Ther Adv Med Oncol
2018, Vol. 10: 1–10
DOI: 10.1177/1758835918776923

Should age impact breast cancer management in young women? Fine tuning of treatment guidelines

Matteo B. Suter and Olivia Pagani

Abstract: Despite breast cancer being uncommon in young women, it is still the most frequent cancer diagnosed in women aged 15–39 years, and the leading cause of death in this age group in high-income countries, after accidents and self-injury. The present review summarizes the most recent guidelines and offers an expert perspective on the many challenges associated with treatment of young women with breast cancer. We will especially focus on early breast cancer, exploring the specificities of the diagnostic process, imaging techniques, locoregional and systemic treatments, and the added value of dedicated multidisciplinary teams. Specific differences in adjuvant treatment between premenopausal and postmenopausal women, especially regarding endocrine therapy, will be addressed in detail. Research questions and current gaps in important fields, such as the paucity of age-specific data regarding antihuman epidermal growth factor receptor 2 (anti-HER2) therapy and gene panels such as OncotypeDX or MAMMAPRINT will be highlighted. A consistent part of this review is dedicated to the issues defining 'young women', such as fertility preservation, managing long-term side effects of oncological treatments and genetic counselling, by detailing current strategies and future perspectives.

Keywords: breast cancer, fertility, premenopausal, review, young women

Received: 20 January 2018; revised manuscript accepted: 12 April 2018

Epidemiology

Breast cancer (BC) is the most common cancer and the first cause of cancer death among women worldwide: in 2016, more than half a million people died across the world from this disease.[1,2] The scientific community defines 'young' women those aged ⩽40 years at BC diagnosis to better frame a cluster of patients with specific issues (e.g. fertility preservation, family planning, genetic counselling), different not only from postmenopausal women but also from older premenopausal patients. BC incidence grows with age, being an uncommon disease in young women: with a cumulative risk of 0.4% it represents less than 7% of all BC patients in developed countries. Nonetheless, BC is the most common cancer diagnosed in women between 15 and 39 years of age.[3] Even if it is not a frequent disease, BC in young women (BCYW) is the leading cause of death in this age group in high-income countries, after road accidents and self-injury.[1,3] One explanation is the frequency of more aggressive biology compared with older women: BCYW is often of high grade, especially in the hormone-responsive subtype, with a shift from luminal A-like (30% *versus* 60–70%) to luminal B-like disease (35% *versus* 10–25%), and a higher proportion of human epidermal growth factor receptor 2 (HER2)-positive and triple-negative histology.[4,5] Unique biology and more aggressive phenotypes of tumours arising in younger patients, beyond traditional immune-histochemical profiles, have been suggested,[4,6] but definitive evidence is still lacking. Another relevant factor is the stage of the disease at diagnosis: young women are more likely to present with symptoms and a more advanced stage due to diagnostic delay.[7] An additional challenge

Correspondence to:
Olivia Pagani
Institute of Oncology and Breast Unit of Southern Switzerland, Bellinzona, Switzerland
Hopitaux Universitaires de Geneve, Department of Oncology and Breast Cancer Centre
olivia.pagani@eoc.ch

Matteo B. Suter
Oncology Unit, ASST Settelaghi, Varese, Italy
Institute of Oncology and Breast Unit of Southern Switzerland, Bellinzona, Switzerland

in BCYW treatment is the small number of cases: many of the available data, and the subsequent recommendations, derive from studies in older patients.

Diagnosis and staging

Dedicated programmes for BCYW

Young women with BC should be cared for by dedicated multidisciplinary teams, ideally within specialized breast units,[8] to properly address age-specific diagnostic, therapeutic and psychosocial issues, for example, breast density, treatment-related body image changes, fertility preservation and family planning, sexuality, return to work. Many, if not all of these issues, require dedicated professionals and integrated services, allowing for coordinated, efficient but also individualized interventions to address all the sensitive issues young women face when diagnosed with BC in a tight timeframe.[9] In fact, one of the main concerns raised by young women with BC is a sense of confusion at decision making and lack of patient's view consideration, which can be aggravated when confronted with several specialists. Navigators, ideally breast nurses or adequately trained healthcare professionals, are being explored as potential facilitators of great help in assisting patients throughout their cancer journey.[10]

Imaging techniques

As mentioned before, young women with BC are generally symptomatic at diagnosis. Despite that, as of today, there is no clear role for routine breast screening in young women with an average BC risk. The use of breast magnetic resonance imaging (MRI) as a screening test should be restricted to patients with a germline mutation in a known cancer predisposition gene, a lifetime BC risk greater than 20%, a significant family history, or an established risk factor such as ionizing radiation to the chest.[11,12] Young age alone should not modify the standard diagnostic procedures, despite acknowledging that tissue density can reduce both sensitivity and specificity of standard diagnostic tools. The use of preoperative MRI should follow the same indication as in older women (i.e. axillary node involvement with unknown primary, monitoring of neoadjuvant therapy, very dense breast).[13] A particular issue in this population is timing the imaging with the menstrual cycle: breast MRI and mammography should be performed between day 5 and 12 of the menstrual cycle to minimize the risk of false positives due to functional contrast enhancement.[14]

Genetic counselling and testing

Genetic counselling should be offered to all young women in keeping with local/national guidelines, resources and testing availability. As a general rule, every young woman should be referred to a genetic counsellor, especially, but not exclusively, those with a family history suggestive for hereditary cancer predisposition or with triple-negative BC. Timing of genetic counselling should be based both on its impact on patient care (e.g. type of surgery) and on the psychological resources of the patient (see also chapter 5). Women who are not ready to discuss genetic counselling and testing at diagnosis should be offered the opportunity during follow up, given also the implications for the rest of the family. Genes beyond BRCA 1-2, p53 (Li-Fraumeni Syndrome) and PTEN (Cowden's Syndrome), with moderate to high penetrance (e.g. PALB2, CHEK 2), should be tested for as deemed necessary by the geneticist.[8]

Early breast cancer

Locoregional therapy: surgery and radiation therapy

Although young age at BC diagnosis is an independent risk factor for local recurrence,[15] a meta-analysis, incorporating >20,000 cases of BCYW, showed no difference in survival between patients undergoing a mastectomy compared with those undergoing breast-conserving surgery (BCS).[16] Also, in breast surgery, young age alone should not be a decisive factor in escalating treatment: BCS, whenever suitable, should be the first option. BCS has a lower impact than mastectomy on self-image changes, but it can still be associated with poor cosmetic results in as many as 20–30% of patients. Oncoplastic techniques, performed by a dedicated breast surgical team, can improve aesthetic results, with complications delaying adjuvant treatments in <2% of cases.[17] Whenever a mastectomy is the preferred choice, skin and nipple-sparing techniques have locoregional recurrence rates comparable with standard mastectomy but better cosmetic results should be considered.[18] Immediate breast reconstruction has the same survival rate as mastectomy without reconstruction and should be offered to every patient, irrespective of the indication for postoperative radiation therapy. The surgical management of women with known BC genetic

predisposition is discussed in chapter 5. The indications of lymph node management, either sentinel node biopsy or axillary dissection, should not differ from those of older women. The optimal locoregional strategy after neoadjuvant chemotherapy is also independent of age. Radiation therapy should be administered in accordance to standard practice, with modern techniques and high-quality standards to maximize efficacy and minimize long-term side effects, crucial in women with a potential long life expectancy. Given the higher risk of local and intra-breast recurrence, a boost to the site of the radical local excision is routinely indicated and partial breast irradiation is still contraindicated outside of a clinical trial. Hypofractionation is of particular interest for young women who need to fit in treatment requirements in busy familial and professional lives. Despite young women being underrepresented in randomized clinical trials, subgroup analysis and long-term data do not suggest differential effects according to age.[19,20] Hypofractionation may be therefore considered also in this age group.

Systemic therapy

Regardless of age, systemic therapies (chemotherapy, endocrine therapy or targeted therapy) should be tailored according to both the biological characteristics (hormone and HER2 receptor status, proliferation, grade) and the stage of the tumour. Patients' comorbidities and preferences should also be taken into account when planning the individual treatment programme.

Endocrine therapy. Hormone-responsive BCYW should be treated with adjuvant endocrine therapy, as numerous trials and patient-level meta-analyses have proven a substantial reduction in both recurrence and mortality.[21] The endocrine therapy choice should be based on the individual risk profile, defined by stage (tumour size and nodal involvement) and tumour immunohistochemistry. Aromatase inhibitors (AIs) are contraindicated in premenopausal women because of the loop stimulation of ovarian function through the increase of the hypothalamic secretion of gonadotrophin-releasing hormones (GnRH). The recent updates of the TEXT and SOFT trials[22,23] confirm previous data[24,25] and support the current guidelines.[8,26,27] In summary, low-risk patients (e.g. small tumour, low proliferation/grade, node negative) have excellent outcomes with tamoxifen alone for 5 years.[22,28] Adding ovarian function suppression (OFS), by GnRH agonists (GnRHa) or oophorectomy, to oral endocrine therapy (either tamoxifen or exemestane) substantially decreases BC relapses in high-risk patients (e.g. higher proliferation/grade, higher stage) with a significantly superior benefit associated with AI over tamoxifen.[22,23] The optimal GnRHa duration remains a matter of debate; older studies used 2–3 years of GnRHa in combination with 5 years of tamoxifen; in TEXT and SOFT, the combination was given for 5 years. In the Austrian Breast and Colorectal Cancer Study Group–12 trial (ABCSG-12) 3 years of anastrozole or tamoxifen plus the GnRHa goserelin were associated with excellent 10-year outcomes.[29] When indicated, OFS can be started together or after chemotherapy, with no detrimental effect of concomitant administration, which can also contribute to fertility preservation.[30] The extension of endocrine therapy beyond 5 years should also be considered in high-risk women. The ATLAS trial included up to 18–19% of premenopausal patients, being the only published evidence in young women of an outcome benefit associated with extended endocrine therapy (i.e. 10 years of tamoxifen).[31] From a clinical perspective, it should be kept in mind that nonadherence to endocrine therapy in premenopausal women is about 20%[32] and is associated with reduced overall survival.[33] Compliance to endocrine therapy, in particular when extension is indicated, should therefore be closely monitored and motivated.

With regards to neoadjuvant endocrine therapy, no results from randomized controlled trials are yet available in this age group. A phase II trial is currently ongoing (IBCSG 41-13 TREND), comparing degarelix (a GnRH antagonist) *versus* triptorelin in combination with letrozole.[34] As of today, neoadjuvant endocrine therapy is not recommended in young women.

Chemotherapy. Gene expression signatures, such as MammaPrint[35] or Oncotype DX,[36] are increasingly used to add prognostic information to classic clinicopathologic factors and better select patients with hormone-responsive disease most likely to benefit from adjuvant chemotherapy. As shown in Table 1, young patients were a small fraction of those enrolled in clinical trials assessing the role of these signatures and caution is therefore required in this population. As mentioned above, young age alone should not prompt treatment escalation and expand chemotherapy indications. We lack randomized evidence of the benefit of adding chemotherapy to endocrine therapy in low-risk, hormone-responsive BCYW, but indirect data

Table 1. Young patients' enrolment in gene assay validation trials.

Trial	Test	Patients	<35-years old	35–50-years old	Mean age
TailorX	Oncotype DX	10253	377*	2336**	55–58
PlanB	Oncotype DX	3198	NA	NA	56
WSG PRIMe	MammaPrint BluePrint TartgetPrint	452	NA	NA	58***
MINDACT	MammaPrint	6693	112	2104	55

NA, not available.
*<40 years old; *41–50 years old; ***0% premenopausal.

support the indication to avoid chemotherapy in these patients, given the very good outcome with optimal endocrine therapy alone.[29,37] For high-risk patients, adjuvant chemotherapy should follow standard guidelines, as for older patients. The latest published Early Breast Cancer Trialists' Collaborative Group's meta-analysis in >100,000 patients was not able to identify a more effective chemotherapy regimen,[38] with age having little to no effect. Early results of a subgroup analysis of the same data set, presented at the San Antonio Breast Cancer Symposium in 2017, seem to suggest that dose-dense regimens significantly reduce disease recurrence and BC mortality in high-risk patients.[39,40] As a general rule, sequential chemotherapy regimens have the same efficacy of simultaneous combination schedules but have a better safety profile.[41,42]

As for neoadjuvant chemotherapy, young women are more likely to achieve a pathological complete response (pCR), especially those with hormone-responsive and HER2-negative disease, as showed in a pooled analysis of the German Breast Group randomized trials.[43] Young age does not seem to affect response in HER2-positive[44] and triple-negative patients. However, in this last subgroup, clinical trials have shown a pCR rate increase when adding carboplatin to standard taxane and anthracycline regimens.[45,46] The impact on survival is controversial and toxicity is increased but, given the dismal outlook of triple-negative patients, the higher frequency in young women, and the prognostic impact of pCR in this subset, the addition of carboplatin to neoadjuvant chemotherapy should be considered and discussed at least in selected high-risk patients. In triple-negative patients not achieving a pCR after neoadjuvant chemotherapy, adjuvant capecitabine provided a benefit in terms of disease-free and overall survival in the CREATE-X trial,[47] which enrolled patients with a median age of 48 years. This approach, based on only one positive trial conducted in Japanese women with possible different fluoropyrimidine bioavailability, should not become a standard of care but individually discussed in high-risk patients, given the absence of further active standard treatment.

antiHER2 therapy. HER2-positive patients should be evaluated for neoadjuvant therapy with pertuzumab in combination with trastuzumab and taxanes, given the increased pCR rate with this combination,[44] using the same criteria as for older patients. For adjuvant therapy, the benefit of trastuzumab is independent of age;[48] 1 year of trastuzumab representing the standard duration. The subcutaneous administration of trastuzumab could be particularly attractive in young women who need to fit BC treatment into complex personal/familial commitments.[49] The additional absolute benefit of adjuvant pertuzumab[50] and neratinib[51] doesn't allow, at present, recommendation of adding these agents in routine clinical practice, especially considering the very small number of young women enrolled in the recently published APHINITY and ExteNET trials.

Fertility preservation and family planning

One of the characteristics clearly distinguishing women <40 years is that family planning is frequently not yet complete. In general, pregnancy after BC has shown not to impair patients' outcomes, also in hormone-responsive disease.[52] Fertility preservation is a sensitive though crucial topic to discuss at BC diagnosis, given the limitation of the available data, the intrinsic emotional impact and the need to tackle it early on in the

treatment journey, when the psychological burden of the new cancer diagnosis is so heavy to deal with. This is one of the specific issues to be cared for in specialized breast units, where an early referral to fertility specialists and preservation techniques, coupled with individualized psychosocial support, can be easily put in place.[9]

Different fertility preservation techniques are available: their indication and expected efficacy depend on the individual patient's situation and country's availability.[53] The use of GnRHa to preserve fertility in patients candidate to chemotherapy is still a matter of debate. A recent meta-analysis, incorporating >1000 patients, has shown a benefit from GnRHa administration in terms of preventing premature ovarian failure 1 year after chemotherapy completion. The meta-analysis also showed a doubling in the chance of pregnancy.[54] As administering GnRHa during chemotherapy can also prevent premature menopause, this option should be routinely discussed.

In patients receiving endocrine therapy, the POSITIVE trial (IBCSG 48-14 NCT02308085), currently recruiting, is studying if temporary interruption of endocrine therapy to permit pregnancy is associated with a higher risk of BC recurrence. The study aims also to evaluate different specific indicators related to fertility, pregnancy outcomes, breastfeeding and BC biology in young women.[55]

Pregnancy is, on the other hand, prohibited during active BC treatment, due to the teratogenic risk of anticancer therapies. Proactive counselling should be provided, favouring barrier methods as a safer alternative to hormonal contraception, which is generally contraindicated for BC survivors.[56,57] Levonorgestrel-releasing intra-uterine devices, which could also help controlling tamoxifen-induced hyperplasia, remain controversial, with further studies needed in this particular population.[58] Contraception also provides the opportunity to discuss sexuality: vaginal dryness, loss of libido, and dyspareunia are among the main complaints of women with chemotherapy-induced amenorrhoea[59] or undergoing OFS and endocrine therapy.[32] For these patients, appropriate counselling should be offered and medication such as vaginal moisturizers or lubricants prescribed.

Follow-up care and survivorship

BCYW follow up should not differ from the standard of care, with annual mammography and clinical examination every 6 months for at least the first 5 years after diagnosis.[60] The peculiarities of BCYW follow up involve age-specific issues. The frequent induction of premature menopause is associated with a sudden change in many aspects of routine daily life, which should be individually addressed and managed. For instance, early iatrogenic menopause, especially in patients also treated with AIs, can result in significant bone loss. Unexpectedly, tamoxifen can also induce bone loss in premenopausal patients, likely because its agonistic effect in the bones is weaker than that of the endogenous estrogens it is blocking.[61] The standard use of bisphosphonates as part of adjuvant treatment has been recently included in guidelines[27] based on the results of a large meta-analysis in >18,000 women, showing a significant reduction of the rate of bone relapse and an improvement of BC survival in menopausal women.[62] Young women with chemotherapy-induced menopause or under OFS and at a significant risk of disease relapse should therefore be considered for adjuvant bisphosphonates. In the overall population, bone density should be regularly monitored and treated in accordance with local guidelines.

Cognitive impairment is frequently reported by BC survivors: forgetfulness, difficulty to concentrate, and distractibility, among the others, can severely impair daily life. Neurocognitive evaluation is often inconclusive, because of frequent discrepancies between tests, imaging findings and patients' subjective difficulties. Only in recent years, changes in white matter after chemotherapy have been described[63]; the effects of endocrine therapy on cognitive function remain poorly understood, as also shown in the Co-SOFT substudy in which, in a small subset of patients enrolled in the SOFT trial, adding OFS to adjuvant oral endocrine therapy didn't substantially affect global cognitive function.[64] Several ongoing studies will hopefully provide etiologic explanations and practical indications on how to manage one of the most bothersome long-term side effects of BC treatment in young women.

Weight control and lifestyle changes should be systematically proposed, given their proven benefit,[65] a BMI below 25 and smoking cessation being the main targets. To this extent, a breast unit should also include a physiotherapist, a nutritionist and dedicated nurses to promote rehabilitation and weight control programmes. The latest guidelines[8] strongly suggest implementing dedicated

clinics to assess and manage early and late treatment side effects, adherence to treatment and follow-up programmes.

Advanced breast cancer

Even in advanced disease, young age should not be a reason to prescribe more aggressive treatments. Established consensus guidelines should be applied as in older women,[66] the focus being quality of life, management of age-related side effects and treatment specificities (e.g. endocrine therapy in the era of targeted therapies). Detailing treatments is beyond the scope of the present review.

Breast cancer gene (BRCA) mutation carriers

Timing of genetic testing in BCYW should be defined based on the therapeutic programme (e.g. if the patient is scheduled to receive breast surgery upfront), as well as on the patient's priorities and psychological resources. This is another setting where a specialized multidisciplinary team, including the geneticist, the oncologist, the psychologist and the plastic/surgeon, with the assistance of a dedicated nurse or navigator, can really empower the patient, allowing for a timely and informed decision. Genes to be tested for depend on personal/family history. BRCA1/2 are the most frequently mutated genes: other moderate-to high-penetrance genes may be considered in the individual patient, if appropriate. With modern techniques, genetic testing can be performed in really tight timeframes but this should not lead to indiscriminate testing and force rushed decisions.

Faced with a diagnosis of BRCA mutation, the first topic to discuss in patients with early BC is the extent of the surgical approach (mastectomy *versus* BCS). As of today, no conclusive data have shown a survival benefit for therapeutic/risk-reducing bilateral mastectomy in women with early BC and a genetic susceptibility syndrome, given the small numbers and the retrospective nature of most of the evidence available.[67,68] The role of bilateral breast surgery in carriers of moderate-risk genes is not yet established. When discussing the options with the patient, the physician should point out, beside the lack of impact on survival, the differences in follow up in the absence of risk-reducing mastectomy and the increased risk of contralateral BC. Women undergoing BCS should be followed with clinical examination every 6 months and annual breast MRI and mammography, while the use of ultrasound every 6 months is still a matter of debate.[69]

Risk-reducing salpingo-oophorectomy (RRSO) should be proposed to all women harbouring a BRCA1/2 mutation and planned after a thorough discussion specifically covering childbearing and premature menopause. In BRCA1 mutation carriers, RRSO is recommended earlier (between age 35 and 40) than in BRCA2 mutation carriers (from age 40) based on the different prevalence of ovarian cancer, always considering the patient's personal and family history. In women who decline RRSO, gynaecological surveillance every 6 months is an appropriate follow-up strategy; routine determination of CA125 serum levels or transvaginal ultrasound is not supported in current guidelines.[70]

As of today, there is no clear indication of a preferred chemotherapeutic regimen for women with BRCA mutations. Based on the available evidence, platinum agents should be considered in both the early and advanced disease setting.[45,71]

The development of BRCA-targeted agents has been less rapid in BC than in ovarian cancer. Only in 2017 the results of the OlympiAD trial have proved the benefit of olaparib, a polyadenosine diphosphate ribose polymerase inhibitor, in metastatic pretreated BRCA-mutated BC patients compared with investigator's choice chemotherapy.[72] The results of the OlympiA trial, assessing olaparib as maintenance therapy after standard treatment in the adjuvant setting, are expected not earlier than 2020.[73]

Conclusions and take-home messages

Management of young women with BC is complex and requires a dedicated approach not only in medical treatment but also in supportive care and during follow up. Given its rarity, medical treatment, apart from endocrine therapy, is largely based on data collected in older patients, highlighting the need to develop dedicated clinical and biologic research programs in this age population. Many clinical aspects and concerns of young women with BC need to be addressed by well-trained and motivated multidisciplinary healthcare professionals. Specific communication and psychosocial support tools also need to be implemented in these women who face a

life-threatening disease in the middle of their personal, professional and reproductive life.

Authors' Note

Olivia Pagani is also affiliated to Department of Oncology and Breast Cancer Centre, Hopitaux Universitaires de Geneve.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Global Burden of Disease 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1151–1210.
2. Global Burden of Disease 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–1259.
3. Fidler MM, Gupta S, Soerjomataram I, *et al.* Cancer incidence and mortality among young adults aged 20–39 years worldwide in 2012: a population-based study. *Lancet Oncol* 2017; 18: 1579–1589.
4. 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: 1061–1066.
5. Keegan TH, DeRouen MC, Press DJ, *et al.* Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res* 2012; 14: R55.
6. 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: 1341–1351.
7. Partridge AH, Hughes ME, Ottesen RA, *et al.* The effect of age on delay in diagnosis and stage of breast cancer. *Oncologist* 2012; 17: 775–782.
8. Paluch-Shimon S, Pagani O, Partridge AH, *et al.* ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). *Breast* 2017; 35: 203–217.
9. Partridge AH, Ruddy KJ, Kennedy J, *et al.* Model program to improve care for a unique cancer population: young women with breast cancer. *J Oncol Pract* 2012; 8: e105–e110.
10. Gabitova G and Burke NJ. Improving healthcare empowerment through breast cancer patient navigation: a mixed methods evaluation in a safety-net setting. *BMC Health Serv Res* 2014; 14: 407.
11. Chiarelli AM, Prummel MV, Muradali D, *et al.* Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the Ontario high risk breast screening program. *J Clin Oncol* 2014; 32: 2224–2230.
12. Oeffinger KC, Fontham ET, Etzioni R, *et al.* Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA* 2015; 314: 1599–1614.
13. Houssami N, Turner R, Macaskill P, *et al.* An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *J Clin Oncol* 2014; 32: 392–401.
14. Kajihara M, Goto M, Hirayama Y, *et al.* Effect of the menstrual cycle on background parenchymal enhancement in breast MR imaging. *Magn Reson Med Sci* 2013; 12: 39–45.
15. Botteri E, Bagnardi V, Rotmensz N, *et al.* Analysis of local and regional recurrences in breast cancer after conservative surgery. *Ann Oncol* 2010; 21: 723–728.
16. Vila J, Gandini S and 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: 175–181.
17. Fitoussi AD, Berry MG, Famà F, *et al.* Oncoplastic breast surgery for cancer: analysis of 540 consecutive cases [outcomes article]. *Plast Reconstr Surg* 2010; 125: 454–462.
18. Headon HL, Kasem A and Mokbel K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch Plast Surg* 2016; 43: 328–338.
19. Kim KS, Shin KH, Choi N, *et al.* Hypofractionated whole breast irradiation: new standard in early breast cancer after breast-conserving surgery. *Radiat Oncol J* 2016; 34: 81–87.
20. 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. *The Lancet Oncology* 2013; 14: 1086–1094.

21. Davies C, Godwin J, Gray R, *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: 771–784.
22. Fleming G, Francis PA, Láng I, *et al*. SOFT Investigators, International Breast Cancer Study Group, Breast International Group, and North American Breast Cancer Group. *Randomized comparison of adjuvant tamoxifen (T) plus ovarian function suppression (OFS) versus tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Update of the SOFT trial*. Paper presented at 2017 San Antonio Breast Cancer Symposium, 5–9 December 2017; San Antonio, TX. Abstract GS4–03.
23. Pagani O, Regan MM, Walley B, *et al*. *Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials*. Paper presented at 2017 San Antonio Breast Cancer Symposium, 5–9 December 2017; San Antonio, TX.
24. Pagani O, Regan MM, Walley BA, *et al*. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; 371: 107–118.
25. Francis PA, Regan MM and Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; 372: 1673.
26. Burstein HJ, Lacchetti C, Anderson H, *et al*. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American society of clinical oncology clinical practice guideline update on ovarian suppression. *J Clin Oncol* 2016; 34: 1689–1701.
27. Curigliano G, Burstein HJ, P Winer E, *et al*. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the primary therapy of early breast cancer 2017. *Ann Oncol* 2017; 28: 1700–1712.
28. Francis PA PO, Regan MM, Fleming GF, *et al*. *SOFT and TEXT Investigators, International Breast Cancer Study Group, Breast International Group and North American Breast Cancer Group. SABCS Abstract #851 GS4–02 (Update of the combined TEXT and SOFT trials) and SABCS Abstract #844 GS4–03 (update of the SOFT trial)*. Paper presented at 2017 San Antonio Breast Cancer Symposium, 7 December 2017; San Antonio, TX.
29. Gnant M, Mlineritsch B, Stoeger H, *et al*. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011; 12: 631–641.
30. Regan MM, Walley BA, Francis PA, *et al*. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. *Ann Oncol* 2017; 28: 2225–2232.
31. 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: 805–816.
32. Saha P, Regan MM, Pagani O, *et al*. Treatment efficacy, adherence, and quality of life among women younger than 35 years in the international breast cancer study group TEXT and SOFT adjuvant endocrine therapy trials. *J Clin Oncol* 2017; 35: 3113–3122.
33. Hershman DL, Shao T, Kushi LH, *et al*. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat* 2011; 126: 529–537.
34. TRial on the Endocrine Activity of Neoadjuvant Degarelix (TREND). https://clinicaltrials.gov/ct2/show/NCT02005887 (accessed November 2017).
35. Cardoso F, Van't Veer LJ, Bogaerts J, *et al*. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med* 2016; 375: 717–729.
36. Sparano JA, Gray RJ, Makower DF, *et al*. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015; 373: 2005–2014.
37. Tevaarwerk AJ, Wang M, Zhao F, *et al*. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2014; 32: 3948–3958.
38. Peto R, Davies C, Godwin J, *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: 432–444.

39. Gray R, Bradley R, Braybrooke J, *et al*. *Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials*. Paper presented at 2017 San Antonio Breast Cancer Symposium, 5–9 December 2017; San Antonio, TX.
40. 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.
41. Swain SM, Tang G, Geyer CE Jr, *et al*. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol* 2013; 31: 3197–3204.
42. Mackey JR, Pienkowski T, Crown J, *et al*. Long-term outcomes after adjuvant treatment of sequential versus combination docetaxel with doxorubicin and cyclophosphamide in node-positive breast cancer: BCIRG-005 randomized trial. *Ann Oncol* 2016; 27: 1041–1047.
43. Loibl S, Jackisch C, Lederer B, *et al*. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials. *Breast Cancer Res Treat* 2015; 152: 377–387.
44. Gianni L, Pienkowski T, Im YH, *et al*. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800.
45. 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: 747–756.
46. 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.
47. Masuda N, Lee SJ, Ohtani S, *et al*. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017; 376: 2147–2159.
48. 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: 2692–2698.
49. Pivot X, Verma S, Fallowfield L, *et al*. Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: final analysis of the randomised, two-cohort PrefHer study. *Eur J Cancer* 2017; 86: 82–90.
50. Von Minckwitz G, Procter M, de Azambuja E, *et al*. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; 377: 122–131.
51. Martin M, Holmes FA, Ejlertsen B, *et al*. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1688–700.
52. Lambertini M, Kroman N, Ameye L, *et al*. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. *J Natl Cancer Inst* 2018; 110: 426–429.
53. De Simone V and Pagani O. Pregnancy after breast cancer: hope after the storm. *Minerva Ginecol* 2017; 69: 597–607.
54. Lambertini M, Ceppi M, Poggio F, *et al*. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol* 2015; 26: 2408–2419.
55. Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE). https://clinicaltrials.gov/ct2/show/NCT02308085 (accessed November 2017).
56. Schwarz EB, Hess R and Trussell J. Contraception for cancer survivors. *J Gen Intern Med* 2009; 24(Suppl. 2): S401–S406.
57. Han SN, Van Peer S, Peccatori F, *et al*. Contraception is as important as fertility preservation in young women with cancer. *Lancet* 2015; 385: 508.
58. Dominick S, Hickey M, Chin J, *et al*. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev* 2015; (12): CD007245.
59. Rosenberg SM, Tamimi RM, Gelber S, *et al*. Treatment-related amenorrhea and sexual

functioning in young breast cancer survivors. *Cancer* 2014; 120: 2264–2271.

60. 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–v30.
61. Vehmanen L, Elomaa I, Blomqvist C, *et al*. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. *J Clin Oncol* 2006; 24: 675–680.
62. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; 386: 1353–1361.
63. Deprez S, Vandenbulcke M, Peeters R, *et al*. Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. *J Clin Oncol* 2014; 32: 2031–2038.
64. Phillips KA, Regan MM, Ribi K, *et al*. Adjuvant ovarian function suppression and cognitive function in women with breast cancer. *Br J Cancer* 2016; 114: 956–964.
65. Schmid D and Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014; 25: 1293–1311.
66. Cardoso F, Costa A, Senkus E, *et al*. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol* 2017; 28: 16–33.
67. Van Sprundel TC, Schmidt MK, Rookus MA, *et al*. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. *Br J Cancer* 2005; 93: 287–292.
68. Metcalfe K, Gershman S, Ghadirian P, *et al*. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ* 2014; 348: g226.
69. Paluch-Shimon S, Cardoso F, Sessa C, *et al*. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO clinical practice guidelines for cancer prevention and screening. *Ann Oncol* 2016; 27(Suppl. 5): v103–v110.
70. Moyer VA and U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2012; 157: 900–904.
71. Gampenrieder SP, Rinnerthaler G and Greil R. SABCS 2016: systemic therapy for metastatic breast cancer. *Memo* 2017; 10: 86–89.
72. Robson M, Goessl C and Domchek S. Olaparib for metastatic germline BRCA-mutated breast cancer. *N Engl J Med* 2017; 377: 1792–1723.
73. OlympiA. Olaparib as adjuvant treatment in patients with germline BRCA mutated high risk HER2 negative primary breast cancer. https://clinicaltrials.gov/ct2/show/NCT02032823 (accessed November 2017).