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Breast Cancer (P Neven, Section Editor)

Breast Cancer Under Age 40: a Different Approach

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Opinion statement

Breast cancer (BC) under age 40 is a complex disease to manage due to the additionally fertility-related factors to be taken in consideration. More than 90 % of young patients with BC are symptomatic. Women <40 years are more likely to develop BC with worse clinicopathological features and more aggressive subtype. This has been frequently associated with inferior outcomes. Recently, the prognostic significance of age <40 has been shown to differ according to the BC subtype, being associated with worst recurrence-free survival (RFS) and overall survival (OS) for luminal BC. The biology of BC <40 has also been explored through analysis of large genomic data set, and specific pathways overexpressed in these tumors have been identified which can lead to the development of targeted therapy in the future. A multidisciplinary tumor board should determine the optimal locoregional and systemic management strategies for every individual patient with BC before the start of any therapy including surgery. This applies to both early (early

breast cancer (EBC)) and advanced (advanced breast cancer (ABC)) disease, before the start of any therapy. Mastectomy even in young patients confers no overall survival advantage when compared to breast-conserving treatment (BCT), followed by radiotherapy. Regarding axillary approach, indications are identical to other age groups. Young age is one of the most important risk factors for local recurrence after both breast-conserving surgery (BCS) and mastectomy, associated with a higher risk of distant metastasis and death. Radiation after BCS reduces local recurrence from 19.5 to 10.2 % in BC patients 40 years and younger. The indications for and the choice of systemic treatment for invasive BC (both early and advanced disease) should not be based on age alone but driven by the biological characteristics of the individual tumor (including hormone receptor status, human epidermal growth factor receptor 2 (HER-2) status, grade, and proliferative activity), disease stage, and patient's comorbidities. Recommendations regarding the use of genomic profiles such as MammaPrint, Oncotype Dx, and Genomic grade index in young women are similar to the general BC population. Especially in the metastatic setting, patient preferences should always be taken into account, as the disease is incurable. The best strategy for these patients is the inclusion into well-designed, independent, prospective randomized clinical trials. Metastatic disease should always be biopsied whenever feasible for histological confirmation and reassessment of biology. Endocrine therapy is the preferred option for hormone receptor-positive disease (HR+ve), even in presence of visceral metastases, unless there is concern or proof of endocrine resistance or there is a need for rapid disease response and/or symptom control. Recommendations for chemotherapy (CT) should not differ from those for older patients with the same characteristics of the metastatic disease and its extent. Young age by itself should not be an indication to prescribe more intensive and combination CT regimens over the sequential use of monotherapy. Poly(ADP-ribose) polymerase inhibitors (PARP inhibitors) represent an important group of promising drugs in managing patients with breast cancer susceptibility gene (BRCA)-1- or BRCA-2-associated BC. Specific age-related side effects of systemic treatment (e.g., menopausal symptoms, change in body image, bone morbidity, cognitive function impairment, fertility damage, sexual dysfunction) and the social impact of diagnosis and treatment (job discrimination, taking care for children) should also be carefully addressed when planning systemic long-lasting therapy, such as endocrine therapy. Survivorship concerns for young women are different compared to older women, including issues of fertility, preservation, and pregnancy.

Introduction

Breast cancer in young women is a rare condition; however, in the USA, an estimated 14,000 women under age 40 are diagnosed with breast cancer (BC) annually, and nearly 3,000 young women die each year from their disease [1]. BC is the leading cause of cancer death in young women.

The prognostic relevance of young age (age <40 years) by itself it is highly controversial. Some data suggest worse outcome, mainly in age <35 years, while other propose it is mostly related with biology. Recent research suggests that age as a prognostic factor differs by biologic subtype. Young women have increased risk of psychosocial distress after BC diagnosis, not only due to less favorable disease on average but also to their stage of life at diagnosis and need to cope with multiple tasks linked to a young family, work, and career [2•]. There are other special areas in young BC patients such as fertility preservation and family planning, sexual functioning, beauty and body image, launching careers, and raising young children.

In recent years, there has been an improvement in the understanding of the biology of BC in young women. The most important message is that although age is an important factor to consider, it should not be the main or only factor for the choice of treatment (both for early (early breast cancer (EBC)) and advanced (advanced breast cancer (ABC)) disease). Treatment choices should be driven by the biological characteristics of the individual tumor, stage, and characteristics of each individual young patient [3, 4].

In this review article, we will focus on current treatment modalities recommended for women <40 years with EBC and ABC. We will also address studies that allowed us to better understand the biology of BC in this population. Survivorship with emphasis on fertility preservation, contraception, and pregnancy after BC diagnosis will also be discussed.

Diagnosis and staging

General considerations

Imaging evaluation of breast suspicious abnormalities should be done as fast as possible by experienced professionals in departments of radiology with expertise of breast diagnostic and interventional procedures [3, 4]. Mammography should be preferably done during the first 2 weeks of the menstrual cycle, while ultrasound can be performed at any time. Magnetic resonance imaging (MRI) should be performed in the second week of the menstrual cycle (to reduce the risk of false positives) following the standard technical recommendations [5].

Screening

Women with a family history suggesting a genetic predisposition to BC should have their risk assessed by a professional, e.g., a clinical geneticist [3, 4]. If they are found to be at high risk (20–30 % lifetime risk or higher), they should be given oral and written data regarding their actual risk and benefits of mammography and MRI screening techniques as well as of prophylactic procedures. Breast cancer susceptibility gene (BRCA)-1 and BRCA-2 mutation carriers should be offered an annual MRI screening starting between age 25 and 29 years or on an individualized timetable based on the earliest age of cancer onset in family member. Tumor protein p53 (TP53) mutation carriers should start at age 20.

Other subgroups of high-risk women with a predisposition to BC should also be offered an annual MRI screening, and they include first-degree relatives of BRCA-1, BRCA-2, and TP53 mutation carriers, women from families not being tested for BRCA mutation but with a 20–30 % lifetime risk or greater, women with previous radiotherapy (RT) before age 30 (e.g., for Hodgkin lymphoma) starting 8 years after the treatment, and women at high risk and being already diagnosed and treated for BC. In TP53 mutation carriers of any age, annual mammography should be avoided due to high risk of radiation-induced cancer(s) [3].

After finding suspicious abnormalities with MRI, there is always a need for reevaluation with conventional imaging (mammography and ultrasound). If

solely MRI discloses the suspicious lesion, MR-guided biopsy localisation should be performed [3, 4].

Diagnosis

Because of the challenge that BC diagnosis often represent in young patients, imaging evaluation of breast lesions should be performed only by an experienced professional, and in case of a strong suspicion of BC, triple assessment must be done (clinical examination, imaging, and cytological/histological confirmation) [3, 4]. When a palpable mass is present, patients should have ultrasound followed, in case of Breast Imaging Reporting and Data System 3-5 (BIRADS 3-5), by core biopsy preferred or fine needle aspirate cytology. The use of mammography should be based on the biopsy result; in case of malignancy, mammography is indicated to determine the extent of the disease [3, 4], and ultrasound of breast and axilla bilaterally should be performed.

It is highly recommended to have a histopathological confirmation of malignancy before any surgical procedures, and immunophenotype of the disease (estrogen receptor (ER), PR, human epidermal growth factor receptor 2 (HER-2) status, and Ki-67 index) should ideally be determined in the core biopsy [6].

There are no data advising the routine use of MRI in the preoperative setting in young women with BC. It should be used for the same indications as in older patients in case of newly diagnosed invasive lobular carcinoma [7], patients being at high risk for BC, those with a size discordancy of more than 1 cm between mammography and ultrasound, and expected impact on the surgical intervention. Multifocality and/or multicentricity found by MRI should be assessed with mammography and ultrasound and confirmed by biopsy.

Staging

Age alone should not be an indication for performing additional staging procedures in asymptomatic patients [3, 4]. In young women with BC, the standard staging procedures for distant metastases should be used and consist of thorax x-ray, bone scan, liver ultrasound (US), and blood tests including a tumor marker.

Biology

Pathohistological features of BC in young women

Results of the POSH study, the largest prospective observational study evaluating the pathological characteristics of 2,956 BC women under age 40, have recently been reported [8]. The majority had ductal histology (86.5 %) and grade III (58.9 %) tumors. Of patients, 50.2 % had node-positive disease, and multifocality was observed in 27 % of patients. One third of tumors were ER-negative and one quarter were HER-2 positive. Similar results were found among the first 399 patients evaluated in the Young Women's BC Study [9], also with high rates of lymphovascular invasion (34 %) and lymphocytic infiltration (24 %). Many other retrospective studies have evaluated differences in pathological features according to age [10]. Gnerlich et al. demonstrated that young patients were more often diagnosed with larger tumors, nodal involvement,

grade III tumors, and ER-negative disease [10]. A population-based study from the California Cancer Registry, which included 5,605 patients aged under 40 at diagnosis, further showed higher proportion (28.2 %) of HER-2-positive tumors in the younger population [11]. In addition, it should be recognized that there is a rare histological subtype, secretory breast carcinoma, which is more common in the (very) young women. Despite the fact that they belong to the phenotypic spectrum of basal-like BC, they are associated with good long-term survival [12].

Recently published retrospective analysis of prospectively collected data by Bayraktar et al. showed that BRCA-1 carriers were more likely to have high nuclear grade and triple negative tumors than BRCA-2 carriers and non-carriers [13]. Moreover, they were more likely to have medullary BC. BRCA-1 carriers were also more likely to be lymph node negative than non-carriers and BRCA-2 carriers. This is a new finding and could be a result of screening differences [13].

Pattern of BC subtypes in young women

The advent of genomic signatures allowed us to better understand the biology of BC, and four main intrinsic subtypes of BC with clinical implications are now recognized: luminal A, luminal B, HER-2 overexpressed, and basal-like. These subtypes generated by genomic signatures are correlated with the classical classification and have clinicopathologic surrogates: luminal A-like, luminal B-like, HER-2 positive (non-luminal), and triple negative. Luminal A type tumors are characterized by endocrine-responsive disease (ER+ and PR+) and low proliferative rate (low grade and low Ki-67). Luminal B tumors are also endocrine-responsive but have higher proliferative rate and are associated with worse prognosis compared to luminal A tumors. HER-2-positive disease (as defined by ASCO/CAP guidelines) [14] is characterized by more aggressive biological behavior and a usually good response to anti-HER-2 therapy. Finally, triple negative disease (ER-negative, PR-negative, and HER-2 negative) usually have a very aggressive behavior being chemotherapy (CT) the mainstay of treatment [15]. More recently published research has depicted even further the heterogeneity of breast cancer recognizing additional subgroups within main intrinsic subtypes already described [16, 17].

In the largest published study to date, Azim et al. evaluated tumors of 3,522 patients in whom 451 were aged ≤40 at diagnosis [18•]. There was a significantly higher proportion of basal-like tumors (34.3 %) in this cohort compared to those aged 41–52 (27.7 %). A higher proportion of HER-2-enriched cancers was also observed in young patients. On the other hand, young women were less likely to have luminal A tumors (17.2 %) compared to other age groups.

Prognostic genomic signatures in young BC patients

Since genomic assays were mainly developed using populations of postmenopausal women, there have been concerns about whether they have the same prognostic value in young patients. First-generation gene signatures, MammaPrint and Oncotype Dx, were evaluated in young patients in two studies. The Dutch group reported that 52/63 (82 %) young patients were

classified as high risk on MammaPrint [19]. The same findings were observed for Oncotype Dx, where the majority of patients under age 40 had a high-risk score (56 %) [20].

An analysis of 755 patients with ER-positive disease, of whom 87 were aged ≤40 years, demonstrated that all three gene expression profiles, MammaPrint, genomic grade index, and GENE 76, were significantly associated with disease-free survival (DFS) and added significant prognostic information to clinico-pathologic parameters (tumor size, nodal status, ER status, and histological grade) [18•].

Because of the longer life expectancy of young women, genomic assays could be useful not only to decide whether to use adjuvant CT but also to identify those who would benefit from extended adjuvant endocrine treatment (ET). However, the late recurrence genomic signatures developed so far have not yet been validated in patients under 40 years.

Gene expression differences in young BC patients

One of the first analyses of the biology of BC in young women using gene expression profiling done by Anders et al. showed a higher proportion of phosphatidylinositide 3-kinase (PI3K) and Myc pathway deregulation [21], but this analysis was not adjusted for potential differences in BC molecular subtypes.

More recently, Azim et al. evaluated the association between patients' age and nearly 50 genes that were identified to be related to early-onset BC. It was found that younger patients have higher expression of RANK-ligand, mammary stem cell and luminal progenitors, and BRCA-1 mutation signatures independently of grade, stage, and intrinsic subtype of BC [18•]. There was also more disruption of MAPK-PI3K pathways and lower expression of many apoptosis-related genes, especially FAS.

There is a high prevalence of BRCA-1 mutations in younger patients [22]. These patients are frequently diagnosed with basal-like tumors [23].

Age as biomarker (prognostic and predictive)

For a long time, young age at diagnosis of BC has been considered as an independent factor associated with higher risk of relapse and death [24, 25]. However, several data, namely lower incidence of luminal A type tumor and enrichment in aggressive subtypes [26, 27], have led to question whether the prognostic significance of age remains when stratified on the basis of biologic subtype. In a recent analysis, Sheridan et al. [28] suggested that the effect of age varies with subtype. In this study, hormone receptor-positive disease (HR+ve) BC in young women carried a worse prognosis than in older women. Age <40 predicted inferior survivals within the luminal subgroup. One must acknowledge that an important limitation of the study is the lack of further subtyping within the luminal group. It is possible that the inferior outcomes are driven by luminal B cancer in this group. In the HERceptin Adjuvant (HERA) trial (HER-2 positive BC), age <40 years was not prognostic for DFS or overall survival (OS) in the CT plus trastuzumab arm [29]. Such data supports the concept that age <40 years as a prognostic factor differs by biologic subtype.

Regarding prediction, age is not a discriminative factor between different types of CT. Additionally, in the HERA trial, age <40 years did not predict for trastuzumab benefit [29].

Treatment

General recommendations

The optimal locoregional and systemic management strategies should be determined by a multidisciplinary tumor board for every individual patient with BC before the start of any therapy including surgery. This applies to both EBC and ABC before the start of any therapy [3, 4, 30, 31].

Locoregional treatment

Surgery

Surgical treatment of BC in young women consisted, for many years, of mastectomy that was considered to be safer leading to less locoregional recurrences (LRR) and better OS. In the last decade, this concept was challenged with the results from large randomized trials in all age groups [32], and mastectomy even in young patients confers no OS advantage when compared to breast-conserving treatment (BCT) [33], followed by RT. Young age however remains as an independent risk factor for increased LRR after BCT [34] for both intraductal and invasive disease [35], despite the use of more effective adjuvant therapies [36]. Even considering the higher LRR in young women compared to other age groups, BCT if feasible should always be the preferred option [37]. The use of oncoplastic techniques is considered safe and seems particular useful when more extensive resections are needed. Young age is also a predictor of a gradual asymmetry between the treated and non-treated breast making oncoplastic techniques more important [38].

Based on current evidence, nipple-sparing mastectomy seems to have identical results regarding local recurrences as classic mastectomies, conveying higher cosmetic results [39]. Reconstruction options should be thoroughly discussed with the patient [37]. Patients should be fully informed of the impact of radiotherapy in breast reconstruction. Current evidence shows similar results when comparing immediate with delayed reconstruction regarding complications. Results favor delaying the procedure when an implant only based technique is the selected method.

Regarding axillary approach, indications are identical to other age groups with no special indications for the young age group.

Young patients submitted to neoadjuvant CT, with incomplete pathologic response, have a higher LRR after BCT [40]. Although surgical guidelines are similar to other age groups regarding resection margins and axillary approach, there is an unnecessary trend towards mastectomy in younger patients after primary systemic treatment [41], eventually explained by a reported greater risk of LRR, less imaging accuracy with higher false-positive rates, and a higher possibility of hereditary BC [40].

Breast conservation can also be an option in BRCA mutation carriers with recently diagnosed BC with the same survival benefit than mastectomy [42]. A recent meta-analysis [43] concerning surgical management of BRCA mutation carriers concludes however that LRR after BCT is significantly higher in

mutation carriers when longer follow-up (more than 7 years) studies were included. There were no differences in LRR between BRCA-1 and 2 mutation carriers. Adjuvant radiotherapy, CT, and prophylactic oophorectomy were all associated with a significant risk reduction of LRR [44].

The risk for contralateral breast cancer (CBC) is increased in BRCA mutation carriers and significantly higher in BRCA-1 mutation carriers, but data about an OS benefit of contralateral prophylactic mastectomy is not clear [42, 45].

Risk reduction surgery with bilateral mastectomy and eventual oophorectomy should be extensively discussed before initial surgery if genetic test results are available at diagnosis. However, adding the impact of a recently diagnosed cancer with the complex discussion about harms and benefits of prophylactic surgery in mutation carriers can be overwhelming and can be delayed to a second phase after the treatment of the recently diagnosed cancer [46]. If bilateral mastectomy is indicated, immediate reconstruction should be offered, and nipple- or skin-sparing mastectomies are proven good options regarding both oncological and cosmetic outcomes [47].

Radiotherapy

Young age is one of the most important risk factors for local recurrence after both BCS and mastectomy associated with a higher risk of distant metastasis and death [34]. Local recurrence rates are reported three times higher at 5 years in patients under 40 years [48]. Biological subtypes are known to have a great impact on both local control and distant failure in all BC patients. Several reports state higher risk for local recurrence after BCS for women younger than 50 years and high-grade tumors [34, 48–50]. There are several hypotheses to account for the effect of age on local control. First, young women may be more likely to have HER-2-positive and triple negative BC [51–53]. The reason for association of the HER-2 subtype with ipsilateral breast tumor recurrence (IBTR) in younger patients is unclear; however, some studies suggest that this subtype may be relatively resistant to post-lumpectomy RT [54–57]. HER-2 inhibitors can affect cellular responses to ionizing radiation by induction of apoptosis and cell cycle arrest and by impeding DNA repair [58–63]. Targeting of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway may help to overcome resistance to currently available HER-2 inhibitors plus irradiation. Second, dense breasts, which are more common in younger women, may be a risk factor for local recurrence [64, 65]. The mechanisms underlying the association of dense breasts and tumor recurrence are largely unknown, although previous research indicated that circulating growth factors and proteins may influence breast density and tumor recurrence [64–66]. Moreover, dense breasts may have a masking effect on tumor detection by mammography [64].

RT after BCS reduces local recurrence from 19.5 to 10.2 % in BC patients 40 years and younger ($P=0.002$) [48]. The 10-year results of the EORTC 22991/10883 trial (boost vs no boost trial) demonstrated that additional radiation had the largest absolute benefit on local control in younger patients and reported that close margin was associated with higher local recurrence rate only in younger patients (less than 45 years old), suggesting the importance of strict surgical local control for this patient population [67, 68].

Systemic treatment

General recommendations

The indications for and the choice of systemic treatment for invasive BC (BC) (both early and advanced disease) should not be based on age alone but driven by the biological characteristics of the individual tumor (including hormone receptor status, HER-2 status, grade, and proliferative activity), disease stage, and patient's comorbidities [3, 4].

Recommendations regarding the use of genomic profiles such as MammaPrint, Oncotype Dx, and Genomic grade index in young women are similar to the general BC population.

In view of the longer expected life time of young women, special attention must be taken into account to potential long-term toxicities of systemic treatment such as secondary cancers, cardiovascular toxicity, bone morbidity, cognitive change ("onco-brain"), and irreversible ovarian failure with consequent infertility. Young women with BC are also more likely to suffer from psychosocial distress and anxiety compared to older patients and are more likely to be concerned with maintaining high function at home and/or work, attractiveness, and sexual dysfunction [2•].

Young women must be advised to appropriate and early referrals to fertility clinics, mental health professionals, and supportive resources, and genetic testing must be an integral aspect of caring for the young patient with BC [69•].

EBC

Indications for neoadjuvant systemic therapy are the same for young as in older women. Neoadjuvant CT approach and subsequent breast conservation have no detrimental effect on survival in young BC patients [3, 4].
It is recommended to start adjuvant systemic CT within 8 weeks of completion of surgery. If both chemo- and radiotherapy are indicated in adjuvant setting, CT should be given first in young women, as in other age categories [3, 4].

(Neo)adjuvant chemotherapy

In the (neo)adjuvant setting, there is currently no evidence to recommend a specific CT regimen for young women. Therefore, regimens including anthracyclines with or without a taxane represent the preferred standard treatment option [3, 4, 15]. Based on the tolerability profile, and on the possible higher efficacy, sequential anthracycline-taxane-based regimens are the preferred combination regimens [70]. A combination of a taxane and cyclophosphamide is also an option in case of contraindications for anthracyclines (cardiac disease, previous exposure to anthracyclines, etc.). There are currently no data supporting the use of platinum in the adjuvant setting.

Young age alone should not be a surrogate factor for use of dose-dense CT approach, as it was shown in a systematic review and meta-analysis that mainly patients with hormone receptor-negative aggressive biology disease benefit from this regimen [71]. The neoadjuvant Gepartrio trial showed that age below 40 was a significant independent predictive factor for efficacy of a docetaxel, adriamycin, and cyclophosphamide (TAC)-based therapy and in the subgroup of patients with triple negative or grade 3 tumors [72]. However, TAC regimen is

associated with more grade 3/4 toxicity, mainly as febrile neutropenia and diarrhea in comparison with the dose-dense one [70].

Approximately 15 % of triple negative breast cancers (TNBCs) are BRCA-mutated [73]. Results of recent randomized phase II trials and meta-analysis suggest that TNBC patients who are BRCA carriers and/or those with a family history of breast/ovarian (BC/OC) cancer seem to benefit from neoadjuvant CT (combination/sequence) incorporating platinum salts [74•, 75, 76•]. These patients respond better compared with non-TNBC patients and achieve a significant improvement in pathologic complete response (pCR) rates when platinum salt is added to standard anthracycline- and/or taxane-based therapy. However, all these trials had small number of patients, and the true value of pCR, particularly in BRCA-mutated tumors, is still unclear. Therefore, use of platinum in the early BC setting cannot yet be considered standard of care.

An indirect endocrine effect of CT in ER-positive BC is based on the induction of ovarian function suppression (OFS). Amenorrhea is associated with improved treatment outcome, even if transient [77•]. In the IBCSG trial, 13–93 (adjuvant CT ± tamoxifen) premenopausal patients with node-positive ER-positive BC who experienced CT-induced amenorrhea (CIA) had a significantly improved outcome (hazard ratio (HR) for amenorrhea vs no amenorrhea= 0.61), whether they received tamoxifen or not.

(Neo)adjuvant endocrine therapy

Neoadjuvant ET should not be proposed to young women outside clinical trials [77•]. In the STAGE study, 95 patients treated with 2 years neoadjuvant combined therapy with goserelin plus anastrozole achieved a significantly better overall response rate (ORR) than 90 patients that were treated with goserelin and tamoxifen (70.4 vs 50.5 %; $p=0.004$) [78].

There are currently many treatment options available for adjuvant ET for young patients with HR+ve. According to the 2011 EBCTCG meta-analysis, 5 years of tamoxifen compared to no ET is associated with a reduction in BC recurrence by 39 %, which is translated into a 13 % absolute reduction in the risk of recurrence at 15 years (33 vs 46 %) [79]. The risk of BC mortality is reduced by 30 %, which is translated into a 9 % absolute reduction in BC-related death (24 vs 33 %). An important issue of adjuvant ET is the so-called carryover effect, which means the mortality reduction is significant throughout at least the first 10 years [79]. The substantial benefit was seen in both pre- and postmenopausal women with ER-positive disease regardless of age, stage, and grade of the disease.

The optimal duration of ET has not been sufficiently studied in young women. Extending tamoxifen up to 10 years should be considered in premenopausal patients that are at high risk for late relapse (such as those with high tumor burden). The results of the recently published ATLAS trial showed a significant reduction in the risk of recurrence, BC-specific mortality, and overall mortality in women with ER-positive disease continuing with tamoxifen treatment up to 10 years [80•]. At 15 years, the recurrence rate for women treated with tamoxifen for 5 years was 25.1 vs 21.4 % for women who received tamoxifen for 10 years. The rate of BC mortality for women treated for 5 years was 15 vs about 12 % for women who received tamoxifen for 10 years (an absolute gain of 2.8 %). Another "extended" tamoxifen adjuvant trial (aTTom) confirmed the ATLAS reduction in recurrence and death from BC [81]. In both

extended tamoxifen trials, ATLAS and aTTom, the relapse risk reduction was time dependent, with practically no benefit seen with longer treatment on years 5–9, followed by an abrupt significant improvement on year 10 and subsequent years [82]. This can be explained by the carryover effect of the first 5 years of tamoxifen, extended its benefit to the period of years 5 to 9.

Benefit of luteinizing-hormone releasing hormone (LHRH) agonists' use has also been shown specifically in the absence of CT. In the meta-analysis by Cuzick et al. that analyzed the role of OFS in 11,906 premenopausal women with EBC, randomized in 16 trials, there was no significant benefit for the use of LHRH agonists alone, but adding these agents to CT, to tamoxifen or both, significantly reduced recurrence by 12.7 % and death after recurrence by 15.1 % [83]. Moreover, the benefit of LHRH agonists after CT was seen in women under age 40 but not in older premenopausal patients. The SOFT trial was designed to assess the benefit of the addition of OFS to adjuvant tamoxifen in premenopausal HR+ve BC patients. The results already reported [84] show a lack of benefit with the addition of OFS to tamoxifen in the overall population. However, prespecified subgroup analysis demonstrates that in the cohort of patients at high enough risk to be treated with chemotherapy (and who remained premenopausal), the addition of OFS to tamoxifen or exemestane led to an improvement in 5-year BC-free interval of 4.5 and 7.7 %, respectively. In the cohort of women not requiring chemotherapy, no statistically significant difference in DFS at 5 years (HR=0.83, 95 % confidence interval (CI)=0.66–1.04) was seen. In an important subgroup analysis of patients younger than 35 years, the most striking advantage from the addition of OFS to endocrine therapy was seen. The rate of freedom from BC at 5 years was 67.7 % for patients in the tamoxifen alone arm, 78.9 % for those in tamoxifen plus OFS arm, and 83.4 % for those assigned to exemestane plus OFS. OS data is not mature, and longer follow-up is needed.

OFS resulted in increased adverse events—menopausal symptoms, depression, osteoporosis, and hypertension—and this must be balanced with the expected benefits and discussed with each patient.

It is still unknown what is the optimal duration of LHRH agonists, although most studies have utilized 2–3 years of LHRH agonists (monthly injection) with 5 years of tamoxifen. Estradiol levels should be monitored on a regular basis (at least every 6 months), always in the same laboratory and preferably in a central reference laboratory. In case of insufficient ovarian suppression, bilateral ovariectomy or continuation of tamoxifen alone should be considered [3].

Aromatase inhibitors (AIs) alone are contraindicated in premenopausal women because the suppression of peripheral aromatase results in reduced feedback to the hypothalamus and consequently ovarian stimulation occurs [77•]. Because of this, AIs alone should also not be used in young women who have had CIA, unless postmenopausal status is definitively proven [3]. At ASCO 2014, the combined analysis of the TEXT and SOFT trials, evaluating the role of adjuvant AIs in premenopausal BC patients, was presented. Exemestane (EXE) plus OFS significantly improved DFS, BCFI, and DRFI in comparison with tamoxifen (a 3.8 % absolute difference in DFS in favor of EXE, no difference in OS after a median follow-up of 5.7 years). Safety profile of EXE + OFS was similar to that seen with AIs in postmenopausal women after a median follow-up of 5.7 years. This combination of ET represents a new treatment option for premenopausal women with early ER-positive BC [85•], particularly for those with contraindications for tamoxifen.

Young women with contraindications for the use of tamoxifen, intolerant, or who develop symptoms/signs of hyperestrogenism induced by tamoxifen, namely ovarian cyst formation, may also be treated with a LHRH agonist alone or in combination with AI; the optimal duration of this treatment is unknown [3, 4]. In young women with BRCA-1/2 mutation or in those patients belonging to hereditary BC families, prophylactic ovariectomy may be considered when adjuvant ET is discussed [77•].

Adjuvant anti-HER-2 therapy

Young women with HER-2-positive early BC should be treated with standard 1-year adjuvant trastuzumab treatment [3, 4]. Adjuvant trastuzumab is indicated for patients with T1b tumors (more than 5 mm in maximum size) and for all patients with node-positive HER-2 positive disease irrespective of its size [15].

A subgroup analysis of the HERA trial showed that patients under the age 35 have the same benefit from 1-year trastuzumab treatment as older ones [29].

Adjuvant bisphosphonates

The meta-analysis of the three largest adjuvant bisphosphonate trials reported an apparent harm of these agents in pre- and perimenopausal women [86]. This finding had been already previously shown in the AZURE trial, in which there was a significant detrimental effect of zoledronic acid (ZA) on the rate of non-skeletal metastases in premenopausal women that was independent of ER status [87]. An older Finnish study also demonstrated similar conclusions, when oral clodronate was given in the adjuvant setting, with non-skeletal recurrences being significantly more frequent in the clodronate group vs control group, especially in ER-negative disease [88]. The only trial showing a potential benefit was the Austrian where ZA at 4 mg per 6 months effectively prevented bone loss in ER-positive premenopausal patients whose treatment regimens included LHRH agonist or those who developed complete ovarian suppression following adjuvant CT [89]. Based on all these data, bisphosphonates should not be given to young women in the adjuvant setting independently of "intrinsic subtype" of BC.

Locally advanced and inflammatory breast cancer

Inflammatory BC is slightly more common in young women, specially in women of African descent in the USA and in North African countries [3, 4]. The management of inflammatory BC in young women should be the same as in the older BC population since there are no data indicating a different biology or a different prognosis [90].

ABC

The treatment for a young individual BC patient with advanced disease must be determined by a multidisciplinary team as for the overall ABC population. Specially in the metastatic setting patient preferences should always be taken into account, as the disease is incurable. The best strategy for these patients is the inclusion into well-designed, independent, prospective randomized clinical trials. Metastatic disease should always be biopsied whenever feasible for histological confirmation and reassessment of biology [3, 4, 30, 91].

Endocrine therapy for advanced disease

Endocrine therapy is the preferred option for HR+ve, even in presence of visceral metastases, unless there is concern or proof of endocrine resistance or there is a need for rapid disease response and/or symptom control [30, 91].

In young patients with ER-positive MBC, tamoxifen in combination with OFS (a LHRH agonist or bilateral ovariectomy) is currently recommended as the standard first-line therapy [3, 4, 30, 77•, 91].

AIs in combination with OFS (a LHRH agonist/bilateral ovariectomy) can be considered in young patients after progression on tamoxifen plus OFS based on the available evidence [3, 4, 30, 91].

Based on findings of the efficacy of fulvestrant in metastatic setting for postmenopausal BC patients and its mechanism of action, this drug should also be effective in young patients. However, it has not been properly studied in premenopausal patients. Bartsch et al. demonstrated a clinical benefit rate of 58 % with fulvestrant plus goserelin in 26 patients pretreated with TAM and AIs in combination with goserelin; median TTP was 6 months and OS 32 months [92].

No specific endocrine resistance mechanisms have been identified in premenopausal ABC patients. mTOR inhibitors have not been studied in premenopausal women. However, from their mechanism of action and in cases where a OFS is given (and therefore the patient becomes postmenopausal), it is acceptable to consider this treatment option for the same indications of postmenopausal women.

Chemotherapy for advanced disease

Recommendations for CT should not differ from those for older patients with the same characteristics of the metastatic disease and its extent. Young age by itself should not be an indication to prescribe more intensive and combination CT regimens over the sequential use of monotherapy [3, 4].

Platinum agents are facing a renewed interest in TNBC and BRCA-1/2-related BC, based on preclinical and some clinical data and several studies to confirm their efficacy is underway. However, in an unselected TNBC population, there are yet no randomized data supporting platinum-based CT as the optimal regimen [93]. In BRCA, mutation carrier's recent data—TNT trial—suggests advantage of platinum-based CT over taxane in first-line metastatic setting [94]. The TNT trial is a randomized, phase 3 trial, comparing six cycles of carboplatin at the full AUC6 vs docetaxel. In the BRCA-related BC, a benefit for single agent platinum with an ORR of 68 vs 33 % ($p=0.03$) was seen.

Anti-HER-2 therapy for advanced disease

Anti-HER-2 therapy recommendations should not differ from those for older patients with HER-2-positive MBC [3, 4].

Systemic treatment of specific sites of metastases

Therapeutic recommendations should not differ from those for older women with the same biology of metastatic disease and its extent [3, 4].

In case of bone metastases in young women, a bone-modifying agent (a bisphosphonate or denosumab) should be routinely used in combination with other systemic therapy, like in older patients [3, 4, 30, 91].

Systemic treatment of locoregional relapse

It has been shown that systemic therapy (both endocrine and CT) has a beneficial effect after complete resection of a first isolated LRR [95]. The CALOR study, a randomized phase III study, evaluating the role of CT after surgery of isolated locoregional recurrence, showed a significant reduction in systemic recurrence with the use of CT in this setting (HR=0.59; p=0.046). A significant improvement in survival was seen only in ER-negative disease. Patients with a HER-2-positive LRR who have not received trastuzumab in adjuvant setting or whose primary tumor was HER-2 negative should receive trastuzumab for 1 year ("pseudo-adjuvant" therapy). These recommendations should not differ in young women from older patient population [3, 4].

New targeted treatment options—BRCA carriers

PARP inhibitors

BRCA mutation-associated BCs are characterized by deficient homologous recombination of DNA, and most of BRCA-1-associated BCs display the basal-like molecular subtype. Traditionally, BRCA-associated BCs have been treated with conventional systemic CT. With the growing understanding of the functions of BRCA-1/2 proteins in homologous DNA repair, it is recognized that BRCA-associated breast tumors may have distinct biochemical characteristics and thus could require tailored treatment strategies. These tumors were shown to be particularly sensitive to platinum compounds or inhibitors of poly(ADP-ribose) polymerase.

Over the past years, increasingly potent poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have been developed and their potential role in treatment of TN and BRCA-associated tumors evaluated.

Phase II studies evaluating single agent therapy with olaparib [96] or veliparib combined with temozolamide [97] in this patient population confirmed the activity of this class of drugs with especially impressive ORR of 41 % (11 of 27) and an additional 44 % (12/27) rate of stable disease (SD) with olaparib monotherapy. Several phase III studies in ABC and neo/adjuvant setting are recruiting patients. In the metastatic setting, the EMBRACA study is evaluating talazoparib after second line [98]. Veliparib is being studied in association with carboplatin and paclitaxel in first and second line (https://clinicaltrials.gov/ct2/show/NCT02163694?term=Breast+cancer+AND+PARP+AND+BRCA&phase=2&rank=2) and inaparib as single agent in the BRAVO study [99].

Imaging for follow-up (EBC and ABC)

General considerations

The aim of follow-up after BC treatment is to detect local recurrences or contralateral BC and to evaluate therapy-related complications [100].

In women treated for sporadic BC by BCS and adjuvant therapy, the risk of ipsi- or contralateral recurrence after 10 years is low (at about less then 5 %) [101].

For women diagnosed at the age of 40 years or less, the risk of a local recurrence at 5 years is equal to 10 %, and there is currently no evidence supporting any differences in follow-up examinations or imaging based on patient age alone [3, 4].

Because the risk of ipsi- or contralateral relapse is constant over time, at least for the first 14 years after primary treatment, routine long-term follow-up is recommended [102].

Conventional breast imaging

In terms of imaging, annual mammography followed by bilateral breast ultrasound, depending on breast density and/or presence of post-surgical and post-radiotherapy changes, represents the standard of care in patients treated for sporadic BC [3, 4].

Ultrasound could represent the first imaging modality, after clinical examination, in patients treated by mastectomy (level of evidence (LOE) 4 and 5) [3, 103].

Ultrasound of the axillary and supraclavicular region is useful in identifying nodal recurrence, both in symptomatic and asymptomatic patients.

Breast MRI

As in older patients, there is not enough evidence to support the routine use of MRI in following up young patients treated for sporadic BC.

MRI may be useful if conventional imaging results are inconclusive for the differential diagnosis between scar and recurrence, where a needle biopsy cannot be performed [3, 4]. If conventional imaging shows a high likelihood of recurrence and a needle biopsy can be performed, MRI should not be used as an alternative to needle biopsy [5].

MRI imaging should be the first choice in monitoring patients at high genetic-familial risk and previously treated BC [3, 4].

MRI has been shown to provide better monitoring of neoadjuvant CT (NAC) response than clinical breast examination (CBE) and/or conventional breast imaging. It should preferably be performed 2 weeks after the last NAC cycle and within 2 weeks before surgery.

Measurements of residual disease after NAC must be performed according to RECIST or WHO criteria. Multifocal or multicentric disease should be evaluated by summing the largest diameter of the visible tumors [5].

MRI evaluation is not recommended as routine surveillance for patients treated for BC with implant prostheses. In asymptomatic patients, dynamic contrast-enhanced MRI is recommended only in higher risk groups that would qualify for MRI screening. In symptomatic women, non-contrast and dynamic contrast-enhanced MRI is indicated when conventional imaging is negative or equivocal [5].

Imaging follow-up (other than breast) in patients treated for BC

An annual gynecological examination with cytology and an endovaginal ultrasound are recommended for all patients on tamoxifen (LOE 5). For patients on hormone therapy, regular bone density evaluation is indicated: annually for

patients on AIs and every 2 years for patients on tamoxifen (or annually for those with osteoporosis or osteopenia).

Fertility preservation plus pregnancy after BC diagnosis and treatment

Major concerns in young BC patients who plan to have children in the future are treatment-induced premature menopause and accompanying infertility [104]. Oncofertility is a new discipline born from the junction of reproductive medicine and oncology and stresses the attention that should be given to childbearing desires and preservation options for every BC patient when her therapeutic plan is designed; whenever possible, the patient should be referred to a specialized reproductive unit [105–107].

Impact of cancer treatments in gonadal function

Systemic treatments may hasten the quality deterioration oocytes naturally suffer during a woman's fertile lifespan [108].

The total effect of CT on the gonadal function depends on several factors, namely the chemotherapeutic agent, the total dose, the dose intensity, the treatment duration, the patient's age, and, of course, the woman's innate ovarian reserve (the latter two being the most important) [109]. The incidence of treatment-related premature ovarian failure rises with age, being in the range of 6–20 % in patients under 31 years, 22–61 % in patients younger than 40 years, and 61–97 % in patients older than 40 years [6].

Alkylating agents have the greatest gonadotoxic potential; anthracyclines, methotrexate, and fluorouracil seem to be in an intermediate position, and taxanes and trastuzumab have an unknown risk [110].

One important aspect to underline is that the majority of research conducted in this context has used amenorrhea as a surrogate marker of ovarian function, which is not reliable since the fertility potential declines well before the cessation of menses, and predictors such as estradiol, anti-Müllerian hormone, inhibin B, and antral follicle count by pelvic ultrasound still await validation [111, 112].

Contraception

Convenient, safe, and effective contraception should be discussed and made available to all women undergoing diagnosis, treatment, and surveillance for BC, namely the young where the fertility potential is high. Hormonal methods should be withheld, particularly in hormone-dependent tumors, but proper counseling regarding adequate methods must always be made. Women who do not consider future motherhood should consider male or female sterilization (failure rates <1 %) [113, 114]. Regarding non-hormonal methods, the copper intrauterine device—IUD—(failure rates <1 %) and condoms (failure rate between 2 and 18 %) [113, 114] are reversible and easily accessible methods. Cases of endometrial proliferation, menorrhagia, and dysmenorrhea may require use of local progestin such as the IUD Mirena® or Skyla® [115].

Fertility preservation strategies in breast cancer patients

Oocyte and embryo cryopreservation	These are considered the gold standard option in cancer patients [116]. The oocyte preservation is mainly used in patients without partners at the time of diagnosis, while the embryo cryopreservation is the standard strategy for partnered patients. Feasibility criteria (ovarian reserve, possibility to delay CT start) need to be fulfilled for the use of these techniques. Data on the pregnancy outcome through these methods is still scarce, and patients should be warned of possible inferior success rates compared to age-matched infertile couples in the non-cancer setting [117].
Cryopreservation of ovarian cortical tissue	This is a promising strategy but still experimental [116].
Ovarian suppression with LHRH agonist	Ovarian protection using GnRH agonists can be safely considered for young women with BC in terms of oncologic outcomes [104]. This treatment did not seem to negatively interact with CT; moreover, it seems to improve disease outcome in ER-positive BC. In the recent presented POEMS study, Moore et al. showed that ovarian protection using LHRH analog (either leuprorelin or goserelin) concomitantly with adjuvant CT is a treatment option for premenopausal hormone receptor-negative BC patients interested in fertility preservation [118]. On the other hand, the ZORO trial did not show a decrease of amenorrhea 5–8 months after end of CT in premenopausal women receiving (neo-)adjuvant CT with goserelin, although a non-significant tendency towards a shorter median time to restoration of menstruation in patients receiving goserelin was seen (6.25 vs 7.13 months, $p = 0.302$) [119]. In view of the conflicting results, ovarian suppression with LHRH is not considered a standard strategy for fertility preservation in ASCO or ESMO guidelines [116, 120] and more randomized data are necessary.
Adoption and third-party reproduction	Although studies have shown biological babies are preferred by cancer patients, this population often suffers from discrimination in adopting [121].

Pregnancy after breast cancer

There is no current evidence suggesting that pregnancy in BC survivors would be associated with any risk to the infant's health, neither for the occurrence of congenital abnormalities nor for potential obstetric and birth complications [122•]. Furthermore, pregnancy after successfully treated BC appears to be safe, even in women with HR+ve BC, as has been shown by Azim et al. [123, 124]. The same holds true for breastfeeding [125].

Regarding the timing of pregnancy after BC, a definite recommendation is still lacking, although some experts recommend avoiding it within 2 years after diagnosis, especially for those patients at greater early relapse risk. Guidelines state that women should wait at least 6 months after the end of CT to allow for oocyte maturation and at least 3–6 months after the end of hormonal treatment

due to the teratogenic potential of tamoxifen [122•]. A similar time period is advised for those receiving trastuzumab [126].

Sporadic cancer patients and carriers of BRCA-1 and BRCA-2 mutations

To date, there is still limited information on the pregnancy outcome of women at risk for hereditary BC and on the impact of that pregnancy on their cancer prognosis.

A large international multicentric cohort of 12,084 women with a BRCA-1 or BRCA-2 mutation identified 128 case subjects who were diagnosed with BC while pregnant or who became pregnant after a diagnosis of BC [127]; they were age-matched to 269 controls (mutation carriers with BC who did not become pregnant). The 15-year survival rate was 91.5 %, compared to a survival of 88.6 % for women who did not become pregnant (adjusted hazard ratio=0.76; 95 % CI= 0.31–1.91; p=0.56), and hence, the authors concluded that pregnancy concurrent with/after a diagnosis of BC does not appear to adversely affect survival among BRCA-1/2 mutation carriers [127]. These results were in accordance with the findings of Milne et al. that particularly studied the effect of parity in the risk of breast and ovarian cancer in BRCA 1/2 mutation carriers: as in the general population, parity appears to confer protection from BC in women with mutations in BRCA-1 and BRCA-2 [128]. Nonetheless, some authors had already pointed out that age at first birth might have an impact [129], and a recent fixed effects meta-analysis was carried out [130] that showed the only variable examined that produced a probable association was late age at first live birth; the meta-analysis showed a decrease in the risk of BC in BRCA-1 mutation carriers with women aged 30 years or older vs women younger than 30 years (effect estimates (ES)=0.65; 95 % CI=0.42 to 0.99). The same was shown for women aged 25 to 29 years vs those aged less than 25 years (ES=0.69; 95 % CI=0.48 to 0.99). Breastfeeding was also associated with reduced ovarian cancer risk in BRCA-1 mutation carriers [130].

Conclusions

Young BC patients represent a unique group of patients who face particular challenges. Early administration of optimal supportive care and psychosocial attention is indispensable for the accurate management of these patients.

Current treatment modalities for young women are based specifically on biological characteristics of an individual tumor and the stage of the disease and should not be based on age alone.

There are data supporting a differential activation of many activated signalling pathways in tumors of young BC patients, which could represent a target for future directed therapy. As we continue to develop ways to tailor an optimal adjuvant treatment, we also need to improve the ability to avoid long-term complications. Second-generation gene signature profiling may provide additional answers, regarding which patients will benefit from the extended adjuvant endocrine therapy.

Additional focus on psychosocial and fertility issues is paramount and should be a priority for ongoing research.

ABC in this group of patients should be treated according to international guidelines, and they should not be overtreated solely based on age.

Despite some advances, few data still exist regarding the management of EBC and, particularly ABC, in young patients. Therefore, randomized prospective trials designed specifically for this BC population are urgently needed.

Take-home messages

- BC in young women represents a big challenge in current oncological practice.
- Current management strategies for young patients should be based on biology and stage of the disease and not on age alone, in both adjuvant and metastatic setting.
- A deeper knowledge of this disease is being acquired, and in the near future, it is expected that a more personalized approach will be feasible.
- Special attention must be paid to specific age-related side effects of systemic therapy such as cognitive dysfunction and fertility issues and to the social impact of diagnosis and treatment (e.g., raising children, job discrimination).
- Few data exist regarding the management of EBC and specially ABC in young patients; therefore, randomized, prospective trials designed especially for this population are urgently needed.

Compliance with Ethics Guidelines

Conflict of Interest

Fatima Cardoso is a consultant to Astellas, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GSK, Merck-Sharp, Merus, Novartis, Pfizer, Roche, and Sanofi.

D Ribnikar, JM Ribeiro, D Pinto, B Sousa, AC Pinto, E Gomes, EC Moser, and MJ Cardoso declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. American Cancer Society. Breast cancer facts & figures 2011–2012. Atlanta: American Cancer Society, Inc.; 2012.
2.• Freedman RA, Partridge AH. Management of breast cancer in very young women. Breast. 2013;22 Suppl 2:S176–9.

This article highlights the importance of special considerations for young patients when deciding/selecting adjuvant treatment options.

3. Cardoso F, Loibl S, Pagani O, Graziottin 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.
4. 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.
5. 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.
6. Yamamoto S, Chishima T, Mastubara Y, Adachi S, Harada F, Toda Y, et al. Variability in measuring the ki-67 labeling index in patients with breast cancer. Clin Breast Cancer. 2015;15(1):e35–9.
7. Mann RM, Loo CE, Wobbes T, Bult P, Barentsz JO, Gilhuijs KG, et al. The impact of preoperative breast MRI

on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat. 2010;119(2):415–22.
8. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study. J Natl Cancer Inst. 2013;105(13):978–88.
9. Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kereakoglow 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.
10. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg. 2009;208(3):341–7.
11. 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.
12. Acevedo C, Amaya C, Lopez-Guerra JL. Rare breast tumors: review of the literature. Rep Pract Oncol Radiother. 2014;19(4):267–74.
13. Bayraktar S, Amendola L, Gutierrez-Barrera AM, Hashmi SS, Amos C, Gambello M, et al. Clinicopathologic characteristics of breast cancer in BRCA-carriers and non-carriers in women 35 years of age or less. Breast. 2014.
14. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997–4013.
15. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann 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.
16. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70.
17. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67.
18.• 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.

This reference explains the complexity of BC in young patients and stresses independency of this complexity among different BC intrinsic subtypes. Furthermore, it discusses the importance of well designed prospective clinical trials in this subgroup population of BC patients—targeting specific signal pathways.

19. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347(25):1999–2009.
20. 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.
21. Anders CK, Acharya CR, Hsu DS, Broadwater G, Garman K, Foekens JA, et al. Age-specific differences in oncogenic pathway deregulation seen in human breast tumors. PLoS ONE. 2008;3(1):e1373.
22. Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer. 2009;9:86.
23. Criscitiello C, Azim Jr HA, Schouten PC, Linn SC, Sotiriou C. Understanding the biology of triple-negative breast cancer. Ann Oncol. 2012;23 Suppl 6:vi13–8.
24. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Semin Oncol. 2009;36(3):237–49.
25. Bharat A, Aft RL, Gao F, Margenthaler JA. Patient and tumor characteristics associated with increased mortality in young women (< or =40 years) with breast cancer. J Surg Oncol. 2009;100(3):248–51.
26. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. J Clin Oncol. 2008;26(20):3324–30.
27. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PLoS ONE. 2009;4(11):e7695.
28. Sheridan W, Scott T, Caroline S, Yvonne Z, Vanessa B, David V, et al. Breast cancer in young women: have the prognostic implications of breast cancer subtypes changed over time? Breast Cancer Res Treat. 2014;147(3):617–29.
29. 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.
30. 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.
31. 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). Breast. 2014;23(5):489–502.
32. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with

radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32.
33. Kroman N, Holtveg H, Wohlfahrt J, Jensen MB, Mouridsen HT, Blichert-Toft M, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer. 2004;100(4):688–93.
34. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707–16.
35. Donker M, Litiere S, Werutsky G, Julien JP, Fentiman IS, Agresti R, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol. 2013;31(32):4054–9.
36. van Laar C, van der Sangen MJ, Poortmans PM, Nieuwenhuijzen GA, Roukema JA, Roumen RM, et al. Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients. Eur J Cancer. 2013;49(15):3093–101.
37. Rosenberg SM, Tamimi RM, Gelber S, Ruddy KJ, Kereakoglow S, Borges VF, et al. Body image in recently diagnosed young women with early breast cancer. Psychooncology. 2013;22(8):1849–55.
38. Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, van der Hulst-Vijgen MH, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol. 2012;23(10):2591–8.
39. de Alcantara FP, Capko D, Barry JM, Morrow M, Pusic A, Sacchini VS. Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience. Ann Surg Oncol. 2011;18(11):3117–22.
40. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer Jr CE, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960–6.
41. Adkisson CD, Vallow LA, Kowalchik K, McNeil R, Hines S, Deperi E, et al. Patient age and preoperative breast MRI in women with breast cancer: biopsy and surgical implications. Ann Surg Oncol. 2011;18(6):1678–83.
42. Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat. 2010;121(2):389–98.
43. Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144(3):443–55.
44. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, Olopade OI, et al. Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2011;127(1):287–96.
45. Heemskerk-Gerritsen B, Hooning M, van Asperen CJ, et al. Efficacy of risk-reducing mastectomy (RRM) on overall survival (OS) in BRCA1/2-associated breast cancer (BC) patients. J Clin Oncol (Meeting Abstracts). 2013;(Meeting Abstracts) 31(15 suppl):1502.
46. Lokich E, Stuckey A, Raker C, Wilbur JS, Laprise J, Gass J. Preoperative genetic testing affects surgical decision making in breast cancer patients. Gynecol Oncol. 2014;134(2):326–30.
47. 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.
48. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys. 1998;40(4):859–67.
49. Han W, Kang SY. Relationship between age at diagnosis and outcome of premenopausal breast cancer: age less than 35 years is a reasonable cut-off for defining young age-onset breast cancer. Breast Cancer Res Treat. 2010;119(1):193–200.
50. O'Rourke MT, Ellison PT. Age and prognosis in premenopausal breast cancer. Lancet. 1993;342(8862):60.
51. Ahn SH, Son BH, Kim SW, Kim SI, Jeong J, Ko SS, et al. Poor outcome of hormone receptor-positive breast cancer at very young age is due to tamoxifen resistance: nationwide survival data in Korea—a report from the Korean Breast Cancer Society. J Clin Oncol. 2007;25(17):2360–8.
52. Bollet MA, Sigal-Zafrani B, Mazeau V, Savignoni A, de la Rochefordiere A, Vincent-Salomon A, et al. Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first. Radiother Oncol. 2007;82(3):272–80.
53. Kim HJ, Han W, Yi OV, Shin HC, Ahn SK, Koh BS, et al. Young age is associated with ipsilateral breast tumor recurrence after breast conserving surgery and radiation therapy in patients with HER2-positive/ER-negative subtype. Breast Cancer Res Treat. 2011;130(2):499–505.
54. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345(19):1378–87.
55. Botteri E, Bagnardi V, Rotmensz N, Gentilini O, Disalvatore D, Bazolli B, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol. 2010;21(4):723–8.

56. Komoike Y, Akiyama F, Iino Y, Ikeda T, Akashi-Tanaka S, Ohsumi S, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: risk factors and impact on distant metastases. Cancer. 2006;106(1):35–41.
57. Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breast-conserving therapy. Breast Cancer Res Treat. 2007;101(1):51–7.
58. Albert JM, Gonzalez-Angulo AM, Guray M, Sahin A, Strom EA, Tereffe W, et al. Estrogen/progesterone receptor negativity and HER2 positivity predict locoregional recurrence in patients with T1a, bN0 breast cancer. Int J Radiat Oncol Biol Phys. 2010;77(5):1296–302.
59. Anders CK, Fan C, Parker JS, Carey LA, Blackwell KL, Klauber-DeMore N, et al. Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes? J Clin Oncol. 2011;29(1):e18–20.
60. Antonini N, Jones H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. Radiother Oncol. 2007;82(3):265–71.
61. Coulombe G, Tyldesley S, Speers C, Paltiel C, Aquino-Parsons C, Bernstein V, et al. Is mastectomy superior to breast-conserving treatment for young women? Int J Radiat Oncol Biol Phys. 2007;67(5):1282–90.
62. Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi Raad RF, Boon WL, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008;26(14):2373–8.
63. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 2010;28(10):1684–91.
64. Fowble BL, Schultz DJ, Overmoyer B, Solin LJ, Fox K, Jardines L, et al. The influence of young age on outcome in early stage breast cancer. Int J Radiat Oncol Biol Phys. 1994;30(1):23–33.
65. Jones HA, Antonini N, Hart AA, Peterse JL, Horiot JC, Collin F, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. J Clin Oncol. 2009;27(30):4939–47.
66. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol. 2001;19(6):1688–97.
67. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007;25(22):3259–65.
68. Neuschatz AC, DiPetrillo T, Safaii H, Price LL, Schmidt-Ullrich RK, Wazer DE. Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy. Cancer. 2003;97(1):30–9.
69.• [?tlb9pt]?Letourneau JM, Melisko ME, Cedars MI, Rosen MP. A changing perspective: improving access to fertility preservation. Nat Rev Clin Oncol. 2011;8(1):56–60.

An important issue about fertility in young BC patients.

70. Ribeiro J, Sousa B, Cardoso F. Optimal approach in early breast cancer: adjuvant and neoadjuvant treatment. EJC Supplements II 2013; 3–22. 2013.
71. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. J Natl Cancer Inst. 2010;102(24):1845–54.
72. Huober J, von Minckwitz G, Denkert C, Tesch H, Weiss E, Zahm DM, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat. 2010;124(1):133–40.
73. Anders CK, Zagar TM, Carey LA. The management of early-stage and metastatic triple-negative breast cancer: a review. Hematol Oncol Clin N Am. 2013;27(4):737–49. 4.
74.• Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144(2):223–32.

An important meta-analysis of the value of platinum compound in the management of triple-negative BCs.

75. 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.
76.• Paluch-Shimon S, Friedman E, Berger R, et al. Does pathologic complete response predict for outcome in BRCA mutation carriers with triple-negative breast cancer? J Clin Oncol. 2014;32:5s,(suppl; abstr 1023).

Important issue of predictive value of pCR in BRCA-positive triple-negative BC patients.

77.• Christinat A, Di Lascio S, Pagani O. Hormonal therapies in young breast cancer patients: when, what and for how long? J Thorac Dis. 2013;5 Suppl 1:S36–46.

Extensive discussion of many endocrine treatment options for young BC patients.

78. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol. 2012;13(4):345–52.

79. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, 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.

80.• 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.

An important large clinical trial evaluating the role of TAM 10 vs 5 years with special attention to benefit that was the biggest in the year 10 and beyond – carry over effect.

81. Gray RG, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol. 2013;31(suppl):abstr 5.

82. Azim HA, Saadeldeen A. Commentary on "aTTom": long-term effects of continuing adjuvant Tamoxifen to 10 years. Chin Clin Oncol. 2014;3(1):7.

83. Cuzick J, Ambroisine L, Davidson N, Jakesz R, Kaufmann M, Regan 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.

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.

85.• Olivia Pagani M, on behalf of the TEXT and SOFT Investigators and International Breast Cancer Study Group (IBCSG). Randomized comparison of adjuvant aromatase inhibitor exemestane plus ovarian function suppression vs tamoxifen plus ovarian function suppression in premenopausal women with hormone receptor positive early breast cancer: joint analysis of IBCSG TEXT and SOFT. J Clin Oncol. 2014;ASCO 2014. Abstract LBA1.

The role of AIs in premenopausal patients with early BC.

86. Vidal LBAI, Rizel S, et al. Bisphosphonates in the adjuvant setting of breast cancer therapy: effect on survival—a systematic review and meta-analysis. J Clin Oncol. 2012;30:abstr 548.

The role of bisphosphonates in adjuvant setting as »preventive« agents in EBC patients. Young (premenopausal) patients receiving bisphosphonates in adjuvant setting have higher rate of non-skeletal distant events.

87. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, et al. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med. 2011;365(15):1396–405.

88. Azim HA, Kamal NS, Malak RA. Bisphosphonates in the adjuvant treatment of young women with breast cancer: the estrogen rich is a poor candidate! J Thorac Dis. 2013;5 Suppl 1:S27–35.

89. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Long-term follow-up in ABCSG-12: significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer. Cancer Res. 2011;71:S1–2.

90. Robertson FM, Bondy M, Yang W, Yamauchi H, Wiggins S, Kamrudin S, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin. 2010;60(6):351–75.

91. 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.

92. Bartsch R, Bago-Horvath Z, Berghoff A, DeVries C, Pluschnig U, Dubsky P, et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. Eur J Cancer. 2012;48(13):1932–8.

93. Isakoff SJ. Triple-negative breast cancer: role of specific chemotherapy agents. Cancer J. 2010;16(1):53–61.

94. Tutt A, Ellis P, Kilburn L, et al. The TNT trial: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). Program and abstracts of the 2014 San Antonio Breast Cancer Symposium December 9–13, 2014; San Antonio, Texas Abstract S3-01. 2014.

95. Aebi S, Gelber S, Anderson SJ, Lang I, Robidoux A, Martin M, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol. 2014;15(2):156–63.

96. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235–44.

97. Isakoff SJ, Overmoyer B, Tung NM, Gelman RS, Giranda VL, Bernhard KM, et al. A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer. J Clin Oncol. 2010;28:15s, 2010(suppl; abstr 1019).

98. EMBRACA study. https://clinicaltrials.gov/ct2/show/NCT01945775

99. Study B. https://clinicaltrials.gov/ct2/show/NCT01905592?term=Breast+cancer+AND+PARP+AND+BRCA&phase=2&rank=3.

100. Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi7–23.

101. Gorechlad JW, McCabe EB, Higgins JH, Likosky DS, Lewis PJ, Rosenkranz KM, et al. Screening for recurrences in patients treated with breast-conserving surgery: is there a role for MRI? Ann Surg Oncol. 2008;15(6):1703–9.

102. Kontos M, Allen DS, Agbaje OF, Hamed H, Fentiman IS. Factors influencing loco-regional

relapse in older breast cancer patients treated with tumour resection and tamoxifen. Eur J Surg Oncol. 2011;37(12):1051–8.
103. Kim HJ, Kwak JY, Choi JW, Bae JH, Shin KM, Lee HJ, et al. Impact of US surveillance on detection of clinically occult locoregional recurrence after mastectomy for breast cancer. Ann Surg Oncol. 2010;17(10):2670–6.
104. Kim J, Kim M, Lee JH, Lee H, Lee SK, Bae SY, et al. Ovarian function preservation with GnRH agonist in young breast cancer patients: does it impede the effect of adjuvant chemotherapy? Breast. 2014;23(5):670–5.
105. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. N Engl J Med. 1990;322(10):659–64.
106. Cooke A, Mills TA, Lavender T. 'Informed and uninformed decision making'—women's reasoning, experiences and perceptions with regard to advanced maternal age and delayed childbearing: a meta-synthesis. Int J Nurs Stud. 2010;47(10):1317–29.
107. Lange S, Tait D, Matthews M. Oncofertility: an emerging discipline in obstetrics and gynecology. Obstet Gynecol Surv. 2013;68(8):582–93.
108. Meirow D, Dor J, Kaufman B, Shrim A, Rabinovici J, Schiff E, et al. Cortical fibrosis and blood-vessels damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. Hum Reprod. 2007;22(6):1626–33.
109. Christinat A, Pagani O. Fertility after breast cancer. Maturitas. 2012;73(3):191–6.
110. Rodriguez-Wallberg KA, Oktay K. Options on fertility preservation in female cancer patients. Cancer Treat Rev. 2012;38(5):354–61.
111. Ronn R, Holzer HE. Oncofertility in Canada: the impact of cancer on fertility. Curr Oncol. 2013;20(4):e338–44.
112. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol. 2006;24(36):5769–79.
113. Casey PM, Faubion SS, MacLaughlin KL, Long ME, Pruthi S. Caring for the breast cancer survivor's health and well-being. World J Clin Oncol. 2014;5(4):693–704.
114. Hatcher Trussel J, Nelson AL, Cates Jr W, Kowal D, Policar MS, editors. Contraceptive technology (20th revised ed.). New York: Ardent Media; 2011.
115. Dinger J, Bardenheuer K, Minh TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. Contraception. 2011;83(3):211–7.
116. 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.
117. Friedler S, Koc O, Gidoni Y, Raziel A, Ron-El R. Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis. Fertil Steril. 2012;97(1):125–33.
118. Moore H. Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). J Clin Oncol 32:5s, 2014(suppl; abstr LBA505). 2014.
119. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011;29(17):2334–41.
120. Peccatori FA, Azim HA, Azim Jr HA, Orecchia R, Hoekstra HJ, Pavlidis N, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.
121. Rosen A. Third-party reproduction and adoption in cancer patients. J Natl Cancer Inst Monogr. 2005;34:91–3.
122.• Pagani O, Azim Jr H. Pregnancy after breast cancer: myths and facts. Breast Care (Basel). 2012;7(3):210–4.
An important discussion on pregnancy after BC diagnosis and treatment.
123. 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.
124. Azim Jr HA, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011;47(1):74–83.
125. Helewa M, Levesque P, Provencher D, Lea RH, Rosolowich V, Shapiro HM. Breast cancer, pregnancy, and breastfeeding. J Obstet Gynaecol Can. 2002;24(2):164–80. quiz 81-4.
126. Azim Jr HA, Metzger-Filho O, de Azambuja E, Loibl S, Focant F, Gresko E, et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). Breast Cancer Res Treat. 2012;133(1):387–91.
127. Valentini A, Lubinski J, Byrski T, Ghadirian P, Moller P, Lynch HT, et al. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2013;142(1):177–85.
128. Milne RL, Osorio A, Ramon y Cajal T, Baiget M, Lasa A, Diaz-Rubio E, et al. Parity and the risk of breast and ovarian cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2010;119(1):221–32.
129. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, et al. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer. 2005;117(6):988–91.
130. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju091.