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EDITORIAL

Introduction and impact of the young breast cancer in China consensus

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Introduction

Breast cancer is the most common cancer type in adolescents and young adults < 40 years of age, accounting for 30% of cancers in this age group[1]. Breast cancer in the young presents significant challenges for patients and society, including more aggressive tumor biology, poor prognosis, genetic susceptibility, fertility preservation, and complex psychosocial issues. Moreover, because of the markedly younger median age of breast cancer, the proportion of young breast cancer patients in China is significantly higher than Western countries[2]. The first Young Breast Cancer in China (YBCC) consensus meeting was held in Guangzhou, China in December 2021 to address exclusive challenges and requirements facing young patients with breast cancer. Chinese medical experts from multiple specialties had an extensive discussion and formulated a consensus over several hot topics in young patients with breast cancer. The "Expert Consensus on the Diagnosis and Treatment of Young Breast Cancer in China (2022 edition)" published in the *Chinese Medical Journal* has garnered significant attention[3], highlighting enormous interest in the YBCC consensus in the medical community and public.

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YBCC epidemiology

Studies indicate that breast cancer among young patients in China imposes an enormous disease burden for society. First, China has the largest global share of breast cancer in all age groups (15.6%) as well as young patients (13.2%)[2]. Second, the proportion of young breast cancer patients in China is markedly higher than Western countries. Several large population studies showed that 15%–19.9% of breast cancer patients are < 40 years of age[4,5] and approximately 10% of patients are ≤ 35 years of age[6]. Moreover, the incidence of breast cancer in young patients increases by approximately 2% annually[7]. In fact, the median age of breast cancer onset in the United States is 62–64 years but the median age of breast cancer onset is much younger (45–49 years) in East Asia countries, including China[4,8].

Unmet needs of young patients with breast cancer in China

Lack of breast cancer awareness and a standard screening program

Breast cancer screening has a crucial role in establishing an early diagnosis. Nevertheless, the participation rate in breast cancer screening is low in China with < 5% of cases identified through screening initiatives[9,10]. In addition, the optimal strategy for breast cancer screening in young women is controversial for the following reasons: dense breast tissue; lack of a standard protocol; and low cost-effectiveness.

Clinical questions without a standard answer or high-level evidence

The optimal surgical approach for patients with *BRCA1/2* genes mutations is controversial[11-13]. Because breast reconstruction

is less affordable and accessible in China, young breast cancer patients often express preferences for breast-conserving surgery (BCS), even in the presence of a *BRCA* mutation. The risk of ovarian cancer is also increased in patients with *BRCA1/2* germline mutations[14,15] but the optimal timing of prophylactic oophorectomy has not been determined.

The higher risk of recurrence and metastasis in young breast cancer patients raises the question of whether more or stronger adjuvant chemotherapy should be administered. Moreover, incomplete ovarian function suppression (OFS) during treatment has a higher incidence in younger patients[16,17]. The definition, incidence, monitoring, prognostic impact, and treatment strategy of ovarian escape is not completely understood.

Tamoxifen use is associated with endometrial proliferation and a potential increase in endometrial cancer risk[18,19], prompting several unresolved clinical questions, including the necessity and optimal frequency of endometrial surveillance in tamoxifen-treated patients, the endometrial thickness threshold for intervention, and standardized indications for diagnostic dilation and curettage in asymptomatic patients with a thickened endometrium. Fertility preservation is a common request in young breast cancer patients. Unresolved issues include optimal conception timing and the development of individualized fertility preservation protocols that balance oncologic safety with reproductive outcomes.

The current international guidelines or consensus is insufficient

Several international guidelines and consensus statements have been developed to help manage young breast cancer patients [Breast Cancer in Young Women (BCY), European Society of Breast Cancer Specialists (EUSOMA), and American Society of Clinical Oncology (ASCO)]. These statements provide recommendations on fertility preservation, psychosocial support, and long-term survivorship issues. However, because of different culture and healthcare resources, there are many questions from young breast cancer patients in China that are not addressed in the international guidelines. Therefore, it is necessary to develop a consensus that suits the needs of young breast cancer patients in China.

The first YBCC expert consensus[3]

Definition of YBCC

Although the median age of breast cancer onset in China is 45–49 years, 62% of the YBCC panelists were of the opinion that the definition of young breast cancer is < 40 years, which is the same as the BCY international consensus, and 32% of the panelists chose < 35 years of age as the definition of young breast cancer. Consequently, a consensus was reached by YBCC expert panel to define young patients with breast cancer as < 40 years of age.

BRCA1/2 gene mutation

The YBCC experts were more conservative with respect to the indications for *BRCA1/2* mutation testing. Of the panelists, 63% supported testing in young patients (< 40 years of age), 97% endorsed testing for patients with a family history of breast cancer, and 91% recommended testing for triple-negative breast cancer (TNBC). These outcomes reflect the different epidemiologic characteristics and socioeconomic status of the Chinese breast cancer population.

For young breast cancer patients with a *BRCA1/2* mutation who are candidates for BCS, 72% of YBCC experts recommend that the surgical decision should be based on an individualized recurrence risk assessment, including age, family history, and personal preference. For patients with a *BRCA1/2* mutation who will undergo a nipple-sparing mastectomy (NSM) with implant reconstruction, 66% of experts suggest the choice of contralateral prophylactic mastectomy should be made considering patient age, family history, and contralateral breast cancer risk. In addition, for patients with a *BRCA1/2* mutation choosing BCS or not opting for contralateral prophylactic mastectomy, 82%, 71%, and 87% of experts recommend close surveillance with ultrasonography, mammography, and MRI, respectively.

The clinical utility of platinum-based chemotherapy in the adjuvant setting for *BRCA1/2* mutation carriers is controversial but no consensus has been reached by the YBCC expert panel.

The decision regarding prophylactic bilateral salpingo-oophorectomy and the timing should consider the mutation type, family history, and personal preferences according to 72% of experts.

Chemotherapy

YBCC experts suggest that young patients, like the older patients, should have the chemotherapy regimen chosen based on factors, such as disease stage and molecular subtype, but not age. Choosing more aggressive chemotherapy solely due to younger age may pose a risk of overtreatment.

Of the YBCC panelists, 84% were in favor of the anthracycline-taxane sequential regimen for medium-high risk (defined as stage II or III with positive lymph nodes) human epidermal growth factor receptor 2 (HER2)-positive young breast cancer patients, while 70% of the panelists chose a taxane combined with platinum regimen in addition to dual HER2 blockade. Most panelists chose an anthracycline-taxane sequential regimen and only 17% of the panelists chose an anthracycline-free regimen consisting of six cycles of docetaxel and cyclophosphamide (6TC) for medium-high risk

HER2-negative young breast cancer patients. Of the YBCC panelists, 71% were opposed to routinely considering platinum as a substitute for anthracyclines in adjuvant chemotherapy regimens for medium-high risk HER2-positive or TNBC young breast cancer patients.

Endocrine therapy

Hormone receptor (HR)-positive young breast cancer patients often need OFS to lower relapse risk. A gonadotropin-releasing hormone agonist (GnRHa) is the most frequently used drug to achieve OFS. Of the YBCC panelists, 81% supports both formulations as options for OFS when used together with selective estrogen receptor modulators (SERMs). However, 50% of the panelists were cautious when aromatase inhibitors (AIs) were used with a three month (3M) GnRHa in young patients because younger patients are more likely to experience OFS escape (defined as failure to achieve complete OFS with a GnRHa) due to potent ovarian function.

The optimal timing for initiating AI has not been established for patients using a GnRHa in combination with an AI. The YBCC expert panel has not reached a consensus on this issue with 43% recommending that AI should only be used after confirming ovarian suppression to avoid the increase in plasma estradiol levels caused by AI monotherapy when OFS is not successful. Nevertheless, 53% of YBCC panelists proposed simultaneous initiation of a GnRHa and AI when GnRHa begins to control hormone levels from the hypothalamic-pituitary axis because the stimulatory effect of an AI on the hypothalamic-pituitary pathway is limited.

Regular estradiol (E2) monitoring facilitates early detection and management of ovarian function escape, ensuring effective treatment. However, a unified frequency and standard for E2 monitoring have not been established in clinical practice. The YBCC expert panel did not reach a consensus because 45% did not support the routine monitoring of E2 levels in patients receiving GnRHa treatment.

Fertility preservation

The YBCC expert panel suggested that suitable fertility preservation strategies should be considered prior to initiating systemic therapy for young patients with desired fertility. In addition, a chemotherapy regimen without cyclophosphamide should be considered to minimize ovarian damage. A GnRHa, although not sufficient alone, should be used for ovarian protection during chemotherapy in addition to the aforementioned measures.

Gynecologic conditions

Of the YBCC panelists, 90% agreed that tamoxifen increases the risk of endometrial cancer in peri- and post-menopausal patients. However, 48% of the YBCC panelists never encountered a patient with endometrial cancer after tamoxifen use, indicating the low incidence of tamoxifen-related endometrial cancer in China. Moreover, 67% and 91% of the YBCC panelists supported regular monitoring of endometrial thickness in premenopausal and peri-/post-menopausal patients, respectively. However, the YBCC expert panel did not reach a consensus within the gynecologic community on the appropriate threshold for diagnostic curettage in asymptomatic patients receiving tamoxifen.

The YBCC expert panel did not reach a consensus on whether breast cancer patients can use progestin-containing intrauterine devices or long-term oral contraceptives due to the low level of existing evidence.

Guideline differences for young breast cancer patients

The YBCC consensus is more focused on the questions and needs in young Chinese patients compared to the comprehensive coverage of the BCY5 consensus[20]. More importantly, the YBCC consensus references research data from the Chinese population and aligned recommendations with the Chinese context. The guidelines related to young breast cancer patients are summarized in **Table 1**, offering a comparative view of similarities and differences.

Impact of the YBCC consensus in China

As the first Chinese consensus of young breast cancer patients, the YBCC consensus selected 50 issues for voting, taking into account specific characteristics of China. The final consensus included six sections: epidemiology; *BRCA* mutation; chemotherapy; endocrine treatment; fertility issues; and gynecologic concerns in young breast cancer patients. These sections address the most common concerns of young patients and highlight areas where treatment approaches may differ and require additional study.

The first edition of the "The Expert Consensus on the Diagnosis and Treatment of Young Breast Cancer in China (YBCC consensus)" was published in the *Chinese Medical Journal* in February 2023. To date, the YBCC consensus has garnered > 21,000 reads and nearly 4000 downloads, highlighting the enormous interest from the medical community and public. Furthermore, the Second YBCC Consensus Conference was held in December 2024, with the hope to address more specific questions for such a large and growing population.

Greater than 20 symposia were held in different cities in China to facilitate a better understanding and application of

Table 1 Consensus and guideline comparisons

Consensus/ Guideline	YBCC[3]	BCY5[20]	ESMO[21]	NCCN[22,23]	ASCO[24,25]
Age definition	< 40 years	< 40 years	Not specified	Not specified	Not specified
BRCA1/2 testing criteria	Recommended for patients with a family history, TNBC, or age < 40 years	Follow national/international guidelines	/	Patients ≤ 50 years	Recommended for all newly diagnosed patients ≤ 65 years
Surgical approaches (patients with *BRCA* mutation)	1. BCS based on individual risk	1. Encourage BCS	1. BCS with radiotherapy is a safe alternative to RRM for high-risk PV-associated patients	1. BCS possible; discuss risk reduction	1. BCS requires weighing risks and surveillance capabilities
	2. Contralateral mastectomy depends on age/family history	2. Consider bilateral mastectomy	/	/	/
	3. RRSO timing by mutation type/patient preference	3. RRSO: *BRCA1* (35–40 years) *BRCA2* (~40 years)	3. RRSO: *BRCA1* (35–40 years) *BRCA2* (~40 years)	3. RRSO: *BRCA1* (35–40 years) *BRCA2* (~40 years)	/
Chemotherapy	1. Intensification of chemotherapy solely based on age is not recommended	1. Intensification of chemotherapy solely based on age is not recommended	/	/	/
	2. Avoid platinum replacing anthracycline	2. Anthracycline remains standard	/	/	/
	3. No consensus on platinum for patients with BRCA mutation	3. Consider platinum for patients with TNBC or BRCA mutation in neoadjuvant	/	/	/
	4. Prefer liposomal doxorubicin because of less toxicity, such as cardiotoxicity and alopecia	/	/	/	/
Endocrine therapy	1. OFS + AI for high-risk patients	1. OFS + AI for high-risk patients	/	1. OFS + ET for premenopausal and high-risk patients	/
	2. 3M GnRHa or 1M GnRHa	2. Prefer 1M GnRHa	/	2. 3M GnRHa or 1M GnRHa	/
	3. Estrogen monitoring debated	3. Monitor estradiol if ovarian escape suspected	/	/	/
Fertility preservation	1. GnRHa during chemotherapy	1. GnRHa during chemotherapy	/	1. GnRHa during chemotherapy	1. GnRHa (When proven fertility preservation methods are not feasible)
	2. Avoid cyclophosphamide during chemotherapy	/		/	/

Table 1 Continued

Consensus/ Guideline	YBCC[3]	BCY5[20]	ESMO[21]	NCCN[22,23]	ASCO[24,25]
	3. Using ART before treatment	3. Using ART before treatment		3. Patients should be advised not to become pregnant while on any systemic therapy	3. Various ARTs are recommended
	4. Postpone pregnancy post-recurrence peak	4. HR+ patients: complete 18–24 months of ET before pregnancy	/	/	/
Gynecologic management	1. Monitor endometrial thickness (tamoxifen users)	/	/	/	/
	2. Use barrier contraception and avoid hormonal methods	2. Hormonal contraception contraindicated in young survivors	/	2. Use IUD, barrier, tubal ligation, or vasectomy (patients with no intent of future pregnancies) for contraception and avoid hormonal methods	/

AI, aromatase inhibitor; ART, assisted reproductive technology; BCS, breast-conserving surgery; GnRHa, gonadotropin-releasing hormone agonist; IUD, intrauterine device; OFS, ovarian function suppression; PV, pathogenic variant; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; TNBC, triple-negative breast cancer.

the YBCC consensus. These meetings often attracted a huge interest from local physicians and fostered collaboration among different medical disciplines. Moreover, researchers in China have begun to focus on young breast cancer patients and published several prominent papers to address concerns. A population-based cohort study has shown a consistently increasing trend of breast cancer patients < 35 years of age in China[7]. Researchers have utilized large patient datasets to compare the efficacy of different dosages of GnRHa, aiding both patients and physicians in selecting the most suitable option[26]. In addition, researchers conducted a comprehensive systematic review addressing the issue of incomplete OFS during GnRHa administration, thereby providing clinicians with insights that better understand and manage incomplete OFS[27].

In March 2023 the first "YBCC Outpatient Clinic" was opened in the Breast Tumor Center of Sun Yat-sen Memorial Hospital. This clinic brings together expertise from genetics, breast surgery, plastic surgery, reproductive medicine, and gynecology, focusing on providing a "one-stop" comprehensive medical consultation for young breast cancer patients < 40 years of age. The YBCC Outpatient Clinic has now been expanded to 14 high-level hospitals in different cities across China. To date, > 50,000 patients have visited the YBCC Outpatient Clinic, demonstrating that YBCC is welcomed by patients and physicians alike. Implementing the YBCC consensus across different levels of hospitals is a complex task that requires systematic planning and multi-dimensional support. Recognizing the comprehensive and multi-disciplinary nature of these challenges is essential for achieving high-quality care of young breast cancer patients.

The future of YBCC consensus

There are still many unanswered questions with respect to young breast cancer patients. With the number of young breast cancer patients growing, many clinical trials have begun to address the concerns and needs, although a large scale randomized trial is more difficult than trials involving elderly patients. Because China has the largest number of young breast cancer patients worldwide, the YBCC consensus, which is based on the clinical experience of Chinese experts, could also be helpful for young breast cancer patients outside of China. Currently, several studies focusing on young breast cancer patients are ongoing. The NCT06793306 and NCT06027541 trials are primarily analyzing the prognosis and molecular characteristics of young breast cancer patients, while the ChiCTR2300068147 and ChiCTR2500098174 studies are investigating the impact of a GnRHa on this patient population. In addition, research is being conducted on the development of Young Breast Cancer Patients' Report Outcome Scale (YBCC-PRO) in China. These studies are expected to provide stronger evidence and guidance for the diagnosis and

treatment of young breast cancer patients. It is hoped that with additional collaboration we can work together to offer more high-level evidence to address the questions and concerns of young breast cancer patients worldwide and provide more comprehensive and higher-quality medical care treatments.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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