

## REVIEW ARTICLE

## Unique Features of Young Age Breast Cancer and Its Management

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Young age breast cancer (YABC) has unique clinical and biological features that are not seen in older patients. Breast tumor biology is more aggressive and is associated with an unfavorable prognosis in younger women. The diagnosis of breast cancer is often delayed, resulting in their initial presentation with more advanced disease. Together, these characteristics lead to a poorer prognosis in younger women than in older women. Young women who receive breast-conserving therapy have a higher rate of local recurrence. Therefore, it is important to secure sufficient resection margins and consider boost radiotherapy to prevent lo-

cal treatment failure. Based on age alone, patients with YABC should be regarded as high-risk cases, and they should be treated with adjuvant chemotherapy. Special considerations regarding psychosocial factors and fertility should be taken into account for young patients. This review discusses the major considerations and principles concerning the management of patients with YABC.

**Key Words:** Age factors, Age of onset, Breast neoplasms, Disease management

## INTRODUCTION

Breast cancer is the most common invasive cancer in women worldwide and it is also the leading cause of death from cancer among women. Despite high incidence rates, the 5-year survival rate of women diagnosed with breast cancer is nearly 90% in Western countries and developed Asian countries. Although improvements in breast cancer treatment and earlier detection have reduced breast cancer mortality in all age groups, young age remains a risk factor for poorer survival [1]. Breast cancer in very young women is rare, but it has unique features that are not observed in older patients. Young age breast cancer (YABC) has aggressive biological characteristics and tends to be diagnosed at an advanced stage, resulting in poorer outcomes than breast cancer in older premenopausal and postmenopausal women. Accordingly, different treatment approaches are required for YABC to achieve optimal therapeutic results. In addition, these patients require special consideration regarding psychosocial factors and fer-

tility. It is important to appreciate the differences between breast cancers in young and older women. This review discusses the major considerations and principles concerning the management of patients with YABC (Table 1).

## OCCURRENCE AND DEFINITIONS

In the United States, approximately 11,000 women aged < 40 years are diagnosed annually with invasive breast cancer, accounting for 4.7% to 4.9% of all patients diagnosed with breast cancer [2,3]. In Western women, < 4% of breast cancer patients are aged < 35 years [4,5]. In contrast, the mean age at diagnosis is about 10 years lower in Korea, as in other Asian countries, and the proportion of patients with YABC is higher in Asian than in Western countries. According to the 2011 Annual Report of the Korea Central Cancer Registry, 13.2% of women diagnosed with breast cancer were aged < 40 years, and 4.7% were aged < 35 years [6].

To date, no consensus has been reached about the definitions of “young age” and “very young age” breast cancer, with various studies arbitrarily or empirically using age cutoffs of 30, 35, and 40 years, depending on the end points being assessed. A systematic analysis of a large number of Korean patients found that age < 35 years was a reasonable cutoff for defining YABC in terms of disease outcome [7]. In addition, the St. Gallen Expert Consensus Report found that an age cutoff of

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Received: August 29, 2014 Accepted: November 5, 2014

**Table 1.** Unique features of young age breast cancer compared to breast cancer in older women

Considerations	Unique features
Biological characteristics	Higher proliferation rates (Ki-67), more grades 3/4 & higher ER negativity [9-13] More BRCA1/2 mutations [22-32]
Diagnostic delay	More advanced stage at presentation [33-35]
Prognosis	Worse in ER-positive breast cancer [14,40-42] 5% increased risk of death/1-year reduction in age [7]
Local therapy	More IBTR [43-47] Higher importance of sufficient resection margins [52] Boost radiotherapy should be considered [47]
Adjuvant chemotherapy	Less chemotherapy-induced amenorrhea [41-42] Greater benefits from chemotherapy [58-59]
Adjuvant hormonal therapy	Tamoxifen resistance [14]
Others	Premature ovarian failure and infertility [66-69] More emotional distress and poorer quality of life [72,73]

ER=estrogen receptor; IBTR=ipsilateral breast tumor recurrence.

< 35 years was an indication for adjuvant chemotherapy [8].

## BIOLOGICAL CHARACTERISTICS OF YOUNG AGE BREAST CANCER

Breast tumor biology was found to be more aggressive in women with YABC than in older premenopausal women, with the former having many factors associated with an unfavorable prognosis, including high proliferation rates, grades 3 and 4 disease, and estrogen receptor (ER) negativity [9-13]. A report from the Korean Breast Cancer Society registration program found that T-stage and the incidence of lymph node positivity were significantly higher and the hormone receptor expression was significantly lower in younger patients (aged < 35 years) than in older premenopausal women (aged  $\geq$  35 but < 50 years) [14].

An analysis of Oncotype DX<sup>®</sup> (Genomic Health Inc., Redwood City, USA) Recurrence Scores (RS) in women with ER-positive breast cancer found that patients aged < 40 years had higher average RS, lower ER expression, and higher expression of genes related to cell proliferation compared with older women [15]. Immunohistochemical assays also showed higher Ki-67 expression in tumors from younger than older patients [16,17]. Moreover, a recent large study of 9,061 ER-positive breast cancer patients showed that Ki-67 expression was inversely proportional to age at diagnosis and was significantly higher in tumors from patients aged < 40 than in those aged  $\geq$  40 years [18].

Studies have also investigated gene expression profiles in

YABC. For example, an analysis of microarray data from several large, publicly available data sets found that the expression of 367 biologically relevant gene sets was higher in tumors from younger women than in those from older women [19]. A subsequent study by the same researchers, however, found that the differences in gene expression were negligible in breast tumors from women aged  $\leq$  45 years and  $\geq$  65 years, after controlling for clinicopathological features, including tumor grade, nodal status, ER expression, and intrinsic breast cancer subtype [20]. Breast tumors in women aged  $\leq$  40 years were found to be biologically distinct, beyond subtype distribution, and enriched with processes associated with immature mammary epithelial cells (e.g., luminal progenitors, mammary stem cells, and expression of c-kit and receptor activator of nuclear factor  $\kappa$ -B ligand) and growth factor signaling [21]. It remains unclear whether YABC itself has distinct molecular features beyond the intrinsic subtypes of breast cancer.

The occurrence of germline mutations in highly penetrant genes, such as BRCA1 or BRCA2, results in breast cancer developing at a younger age. For example, 5.9% to 12.4% of patients aged < 35 years and 11.6% to 17% of patients aged < 40 years had either a BRCA1 or BRCA2 mutation, compared with 1.2% to 6.1% of all patients with breast cancer [22-28]. In selected ethnic groups, such as Ashkenazi Jews, BRCA mutations are present in 29.3% to 44.4% of young women [29-31]. Among Asian women, 8.1% of Korean patients aged < 35 years had BRCA mutations, compared with only 2.8% of non-age-selected patients [32].

## DIAGNOSTIC DELAY

The diagnosis of breast cancer is often delayed in young women, resulting in their initial presentation with more advanced disease. These delays are caused primarily by the younger women themselves, as they are often less concerned about and aware of breast cancer, and by physicians, who have less suspicion of this disease in younger women [33-35]. Current guidelines for breast cancer screening recommend mammograms for women > 40 or > 50 years of age. In addition, mammograms in young women have a markedly lower sensitivity for breast cancer due to the higher incidence of dense breasts in this age group. Diagnosis is also complicated by the various physiological changes and parenchymal development occurring during periods of pregnancy and lactation. The generally more aggressive tumor biology and the more rapid tumor progression in younger patients are indicative of more advanced disease at diagnosis.

However, it has also been shown that presentation with symptoms of breast cancer, rather than age, predicts delay and

higher stage at diagnosis. In a study evaluating the relationship among age, delay in breast cancer diagnosis, and stage, younger women ( $\leq 40$  years) were not more likely to have a delay in diagnosis after adjustment for type of initial sign or symptom [36].

## PROGNOSIS

YABC patients were found to have a poorer prognosis than older women with breast cancer, even after adjusting for the delay in diagnosis of younger patients [37-39]. Studies evaluating the hormone receptor status of tumors suggested that the difference in prognosis between age groups was particularly evident for ER-positive patients [14,40-42]. ER-positive patients aged  $< 35$  years are predicted to be at a 1.5-fold higher risk of mortality on Adjuvant! Online (<http://www.adjuvantonline.com>; Adjuvant! Inc.).

Prognosis has been reported to worsen drastically in patients aged  $< 35$  years and to be inversely associated with age, whereas there was no difference in the prognosis between patients aged 35 to 39 years and older patients [7]. In patients aged  $< 35$  years, the risk of death increased 5% for every 1-year reduction in age, whereas the risk of death was not significantly associated with age in patients aged 35 to 50 years [7].

## LOCAL THERAPY

Ipsilateral breast tumor recurrence (IBTR) after breast-conserving therapy (BCT) has been reported to be significantly higher in younger patients than in older patients (Table 2) [43-47]. Similarly, another study found that IBTR increased with decreasing age, and they further showed that boost radiation resulted in a greater absolute reduction of local failure in younger patients [47]. Women aged  $< 35$  years had an even higher risk of IBTR than those aged 35 to 40 years [48]. Moreover, the relative risk of locoregional recurrence was found to increase 7% for every 1-year decrease in age [49]. In a study investigating age and cancer subtype, the IBTR rate was significantly higher in women aged  $\leq 40$  years, especially in those with the human epidermal growth factor receptor 2 (HER2)

subtype (ER-negative/HER2-positive) breast cancer [50].

Despite this higher risk of IBTR after BCT, the risk of death in young women who received BCT was similar to that of patients who underwent radical mastectomy [51]. Thus, young age itself should not be considered a contraindication for BCT.

Another study evaluated the significance of resection margins after BCT as a function of patient age [52]. Although local failure rates in patients aged  $\geq 45$  years were similar in those having resection margins  $\leq 2$  mm and  $> 2$  mm, differences were observed in patients  $< 45$  years of age [52]. Younger patients with resection margins  $\leq 2$  mm had a local failure rate of 19%, whereas those with wider margins had a local failure rate of 7% [52], suggesting that securing sufficient resection margins is important in younger patients.

Treatment of stage II breast cancer patients aged  $\leq 35$  years with postmastectomy radiotherapy (PMRT) resulted in a significant improvement in local recurrence rates compared with mastectomy alone or BCT [53]. Another study reported that the hazard ratio for locoregional recurrence was 0.54 for PMRT versus mastectomy alone, but PMRT failed to show a survival benefit [54]. Further studies are needed to assess the effectiveness of PMRT in young women according to lymph node status.

An analysis of women included in the Surveillance, Epidemiology, and End Results (SEER) database in the United States who underwent mastectomy for unilateral breast cancer during 1998 to 2002 showed that contralateral mastectomy performed at the same time was associated with an improvement in breast cancer-specific survival only in younger women, aged 18 to 49 years, with stage I/II, ER-negative breast cancer [55]. National Comprehensive Cancer Network guidelines recommend that breast cancer patients aged  $\leq 35$  years or premenopausal and carriers of a known BRCA1/2 mutation should consider additional risk reduction strategies such as contralateral prophylactic mastectomy [56].

Younger women experience greater physical and psychosocial impact after breast surgery than older women [57]. Accordingly, reconstructive surgery using implants or autologous tissue should be strongly considered when mastectomy is inevitable.

**Table 2.** Young age and ipsilateral breast tumor recurrence after breast-conserving surgery

Study	No. of patients	Age cutoff	Risk	p-value	Remark
Fourquet et al. [43]	518	$\leq 32$	RR, 2.44	$< 0.0001$	Breast cancer with T1 or T2, and N0 or N1a
Voogd et al. [44]	879	$\leq 35$ vs. $> 60$	HR, 9.24	$< 0.0001$	From two randomized trials; stage I and II
Jobsen et al. [45]	1,085	$\leq 40$	OR, 2.4	0.027	pT1; lumpectomy with ALND, RT with boost RT
Arriagada et al. [46]	717	$\leq 40$ vs. $> 60$	RR, 4.4	0.0001	Tumor size $\leq 25$ mm
Komoike et al. [47]	1,901	Serial variable	1.06/yr	$< 0.0001$	Age was risk factor regardless of age cut-point

RR=relative risk; HR=hazard ratio; OR=odds ratio; ALND=axillary lymph node dissection; RT=radiotherapy.

## ADJUVANT CHEMOTHERAPY

Although few clinical trials have assessed the effects of adjuvant chemotherapy in younger women alone, large scale trials have shown similar efficacy of chemotherapeutic agents in all age groups. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that anthracycline-based polychemotherapy reduced the annual breast cancer death rate by 38% in women aged < 50 years [58]. In addition, a study by the Danish Breast Cancer Cooperative Group of 10,356 patients aged < 50 years found that the relative risk of death following adjuvant chemotherapy was 1.5- and 2-fold higher in patients aged 35 to 39 and < 35 years, respectively, compared with patients aged  $\geq$  45 years [59]. These results suggest that, based on age alone, young women with breast cancer should be regarded as high-risk patients and be given adjuvant chemotherapy.

A meta-analysis of four randomized controlled trials of 3,700 premenopausal and perimenopausal patients who had received adjuvant cyclophosphamide, methotrexate, and fluorouracil found that overall survival was better in ER-positive than in ER-negative patients aged  $\geq$  35 years, whereas there was no difference between ER-positive and ER-negative patients aged < 35 years [42]. These results suggest that the ovarian-suppressive effects of chemotherapy alone are insufficient for younger patients and that additional endocrine therapies should be considered for patients with ER-positive tumors [42]. The poorer prognosis of young women with ER-positive tumors following adjuvant chemotherapy alone was likely to be due to differences in the incidence of chemotherapy-induced ovarian dysfunction between the age groups [41]. Temporary and permanent amenorrhea occurred in 66% and 59%, respectively, of patients aged  $\geq$  35 years, but in only 12% and 8%, respectively, of patients aged < 35 years [41].

A meta-analysis of randomized trials that evaluated the efficacy of incorporating taxanes into anthracycline-based regimens showed that the addition of taxanes was associated with superior results in all age groups [60]. Similarly, the Herceptin Adjuvant Trial evaluating women with early-stage HER2-positive breast cancer found that age was not strongly associated with the risk of early recurrence and was not a predictor of the benefit derived from trastuzumab therapy [61].

## ADJUVANT HORMONAL THERAPY

Meta-analyses by the EBCTCG in 2005 found that adjuvant tamoxifen therapy for 5 years was effective in lowering death rates for patients of all ages with ER-positive or ER-unknown breast cancer; in particular, tamoxifen reduced the death rate

by 39% in patients aged < 40 years [58]. As mentioned above, however, the prognosis of YABC patients worsens rapidly for patients aged < 35 years, but only in those with ER-positive tumors. A recent report from the Adjuvant Tamoxifen: Longer Against Shorter Trial demonstrated that continuing tamoxifen treatment for 10 years provides further protection against recurrence and breast cancer mortality [62]. Young patients with ER-positive tumors may be the true beneficiaries of longer tamoxifen treatment because their time to natural menopause is longer than that of older patients. No prospective study to date, however, has evaluated the effectiveness of adjuvant tamoxifen in patients aged < 35 years.

The poor prognosis observed in young patients with ER-positive breast cancer may be a result of their reduced compliance with tamoxifen treatment due to their concerns about the adverse effects of tamoxifen, especially on fertility. A large-scale study found that the proportion of patients who received hormone therapy decreased as the age group became younger [7]. However, the age-associated difference in survival in patients with hormone receptor positive disease was significant both in patients who did and did not receive hormone therapy, suggesting that tumors in very young patients may be resistant to tamoxifen [14].

An alternative form of hormone therapy in premenopausal women is ovarian suppression. Recovery of menstruation after chemotherapy-induced amenorrhea is more frequent in younger than in older women [63], suggesting that younger patients may benefit more from ovarian suppression. We await results from randomized controlled trials comparing standard treatment using oral endocrine therapy with additional ovarian suppression in premenopausal women, including those aged < 35 years [64,65].

## OTHER CONSIDERATIONS

Preserving fertility and preventing premature ovarian failure (POF) is one of the most important considerations in young breast cancer patients. Embryo and oocyte cryopreservation are considered standard practice for fertility preservation in cancer patients [66]. However, premenopausal women receiving chemotherapy plus luteinizing hormone-releasing hormone analogues have been shown to prevent POF in both hormone receptor-positive and -negative breast cancer [67-69]. These options should be discussed with YABC patients who will undergo cytotoxic chemotherapy.

Young women have a longer life expectancy after a diagnosis of breast cancer. Nevertheless, there is no consensus as to whether and how postoperative radiotherapy and chemotherapy affects organs such as the heart and lungs decades after



treatment [70]. Efforts have been made to develop recommendations for the surveillance of YABC survivors who were given chest radiation before the age of 30 years [71].

Furthermore, ovarian cysts occurred frequently in younger women who received tamoxifen [72]. Younger women also experience more emotional distress and poorer quality of life than older women during breast cancer diagnosis and treatment [72,73].

## CONCLUSIONS

Although its incidence is low, YABC has many clinical and biological features that must be considered during treatment. First, its diagnosis is usually delayed, resulting in an advanced stage at presentation. This may be due to a lack of screening programs for young women or to the aggressiveness of the disease itself. Second, IBTR after BCT is significantly more frequent. Although total mastectomy is not mandatory, securing a sufficiently wide resection margin is required for lumpectomy, and boost radiotherapy should be considered in local treatment of YABC. Third, systemic recurrence and mortality after treatment is more frequent in younger patients than in older women, especially in those with hormone receptor positive breast cancer. This may be caused by the lower incidence of menopause after chemotherapy, poor compliance with appropriate hormone therapy, and/or intrinsic tumor resistance to tamoxifen. Fourth, chemotherapy has greater benefits in younger women, suggesting that aggressive chemotherapy should be considered, even in patients at low to intermediate risk. Finally, younger women require greater psychosocial support because they experience more emotional distress and poorer quality of life than older women, before and after treatment. Younger women also require appropriate counseling and other measures regarding fertility preservation and possible pregnancy. These women must be tested for BRCA1/2 mutations to determine if they have hereditary breast cancer.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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