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General Overview and Treatment Recommendations for Young Women with Breast Cancer

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ABSTRACT

Breast cancer in young women is a complex disease to manage due to its biological heterogeneity and special issues related to toxicity of different treatment strategies. Defining a cut-off for young age has been challenging since it is not clear whether the prognostic effect of age is continuously variable or whether there are certain thresholds at which the prognosis changes (e.g. those < 50 years of age or ≤ 35 years of age). In this review article, we define young patients as those being premenopausal. In addition, we discuss the most recent data of the biological diversity of breast cancer arising in premenopausal patients and current treatment modalities in early and advanced settings. Survivorship, with special emphasis on the importance of early supportive care, is also discussed. (REV INVES CLIN. 2017;69:77-93)

Key words: Age. Biology. BRCA. Breast cancer. Menopause. Treatment. Young women.

INTRODUCTION

Breast cancer in young women is an uncommon disease. However, despite the relatively low absolute risk, it is the leading cause of death amongst women under age 45 in high-income countries, and therefore it presents a substantial public health concern[1]. In addition, it was found that breast cancer incidence and mortality for Latin American women aged < 45 years were significantly higher in comparison to those of developed countries[2].

Breast cancer in young patients represents a special entity. The main reason for this is its unique biology which, compared to older patients, is more aggressive and typically presents at a more advanced stage[3,4]. Additionally, young patients are faced with the threat of a potentially fatal illness at the peak of their professional careers and family planning years. Furthermore, the toxicity profile of the treatments they receive may be much more difficult to tolerate than in older patients, with a detrimental effect on fertility and risk of premature menopause and its associated short-term and long-term risks. For these reasons, young patients tend to be less adherent to systemic adjuvant therapies, especially to endocrine therapy (ET), which can increase the chance of recurrence[5].

In recent years there has been a significant improvement in the understanding of the biology of breast cancer in young women. The most important finding

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is that although age is a significant factor to consider, it should not be the only or the most important factor for the choice of treatment for both early and advanced disease. To avoid overtreatment of young breast cancer patients, treatment planning should be made according to the biological characteristics of the tumor, its stage, and the patient's characteristics[6,7].

A cut-off of age to define "young breast cancer patients" cannot be determined accurately since the biological, hormonal, and environmental milieu underlying tumor biology is continuously changing during a lifetime[8]. Most research refers to young patients as those being under age 35 or 40; however, it is still unclear whether young age as a prognostic factor represents a continuous variable or may be an inherent feature of wider subgroups, i.e. premenopausal (< 50 years) or very young patients (< 35 years of age)[9,10].

For this review article, we define young patients as those before menopause as we will focus on the biology and current treatment modalities in this important subgroup of breast cancer patients. Survivorship, with special emphasis on the importance of early supportive care, is also discussed.

DEFINING MENOPAUSE

The accurate identification of a woman's menopausal status is crucial for treatment planning. Aromatase inhibitors (AI) are contraindicated in pre- and perimenopausal women as they can induce ovarian hyperstimulation and cause an increase in ovarian production of estrogens, which may lead to a hypothetical increased risk of breast cancer relapse[11,12]. Additionally, there is an increased risk of unplanned pregnancy with their use.

The term "natural menopause" is defined as the permanent cessation of menstruation resulting from the loss of ovarian activity. It is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological and physiological cause[13]. Since breast cancer patients can become amenorrheic during or after adjuvant systemic chemotherapy and may receive tamoxifen as adjuvant endocrine treatment, it is inappropriate to use the definition for menopause described above. Additionally, the National Comprehensive Cancer Network's definition of menopause specifically notes that it is not possible to identify the menopausal status of women receiving luteinizing hormone-releasing hormone (LHRH) analogues, and that amenorrhea after chemotherapy is not a reliable indicator of menopausal status[14]. Furthermore, the criteria for identifying patients as postmenopausal vary between trials and research groups[15-17]. It is important to highlight also that levels of sex hormones "in the postmenopausal range" can occur during the perimenopausal stage and additional factors such as body mass index, lifestyle, and menstrual irregularity may also lead to a misdiagnosis of menopause when based on amenorrhea alone[18]. Confirmatory biochemical tests can also be uninformative in patients being treated with tamoxifen since the latter is associated with a marked fall in follicle-stimulating hormone levels[19]. In addition, estradiol levels can be elevated by tamoxifen due to cross-reactivity of tamoxifen and its metabolites and the estradiol assay[20]. In summary, the clinical significance of amenorrhea and determination of follicle-stimulating hormone levels and estradiol levels as surrogates for menopause are not clear in this patient population[21].

Defining menopause in amenorrheic breast cancer patients after chemotherapy (CT) is also challenging. It is not adequate to use cessation of menstruation as the only surrogate marker of menopause after chemotherapy as there have been case reports of spontaneous conception in women with amenorrhea after chemotherapy[22].

Additionally, there are data suggesting that 27% of patients achieving chemotherapy induced amenorrhea regained ovarian function after starting AI treatment at a median time of 12 months (range 4-59)[12]. These data suggest that an arbitrary cutoff of 12 months period of amenorrhea is not suitable for menopause determination and in such patients, AIs should not be used in the absence of concurrent ovarian function suppression (OFS). Consequently, we urge extreme caution in the use of AIs without ovarian function suppression in women < 50 years old with amenorrhea after chemotherapy or tamoxifen use. Table 1 represents sources of estrogen in pre- and postmenopausal women.

BIOLOGY

Clinicopathological characteristics of breast cancer in young women

Two large analyses were performed to evaluate whether differences exist within the premenopausal breast cancer

Table 1. Sources of estrogen in premenopausal and postmenopausal women.

Sources of estrogen	Premenopausal women	Postmenopausal women
Major	Ovaries	-
Minor	Extragonadal sites: – Mesenchymal cells of adipose tissue – Osteoblasts and chondrocytes of bone – Skin fibroblasts – Numerous sites in the brain – Vascular endothelium and aortic smooth muscle cells – Placental syncytiotrophoblast (in pregnant women)	Extragonadal sites: – Mesenchymal cells of adipose tissue – Osteoblasts and chondrocytes of bone – Skin fibroblasts – Multiple sites in the brain – Vascular endothelium and aortic smooth muscle cells

population according to actual age. The first one, which included 1,427 premenopausal patients aged ≤ 50 years at the time of primary diagnosis, demonstrated significant age-related differences in aggressive features: estrogen receptor (ER) and/or progesterone receptor (PR) negativity, human epidermal growth factor receptor 2 (HER2) positivity, presence of lymphovascular invasion, grade 3, Ki67 ≥ 20%[23]. These pathological features were observed more frequently in cancers arising in younger patients. Similar results were reported by the study of Han, et al., which included 9,885 premenopausal patients aged ≤ 50 years at the time of primary breast cancer diagnosis[24]. Survival outcomes of patients aged 35-39 years were not different from those of patients aged 40-50 after adjustment for important prognostic factors. However, in patients aged < 35 years, the risk of death rose by 5% for every year of decrease in age.

More recently, published data of the POSH study, the largest prospective observational study evaluating pathological characteristics of breast cancer patients under age 40, have shown that the majority of these patients had high-grade tumors (59%) of ductal histology (87%)[25]. Half of the patients had node-positive disease and multifocality was observed in 27% of patients. One third of tumors were ER-negative and one-quarter HER2-positive.

The advent of genomic signatures has allowed a better understanding of the biological heterogeneity of breast cancer. Four main intrinsic subtypes of breast cancer are recognized: luminal A, luminal B, HER2-enriched, and basal-like[26-28]. Azim, et al. published the results of the largest study including 3,522 patients, evaluating the pattern of breast cancer molecular subtypes according to age using gene-expression profiling[29]. Out of 3,522 patients, 1,611 were aged ≤ 52 years at diagnosis. There were a significantly higher proportion of basal-like cancers (31%) in this cohort compared to older women (21%). Another recently reported study has found significant differences in the distribution of molecular subtypes when comparing the different groups according to age[30]. The proportion of luminal B-like cancers was ~ 14% in patients ≤ 35 years of age[31]. This high proportion is consistent with the greater percentage of high-grade cancers and the more frequent presence of HER2-positive cancer in young women with hormone receptor-positive disease. Conversely, young patients were less likely to present with luminal A cancers, but the difference was significant only when comparing those aged ≤ 40 years to those > 40 years.

Studies found that younger patients are more likely to be diagnosed with stage IV disease at first presentation with breast cancer[32-35]. A study of the incidence and survival rates of women with breast cancer from the SEER database found a small but statistically significant increase (~ 2% per year) in the incidence of *de novo* metastatic breast cancer in patients aged < 40 years[35]. The same study showed a higher incidence of *de novo* metastatic disease for women with ER-positive subtypes compared to women with ER-negative subtypes[35].

Young age itself, basal-like, and HER2-enriched tumors are associated with a higher risk of brain metastasis in most reported studies[36,37]. A population-based study reported that younger patients (< 50 years) were more likely to have liver metastases (31 vs. 20%; p < 0.001) than older patients, while frequency of bone, lung/pleural, and skin metastasis did not vary significantly[38].

Prognostic genomic signatures in young women with breast cancer

Currently there are several gene-expression profiles available in routine clinical practice to improve prognostication and aid decision-making in the adjuvant setting[26]. They are not used as the only parameter for decision-making about adjuvant chemotherapy, but can be integrated with classical clinicopathological features. However, there have been some concerns about whether they offer the same prognostic value in young patients as they were developed mainly in populations of postmenopausal women.

Two first-generation gene signatures, MammaPrint® and Oncotype DX®, were evaluated in young breast cancer patients in a Dutch study. Data revealed that 82% (52/63) of young patients were classified as high-risk on MammaPrint®[39]. Similar data were observed for Oncotype DX®, where the majority of patients ≤ 40 years of age had a high-risk score (RS: >30; 56%). The proportion of patients aged 40-50 being classified as high risk was only 29%[40].

In an analysis of 755 patients with ER-positive disease, of whom 87 were aged ≤ 40 years, each of the three genomic profiles including MammaPrint®, Genomic grade index, and GENE 76 were significantly associated with disease-free survival and added significant prognostic information to the clinical risk classifier, Adjuvant! Online[29].

Additionally, young patients with luminal types of breast cancer have a high risk for late distant relapse, since 40-50% of recurrences occur beyond the initial five years[25]. Therefore, second-generation gene expression profiles (PAM50, EndoPredict® and BC Index) might serve as tools to predict the residual risk of distant relapse and to identify those young patients that would benefit from extended endocrine treatment. However, the late recurrence genomic signatures developed so far have not yet been validated in young patients.

Gene expression and genomic aberrations in young women with breast cancer

One of the first analyses of the biology of breast cancer in young women using gene-expression profiling showed a higher proportion of phosphatidylinositide 3-kinase (PI3K) and Myc pathway dysregulation, but the analysis was not adjusted for known prognostic factors and potential differences in molecular subtypes[41].

More recently, a large gene-expression analysis has been performed to evaluate the association between patients' age and nearly 50 genes that were thought to be related to early onset breast cancer. Importantly, the analysis was adjusted for differences in molecular subtype, histological grade, tumor size, and nodal status. It was found that younger patients have higher expression of RANK-ligand, c-kit, mammary stem cell, luminal progenitors, and BRCA1 mutation signatures than older patients[29]. In addition, there were more aberrant MAPK-PI3K pathways and lower expression of many apoptosis-related genes, particularly FAS. Furthermore, the high frequency of BRCA1 mutation signature is consistent with the already known relatively high prevalence of BRCA1 mutations in younger women[42]. The latter are more commonly diagnosed with basal-like tumors[43].

More recent work has explored the prevalence of somatic mutations and chromosomal copy number variations according to age[44]. Data showed that GATA3 mutations were the main somatic event that characterized tumors arising in young women. Some preclinical data suggest that mutations in GATA3 affect ER binding to DNA, promote tumor growth, and may be associated with endocrine resistance[45-47]. These findings are extremely important since the worst prognosis in young breast cancer patients has been observed mainly in ER-positive disease, especially luminal B-like tumors[31]. Moreover, these data clearly indicate that breast cancer in young women is a disease associated with unique molecular features that are independent of tumor stage, histology, and molecular subtyping.

Young age as prognostic and predictive biomarker

Young age at diagnosis of breast cancer has long been considered as a poor prognostic factor because young patients, on average, have increased risk of disease relapse and decreased survival as well as fewer competing risks[48]. In recent years, however, with the advent of genomic signatures that have helped us to better understand the biological heterogeneity of breast cancer, there have been some concerns and questions whether age alone remains solely prognostic when adjusted to molecular subtyping and classical clinicopathological characteristics. Breast

cancer-specific survival varies by tumor subtype. Young age alone does not seem to be an independent predictor of poor outcome in triple-negative and HER2-positive disease[49]. However, in patients with luminal tumors, younger age has an important prognostic role.

There are controversial data regarding age as a determinant of benefit for adjuvant chemotherapy. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, the mean annual risk reduction of relapse attributable to chemotherapy (mainly CMF and anthracyclines) was 40% in patients under age 40, 36% in those aged 40-49, and 23% in patients aged 50-59[50]. However, when ER status is taken into account, age loses its independent predictive utility for chemotherapy. All ER-negative patients benefit from chemotherapy to the same relative extent[50]. More recent data with regimens including taxanes in the adjuvant setting have been even more controversial.

The results from the GeparTrio trial showed that patients < 40 years of age with triple-negative disease had much higher pathologic complete response rates after neoadjuvant chemotherapy with anthracyclines and taxanes than those aged > 40 (57 vs. 34%)[51]. Age was the only independent predictor for chemotherapy response in the triple-negative group of patients. Conversely, the benefit of adjuvant trastuzumab appears independent of age in studies published so far[52].

TREATMENT

General considerations

Young women with breast cancer need, on average, more treatment modalities than their older counterparts and have unique needs including fertility preservation, genetic counseling, and sexual health and psychosocial considerations. Therefore, they should be referred to specialized breast clinics and discussed within a multidisciplinary tumor board in order to avoid any gaps in management[53].

Surgical treatment

Younger age has consistently been associated with high mastectomy rates. Proponents of mastectomy argue that it offers better locoregional control and that this might translate in improved survival. However, a recent meta-analysis did not show any survival advantage amongst young breast cancer patients who underwent mastectomy compared to breast-conserving surgery (BCS), which is consistent with the results of individual randomized trials[54-56].

Long-term results of EORTC studies, however, showed that younger age and breast conservation were independent risk factors for isolated locoregional recurrence[57]. Other series also confirmed that young age is associated with increased risk for local recurrence after BCS[58-60]. Nevertheless, a recent population-based study from The Netherlands showed that five-year rates of developing local or regional recurrence in women < 35 years of age were only 3.5 and 3.7%, respectively[61]. These were not influenced by surgery type (BCS vs. mastectomy) and were substantially lower than reported in the past[60,62]. A trend for decreasing risk of locoregional breast cancer recurrence has been observed among all breast cancer patients and likely represents screening-associated stage migration, with an increasing proportion of patients diagnosed with smaller tumors as well as improvements in adjuvant therapies[61].

Given the similar overall survival, the low risk of locoregional recurrence in contemporary studies, and improved cosmetic results, BCS with or without oncoplastic repair is the surgical treatment of choice whenever technically feasible, even in young breast cancer patients[53,61,63].

Although BCS is the preferred option, some young breast cancer patients still need mastectomy because of multicentricity or large tumors. When mastectomy is indicated, immediate breast reconstruction should be discussed with all patients except those with inflammatory breast cancer[53]. The decision regarding the type of reconstruction is influenced by patient characteristics such as body habitus and comorbidities, the expertise of the reconstructive surgeon, patient preferences, and indications for post-mastectomy irradiation. The latter is not a contraindication for immediate reconstruction, but expander placement followed by implant placement or autologous tissue transplantation after the completion of irradiation is the preferred option for such patients[64].

Based on current evidence, nipple-sparing mastectomy has favorable oncologic outcomes with superior cosmetic results in carefully selected patients[65].

Figure 1. Forest plots for the benefit of radiation therapy after breast conserving surgery (BCS) (node negative disease; **A:** Disease-free survival, **B:** Overall survival)

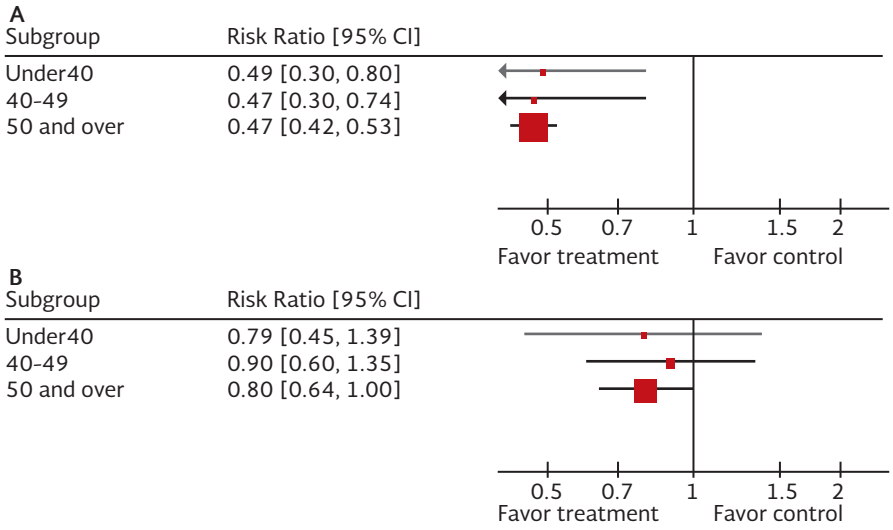
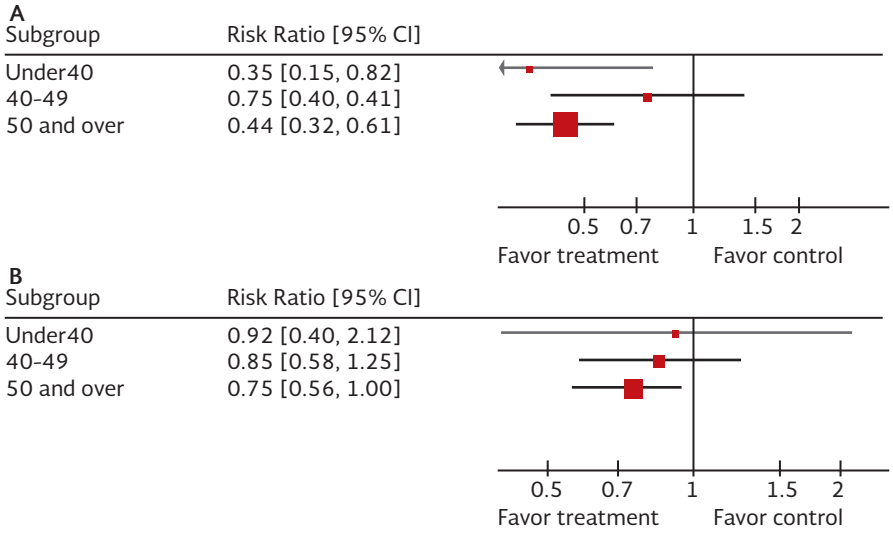


Figure 2. Forest plots for the benefit of radiation therapy after breast conserving surgery (BCS) (node positive disease; **A:** Disease-free survival, **B:** Overall survival)



Moreover, robotic techniques are evolving in breast surgery, further improving cosmetic issues[66].

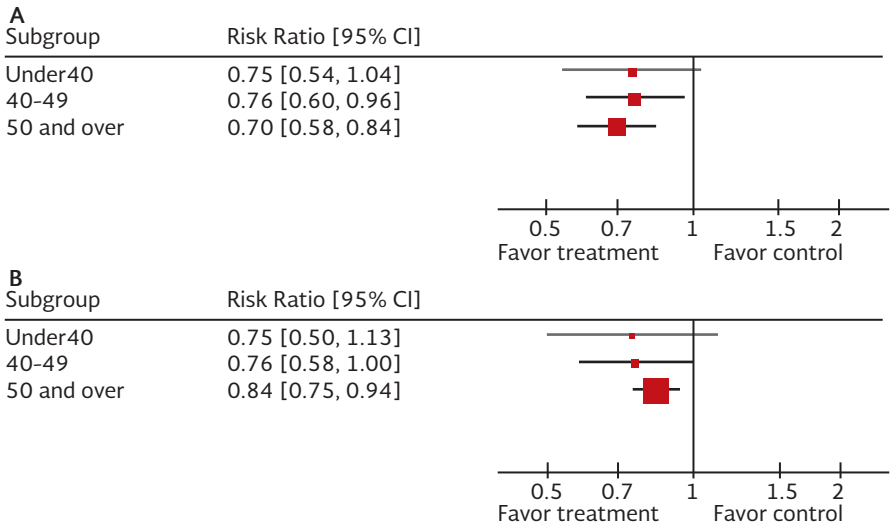
The management of the axilla is similar in young women and those that are older[53].

Radiotherapy

Adjuvant radiotherapy after BCS in women with pathologically node-negative disease (pN0) roughly halved the risk of first recurrence at nine years from 11.5 to 5.9% (RR: 0.52; 95% CI: 0.38-0.72) in women aged < 40 and from 6.1 to 2.7% (RR: 0.48; 95% CI: 0.39-0.59) in women aged 40-49 years, as demonstrated in the EBCTCG meta-analysis[67]. The risk of death was also modestly reduced (see Figs. 1 and 2; which are based on data reported by EBCTCG)[67]. Compared to older studies included in the EBCTCG meta-analyses, more contemporary data show lower five- and 10-year locoregional recurrence rates after BCS and radiotherapy in all patients with early breast cancer, including patients aged 40 or younger[67-72].

In node-positive disease (pN+), increasing evidence suggests that regional lymph node radiotherapy in addition to whole breast/chest wall radiotherapy improves outcomes, not only in locally advanced breast cancers, but also in those with lower volume nodal

Figure 3. Forest plots for the benefit of postmastectomy radiation therapy (**A:** Disease-free survival, **B:** Overall survival)



disease (one to three lymph nodes involved) (Fig. 3; forest plot for the benefit of radiation therapy after mastectomy)[68,73-76]. Locoregional radiotherapy is internationally accepted as a recommended adjuvant treatment in locally advanced breast cancer (T3-4 and N2-3 tumors), while adjuvant radiotherapy of N1 disease is a subject of ongoing discussion and research[64,71,77-82]. Recent postmastectomy radiotherapy guidelines focusing on T1-2 and N1 tumors could not agree on specific patient subgroups in whom radiotherapy could be safely omitted, but recommended younger age (< 45 years) as a potential factor for clinical decision-making in favor of radiation[71,83,84]. The absolute benefit of regional nodal radiotherapy in individual patients with 1-3 positive lymph nodes is not known accurately, and the estimation of relative risk reduction with radiotherapy is extrapolated from results of reported randomized trials in unselected patients. The interaction between systemic therapy and locoregional radiation treatment is not fully understood and it is proposed that the two treatments may complement each other[71,79]. The balance between potential benefits of regional nodal irradiation and toxicity should be discussed with the patient[71,78].

Moderately hypofractionated radiotherapy schedules of breast/chest wall and/or lymph node areas with higher dose per fraction (> 2 Gy) and shortened overall treatment time are increasingly gaining popularity around the globe including in patients younger than 50 years[85-88]. Shortened treatment schedules demonstrated equivalent local control and similar or lower toxicity rates, regardless of the patient's age[87,89]. Up to one third of included patients in randomized trials of hypofractionated radiotherapy were aged < 50 years[87,89,90]. Moderately hypofractionated radiation schedules in locoregional radiotherapy or in patients with reconstructed breast are still not used routinely because of normal tissue toxicity concerns as those patients were underrepresented in randomized controlled trials and toxicities were not separately reported[87,89]. It is not expected that a higher dose per fraction with a lower total prescribed dose and similar biologically effective dose would produce more detrimental normal tissue side effects than conventional fractionation (e.g. radiation-induced brachial plexopathy or lymphedema), but long-term results from clinical trials are still pending[87,91-93]. Some authors suggest that patients with postoperative complications, such as those with large breasts for whom a maximum dose of < 107% is not achievable, or patients with breast implants who have an increased risk for late fibrosis or cosmetic deterioration following radiotherapy, should receive a biologically less-intense dose[94]. Adjuvant radiotherapy after breast reconstruction (especially implant-based) is a risk factor for higher tissue toxicity[95].

A schedule of 3-4 weeks seems to be more convenient than the standard five or six as fewer daily treatments mean less time and costs spent travelling and less time away from family and work[85]. Shorter courses of breast radiation therapy allow more women access to life-saving treatments, especially in countries where there are limited radiotherapy facilities[96].

Additional dose to tumor bed for patients treated with BCS further improves local control in all age groups and all tumor types, with the largest absolute benefit in young patients, although it increases the risk of worse cosmetic results and fibrosis[62,97]. Guidelines on margin status after BCS suggest that, similarly to older patients, larger margin widths than no ink on tumor after BCS are not needed in younger patients[98]. It is important to note that positive margins are associated with an elevated risk of breast cancer recurrence regardless of a higher radiation boost-dose delivery, systemic treatments, or favorable tumor biology[98,99].

In a recently published randomized trial evaluating radiation boost after whole-breast irradiation, the absolute risk reduction in local recurrence was greatest in the youngest patient group: the addition of a radiation boost resulted in an absolute risk reduction at 20-years of 11.6% in women < 40 and of 5.9% in those aged 41-50 years[97]. The final results of a radiation dose-intensity study in young women (Young boost trial, ClinicalTrials.gov identifier: NCT00212121) will provide us more data on the local recurrence risks and cosmetic outcome[100]. In the future, the decision of adjuvant radiation treatment could be supported by individual tumor prognostic and predictive factors based on gene-expression profiles as some reports suggest[72,101-103].

In selected patients, accelerated partial breast irradiation (APBI) is an alternative to whole breast irradiation, but patients < 50 years old are underrepresented (up to 23%) in key published APBI trials, and off-protocol use of APBI in younger patients is not recommended[104]. Results of the phase III clinical trial NSABP B-39/RTOG 0413 are awaited and should provide greater clarity regarding this treatment in younger women (ClinicalTrials.gov identifier: NCT0010318)[105].

Modern radiation techniques are continuously improving and are based on CT delineation of target volume and adjacent organs at risk[106,107]. Tangential three-dimensional conformal or intensity modulated radiotherapy planning approaches allow for more homogenous target coverage, and at the same time, dose-volume estimations of delivered dose to organs at risk. Different strategies to reduce the dose to thoracic organs are being researched[108-110]. Image-guided deep inspiratory breath hold is a reproducible and stable radiotherapy technique, which can be implemented as a voluntary, non-computer-controlled technique in breast/chest wall and/or locoregional radiotherapy, including its use in low-resource settings[111]. Deep inspiratory breath hold has been shown to significantly reduce dose to heart, left anterior descending coronary artery, and lung[108,112].

Contralateral breast cancers and secondary tumors after adjuvant radiotherapy

Adjuvant breast cancer radiotherapy is one of the factors that contribute to the risk of contralateral breast cancer and secondary tumors. Younger age (< 40-45), dose of radiation, and volume of normal tissue in the radiation field all increase the risk for secondary primary cancers after breast radiotherapy[113,114].

Women < 40 years of age who received an absorbed radiation dose > 1.0 Gy to the part of contralateral breast had a 2.5-fold greater long-term risk of developing a second primary contralateral breast cancer compared to unexposed women. Interestingly, no excess risk was observed in women > 40 years of age[113].

Radiotherapy was significantly associated with an increased risk of second lung and esophagus cancer or second sarcomas (RR: 1.12; 95% CI: 1.06-1.19) in a recent large meta-analysis of 762,468 patients[114]. The risk increased over time, and was highest 15 or more years after breast cancer diagnosis, especially for second lung and second esophageal cancer[114]. The absolute risk was relatively small, but special attention should be paid to minimizing radiation exposure to organs at risk as the number of long-term survivors after breast cancer radiotherapy is growing.

In a systematic review of small and retrospective studies, comparing BCS with radiotherapy versus unilateral mastectomy, in carriers of BRCA1/BRCA2 mutations, authors found similar risks of ipsilateral breast tumor recurrence and survival rates in both groups[115]. Evidence further suggests that treatment with ionizing radiation after BCS or mastectomy in BRCA1/BRCA2 carriers does not affect the rates of contralateral breast cancers or rates of acute/late radiation toxicities[115,116]. Large randomized trials are required to determine the most effective and least toxic treatment in this special population of patients. Radiation therapy is usually avoided in breast cancer patients with germline p53 mutations (Li-Fraumeni syndrome) as they are at a high risk of developing radiation-induced secondary cancers[117].

Figure 4. Forest plots for the benefit of chemotherapy (CT) (**A:** Disease-free survival, **B:** Overall survival)

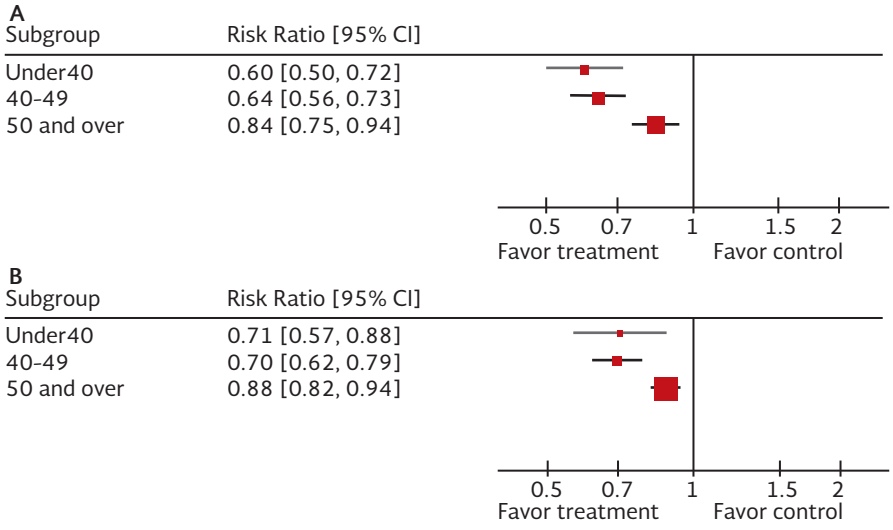
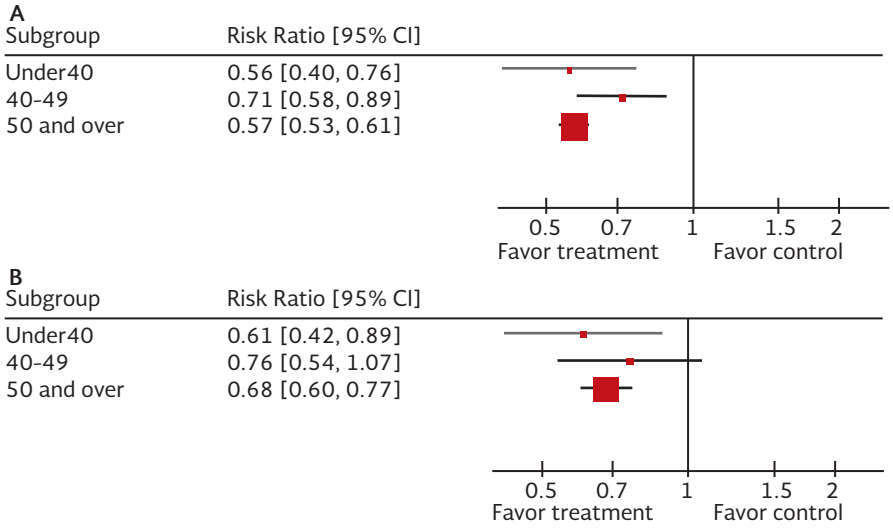


Figure 5. Forest plots for the benefit of endocrine therapy (ET) (**A:** Disease-free survival, **B:** Overall survival)



Systemic treatment

General recommendations

Decisions about adjuvant systemic treatment for invasive breast cancer (in both early and metastatic settings) should be made according to the anatomical extent of the disease, biological features of the tumor, and characteristics (comorbidities and preferences) of each individual patient and not based on age alone[53]. Figures 4 and 5 represent forest plots of the benefit of different systemic treatments (CT and ET).

In view of the longer life expectancy of young women, not only efficacy but particularly also long-term toxicities of systemic therapy should be taken into account. These include cardiovascular disease, bone loss, cognitive impairment, sexual dysfunction, secondary cancers, and infertility. Young patients with breast cancer are more likely to have concerns about maintaining high function at home and work and are more likely to suffer from depression compared to older patients[118].

All young breast cancer patients should be counseled about the risks, associated symptoms, and outcomes of treatment-related amenorrhea and premature

menopause before starting with systemic therapy (either CT or ET) and those aged < 45 should be referred to fertility clinics[53].

Systemic chemotherapy in early stage disease

There is no evidence to recommend a specific chemotherapy regimen for young women requiring neo/adjuvant chemotherapy. In the EBCTCG meta-analysis involving anthracycline- or taxane-based regimens, relative risk reductions were not influenced by age[119]. The landmark NSABP-B18 trial not only moved neoadjuvant chemotherapy to the setting of operable disease, but also demonstrated a non-significant trend for younger women benefiting from neoadjuvant rather than adjuvant CT[120].

In a recent pooled analysis, including premenopausal patients enrolled in two phase III adjuvant trials, investigators reported that dose-dense scheduling of chemotherapy was associated with a significant improvement in overall survival as compared to standard-interval treatment hazard ratio [HR]: 0.71; p = 0.021)[121]. This may be confounded by higher proportions of triple-negative breast cancer (TNBC) in younger patients. ER-negative breast cancer has been shown to benefit from dose-dense scheduling, unlike ER-positive disease[122]. Additionally, there was no increased risk of chemotherapy induced amenorrhea, suggesting the greater efficacy of dose-dense treatment does not seem to be related to a greater activity in suppressing ovarian function. This needs to be further explored in prospective randomized trials.

Around 15% of unselected triple-negative breast cancers occur in BRCA1/2 mutants[123]. The benefit of addition of platinum compound has been observed in some randomized phase II trials and a meta-analysis in triple-negative breast cancer patients with BRCA-mutations and/or positive family history of breast or ovarian cancer[124,125]. The latter tend to respond better compared with non-TNBC patients and achieve higher rates of pathologic complete response when platinum agent is added to standard anthracycline- and taxane-based therapy. However, there are limited data supporting platinum therapy in BRCA2 carriers with ER-positive disease. As the true value of pathologic complete response, especially in BRCA-associated patients, is unclear and no long-term survival data are available, the use of platinum agents is currently not recommended as a standard of care in the neo/adjuvant setting.

Endocrine therapy in early stage disease

Neoadjuvant endocrine therapy (ET) should not be routinely prescribed to any young patient with breast cancer outside of clinical trials since there are insufficient data regarding its efficacy in this breast cancer population[126]. The STAGE study, evaluating neoadjuvant ET in premenopausal breast cancer patients, was underpowered to assess long-term outcome[127].

All young women with invasive hormone receptor positive breast cancer should be offered adjuvant ET. In the EBCTCG meta-analysis, five years of tamoxifen (TAM) compared to no ET was associated with a relative reduction in breast cancer recurrence of 39%, which translates into a 13% absolute reduction in the risk of recurrence at 15 years (33 vs. 46%). The relative risk of breast cancer mortality was reduced by 30%, which translated into a 9% absolute reduction in breast cancer-related death (24 vs. 33%)[128]. Tamoxifen has a carryover effect, meaning its efficacy after five years of treatment persists even after its discontinuation, and the mortality reduction remains significant throughout at least the first 10 years of survival[128]. A significant benefit was seen in both pre- and postmenopausal women with hormone receptor positive disease, regardless of age, stage, and grade of the disease.

A very important issue that unfortunately has not been studied sufficiently in young patients is the optimal duration of ET. Lower-risk patients (older premenopausal patients with small, node-negative and low-grade disease) who do not receive adjuvant CT have excellent outcomes with TAM given for five years[129]. Extending TAM up to 10 years should be considered in premenopausal patients that are at high risk for late relapse (high tumor burden such as large tumor size or nodal involvement). In the ATLAS trial, the recurrence rate for women treated with TAM for five years was 25.1 vs. 21.4% for those who received TAM for 10 years. An absolute gain of 2.8% in the rate of breast cancer mortality was demonstrated with extended TAM[130]. Similar findings were seen in the yet to be published aTTom trial and an important message is that the benefit of extended TAM treatment was seen only from year 10 onwards, which could be explained by the carryover effect of the first five years of TAM[131]. For older premenopausal patients who have received 4.5-6.0 years of TAM and become definitely postmenopausal, switching to an AI may be preferable,

especially for those with high-risk tumor characteristics, as the reduction in risk of recurrence is observed even within the initial 2-3 years of AI therapy[132].

Aromatase inhibitors alone are contraindicated in premenopausal breast cancer patients and should not be used in those patients who develop chemotherapy induced amenorrhea. Two large phase III trials, TEXT and SOFT, evaluated the role of AIs and ovarian function suppression (OFS) in premenopausal patients. Patients with higher risk of relapse (those with large tumors, node-positive and high-grade disease) requiring adjuvant CT and remaining premenopausal after CT now may benefit from OFS in combination with either TAM or exemestane. The absolute improvement in the five-year breast cancer-free survival rate with exemestane and OFS (as compared with tamoxifen) OFS was 5.5% in TEXT and 3.9% in SOFT in patients who received CT. The impact of adding OFS to either TAM or exemestane was particularly striking in patients aged < 35; the five-year breast cancer-free rate was 67.7% for patients receiving TAM alone, 78.9% for those assigned TAM/OFS, and 83.4% for those treated with exemestane-OFS[129]. The ABCSG-12 trial also explored the value of addition of OFS to an AI anastrozole (ANA) in premenopausal breast cancer patients, where the majority of patients did not receive CT[133]. There was no difference in disease-free survival after treatment with three years of goserelin plus either TAM or ANA after 94.4 months of median follow-up. However, there was an apparent inferior overall survival in the AI arm (HR: 1.63; p = 0.030). These discordant results between the TEXT/SOFT and ABCSG/12 trials may be due to different patient characteristics and different treatment durations. In addition, only 18% of women in the ABCSG/12 trial were aged < 40 in comparison with 30% in the SOFT/TEXT trials.

While AIs in young women require concurrent LHRH analogue, the optimal duration of the latter in combination with TAM remains unknown; most old generation studies utilized 2-3 years of LHRH agonist with five years of TAM, while in the SOFT and TEXT trials, five years of treatment was used[129,134]. In a meta-analysis that analyzed the role of OFS in 11,906 premenopausal patients with early breast cancer, there was no significant benefit for the use of LHRH agonists alone, but the addition of these agents to CT, TAM, or both significantly reduced recurrence by 12.7% and death after recurrence by 15.1%[135]. Patients that derived the most benefit from LHRH agonists after CT were those aged < 40 and not older premenopausal women.

Comprehensive OFS is not always successfully achieved with LHRH analogues; suboptimal estrogen suppression has been reported in up to one third of patients[136]. Despite the fact that estradiol assays are not standardized and their accuracy and interpretation can be problematic in the presence of very low levels of estradiol, it is recommended to check hormone levels if there are concerns about suboptimal ovarian function suppression (such as in response to breakthrough vaginal bleeding in patients receiving an AI)[137]. In situations of doubt, OFS with TAM may be preferable to OFS and AI.

Unfortunately, we do not have any data about extended ET after five years of combined OFS and either AI or TAM. Worrisome is the fact that there are no ongoing or planned trials that might give us an answer to this very important question in the near future. Figure 6 represents a suggested algorithm for adjuvant ET in premenopausal women with breast cancer.

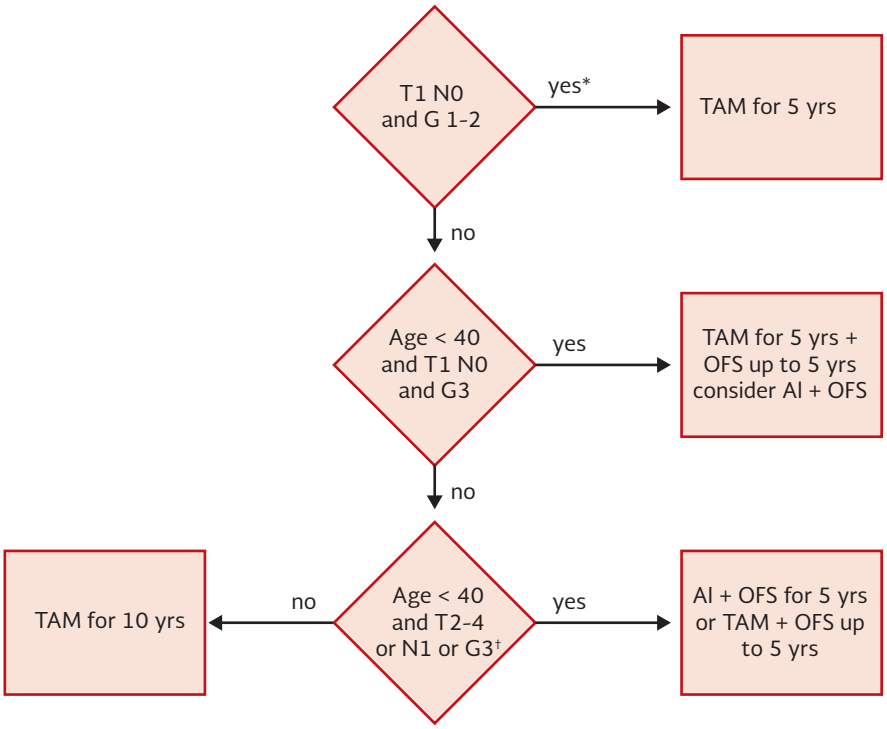
Adjuvant anti-HER2 therapy

The benefit of adjuvant trastuzumab appears independent of age in all published studies[52]. As such, treatment of HER2-positive early breast cancer should mirror that of older patients with the same disease. All young women with HER2-positive early breast cancer should be treated with standard one-year adjuvant trastuzumab unless contraindicated[6]. Adjuvant trastuzumab with chemotherapy is indicated for patients with tumors measuring more than 1 cm and for all patients with node-positive HER2-positive disease regardless of tumor size[27]. Consideration of adjuvant chemotherapy and trastuzumab in women with smaller (< 1 cm) node-negative tumors is appropriate. However, patients should be counseled about the uncertainty regarding available data in these tumor types.

Adjuvant bisphosphonates

No benefit from adjuvant bisphosphonates in pre- and perimenopausal patients was reported in the meta-analysis of adjuvant bisphosphonate trials[138]. Figure 7 represents a forest plot for the benefit of adjuvant bisphosphonates on bone recurrence. The only trial

Figure 6. Suggested algorithm for adjuvant endocrine treatment of premenopausal breast cancer patients.
*May confirm low-risk disease with molecular tests, e.g. Oncotype DX®/MammaPrint®;
†Factors demanding CT.
AI: aromatase inhibitor; CT: chemotherapy; G: grade of malignancy; N: nodal status; OFS: ovarian function suppression; T: tumor; TAM: tamoxifen.

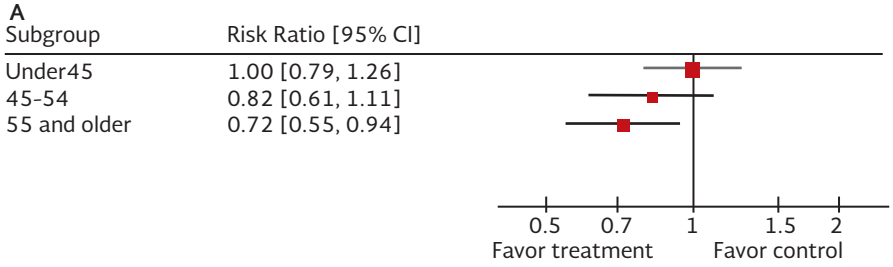


showing a potential benefit was the ABCSG-12 trial, where zoledronic acid once every six months effectively prevented bone loss in hormone receptor positive premenopausal patients whose endocrine treatment included LHRH analogues, or those who developed complete ovarian suppression following adjuvant CT[133]. Interestingly, in this trial, patients aged > 40 years had significantly improved disease-free survival in comparison to those ≤ 40 years of age. This may relate to those patients aged < 40 not achieving comprehensive OFS and therefore not being "postmenopausal" (the group of patients thought to benefit from adjuvant bisphosphonates). The characteristics of patients benefiting from zoledronic acid in the ABCSG-12 study is at odds with the characteristics of those benefiting from OFS in the SOFT and TEXT trials. Therefore, the benefit of adjuvant bisphosphonates in women receiving OFS remains uncertain.

Systemic therapy for metastatic disease

In the metastatic setting, patients' preferences should always be taken into account as the disease is incurable. Metastatic disease should be biopsied, whenever

Figure 7. Forest plot for the benefit of adjuvant bisphosphonates.



feasible, for confirmation and determination of receptor status[6,139].

Cytotoxic therapy for metastatic breast cancer in young women

General recommendations for CT should not differ from those for older women with the same biological features of metastatic disease and its extent. Young age by itself must not be an indicator for more intensive treatment nor use of combination CT in a metastatic setting. There is no survival advantage for combination CT over sequential single-agent chemotherapy and combination treatment leads to higher toxicity, which is of special importance in the treatment of advanced, incurable disease[6].

Platinum compounds have been seeing a renewed interest in TNBC, especially those associated with BRCA1/2 mutations. The TNT trial compared standard docetaxel to carboplatin in unselected TNBC patients[140]. Carboplatin was found to be superior among BRCA-mutated patients, but not in the unselected TNBC population. It is important to highlight that 15% of patients did not receive prior systemic chemotherapy in early disease setting, and only 35% had received taxanes in the neo/adjuvant setting. Carboplatin was better tolerated than docetaxel.

Endocrine therapy for metastatic disease

Endocrine therapy should be the preferred systemic treatment for young patients with metastatic hormone receptor positive breast cancer, unless there is visceral crisis present or concern about endocrine resistance[139].

Ovarian suppression/ablation with additional endocrine agent (TAM or an AI) remains a standard treatment option for first-line treatment for young metastatic breast cancer women with hormone receptor positive disease[139]. The choice of an additional endocrine agent depends on the type of previous adjuvant therapy, as well as time elapsed from completion of adjuvant therapy and onset of metastatic disease.

There has been increased interest in fulvestrant in the metastatic setting for postmenopausal breast cancer patients. Hypothetically, it should also be effective in pre- and perimenopausal patients. However, it has not been studied adequately in premenopausal patients. Therefore, the use of OFS concomitantly with fulvestrant is often required when used in this group.

An important advance in the management of hormone receptor positive metastatic breast cancer has been the introduction of a new class of agents, the CDK4/6 inhibitors, in combination with endocrine agents. Palbociclib, a CDK4/6 inhibitor, was evaluated in the phase III PALOMA 2 trial together with letrozole as first-line treatment in postmenopausal patients with hormone receptor positive metastatic breast cancer and demonstrated a 10-month improvement in progression-free survival, with the main toxicity being hematological (neutropenia)[141]. Its use together with an AI in pre- and/or perimenopausal patients mandates the use of ovarian suppression/ablation, but lacks a robust evidence base. The future role of mammalian target of rapamycin (mTOR) inhibitors is uncertain due to their high toxicities and lack of overall survival benefit. Additionally, there is a lack of data supporting the use of mTOR inhibitors after CDK4/6 inhibitors, which are increasing being used in earlier lines of therapy.

Anti-HER2 therapy for metastatic disease

Similar to HER2-positive early breast cancer, management of HER2-positive metastatic breast cancer is similar in younger and older women.

New targeted treatment options for patients with BRCA-associated breast cancer

An important characteristic of BRCA-mutated cancers is defective function of one of the major DNA damage repair pathways, the homologous recombination pathway[142]. The discovery of the family of nuclear enzymes poly(ADP-ribose) polymerases (PARP), and their role in DNA damage repair pathways led to development of a new class of drugs, so-called PARP inhibitors, which have the ability to interfere with the DNA damage repair systems of cancer cells. Over the past years, many different PARP inhibitors have been developed and their potential role has been evaluated especially in the treatment of TNBC and BRCA-associated tumors.

It has been shown that activity of PARP inhibitor monotherapy is modest, and the toxicity of combination therapy with PARP inhibitors and chemotherapy is quite

high[143]. There are several phase III trials currently ongoing in both the metastatic and neo/adjuvant and are limited to patients with BRCA1/2-associated tumors[142].

PSYCHOLOGICAL AND SOCIAL BURDEN OF BREAST CANCER IN YOUNG SURVIVORS

Diagnosis of breast cancer can have a substantial effect on the life of a young woman. A prospective cohort study from the Netherlands demonstrated that health-related quality of life (which includes the role functioning, emotional and cognitive functioning, fatigue, and pain) in the first year after BCS and radiotherapy is more strongly affected in young breast cancer survivors than in older patients, but improves over time[144].

Emotional burden can be high for patients and family members[145]. A cross-sectional study from Canada found that breast cancer survivors with children experience higher levels of fear of cancer recurrence and report more problems in intimacy many years after diagnosis[146]. It seems that parenting adolescent children can be particularly challenging and emotionally stressful for a young woman with breast cancer[147].

Prolonged adjuvant treatments after breast cancer surgery have a financial impact on the lives of young patients along with their extended families. Higher risk of losing paid employment and seeking of unemployment and disability benefits up to 5-10 years after diagnosis are reported in young breast cancer survivors[148]. Work and home productivity losses among survivors aged 18-44 years are of considerable importance and call for the support and understanding of healthcare systems around the globe[149].

Rehabilitation strategies are important to improve all aspects of quality of life, including physical, psychological, social, and vocational well-being. Younger women report the need for their healthcare professionals to be more active in recommending rehabilitative care after initial breast cancer treatment has been completed[150].

CONCLUSIONS

Breast cancer in young women represents a special entity of the disease. Not only do young patients face particular challenges and experience different social impacts of diagnosis and treatment, but also the biology of their disease is distinct, even independently of stage and molecular subtyping.

Current treatment modalities for young women with breast cancer are based on biological features of an individual tumor, and the stage of the disease and should not be based on age alone. Data show that breast cancer in young women is complex and heterogeneous, with many activated signaling pathways, which may represent therapeutic targets for future drug development. It is important to further investigate the reasons for a worse outcome of young breast cancer patients with luminal subtypes of the disease and find alternative treatment strategies for this important subgroup of young patients.

At present, there is a lot of uncertainty regarding which young breast cancer patients need OFS as adjuvant endocrine treatment, since the trials demonstrated discordant results. The decision is important from both the perspective of efficacy and toxicity as young women have a lower adherence with adjuvant therapy than older patients.

Early supportive care with special focus on fertility issues and psychosocial morbidity is crucial for optimal management of these patients.

Despite some advances, only few data still exist regarding the management of young breast cancer patients, especially in advanced disease setting, therefore prospective randomized trials designed in this breast cancer population are desirable.

REFERENCES

1. WHO. Women and health. 2009. Available at: http://www.who.int/gender/women_health_report/full_report_20091104_en.pdf
2. Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, et al. Breast cancer in young women in Latin America: an unmet, growing burden. Oncologist. 2013;18:1298-306.
3. Collins LC, Marotti JD, Gelber 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;131:1061-6.
4. Partridge AH, Hughes ME, Ottesen RA, et al. The effect of age on delay in diagnosis and stage of breast cancer. Oncologist. 2012;17:775-82.
5. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat. 2012;134:459-78.
6. Cardoso F, Loibl S, Pagani O, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48:3355-77.
7. Partridge AH, Pagani O, Abulkhair O, et al. First international consensus guidelines for breast cancer in young women (BCY1). Breast. 2014;23:209-20.
8. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ. 2000;320:4748.

9. Gabriel CA, Domchek SM. Breast cancer in young women. Breast Cancer Res. 2010;12:212.
10. De La Rochefordiere A, Asselain B, Campana F, Scholl SM, Fenton J, Vilcoq JR. Age as prognostic factor in premenopausal breast carcinoma. Lancet. 1993;341:1039-43.
11. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001;75:305-9.
12. Smith IE, Dowsett M, Yap Y-S, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: Caution and suggested guidelines. J Clin Oncol. 2006;24:2444-7.
13. World Health Organization. Tech Rep Ser Res menopause Geneva Switz WHO. 1991;670.
14. National Comprehensive Cancer Network practice guidelines in oncology. 2005. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
15. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004;350:1081-92.
16. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349:1793-802.
17. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002;359:2131-9.
18. Cooper GS, Baird DD, Darden FR. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35-49 years. Am J Epidemiol. 2001;153:1159-65.
19. Delrio G, De Placido S, Pagliarulo C, et al. Hypothalamic-pituitary-ovarian axis in women with operable breast cancer treated with adjuvant CMF and tamoxifen. Tumori. 1986;72:53-61.
20. Lum SS, Woltering EA, Fletcher WS, Pommier RF. Changes in serum estrogen levels in women during tamoxifen therapy. Am J Surg. 1997;173:399-402.
21. Amir E, Seruga B, Freedman O, Clemons M. Amenorrhoea, menopause, and endocrine therapy for breast cancer. BMJ. 2009; 339:b4261.
22. Vital-Reyes V, Tellez-Velasco S, Chhieng D, Grizzle W, Reyes-Fuentes A. Spontaneous pregnancy in a woman with premature ovarian failure: a case report. J Reprod Med. 2004;49:989-91.
23. Colleoni M, Rotmensz N, Robertson C, et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. Ann Oncol Off J Eur Soc Med Oncol. 2002;13:273-9.
24. Han W, Kang SY, Korean Breast Cancer Society. 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;119:193-200.
25. Copson E, Eccles B, Maishman T, 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;105:978-88.
26. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med. 2009;360:790-800.
27. Goldhirsch A, Winer EP, Coates AS, 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;24:2206-23.
28. Koboldt DC, Fulton RS, McLellan MD, et al. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490:61-70.
29. Azim HA, Michiels S, Bedard PL, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res. 2012;18:1341-51.
30. Sabiani L, Houvenaeghel G, Heinemann M, et al. breast cancer in young women: Pathologic features and molecular phenotype. Breast. 2016;29:109-16.
31. Azim HA, Partridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014;16:427.
32. Rudra S, Yu DS, Yu ES, Switchenko JM, Mister D, Torres MA. Locoregional and distant recurrence patterns in young versus elderly women treated for breast cancer. Int J Breast Cancer. 2015;2015:213123.
33. Seneviratne S, Lawrenson R, Harvey V, et al. Stage of breast cancer at diagnosis in New Zealand: impacts of socio-demographic factors, breast cancer screening and biology. BMC Cancer. 2016;16:129.
34. Paluch-Shimon S, Wolf I, Sadetzki S, et al. Association between very young age and adverse characteristics of breast cancer at presentation amongst Israeli women. Am J Clin Oncol. 2011;34:219-22.
35. Johnson RH, Chien FL, Bleyer A, et al. Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. JAMA. 2013;309:800.
36. Hung M-H, Liu C-Y, Shiau C-Y, et al. Effect of age and biological subtype on the risk and timing of brain metastasis in breast cancer patients. PLoS One. 2014;9:e89389.
37. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28:3271-7.
38. Ernst MF, van de Poll-Franse LV, Roukema JA, et al. Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002. Breast. 2007;16:344-51.
39. van de Vijver MJ, He YD, van 't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347:1999-2009.
40. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817-26.
41. Anders CK, Acharya CR, Hsu DS, et al. Age-Specific Differences in Oncogenic Pathway Deregulation Seen in Human Breast Tumors. Wu X, editor. PLoS One. 2008;3:e1373.
42. Young S, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer. 2009;9:86.
43. Criscitiello C, Azim HA, Schouten PC, Linn SC, Sotiriou C. Understanding the biology of triple-negative breast cancer. Ann Oncol. 2012;23(Suppl 6):vi13-18.
44. Azim H, Nguyen B, Brohee S, Zoppoli G, Sotiriou C. Genomic aberrations in young and elderly breast cancer patients. BMC Med. 2015;13:266.
45. Liu Z, Merkurjev D, Yang F, Li W, Oh S, Friedman MJ. Enhancer activation requires trans-recruitment of a mega transcription factor complex. Cell. 2014;159:358-73.
46. Chou J, Provot S, Werb Z. GATA3 in development and cancer differentiation: Cells GATA have it! J Cell Physiol. 2010;222:42-9.
47. Adomas AB, Grimm SA, Malone C, Takaku M, Sims JK, Wade PA. Breast tumor specific mutation in GATA3 affects physiological mechanisms regulating transcription factor turnover. BMC Cancer. 2014;14:278.
48. Anders CK, Johnson R, Litton J. BC before age 40 years. Semin Oncol. 2009;36:237-49.
49. Partridge AH, Hughes ME, Warner ET, Ottesen RA, Wong YN, Edge SB. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol. 2016;34:3308-14.
50. Clarke M, Coates AS, Darby SC. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomized trials. Lancet. 2008;371:29-40.
51. Huober J, von Minckwitz G, Denkert C. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological BC phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat. 2010;124:133-40.
52. Partridge AH, Gelber S, Piccart-Gebhart MJ, 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;31:2692-8.
53. Paluch-Shimon S, Pagani O, Partridge AH, et al. Second international consensus guidelines for breast cancer in young women (BCY2). Breast. 2016;26:87-99.
54. 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;24:175-81.
55. Veronesi U, Cascinelli N, Mariani L, 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;347:1227-32.
56. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer. 2004;100:688-93.
57. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: Long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer. 2006;42:351-6.
58. Botteri E, Bagnardi V, Rotmensz N, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol. 2010;21:723-8.
59. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer. Cancer. 2006;106:35-41.
60. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the

treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤40 years. Breast Cancer Res Treat. 2011;127:207-15.
61. Aalders KC, Postma EL, Strobbe LJ, et al. Contemporary locoregional recurrence rates in young patients with early-stage breast cancer. J Clin Oncol. 2016;34:2107-14.
62. Bartelink H, Horiot J-C, Poortmans PM, 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.
63. Plichta JK, Rai U, Tang R, et al. Factors associated with recurrence rates and long-term survival in women diagnosed with breast cancer ages 40 and younger. Ann Surg Oncol. 2016;23:3212-20.
64. Gradishar WJ, Robert CH, Anderson BO, et al. NCCN Guidelines Version 2.2016 Breast Cancer Panel Members NCCN Evidence Blocks TM. 2016. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf
65. Hieken TJ, Boolbol SK, Dietz JR. Nipple-sparing mastectomy: Indications, contraindications, risks, benefits, and techniques. Ann Surg Oncol. 2016;23:3138-44.
66. Toesca A, Peradze N, Manconi A, et al. Robotic nipple-sparing mastectomy for the treatment of breast cancer: Feasibility and safety study. Breast. 2017;31:51-6.
67. Darby S, McGale P, Correa C, 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;378:1707-16.
68. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year Breast Cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383:2127-35.
69. van Laar C, van der Sangen MJ, Poortmans PM, 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;49:3093-101.
70. Bosma SCJ, van der Leij F, van Werkhoven E, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Cancer Res Treat. 2016;156:391-400.
71. Recht A, Comen EA, Fine RE, et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Pract Radiat Oncol. 2016;6:e219-34.
72. Bartelink H. The changing landscape in radiotherapy for breast cancer: Lessons from long term follow-up in some European breast cancer trials. Radiother Oncol. 2016;121:348-56.
73. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015;373:307-16.
74. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015;373:317-27.
75. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials-an update. Radiat Oncol. 2015;10:258.
76. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366:2087-106.
77. Brackstone M, Fletcher GG, Dayes IS, et al. Locoregional therapy of locally advanced breast cancer: a clinical practice guideline. Curr Oncol. 2015;22(Suppl 1):S54-66.
78. Poortmans PM, Whelan TJ. Locoregional treatment in early stage breast cancer: More evidence and yet more questions? J Clin Oncol. 2015;27:689-91.
79. Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. Lancet. 2014;383:2104-6.
80. Kunkler IH, Canney P, van Tienhoven G, Russell NS, MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group. Elucidating the role of chest wall irradiation in "intermediate-risk" breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol). 2008;20:31-4.
81. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol. 2016;34:314-20.
82. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v8-30.
83. Yildirim E, Berberoglu U. Local recurrence in breast carcinoma patients with T1-2 and 1-3 positive nodes: Indications for radiotherapy. Eur J Surg Oncol. 2007;33:28-32.
84. Su Y-L, Li S-H, Chen Y-Y, et al. Post-mastectomy radiotherapy benefits subgroups of breast cancer patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis. Radiol Oncol. 2014;48:314-22.
85. Ashworth A, Kong W, Whelan T, Mackillop WJ. A population-based study of the fractionation of postlumpectomy breast radiation therapy. Int J Radiat Oncol. 2013;86:51-7.
86. Nguyen K, Mackenzie P, Allen A, et al. Breast interest group faculty of radiation oncology: Australian and New Zealand patterns of practice survey on breast radiotherapy. J Med Imaging Radiat Oncol. 2016. [Epub ahead of print].
87. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086-94.
88. Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. JAMA. 2014;312:2542.
89. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-20.
90. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006;7:467-71.
91. Caudrelier J-M, Truong PT. Role of hypofractionated radiotherapy in breast locoregional radiation. Cancer/Radiothérapie. 2015;19:241-7.
92. DBCG; Danish Breast Cancer Cooperative Group. The SKAGEN Trial 1 Moderately hypofractionated loco-regional adjuvant radiation therapy of early breast cancer combined with a simultaneous integrated boost in patients with an indication for boost: DBCG HYPO II, a randomised clinically controlled trial. 2015. p. 1-33. Available from: www.dbcg.dk/
93. Ain Shams University. Conventional Versus Hypofractionated Radiotherapy in Node Positive Breast Cancer. ClinicalTrials.gov Identifier: NCT02690636.
94. Koulis TA, Phan T, Olivotto IA. Hypofractionated whole breast radiotherapy: current perspectives. Breast Cancer. 2015;7:363-70.
95. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. Breast Cancer Res Treat. 2011;127:15-22.
96. Khan AJ, Rafique R, Zafar W, et al. Nation-scale adoption of shorter breast radiation therapy schedules can increase survival in resource constrained economies: Results from a Markov chain analysis. Int J Radiat Oncol. 2017;97:287-95.
97. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16:47-56.
98. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol. 2014;32:1507-15.
99. Houssami N, Macaskill P, Luke Marinovich M, Morrow M. The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive breast cancer Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2014;21:717-30.
100. Brouwers PJ, van Werkhoven E, Bartelink H, et al. Factors associated with patient-reported cosmetic outcome in the Young Boost Breast Trial. Radiother Oncol. 2016;120:107-13.
101. Tramm T, Mohammed H, Myhre S, et al. Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. Clin Cancer Res. 2014;20:5272-80.
102. Cheng SH, Horng C-F, Huang T-T, et al. An eighteen-gene classifier predicts locoregional recurrence in post-mastectomy breast cancer Patients. EBioMedicine. 2016;5:74-81.
103. Torres-Roca JF, Fulp WJ, Caudell JJ, et al. Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast cancer. Int J Radiat Oncol Biol Phys. 2015;93:631-8.
104. Vicini F, Shah C, Tendulkar R, et al. Accelerated partial breast irradiation: An update on published Level I evidence. Brachytherapy. 2016;15:607-15.

105. NSABP B-39, RTOG 0413: A Randomized Phase III Study of conventional whole breast irradiation versus partial breast irradiation for women with stage 0, I, or II breast cancer. Clin Adv Hematol Oncol. 2006;4:719-21.
106. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol. 2015;114:3-10.
107. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2011;79:10-18.
108. Smyth LM, Knight KA, Aarons YK, Wasiak J. The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review. J Med Radiat Sci. 2015;62:66-73.
109. Taylor CW, Kirby a M. Cardiac side-effects from breast cancer radiotherapy. Clin Oncol (R Coll Radiol). 2015;27:621-9.
110. Latty D, Stuart KE, Wang W, Ahern V. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. J Med Radiat Sci. 2015;62:74-81.
111. Bartlett FR, Colgan RM, Donovan EM, et al. Voluntary breath-hold technique for reducing heart dose in left breast radiotherapy. J Vis Exp. 2014;89.
112. Conway JL, Conroy L, Harper L, et al. Deep inspiration breath-hold produces a clinically meaningful reduction in ipsilateral lung dose during locoregional radiation therapy for some women with right-sided breast cancer. Pract Radiat Oncol. 2016. [Epub ahead of print].
113. Stovall M, Smith SA, Langholz BM, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE Study. Int J Radiat Oncol Biol Phys. 2008;72:1021-30.
114. Grantzau T, Overgaard J. Risk of second non- breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. Radiother Oncol. 2015;114:56-65.
115. Hallam S, Govindarajulu S, Huckett B, Bahl A. BRCA1/2 mutation-associated breast cancer, wide local excision and radiotherapy or unilateral mastectomy: A systematic review. Clin Oncol (R Coll Radiol). 2015;27:527-35.
116. Bernstein JL, Thomas DC, Shore RE, et al. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: A WECARE Study Report. Eur J Cancer. 2013;49:2979-85.
117. Heymann S, Delaloge S, Rahal A, et al. Radio-induced malignancies after breast cancer post-operative radiotherapy in patients with Li- Fraumeni syndrome. Radiat Oncol. 2010;5:104.
118. Freedman RA, Partridge AH. Management of breast cancer in very young women. Breast. 2013;22:S176-9.
119. Wolmark N, Wang J, Mamounas E, Project B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. Cancer Inst Monogr. 2001;30:96-102.
120. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, 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;379:432-44.
121. Lambertini M, Ceppi M, Cognetti F, et al. Dose-dense adjuvant chemotherapy in premenopausal breast cancer patients: A pooled analysis of the MIG1 and GIM2 phase III studies. Eur J Cancer. 2017;71:34-42.
122. Amir E, Ocana A, Freedman O, Clemons M, Seruga B. Chemotherapy: dose-dense treatment for triple-negative breast cancer. Nat Rev Clin Oncol. 2010;7:79-80.
123. Anders CK, Zagar TM, Carey LA. The management of early-stage and metastatic triple-negative breast cancer: a review. Hematol Oncol Clin North Am. 2013;27:737-49.
124. Sikov WM, Berry DA, Perou CM, 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;33:13-21.
125. von Minckwitz G, Schneeweiss A, Loibl S, 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;15:747-56.
126. 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.
127. Iwata H, Masuda N, Sagara Y, et al. Analysis of Ki-67 expression with neoadjuvant anastrozole or tamoxifen in patients receiving goserelin for premenopausal breast cancer. Cancer. 2013;119:704-13.
128. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, 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;378:771-84.
129. Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:1672-3.
130. Davies C, Pan H, Godwin J, 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;381:805-16.
131. Azim HA, Saadeldeen A. Commentary on "aTTom": long-term effects of continuing adjuvant Tamoxifen to 10 years. Chin Clin Oncol. 2014;3:7.
132. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005;97:1262-71.
133. Gnant M, Mlineritsch B, Stoeger H, 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;26:313-20.
134. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Goel S, editor. Cochrane Database Syst Rev. 2009;4:CD004562.
135. LHRH-agonists in Early Breast Cancer Overview group, Cuzick J, Ambroisine L, 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;369:1711-23.
136. Bellet M, Gray KP, Francis PA, et al. Estrogen levels in premenopausal patients with hormone-receptor positive (HR+) early breast cancer (BC) receiving adjuvant triptorelin plus exemestane or tamoxifen in the SOFT trial: SOFT-EST substudy. J Clin Oncol. 2014;32. [Abstract 585].
137. Dowsett M, Folkerd E, Res BC. Deficits in plasma oestradiol measurement in studies and management of breast cancer. Breast Cancer. 2005;7:1-4.
138. Ben-Aharon I, Vidal L, 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. [Abstract 548].
139. Cardoso F, Costa A, Senkus E, et al. 3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017;31:244-59.
140. Tutt A, Ellis P, Kilburn L. TNT: a randomized phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced triple-negative or BRCA1/2 breast cancer. Cancer Res. 2015;75:S3-1.
141. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25-35.
142. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med. 2015;13:188.
143. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244-50.
144. Bantema-Joppe EJ, de Bock GH, Woltman-van Iersel M, et al. The impact of age on changes in quality of life among breast cancer survivors treated with breast-conserving surgery and radiotherapy. Br J Cancer. 2015;112:636-43.
145. Ali A, Fergus K, Wright FC, Pritchard KI, Kiss A, Warner E. The impact of a breast cancer diagnosis in young women on their relationship with their mothers. Breast. 2014;23:50-5.
146. Arès I, Lebel S, Bielajew C. The impact of motherhood on perceived stress, illness intrusiveness and fear of cancer recurrence in young breast cancer survivors over time. Psychol Health. 2014;29:651-70.
147. Grabiak BR, Bender CM, Puskar KR. The impact of parental cancer on the adolescent: an analysis of the literature. Psychooncology. 2007;16:127-37.
148. Paalman CH, van Leeuwen FE, Aaronson NK, et al. Employment and social benefits up to 10 years after breast cancer diagnosis: a population-based study. Br J Cancer. 2016;114:81-7.
149. Ekwueme DU, Trogdon JG, Khavjou OA, Guy GP. Productivity costs associated with breast cancer among survivors aged 18-44 years. Am J Prev Med. 2016;50:286-94.
150. Easley J, Miedema B. Rehabilitation after breast cancer: Recommendations from young survivors. Rehabil Nurs. 2012;37:163-70.