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Position Paper

The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer

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Abstract EUSOMA (The European Society of Breast Cancer Specialists) is committed to writing recommendations on different topics of breast cancer care which can be easily adopted and used by health professionals dedicated to the care of patients with breast cancer in their daily practice.

In 2011, EUSOMA identified the management of young women with breast cancer as one of the hot topics for which a consensus among European experts was needed. Therefore, the society recently organised a workshop to define such recommendations. Thirteen experts from the different disciplines met for two days to discuss the topic. This international and

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multidisciplinary panel thoroughly reviewed the literature in order to prepare evidence-based recommendations. During the meeting, two working groups were set up to discuss in detail diagnosis and loco-regional and systemic treatments, including both group aspects of psychology and sexuality. The conclusions reached by the working groups were then discussed in a plenary session to reach panel consensus. Whenever possible, a measure of the level of evidence (LoE) from 1 (the highest) to 4 (the lowest) degree, based on the methodology proposed by the US Agency for Healthcare Research and Quality (AHRQ), was assigned to each recommendation.

The present manuscript presents the recommendations of this consensus group for the management of young women with breast cancer in daily clinical practice.

1. General introduction and methods

For the purpose of these guidelines, The European Society of Breast Cancer Specialists (EUSOMA) working group decided to define "young women" as women under the age of 40. We acknowledge that both biology and endocrine milieu are a continuum and that age group definition will always be arbitrary. However, women under the age of 40 have specific issues related to fertility preservation, pregnancy and lactation that deserve a different approach and management from slightly older pre- and peri-menopausal women.

The risk of breast cancer is age-dependent. The probability of developing breast cancer is equal to 0.04% per year for average risk women between age 30 and 39 and increases to >10% per year in those over 80 years.[1]

Breast cancer in women under 40 years is not a common condition (Fig. 1). However, a dramatic increase in the number of breast cancers diagnosed in premenopausal women has been reported in several countries. In the United States, 5.5% of breast cancers occur in women younger than the age of 40 years.[2]

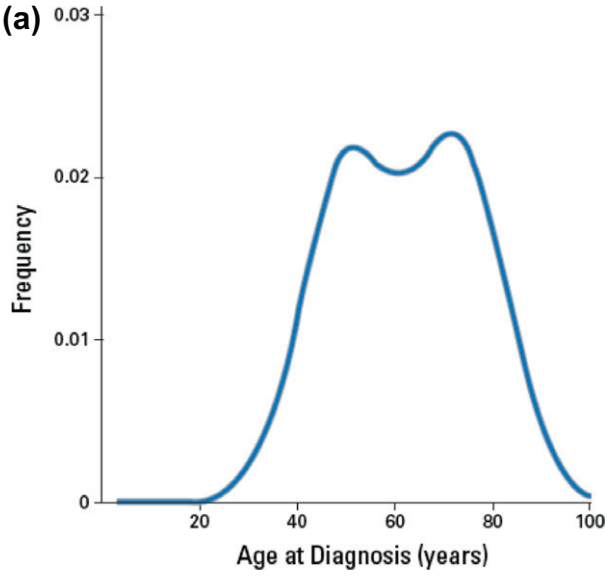
Approximately one in forty women diagnosed with early breast cancer is very young (<35 years). Breast cancer in young women is associated with a positive family history and gene mutations more frequently than in older women.[2]

In addition, the working group also decided to focus on recommendations specific for this age group. Yet, we still want to emphasise those general recommendations that do not necessarily differ with age but are particularly important for young women. We, thus, want to avoid over- and under-treatment based more on physicians' concern than on actual evidence.

During the review of all available evidence, we realised that there are many issues regarding the management of young women for which evidence is lacking. Such issues are, therefore, highlighted in the article as research priorities.

Issues of body image, sexuality, fertility and lactation must be discussed with young women with breast cancer. These issues are of course important for women of all ages albeit the actual importance is weighted on an individual basis that is not necessarily related to age. Issues of fertility and lactation are, by definition, related to age and menopausal status even outside breast

(a)



(b)

Age	Annual incidence/100 000 women
<20	0.1
20-24	1.4
25-29	8.1
30-34	24.8
35-39	58.4
40-44	116.1
45-49	198.5

Fig. 1. (a) Bimodal distribution of breast cancer according to age. (b) Annual incidence of breast cancer according to age categories. Modified from Pagani O, Goldhirsch A. Breast cancer in young women: climbing for progress in care and knowledge. (a) Anderson WF, et al. J Clin Oncol 2009;27(32):5308–11. Reprinted with permission from ASCO (American Society of Clinical Oncology). (b) Women's Health 2006;2(5):717–32.

cancer. In particular, fertility issues must be discussed before the start of any type of anticancer treatment, since treatment consequences may be irreversible and there is a predefined time schedule specific to each fertility preservation intervention that may also impact on anticancer therapy. All these issues must continue to be discussed throughout follow-up.

Age has been shown in several studies to be an independent adverse prognostic factor for women with a diagnosis of breast cancer.[3–8] There is a continuous linear effect, with a 4% decrease in distant recurrence and 6% in local recurrence for every additional year of age.[9] There are also data showing a higher risk of contralateral BC in young women,[10] in particular in BRCA mutation carriers[11] and increased mortality in young women.[12]

While some preliminary studies suggest that the distribution of the different biological subtypes of breast cancer is different in young women with a higher prevalence of triple negative and Human Epidermal Growth Factor Receptor 2 (HER-2)+ disease[7,8], a clear molecular characterisation of breast cancer in these patients is lacking and is a RESEARCH PRIORITY. In addition, it should be recognised that there are some rare histological subtypes such as "juvenile secretory adenocarcinoma" that are more frequent in the very young women. Despite the fact that they are triple negative their prognosis is good.

2. Screening, diagnosis and staging

2.1. General considerations

The aim of this section of the paper is to evaluate the currently recognised radiological imaging modalities (mammography, ultrasound and magnetic resonance) for diagnosis and staging of breast cancer. To date, there is no evidence in the literature suggesting clinical utility of other emerging diagnostic tools in both diagnosis and local staging of breast cancer.

For young women, due to the intrinsic difficulties in diagnosis, imaging evaluation of breast abnormalities should be done by experienced professionals, preferably in departments of radiology with experience on breast diagnostic and interventional procedures. In addition, when suspicious breast abnormalities are identified, fast diagnosis is the highest priority. With regard to the timing of imaging, if not urgent, mammography should preferably be performed during the first 2 weeks of the menstrual cycle while ultrasound can be performed at any time point. Magnetic resonance imaging (MRI) should be performed in the second week of the menstrual cycle (day 6–13 counting from the first day of bleeding), and should follow the recommended technical requirements.[13] It should also be noted that imaging is not influenced by hormonal contraception.

2.2. Screening

2.2.1. Women at average risk

At the present time, mammography is the diagnostic modality of choice for screening for early breast cancer.[14,15] The sensitivity of mammography in women over the age of 50 has been estimated to be around 85% (range 68% to >90%) while it was reported to be lower (range 62–76%) in women between 40 and 49 years.[16] The advent of full-field digital mammography suggests a further positive clinical impact on early detection of breast cancer.[17] Studies comparing the diagnostic performance of full-field digital mammography with screen-film mammography in a corporate screening, showed a significantly higher cancer detection rate and positive predictive value for full-field digital mammography, especially in women under the age of 50.[18] Results from randomised clinical trials (RCTs) showed that screening mammography reduces the number of deaths from breast cancer in women between 40 and 74 years of age.[19,20] A recent systematic analysis of major RCTs showed that screening mammography provides an average mortality reduction of about 19% with its major impact (mortality reduction of 30%) in the age group of 49–59 years.[21] Screening programmes must consider the incidence of the disease, the performance of the diagnostic tests as well as the costs to both patients and society. The low incidence of sporadic breast cancer before the age of 40 and the suboptimal performance of diagnostic modalities in these women justify the absence of trials investigating not only the efficacy but also the feasibility of breast cancer screening programmes in women under 40 years of age. In addition, studies conducted in women under the age of 40 years not only failed to show a benefit from regular screening mammography but also demonstrated high recall rates, high rates of additional imaging and low cancer detection rates.[22] The efficacy of a baseline mammogram for women at average risk at the age of 35–40 years to provide a comparison image available when regular screening begins at the age of 40 years or older, was tested in the past, yet there was no sign of benefit from such a baseline screening.[23]

Breast augmentation is increasingly performed in young women for cosmetic purposes. The presence of breast implants does not represent a risk factor. Several case control and cohort studies have not shown an increased risk for breast cancer due to augmentation mammoplasty.[24] To date no studies have investigated screening programmes or imaging surveillance in aesthetically augmented women under 40 years who are at average risk. There are some data suggesting that the presence of implants may lead to a loss of 28–49% of the breast on mammographic view.[25] The sensitivity of a screening mammography in asymptomatic women is lower in women with breast augmentation in comparison to those

without (45.0% versus 66.8%); yet, the specificity is slightly higher in women with augmentation (97.7% versus 96.7%).[26] It was reported that – at time of diagnosis – breast cancers are more frequently palpable in augmented women than in those without implants (75% versus 54%).[27] This observation raises the hypothesis that the presence of breast implants may lead to a delayed diagnosis with all its consequences. Young women planning to have a breast augmentation surgery should be specifically informed about this issue. However, published studies confirmed that prognosis, disease-free time and survival rates are similar between augmented and non-augmented women with breast cancer.[26–28]

No evidence exists for recommending periodic contrast-enhanced MRI in women at average risk, both with or without cosmetic breast implants.[13] The available evidence for the benefit of breast self examination (BSE) is limited and mostly relates to increased breast health awareness.[14,15]

2.2.1.1. In summary.

- Regular breast self-examination and clinical breast examination should be recommended for all the women at average risk under 40 years of age. Women also need to be informed about the limitations and risks of breast examination. The ideal time for breast examination is after menstruation (level of evidence (LoE) expert opinion).
- The panel emphasises that any new breast abnormality in young women should be thoroughly investigated (imaging, needle biopsy), even though the incidence of breast cancer is lower in this age group, to avoid misdiagnosis and delayed diagnosis, and importantly to minimise unnecessary surgical intervention for non-malignant conditions.
- Adequate information about genetic counselling and imaging surveillance programmes should be provided to all young women with a strong family history of breast cancer (LoE expert opinion).
- There is no evidence to recommend regular diagnostic surveillance in augmented and non-augmented women at average risk under 40 years of age (LoE III).
- A pre-operative diagnostic check, including clinical examination, mammography (if the women are between age 35 and 40 years) and/or ultrasound is suggested in women at average risk under the age of 40 years, undergoing aesthetically breast augmentation (LoE expert opinion).

2.2.2. High-risk women

In 2010, EUSOMA published a paper evaluating the available evidence regarding clinical value of and indications for breast MRI.[13] This paper reported the results of all the cohort studies investigating the diagnostic performance of different imaging modalities in the surveillance of high-risk women. Because no significant modifications have occurred since that publication, we summarise these EUSOMA recommendations and refer to that particular paper for more detailed information.

2.2.2.1. In summary.

- Women with a family history suggesting an inherited predisposition to breast cancer should have their risk assessed by an appropriately trained professional group (e.g. genetic counselling) (LoE expert opinion). If found to be at high risk (20–30% lifetime risk or greater), these women should be given oral and written information regarding their risk and the risks and benefits of mammography and MRI screening or alternative risk-reducing interventions; if these women accept to be screened by MRI, they should be informed about screening intervals and logistics (LoE expert opinion). Lifetime risk thresholds for including women in surveillance programmes with annual MRI may be determined on the basis of regional or national considerations reflecting an area-specific cumulative risk in the general population, resource availability and practical feasibility (LoE expert opinion).
- High-risk breast screening utilising MRI should be conducted only by a nationally/regionally approved and audited service or as part of an ethically approved research study. Periodical audits should be undertaken to ensure that high sensitivity is achieved and that the early recall rate (MR imaging more frequent than annually) is less than 10%, and to monitor detection rate, needle biopsy rate and interval cancers (LoE expert opinion).
- Annual MRI screening should be available starting at age 30. Starting annual screening before age 30 may be discussed, such as in BRCA1 or BRCA2 mutation carriers (starting between age 25 and 29 years) and TP53 mutation carriers (starting at age 20) (LoE IIb).
- Annual MRI screening should be offered to:
  - o BRCA1, BRCA2 and TP53 mutation carriers'.
  - o Women at 50% risk to be carriers of BRCA1, BRCA2 or TP53 mutation (first-degree relatives of mutation carriers) (LoE-Ib).
  - o Women from families not tested or inconclusively tested for BRCA mutation with a 20–30% lifetime risk or greater (LoE-II).
  - o Women with prior mantle radiotherapy before age 30 (e.g. for Hodgkin disease), starting 8 years after their treatment (LoE III).
  - o Women at high risk and who were already diagnosed and treated for breast cancer should be included in screening programmes including MRI (LoE-IIb).
- Women of any age undergoing prophylactic mastectomy should have a MRI examination within the 3 months before surgery to screen for occult breast cancer (LoE expert opinion).

- Screening mammography should not be performed in high-risk women below 35 years as there is no evidence that the benefits outweigh the risks in this young age group (LoE expert opinion).
- In TP53 mutation carriers of any age, annual mammography can be avoided based on the discussion of risks and benefits from radiation exposure (LoE expert opinion).
- Annual mammography may be considered for high-risk women starting at age 35 years (LoE III).
- If annual MRI is performed, additional screening with breast ultrasound (US) and clinical breast examination (CBE) are not necessary as there is no evidence of any benefit added to MRI (LoE II). They are however recommended in women under 35 years who do not tolerate or have contraindications to MRI or gadolinium-based contrast administration (LoE expert opinion).
- Cases requiring workup after MRI should be initially assessed with conventional imaging – re-evaluation of mammography and targeted US (LoE II). In cases of suspicious findings solely detected by MRI, MR-guided biopsy localisation should be performed (LoE I).
- Risk factors such as prior diagnosis of invasive breast cancer or Ductal Carcinoma In Situ (DCIS), atypical ductal hyperplasia, lobular intraepithelial neoplasia, heterogeneous or dense breasts on mammography, if not associated with other risk factors, do not confer an increased risk justifying the use of screening MRI (LoE III).

2.3. Diagnosis

The diagnosis of breast cancer in young women may be difficult because of dense breast tissue, lack of previous routine breast screening and shorter tumour doubling times. For this age group, due to these intrinsic difficulties in diagnosis, imaging evaluation of breast lesions should only be done by experienced professionals. Breast cancer in young women more frequently presents with a higher disease stage and poorer prognosis than in older women. In fact, >90% of young women with breast cancer are symptomatic, but it is important to consider that most of the young women presenting with breast symptoms do not have breast cancer.

Only a few studies in the literature have investigated the diagnostic performance of imaging in young women with breast symptoms. The cancer detection rate of mammography in symptomatic women under 40 years ranges in the literature between 55% and 86%.[2] In a retrospective study investigating 239 cases of breast cancer in women less than 40 years during a period of 10 years, Foxcroft and colleagues reported that 70.8% of the subjects had a mammographic abnormality which was correctly classified as malignant in 52.8%. Mammography was the only satisfactory imaging modality for demonstrating small clusters of microcalcifications.[29] Houssami and colleagues retrospectively evaluated the diagnostic performance of conventional imaging in 240 patients with breast cancer of whom 64 were under 40 years. In this subgroup, the sensitivity of mammography ranged between 69% and 76% while the specificity was between 83% and 96%.[30]

Since ultrasound is less affected by breast density, it shows a better diagnostic performance than mammography in symptomatic young patients. In the series of Foxcroft, it showed an abnormality in 95.5%, which was correctly classified as benign or probably benign in 25.5% of the cases. In the study of Houssami, the breast cancer detection rate of ultrasound was 84% with a specificity between 84% and 91%.

These results, associated with the potential damage from ionising radiation exposure, suggest that ultrasonography could be the primary imaging test in symptomatic women younger than 40 years (LoE Expert Opinion). As in older women, ultrasound guided biopsy should be performed if a sonographically suspicious finding is detected. Since malignant lesions may mimic benign lesions in high-risk women, ultrasound guided biopsy should also be considered when a probably benign sonographic finding is detected in these patients. The subsequent use of mammography should be decided on the basis of the biopsy result. If the result is positive or inconclusive, mammography is indicated to define the extent of the disease or to add further diagnostic information, respectively. If ultrasound is negative, the potential benefit of a clinical biopsy and/or mammography is related to the degree of clinical suspicion and the breast cancer prevalence.

As in older women, accurate pre-surgical local staging of breast cancer is required to ensure a complete excision of the disease. In the study of Foxcroft, mammography was unreliable for diagnosing multifocality while ultrasound was useful in the detection of other disease foci. In addition, ultrasound was also more reliable in the assessment of the size of the lesion as confirmed by pathology. These findings suggest that bilateral breast ultrasound, including the axilla, should be performed in the diagnostic workup of all breast cancer patients less than 40 years.

The role of MRI in the preoperative setting is still controversial. MRI is recognised as the most sensitive modality both in identification and local staging of breast cancer[13] but shows limitations in terms of variable specificity[31] MRI shows a better diagnostic performance in staging invasive lobular breast cancer[32] and in identifying contralateral disease foci.[33] It has been shown that MRI is more sensitive than conventional imaging in the evaluation of an extensive intraductal component (EIC) and DCIS without microcalcifications, both of which are more frequent in young and in high-risk women.[34]

MRI also has a higher negative predictive value (97% for a lesion of $\geqslant 2$ cm) for measuring the distance between nipple/areolar complex and the lesion itself,[35] which is useful for planning nipple sparing mastectomy. On the other hand, the main concerns regarding MRI are its unclear impact on clinical outcome and the potential risk of surgical overtreatment. Two randomised prospective trials evaluated the impact of preoperative MRI on surgical outcome.[35,36] In both trials, the introduction of MRI in the management of patients undergoing surgery did not lead to a reduction of re-excision rate. Moreover, in the COMICE trial[35] the mastectomy rate was significantly higher in the arm with MRI with respect to that without (7% versus 1%). Only retrospective studies investigated the impact of MRI on long-term clinical outcomes. In the study of Fischer et al.[37] the IBTR rate at a follow-up of 40 months was 1.2% for the 86 patients who underwent pre-operative MRI with respect to 6.8% for the 133 without pre-operative MRI. Conversely, the studies of Solin et al.[38] and Hwang et al.[39] reported no differences in IBTR rate between patients with and without preoperative MRI. In brief, even though MRI is the most sensitive modality in the identification of breast cancer, at present there is no evidence that detection of additional malignant foci with MRI before treatments translates into patient benefit from both surgical care and prognosis.[31,40,41] However, it should be taken into account that published evidence does not reflect breast cancer patients under 40 years.[3,12]

2.3.1. In summary

- As in older women, young women presenting with breast symptoms and a strong suspicion of breast cancer should be evaluated by triple assessment (clinical examination, imaging and cytological/histological examination) in order to exclude or confirm a diagnosis of cancer (LoE IIa) When a palpable abnormality is present, patients should have ultrasound followed, if required (in case of Breast Imaging-Reporting And Data System (BIRADS) 3–5), by core biopsy and/or fine needle aspirate cytology (LoE IIa). The subsequent use of mammography should be based on the biopsy result (LoE expert opinion). If the result is positive or inconclusive, mammography is indicated to define the extent of disease or to add further diagnostic information (LoE expert opinion).
- If the ultrasound is negative (BIRADS 1–2), the benefit of a clinical biopsy and/or mammography is related to the degree of clinical suspicion and the breast cancer prevalence (LoE expert opinion).
- As in older women, a lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have a histopathological confirmation of malignancy before any surgical procedure takes place. Immunohistochemical biomarkers (oestrogen and progesterone receptors status, HER-2 status and proliferation (e.g. Ki67)) should be measured on all invasive primary breast cancers, ideally in both core biopsy and surgical specimen.
- As in older women, in cases of possible or scheduled primary chemotherapy, immunohistochemical biomarkers (oestrogen receptor (ER), partial response (PR), HER-2 and proliferation) should be measured in the core biopsy before the beginning of medical treatment.
- If malignancy is diagnosed, bilateral ultrasound of the breast and axilla should be performed for local staging of the disease (LoE IIa).
- There is no evidence to recommend routine preoperative MRI in young women with breast cancer. Indications for MRI are the same as for older women, including patients with newly diagnosed invasive lobular cancer (LoE IIa), patients at high-risk for breast cancer (LoE IIb), patients with a size discrepancy of more than 1 cm between mammography and ultrasound and an expected impact on the treatment decision (LoE IIb). Because of the special characteristics of young patients, multidisciplinary evaluation of the advantages and disadvantages of pre-operative MRI taking into account the planned surgical approach, is recommended (LoE expert opinion).
- Additional lesions identified by MR that may modify the already planned surgical treatment should be initially assessed with conventional imaging (re-evaluation of mammography and targeted US) and verified by imaging-guided biopsy (LoE II). In cases of suspicious findings solely detected by MRI, MR-guided biopsy localisation should be performed (LoE I).

2.4. Staging

There is no evidence to support routine staging for metastatic disease merely based on patient age. In young women with breast cancer, the recommended staging, including assessment of axillary nodal status, does not differ from that in all other older patients.

3. Management of pre-invasive disease

3.1. Chemoprevention

The panel agrees that chemoprevention treatments should preferably be administered within study protocols.

3.2. Pre-invasive lesions (DCIS–DIN) Ductal Intraepithelial Neoplasia

3.2.1. Counselling

Counselling in young women at increased risk for invasive recurrence or breast cancer should include family planning issues (fertility and contraception), even at diagnosis of a pre-invasive lesion.

3.2.2. Surgery

The panel agrees that the surgical treatment of young patients presenting with intraductal neoplasia should in general not differ from that in older patients. Nevertheless, young age is a variable that independently increases the local recurrence rate.[42] Therefore, the lesion must be removed with adequate surgical margins of at least 2 mm. Achievement of clear margins (at least 2 mm) is strongly recommended. For those women who do not want to undergo re-excision or mastectomy in cases of close proximity to or focal positivity of margins, information needs to be given concerning the increased risk of local recurrence. As there is lack of data regarding safety of skin-sparing mastectomy in young patients, careful preoperative evaluation must be performed in order to properly select patients suitable for skin-sparing mastectomy, especially with nipple-areola complex (NAC) preservation. In such patients, evaluation of the retro-areolar margin, both intra-operatively by frozen section and post-operatively, is recommended. There is NO evidence for the necessity to perform prophylactic contralateral surgery in young women with unilateral DCIS or LIN (lobular in situ neoplasia) unless they are BRCA positive.

As in older patients, sentinel lymph node biopsy (SLNB) is not routinely indicated in young patients with intraductal neoplasia. Nevertheless, it should be considered whenever there is a substantial risk of underestimating the real disease extent by the pre-operative diagnosis (for example, a large cluster of microcalcifications or extensive multifocal lesions) in order to avoid the risk of a second operation in the event that invasive disease is diagnosed at the final histology. The panel agrees that SLNB is strongly recommended in all patients undergoing mastectomy.

3.2.3. Radiotherapy

The radiotherapy trial evidence is supported by retrospective subgroup analyses according to age in large prospective trials. There is NO role for post-mastectomy radiation therapy in cases of DCIS with clear margins. However, it should be noted that older evidence refers to mastectomy that almost invariably included excision of the NAC. There is NO current evidence regarding preservation of the NAC, particularly not for young women with their known high-risk of recurrence. For this reason, data are urgently needed and this topic thus constitutes a RESEARCH PRIORITY. The current lack of evidence means that the issue of post-mastectomy radiotherapy after preservation of the NAC requires a full discussion and decision by the multidisciplinary team with psychosocial issues considered.

After breast conserving surgery, whole breast radiotherapy (WBR) should be given (LoE I). An additional radiation dose to the tumour bed (boost) should be considered or entry into an appropriate prospective clinical boost trial[43] (LoE II). There is NO evidence to support withholding radiotherapy after breast conserving therapy for DCIS in young women. It should be noted, however, that all studies addressing this point predominantly looked at older women. Partial breast irradiation (PBI), such as intra-operative radiotherapy (IORT) or other techniques, is not recommended as there are no data for DCIS. All randomised data on PBI so far refer to invasive cancers.

4. Surgery

4.1. Breast surgery

Young age is an independent risk factor for increased local recurrence after breast conserving surgery and radiotherapy without affecting overall survival.[44,45] Some of the histopathological characteristics such as larger size, higher grade, presence of peripheral extensive intraductal component, vascular embolies and lymphoid stroma have been related to a higher risk of local recurrence. Nevertheless, the panel agrees that surgical treatment of young patients presenting with invasive cancer – while being tailored to the individual patient – should in general not differ from that of older patients. Breast-conserving surgery followed by radiotherapy offers the same survival benefits as modified radical mastectomy in women with stage I or II breast cancer[46,47] and should therefore be considered as the first option whenever suitable This may be particularly relevant for young women with breast cancer. Modern breast conserving surgery is aimed to remove the cancer while excising the smallest possible volume of tissue. Besides, and especially in young women, aesthetic outcomes and concept of female identity need to be taken into account. Skin-sparing and nipple-sparing mastectomy techniques seem to be ideal options both from an oncological and a cosmetic point of view.[48] Oncoplastic repair techniques should be offered to patients treated by breast conserving surgery in order to maximise cosmetic results whenever an obvious postoperative asymmetry can be estimated (LoE IC). Immediate breast reconstruction after mastectomy offers the same survival benefits as mastectomy without reconstruction (LoE IC). The options of immediate breast reconstruction should be discussed prior to surgery, ideally by a multidisciplinary team, in order to consider the issues related to possible indications for post-mastectomy radiotherapy.

In young women with the diagnosis of either invasive disease or pre-invasive lesions, who are not BRCA mutation carriers, there is no evidence for improved overall survival by performing risk-reducing bilateral mastectomy. The risk for contralateral disease in young women with a family history who are not BRCA carriers does not seem to be substantially increased.[49] Nevertheless, if, after receiving proper and thorough information based on the available data and on an appreciation of

the possible surgical complications and consequences, the patient still shows a strong motivation to undergo prophylactic surgery, this preference should be respected. In this situation, adequate time should be given to the patient to allow the proper understanding of all information and to avoid "rush decisions"

4.2. Loco-regional therapy in high-risk women

Management of young high-risk women with breast cancer is very complex and should therefore be performed within specialised centres. The evidence regarding the necessity of ipsilateral mastectomy is inconclusive in this subset of patients[50,51] and, therefore, breast conservation remains a suitable option after a thorough discussion with a patient motivated to retain her breast. Radiation does not lead to increased toxicities in BRCA mutation carriers.[52] In known BRCA mutation carriers, risk-reducing surgery, such as bilateral mastectomy and oophorectomy, needs to be discussed as part of the *initial* treatment concept. Rapid BRCA testing is indicated if knowledge of the mutation status would impact on the BC treatment plan (e.g. radiotherapy/reconstruction). Nevertheless, if the patient needs more time to decide about any possible prophylactic surgery or if a rapid test is not achievable, stage-adapted treatment of the breast cancer should be performed while postponing any potential prophylactic procedure to a second stage.

4.3. Surgical treatment of the axilla

Sentinel lymph node biopsy (SLNB) is, worldwide, considered to be the first choice of axillary staging in patients with early breast cancer. There is no evidence of an increased false negative rate or a worse outcome in young patients undergoing (SLNB).[53] In young women, indications for (SLNB) are the same as in older patients. The procedure should be performed according to national and institutional guidelines and young age *per se* is not a reason to prefer axillary dissection over (SLNB). In pregnant patients with breast cancer, lymphoscintigraphy and (SLNB) can be performed as low injected doses are utilised and dosimetric studies confirm negligible effects on both the mother and the foetus.[54,55] Nevertheless, the panel strongly recommends that management of pregnant patients with breast cancer is performed in specialised centres and involving the multidisciplinary team.

Surgical management of patients with minimal Sentinel Lymph Node (SLN) involvement is still matter of debate. In particular, no data are available for this specific topic in young women. When isolated tumour cells are found in the SLN, general agreement is not to perform Axillary Lymph Node Dissection (ALND). At the moment, the trend is moving towards minimising axillary surgery with sparing the axillary nodes even in the presence of micrometastases in the SLN.[56] Recent data from a randomised trial[57] enrolling patients of any age showed that ALND did not significantly affect disease-free or overall survival of patients with clinical T1–T2 cN0 breast cancer and at the most two positive SLN treated with lumpectomy, adjuvant systemic therapy and tangential-field whole breast irradiation. Therefore, avoidance of axillary dissection can and should be discussed even in young patients with involved SLN who will undergo breast conservation with whole-breast radiotherapy and appropriate systemic treatment.

5. Adjuvant radiotherapy

High quality standards are mandatory in order to minimise side effects and maximise benefits. This is particularly relevant in young women with their potential long-term survival. Treatment planning should be performed using CT scan imaging and three-dimensional dosimetric systems. Doses to the breast and tumour bed should be homogenised within recommended tolerance margins, and doses to organs at risk (mainly ipsilateral lung, heart and contralateral breast) should be kept below consensus thresholds in all instances.

In patients with early breast cancer, adjuvant irradiation is indicated after breast conserving surgery (LoE IA). Adjuvant chest wall radiotherapy after mastectomy should be offered to patients with early invasive breast cancer and a high risk of local recurrence including where there are four or more positive axillary lymph nodes or involved resection margins (LoE IA). Until data from a large ongoing randomised trial[58] become available, radiotherapy after mastectomy should be discussed with patients with 1-3 positive nodes (LoE IA). Young patients should be informed about the high local recurrence risk if radiotherapy is avoided[59] and about the evidence for the advantages of radiotherapy regarding reduction of local recurrence and improvement in overall survival.[60] This must be balanced with information on the potential long-term toxicities. Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion). The target volume of percutaneous adjuvant radiotherapy encompasses the entire breast and the adjacent thoracic wall. The dose amounts to approximately 50–50.4 Gray fractionated in the conventional manner (1.8–2.0 Gray per fraction) with an additional local boost (LoE IA). Alternative fractionation regimes such as those utilising hypofractionation with a higher dose per fraction enabling the use of fewer fractions should – at the present time – be considered with caution as the randomised trials of hypo-fractionation included few younger women[61] (LoE IB). An additional boost to the site of local excision must be offered to young patients with early invasive breast cancer following breast-conserving surgery with

clear margins and whole breast radiotherapy, particularly to those at high risk of local recurrence[62] (LoE IIA). Axillary radiotherapy should be discussed on an individual basis in the multidisciplinary team and will depend on surgical, histopathological and where available, radiological findings (LoE IA). Partial breast irradiation (PBI), by whatever method, is best delivered within the protocol of a clinical trial until the results of all current trials[63] are reported or are more mature.

Young age is a recognised risk factor increasing local relapse after mastectomy.[64] Therefore, patients should be informed prior to surgery about the possibility of undergoing post-mastectomy radiotherapy in order to facilitate any necessary discussions with the plastic surgeon about options for immediate breast reconstructions and their potential limitations. Young age is one of the risk factors for involvement of the internal mammary chain (IMC). Evidence (LoE II) from retrospective generally under-powered series suggests that IMC radiation is an option. It will remain such until mature results from large clinical trials are available. However, side effects from IMC irradiation may be severe if high standards of radiotherapy are not followed and, in particular, radiation doses to the major vessels and coronary arteries must be kept to absolute minima. It is imperative that long-term side effects are carefully balanced against published benefits.

6. Imaging and clinical follow-up of patients with breast cancer

In women treated for sporadic breast cancer by breast-conserving surgery and adjuvant therapy, the risk of ipsi- or contra-lateral recurrence after 10 years is low at about <5%.[65] Young age represents an unfavourable factor in terms of clinical outcomes. In fact, for women diagnosed at the age of 40 years or less, the risk of a local recurrence at 5 years is equal to 10%. Conversely, in patients treated by mastectomy, the risk of local relapse is not affected by the age at diagnosis.[44,60] Because the risk of ipsi- or contra-lateral relapse is constant over time, at least for 14 years, routine long-term follow up is recommended.[66]

In terms of imaging, annual mammography (followed by ultrasound depending on breast density and/or presence of post-surgical and post-radiotherapy changes) represents the standard of care for follow-up of patients treated by breast-conserving surgery. However, a study on accuracy and outcomes of screening mammography in 58,870 women with a personal history of early-stage breast cancer showed that in patients under 40 years the risk of a second breast cancer within 1 year of screening is around 2% with respect to 0% of those without a personal history of breast cancer. The same study demonstrated that screening mammography in younger women detects early-stage second breast cancer but shows lower sensitivity (51% in patients <50 years versus >64% in those ⩾50 years) and higher interval cancer rate (7.5/1000 screens in patients <50 years versus >3.7/1000 screens in those ⩾50 years).[67]

Ultrasound could represent the first imaging modality after clinical examination in patients treated by mastectomy. Diagnostic performance of ultrasound in the identification of a relapse after mastectomy is higher than that of clinical examination (91% versus 79%) and mammography (91% versus 45%).[68]

As in older women, there is not enough evidence to support the routine use of MRI in following up young patients treated for sporadic breast cancer. In particular, there are no trials demonstrating improved prognosis after early detection of a recurrence by MRI. Currently, MRI examination may be useful if conventional imaging results are inconclusive for the differential diagnosis between scar and recurrence and where a needle biopsy cannot be performed. However, MRI imaging should be the first choice in breast cancer for patients at high genetic-familial risk.[13]

Regional nodal recurrence is not a frequent condition and occurs in only about 1–16% of patients with prior breast cancer. It is related to poor prognosis. Clinical examination and mammography show a high false negative rate in the evaluation of the axillary or supraclavicular region. A large retrospective study, evaluating 1817 patients after breast-conserving surgery demonstrated that ultrasound is useful in the identification of nodal recurrence in asymptomatic subjects, with an accuracy approaching 99%.[69] In this study, the false negative rate of ultrasound was significantly lower compared to that of clinical examination and mammography (23% versus 39% and 23% versus 100%, respectively).

6.1. Organ staging

There is no evidence for any differences in follow-up examinations or imaging based on patient age alone.

6.1.1. In summary

- Annual mammography (followed by ultrasound depending on breast density and/or presence of post-surgical and post-radiotherapy changes) represents the standard of care in follow-up of patients treated for sporadic breast cancer (LoE II).
- Ultrasound could represent the first imaging modality after clinical examination in patients treated by mastectomy (LoE expert opinion).
- Ultrasound of the axillary and supraclavicular region is useful in identification of nodal recurrence (LoE expert opinion) in both symptomatic and asymptomatic patients.
- MRI imaging should be the first imaging of choice in patients at high genetic-familial risk and previously treated for breast cancer (LoE II).

- There is not enough evidence to support the routine use of MRI in the follow-up of patients treated for sporadic breast cancer (LoE III). MRI examination may be useful if conventional imaging results are inconclusive for differential diagnosis between scar and recurrence and where needle biopsy cannot be performed (LoE expert opinion).
- Accuracy and clinical effects of additional modalities (US and MRI) to follow-up mammography should be considered as a research priority.

7. Systemic therapy

7.1. General issues

7.1.1. Age as a prognostic factor

All classical studies dealing with factors predictive of general prognosis in localised breast cancer have shown young age to be a constant adverse general prognostic factor,[70] and this was thought to be related to a specific biology of the tumour.[71] Recent studies integrating modern multi-gene biology fail to demonstrate such an independent adverse prognostic effect: age disappears as a prognostic factor when a multigene assay is included in all such major studies either using Oncotype-DX™,[72,73] MammaPrint®[74] or Genomic Grade/MapquantDX®[75] (LoE II). Prospective data from the two major randomised trials MINDACT and TailorX are awaited to reassess the prognosis and benefit of chemotherapy according to age and tumour biology in the modern era.

Taking the above into consideration, young age alone should not be a reason to prescribe more aggressive therapy and the biology of the tumour should always be taken into account together with tumour burden. However, some epidemiological studies[4] suggest that young women are almost never of low risk: therefore in cases of favourable-biology, low-stage invasive breast cancer, young women should always receive at least endocrine therapy (LoE III).

Even though the available version of Adjuvant Online includes age <35 as an independent adverse prognostic factor (with a 1.5 fold factor, chosen arbitrarily) this tool should not be used alone for treatment-decision making, as it is also the case in older patients.

7.1.2. Age as a predictive factor

There are some controversial data regarding age as a determinant of benefit for adjuvant chemotherapy. In the Oxford meta-analysis, the mean annual reduction of risk of relapse attributable to chemotherapy (mainly CMF and anthracyclines) was $40 \pm 6\%$ in patients less than 40, $36 \pm 6\%$ in patients 40–49 and $23 \pm 3\%$ in patients 50–59.[60] However, when ER status is taken into account, age disappears as an independent prognostic factor for the benefit of chemotherapy with all ER-negative patients benefiting from chemotherapy at the same extent.[76]

Data with more recent regimens including taxanes are much more controversial, with some studies suggesting a higher and others a lower benefit in younger women. Obviously, these data have to be carefully interpreted, the effects observed being in part related to the degree of amenorrhoea induced by the diverse regimens.[77]

Recent data in the neoadjuvant setting suggest that young age is constantly associated with greater benefit from preoperative anthracycline–taxane-based chemotherapy[78] (LoE III). In the triple negative setting, age was the only independent predictive factor for chemotherapy response in this setting.

The identification of the optimal chemotherapy regimen for young women regarding efficacy and long-term tolerance is a RESEARCH PRIORITY.

In the adjuvant setting, the benefit of adjuvant trastuzumab appears independent of age in all published studies (LoE II).

7.1.3. General recommendations

The indications for and the choice of type of adjuvant systemic treatment for invasive breast cancer should be driven, as in other age categories, by the biological characteristics of the tumour (including steroid hormone and HER-2 receptors, proliferation and grade), the tumour stage and patient's comorbidities (LoE IA).

For the time being, the type of systemic treatment of early breast cancer is independent of BRCA or any other constitutional genetic status. However, with the development of new targeted agents, BRCA status may become more important for systemic treatment decision (RESEARCH PRIORITY).

Recommendations regarding the use of new prognostic tools such as uPA-PAI1, MammaPrint™, Oncotype DX™ and Genomic Grading in young women are similar to the general breast cancer population.

In most studies, young women are not classically identified as a high-risk group for secondary visceral morbidity of chemotherapy except ovarian (LoE II). Of note, however, in a Swedish cohort the incidence of secondary non-haematologic malignancies appears specifically elevated among women with lower age at initial diagnosis.[79] In addition, in view of the longer expected life-time of young women, particular attention should be paid to potential long-term toxicities such as secondary cancers, cardiovascular toxicity and irreversible ovarian failure with its consequences. Furthermore, bone morbidity as well as weight gain and cognitive impairment should be considered carefully in young women with long life expectancy (RESEARCH PRIORITIY).

Before any treatment decision, young women must be advised to have fertility and contraception counselling (details on Section 11)[80]

7.2. Early breast cancer

All patients with breast cancer should be discussed within the multidisciplinary team before any treatment decision making.

In patients with unifocal operable tumours too large for breast conserving surgery, downstaging with neoadjuvant systemic therapy should be considered (LoE IA). Although there has been a suggestion of higher local relapse rates after neoadjuvant chemotherapy and breast conservation, especially in young women,[81,82] there appears to be no long-term significant survival harm from neoadjuvant chemotherapy and subsequent conservative surgery in young women.[81] The NSABP B-24 study demonstrated that women <50 years was the only group benefitting long term from neoadjuvant compared to adjuvant treatment.[83]

Outside clinical trials, if adjuvant chemotherapy and radiotherapy are indicated, chemotherapy should be given first in young women, as in other age categories (LoE IA).

It is recommended to start adjuvant chemotherapy or radiotherapy within 8 weeks of completion of surgery (LoE IC).

7.2.1. (Neo)adjuvant chemotherapy

There are no evidence to recommend a specific chemotherapy regimen for young women. Therefore, as for all stage I–III breast cancer patients, the preferred regimens are standard anthracycline-based regimens with or without a taxane (LoE IA). A sequential regimen of anthracycline-based chemotherapy followed by adequately dosed CMF (oral or day 1&8 iv) or a combination of taxane and cyclophosphamide are also valid options in some circumstances.

However, as mentioned above, young age might be just the phenotype for a genetic/biologically different cancer associated with an adverse prognosis.[4,84] Accordingly, very young women should probably be treated with a standard regimen including at least an anthracycline and a taxane. The neoadjuvant Gepartrio trial demonstrated that age below 40 was a significant independent predictive factor for efficacy of a Taxotere, Adriamycin and Cyclophosphamide (TAC)-based therapy overall, and in the subgroup of triple negative breast cancer.[78] Some oncologists use dose-dense regimens more often in young women, but to date, only patients with hormone receptor-negative breast cancer have shown benefit from this approach.[85] There are several acceptable regimens recommended, for example, those suggested by the German AGO Breast Kommission.[86]

Standard duration of treatment (minimum of four and maximum of eight cycles) should also be prescribed.

Data available suggest at least equal or superior efficacy for sequential regimens over combinations (for example of anthracyclines and taxanes)[77,87,88]: Young age by itself should not be an indication to prescribe a combination of cytotoxic agents.

Despite older age being an additional risk factor for febrile neutropenia, young women have also a risk of developing (febrile) neutropenia if treated with a chemotherapy regimen associated with a risk of febrile neutropenia greater than 20%, such as TAC or dose-dense regimens.[89] According to the updated European Organisation for Research and Treatment of Cancer (EORTC) guidelines on G-CSF (granulocyte colony-stimulating factor) use, primary prophylactic G-CSF is recommended if the individual patient's risk of febrile neutropenia is 20% or higher. Secondary prophylaxis with G-CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (LoE IA).[89] Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia, independently of age.

High-dose chemotherapy with stem-cell transplantation cannot be recommended for patients with primary or metastatic breast cancer (LoE IA).

7.2.2. (Neo)adjuvant endocrine therapy

Neoadjuvant endocrine therapy should not be used in young women outside clinical trials.

Young patients with hormone receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years (LoE IA), with or without an Gonadotropin-releasing hormone (GnRH) analogue. Patients should be informed of the possibility of getting pregnant while on tamoxifen, despite developing amenorrhoea, and of the need for adequate non-hormonal contraception.

If a GnRH analogue is used in this age group, it should be given on a monthly basis (and not on a 3-monthly basis) to optimise ovarian suppression and efficacy. If the combination of tamoxifen and GnRH analogue is given, estradiol levels should be checked on a regular basis (at least every 6 months) because in some patients ovarian suppression is not achieved. Due to the lack of reproducibility, estradiol levels should be measured always in the same laboratory and preferably in a central reference laboratory. As a consequence, patients should also be informed to undertake effective non-hormonal contraception while on treatment. In cases of inadequate suppression alternative strategies should be discussed (oophorectomy or continuation of tamoxifen alone).

Women should be fully informed about the risk of stopping tamoxifen treatment early (the earlier the interruption the higher the risk).

Young women with stage I or II breast cancer who cannot take tamoxifen (due to contraindications or severe side effects) should receive a GnRH analogue (LoE IA). The optimal duration of this treatment is currently unknown and is a RESEARCH PRIORITY.

There are conflicting data (ZORO and PROMISGIM6 studies) regarding the use of GnRH analogues

to protect ovarian function during chemotherapy and additional studies are ongoing (see also below).[90–92]

Aromatase inhibitors alone are contra-indicated in pre-menopausal women. Aromatase inhibitors combined with GnRH analogue should not be used in young early breast cancer patients outside clinical trials, before the results of the SOFT and TEXT trials are available. Additionally, aromatase inhibitors alone should not be used in young patients with chemotherapy-induced amenorrhoea, unless postmenopausal status is definitively proven.

CYP2D6 polymorphism analysis cannot be recommended outside clinical studies.

Usually, the younger the woman, the worse are the side effects of endocrine therapy; therefore supportive measures are needed. Research on age-related quality of life issues should be a RESEARCH PRIORITY.

The optimal duration of endocrine therapy for high-risk premenopausal women to balance potential benefits and side effects associated with the treatment still needs to be determined and is a RESEARCH PRIORITY.

7.2.3. Adjuvant anti-HER-2 therapy

One year treatment with adjuvant trastuzumab, together or after chemotherapy, is indicated for women with HER-2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm), having a left ventricular ejection fraction of $\geqslant 55\%$ and without important cardiovascular risk factors, regardless of age (LoE Ia).

A subgroup analysis of the HERA trial[93] demonstrated that women below the age of 35 derive the same benefit from one year trastuzumab as the overall population.

7.2.4. Adjuvant bisphosphonates

Until definitive results of clinical trials are available, bisphosphonates should not be routinely used in the adjuvant treatment of young women with breast cancer to improve disease outcome, (LoE IV). In the setting of combined endocrine therapy alone (i.e. LHRH agonist in combination with tamoxifen or aromatase inhibitor), there are data suggesting that zolendronic acid improves disease-free survival and maintains bone mineral density in pre-menopausal women.[94]

7.3. Metastatic breast cancer

For this section, we have considered women with metastatic disease diagnosed before the age of 40.

The treatment of metastatic breast cancer (MBC) should be discussed within the multidisciplinary team and patient preferences should always be taken into account.

As recommended for early breast cancer, also in the metastatic setting, age alone should not be a reason to prescribe more aggressive therapy.

There are few proven standards of care in MBC management overall[86,95–100] and even fewer in young women. Therefore, inclusion of patients in well-designed, independent, prospective randomised trials must be a priority whenever available.

Whenever feasible the tumour should be tested for confirmation of diagnosis, histology and biology, especially in case of late relapse.

Local treatment in case of isolated single visceral metastasis should be discussed.[97]

The specific psychosocial issues related to metastatic breast cancer in young women (i.e. information to family/children, job and social insurance) should be addressed in a multidisciplinary setting.

Research on age-related quality-of-life issues and supportive interventions should be a RESEARCH PRIORITY.[101]

In endocrine-responsive metastatic breast cancer, most studies addressing the combination of endocrine treatment and chemotherapy showed an increased response rate or an increased time to progression but no improvement in overall survival.[102] This is in contrast to the early breast setting where combination of tamoxifen with chemotherapy was found to be detrimental and hence sequential use is recommended. Trials examining concurrent versus sequential treatment with endocrine therapy and chemotherapy need to be conducted. In addition, endocrine therapy can frequently be used as maintenance treatment after obtaining the maximum benefit from chemotherapy (LoE expert opinion). However, trials clearly evaluating the role of maintenance therapy for MBC (be it endocrine, biological or cytotoxic) are urgently needed (RESEARCH PRIORITY).

7.3.1. Endocrine therapy for advanced disease

Endocrine therapy is the preferred option for hormone receptor-positive disease, unless there is concern or proof of endocrine resistance (i.e. early relapse under adjuvant endocrine therapy) or need for rapid disease and/or symptom control.

In young patients with hormone receptor-positive or hormone receptor unknown metastatic breast cancer, tamoxifen in combination with suppression/ablation of ovarian function is the first-line endocrine therapy of choice (LoE IA).[103]

Aromatase inhibitors together with ovarian suppression/ablation can be considered after progression on tamoxifen $\pm$ ovarian suppression/ablation (LoE IIB).[104–106]

Fulvestrant has not yet been studied in pre-menopausal women and specific studies are needed (RESEARCH PRIORITY).[107,108]

7.3.2. Chemotherapy for advanced disease

Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.

Young age by itself is not an indication to prescribe combination chemotherapy over sequential use of monotherapy.

The fact that young women tolerate chemotherapy better than their older counterparts should not be a reason to prescribe more aggressive regimens.

7.3.3. Biological therapy for advanced disease

Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.

7.3.4. Treatment of specific sites of metastases

7.3.4.1. Bone. Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.

7.3.4.2. Brain. Young age has been associated with an increased risk of brain metastases despite clinical and pathologic characteristics predicting for CNS recurrence often overlap with factors that indicate an increased risk for general metastatic dissemination (i.e. young age, ER- and PR-negativity, high proliferation and genomic instability).[109–112]

Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.

7.3.5. Palliative and terminal care

The problems faced by young women at a palliative setting are different and should be addressed specifically (for example those related to her children and spouse).

8. Treatment of locoregional relapse

Young age per se is a risk factor for local relapse (LoE IA). The recommendations for young women do not differ from those for the general patient population. In case of a local or regional relapse, the tumour should be tested for confirmation of diagnosis, histology and biology.

An isolated local recurrence after breast-conserving treatment should be preferably treated by mastectomy to obtain a R0 situation (LoE IC). Even if tumour free margins can be obtained by a second breast conserving operation, a disadvantage in overall survival as well as in local tumour control cannot be completely ruled out. A second breast conservation is therefore an individual decision after an informed decision making process. In a curative situation, a R0 situation must be obtained (LoE IIA). The role of surgery for locoregional relapse in patients with additional distant metastasis has not yet been completely clarified.

An isolated thoracic wall recurrence should be preferentially treated by surgery and adjuvant radiotherapy, whenever possible (LoE IC).

Systemic treatment for a completely excised locoregional recurrence should be discussed in a multidisciplinary team. Although local relapses are more frequent in women of young age at initial diagnosis, there are no specific data to guide treatment choices at the time of local relapse. Decisions on adjuvant systemic treatment after local relapse should be influenced both by the initial biology and prior therapy, as well as by the biology of the relapse and the disease-free interval (LoE III).

Systemic treatment for a completely excised locoregional recurrence should be discussed in the multidisciplinary team. So far, only the benefit of an additional endocrine therapy has been proven, and this treatment can therefore be recommended (LoE I). There is less data on the added value of chemotherapy in this setting, and randomised trials in this setting have been very difficult to run. Patients with a HER-2 positive local recurrence who have not received trastuzumab before or whose primary tumour was HER-2 negative (trastuzumab naïve patients) should receive trastuzumab for one year in this "pseudo-adjuvant" situation (LoE expert opinion).

Patients with a primary inoperable local relapse should receive systemic therapy to improve operability and increase the chance of tumour free margins (LoE III).

9. Locally advanced and inflammatory breast cancer

Inflammatory breast cancer is slightly more frequent in young women, especially in women of African descent in the United States and in North African countries. Mean age at onset of inflammatory breast cancer in registries in western countries is 55 (as compared to 62 for non inflammatory cases).[113,114] Inflammatory breast cancer in young women does not appear to be linked to the constitutional genetic background.

Since there are no data to indicate a different biology or a different prognosis[114] the management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.

10. Supportive care for patients with breast cancer

Even if breast cancer diagnosis is a difficult charge at any age, young women face specific psychosocial and sexual issues that should be addressed by a multidisciplinary group of providers including breast nurses, breast oncologists and gynaecologists among others (LoE III).[115–117]

Some supportive measures, including physiotherapy for arm mobility after axillary clearance, regular physical activity, weight loss if overweight or obese and a low calories diet are not age specific, but should be implemented also in the young patient population (LoE II).[118] Smoking should be discouraged as it is

associated with an increased risk of secondary tumours, including breast cancer (LoE III).[119] Alcohol should be avoided as well, or limited to one alcohol unit per day, as it increases the lifetime risk of breast cancer. Psychosocial support should be routinely offered also to spouse and children with directed interventions, if required (LoE III).[120–122] Breast nurses (or experienced nurses) are of crucial important for the support of the patient and the family.

Some of the specific issues for the young breast cancer population include:

10.1. Premature menopause

The risk of chemotherapy induced premature menopause is related to the agents used, the total dose delivered and patient's age.[123,124] Combination regimens used as adjuvant treatment have different rates of premature menopause (Table 1) and risk estimating nomograms can be found on-line (www.fertilehope.com). High cumulative doses of alkylating agents after the age of 35 years are associated with a high probability of premature menopause. Premature menopause remains a major concern for young women with breast cancer, and can influence therapeutic decisions and treatment adherence.[125–128] There is some evidence that amenorrhoea is a good prognostic marker[77] but the therapeutic consequences of these preliminary data are not yet clear.

Menopausal symptoms can be particularly bothersome in young patients with iatrogenic ovarian exhaustion.[129,130] Hot flashes can be reduced with non-hormonal treatments such as SSRI (Selective Serotonin Reuptake Inhibitors) (LoE I)[131–134] but attention should be paid to potential interactions of some of these agents with tamoxifen activity. Their combined action as antidepressants and hot flash reducers may be specifically helpful in young breast cancer patients where depression is significantly prevalent and often unaddressed. Fatigue, a common complaint in breast cancer patients, may be worsened by menopausal symptoms, insomnia and restlessness, and be of special concern in young patients who have to cope with multiple tasks linked to a young family, work and career. Other available non-hormonal treatments against hot flashes include gabapentine, clonidine and acupuncture.[135,136]

10.2. Infertility

The risk of infertility is strictly related to that of premature menopause. Even women with regular menses after chemotherapy have a reduced ovarian reserve and experience impaired fertility and an earlier menopause.[123,137] This is mainly due to the direct toxicity of chemotherapy on the primordial ovarian oocyte pool, which physiologically diminishes with age and is significantly reduced after chemotherapy (Fig. 2). Chemotherapy might also damage ovarian granulosa cells, thus accounting for menstrual irregularity during treatment.[138] The risk of genetic foetal anomalies, when pregnancy occurs during chemotherapy should prompt a thorough discussion about contraception before this treatment is initiated.

Table 1
Rates of chemotherapy induced amenorrhoea by combination regimen. Modified from Stearns V, Schneider B, Henry NL, Hayes DF, Flockhart DA. Breast cancer treatment and ovarian failure: risk factors and emerging genetic determinants, Nat Rev Cancer 2006:6(11):886–93.

Regimen	Age	Chemotherapy-induced amenorrhoea (%)
CMF × 6	<40	30–80
	⩾40	60–96
AC × 4	<40	13–30
	⩾40	57–63
FEC/FAC × 6-8	<40	10–25
	⩾40	80–90
AC × 4 → Paclitaxel × 4	<40	35
	⩾40	77
AC × 4 → Docetaxel × 4	<40	29–42
	⩾40	66–75
TAC × 6		62

10.3. Contraception

Young women are potentially fertile also if they have menstrual irregularities or even if they are amenorrheic during or after treatment.[139] Therefore, the issue of contraception needs to be addressed in all young BC patients (LoE III). Reliable and reversible non-hormonal methods including barrier methods (such as condoms, cervical diaphragm and copper IUDs) can be suggested (LoE III). For women asking for permanent contraception, laparoscopic tubal ligation or hysteroscopic tubal plugging can be used. In case of a steady partner, vasectomy is an option that needs to be discussed. The methods need to be chosen after thorough discussion with the woman/couple about the necessity of fertility preservation. Oestrogen ± progestin-containing contraceptives should not be used (LoE II),[140] particularly not in women with endocrine-responsive BC. Although it is currently unknown if this also applies to non-endocrine-responsive disease, caution should be taken also in this subset of women.

10.4. Cancer therapy-associated cognitive change ("*chemobrain*")[141]

Increasingly reported complaints include attention deficit, memory and concentration difficulties, which may affect cognition, psychological well being and the ability to perform professional and daily activities, a problem of special relevance in young patients committed to excellence at work and career. A randomised trial

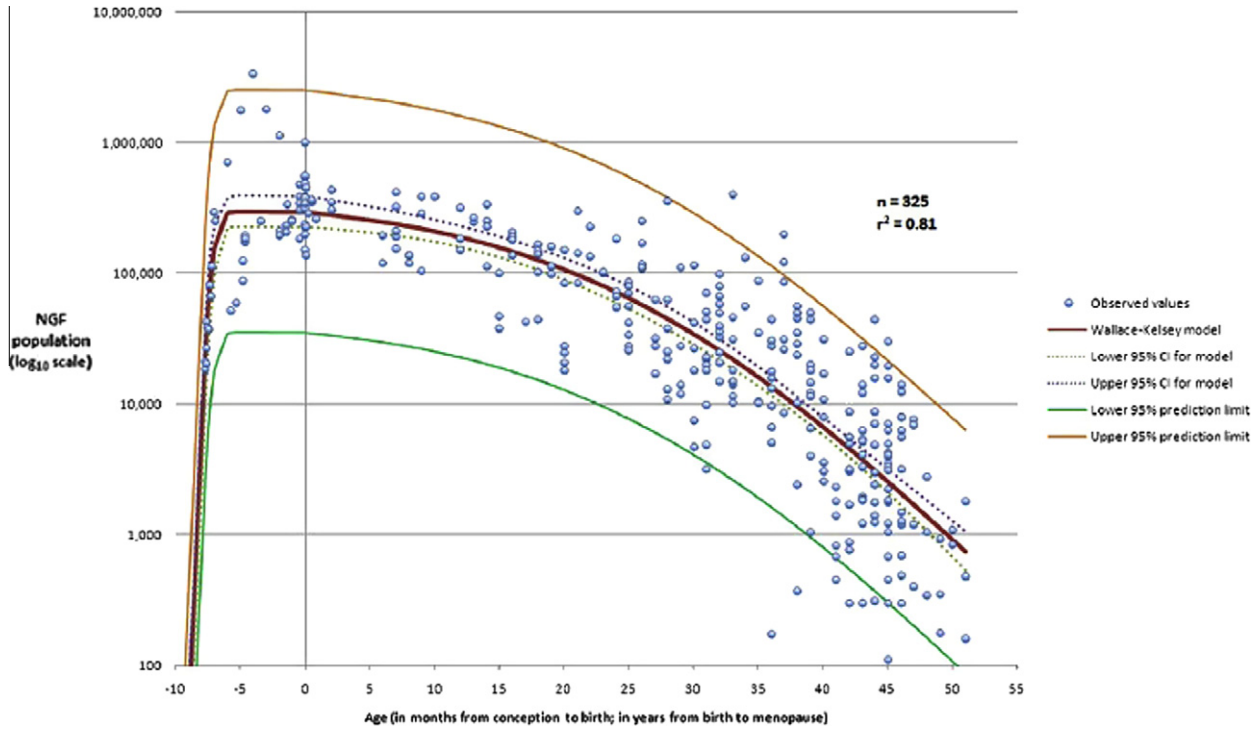


Fig. 2. Ovarian reserve by age. Open Access Article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited. Wallace WHB, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS ONE 5(1):e8772. http://dx.doi.org/10.1371/journal.pone.0008772.

suggests that modafinil (a novel wakefulness and alertness enhancing agent, with the potential to act as a cognitive enhancer without the side effects produced by other stimulants) may significantly improve speed of memory and quality of episodic memory, with improvement of continuity of attention in patients who continued the active treatment, with parallel significant improvement of the quality of sleep (another underevaluated complaint after chemotherapy).[142] Unfortunately, this study does not specifically analyse the impact of the drug on the younger cohort of breast cancer patients. Cancer therapy-related cognitive decline, along with fatigue, anxiety and depression, are among the most common symptoms affecting the quality of life of breast cancer patients. They are becoming increasingly relevant, as post-treatment survivorship issues, with the improvement in survival of breast cancer patients seen in the last decades. In addition, cancer therapy associated cognitive changes may be affected by the menopausal status and its associated symptoms (insomnia, hot flashes, depression and anxiety) and comorbidities. Accurate understanding of the different potential contributors is crucial to optimise the treatment of this syndrome generically called "chemobrain".

10.5. Bone health

Young women with chemotherapy-induced permanent amenorrhoea or those undergoing ovarian suppression may be considered at high risk for osteopenia/osteoporosis. Despite acting as a partial oestrogen agonist on the skeleton, tamoxifen can cause bone loss in premenopausal patients, probably because it has a weaker effect on bone than endogenous estrogens. As a consequence, in all young patients special emphasis on regular exercise and dietary education is needed (LoE III). Bone density scan monitoring may be considered and calcium (1000 mg/day) and vitamin D (800 UI/day) supplements can be recommended, especially in cases of lactose or gluten intolerance and/or when the diet is poor in calcium. Bisphosphonates should be prescribed according to the degree of bone loss. Current general guidelines in postmenopausal patients (including premature menopause either spontaneous or iatrogenic) recommend their use in case of osteoporosis but not osteopenia (LoE II). No general recommendation regarding the use of prophylactic bisphosphonates for bone health preservation can be made at the present time.

10.6. Lymphoedema

Lymphoedema is the second most feared complication after recurrence of breast cancer. It may affect 32–40% of women undergoing axillary dissection and 1.8% of those undergoing sentinel lymph node biopsy. It may dramatically affect quality of life for functional and cosmetic reasons. Treatment may include drugs such as diosmine–hesperidine that may increase lymph drainage and hence reduce lymphoedema, particularly

if started early.[143,144] It is also important to reduce modifiable risk factors such as high BMI, infection and injury.[145] Physiotherapy and strength training intervention can lead to significant improvement of lymphoedema, but particularly of mobility.

10.7. Sexual dysfunction

Sexuality encompasses three major dimensions: *sexual identity*, *sexual function* and *sexual relationship*, which may be variably wounded in young women with breast cancer.[146,147]

Sexual identity and body image are more vulnerable in younger women,[148,149] the breast being a prominent sign of femininity and beauty. If mastectomy is required, attention to immediate reconstruction and nipple sparing techniques (if oncologically feasible) to maintain the nipple sensitivity may positively improve the psychosexual outcome in terms of body image and sexual identity.

Young women with breast cancer are at particular risk for *sexual dysfunction*, which is being increasingly reported during and after treatment. Prospective data indicate that the quality of sexual intimacy worsens over time,[150] with increasing percentage of women reporting sexual dysfunction. For vaginal dryness and dyspareunia, non-hormonal methods, including moisturising and lubricating agents are preferred (LoE III)[151] Local estrogens with low/minimal (<1%) systemic absorption like promestriene could be helpful,[152] yet few safety data in women with breast cancer are available.[153,154] In women with oestrogen-receptor negative breast cancer twice a week vaginal estradiol or estriol, that have low systemic absorption and stronger efficacy on the vaginal mucosa, lubrication and vaginal ecosystem, can be considered in cases with severe symptoms. Special attention should be devoted to the complaint of dyspareunia that can be triggered by vaginal dryness and worsened by the defensive contraction of the pelvic floor (levator ani muscle), more likely in childless women.[129,130] While specific studies in breast cancer patients are lacking, in general patients with dyspareunia pelvic floor rehabilitation, levator ani stretching, electromyographical biofeedback aiming at relaxing the pelvic floor are supported by significant evidence (LoE II).[149] If loss of desire and central arousal difficulties persist after correction of physical symptoms and depression, psychological support should be offered (III).[155]

Sexual relationship: breast cancer diagnosis and treatment may dramatically impair the quality of the couple relationship. Data indicate that the emotional intimacy, the sense of bonding, affection and commitment may be improved in the majority of couples (60–70%) while the physical, erotic intimacy may be variably affected. The longer the time is between surgery and having intercourse again, the higher the probability of sexual dysfunction. Patients and their partners should be reassured that there is no medical contraindication to sexual intimacy including touching the operated breast during breast cancer therapy and afterwards.[130,156] These issues should be addressed promptly, as sexual prognosis improves if effective management/treatment is implemented early (LoE III).[148] Unfortunately, the quality of sexual life remains unaddressed in the majority of consultations, with a major burden for younger couples. Younger husbands seem to have the highest vulnerability as caregivers, as they have more difficulty in coping with the wife/partner illness and the responsibility of small children.[157] Data indicate that addressing intimacy and partner communication in breast cancer patients may improve relationship adjustment[158], with specific attention to young women with breast cancer.

In post-diagnosis counselling, it is important not to overwhelm patients with too much information and too many issues. Time for a second or third discussion should be offered and referral for specific professional consultation should be facilitated within the context of the individual oncologic situation.

11. Fertility preservation

Fertility issues should always be discussed before the start of any breast cancer therapy (LoE III).[159] Discussion should allow appropriate time for reflection and should possibly involve the partner, if present.[128,160,161] An early referral to the reproductive endocrinologist is warranted (LoE III).[127,159,162]Methods to preserve fertility in young breast cancer patients include:

11.1. GnRH analogues co-administration during chemotherapy

Conflicting results are reported in the literature. Published trials have heterogeneous endpoints and are difficult to interpret.[90,92] Even if some experts advocate the routine use of GnRH analogues during chemotherapy to reduce the risk of infertility and premature menopause,[163] current data are not valid enough to make a strong recommendation outside clinical trials (LoE II).

11.2. Oocytes/embryo cryopreservation

Oocytes harvesting prior to gonadotoxic chemotherapy is an established method of fertility preservation.[164,165] Embryo cryopreservation is endorsed by the American Society of Clinical Oncology as the most efficient mean to preserve fertility in cancer patients, but requires a partner or a sperm donor.[160] The recent technology advances in oocytes freezing and thawing allow oocyte cryopreservation as an alternative method.[166] The most appropriate protocol of ovarian stimulation remains a matter of discussion and research.[167] Adapted

regimens including the use of letrozole, GnRH antagonists or in vitro maturation of immature oocytes are under investigation.[168] Limited data on hormonal stimulation methods and breast cancer outcome are available.[169] As a consequence, the risk/benefit ratio has to be thoroughly discussed before suggesting any of these methods to the individual woman and couple.

11.3. Ovarian tissue freezing

Ovarian tissue harvesting and cryopreservation with subsequent re-implantation have been reported as a potential effective fertility sparing procedure in patients undergoing chemotherapy for various malignancies.[170] Thirteen healthy deliveries have been reported after this technique, but the pregnancy rate is still unknown and the procedure remains experimental.[171] The risk of tumour cell contamination of the frozen ovarian tissue is probably overestimated in early breast cancer, but remains a concern.[172] Future improvements of in vitro oocyte maturation will open new perspectives in the applicability of this technique.[173]

A number of websites are available and can be used for patient information and counselling (www.fertiprotect.de, www.fertilehope.org, www.myoncofertility.org, www.youngsurvival.org). Referral to the experienced multidisciplinary team is essential to ensure the optimal risk/ benefit discussion for the individual patient/couple and coordination with planned anticancer treatment.

12. Breast cancer and pregnancy

12.1. Pregnancy after breast cancer

All retrospective available data report not only no detrimental effect of a subsequent pregnancy on breast cancer outcome but also a potential favourable impact on prognosis. Therefore, pregnancy after breast cancer should not in principle be discouraged (LoE III).[174,175]

Nonetheless, a thorough staging should be performed before trying for conception, depending on the individual risk of relapse (LoE IV) and patients should be informed about the possibility of breast cancer recurrence even many years after diagnosis.

There is no definitive evidence to recommend a fixed time frame from diagnosis to pregnancy. Despite absence of supporting evidence, some experts recommend avoiding early pregnancy (within 2 years from diagnosis) in cases of higher risk of early relapse. In addition, potential disadvantages of early stopping of ongoing recommended anti-cancer treatments must be discussed and balanced with the risk of infertility due to ageing and iatrogenic effects of cancer treatment. In particular, women should be fully informed about the risk of stopping tamoxifen treatment prematurely (the earlier the interruption, the higher the risk of relapse). For the moment, it is recommended to complete endocrine therapy after pregnancy and an ongoing worldwide clinical trial is addressing this issue. A delay of pregnancy should be discussed on an individual basis in order to allow for continuation/completion of adjuvant therapy, and discussion should include taking into account the half life of administered treatment (to prevent detrimental effects on foetus), the detection of early relapse in high-risk disease and/or overcoming early treatment related side effects. In general, an interval of at least 4–6 months from the end of chemotherapy and the attempt to conceive is recommended (LoE expert opinion). Data on endocrine treatment are less conclusive: as a practical advice, an interval of at least 3 months from the end/interruption of therapy is recommended due to the half-life of tamoxifen. Limited data on the efficacy and safety of ovarian stimulation after treatment of breast cancer are available. Caution and individualised decision making are recommended.

Data about pregnancy and foetal outcome after breast cancer treatment are reassuring. No increased foetal malformation rates have been reported after completion of chemotherapy or endocrine treatment, but some population-based data report an increased risk of delivery complications, caesarean section, very preterm birth (<32 weeks) and low birth weight (<1500 g), highlighting the need for careful pregnancy surveillance and management in this population.

Breastfeeding after breast cancer is not contra-indicated and should be supported with adequate information and counselling.[176,177] Milk production after breast conserving surgery and radiotherapy is reduced, but breastfeeding from the other breast is feasible and safe for the mother and the child, provided the patient is not taking any medications that may be harmful for the child (LoE III).

If a woman prematurely stops endocrine treatment to achieve a pregnancy, resuming tamoxifen after breastfeeding completion can be considered (LoE expert opinion). A clinical trial evaluating this issue is a RESEARCH PRIORITY.[175]

Given the retrospective nature of the data available and the degree of uncertainty on many aspects of fertility and pregnancy after breast cancer, this field should be considered as a RESEARCH PRIORITY.

12.2. Breast cancer during pregnancy

In 2010 an international, multidisciplinary group met to update recommendations on treatment of breast cancer during pregnancy.[178]

There are some key issues which need to be addressed in this particularly difficult situation. The experienced multidisciplinary team expanded to include obstetricians and perinatologists should decide on diagnostic and therapy interventions, on an individual basis.

Any suspicious breast lump appearing during pregnancy should be clarified starting with ultrasonography. A core biopsy under local anaesthesia should be undertaken if doubt persists. To rule out multiple lesions or bilateral breast cancer, mammography can be recommended. Further staging using other imaging techniques should only be undertaken if the results would lead to an important change in the treatment approach.

Any type of therapy should follow the guidelines for non-pregnant women as closely as possible. Surgery can be safely performed, and the indications for mastectomy or breast conserving therapy are the same as for non-pregnant women. There are increasing data suggesting that sentinel node biopsy with radionuclide mapping can be safely performed during pregnancy, using a one day protocol to keep the radioactivity to a minimum.

There is an important amount of data demonstrating that chemotherapy can be safely administrated to pregnant breast cancer patients using standard anthracycline-based regimens (e.g. FEC, FAC, EC, AC). These regimens should be followed by a taxane whenever indicated. The taxane can also be administered during pregnancy, although there are less available data. A more widely used approach is to administer the anthracycline-based part of the regimen during pregnancy and the taxane-based part, whenever indicated, after delivery. Since there are sufficient alternatives and given the potential foetal toxicity of M, CMF should not be used during pregnancy.[178] The regimens of chemotherapy recommended to pregnant breast cancer patients are the same as the ones recommended to non-pregnant counterparts.

Trastuzumab and endocrine therapy must not be prescribed during pregnancy but must be postponed until after delivery. Radiotherapy should also be postponed until after delivery.

Delivery should be done according to obstetrical needs with an interval of 2–3 weeks between chemotherapy and delivery. It is believed that the risks associated with premature delivery are higher than the risks associated with chemotherapy administration during pregnancy. However, longer follow-up is needed in the several existent series of children whose mothers received chemotherapy during pregnancy, to better evaluate potential long term consequences.

To increase the knowledge in this specific patient population, the German Breast Group is coordinating an international prospective registry with translational research and pharmacokinetics studies associated (www.germanbreastgroup.de/pregnancy).

13. Final comments

Attention needs to be paid to the definition of age groups since too crude or too narrow grouping or inadequate assessment of menopausal status may not be clinically useful. The authors thus suggest to group age either by actual menopausal status if the trial addresses issues different according to endocrine situation or to group by young age (under 40 years-old) versus older in order to ensure large enough numbers within the age groups. In some situations it may also be important to evaluate separately the group of very young women (under 35 years-old), if appropriate.

Medical treatment of breast cancer in young women is not substantially different from other age groups except for some specific issues on endocrine therapy, since therapy is mainly linked to the biology of the tumour. However, counselling of these women must emphasise different issues specific to their age and life situation. Fertility and pregnancy-related issues are confined to this age group. It may not be possible to address a number the research questions identified in this article by clinical trials because of a lack of patient numbers or difficulty of randomisation due to very personal issues such as pregnancy. However, all efforts should be made globally by the research community, to develop research programmes encompassing the specificities of breast cancer in young women, whose needs are not yet met. Additionally, prospectively planned subgroup analyses in trials across age groups may add important knowledge and thus help to improve management in young women.

Multidisciplinary management and care is strongly recommended to avoid an opinionated standard of practice and the risk of overtreatment. The role of patients' advocacy for this age group is also of crucial important, particularly for dissemination of information and knowledge.

Conflict of interest statement

None declared.

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