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

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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

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. 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. 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. 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. Unique biology and more aggressive phenotypes of tumours arising in younger patients, beyond traditional immune-histochemical profiles, have been suggested, 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. An additional challenge...
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, 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. 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.

**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. 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). 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.

**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 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.

**Early breast cancer**

*Locoregional therapy: surgery and radiation therapy*

Although young age at BC diagnosis is an independent risk factor for local recurrence, 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). 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. 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. 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. 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. 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 confirm previous data and support the current guidelines. In summary, low-risk patients (e.g. small tumour, low proliferation/grade, node negative) have excellent outcomes with tamoxifen alone for 5 years. 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. 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 (ABCDSG-12) 3 years of anastrozole or tamoxifen plus the GnRHa goserelin were associated with excellent 10-year outcomes. When indicated, OFS can be started together or after chemotherapy, with no detrimental effect of concomitant administration, which can also contribute to fertility preservation. 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). From a clinical perspective, it should be kept in mind that nonadherence to endocrine therapy in premenopausal women is about 20% and is associated with reduced overall survival. 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 TREAT), comparing degarelix (a GnRH antagonist) versus triptorelin in combination with letrozole. As of today, neoadjuvant endocrine therapy is not recommended in young women.

**Chemotherapy.** Gene expression signatures, such as MammaPrint or Oncotype DX, 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...
support the indication to avoid chemotherapy in these patients, given the very good outcome with optimal endocrine therapy alone. 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, 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. As a general rule, sequential chemotherapy regimens have the same efficacy of simultaneous combination schedules but have a better safety profile.

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. Young age does not seem to affect response in HER2-positive 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. The impact on survival is controversial and toxicity is increased but, given the dismal outlook of triple-negative patients, 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, 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.

**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    | 452      | NA            | NA              | 58***    |
|             | BluePrint     |          |               |                 |          |
|             | TargetPrint   |          |               |                 |          |
| MINDACT     | MammaPrint    | 6693     | 112           | 2104            | 55       |

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

As for 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, using the same criteria as for older patients. For adjuvant therapy, the benefit of trastuzumab is independent of age; 1 year of trastuzumab is associated with increased survival. The subcutaneous administration of trastuzumab could be particularly attractive in young women who need to fit BC treatment into complex personal/familial commitments.

The additional absolute benefit of adjuvant pertuzumab and neratinib 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. 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 amenorrhea59 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 guidelines27 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 described63; the effects of endocrine therapy on cognitive function remain poorly understood, as also shown in the Co-SOFT sub-study 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 guidelines8 strongly suggest implementing dedicated
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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, 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-penetration 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. 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.

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.

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. 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. The results of the OlympiA trial, assessing olaparib as maintenance therapy after standard treatment in the adjuvant setting, are expected not earlier than 2020.

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.

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