



Original article

Second international consensus guidelines for breast cancer in young women (BCY2)



Shani Paluch-Shimon ^{a,1}, Olivia Pagani ^{b,1}, Ann H. Partridge ^c, Eran Bar-Meir ^d,
 Lesley Fallowfield ^e, Deborah Fenlon ^f, Eitan Friedman ^a, Karen Gelmon ^g,
 Oreste Gentilini ^h, James Geraghty ⁱ, Nadia Harbeck ^j, Stephen Higgins ^k, Sibylle Loibl ^l,
 Elizabeth Moser ^m, Fedro Peccatori ⁿ, Hila Raanani ^a, Bella Kaufman ^{a,2},
 Fatima Cardoso ^{m,o,*,2}

^a Sheba Medical Center, Ramat Gan, Israel

^b Oncology Institute of Southern Switzerland and Breast Unit of Southern Switzerland, Bellinzona, Switzerland

^c Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

^d Faculty of Medicine, Bar-Ilan University, Israel

^e SHORE-C, Brighton & Sussex Medical School, University of Sussex, Falmer, UK

^f University of Southampton, Southampton, UK

^g British Columbia Cancer Agency, Vancouver, Canada

^h Breast Surgery Unit, San Raffaele Hospital, Milan, Italy

ⁱ St Vincent Hospital, Dublin, Ireland

^j Breast Center, Dept. OB&GYN, University of Munich (LMU), Munich, Germany

^k Tallaght Hospital & Our Lady's Hospice, Dublin, Ireland

^l German Breast Group, Neu-Isenburg, & Sana Klinikum Offenbach, Germany

^m Breast Unit, Champalimaud Cancer Center, Lisbon, Portugal

ⁿ European Institute of Oncology, Milan, Italy

^o European School of Oncology, Italy

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ABSTRACT

The 2nd International Consensus Conference for Breast Cancer in Young Women (BCY2) took place in November 2014, in Dublin, Ireland organized by the European School of Oncology (ESO). Consensus recommendations for the management of breast cancer in young women (BCYW) were updated from BCY1 with incorporation of new evidence to inform the guidelines, 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

Breast cancer is the leading cause of cancer and of cancer death amongst women worldwide [1]. BCYW (≤ 40 years) women is uncommon, with a 0.40–0.45% cumulative risk by that age [1]. Overall, they represent less than 7% of women diagnosed with

breast cancer in developed countries [2]. Despite the relatively low cumulative risk, in high-income countries breast cancer is the leading cause of death amongst women under the age of 45 years, following road traffic accidents and self-injury, making BCYW a significant public health issue [3]. While the incidence has not increased in many countries young women are a growing population and thus the absolute number of women at risk has increased. Data on breast cancer epidemiology and clinical-biological behavior is based predominantly on older breast cancer patients resulting in a relative paucity of data in young women.

BCYW is a distressing and far-reaching disease - it strikes the women at the peak of their careers, motherhood plans and family

* Corresponding author. Breast Unit, Champalimaud Clinical Center, Av. De Brasília, s/n, 1400-038 Lisbon, Portugal. Tel.: +351 210 480 004.

E-mail address: fatimacardoso@fundacaochampalimaud.pt (F. Cardoso).

¹ Co-first authors.

² Co-last authors.

life. The treatments they receive may adversely affect their fertility and induce premature menopause. Thus they face not only the threat of a potentially fatal illness, but they have the added burden, specific to their age-group and stage in life, of unique concerns on the long-term disease impact. Most concerning, young women on average experience increased risk of both local and systemic recurrence and death after a diagnosis of breast cancer [4]. This is largely due to their increased risk of biologically aggressive cancer types (i.e., more high grade when ER+, increased HER2-positive and triple negative disease) and more advanced stage [5–9]. 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 sub-typing. Consequently, 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 long-term side effects and influence quality of life. Additionally, because they have generally not been studied in large numbers, young women may not benefit from our increasing ability to better risk stratification of breast cancer, and some young women may be at risk of being overtreated based solely on age.

Young women are also more likely to harbor a genetic predisposition to breast cancer (e.g., a BRCA1 or BRCA2 mutation) than older women, especially if the disease is triple negative. This hereditary predisposition may impact on their local treatment decisions and considerations for risk-reducing surgeries, such as contralateral mastectomy and salpingo-oophorectomy [10] to actively reduce future cancer risks, which may result in additional psychosocial adjustments [11–13]. Research has consistently shown that young women with breast cancer are at increased risk of psychological distress at diagnosis and in long-term follow-up [14,15] and yet have traditionally had far less organized peer- and professional support available to them.

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 to understand and improve outcomes in this population [6,16,17].

For the purpose of these recommendations, consistent with previous guidelines [18,19], the panel decided to define “young women” as women under the age of 40 at breast cancer diagnosis in recognition that these women have specific issues (e.g. fertility, genetics and psychosocial concerns) that often deserve a different approach compared to older premenopausal patients. The application and use of consensus guidelines have previously been demonstrated to have a positive impact on breast cancer care [20,21].

Methodology

Recommendations from BCY1 formed the basis for the current recommendations [19]. The updated statements from BCY2 were presented, discussed and voted on during the consensus session of BCY2. 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. These recommendations were circulated to panel members by email for comments, updating based on recent reports, and corrections on content and wording.

Table 1 describes the grading system used [22]. Statements without grading were considered justified standard clinical practice by the panel experts.

Appendix 1 lists all members of the BCY2 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 panel reinforced the concept that the complex care of BCYW requires additional specialists (e. g. geneticists, fertility and psycho-social experts). Specialized breast clinics allow for such a multidisciplinary approach, for women with breast cancer in general [23,24], and specifically young patients [25]. Thus, the panel agreed that all young patients should be cared for in specialized breast clinics that incorporate treatment coordinators. 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, psycho-social health professionals, physiotherapists and sexual experts) recognizing that access to such professionals may be limited, particularly in lower resource settings. Keeping this in mind the panel stated that navigators/navigation tools may be of great assistance in optimizing patient care. Navigators should ideally be breast nurses but lay-health professionals with strong communication skills and sufficient experience may also address complex care and mixed cultural settings [26]. Studies have shown that incorporating navigators in health clinics improves patients' sense of empowerment and increases the uptake of standard therapies [26–28]. Where human resources may be more limited, internet/technology based-tools may be an option to assist in patient navigation.

Panel members reemphasized that many specific issues in the treatment of young women with breast cancer, both in the early and in the advanced settings, still lack definitive proven standards. Therefore, well-designed, independent, prospective randomized trials should be a global research priority.

Extensive data suggest that tumors in younger women tend to be of more aggressive phenotypes [5–9,16]. Recent studies suggest potentially unique biology of tumors arising in younger patients [6,7,29,30]. Whether young age alone represents an independent prognostic or predictive factor as we improve our understanding of tumor sub-typing remains an area of active research with significant clinical implications. At this time the choice of most treatments for young women, both in the early and the advanced setting, should be driven by similar factor as for older women, i.e. by the biological characteristics of the tumor (i.e. hormone receptors, HER2, proliferation, grade), tumor stage, hormonal milieu (i.e. the panel wished to emphasize that chemotherapy or treatment induced amenorrhea is not equivalent to menopause), patient's co-morbidities and personal preferences, especially when benefits may be modest or options are equivalent in outcome (e.g. mastectomy versus breast conservation) [23,31]. The panel reinforced the concept that young age alone should not be a reason to prescribe more aggressive therapy.

Diagnosis & imaging for staging and follow-up (Table 3)

The panel re-discussed ultrasound (US) and magnetic resonance (MRI) as specific diagnostic tools in young women and confirmed the previous agreement on the lack of evidence that addition of MRI improves outcomes both in young and older women [32–34]. At the present time, there is no clear role for routine screening by any imaging for early detection in healthy, average risk young women.

Table 1
Levels of evidence grading system [22].

Grade of recommendation/ description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A/Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

Table 2
General recommendations.

Guideline statement	LoE
1. 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, independent, prospective randomized trials should be a global research priority	Expert opinion
2. The care of all young patients with breast cancer (either early stage, EBC, or advanced disease, ABC) should be discussed within a multidisciplinary team before any treatment decision-making, and provided in specialized breast clinics.	Expert opinion
3. Navigators/navigation tools are of great assistance in optimizing patient care. Navigators should ideally be breast nurses but lay-health professionals with strong communication skills and sufficient experience may also address complex care and mixed cultural settings.	Expert opinion
4. In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, & socio-economic impact are highly recommended as part of the individual treatment planning.	Expert opinion
5. Young age by itself should not be the reason to prescribe more aggressive therapy than other age groups. Factors influence choice of treatment should include but not be limited to the complete biological characteristics of the tumor (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumor stage, hormonal milieu, genetic status (if available) and patient's co-morbidities and preferences.	Expert opinion

However, in the presence of a cancer predisposition syndrome, germline mutation in a known cancer predisposition gene, significant family history, or prior personal history of ionizing radiation to the chest, consideration may be given to screening breast MRI [35,36]. Of note, some members of the panel considered that women harboring p53 mutations should minimize exposure to ionizing radiation and thus avoid mammography, and be screened by ultrasound and MRI (level of evidence: Expert Opinion) [37]. The recommended staging, including axillary assessment, does not differ from that for older breast cancer patients.

The panel strongly supported that, when MRI is used, it should be done by nationally/regionally approved and audited services. It also noted that the timing of the menstrual cycle should be taken into account when planning and performing MRI (and mammography, if done) in order to optimize accuracy of imaging with optimal timing being in the first half of the menstrual cycle (day 7–10) [38].

For BRCA 1/2 mutation and other cancer susceptibility genes carriers (eg RAD51C, p53) who have not undergone salpingo-oophorectomy, gynecologic surveillance every six months is

Table 3
Screening, diagnosis & imaging for staging and follow-up.

Guideline statement	LoE
6. There is no clear role for routine screening by any imaging for early detection in healthy, average risk young women. However, in the presence of a cancer predisposition syndrome, germline mutation in a known cancer predisposition gene, significant family history, or prior personal history of ionizing radiation to the chest, consideration may be given to screening breast MRI.	1A Expert opinion
7. Diagnosis, imaging and staging in young women should follow standard algorithms consistent with older women. Additional consideration may be given to ultrasound and breast MRI in young women particular in the setting of very dense breast tissue or consideration of a genetic predisposition or other high risk individuals (i.e. radiotherapy for childhood malignancy).	2C
8. For BRCA 1/2 mutation carriers and others at extremely high risk based on family history or predisposing mutations in other genes, and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with mammography and MRI with or without ultrasound is recommended.	1C
9. For BRCA 1/2 mutation and other cancer susceptibility genes carriers (eg RAD51C, p53) who have not undergone salpingo-oophorectomy, gynecologic surveillance every six months is recommended, beginning at age 30 or 5 years younger than the earliest diagnosis of a gynecological malignancy in the family, whichever comes earlier.	Expert opinion

recommended, beginning at age 30 or 5 years younger than the earliest diagnosis of a gynecological malignancy in the family, whichever comes earlier. While these are the current recommendations, data supporting this approach as an effective screening method remain limited. In addition, the best method to perform this gynecologic surveillance (i.e. gynecologic exam or ultrasound) is unknown.

Genetic counseling and testing (Table 4)

There was discussion among the panel of whether genetic counseling should be only family based or considered in all breast cancer patients under 40 years. The panel concluded that genetic counseling should be offered for every young woman, particularly if there's a family history of breast cancer or the tumor is of triple negative subtype. When possible and relevant to patient care (e.g. selection of breast surgery), counseling should be offered before the commencement of treatment. The panel did emphasize that practice should be in keeping with local guidelines and testing availability on a country-by-country basis. 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 issues of specific intensive surveillance and risk reduction of additional primary tumors, and risk assignment and stratification for relatives.

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. In addition to BRCA 1/2 mutations, young women with breast cancer are also at risk of having rare genetic cancer syndromes including a germline p53 mutation (Li-Fraumeni Syndrome) or a PTEN mutation (Cowden's Syndrome) [39,40]. Other moderate-high-penetrance genes (e.g., CDH1, CHEK2, PALB2, RAD51C, BRIP1) should be tested for as deemed necessary by the geneticist. The patient must be made aware that the presence of a predisposing mutation may have an impact on clinical management, follow-up and decision making, as well as for other family members.

Early breast cancer

Loco-regional treatment (Table 5)

Surgery

Despite the fact that young age is an independent risk factor for increased local recurrence [41,42], a recent meta-analysis confirmed no improvement in overall survival (OS) amongst young breast cancer patients who underwent mastectomy compared to breast conservation [43]. The panel therefore confirmed conservative surgery as the first option whenever suitable, and expressed concern at the growing trend for routine mastectomies particularly in younger women. Oncoplastic repair

techniques by a dedicated breast surgical team should be offered to all patients treated by BCS in order to maximize cosmetic and self-image results whenever an obvious postoperative asymmetry is expected. When mastectomy is indicated, skin- and nipple-sparing techniques with immediate breast reconstruction when feasible, can provide adequate oncological control while also addressing the cosmetic needs [44,45]. Immediate breast reconstruction after mastectomy offers the same survival rates as mastectomy without reconstruction, and should be offered to all patients except those with inflammatory breast cancer. With the new radiotherapy (RT) techniques there is no need to postpone reconstruction.

The panel also confirmed that the indications for SLNB and surgical management of patients with SLN involvement should be the same as in older patients.

Radiotherapy

The panel reiterated BCY1 recommendations on; the need of modern techniques and high quality standards to minimize long-term side effects, and the routine indication for a boost to the site of the radical local excision. Given the high recurrence risk also outside the initial tumor area, partial breast irradiation is contraindicated and should only be proposed within a clinical trial. Post-mastectomy radiotherapy and internal mammary chain irradiation should continue to be discussed on an individual basis, as in older women, and based on initial staging if neoadjuvant treatment is given.

Regarding hypo-fractionated abbreviated schedules with a higher dose/fraction, a population-based study from Canada indicated that its use in women under 50 is growing (52% of women <50 years) [46] with shared satisfactory safety and cosmetic outcome. With the lack of long-term outcome data, the majority of the panel continued to agree that hypo-fractionation could be proposed in young patients on a case by case basis. Modern RT techniques should be used to assure target coverage (including nodal areas) while reducing normal tissue exposure and guaranteeing homogeneous dose delivery to avoid higher risk of fibrosis and worse cosmetic outcomes.

Adjuvant systemic treatment (Table 6)

Adjuvant systemic treatment decisions for invasive breast cancer should be driven, as for women in other age categories, by extent of disease and the biological characteristics of the tumor (including, but not limiting to, hormone- and HER-2 receptors, proliferation, and grade), patient's co-morbidities and preferences.

Available gene expression signatures are considered to add prognostic information to classic clinico-pathologic factors [7,9,47,48]. That being said, women <40 are grossly under-represented in the retrospective studies performed to date. Prospective data from randomized trials (MINDACT, TailorX, X-PONDER, PLAN B) are awaited to assess the prognosis and benefit of

Table 4
Genetic counseling and testing.

Guideline statement	LoE
8. Every young woman with breast cancer should be offered genetic counseling preferably before starting the treatment. Practice should be consistent with local-guidelines on a country-by-country basis. 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 issues of surveillance and risk reduction of additional primary tumors for the patient, and risk issues for relatives.	Expert opinion
9. 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. The patient must be made aware that the presence of a predisposing mutation may have an impact on her management, follow-up and decision making, as well as family members. Genes to be tested for are BRCA1 and BRCA2 (other additional high-penetrance genes can be tested if deemed necessary by the geneticist)	Expert opinion

Table 5

Early breast cancer loco-regional treatment.

Guideline statement	LoE
10. Surgical treatment of young patients with EBC – while being tailored to the individual patient – should in general not differ from that of older patients. Breast conserving surgery should be performed as the first option whenever suitable, as it provides the same OS than mastectomy.	I B I A
11. Oncoplastic repair techniques should be offered to all patients treated by BCS in order to maximize cosmetic and self image results whenever an obvious postoperative asymmetry can be estimated by dedicated breast surgical team. Immediate breast reconstruction after mastectomy offers the same survival rates as mastectomy without reconstruction and should be offered to all patients except those with inflammatory breast cancer.	I C
12. There is no evidence of an increased false negative rate or a worse outcome in young patients undergoing SNLB, therefore the indications for SNLB are the same as in older patients.	I B
13. 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 bilateral mastectomy.	IC
14. For all surgical decisions and particularly for risk-reducing mastectomy, patients must be given proper, thorough and unbiased information based on the available data, and adequate time to decide, since breast surgery is not an emergency. Once an informed decision is taken by the patient it should be respected. Additional psychosocial support should be offered given the potentially high anxiety and long term sequela of patients making these difficult decisions.	Expert opinion
15. Indications for adjuvant RT are the same as for older patients. Data are more robust in support of the benefits of post-mastectomy (PM) RT and internal mammary chain RT for young women.	I B
16. After breast-conserving surgery, breast radiation + boost is recommended. Young patients should be informed about the high local recurrence risk if RT is avoided after BCS and about the benefit of RT on reduction of local recurrence and improvement in OS. This must be balanced with information about the potential long-term toxicities.	IB
17. Hypofractionation can be discussed in selected cases	2B
18. Indications of adjuvant RT are independent of BRCA status	Expert opinion

chemotherapy according to age and tumor biology in the modern era. In the post-BCY2 preliminary report of the TailorX trial, young women were <5% of the total [49]. Thus, these tests should be used with caution in young women.

Taking the above into consideration, the panel believes young age alone should not be a reason to prescribe more aggressive therapy but biology and stage of the tumor should always be taken into account when planning adjuvant treatments.

Table 6

Adjuvant systemic treatment.

Guideline statement	LoE
19. All young women should be counseled about the risks, 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 counselling/consultation.	Expert opinion
20. Neoadjuvant ET should not be used in young women outside clinical trials.	Expert opinion
21. All patients with HR positive disease should receive adjuvant ET. Tamoxifen alone for 5 years is indicated for low risk patients. Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively post-menopausal. Tamoxifen for 10 years should be considered in high-risk patients, if tolerated. The addition of a GnRH agonist to tamoxifen is indicated in patients at higher risk who remain premenopausal after chemotherapy.	IA IA IA IA IA
22. AIs alone are contra-indicated in pre-menopausal women. The combination of an aromatase inhibitor and a GnRH agonist (or ovarian ablation) should be considered in high risk patients if tolerated.	IA IA
23. Young women with stage I or II breast cancer who cannot take tamoxifen (due to contraindications or severe side effects) may receive a GnRH agonist alone, oophorectomy or an aromatase inhibitor + GnRH agonist. The optimal duration of GnRH agonist alone is currently unknown. The choice will depend on risk of relapse, toxicity and patient preferences.	IA
24. If a GnRH agonist 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. Estradiol levels should be checked if there are concerns ovarian function is not suppressed, especially if a breakthrough bleeding occurs and/or the patient is on an AI; if done, the analysis should be always performed in the same laboratory, and preferably in a central reference laboratory. In cases of inadequate suppression alternative strategies should be discussed (oophorectomy or continuation of tamoxifen alone).	2 B Expert opinion
25. Young patients (>35 years at diagnosis) with low risk HR positive disease have excellent outcomes with ET alone: the addition of adjuvant chemotherapy should not be standard but discussed on an individual basis.	IB
26. The indications for and the choice of adjuvant systemic treatment for invasive breast cancer should be driven, as for women in other age categories, by extent of disease and the biological characteristics of the tumor (including, but not limiting to, ER/PR and HER-2 receptors, proliferation, and grade), patient's comorbidities.	LoE IA
27. For the time being, the type of systemic treatment of EBC is independent of BRCA or any other constitutional genetic status.	Expert opinion
28. The optimal (neo)adjuvant CT regimen specifically 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.	IA
29. 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 combination of cytotoxic agents.	IA IA
30. One year treatment with adjuvant trastuzumab, together with chemotherapy, is indicated for women with HER-2-positive, node-positive or high-risk node-negative breast cancer (tumor size > 0.5 cm), having a left ventricular ejection fraction of ≥55% and without important cardiovascular risk factors, regardless of age.	I A
31. 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, weight gain, cognitive function, bone health).	Expert opinion
32. The management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.	Expert opinion

Neo-adjuvant endocrine therapy (ET)

The STAGE study evaluated neo-adjuvant endocrine therapy amongst 197 pre-menopausal patients by assessing clinical response, however pathologic response was not reported and the study was underpowered to assess long-term outcome [50]. An International Breast Cancer Study Group (IBCSG) randomized phase II Trial (IBCSG 41-13 TREND) is evaluating the efficacy of the GnRH antagonist degarelix versus triptorelin as neo-adjuvant treatment in 50 pre-menopausal patients receiving letrozole.

In the absence of new data, BCY2 reinforces the BCY1 recommendation that neo-adjuvant ET should not be routinely recommended for young women outside of clinical trials.

Adjuvant endocrine therapy

Young women with invasive hormone receptor-positive (HR+) breast cancer should be offered adjuvant ET given the substantial risk reduction afforded [51,52]. In the course of 2014, the long awaited results of the Tamoxifen and Exemestane Trial (TEXT) [53] and Suppression of Ovarian Function Trial (SOFT) [54] trials provided new insight to better individualize ET according to risk factors (e.g. disease characteristics, stage, adjuvant chemotherapy) and age.

Low risk patients (e.g. older pre-menopausal patients with small, low-grade, node negative tumors) who do not receive adjuvant chemotherapy have excellent outcomes with 5 years of tamoxifen alone (>95% 5 year Breast Cancer Free Interval (BCFI) in the SOFT trial) [52,54]. Women at higher risk of recurrence (e.g. with node positive, larger and high-grade tumors) demanding adjuvant chemotherapy and remaining pre-menopausal afterwards significantly benefit from the addition of ovarian function suppression (OFS), by GnRH agonist (GnRHa) or oophorectomy, to tamoxifen in the SOFT trial, the only trial comparing a GnRHa after chemotherapy with tamoxifen in both arms (82.5% 5 year BCFI- in patients receiving tamoxifen plus OFS and 78.0% in patients with tamoxifen alone).

Aromatase inhibitors (AIs) alone are contra-indicated in pre-menopausal women. In the TEXT and SOFT combined analysis OFS plus the AI exemestane significantly reduced the risk of recurrence, as compared with tamoxifen plus OFS and represents a new treatment option in high risk pre-menopausal patients [53,54]. The only additional evidence of AIs combined with GnRHa, provided by the ABCSG-12 trial in patients with favorable prognosis, the majority of whom did not receive adjuvant chemotherapy, did not demonstrate a difference in DFS after treatment with 3 years of goserelin plus either tamoxifen or anastrozole after 94.4 months median follow-up [55]. Further, there is a long-term unfavorable trend for the anastrozole arm with respect to OS (HR = 1.63; 95%CI, 1.05–1.45; $p = .030$). The conflicting results between the TEXT/SOFT and ABCSG-12 trials may be attributable to a number of factors: different patient populations, greater statistical power of TEXT/SOFT and different treatment duration (5 years versus 3 years). Of note, only 18% of women were <40 years of age when randomized in the Austrian trial as compared to 30% and 27% in the SOFT and TEXT trials, respectively. Data on post-relapse treatment, body mass index (BMI) and long-term follow-up from the TEXT and SOFT trials will help to better interpret these differences and identify women most likely to benefit from OFS plus AIs.

Very young women (<35 years) represent the subgroup who appeared to derive the greatest benefit from combined ET after adjuvant chemotherapy [56,57].

While AIs require concurrent GnRHa, the optimal duration of GnRHa plus Tamoxifen remains unknown: most old generation studies utilized 2–3 years of GnRH agonist with 5 years of tamoxifen [58,59] while in SOFT and TEXT 5 years were used [53,54].

When to commence with GnRH agonist in patients receiving adjuvant chemotherapy remains a matter of debate. Both concomitant and sequential administrations are valuable options. In the TEXT combined analysis [60], the 5 years BCFI was 82.2% in SOFT patients, who received triptorelin a median of 8 months after the end of chemotherapy (patients could receive tamoxifen while waiting for ovarian function to resume), and 86% in the TEXT trial in which patients received triptorelin together with chemotherapy. Extended ET for premenopausal women remains understudied. The ATLAS and aTTom studies included premenopausal patients (10% of the overall population in the ATLAS trial) and provide the first and only evidence of a significant long-term reduction in breast cancer mortality with 10 years of adjuvant tamoxifen as compared to 5 years, with an impressive carry-over benefit during the 5 years of follow-up after treatment completion [61,62]. BCY2 reinforces the BCY1 recommendation that extending tamoxifen beyond 5 years should be considered in higher-risk patients, considering the estimated absolute benefit, the risk for late relapse, and quality-of-life issues for the individual patient. Given the higher benefit, demonstrated in the MA.17 trial, of switching to the AI letrozole after 4.5–6 years of tamoxifen in women who were pre-menopausal at diagnosis who became definitively post-menopausal at the time of randomization [63], consideration of AI for young women who became postmenopausal was confirmed in BCY2. Great caution is however recommended given the potential recovery of ovarian function [64].

Chemotherapy may cause transient or permanent damage to the oocyte pool and ovarian reserve, depending on the chemotherapy regimen and cumulative dose, the pre-existing ovarian reserve, and the age of the woman [65]. Menopause occurs when the remaining follicle count reaches 1000 or below. While natural onset menopause is defined as twelve months after the last menstrual period, chemotherapy induced amenorrhea is often mistaken for true menopause, even though menses may resume even after more than a year from the end of chemotherapy. As such, in the absence of a clear-cut definition, menopausal status following chemotherapy can be empirically diagnosed in case of amenorrhea for ≥ 2 years, a post-menopausal hormonal profile and a vaginal ultrasound indicating the ovaries are no longer functioning.

OFS is not always successfully achieved with GnRH agonists: suboptimal estrogen suppression has been reported in up to 1/3 of patients [66,67]. Despite the fact that estradiol assays are not standardized and their accuracy and interpretation can be problematic in presence of very low levels of estradiol [68], the panel suggests to check hormone levels if there are concerns ovarian function is not suppressed, especially if a breakthrough bleeding occurs and/or the patient is on an AI; if done, the analysis should be always performed in the same laboratory, preferably in a central reference laboratory.

Data comparing the efficacy of monthly and trimonthly formulations of GnRH agonists are lacking. Estradiol levels did not differ significantly between monthly goserelin and trimonthly leuprolide in 79 early breast cancer patients receiving GnRH agonists for at least 6 months [69] but further research is needed before trimonthly administration can be routinely recommended in women <40 years of age.

Younger age is associated with low adherence and persistence to adjuvant ET [70,71]. The mean adherence to adjuvant AIs in post-menopausal women is also known to decrease over time [72]. In SOFT, tamoxifen was discontinued early in 16.7% of the tamoxifen–OFS group and non-adherence with OFS reached 21.9% at 4 years [54]. In TEXT, 16.1% of the patients in the exemestane–OFS group stopped all protocol assigned treatments early [53]. Healthcare professionals should therefore encourage young patients to

persist with the assigned ET or discuss all toxicity issues and ways to overcome them, as well as any possible treatment modification.

Many of the side effects of adjuvant ET mimic menopause and may significantly impact quality of life (QoL). The self-reported QoL showed increased menopausal symptoms and decreased sexual activity of OFS over tamoxifen alone in the E-3193 trial [73] and of exemestane over tamoxifen in the TEXT trial, but symptoms diminished over time and the overall QoL was not significantly different between treatment arms [74]. Healthcare providers should follow young patients on ET closely in order to promptly manage side effects or discuss treatment adjustments according to individual tolerance which may require a change of therapy.

The inconvenience, cost, and availability of the different treatment options must also be considered when tailoring ET for the individual patient.

GnRH agonists & ovarian function preservation

The effectiveness of GnRH agonists to preserve ovarian function in women receiving chemotherapy, thus reducing the risk of early menopause and increasing the chances for future fertility, has not yet been fully elucidated. Despite limitations in study design and statistical power, the most recent randomized controlled trials suggest a protective ovarian effect in both HR+ and HR– patients and no signal for harm from a breast cancer recurrence standpoint [75,76]. A recent meta-analysis supports these findings [77]. The BCY2 panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.

Adjuvant bisphosphonates

After BCY2 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis was published which confirmed the lack of benefit of adjuvant bisphosphonates among premenopausal women [78]. The BCY2 panel, in keeping with the recommendation of BCY1, 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 [79–81].

Neo/adjuvant chemotherapy

The additional benefit, if any, of adjuvant chemotherapy in young patients with low risk HR+ early breast cancer under optimal endocrine therapy is still undetermined. All prospective randomized trials have failed in recruiting enough patients to definitively answer this question [82,83]. To overcome the scarcity of randomized data, a growing bulk of indirect evidence seems to suggest that young women with low-risk HR+ early breast cancer could be spared chemotherapy. The phase III Eastern Cooperative Oncology Group trial (E-3193, INT-0142) in premenopausal patients with node-negative HR+ early breast cancer [73], showed a greater than 95% 10 year OS in the absence of chemotherapy; in the SOFT and TEXT patients who did not receive chemotherapy (8% and 21% node-positive, respectively) the 5 year BCFI was 96% and 97%, respectively with similar favorable outcomes in the ABCSG trial [53,55,84].

The panel restated that there is no evidence to recommend a specific chemotherapy regimen for young women requiring neo/adjuvant chemotherapy. In the last EBCTCG meta-analyses involving taxane- or anthracycline-based regimens, proportional risk reductions were little affected by age [85]. Sequential regimens have at least equal or superior efficacy over combination regimens and may be better tolerated although this has not been evaluated specifically in young women [86]. A sequential regimen of anthracycline based chemotherapy followed by adequately dosed CMF (oral or Day1,8 every 21 days intravenously) or a combination

of a taxane and cyclophosphamide may be valid alternatives [87,88]. Similar to older women, standard duration of treatment should include between 4 and 8 cycles of treatment.

Although higher local relapse rates after neo-adjuvant chemotherapy and breast conservation have been seen in young women, no long-term significant survival harm from neo-adjuvant chemotherapy and subsequent conservative surgery in young women has been demonstrated [89]. A pooled analysis of individual patient data from eight prospectively randomized controlled trials of the German Breast Group, published after BCY2, showed that young women (n = 1453) are more likely to achieve pCR after neoadjuvant chemotherapy, especially in HR+/HER2– and triple negative disease (20.9 vs. 17.7 vs. 13.7%; p < 0.001). Age was not prognostic in triple negative and HR–/HER2+ patients as opposed to HR+/HER2– disease [102]. The Geparsixto trial & CALGB trials demonstrated improved pCR amongst triple negative disease with the incorporation of platinum agents. No long term survival data is available therefore platinum agents while may be considered should not be routinely incorporated into neo-adjuvant regimens until further data is available [90,91].

Adjuvant anti-HER-2 therapy

There is still no evidence to recommend a specific HER2-targeted regimen and treatment duration for young women with HER-2+ early breast cancer: the benefit of adjuvant trastuzumab appears independent of age in all published studies [9].

Side effects of adjuvant therapy

In view of the longer life expectancy of young women, the panel reinforced the need to monitor potential long-term toxicities (i.e. cardiovascular, bone morbidity, cognitive impairment). Further, young women have been documented to be at greater risk of psychosocial morbidity after a diagnosis of breast cancer, particularly those who receive chemotherapy and undergo a menopausal transition with treatment [92,93].

Inflammatory breast cancer

Inflammatory breast cancer should be managed the same as for the older breast cancer population.

Advanced breast cancer (ABC) (Table 7)

There are few proven standards of care in ABC management overall and even more so in young women. Thus, the development of well-designed, independent, prospective randomized trials in ABC was stressed in BCY2, with efforts to augment inclusion of young patients [23].

Further, as is the recommendation for early breast cancer, young age alone should not be a reason to prescribe more aggressive therapy, and international consensus guidelines for management of ABC should be applied [51,94].

The BCY2 panel endorses the ESO-ESMO ABC 2 guidelines for the management of Luminal ABC in pre-menopausal women.

BCY2 recommendations reiterated that treatment strategies should not differ from those for older women with the same disease characteristics and young age by itself is not an indication to prescribe combination chemotherapy over sequential use of monotherapy. The unique medical and psychosocial concerns of young women should be addressed and individualized when caring for young women in the metastatic disease setting.

Loco-regional relapse

Young age is a risk factor for local relapse. The recommendations for young women do not differ from those for the general patient population although particular attention to margin status may be

Table 7
Advanced breast cancer.

Guideline statement	LoE
33. 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 2, ESMO and NCCN guidelines). Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.	Expert opinion IC
34. The BCY2 panel endorses the ESO-ESMO ABC 2 guidelines for the management of Luminal ABC in pre-menopausal women.	IA
35. Well designed prospective randomized trials evaluating the role of platinum agents in the population of BRCA 1/2 mutation associated ABC are urgently needed. For now, in women who BOTH harbor a BRCA mutation AND have “triple negative” subtype use of platinum agents may be considered in the advanced disease setting.	Expert opinion IB
36. 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).	I C

warranted in young women. In keeping with practice for older women, chemotherapy after loco-regional therapy should be considered, particularly in women with HR-negative tumors, based on evidence for benefit in DFS and OS seen in the CALOR trial [95].

BRCA mutation carriers (Table 8)

The indications and modalities of MRI surveillance in high-risk patients still refer to the 2010 EUSOMA guidelines which considered different imaging modalities in the surveillance of high-risk women [35].

The BCY2 panel confirmed BCY1 recommendations for prevention, surveillance, treatment and risk reducing strategies. In particular (i) there is still no definitive evidence that therapeutic mastectomy plus contralateral risk-reducing mastectomy has an impact on survival in a woman with early breast cancer in the context of a hereditary cancer syndrome and, (ii) breast imaging is a screening/surveillance tool for detecting early disease whereas surgery is a risk-reducing procedure for actively reducing the risk of the development of disease [96–98].

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 genetic based information and its consequences to avoid “rush decisions”.

Regarding bilateral risk-reducing salpingo-oophorectomy (RRSO) for the prevention of ovarian cancer amongst women harboring a BRCA 1/2 mutation, the panel members recommended this be performed between ages 35–40 (no consensus on the exact age), as recommended by NCCN and NICE guidelines [99,100], taking into consideration the specific family history and provided the woman has completed childbearing [101,102]. In women not considering RRSO, gynecologic surveillance every six months is still recommended: the panel did not endorse routine CA-125 testing, or transvaginal ultrasound, in agreement with

several available guidelines [103]. While 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 BRCA 1/2 carriers with no clinically significant increased breast cancer risk with recent formulations [104–106], the safety of this strategy in breast cancer survivors has not been tested. For women who choose not to undergo risk reducing contralateral mastectomy, RRSO at young age reduces risk of new breast primaries.

Still, there is no definitive conclusion on the best chemotherapy regimen for BRCA-associated breast cancer patients and the panel recommended that standard prognostic features should be used to decide treatment in the early disease setting [107]. Based on the results of the Geoparsixto trial (see above), the use of platinum may be considered in BRCA-associated triple negative breast cancer [91]. Following the results of the TNT study, the use of a platinum agent should be considered in the advanced breast cancer setting of BRCA-associated ABC [108].

Poly (ADP-ribose) polymerase (PARP) inhibitors are being developed as therapeutic agents for germline and somatic BRCA-mutated breast cancer patients, both in the early and advanced settings [109,110].

Supportive and follow-up care (Table 9)

In principle, follow-up care in young women should follow the same guidelines as in older women [111]. Supportive treatment of specific symptoms/side effects should also follow current recommendations as for older women.

In many settings, breast nurses are of crucial importance to address and support the unique psychosocial and sexual issues of young patient and their families. The panel reinforced the need to address social issues (e.g. return to work, family planning, financial

Table 8
Germline BRCA 1/2 mutation carriers.

37. For survivors harboring a BRCA 1/2 or (other) strongly predisposing mutation, bilateral risk-reducing mastectomy may be considered, although there is no definite evidence that it leads to a survival benefit. 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	IIB
38. For survivors harboring a BRCA 1/2 mutation, risk-reducing 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
39. For the time being, the radiotherapy treatment of EBC is independent of BRCA or any other constitutional 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.	I B III
40. The same guiding principles defining treatment decisions should be applied for all women with ABC regardless of genetic status. Systemic therapy recommendation for BRCA-associated early BC are the same as for the non-BRCA-associated, with the exception of possible consideration of platinum in the neo-adjuvant setting of BRCA-associated triple negative BC.	I B IIB(for platinum)
41. A platinum agent should be considered in the treatment of BRCA-associated advanced breast cancer.	IB

Table 9
Supportive and follow-up care.

Guideline statement	LoE
42. Young women with breast cancer face specific physical, psychosocial and sexual issues that should be addressed by a multidisciplinary group of providers including breast medical, surgical and radiation oncologists, breast nurses, social workers, psycho-oncologists, gynecologists and fertility experts, among others.	Expert opinion
43. All young women should be counseled regarding the risk of getting pregnant while on chemotherapy, endocrine or anti-HER-2 therapy, despite developing amenorrhea, and of the need for adequate non-hormonal contraception if they are sexually active and could become pregnant. Exogenous hormonal contraception is generally contraindicated in young cancer survivors, irrespective of disease subtype, and alternative strategies should be considered.	I B Expert opinion
44. All young women should be referred for special counseling/consultation if interested in fertility preservation prior to commencement of any therapy.	Expert opinion
45. The use of GnRH analog concomitant with adjuvant CT should be discussed on a case by case basis to preserve ovarian function and possibly fertility	I C
46. All young women should be counseled about the risks and associated symptoms and outcomes and management of treatment-related amenorrhea and premature menopause before the onset of systemic therapy (either CT or ET) and informed of available ameliorative therapies.	Expert opinion
47. Premature menopause and/or treatment related amenorrhea increase the risk of bone thinning and patients should be counseled, monitored and treated accordingly.	I A
48. Pregnancy after breast cancer should not be discouraged even in patients with HR positive disease, although all data available have limitations.	I B
49. Treatment of patients with breast cancer during pregnancy should be decided on an individual basis according to international guidelines within an expert multidisciplinary team, expanded to include obstetricians and perinatologists, and according to patients' preferences.	Expert opinion
50. Young patients should be strongly encouraged to adopt the following healthy life style changes: <ul style="list-style-type: none"> • maintain BMI ≤ 25 • perform regular aerobic exercise • not to smoke • to limit daily alcohol intake 	Expert opinion

loss) and feelings of inadequacy (e.g. fear of starting a new relationship, partner's strain).

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 [14,112]. 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 [113] and are reinforced here [113]. Appropriate early referrals for fertility preservation strategies, based on existing practice guidelines [113], 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 regards to predicting fertility as well as safety of intervention. Pregnancy is prohibited due to risk of teratogenesis during active treatment of breast cancer so effective contraception is recommended and proactive counseling should be done on this issue for each patient. 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, or male contraception) should be considered [114]. 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 [115]. In the absence of prospective data patients should be advised to use alternative non-hormonal contraception.

Premature menopausal symptoms may include vasomotor symptoms, sleep disturbance, fatigue and weight gain as well as

sexual dysfunction – all of which can be very distressing for young women [116]. For hot flashes studies of megesterol acetate and medroxyprogesterone acetate have been performed and appeared efficacious [117–119], however long term safety data is limited. Numerous studies exist that evaluated the use of non-hormonal medications and acupuncture in the management of hot flashes but this is beyond the scope of these guidelines.

Sexual functioning: sexual dysfunction is a major issue having significant impact on quality of life both amongst women with chemotherapy-induced amenorrhea [120] and amongst women receiving OFS and oral ET [54,60]. This issue encompasses vaginal dryness, dyspareunia, decreased libido, body image concerns, anxiety and depression, fatigue and side-effects from medications (including anti-depressants). Appropriate counseling should be available and vaginal moisturizers and lubricants should be prescribed [121]. Sexual health should be included in the survivorship care plan and further research is needed to improve management of these [122]. In patients where aforementioned measures do not help consideration of limited and selective use of hormonal agents with a conversation about the lack of data on risk may be considered. This may include vaginal estrogens which may be safer in those on tamoxifen than AI, however safety data is limited.

Pregnancy after breast cancer: all retrospective available data report no detrimental effect of a subsequent pregnancy on breast cancer outcome [123–128]. 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 in the HR+ population at a median follow-up of 5 years following conception [125]. Therefore, pregnancy after breast cancer should not be discouraged, even though definitive data from prospective clinical trials are needed [126]. A prospective global cooperative study, the POSITIVE study has been commenced with the aim of assessing the safety and feasibility of

interrupting ET for pregnancy after breast cancer – enrollment in the study should be strongly encouraged among women who desire early pregnancy after diagnosis, as this will likely be the only prospective study on pregnancy after breast cancer.

Bone health: bone health should be checked regularly (similar to older women) in young women with breast cancer, especially in those receiving OFS plus oral ET. Of note, in contrast with its effects on bones in post-menopausal 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 [129,130]. As a consequence, in all young patients special emphasis on dietary education [i.e. adequate intake of calcium through diet and supplements (1000 mg/day) and vitamin D (800–1000 UI/day)] and regular weight-bearing exercise is needed [131]. Treatment-related bone loss should be managed accordingly, independent of age.

Cognitive impairment: Neurocognitive symptoms (“onco or chemo brain”) are frequently described among young breast cancer survivors [92,132]. Patient-reported symptoms (forgetfulness, difficulty with concentration, fatigue, distractibility and difficulty with word finding) rarely correlate with neuro-imaging 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 [133,134]. While much of the prior work has focused on the effects of chemotherapy, ET may also adversely affect cognition [135–138], although few specific investigations have been conducted and none in young women. In the ZIPP trial (6 cycles of CMF \pm 2 years of goserelin, goserelin plus tamoxifen, or tamoxifen), no effect of treatment on patients’ self-evaluation of memory and concentration was shown [139]. Cognitive function is being prospectively investigated in patients participating in the SOFT trial.

Lifestyle changes: The panel endorsed that young patients should be strongly encouraged to adopt healthy lifestyle changes that include maintaining healthy BMI (≤ 25), performing regular aerobic exercise (equivalent of at least 150 min/week of at least moderate intensity) [140], not smoking and limiting alcohol intake.

Breast cancer during pregnancy: management of patients with breast cancer during pregnancy is outside of scope of these guidelines and should follow established recommendations [141]. In general pregnant women can and should be treated as closely as possible to the general guidelines for BCYW. Patients should be enrolled in prospective registration studies [142].

Conclusions

Loco-regional and systemic treatment of breast cancer in young women should not substantially differ from women in other age groups as management is guided by the stage and biology of the tumor, both in the early and advanced disease setting. However, care of young women must emphasize and address the unique issues specific to their age and life situation – ranging from fertility and pregnancy-related issues, long-term toxicities of treatment and psychosocial problems including long-term quality of life and cosmetic outcomes. All efforts should be made globally by the research community (academia, pharmaceutical industries, independent funding sources, advocacy groups) to develop research programs addressing the unanswered questions regarding the optimal management of breast cancer in young women, in order to overcome the lack of statistical power in smaller studies and possible conventional prejudices of the medical community. Additionally, prospectively planned subgroup analyses in

additional trials across age groups may add important knowledge and thus help to improve management in young women.

In routine clinical practice, the culture of multidisciplinary management and care is strongly recommended to avoid a dogmatic standard of practice and the risk of overtreatment, in particular, in young women. The role of patient advocacy for this age group is also crucial, particularly for dissemination of information and knowledge.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.breast.2015.12.010>.

Conflict of interest statement

None declared.

References

- [1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer J Clin Oncol* 2010;127(12):2893–917. Epub 2011/02/26.
- [2] Desantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics. *CA Cancer J Clin* 2014 Jan–Feb;64(1):52–62.
- [3] WHO. Women & health. 2009.
- [4] American Cancer Society. Breast cancer facts & figures 2013–2014. Atlanta: American Cancer Society; 2013.
- [5] Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA. Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res* 2012;14(2):R55. Epub 2012/03/29.
- [6] Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kerekoglow S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat* 2012;131(3):1061–6. Epub 2011/11/15.
- [7] Azim Jr HA, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. *Clin Cancer Res* 2012;18(5):1341–51. Epub 2012/01/21.
- [8] Partridge AH, Hughes ME, Ottesen RA, Wong YN, Edge SB, Theriault RL, et al. The effect of age on delay in diagnosis and stage of breast cancer. *Oncologist* 2012;17(6):775–82. Epub 2012/05/05.
- [9] Partridge AH, Gelber S, Piccart-Gebhart MJ, Focant F, Scullion M, Holmes E, et al. Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2-positive breast cancer: results from a herceptin adjuvant trial. *J Clin Oncol* 2013;31(21):2692–8. Epub 2013/06/12.
- [10] Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015;33(4):304–11. official journal of the American Society of Clinical Oncology. Epub 2014/12/03.
- [11] de Sanjose S, Leone M, Berez V, Izquierdo A, Font R, Brunet JM, et al. Prevalence of BRCA1 and BRCA2 germline mutations in young breast cancer patients: a population-based study. *Int J Cancer* 2003;106(4):588–93. Epub 2003/07/08.
- [12] Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, et al. Expanding the criteria for BRCA mutation testing in breast cancer survivors. *J Clin Oncol* 2010;28(27):4214–20. Epub 2010/08/25.
- [13] Robertson L, Hanson H, Seal S, Warren-Perry M, Hughes D, Howell I, et al. BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. *Br J Cancer* 2012;106(6):1234–8. Epub 2012/02/16.
- [14] Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104(5):386–405. Epub 2012/01/25.
- [15] Phillips-Salimi CR, Andrykowski MA. Physical and mental health status of female adolescent/young adult survivors of breast and gynecological cancer: a national, population-based, case-control study. *Support Care Cancer* 2013;21(6):1597–604. Epub 2013/01/12.
- [16] Copson E, Maishman T, Gerty S, Eccles B, Stanton L, Cutress RI, et al. Ethnicity and outcome of young breast cancer patients in the United Kingdom: the POSH study. *Br J Cancer* 2014;110(1):230–41. Epub 2013/10/24.
- [17] Partridge AH, Ruddy KJ, Barry WT, Greaney M, Sprunck-Harrild K, Meyer ME, et al. Young and strong: a randomized trial to evaluate a program for young women with breast cancer. In: Poster presentation at the 2013 San Antonio breast cancer symposium; 2013. Poster OT2–4–02.
- [18] Cardoso F, Loibl S, Pagani O, Graziotin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the

- management of young women with breast cancer. *Eur J Cancer* 2012;48(18):3355–77. Epub 2012/11/03.
- [19] Partridge AH, Pagani O, Abulkhair O, Aebi S, Amant F, Azim Jr HA, et al. First international consensus guidelines for breast cancer in young women (BCY1). *Breast* 2014;23(3):209–20. Epub 2014/04/29.
 - [20] Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. *J Clin Oncol* 2004;22(18):3685–93. official journal of the American Society of Clinical Oncology. Epub 2004/08/04.
 - [21] Hassett MJ, Hughes ME, Niland JC, Ottesen R, Edge SB, Bookman MA, et al. Selecting high priority quality measures for breast cancer quality improvement. *Med care* 2008;46(8):762–70. Epub 2008/07/31.
 - [22] Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest* 2006;129(1):174–81. Epub 2006/01/21.
 - [23] Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast* 2012;21(3):242–52. Epub 2012/03/20.
 - [24] The requirements of a specialist breast unit. *Eur J Cancer* 2000;36(18):2288–93. Epub 2000/11/30.
 - [25] Partridge AH, Ruddy KJ, Kennedy J, Winer EP. Model program to improve care for a unique cancer population: young women with breast cancer. *J Oncol Pract* 2012;8(5):e105–10. Epub 2013/01/02.
 - [26] Gabitova G, Burke NJ. Improving healthcare empowerment through breast cancer patient navigation: a mixed methods evaluation in a safety-net setting. *BMC Health Serv Res* 2014;14:407. Epub 2014/09/23.
 - [27] Ko NY, Darnell JS, Calhoun E, Freund KM, Wells KJ, Shapiro CL, et al. Can patient navigation improve receipt of recommended breast cancer care? Evidence from the National Patient Navigation Research Program. *J Clin Oncol* 2014;32(25):2758–64. official journal of the American Society of Clinical Oncology. Epub 2014/07/30.
 - [28] Fiscella K, Whitley E, Hendren S, Raich P, Humiston S, Winters P, et al. Patient navigation for breast and colorectal cancer treatment: a randomized trial. *Cancer Epidemiol Biomarkers Prev* 2012;21(10):1673–81. a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Epub 2012/10/10.
 - [29] Colleoni M, Anders CK. Debate: the biology of breast cancer in young women is unique. *Oncologist* 2013;18(4):e13–5. Epub 2013/05/02.
 - [30] Loibl S, Jackisch C, Gade S, Untch M, Paepke S, Kuemmel S, et al. Neoadjuvant chemotherapy in the very young 35 years of age or younger. *Cancer Res* 2012;72(24 Suppl.):965.
 - [31] Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013;24(9):2206–23. Epub 2013/08/07.
 - [32] Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. *Lancet* 2011;378(9805):1804–11. Epub 2011/11/22.
 - [33] Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Ann Surg* 2013;257(2):249–55. Epub 2012/11/29.
 - [34] Houssami N, Turner R, Macaskill P, Turnbull LW, McCready DR, Tuttle TM, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *J Clin Oncol* 2014;32(5):392–401. Epub 2014/01/08.
 - [35] Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer* 2010;46(8):1296–316. Epub 2010/03/23.
 - [36] Chiarelli AM, Prummel MV, Muradali D, Majpruz V, Horgan M, Carroll JC, et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program. *J Clin Oncol* 2014;32(21):2224–30. official journal of the American Society of Clinical Oncology. Epub 2014/06/18.
 - [37] Schneider K, Zelle K, Nichols KE, Garber J. Li-Fraumeni syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LH, et al., editors. *GeneReviews*(R); 1993. Seattle (WA).
 - [38] Kajihara M, Goto M, Hirayama Y, Okunishi S, Kaoku S, Konishi E, et al. Effect of the menstrual cycle on background parenchymal enhancement in breast MR imaging. *Magnetic Reson Med* 2013;12(1):39–45. MRMS : an official journal of Japan Society of Magnetic Resonance in Medicine. Epub 2013/03/12.
 - [39] McCuaig JM, Arnel SR, Novokmet A, Ginsburg OM, Demsky R, Narod SA, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? *Fam Cancer* 2012;11(4):607–13. Epub 2012/08/02.
 - [40] Mester JL, Moore RA, Eng C. PTEN germline mutations in patients initially tested for other hereditary cancer syndromes: would use of risk assessment tools reduce genetic testing? *Oncologist* 2013;18(10):1083–90. Epub 2013/09/17.
 - [41] Bantema-Joppe EJ, de Munck L, Visser O, Willemse PH, Langendijk JA, Siesling S, et al. Early-stage young breast cancer patients: impact of local treatment on survival. *Int J Radiat Oncol Biol Phys* 2011;81(4):e553–9. Epub 2011/05/24.
 - [42] Botteri E, Bagnardi V, Rotmensz N, Gentilini O, Disalvatore D, Bazzoli B, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. *Ann Oncol* 2010;21(4):723–8. Epub 2009/10/17.
 - [43] Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (<=40 years) early breast cancer patients: a systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast* 2015 Jun;24(3):175–81.
 - [44] Niemeyer M, Paepke S, Schmid R, Plattner B, Muller D, Kiechle M. Extended indications for nipple-sparing mastectomy. *Breast J* 2011;17(3):296–9. Epub 2011/04/01.
 - [45] Chung AP, Sacchini V. Nipple-sparing mastectomy: where are we now? *Surg Oncol* 2008;17(4):261–6. Epub 2008/05/06.
 - [46] Ashworth A, Kong W, Whelan T, Mackillop WJ. A population-based study of the fractionation of postlumpectomy breast radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;86(1):51–7. Epub 2013/02/26.
 - [47] Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817–26. Epub 2004/12/14.
 - [48] Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* 2006;98(17):1183–92. Epub 2006/09/07.
 - [49] Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015 Nov 19;373(21):2005–14.
 - [50] Iwata H, Masuda N, Sagara Y, Kinoshita T, Nakamura S, Yanagita Y, et al. Analysis of Ki-67 expression with neoadjuvant anastrozole or tamoxifen in patients receiving goserelin for premenopausal breast cancer. *Cancer* 2013;119(4):704–13. Epub 2012/09/14.
 - [51] NCCN. 2015.
 - [52] Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378(9793):771–84. Epub 2011/08/02.
 - [53] Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Lang I, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371(2):107–18. Epub 2014/06/03.
 - [54] Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372(17):1673. Epub 2015/04/23.
 - [55] Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Knauer M, Moik M, et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol* 2015;26(2):313–20. official journal of the European Society for Medical Oncology/ESMO. Epub 2014/11/19.
 - [56] International Breast Cancer Study G, Castiglione-Gertsch M, O'Neill A, Price KN, Goldhirsch A, Coates AS, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003;95(24):1833–46. Epub 2003/12/18.
 - [57] Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Martino S, White DR, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol* 2005;23(25):5973–82. official journal of the American Society of Clinical Oncology. Epub 2005/08/10.
 - [58] Group LH-aIEBCO, Cuzick J, Ambroisine L, Davidson N, Jakesz R, Kaufmann M, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007;369(9574):1711–23. Epub 2007/05/22.
 - [59] Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database Syst Rev* 2009;(4):CD004562. Epub 2009/10/13.
 - [60] Pagani O, Regan MM, Francis PA, Text, Investigators S, International Breast Cancer Study G. Exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371(14):1358–9. Epub 2014/10/02.
 - [61] Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381(9869):805–16. Epub 2012/12/12.
 - [62] Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, et al. aTOM: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. *J Clin Oncol* 2013;31. 2013 (suppl; abstr 5).
 - [63] Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Livingston RB, et al. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. *Ann Oncol* 2013;24(2):355–61. official journal of the European Society for Medical Oncology/ESMO. Epub 2012/10/03.
 - [64] Henry NL, Xia R, Banerjee M, Gersch C, McConnell D, Giacherio D, et al. Predictors of recovery of ovarian function during aromatase inhibitor

- therapy. *Ann Oncol* 2013;24(8):2011–6. official journal of the European Society for Medical Oncology/ESMO, Epub 2013/04/25.
- [65] Meior D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update* 2001;7(6):535–43. Epub 2001/12/01.
- [66] Carlson RW, Theriault R, Schurman CM, Rivera E, Chung CT, Phan SC, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. *J Clin Oncol* 2010;28(25):3917–21. official journal of the American Society of Clinical Oncology, Epub 2010/08/04.
- [67] Bellet M, GK, Francis PA, et al. Estrogen levels in premenopausal (prem) patients (pts) with hormone-receptor positive (HR+) early breast cancer (BC) receiving adjuvant triptorelin (Tript) plus exemestane (E) or tamoxifen (T) in the SOFT trial: SOFT-EST substudy. *J Clin Oncol* 2014;32(5s) (suppl; abstr 585).
- [68] Dowsett M, Folkler E. Deficits in plasma oestradiol measurement in studies and management of breast cancer. *Breast Cancer Res BCR* 2005;7(1):1–4. Epub 2005/01/12.
- [69] Aydinler A, Kilic L, Yildiz I, Keskin S, Sen F, Kucuk S, et al. Two different formulations with equivalent effect? Comparison of serum estradiol suppression with monthly goserelin and trimonthly leuprolide in breast cancer patients. *Med Oncol* 2013;30(1):354. Epub 2013/01/01.
- [70] Cluze C, Rey D, Huiart L, BenDiane MK, Bouhnik AD, Berenger C, et al. Adjuvant endocrine therapy with tamoxifen in young women with breast cancer: determinants of interruptions vary over time. *Ann Oncol* 2012;23(4):882–90. official journal of the European Society for Medical Oncology/ESMO, Epub 2011/07/27.
- [71] Llarena NC, Estevez SL, Tucker SL, Jeruss JS. Impact of fertility concerns on tamoxifen initiation and persistence. *J Natl Cancer Inst* 2015;107(10). Epub 2015/08/27.
- [72] Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol* 2008;26(4):556–62. official journal of the American Society of Clinical Oncology, Epub 2008/01/09.
- [73] Tevaarwerk AJ, Wang M, Zhao F, Fetting JH, Cella D, Wagner LJ, et al. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2014;32(35):3948–58. official journal of the American Society of Clinical Oncology, Epub 2014/10/29.
- [74] Bernhard, JLW, K. Ribi, et al., Patient-reported endocrine symptoms, sexual functioning, and quality of life (QoL) in the IBCSG TEXT and SOFT trials: adjuvant treatment with exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC). *J Clin Oncol* 32:19s
- [75] Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA J Am Med Assoc* 2011;306(3):269–76. Epub 2011/07/21.
- [76] Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015;372(10):923–32. Epub 2015/03/05.
- [77] Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim Jr HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol* 2015;26(12):2408–19. official journal of the European Society for Medical Oncology/ESMO, Epub 2015/09/09.
- [78] Coleman R, Cameron D, Dodwell D, Bell R, Wilson C, Rathbone E, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol* 2014;15(9):997–1006. Epub 2014/07/19.
- [79] Valachis A, Polyzos NP, Coleman RE, Gnani M, Eidtmann H, Brufsky AM, et al. Adjuvant therapy with zoledronic acid in patients with breast cancer: a systematic review and meta-analysis. *Oncologist* 2013;18(4):353–61. Epub 2013/02/14.
- [80] Coleman R, Gnani M, Paterson A, Powles T, von Minckwitz G, Pritchard K, et al. Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: a meta-analysis of individual patient data from randomised trials. In: Presented at the 2013 San Antonio breast cancer symposium; 2013. Abstract S4–07.
- [81] Coleman RE. Adjuvant bone-targeted therapy to prevent metastasis: lessons from the AZURE study. *Curr Opin Support Palliat Care* 2012;6(3):322–9. Epub 2012/07/18.
- [82] Thurlimann B, Price KN, Gelber RD, Holmberg SB, Crivellari D, Colleoni M, et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. *Breast Cancer Res Treat* 2009;113(1):137–44. Epub 2008/02/09.
- [83] Regan MM, Pagani O, Walley B, Torrisi R, Perez EA, Francis P, et al. Premenopausal endocrineresponsive early breast cancer: who receives chemotherapy? *Ann Oncol* 2008;19(7):1231–41. official journal of the European Society for Medical Oncology/ESMO, Epub 2008/03/08.
- [84] Francis PA, Regan MM, Fleming GF, Lang I, Ciruelos E, Bellet M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372(5):436–46. Epub 2014/12/17.
- [85] Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379(9814):432–44. Epub 2011/12/14.
- [86] Eiermann W, Pienkowski T, Crown J, Sadeghi S, Martin M, Chan A, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIrg-005 trial. *J Clin Oncol* 2011;29(29):3877–84. official journal of the American Society of Clinical Oncology, Epub 2011/09/14.
- [87] Piccart MJ, Di Leo A, Beauduin M, Vindevoghel A, Michel J, Focan C, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol* 2001;19(12):3103–10. official journal of the American Society of Clinical Oncology, Epub 2001/06/16.
- [88] Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-Year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009;27(8):1177–83. official journal of the American Society of Clinical Oncology, Epub 2009/02/11.
- [89] Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97(3):188–94. Epub 2005/02/03.
- [90] Sikov WM, Berry DA, Perou CM, Singh B, Cirincione CT, Tolane SM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015;33(1):13–21. official journal of the American Society of Clinical Oncology, Epub 2014/08/06.
- [91] von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014;15(7):747–56. Epub 2014/05/06.
- [92] Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;21(22):4184–93. official journal of the American Society of Clinical Oncology, Epub 2003/11/15.
- [93] Kroenke CH, Rosner B, Chen WY, Kawachi I, Colditz GA, Holmes MD. Functional impact of breast cancer by age at diagnosis. *J Clin Oncol* 2004;22(10):1849–56. official journal of the American Society of Clinical Oncology, Epub 2004/05/15.
- [94] Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) dagger. *Ann Oncol* 2014;25(10):1871–88. official journal of the European Society for Medical Oncology/ESMO, Epub 2014/09/23.
- [95] Aebi S, Gelber S, Anderson SJ, Lang I, Rבודoux A, Martin M, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol* 2014;15(2):156–63. Epub 2014/01/21.
- [96] Metcalfe K, Gershman S, Ghadirian P, Lynch HT, Snyder C, Tung N, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ* 2014;348:g226. Epub 2014/02/13.
- [97] Evans DG, Ingham SL, Bailem A, Ross GL, Lalloo F, Buchan I, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. *Breast Cancer Res Treat* 2013;140(1):135–42. Epub 2013/06/21.
- [98] van Sprundel TC, Schmidt MK, Rookus MA, Brohet R, van Asperen CJ, Rutgers EJ, et al. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. *Br J Cancer* 2005;93(3):287–92. Epub 2005/07/30.
- [99] NICE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2013 (Amended 2015).
- [100] NCCN. Genetic/familial high risk assessment: breast & ovarian V2. 2015. p. 2015.
- [101] Domchek SM, Friebe TM, Garber JE, Isaacs C, Matloff E, Eeles R, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 2010;124(1):195–203. Epub 2010/02/25.
- [102] Domchek SM, Friebe TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *Jama* 2010;304(9):967–75. Epub 2010/09/03.
- [103] Moyer VA. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2012;157(12):900–4. Epub 2012/09/12.
- [104] Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. *Eur J Cancer* 2010;46(12):2275–84. Epub 2010/06/12.
- [105] Gadducci A, Biglia N, Cosio S, Sismondi P, Genazzani AR. Gynaecologic challenging issues in the management of BRCA mutation carriers: oral

- contraceptives, prophylactic salpingo-oophorectomy and hormone replacement therapy. *Gynecol Endocrinol* 2010;26(8):568–77. Epub 2010/07/17.
- [106] Cibula D, Zikan M, Dusek L, Majek O. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. *Expert Rev Anticancer Ther* 2011;11(8):1197–207. Epub 2011/09/16.
- [107] Balmana J, Diez O, Rubio IT, Cardoso F. BRCA in breast cancer: ESMO clinical practice guidelines. *Ann Oncol* 2011;22(Suppl. 6):vi31–4. Epub 2011/10/20.
- [108] Tutt A. TNT: a randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer. In: *San Antonio Breast Cancer Symposium*; December 2014.
- [109] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009;361(2):123–34. Epub 2009/06/26.
- [110] Yap TA, Sandhu SK, Carden CP, de Bono JS. Poly(ADP-ribose) polymerase (PARP) inhibitors: Exploiting a synthetic lethal strategy in the clinic. *CA Cancer J Clin* 2011;61(1):31–49. Epub 2011/01/06.
- [111] Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31(7):961–5. Epub 2012/11/07.
- [112] Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol* 2004;22(20):4174–83. Epub 2004/10/16.
- [113] Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31(19):2500–10. official journal of the American Society of Clinical Oncology, Epub 2013/05/30.
- [114] Blanc B, Lazard A, Estrade JP, Agostini A, Gurriet B. Contraceptive methods after gynecological and breast cancer. *Bull Acad Natl Med* 2010;194(3):521–7. discussion 9–30. Epub 2010/12/22. *Contraception apres cancer gynecologique et mammaire*.
- [115] Schwarz EB, Hess R, Trussell J. Contraception for cancer survivors. *J Gen Intern Med* 2009;24(Suppl. 2):S401–6. Epub 2009/11/05.
- [116] Rosenberg SM, Partridge AH. Premature menopause in young breast cancer: effects on quality of life and treatment interventions. *J Thorac Dis* 2013;5(Suppl. 1):S55–61. Epub 2013/07/03.
- [117] Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331(6):347–52. Epub 1994/08/11.
- [118] Quella SK, Loprinzi CL, Sloan JA, Vaught NL, DeKrey WL, Fischer T, et al. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer* 1998;82(9):1784–8. Epub 1998/05/12.
- [119] Bertelli G, Venturini M, Del Mastro L, Bergaglio M, Sismondi P, Biglia N, et al. Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. *Ann Oncol* 2002;13(6):883–8. official journal of the European Society for Medical Oncology/ESMO, Epub 2002/07/19.
- [120] Rosenberg SM, Tamimi RM, Gelber S, Ruddy KJ, Bober SL, Kerekoglow S, et al. Treatment-related amenorrhea and sexual functioning in young breast cancer survivors. *Cancer* 2014;120(15):2264–71. Epub 2014/06/04.
- [121] Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. *J Sex Med* 2011;8(2):549–59. Epub 2010/08/21.
- [122] Dizon DS, Suzin D, McIlvenna S. Sexual health as a survivorship issue for female cancer survivors. *Oncol* 2014;19(2):202–10. Epub 2014/01/08.
- [123] Azim Jr HA, Del Mastro L, Scarfone G, Peccatori FA. Treatment of breast cancer during pregnancy: regimen selection, pregnancy monitoring and more. *Breast* 2011;20(1):1–6. Epub 2010/11/30.
- [124] Kroman N, Jensen MB, Wohlfahrt J, Ejlersen B. Pregnancy after treatment of breast cancer—a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol* 2008;47(4):545–9. Epub 2008/05/10.
- [125] Azim Jr HA, Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013;31(1):73–9. Epub 2012/11/22.
- [126] Pagani O, Partridge A, Korde L, Badve S, Bartlett J, Albain K, et al. Pregnancy after breast cancer: if you wish, ma'am. *Breast Cancer Res Treat* 2011;129(2):309–17. Epub 2011/06/24.
- [127] Theriault RL, Litton JK. Pregnancy during or after breast cancer diagnosis: what do we know and what do we need to know? *J Clin Oncol* 2013;31(20):2521–2. Epub 2013/06/05.
- [128] Azim Jr HA, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev* 2012;38(7):834–42. Epub 2012/07/13.
- [129] Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. *J Clin Oncol* 2006;24(4):675–80. Epub 2006/02/01.
- [130] Sverrisdottir A, Fornander T, Jacobsson H, von Schoultz E, Rutqvist LE. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. *J Clin Oncol* 2004;22(18):3694–9. Epub 2004/09/15.
- [131] Hojan K, Milecki P, Molinska-Glura M, Roszak A, Leszczynski P. Effect of physical activity on bone strength and body composition in breast cancer premenopausal women during endocrine therapy. *Eur J Phys Rehabil Med* 2013;49(3):331–9. Epub 2013/02/27.
- [132] Castellon SA, Silverman DH, Ganz PA. Breast cancer treatment and cognitive functioning: current status and future challenges in assessment. *Breast Cancer Res Treat* 2005;92(3):199–206. Epub 2005/09/13.
- [133] Deprez S, Amant F, Yigit R, Porke K, Verhoeven J, Van den Stock J, et al. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. *Hum Brain Mapp* 2011;32(3):480–93. Epub 2010/08/21.
- [134] Deprez S, Amant F, Smeets A, Peeters R, Leemans A, Van Hecke W, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *J Clin Oncol* 2012;30(3):274–81. Epub 2011/12/21.
- [135] Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat* 2000;64(2):165–76. Epub 2001/02/24.
- [136] Leining MG, Gelber S, Rosenberg R, Przypyszny M, Winer EP, Partridge AH. Menopausal-type symptoms in young breast cancer survivors. *Ann Oncol* 2006;17(12):1777–82. Epub 2006/09/15.
- [137] Phillips KA, Aldridge J, Ribi K, Sun Z, Thompson A, Harvey V, et al. Cognitive function in postmenopausal breast cancer patients one year after completing adjuvant endocrine therapy with letrozole and/or tamoxifen in the BIG 1-98 trial. *Breast Cancer Res Treat* 2011;126(1):221–6. Epub 2010/11/04.
- [138] Phillips KA, Ribi K, Sun Z, Stephens A, Thompson A, Harvey V, et al. Cognitive function in postmenopausal women receiving adjuvant letrozole or tamoxifen for breast cancer in the BIG 1-98 randomized trial. *Breast* 2010;19(5):388–95. Epub 2010/04/14.
- [139] Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol* 2003;21(9):1836–44. Epub 2003/05/02.
- [140] Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;25(7):1293–311. official journal of the European Society for Medical Oncology/ESMO, Epub 2014/03/20.
- [141] Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol* 2015;1(8):1145–53.
- [142] Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012;13(9):887–96. Epub 2012/08/21.