The 1st International Consensus Conference for Breast Cancer in Young Women (BCY1) took place in November 2012, in Dublin, Ireland organized by the European School of Oncology (ESO). Consensus recommendations for management of breast cancer in young women were developed and areas of research priorities were identified. This manuscript summarizes these international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

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Introduction

Young women with breast cancer face not only the threat of a potentially fatal illness and burdensome treatment, but they have the added burden of unique concerns. Most concerning, young women on average experience increased risk of recurrence, both local and systemic, and death after a diagnosis of breast cancer [1]. This is due in large part to their increased risk of presenting with biologically aggressive types of cancer (i.e., more high grade when ER+ disease, increased Her-2-positive and triple negative disease) and at more advanced stage [2–6]. The biologic, medical and psychosocial underpinnings of this disparity in disease outcomes are an area of active research, particularly whether or not young age alone will remain an independent prognostic factor as we improve...
our understanding of molecular subtyping of breast cancer. Nevertheless, one of the consequences of this reality is that young women often need and receive aggressive multimodality treatments (i.e., surgery, radiation, chemotherapy, biological therapies and endocrine therapy as appropriate), each of which can cause significant side effects and impact on quality of life. Young women are usually pre-menopausal at diagnosis and systemic therapy may cause amenorrhea (either permanent or temporary, with associated menstrual symptoms) and infertility, a substantial problem for women who are interested in having biologic children in the future. Young women are also more likely to harbor a genetic predisposition to breast cancer (e.g., a BRCA 1 or BRCA 2 mutation) than older women, especially if triple negative, which may impact on their local treatment decisions, considerations for prophylactic contralateral mastectomy and salpingo-oophorectomy, and future risks [7–9]. Further, likely due in part to the issues raised previously, the relative lack of peer support and information available for young women, as well as their developmental stage in life, young women with breast cancer are at increased risk of psychological distress at diagnosis and in long-term follow-up [10,11]. Additionally, some young women may be at risk of being overtreated based solely on age, increasing the burden of breast cancer diagnosis and treatment.

The evidence base for treatment of young women with breast cancer is limited given the demographics of the disease. Women aged younger than 40 at diagnosis represent fewer than 7% of women diagnosed with breast cancer in developed countries [12]. While young women do participate in research studies, there are rarely enough young women in any given study to focus on this subset and results to inform the treatment of young women are generally derived from findings among women of older age. In recent years, there have been an increasing number of prospective studies focused on young women, however there remains an urgent need for intervention studies, in particular, to understand and improve outcomes in this population [3,13,14]. For the purpose of these recommendations, consistent with prior guidelines focused on young women [15], the panel decided to define “young women” as women under the age of 40 at breast cancer diagnosis out of recognition that these women have specific issues including those related to fertility, genetics and psychosocial concerns that often deserve a different approach compared to older premenopausal and post-menopausal women.

Methodology

Prior to the BCY1 Conference, a set of preliminary recommendation statements on the care of young women with breast cancer were prepared building mainly on the previous work of members of the EUSOMA guidelines [15]. These recommendations were circulated to panel members by email for comments and corrections on content and wording. A final set of statements was presented, discussed and voted on during the consensus session of BCY1. All panel members were instructed to vote on all questions; with members with a potential conflict of interest or who did not feel comfortable responding (e.g., due to lack of expertise on the topic) instructed to abstain for that particular question. Where there were areas of substantial controversy or disagreement, it is noted in the discussion of the recommendations.

Levels of evidence (I–V) and grades of recommendation (A–D) as used by the American Society of Clinical Oncology and the European Society of Medical Oncology (ESMO) are given in brackets [16]. Statements without grading were considered justified standard clinical practice by the panel experts (Table 1). Supplementary Table 1 lists all members of the BCY1 consensus panel and their disclosure of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

General considerations when caring for young women with breast cancer (Table 2)

The care of women with breast cancer in the modern era has become increasingly complex and generally requires input from a number of specialists with expertise in surgery, medical oncology, radiation oncology, and other areas. Specialized breast clinics have allowed for a focused, multidisciplinary approach, to the care of women with breast cancer in general [17,18]. In no population is this need more evident and likely to be valuable than in young women with breast cancer given their well-documented additional burdens and concerns [19]. Further, there is evidence that there are
gaps in the care of young women after a diagnosis of breast cancer, particularly with regard to their unique needs including fertility, psychosocial and sexual health, as well as genetic issues [10]. Thus, the panel agreed that all young patients should be attended to in a multidisciplinary fashion and communication prior to beginning of therapy and attention to their unique issues are highly recommended. It was noted by panel members to not forget the importance of breast nurses as part of the team, particularly as a “navigator” (at least in some settings) to guide the patient. The team should be appropriate for the current management of clinical issues and additional specialists should be available for consultation (i.e. fertility service providers, mental health professionals, physiotherapists and sexual experts) recognizing that access to such professionals may be limited, particularly in lower resource settings.

When providers are considering treatment options for young women, it should be recognized that most data are derived from studies of older women. Further, panel members noted that many specific issues in the treatment of young women with BC, both in the early and in the advanced settings, still lack definitive proven standards. Therefore, well-designed, prospective randomized trials should be a global research priority. This may be particularly important for women with a clear hereditary predisposition (e.g., BRCA 1/2 mutation carriers) as at this time there are only limited data in this subpopulation.

Extensive data suggest that tumors that develop in younger women tend to be of more aggressive phenotypes and with more advanced stage disease than older women [2–6,13]. Recent studies have sought to evaluate whether there are factors distinctive to the biology of breast cancer in young women with data suggestive of potentially unique biology of tumors arising in younger patients [4,20,21]. Yet this data requires further validation. Nevertheless, whether young age alone will remain a prognostic or predictive factor as we improve our understanding of tumor subtyping remains an area of active research. Given the lack of definitive evidence for improvements in outcome from an alternative approach, at this time the choice of most treatments for young women, both in the early and the advanced setting, should be driven by the biological characteristics of the tumor (i.e. ER/PR, HER-2, proliferation, grade), tumor stage, menopausal status/hormonal milieu, patient’s comorbidities and personal preferences, especially when benefits may be modest or options are equivalent in outcome (e.g. mastectomy versus breast conservation), similarly to treatment decision in older women [17,22]. The panel strongly supported the concept that young age alone should not be a reason to prescribe more aggressive therapy.

Diagnosis, imaging, and staging

Young women are more likely to present with a mass or symptom due to the lack of screening programs and to inadequate imaging for their frequently dense breasts [5,23]. Screening for breast cancer in young women including women with hereditary risks was beyond the scope of the guideline panel. However, the panel did discuss the presentation of breast cancer in young women and whether there was evidence to support an alternative approach to diagnostic imaging in young women compared with older women. In particular, ultrasound (US) and magnetic resonance (MRI) are often used to delineate the extent of disease given dense breasts in young women, and the fact that most young women present with a symptom compared with older women who are more likely to present with a screening mammogram [5]. However, panel members recommended that particular care be taken in this regard recognizing that there is no evidence that addition of MRI in this setting improves outcomes, and recent evidence suggests no benefit in terms of local recurrence or distant recurrence with pre-operative MRI in young or older women [24–26]. Consideration may also be given to breast MRI in young women if a genetic predisposition to the disease is suspected [27]. The panel strongly supported that, when MRI done, it should be performed by nationally/regionally approved and audited services. There is no evidence to support routine staging for metastatic disease merely based on patient age. In young women with breast cancer, the recommended staging, including assessment of axillary nodal status, does not differ from that for older patients. The panel supported breast self-examination mostly for breast awareness and in low/middle income countries but considered it not reliable as surveillance method.

Genetic counseling and testing (Table 3)

Genetic counseling and testing allows for the identification of women who are at dramatically increased risk of new primary breast cancer and ovarian cancer; further it has implications for the cancer risks of their relatives. Thus, genetic counseling and testing is prudent for all young patients recognizing that 10–15% of unselected patients diagnosed under the age of 35 will harbor a BRCA 1 or BRCA 2 mutation [28]. Further, young women with breast cancer are also at risk of having more rare genetic cancer syndromes including a germline p53 mutation (Li–Fraumeni syndrome).

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<th>Table 2</th>
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<td><strong>Guideline statement</strong></td>
<td><strong>LoE</strong></td>
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<tr>
<td>1. The Care of all young patients with breast cancer (either early stage, ER+, or advanced disease, ABC) should be discussed within a multidisciplinary team before any treatment decision-making.</td>
<td>Expert opinion</td>
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<td>2. In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition and fertility are highly recommended as part of the individual treatment planning.</td>
<td>Expert opinion</td>
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<td>3. Young age by itself should not be the reason to prescribe more aggressive therapy than general recommendations.</td>
<td>Expert opinion</td>
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<td>4. Choice of treatment should include but not be limited to the extensive biological characteristics of the tumor (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumor stage, menopausal status, and patient’s comorbidities and preferences.</td>
<td>Expert opinion</td>
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<td>5. Additional consideration may be given to ultrasound or breast MRI in young women particularly in the setting of very dense breast tissue or consideration of a genetic predisposition to the disease.</td>
<td>Expert opinion</td>
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<td>6. All young women should be counseled about the risks and associated symptoms and outcomes of treatment-related amenorrhea and premature menopause before the onset of systemic therapy (either CT or ET) and referred for special counseling/consultation if interested in fertility preservation.</td>
<td>Expert opinion</td>
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<th>Table 3</th>
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<td><strong>Guideline statement</strong></td>
<td><strong>LoE</strong></td>
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<td>6. Every young woman (under 35–40) with breast cancer should be offered genetic counseling before starting the treatment and in follow-up, if not done initially.</td>
<td>Expert opinion</td>
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<td>7. Genetic testing should be conducted only following genetic counseling with a genetic counselor (or other trained health professional) who explains the implications of the results of the genetic testing. The patient must be made aware that the presence of a predisposing mutation may have an impact on patient management, follow-up and decision making, as well as for family members.</td>
<td>Expert opinion</td>
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Syndrome) or a PTEN mutation (Cowden’s Syndrome) [29,30]. There was discussion among the panel of whether genetic counseling should be only family based or considered in all patients between 35 and 40. National guidelines differ to this extent and a consensus was not reached. For those women who are not ready to consider genetic issues at breast cancer diagnosis, access to genetic counseling should be offered again during follow-up, to address in the patient issues of specific intensive surveillance and risk reduction of additional primary tumors, and risk issues for relatives.

**Early breast cancer**

**Locoregional treatment (Table 4)**

**Surgery**

Breast conserving surgery (BCS) followed by radiotherapy (RT) provides the same long-term survival benefit as modified radical mastectomy in women with stage I—II breast cancer, despite a significantly higher rate of local recurrences [31]. Young age is an independent risk factor for increased local recurrence [32,33]. The available evidence in young women suggests breast conservation followed by radiotherapy is associated with an acceptable local recurrence rate and a survival rate similar to mastectomy and these outcomes have been improving over time. [32,34,35] The panel therefore recommends conservative surgery as the first option whenever suitable. Esthetic outcomes, body image changes and the impact on sexuality may be more relevant in young women: when mastectomy is indicated, skin- and nipple-sparing techniques with immediate breast reconstruction, when feasible, or other oncoplastic techniques can provide adequate oncological control while also addressing the cosmetic needs [36,37].

There is no evidence of an increased false negative rate or a worse outcome in young patients undergoing sentinel lymph node biopsy (SLNB) [38,39]. Indication for SLNB and surgical management of patients with SLN involvement should be the same as in older patients.

**Radiotherapy**

Long-term side effects of radiotherapy to organs at risk (i.e. ipsilateral lung, heart and contralateral breast) are particularly relevant in young women with their potential long-term survival. Modern techniques and high quality standards are therefore mandatory in order to minimize risks/maximize benefits. An additional boost to the site of local excision must be offered after BCS and whole breast radiotherapy to all young patients given that they are at particularly high risk for local recurrence: for patients ≤40 years, the 16 Gy boost to the tumor bed reduced the 5-year local recurrence rate (LRR) from 20% to 10% [40–42].

Young age is also a recognized risk factor of increased local relapse after mastectomy and involvement of the internal mammary chain (IMC) [43]. In light of this, the possibility of post-mastectomy radiotherapy and IMC irradiation should be discussed on an individualized basis, similar to recommendations for older women, balancing potential benefits, adverse cosmetic outcomes and long-term side effects [22].

Hypofractionated, abbreviated schedules with a higher dose per fraction, have been evaluated in several randomized trials: these studies have generally demonstrated equivalent rates of locoregional recurrence (LRR), disease-free survival (DFS) and overall survival (OS) compared with conventional fractionation [44]. The rates of acute and long-term toxicities (one trial providing follow up greater than 10 years) have not been increased: in particular, cosmetic outcomes were not worse in patients treated with abbreviated-course RT and younger patients had slightly better long-term cosmetic results in the randomized trial with the longest reported follow-up [45]. The majority of patients included in these studies were nevertheless of older age with early-stage low-risk invasive ER+ disease; patients not meeting these criteria were relatively underrepresented: in particular ≤30% of patients were ≤50 years and few of the trials reported subgroup analyses. For the time being, the majority of the panel therefore agreed that hypofractionation cannot yet be considered standard of care in young patients but can be proposed in selected cases and discussed on a case by case basis. More sophisticated treatment techniques and mature data may soon extend the indication, possibly reducing the underuse of radiotherapy in young women due to competing family demands and logistic issues [46].

Partial breast irradiation (PBI) is not indicated in young patients outside clinical trials given that all the evidence and international recommendations guidelines apply to women ≥50 years at diagnosis [47].

**Adjuvant systemic treatment (Table 5)**

Recent evidence suggests that the currently available gene expression signatures add prognostic information to classic clinicopathologic factors irrespective of age [4,6,48,49]. Prospective data from the two major randomized trials MINDACT and TailorX are...
The combination of an aromatase inhibitor and a LH-RH analog can be effective but definitive randomized confirmation is warranted [50,51].

Neoadjuvant endocrine therapy

Neoadjuvant ET should not be proposed to young women outside clinical trials. The limited available evidence suggests that the combination of an aromatase inhibitor and a LH-RH analog can be effective but definitive randomized confirmation is warranted [50,51].

Endocrine therapy (ET)

Young women with invasive hormone receptor-positive (HR+) breast cancer should be considered for adjuvant tamoxifen regardless of age, lymph-node status or chemotherapy administration [22,25–54]. The magnitude of benefit of 5 years of tamoxifen on disease recurrence and mortality is similar for younger as compared to older women and comparable benefits are also reported in very young (<35 years) women irrespective of the lower rate of permanent amenorrhea following adjuvant chemotherapy in this population [52].

Data on HER-2 influence on adjuvant ET in younger women are limited, but in the presence of oophorectomy, the impact of adjuvant tamoxifen on outcome is comparable in patients with HER-2-positive and HER-2-negative tumors [55].

The optimal duration of ET for high-risk premenopausal women has not been adequately studied. After the BCT 1 meeting, the ATLAS and aTTom (Adjuvant Tamoxifen: To Offer More?) studies reported that extending adjuvant tamoxifen treatment for a total of 10 years, compared to stopping at 5 years, reduced breast cancer mortality by about one third in the first 10 years following diagnosis and by a half subsequently [56,57]. Yet, definite long-term side effects of tamoxifen, such as hot flashes and venous thromboembolism, which need to be considered when discussing extended tamoxifen in patients with a potential life expectancy. The panel members reviewing this manuscript agreed that extending tamoxifen therapy beyond 5 years should therefore be considered in premenopausal women and that treatment decision should be individualized, balancing the estimated absolute benefit, the risk for late relapse and quality-of-life issues. Given the benefits demonstrated in the MA.17 trial of switching to the aromatase inhibitor letrozole after 4.5–6 years of tamoxifen, this strategy can be considered in women who have become definitively post-menopausal in follow-up [58]. However, it can be difficult to determine that a young woman is definitively post-menopausal and great caution is recommended given the potential for residual ovarian function [59].

The therapeutic impact of a GnRH analog is still a matter of study and debate. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of trials with known HR status suggested GnRH analog to be beneficial whether used alone, in addition to tamoxifen or chemotherapy, and as an alternative to chemotherapy [60–62]. The effects of GnRH analogs were greater in women <40 years in whom chemotherapy is less likely to induce permanent amenorrhea. However, there were few trials testing the addition of GnRH analogs to tamoxifen (with or without chemotherapy) and no trials had compared a GnRH agonist against chemotherapy with tamoxifen in both arms. Additionally, modern standard chemotherapies are generally less associated with premature menopause than those included in the Oxford overview and the question of whether adding a GnRH agonist is only useful when amenorrhea is not achieved with chemotherapy is still unanswered [63].

Optimal duration of LH-RH agonists is also unknown, although most studies have utilized 2–3 years of LH-RH agonist with 5 years of tamoxifen. The results of the International Breast Cancer Study Group (IBCSG)-led Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) trials, awaited in the course of 2014, will clarify the added role of GnRH agonist compared with tamoxifen alone ± chemotherapy [64]. For the time being, the panel therefore endorsed tamoxifen as the standard adjuvant ET in young patients and that the addition of a GnRH analog should be discussed on an individualized basis. The panel however agrees that the upcoming results of the SOFT trial will provide further evidence into this clinically relevant question.

The only available evidence of adjuvant aromatase inhibitors (AIs) combined with GnRH analog provided by the ABCSG-12 trial

Table 5

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<th>Neo/adjuvant systemic treatment</th>
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<tr>
<td>17. The indications for and the choice of type of adjuvant systemic treatment for invasive breast cancer should be driven, as for women in other age categories, by the biological characteristics of the tumor (including, but not limiting to, HR and HER-2 receptors, proliferation markers (e.g. Ki-67), and grade), the tumor stage, patient's comorbidities and menopausal status.</td>
<td>Expert opinion</td>
<td>IA</td>
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<td>18. Neoadjuvant ET should not be used in young women outside clinical trials.</td>
<td>Expert opinion</td>
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<td>19. Patients with HR positive disease should receive adjuvant ET with tamoxifen for at least 5 years and up to 10 years as risk appropriate and tolerated. Switching to an AI can be considered for women who have become definitively post-menopausal. The added value of a GnRH analog is still controversial in the presence of chemotherapy and/or tamoxifen; in the absence of chemotherapy or tamoxifen, it should be considered</td>
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<td>20. If a GnRH analog is used in this age group, it should be given on a monthly basis (and not on a 3-monthly basis) to optimize ovarian suppression and efficacy, and estradiol levels should be checked on a regular basis (at least every 6 months) because in some patients ovarian suppression is not achieved. In cases of inadequate suppression alternative strategies should be discussed (oophorectomy or continuation of tamoxifen alone).</td>
<td>Expert opinion</td>
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<td>21. Young women with stage I or II breast cancer who cannot take tamoxifen (due to contraindications or severe side effects) should receive a GnRH analog or oophorectomy. The optimal duration of this treatment is currently unknown.</td>
<td>Expert opinion</td>
<td>IA</td>
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<tr>
<td>22. AIs alone are contra-indicated in pre-menopausal women. Adjuvant AIs combined with GnRH analog should in principle not be used in young early breast cancer patients outside clinical trials, except in special cases.</td>
<td>Expert opinion</td>
<td>IA</td>
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<td>23. The optimal (neo)adjuvant CT regimen for young women regarding efficacy and long-term tolerance is currently unknown. As for all stage I–III breast cancer patients, the preferred regimens are standard anthracycline, alkylating, and taxane based regimens.</td>
<td>Expert opinion</td>
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<td>24. One year treatment with adjuvant trastuzumab, together or after chemotherapy, is indicated for women with HER-2 positive, node-positive or high-risk node-negative breast cancer (tumor size &gt; 0.5 cm), having a left ventricular ejection fraction of ≥55% and without important cardiovascular risk factors, regardless of age.</td>
<td>Expert opinion</td>
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<td>25. Standard duration of treatment (minimum of 4 and maximum of 8 cycles) should be prescribed. Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated; young age by itself should not be an indication to prescribe a particular combination of cytotoxic agents.</td>
<td>Expert opinion</td>
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<td>26. In view of the long potential life-expectancy, particular attention should be paid to possible long-term toxicities of adjuvant treatments (e.g. secondary cancers, cardiovascular toxicity, irreversible ovarian failure).</td>
<td>Expert opinion</td>
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<td>27. The management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.</td>
<td>Expert opinion</td>
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in patients with favorable prognosis (75% T1, G1–2 tumors, 30% node-positive) and no adjuvant chemotherapy, showed no difference in DFS after treatment with 3 years of goserelin combined with either tamoxifen or anastrozole [65]. Further, overall survival with longer follow-up was worse with anastrozole than with tamoxifen (46 vs 27 deaths; HR 1.75, 95% CI 1.08–2.83; p = 0.02). Of note, only 18% of women were ≤40 years of age when randomized. The panel agrees that the upcoming results of the SOFT and TEXT trials will provide further insight into this clinically important question.

Bisphosphonates

The ABCSG 12 demonstrated that adjuvant zoledronic acid, in young patients rendered post-menopausal by GnRH analog, reduced risk of disease-free survival events overall (HR 0.68, 95% CI 0.51–0.91; p = 0.009) at 62 month follow-up, although the difference was not significant in the tamoxifen (HR 0.67, 95% CI 0.44–1.03; p = 0.067) and anastrozole arms (HR 0.68, 95% CI 0.45–1.02; p = 0.061) assessed separately [65]. Further, zoledronic acid did not significantly affect risk of death (30 deaths with zoledronic acid vs 43 deaths without; HR 0.67, 95% CI 0.41–1.07; p = 0.09). Given recent data from meta-analyses and that the only study with a prespecified subgroup analysis based on age and menopausal status showed no benefit in pre and perimenopausal patients, the panel agreed that bisphosphonates should not be considered standard adjuvant therapy for premenopausal women at this time, although can be used for prevention of loss of bone density [66–68].

Neo/adjuvant chemotherapy

There is no evidence to recommend a specific chemotherapy regimen for young women requiring neo/adjuvant chemotherapy: when ER status is taken into account, age disappears as an independent prognostic factor for the benefit of chemotherapy, with part of the efficacy due to rates of amenorrhea induced by the different regimens [63]. In the last EBCTCG meta-analyses involving taxane- or anthracycline-based regimens, proportional risk reductions were little affected by age [69]. Based on their genetic/biologically adverse prognosis, very young women (<35 years) should probably be treated with a standard regimen including an anthracycline, an alkylating agent, and a taxane. Some oncologists use dose-dense regimens more often in young women, although there has been retrospective data suggesting that women with hormone receptor-negative disease obtain the greatest benefit from this approach [70].

Although higher local relapse rates after neoadjuvant chemotherapy and breast conservation have been suggested in young women, no long-term significant survival harm from neoadjuvant chemotherapy and subsequent conservative surgery in young women has been demonstrated [71]. The neoadjuvant Gepartrio trial demonstrated that age <40 was a significant independent predictive factor for efficacy of a Taxteter, Adriamycin and Cyclophosphamide (TAC)-based therapy overall, especially in the subgroup of patients with triple negative breast cancer [72].

Inflammatory breast cancer (IBC) appears to be slightly more frequent in young women, especially in women of African descent. IBC in young women does not appear to be linked to the constitutional genetic background and its management should be the same as in the older breast cancer population.

Adjuvant anti-HER-2 therapy

There is no evidence to recommend a specific regimen for young women with HER-2 early breast cancer: the benefit of adjuvant trastuzumab appears independent of age in all published studies. Analysis of age and short term outcome in the HERA trial has demonstrated women of all age groups, including very young women, appear to derive similar benefit from adjuvant trastuzumab [6].

Side effects of adjuvant therapy

Overall, young women are not a high-risk group for morbidity of chemotherapy except ovarian failure. However, in a Swedish cohort, the incidence of secondary non-hematologic malignancies ≥30 years after breast cancer diagnosis was specifically elevated among younger women at initial diagnosis [73]. In view of the longer life expectancy of young women, the panel strongly suggests particular attention be paid to potential additional long-term toxicities (i.e. cardiovascular, bone morbidity, cognitive impairment, weight gain).

Advanced breast cancer (ABC) (Table 6)

For the purpose of the Conference and these recommendations ABC in young women is defined as metastatic disease diagnosed <40 years old.

In the United States, the incidence of breast cancer with distant involvement at diagnosis increased in 25–39-year-old women from 1.53/100,000 in 1976 to 2.90/100,000 in 2009 and the 5-year US survival rate for distant disease for 25–39-year-old women is only 31%, compared with 87% for women with loco-regional breast cancer. In addition, ABC as a proportion of all invasive breast cancer in this age group rose from 4.4% in the 1970s to 7.2% in the early 2000s [74].

There are few proven standards of care in ABC management overall and even more in young women, and the development and inclusion of patients in well-designed, independent, prospective randomized trials must be a priority [17]. Whenever feasible the metastatic lesion should be biopsied and tested for confirmation of diagnosis, histology and biology, especially in case of late relapse.

As recommended for early breast cancer, also in the metastatic setting, age alone should not be a reason to prescribe more aggressive therapy.

Table 6

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<td>28. Also in the metastatic setting, age alone is not a reason to prescribe more aggressive therapy and International Consensus Guidelines for management of advanced breast cancer must be applied (ABC 1, ESMO and NCCN guidelines). Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.</td>
<td>Expert opinion IC</td>
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<td>29. Endocrine therapy is the preferred initial option for HR-positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or need for rapid disease and/or symptom control. Tamoxifen + ovarian suppression/ovarian ablation (OS/OA) is the 1st ET of choice. AIs = OS/OA can be considered after progression on tamoxifen + OS/OA. Fulvestrant has not yet been studied in pre-menopausal women and specific studies are urgently needed.</td>
<td>IA IA IB Expert opinion</td>
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<td>30. Although young age has been associated with an increased risk of CNS metastases, surveillance and therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent, since clinical and pathologic characteristics predicting for CNS recurrence often overlap with factors that indicate increased risk for general metastatic dissemination (i.e. young age, ER- and PR-negativity, HER-2 overexpression, high proliferation, and genomic instability).</td>
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Endocrine therapy

Endocrine therapy is the preferred option for HR+ disease, unless there is concern or proof of endocrine resistance (i.e., early relapse under adjuvant endocrine therapy) or need for rapid disease and/or symptom control. A meta-analysis comparing GnRH analogs +tamoxifen showed that the outcomes were significantly improved in patients who received the combination [75].

The combination of GnRH analogs and AIs has proven to be active in small Phase II studies [50,76,77]. In addition, in a phase II parallel group study there was no statistical difference in the median time to progression (TTP) between premenopausal patients receiving letrozole plus goserelin and postmenopausal patients treated with letrozole alone [78]. The exact role of this therapeutic option requires further investigation in randomized trials.

The available evidence of the antitumor activity of fulvestrant in premenopausal patients is limited to small Phase II studies and deserves further evaluation, although the drug does appear to be active in this setting [79–81].

In endocrine-responsive ABC, most studies addressing the combination of ET and chemotherapy showed an increased ORR or an increased TTP but no improvement in OS with no age-related differences [82]. Trials examining concurrent versus sequential treatment with ET and chemotherapy need therefore to be conducted at present time, outside clinical trials, concomitant ET and CT should not be used.

Endocrine therapy is frequently used as maintenance treatment after obtaining the maximum benefit from chemotherapy. However, trials clearly evaluating the role of maintenance therapy for ABC (be it endocrine, biological or cytotoxic) are urgently needed.

No specific endocrine resistance mechanisms have been identified in premenopausal patients and all the compounds developed to address endocrine resistance have been tested predominantly in postmenopausal patients so far. Clinical trials are currently being proposed for premenopausal women combining agents to overcome endocrine resistance with endocrine therapy and GnRH analogs.

Chemotherapy and biological therapy for advanced disease

Therapeutic recommendations should not differ from those for older women with the same disease characteristics. Young age by itself is not an indication to prescribe combination chemotherapy over sequential use of monotherapy. However, the unique medical (e.g., risk of pregnancy) and psychosocial concerns (e.g., body image, hair loss) of young women should be addressed when caring for them in the metastatic disease setting.

BRCA mutation carriers (Table 7)

The panel felt strongly that it is imperative that the oncology providers clarify during the decision-making process that (i) there is no clear evidence that therapeutic mastectomy plus contralateral risk-reducing mastectomy has an impact on survival in a woman with a hereditary cancer syndrome with existing breast cancer and, (ii) breast imaging is a screening/surveillance tool for detecting early disease whereas surgery is a risk-reducing procedure for reducing the risk of the development of disease. Therapeutic decisions should reflect a balance between the risk of recurrence of the diagnosed breast cancer, the potential benefit of preventing an additional primary tumor and patient preferences. The evidence regarding the necessity of ipsilateral mastectomy is inconclusive in this subset of patients and, therefore, breast conservation remains a suitable option after a thorough discussion with a patient motivated to retain her breast [83,84].

In addition, the current evidence show that radiotherapy does not lead to increased toxicities or carcinogenic effects in BRCA mutation carriers than in non-carriers [85].

The calculated risk of contralateral disease in BRCA-negative young patients with a family history is controversial [86,87]. Prophylactic breast surgery should be discussed in this subset of patients. If a patient decides to undergo therapeutic mastectomy plus contralateral risk-reducing mastectomy, immediate reconstruction should be offered: skin-and nipple-sparing mastectomy techniques could be options both from an oncological and a cosmetic point of view [36,37,88]. The availability of rapid BRCA testing would favorably impact on the treatment plan but adequate time should be given to the patient to allow the proper understanding of all information and to avoid “rush decisions”.

Regarding bilateral salpingo-oophorectomy (BSO) for the prevention of ovarian cancer, there was a lack of consensus among panel members on the optimal age for considering this procedure in a BRCA 1 or BRCA 2 mutated patient, according to available data [89,90]. It was recommended that one consider the family history and individual family planning in this regard. In women not considering BSO, gynecologic surveillance every six months is recommended: the panel did not endorse routine CA-125 testing, in agreement with several available guidelines [91]. Recent data in mutation carriers further support the evidence that the use of oral contraceptives is associated with a significant reduced risk of ovarian cancer for BRCA1/2 carriers with no increased breast cancer risk with recent formulations [92–94].

Current evidence suggests that the overall prognosis of early breast cancer in BRCA carriers who receive standard adjuvant treatment is similar to sporadic breast cancers with the same biological characteristics and equivalent stage [95–97]. BRCA deficiency seems to be predictive of chemosensitivity, especially to

<table>
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<th>Table 7: Germline BRCA 1/2 mutation carriers.</th>
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<tr>
<td>31. For survivors harboring a BRCA 1/2 or (other) strongly predisposing mutation, bilateral risk-reducing mastectomy may be considered. Therapeutic decisions should reflect a balance between the risk of recurrence of the diagnosed breast cancer and the potential benefit of preventing an additional primary tumor. Expert opinion Expert opinion</td>
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<td>32. For survivors harboring a BRCA 1/2 mutation, prophylactic salpingo—oophorectomy should be discussed from the age of 35 provided that the woman has completed family planning, and should preferably be done before 40, always respecting patient’s preferences and considering the family history. I B</td>
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<tr>
<td>33. For survivors harboring a BRCA 1/2-mutation carriers who have not undergone oophorectomy, gynecologic surveillance every six months is recommended, beginning at age 30. IC</td>
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<td>34. In young women with the diagnosis of either invasive disease or pre-invasive lesions, who are not BRCA mutation carriers, there is no evidence for improved OS by performing risk-reducing/ prophylactic bilateral mastectomy. I A</td>
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<td>35. For the time being, the type of systemic treatment of EBC is independent of BRCA or any other constitutional genetic status. I B</td>
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<tr>
<td>36. For the time being, the type of systemic or radiation therapies for ABC is independent of BRCA status or any other constitutional genetic status. The same guiding principles defining treatment decisions should be applied for all women with ABC regardless of genetic status. The same guiding principles defining treatment decisions should be applied for all women with ABC regardless of genetic status, with the exception of germline TP53 mutations, for which a very high risk of secondary cancers has been described after radiation therapy. Radiation therapy should be carefully discussed in an individual basis for these patients. III</td>
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<tr>
<td>37. Well-designed prospective randomized trials evaluating the role of platinum agents and PARP inhibitors in the population of women with BRCA 1/2 mutation associated ABC are urgently needed. Expert opinion</td>
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DNA-damaging agents [98–100]. Still, there is no definitive conclusion on the best chemotherapy regimen for BRCA breast cancer patients and the panel recommends standard prognostic features should be used to decide treatment both in the early and advanced disease setting [101].

Poly (ADP-ribose) polymerase (PARP) inhibitors are being developed as therapeutic agents for germline BRCA-mutated breast cancer patients [102,103]. The available evidence with the oral PARP inhibitor olaparib in heavily pretreated ABC patients with BRCA mutations provides positive proof-of-concept of the efficacy and tolerability of this targeted approach. Other PARP inhibitors are being evaluated either alone or in combination with chemotherapy for BRCA associated tumors.

For young women with breast cancer who are BRCA 1/2 mutation carriers and others at extremely high risk (>20–25% in lifetime) for new primary breast cancer based on family history or predisposing mutations in other genes, and for those at increased risk because of a personal history of therapeutic radiation (in adolescence), annual surveillance with mammography and MRI with or without US (of remaining breast tissue) is recommended [104]. Of note, tamoxifen may reduce risk of new primaries in BRCA patients even when the original primary was ER negative [105]. The indications and modalities of MRI surveillance in high-risk patients might refer to the 2010 EUSOMA guidelines which considered different imaging modalities in the surveillance of high-risk women [27].

**Supportive and follow-up care (Table 8)**

In principle, follow-up care in young women should follow the same guidelines as in older women [106]. Supportive treatment of specific symptoms/side effects should also follow current recommendations as for older women.

Young women face specific psychosocial and sexual issues that should be addressed by a multidisciplinary group of providers including breast nurses, breast oncologists, gynecologists and fertility experts among others. In many settings, breast nurses are of crucial importance for the support of the patient and the family. Sources of distress include premature treatment-induced menopause and its related effects (i.e. infertility, alterations in body image, sexual dysfunction, hot flashes/night sweats, bone thinning), long-term side effects of tumor treatment (i.e. cognitive dysfunction and cardiovascular risks), feeling of social inadequacy (i.e. fear of starting a new relationship, partner’s strain, work and financial loss, childcare difficulties). Family planning and return to work must be taken into consideration and specifically addressed.

Some of the specific issues for the young breast cancer population include:

**Fertility, contraception and premature menopause**

Fertility and family planning are major concerns for young women with breast cancer [10,107]. Many young women will still be fertile after treatment and some will be interested in having a future biologic child. Discussion of these issues at diagnosis, elicitation of patient interest in future fertility and appraising patients of the risks of amenorrhea and potential infertility as well as premature menopause have been recommended by other guideline panels as an important component of quality oncology care [108] and are also recommended here [108]. Appropriate early referrals for fertility preservation strategies as well as psychosocial support surrounding this extremely complex issue should also be made. There was recognition by the majority of the panel that this is one of the most difficult and emotionally challenging issues facing young survivors, which is complicated by limitations of the data, particularly with regard to predicting fertility as well as safety of intervention. Pregnancy must be discouraged during active treatment of breast cancer, so effective contraception is recommended. Exogenous hormonal contraception is generally contraindicated in breast cancer survivors and alternative strategies (i.e. barrier methods such as condoms, cervical diaphragm and copper IUDs) should be considered [109]. The safety of levonorgestrel-releasing intra-uterine device (IUD) (Mirena®), which delivers high local but low systemic doses of progestogen is controversial: studies in BC survivors are small and have not included recurrence or new cancers as an endpoint [110]. In the absence of prospective data patients should be advised to use alternative non-hormonal contraception.

**Pregnancy after breast cancer**

All retrospective available data report no detrimental effect of a subsequent pregnancy on breast cancer outcome [111–115]. In particular, in a recent multicenter, retrospective cohort study in which 333 patients who became pregnant any time after BC were matched (1:3) to patients with BC with similar ER status, nodal status, adjuvant therapy, age, and year of diagnosis, no difference in DFS was observed between pregnant and non-pregnant patients which is complicated by limitations of the data, particularly with regard to predicting fertility as well as safety of intervention. Pregnancy must be discouraged during active treatment of breast cancer, so effective contraception is recommended. Exogenous hormonal contraception is generally contraindicated in breast cancer survivors and alternative strategies (i.e. barrier methods such as condoms, cervical diaphragm and copper IUDs) should be considered [109]. The safety of levonorgestrel-releasing intra-uterine device (IUD) (Mirena®), which delivers high local but low systemic doses of progestogen is controversial: studies in BC survivors are small and have not included recurrence or new cancers as an endpoint [110]. In the absence of prospective data patients should be advised to use alternative non-hormonal contraception.

**Bone health**

Bone health has to be regularly checked in young women with breast cancer. Of note, in contrast with its effects on bones in postmenopausal women, tamoxifen can cause bone loss in premenopausal patients, likely because it is a weaker agonist in the bones that the premenopausal endogenous estrogens it is blocking [116,117]. As a consequence, in all young patients special emphasis on dietary education (i.e. adequate intake of calcium [1000 mg/day] and vitamin D [800 UI/day]) and regular weight-bearing exercise is needed [118]. Treatment-related bone loss should be treated accordingly, independent of age.
Cognitive impairment

Neurocognitive symptoms ("chemo brain") are frequently described among young breast cancer survivors [119,120]. Patient-reported symptoms (forgetfulness, difficulty with concentration, fatigue, distractibility and difficulty with word finding) rarely correlate with neuro-image studies and neuro-psychiatric evaluation. Neither the biological basis for this syndrome, nor the predictors, nor any interventions, are well understood although recent investigations suggest a relationship with structural changes occurring in cerebral white matter and several investigations are underway [121,122]. ET may also adversely affect recent investigations suggest a relationship with structural cognition [123].

Tamoxifen, no effect of treatment on patients during CMF cycles of CMF have been conducted and none in young women. In the ZIPP trial (6 cycles of CMF ± 2 years of goserelin, goserelin plus tamoxifen, or tamoxifen), no effect of treatment on patients' self-evaluation of memory and concentration was shown [127]. Cognitive function is being prospectively investigated in patients participating in the SOFT trial.

References


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