Review

Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)

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As the mean age of the global population increases, breast cancer in older individuals will be increasingly encountered in clinical practice. Management decisions should not be based on age alone. Establishing recommendations for management of older individuals with breast cancer is challenging because of very limited level 1 evidence in this heterogeneous population. In 2007, the International Society of Geriatric Oncology (SIOG) created a task force to provide evidence-based recommendations for the management of breast cancer in elderly individuals. In 2010, a multidisciplinary SIOG and European Society of Breast Cancer Specialists (EUSOMA) task force gathered to expand and update the 2007 recommendations. The recommendations were expanded to include geriatric assessment, competing causes of mortality, ductal carcinoma in situ, drug safety and compliance, patient preferences, barriers to treatment, and male breast cancer. Recommendations were updated for screening, primary endocrine therapy, surgery, radiotherapy, neoadjuvant and adjuvant systemic therapy, and metastatic breast cancer.

Introduction

Recommendations for management of breast cancer in older individuals are limited by a lack of level 1 evidence. Treatment is largely based on limited retrospective subgroup analyses and extrapolation of study results from younger patients. Such extrapolation might not be valid since breast-cancer biology differs in older patients, treatment tolerance varies, and there are competing risks of non-breast-cancer mortality. Modified management strategies are often used for older individuals; however, the evidence for such approaches is poor, and resulting under treatment is well documented.[1]

We present recommendations for management of older individuals with breast cancer created by a European Society of Breast Cancer Specialists (EUSOMA) and International Society of Geriatric Oncology (SIOG) multidisciplinary task force. This task force—inclusive of representative specialists from medical oncology, radiation oncology, surgery, geriatric medicine, radiology, and epidemiology—used the SIOG guidelines published in 2007 as a starting document.[2] Existing guidelines for screening, primary endocrine therapy, surgery, radiotherapy, adjuvant systemic therapy, and metastatic breast cancer have been updated. The guidelines have been supplemented with recommendations for geriatric assessment and management, competing causes of mortality, ductal carcinoma in situ, male breast cancer, drug safety and compliance, patient preferences, and barriers to treatment.

The scarcity of robust data on breast cancer in older individuals—particularly on modifying management for frail patients—precludes these recommendations being based on level 1 evidence. Therefore, these recommendations are a consensus by an expert task force on available evidence and expert opinion. Table 1 presents the 2007 and current recommendations. Recommendations unchanged from 20072 because of absence of new data have not been rediscussed (ie, surgery of the primary tumour, radiotherapy after conservative surgery, post-mastectomy radiotherapy, adjuvant trastuzumab, and hormone treatment for metastatic breast cancer).

Age alone should not dictate any aspect of management for older individuals with breast cancer. All decisions should consider physiological age, estimated life expectancy, risks, benefits, treatment tolerance, patient preference, and potential treatment barriers.

Incidence, general characteristics, and prognosis

Breast cancer incidence varies widely between and within continents. In Europe, incidence for women 70 years or older diagnosed between 2000–04 varied from 100 to 350 per 100 000 per year.[3] The incidence for this group has shown a steady increase in most European countries between 1990–2002.3

Compared with younger women, older women are more likely to have breast cancer with oestrogen receptor (ER) and progesterone receptor expression, with or without HER2 overexpression.[4] Variation in receptor status expression mainly exists between very young women (<35 years) compared with other age groups. There is less variation between age groups among postmenopausal women. ER-positive cancers increase from greater than 60% among women aged 30–34 years to 85% among women 80–84 years.[5] HER2-positive tumours decrease from 22% among women younger than 40 years to 10% in women 70 years or older.[6] Tumour size and nodal involvement increase with age,4,7 at least partly explained by delayed diagnosis in older women. However, increased nodal involvement is mainly seen with smaller tumours, suggesting more aggressive small tumours in older women.[7]

5-year and 10-year relative survival of patients 70 years or older are lower than those of patients aged 40–70 years, even when adjusting for disease stage.[8] Under treatment, socioeconomic differences, and unequal access to health care contribute to poorer prognosis. Across Europe, 5-year relative survival for all patients improved significantly from 1990–94 to 2000–04;[8] however, in most countries improvements were larger for patients younger than 70 years.

Competing causes of mortality

Many older patients with operable breast cancer die of non-cancer-related causes. Relative breast-cancer survival is the preferred way to describe the prognosis of older patients with breast cancer, since it considers the risk of dying from other causes.

The benefit of cancer therapy in individuals likely to die at an early stage from non-cancer-related causes is questionable; however, it is difficult for clinicians to identify these individuals. Assessment of comorbidity and the need for assistance in activities of daily living (ADLs) and instrumental activities of daily living (IADLs) predict likelihood of early death from non-breast-cancer causes.[9,10] The presence of comorbidity is particularly important. In a study of more than 900 women with early breast cancer, women with at least three of seven selected morbid conditions were 20 times more likely to die from causes other than breast cancer.[9]

	2007 recommendations (SIOG)	Current recommendations (SIOG/EUSOMA)
General recommendations for all aspects of management	..	All management decisions for an older individual with breast cancer should consider: Physiological age Life expectancy Potential risks vs absolute benefits Treatment tolerance Patient preference Potential barriers to treatment
Competing causes of mortality	..	Relative breast-cancer survival is the preferred way to describe the outcome of older patients with breast cancer Assessment of comorbidity and function can predict likelihood of dying from non-breast cancer causes
Geriatric assessment	..	Collaborative geriatric and oncology management can optimise care General health and functional status can be captured in a multidomain geriatric assessment; however, it is unclear which elderly patients are most likely to benefit and which method is best A screening assessment is a reasonable first step in identifying patients that may benefit from an extended CGA Active intervention for CGA-identified reversible geriatric domains can reduce morbidity and mortality, and improve quality of life Serial geriatric assessment can identify incident deterioration, for which intervention might improve outcomes
Screening mammography	There are no strong data for screening mammography in women older than 70 years Screening in women aged 70–75 years could be appropriate with the individual decision based on risks and benefits, patient preference, physiological age, and life expectancy	There are no strong data for screening mammography in women older than 70 years Screening in women aged 70–75 years could be appropriate with the individual decision based on risks and benefits, patient preference, physiological age, and life expectancy
Ductal carcinoma in situ (DCIS)	..	There are no strong data available for treatment of older women with DCIS Healthy older women with localised DCIS should be considered for BCS and postoperative radiotherapy
Surgery	Patients 70 years or older should be offered the same surgery as younger patients Standard of care is BCS plus WBRT, or mastectomy with or without postoperative radiotherapy Mastectomy is indicated for large or multifocal tumours not amenable to conservative excision, patients who are not fit for WBRT, and patients who prefer mastectomy to BCS plus WBRT ALND is indicated for clinically positive or highly suspected nodes, since nodal status can affect adjuvant therapy SLNB is a safe alternative to primary ALND in patients with clinically node negative disease. Need for ALND after positive SLNB is controversial	Patients 70 years or older should be offered the same surgery as younger patients Standard of care is BCS plus WBRT, or mastectomy with or without postoperative radiotherapy Mastectomy is indicated for large or multifocal tumours not amenable to conservative excision, patients who are not fit for WBRT, and patients who prefer mastectomy to BCS plus WBRT; ALND is indicated for clinically positive or highly suspected nodes In clinically node negative disease, axillary staging by SLNB with completion ALND for tumour-positive SLNB remains the standard of care. Omission of SLNB and completion ALND might be reasonable in some older patients (see text)
Radiotherapy	WBRT after BCS, with a boost to the tumour bed, should be considered in all elderly patients since it decreases risk of local relapse (there is no evidence for an overall survival advantage in analyses restricted to elderly patients) Post-mastectomy chest-wall radiation should be considered for elderly patients with at least four nodes or a pT3/4 tumour The role of omission of postoperative WBRT, partial breast irradiation, and hypofractionation are undefined	WBRT after BCS, with a boost to the tumour bed, should be considered in all elderly patients since it decreases risk of local relapse. There is no subgroup of fit older patients in whom post-BCS WBRT can be systematically omitted (see text) Post-mastectomy chest-wall radiation should be considered for elderly patients with at least four nodes or a pT3/4 tumour Hypofractionated radiation schedules offer similar local-regional control and adverse effects as standard WBRT The evidence for PBI in older patients is not sufficiently robust to recommend it as standard therapy (see text)

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	2007 recommendations (SIOG)	Current recommendations (SIOG/EUSOMA)
(Continued from previous page)		
Primary endocrine therapy	In healthy older women, primary endocrine therapy with tamoxifen is inferior to surgery (with or without hormonal therapy) for local control and PFS, without significant difference in overall survival Data for primary therapy with aromatase inhibitors are missing	Primary endocrine therapy should only be offered to elderly individuals with ER-positive tumours who have a short estimated life expectancy (<2–3 years), who are considered unfit for surgery after optimisation of medical conditions or who refuse surgery The involvement of a geriatrician is strongly recommended to estimate life expectancy and guide management of reversible comorbidities It is reasonable to choose tamoxifen or an aromatase inhibitor based on potential side-effects
Adjuvant hormone therapy	There is no age-dependent efficacy of tamoxifen or aromatase inhibitors Efficacy is slightly greater with aromatase inhibitors in terms of DFS; however, elderly patients are more vulnerable to toxicity and safety is important in choice of agent Initial treatment should be tamoxifen or an aromatase inhibitor Patients given tamoxifen up front should be considered for a switch to an aromatase inhibitor after 2–3 years	There is no age-dependent efficacy of tamoxifen or aromatase inhibitors Efficacy is slightly greater with aromatase inhibitors; however, elderly patients are more vulnerable to toxicity and safety is important in choice of agent Initial treatment should be tamoxifen or an aromatase inhibitor. Patients given tamoxifen should be considered for a switch to an aromatase inhibitor after 2–3 years. Extension of adjuvant treatment with an aromatase inhibitor after 5 years of tamoxifen could be considered for healthy elderly patients Omission of endocrine therapy is an option for patients with a very low-risk tumour (pT1aN0) or life-threatening comorbidities
Adjuvant chemotherapy	The decision to treat with adjuvant chemotherapy should not be age-based Older patients with node-positive, hormone-receptor negative disease potentially derive the largest benefit Four cycles of an anthracycline-containing regimen are usually preferred over CMF In healthy patients with high-risk disease, taxanes should be considered in addition to anthracyclines TC or CMF can replace anthracyclines in patients with cardiac risk Patients with HER2-positive breast cancer, without cardiac disease, should be offered trastuzumab in combination with chemotherapy	The decision to treat with adjuvant chemotherapy should not be age-based Older patients with node-positive, hormone-negative disease potentially derive the largest benefit Four cycles of an anthracycline-containing regimen are usually preferred over CMF Standard AC and CMF chemotherapy are better than single-agent capecitabine Taxanes are associated with increased toxicity compared with younger women, but can be added to anthracyclines in high-risk healthy elderly patients, or replace anthracyclines to reduce the cardiac risk Patients with HER2-positive breast cancer, without cardiac disease, should be offered trastuzumab in combination with chemotherapy (see text)
Metastatic breast cancer	Hormone treatment is the treatment of choice for older women with ER-positive metastatic breast cancer Chemotherapy is indicated for ER-negative, hormone-refractory, or rapidly progressing disease Single-agent chemotherapy is preferred to combination regimens; however, evidence for specific monotherapy in elderly patients is limited Dose reductions and schedule modifications are controversial, but should be considered based on pharmacology and toxicity Patients with HER2-positive disease should receive trastuzumab and chemotherapy Data for bevacizumab efficacy and toxicity is limited	Hormone treatment is the treatment of choice for older women with ER-positive metastatic breast cancer Chemotherapy is indicated for ER-negative, hormone-refractory, or rapidly progressing disease Single-agent chemotherapy and combination oral chemotherapy are feasible options in elderly patients Dose reductions and schedule modifications are controversial, but should be considered based on pharmacology and toxicity Patients with HER2-positive disease should receive HER2-targeted therapy and chemotherapy In patients with HER2-positive ER-positive disease with a contraindication to chemotherapy, or without life threatening disease, anti-HER2 therapy plus endocrine therapy is an option In patients with HER2-positive ER-negative disease, trastuzumab monotherapy could be reasonable Bevacizumab is active in elderly patients in terms of increased PFS; however, toxicity and cost efficacy are important issues that need to be further elaborated
Drug safety and compliance	..	Careful drug prescription is warranted because of physiological age-related pharmacokinetic alteration, comorbidities, and polypharmacy Renal function evaluation is mandatory for treatment with renally excreted or nephrotoxic drugs A thorough medication review is advised, ideally involving a clinical pharmacist Drug compliance should be actively promoted Close adverse event monitoring to allow prompt intervention is recommended, since elderly patients have lower physiological reserve, side-effects can present in an atypical way, and unaddressed toxicity can compromise compliance
Patient expectations	..	Physicians should provide clear information to elderly patients with breast cancer on prognosis, treatment options, expectations of treatment, and potential toxicity Physicians should be attentive to the expectations and preferences of individuals, with particular attention to quality of life
Barriers to treatment	..	Barriers to therapy should be identified and addressed Special attention should be paid to comorbidity (particularly cognitive status, anxiety, and depression) and social setting (particularly transport) that can affect patient decisions Physician bias should not influence management Family and caregivers cannot reliably predict patient preferences, and caregiver bias should not unduly influence management
Male breast cancer	..	In older men with breast cancer, there is only indirect evidence on which to base treatment guidelines It is reasonable to follow guidelines for post-menopausal women for surgery, radiotherapy, chemotherapy, and anti-HER2 therapy Tamoxifen is indicated for ER-positive disease, whereas there is insufficient data on aromatase inhibitors in elderly men with breast cancer to allow recommendations

SIOG=International Society of Geriatric Oncology. EUSOMA=European Society of Breast Cancer Specialists. CGA=comprehensive geriatric assessment. BCS=breast-conserving surgery. WBRT=whole-breast radiotherapy. ALND=axillary lymph-node dissection. SLNB=sentinel lymph-node biopsy. PBI=partial-breast irradiation. PFS=progression-free survival. ER=oestrogen receptor. DFS=disease-free survival. CMF=cyclophosphamide, methotrexate, and fluorouracil. TC=docetaxel and cyclophosphamide. AC=cyclophosphamide plus doxorubicin.

Table 1: **Recommendations for management of older individuals with breast cancer**

Despite competing causes of death, breast cancer is the cause of death in a substantial number of older patients. In women 80 years or older at diagnosis, up to 40% die from breast cancer.[8] Underestimation of life expectancy and fitness for therapy might result in age-related undertreatment, itself a risk factor for breast-cancer recurrence and death.1

Geriatric assessment

Estimation of life expectancy and ability to undergo treatment might be improved by collaborative geriatric and oncology management, and a multidomain geriatric assessment.[11–13] There is currently no standard method for geriatric assessment; however, the comprehensive geriatric assessment (CGA) includes measures of function, comorbidity, nutrition, medication, socioeconomic issues, and geriatric syndromes.[12] There is strong evidence in the general elderly population that implementation of CGA to identify and guide

management of reversible domains—particularly comorbidities, depression, and nutrition—improves compliance, treatment tolerability, quality of life (QoL), and survival.[12] There is some evidence in the cancer population that CGA can contribute to patient management (table 2).[11–17] Pilot studies have found that a mean of six problems are identified during an initial CGA, particularly in the pharmacological, psychological, and nutritional domains.[13]

In breast cancer, robust evidence is lacking on the effect of using CGA results to guide treatment. In one study, 39% (36 of 93) patients had their treatment changed after geriatric assessment; however, the effect of these changes on outcome is unknown.[17] In another study, CGA resulted in some patients with breast cancer undergoing surgery for which they were originally considered unfit.[11]

Preoperative assessment of cancer in the elderly (PACE), which includes CGA, has been used to assess suitability for surgery.[18]

General health and functional independence are key components of QoL in the elderly. Therefore, feasibility endpoints based on function rather than discrete adverse events might be more meaningful in clinical trials with elderly patients. A recent study in elderly women selected for adjuvant chemotherapy for breast cancer used feasibility as a primary endpoint, defined as maintenance of functional autonomy as assessed by ADLs.[16] Chemotherapy was deemed feasible if autonomy was not attenuated. The Cancer and Leukemia Group B (CALGB) reported the feasibility of implementing a brief, mainly self-administered geriatric assessment in future trial design.[19] CGA can be time consuming and labour intensive, taking roughly 45 min to complete and usually implemented by a geriatrician. Therefore, use of an abbreviated screening method has been recommended to identify patients who would benefit from a full CGA.[12,20] Screening methods have been studied, but there is no consensus on which should be used. The G8 screening method was prospectively validated in a large French study, and was chosen by the EORTC as the screening method for EORTC clinical trials.[12,20,21] The abbreviated comprehensive geriatric assessment (aCGA) has been retrospectively validated, with debate as to whether problems in a specific aCGA domain warrant further domain-specific investigation or complete CGA.[22]

	Age, eligibility	Population	Number of patients (median age)	Method	Results
Repetto et al (2002)[14]	≥65 years	Solid and haematological tumours	363 (72 years)	CGA	CGA was compared with ECOG PS, ADLs, IADLs, and comorbidities. CGA provided valuable additional information, even for patients with a good PS
Stotter et al (2010)[11]	Eligible if considered unfit for, or declining, standard treatment	Breast cancer: preoperative	152 (NA)	CGA (or other frailty tool), geriatrician review	Geriatric assessment resulted in several elderly patients undergoing surgery who were originally considered unfit for anaesthesia, and also identified patients with an estimated short life expectancy (<2 years) for whom surgical treatment was considered unlikely to add significant benefit over endocrine therapy alone
Exterman et al (2004)[13]	≥70 years	Breast cancer: postoperative	15 (79 years)	CGA baseline, serial CGA	Baseline CGA identified an average of six problems on initial assessment, particularly in the pharmacological, psychosocial, and nutritional domains, and three new problems during follow-up. Use of CGA directly influenced oncological treatment in four patients
Clough-Gorr et al (2010)[15]	≥65 years	Breast cancer: postoperative	660 (range 70–79 years)	Geriatric assessment domains: clinical, sociodemographic, function, psychosocial	Independent of age and disease stage, geriatric assessment domains were associated with poor treatment tolerance and higher mortality at 7 years of follow-up
Brain et al (2011)[16]	≥70 years	Breast cancer: postoperative	40 (75 years)	ADLs, CGA	Function, as assessed by pre-therapy and post-therapy ADLs and CGA, did not change with chemotherapy. There was an effect on social functioning and nutrition
Girre et al (2008)[17]	>70 years	Solid tumours: 61% of patients had breast cancer	105 (79 years)	Geriatric oncology consultation	The oncology treatment plan, documented before and after geriatric assessment, changed in 39% of patients; however, whether or not these treatment changes affect outcome remains to be seen

CGA=comprehensive geriatric assessment. ECOG=Eastern Cooperative Oncology Group. PS=performance score. ADLs=activities of daily living. IADLs=Instrumental Activities of Daily Living. NA=not available.

Table 2: **Geriatric assessment in elderly individuals with cancer**

Screening

The US Preventive Services Task Force concluded that there is insufficient data on the effect of mammographic screening on breast-cancer mortality among women 70 years or older.[23] While direct evidence is lacking, modelling studies suggest that mortality reduction can be achieved on a cost-effective scale up to 74 years of age,[24] and is recommended in several

European countries. In the absence of an overall survival benefit, however, the decision to screen beyond 70 years should be made by the individual and their clinician, based on risks and benefits of screening, patient preference, and life expectancy.

Ductal carcinoma in situ

Variability in study design and selection criteria makes the occurrence of ductal carcinoma in situ (DCIS) in elderly women difficult to assess. A French survey done in 2003–04 reported that 13·4% of women treated for DCIS were 70 years or older.[25] DCIS in elderly patients was mammographically detected in 83·8%, compared with 91·6% in younger women (p<0·0001).[25]

There is little outcome data for elderly women treated for DCIS. A meta-analysis confirmed significant benefit from adjuvant radiotherapy plus breast-conserving surgery (BCS) over BCS alone in women older than 50 years (10-year local recurrence rate [LRR] 10·8% vs 27·8%, respectively), without specific data in women older than 70 years.[26] However, the proportional benefit in reduced breast events in the adjuvant radiotherapy group increased significantly with age in 10-year cohorts including 60–69 years and 70 years or older (p=0·02).

Despite lower LRR with radiotherapy, randomised trials have not shown a survival benefit from radiotherapy. Therefore, in older women, lower LRR should be weighed against harms of treatment and competing causes of mortality.

Surgery

Standard of care for operable breast cancer is BCS plus whole-breast radiotherapy (WBRT), or mastectomy followed by postoperative radiotherapy in selected patients. For patients with clinically positive or highly suspected nodes, axillary lymph-node dissection (ALND) is recommended, however management of the axilla in clinically and radiologically lymph-node-negative disease is controversial. Standard of care has been sentinel lymph-node biopsy (SLNB) with completion ALND for sentinel lymph node (SLN)-positive patients, ideally with immediate ALND to avoid the increased morbidity associated with delayed ALND, done in a second surgery. However, recent studies suggest that omission of completion ALND in SLN-positive patients, and even omission of SLNB in elderly patients, might be reasonable.

Two large randomised studies compared ALND versus no ALND in older women with clinically node-negative disease (no SLNB was done in these studies).[27,28] Most patients had ER-positive disease and received 5 years of adjuvant tamoxifen. ALND omission did not adversely affect overall survival with the two studies reporting low axillary recurrence of 1·8% and 3%, compared with recurrence rates of 0% and 1% with ALND.[27,28] Median 15-year follow-up of a non-randomised, retrospective study of elderly patients with clinical T1N0 disease treated by surgery and adjuvant tamoxifen with or without ALND revealed no difference in overall survival.[29] Axillary recurrence rates were 5·8% without ALND and 0% with ALND. No data are available on the effect of ALND on QoL in the two studies by Martelli and colleagues;[27,29] however, the IBCSG study[29] showed that avoiding axillary clearance yielded better early QoL.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial assessed non-inferiority of omission of completion ALND in SLN-positive disease.[30] Women with one to two positive SLNs were randomised to no ALND (median age 54 years) or ALND with resection of at least ten nodes (median age 56 years). All patients underwent BCS with WBRT. The primary endpoint was overall survival, with the hypothesis that SLNB alone was non-inferior. Non-inferiority was defined as 5-year overall survival for SLNB alone of not less than 75% of the overall survival for SLNB plus ALND (estimated to be 80%). The trial needed 1900 women and 500 deaths; however, the study closed prematurely because of a low death rate. Analyses were done after 94 deaths in 856 women (median follow-up 6·3 years).

Axillary recurrence rates were 0·9% for SLNB alone and 0·5% for SLNB plus ALND, with no differences in distant recurrence (83·9% and 82·2%, respectively) or overall survival (92·5% and 91·8%, respectively). These results should be interpreted with caution, since the trial did

not reach its target accrual and the population enrolled was highly selected: pT1 (70%), ER-positive (80%), and SLN micrometastases (40%).
An alternative to completion ALND for SLN-positive disease is axillary irradiation, which is being investigated in the AMAROS trial. An early observation indicates that lack of knowledge of the extent of nodal involvement in the axillary irradiation group did not substantially affect administration of adjuvant systemic therapy, suggesting that axillary radiotherapy might be a reasonable option for older patients with positive SLN, avoiding the morbidity of ALND.[31] Thus, axillary staging by SLNB with completion ALND for SLN-positive disease remains the standard of care for elderly patients with clinically node-negative breast cancer.
Further studies are needed before omission of completion ALND becomes standard of care. Omission of SLNB and completion ALND might be reasonable in some elderly patients, since ALND did not affect breast-cancer mortality and subsequent symptomatic axillary disease is rare.
Additionally, since most elderly patients have endocrinesensitive disease and will be given hormone therapy, axillary staging is unlikely to affect adjuvant therapy decisions. Routine omission of SLNB or ALND (or both) in this population will increase LRR, which, although salvageable by secondary surgery, could have psychological effects that should not be underestimated. Regional nodal irradiation might be a reasonable alternative to ALND for SLN-positive disease, but study results are awaited before this could be considered standard of care.

Radiotherapy

Radiotherapy omission

Omission of WBRT after BCS in elderly patients with breast cancer is controversial. Most randomised trials assessing WBRT omission excluded patients older than 70 years. In a meta-analysis by Clarke and colleagues,[32] only 9% (550 of 6097) of node-negative patients who received BCS were older than 70 years. This meta-analysis showed that a 16% reduction in LRR from radiotherapy after BCS led to a 5% reduction in breast-cancer mortality at 15 years.[32] However, none of the randomised trials included in the meta-analysis showed a decrease in overall survival with WBRT omission.
The CALGB 9343 trial[33,34] randomised women 70 years or older with clinical stage 1, ER-positive breast cancer to lumpectomy plus tamoxifen with or without WBRT, with similar proportion of women undergoing ALND in each group (63% and 64% respectively). At 5-year median follow-up, LRRs were 1% for patients with WBRT and 4% for those without.[33] At 10·5-year median follow-up, LRRs were 2% and 9%, respectively, although with no overall survival difference (breast-cancer-specific survival 98% vs 96%; overall survival 63% vs 61%) was observed.[34] The widening absolute difference in local control with longer follow-up argues for radiotherapy even in low-risk patients with an expected survival of longer than 5 years.
Balanced against this are the dominant competing risks of non-breast-cancer mortality and the fact that LRRs after breast-conserving therapy are falling.[35] Additional data will come from the PRIME II trial, which is assessing the effect on local control of WBRT omission after BCS and adjuvant endocrine therapy, in 1380 patients with T1–2 (≤3 cm), node-negative disease.
QoL is an important additional endpoint to consider with radiotherapy in older patients. The PRIME I trial[36] randomised women 65 years or older with T1–2N0M0 disease, considered at low risk of local relapse, to BCS plus endocrine therapy with or without WBRT. The primary outcome was QoL, measured by European Organisation for Research and Treatment of Cancer (EORTC) QoL modules. At 60-month median follow-up, there was no difference in overall QoL scores, although patients identified practical issues of hospital transport and accommodation as important concerns.[36] Ongoing economic modelling is assessing the cost-effectiveness of radiotherapy omission. In the longer term, the potential effect of local relapse on QoL and psychological state in older patients should not be underestimated.

Thus, with available evidence, there is no subgroup of fit older patients in whom post-BCS WBRT can be systematically omitted. However, in view of the absence of overall survival benefit and the fact that local relapses can be successfully secondarily operated, this position should be balanced with the logistics of daily travel necessary to undertake standard external radiotherapy and individual preference regarding the potential of local relapse.

Hypofractionation

Predicated on the hypothesis that breast cancer is sensitive to fraction size, the UK START trials[37,38] and a Canadian trial[39] have shown equivalent local control for standard WBRT and hypofractionated schedules (table 3). Elderly patients were well represented in these trials. A non-randomised series specifically in elderly patients reported similar local recurrence-free and metastasis-free survival for hypofractionation (32·5 Gy in five fractions once a week) and WBRT.[40]

	Inclusion criteria	Treatment: hypofractionation versus WBRT	Local recurrence rate	Comment
Bentzen et al; START A (2008)[37]	BCS or mastectomy	39 Gy in 13 fractions over 5 weeks versus 41·6 Gy in 13 fractions over 5 weeks versus 50 Gy in 25 fractions over 5 weeks	5·2% (5 year) 3·5% (5 year) 3·6% (5 year)	..
Bentzen et al; START B (2008)[38]	BCS or mastectomy	40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks	2·2% (5 year) 3·3% (5 year)	Better breast cosmesis with hypofractionation
Whelan et al; Canadian trial (2010)[39]	BCS, T1–2N0M0, clear resection margins	42·5 Gy in 16 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks	6·2% (10 year) 6·7% (10 year)	No significant difference in breast cosmesis and late cardiotoxicity between treatment groups

WBRT=whole-breast radiotherapy. BCS=breast-conserving surgery.

Table 3: **Studies of hypofractionation versus standard fractionation WBRT**

Partial-breast irradiation

Since most local recurrences occur at or close to the original tumour site, there is interest in partial-breast irradiation (PBI) to deliver most or all radiotherapy to the original site. Techniques include intraoperative or postoperative brachytherapy, targeted intraoperative radiotherapy (TARGIT), and electron intraoperative radiotherapy (ELIOT). TARGIT A,[41] the only published randomised trial of PBI in which older patients were well represented, compared post-BCS TARGIT (single intraoperative 20 Gy fraction) with WBRT. At 4-year follow-up, LRRs were 1·2% and 0·95%, respectively.

Clearly, the avoidance of weeks of tiring external-beam irradiation is appealing; however, follow-up is short and results are confounded by the option of supplementing TARGIT with WBRT for high-risk tumours at the investigator's discretion. A non-randomised series of patients given quadrantectomy and ELIOT (single intraoperative electron dose [3–12 MeV] of 21 Gy) reported a 2·3% LRR after 36-month median follow-up.[42] In our view, PBI evidence in older patients is insufficiently robust to recommend it as standard therapy. Off-study use of PBI might be reasonable in elderly patients for whom standard radiotherapy presents particular difficulty; however, patients should be informed of the longer track record of efficacy of WBRT.

Systemic treatment

Decisions about systemic treatment should reflect the breast-cancer biological subtype. Such an approach is extrapolated from data in the general breast-cancer population, since there are no subtype-specific treatment data for elderly patients.

Neoadjuvant therapy

Patients with locally advanced disease or large tumours relative to breast size might be offered preoperative systemic therapy to render surgery feasible or to make breast conservation possible. Most elderly patients have ER-positive, HER2-negative disease, tumours which are likely to respond to neoadjuvant endocrine therapy. Neoadjuvant aromatase inhibitors are better than tamoxifen.[43–45] Neoadjuvant chemotherapy alone or with

HER2-targeted treatment should be considered for triple negative and HER2-positive disease, respectively. However, specific data in older patients is lacking.

Primary endocrine therapy

Primary endocrine therapy, by contrast with neoadjuvant treatment, refers to systemic endocrine treatment as sole treatment for early stage ER-positive breast cancer.

A Cochrane review showed a decrease in local progression with surgery plus endocrine treatment compared with primary endocrine therapy alone; however, no difference was observed in overall survival.[46] For optimum local control, surgery (with or without radiotherapy) plus adjuvant endocrine therapy is better than primary endocrine therapy.

Evidence exists for disease control of 2–3 years with primary endocrine therapy.46 Therefore, in patients with a short life expectancy (<2 years), considered unfit for surgery after optimisation of their general medical condition, or refusing surgery, primary endocrine therapy might be considered. Geriatrician involvement in management of these patients is strongly recommended to estimate life expectancy, identify and guide management of reversible conditions, and thus, reduce the risk of overtreatment and undertreatment.

Primary endocrine therapy studies have mainly used tamoxifen, although aromatase inhibitors could be preferable on the basis of neoadjuvant, adjuvant, and metastatic data. The ESTEeM trial comparing primary anastrozole with surgery plus adjuvant anastrozole in women 75 years or older closed because of poor accrual.

To evaluate primary aromatase inhibitors in frail older patients with ER-positive tumours, clinical trials are needed, but in view of the difficulty in recruiting for such a trial it is reasonable to assess each individual for tamoxifen or aromatase inhibitors based on potential toxicity. The role of primary endocrine therapy in combination with trastuzumab and lapatinib for ERpositive and HER2-positive disease is unclear.

Adjuvant hormonal treatment

A Danish Breast Cancer Cooperative Group study[47] identified a subgroup of patients who might not benefit from adjuvant systemic treatment. In the absence of any systemic therapy, women aged 60–74 years with small (≤10 mm), node-negative, endocrine-responsive, grade 1 ductal carcinoma or grade 1 or 2 lobular carcinoma did not have increased mortality compared with age-matched women in the general population. In such patients with very low-risk tumours, or patients with life-threatening comorbidities, omission of endocrine therapy is an option.[47,48] Aromatase inhibitors have been compared with tamoxifen in several large, randomised, adjuvant trials (direct comparison, switch to aromatase inhibitor after 2–3 years of tamoxifen, and aromatase inhibitor extension after 5 years of tamoxifen); a small proportion of elderly patients were included in these trials (5–20%).[49] Two analyses have been done specifically in elderly patients. In the MA.17 trial, the advantage conferred by extended letrozole after 5 years of tamoxifen was significant only in patients younger than 60 years.[50] However, since there was no significant interaction between age and treatment for disease-free survival (DFS) or overall survival, extended adjuvant therapy with letrozole could be considered for healthy elderly patients. In the BIG 1-98 trial,[51] letrozole showed age-independent superior efficacy compared with tamoxifen.

Tolerance is an important issue for compliance. In older patients, aromatase inhibitors are preferred to tamoxifen because of the lower risk of increased thrombosis and endometrial cancer, with similar effect on QoL.[50,51] However, aromatase inhibitors are associated with musculoskeletal syndrome, accelerated bone loss, and increased fracture rate, seemingly irrespective of age, as suggested prospectively in BIG 1-98.[50,51] BIG 1-98 results showed significantly more grade 3–5 protocol-specified non-fracture adverse events for letrozole compared with tamoxifen in patients 75 years or older, whereas differences were not significant for thromboembolic or cardiac events.[51] Cognitive impairment has been described in association with adjuvant hormonal treatment, but data are sparse.[52] Bone loss associated with aromatase inhibitors is a particular problem in elderly patients, since pre-existing decreases in bone mineral density and osteoporosis are prevalent. Vitamin D and calcium supplementation should be considered, especially since subclinical vitamin D insufficiency is

common in elderly patients. Antiresorptive therapies are indicated for increasing bone mineral density and reducing fracture risk in elderly patients with osteoporosis.[53]

Adjuvant chemotherapy

Benefit of chemotherapy in older individuals

There is no evidence to support differential use of specific chemotherapy drugs or dose reductions in older patients compared with younger ones. A CALGB study provided important information on the value of adjuvant chemotherapy.[54] Patients 65 years or older were randomised to standard chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF] or cyclophosphamide plus doxorubicin [AC]) or capecitabine. At 3 years, relapse-free survival (RFS) and overall survival were significantly lower with capecitabine than with standard chemotherapy (RFS 68% vs 85%; overall survival 86% vs 91%, respectively). In the capecitabine group, two patients died from treatment-related complications but fewer patients had moderate-to-severe toxicity (64% vs 33%). Chemotherapy benefit was observed mostly in ER-negative disease.

Two large, international randomised trials (CASA and ACTION) comparing adjuvant chemotherapy with no chemotherapy were closed prematurely because of insufficient accrual. It will be difficult to do future randomised studies with a no-treatment control group. Observational studies are much less prone to selection bias and can also provide valuable information.

Chemotherapy is feasible in most patients 70 years or older who are selected for adjuvant chemotherapy, but increasing age, lower function, and comorbidity are associated with dose reductions and treatment breaks.[55] Some studies identify age-related toxicity.[56] Not all studies report age trends, but caution is warranted since selection bias excludes many frail and vulnerable patients who have higher risk of toxic effects.

Choice of chemotherapy

CMF is generally poorly tolerated, and anthracyclinerelated cardiotoxicity might be an issue in elderly patients.

A taxane-based regimen might replace anthracyclines To reduce cardiac risk. Docetaxel and cyclophosphamideshowed superiority over doxorubicin and cyclophosphamide for DFS and overall survival, in a study which included patients older than 65 years.[57] In a retrospective observational study in women older than 70 years, adjuvant therapy with docetaxel and cyclophosphamide was feasible.[58]

Administration of adjuvant taxanes seems feasible in older patients, but carries higher rates of dose delays and reductions, hospitalisation, therapy discontinuation, haematological toxicity, and some non-haematological toxicities (eg, loss of appetite, severe fatigue, and mucositis) than for younger women.[56] There is no published data validating the use of sequential treatment (anthracyclines followed by taxanes) in elderly patients. Therefore, these combinations should be confined to biologically aggressive tumours in healthy elderly women.

Adjuvant trastuzumab

Healthy patients with HER2-positive breast cancer and without cardiac disease should be offered trastuzumab in combination with chemotherapy. There is no clinical data available for treatment with trastuzumab alone in patients who are not candidates for chemotherapy; however, the 2011 St Gallen consensus states that if chemotherapy cannot be given, it might be reasonable in some settings to give trastuzumab without it.[48]

Metastatic breast cancer

Older women are more likely than younger women to present with more advanced breast cancer. There is a delicate balance between overtreatment and undertreatment of advanced disease, in which maintenance of QoL is a priority.

Chemotherapy

Chemotherapy is indicated in older patients with ERnegative disease, hormone-refractory disease, or rapidly progressing disease. Elderly patients with metastatic breast cancer are expected to derive similar benefits from chemotherapy as younger patients. Single-agent chemotherapy is generally preferred to combination regimens, which are usually more toxic and provide, at most, a limited survival gain. Preference should be given to chemotherapy agents with better safety profiles (such as weekly taxanes, pegylated liposomal doxorubicin, capecitabine, and vinorelbine) that have been studied in older patients.[59]
There is limited data on polychemotherapy in elderly patients. Combination oral chemotherapy (vinorelbine and capecitabine) was assessed in patients older than 70 years with advanced cancer, many with breast cancer, and was active and well tolerated.[60] Oral therapy is attractive since it eliminates the constraints and risks of parenteral therapy, but efficacy and tolerability can be compromised by interference with food (eg, lapatinib), concomitant medications (eg, capecitabine with warfarin), and errors in compliance.

HER2-targeted therapy
Trastuzumab and lapatinib are equally effective in younger and older patients with metastatic breast cancer. Data on trastuzumab in elderly women are limited, but a retrospective series showed that benefits and safety seem to be conserved in patients older than 60 years and in those older than 70 years.[61]
Lapatinib plus capecitabine has similar efficacy in older and younger women.[62] In a pooled analysis of nine trials including different tumour types, lapatinib-associated diarrhoea was similar in severity, onset, and resolution in older and younger patients;[63] however, elderly patients are less tolerant of diarrhoea-associated dehydration and need close monitoring. In the breast-cancer subgroup of the analysis, patients 70 years or older experienced more grade 3 events than did younger patients (33% vs 19%).63 In elderly, HER2-positive patients with metastatic breast cancer who are unfit for chemotherapy, or in those without life-threatening disease, trastuzumab monotherapy or anti-HER2 therapy plus endocrine therapy could be reasonable. However, there is no specific efficacy or safety data in elderly patients. First-line trastuzumab monotherapy has shown clinical benefit rates of around 40%.[64] Combination anti-HER2 plus hormone therapy—trastuzumab plus anastrazole, lapatinib plus letrozole—improves progression-free survival (PFS) over hormone therapy alone in HER2-positive and ER-positive disease, but with more toxic effects and higher economic cost.[65,66]

VEGF-targeted therapy
First-line bevacizumab plus chemotherapy confers a PFS but no overall survival benefit in all age groups, although to a lesser extent in elderly patients.[67] A meta-analysis of three trials—E2100, AVADO, and RIBBON-1—showed a PFS benefit in younger and older patients (<65 years:
hazard ratio [HR] 0·62, 95% CI 0·56–0·70; ≥65 years: HR 0·70, 0·56–0·88).[67] In the ATHENA study,68 older women given bevacizumab plus chemotherapy had more grade 3–4 adverse events than younger women, particularly hypertension, but there was no age-related increase in thromboembolic events. An ATHENA substudy highlighted exacerbation of chemotherapy toxicity by bevacizumab, rather than increased bevacizumab-specific toxicity.[68] The clinical value of a PFS benefit and cost-effectiveness need evaluation to define the role of bevacizumab.

Bone health

In elderly patients, decreases in bone mineral density and osteoporosis are prevalent. Antiresorptive therapies are standard of care for maintaining bone health in patients with osteoporosis and those with cancer, particularly when receiving drugs such as aromatase inhibitors.[53,69] Several bisphosphonates and denosumab are currently approved or under evaluation in the USA or Europe, but antiresorptive therapies are underused in elderly patients.[53,69] Special considerations should be made for elderly patients, who might have renal impairment or might be taking concomitant medications for comorbid conditions. In this regard, there could be an advantage for denosumab in elderly patients. Adequate hydration

is particularly important for minimising potential nephrotoxicity, but is often overlooked. Because of non-compliance with oral bisphosphonates, intravenous or subcutaneous administration might be preferable.

Drug safety and compliance

Careful drug prescribing in elderly patients with breast cancer is essential because of physiological age-related pharmacokinetic alteration, comorbidities, and polypharmacy.

Physiological ageing can be associated with altered pharmacokinetics (drug absorption, distribution, metabolism, and excretion) which can affect efficacy and toxicity. Many drugs have reduced liver metabolism in older people, attributable to decreased hepatic blood flow and liver mass rather than altered activity of metabolising enzymes or cytochrome P450 isoforms. Physiological ageing affects renal function. Pretreatment optimisation of hydration, and assessment of renal function is mandatory if treatment with renally excreted or nephrotoxic drugs is considered. Serum creatinine does not correctly reflect renal function in older people. Creatinine clearance should be calculated by the abbreviated modification of diet in renal disease (MDRD) or Cockcroft–Gault equations. SIOG has established guidelines for measurement of renal function in elderly patients with cancer, and chemotherapy dosing adjustment for renal insufficiency.[70,71] Comorbidities can affect choice of breast-cancer treatment (eg, omission of anthracyclines and trastuzumab in cardiomyopathy, and avoidance of tamoxifen in thromboembolic disease) and treatment tolerability. Concurrent medications can have important interactions (eg, warfarin and fluorouracil) or important organ insult (eg, nephrotoxicity of non-steroidal anti-inflammatory drugs and methotrexate). A thorough medication review is recommended, ideally involving a clinical pharmacist, before treatment decisions.

Compliance is an important issue since poor compliance can jeopardise efficacy. Non-compliance with adjuvant capecitabine was reported in 25% of older women with breast cancer in the CALGB 49907 study.[72] Similar non-compliance is reported in elderly patients with adjuvant endocrine therapy and oral bisphosphonates.[51,73] Poor compliance could be a result of poor tolerability. Close adverse-event monitoring to allow prompt intervention is recommended, since side-effects might present in an atypical way and unaddressed toxicity might compromise compliance.

Unfortunately, simple interventions do not improve compliance (eg, provision of information, reminders, self-monitoring, family therapy, telephone follow-up).[74] Health professionals, including clinicians, nurses, and clinical pharmacists, should actively promote compliance with medication in elderly patients with breast cancer.

Patient preferences

Older patients generally prefer to be well informed, with no significant age-dependent information needs.[75,76] Patients might have misperceptions about breast cancer and about excessive treatment toxicity for no or limited benefit. It is necessary for clinicians to provide clear information to elderly patients and discuss the diagnosis, prognosis, expectations of treatment, and the potential negative effect of undertreatment.[1]

A small proportion of older patients want an active role in decision making.[75,76] The recommendation of a cancer specialist is a strong determinant of selection of breast cancer therapy. Acceptance of therapy does not differ between younger and older patients; however, older patients are less willing to compromise QoL and independence for potential increased survival.[59] General health and functional independence are key components of QoL in elderly patients, which should be considered in management decisions.

Barriers to treatment

Age is an independent risk factor for receipt of nonstandard breast-cancer therapies. Even taking into account comorbidity and recurrence risk, women aged 75 years or older are more likely to receive non-standard therapy.[77] Other factors contributing to receipt of nonstandard therapy are ethnic origin, cultural environment, socioeconomic status, comorbidities (particularly cognitive status, depression, anxiety) and physical barriers (eg, sensory

impairment, poor mobility). Another barrier might be transport to general hospitals, radiotherapy centres, and academic hospitals for participation in clinical trials.[77,78] Transport might be particularly problematic for radiotherapy, requiring patients to travel long distances or to temporarily relocate.

Physician bias can be a further barrier to treatment, and might be affected by concerns of toxicities, lack of robust evidence, and limited expectations of long-term benefit.[75,77,78] Barriers to clinical trial inclusion include unnecessarily strict inclusion or exclusion criteria, exclusion because of comorbidities beyond those specified by protocol, and presumed patient difficulty in trial participation.[78] Elderly patients report limited access to information regarding clinical trials, but can be as willing as younger patients to participate.[79] Experience in achieving target accrual in trials with elderly patient has been mixed. Poor accrual might partly reflect trial design, with patient willingness to consider trial participation but unwillingness to be randomised to a no-treatment control group.

Involvement of family members in management and decision making is important.[80] However, elderly patients' preferences cannot be predicted by relatives or caregivers because of high discordance between the real and perceived needs of the patients.[81] Caregiver bias should not unduly influence management.

	Age (years)			p value
	<50	50–70	>70	
Clinicopathological features (%)				
Comorbidities	24%	42%	60%	<0·0001
pT1–2	33%	45%	57%	0·0185
pT3–4	26%	28%	42%	0·0188
Grade 3	20%	23%	19%	NS
Lymph-node positive	62%	53%	50%	NS
Involvement of >50% excised nodes	20%	20%	41%	0·04
Positive hormone receptors	90%	96%	96%	NS
Treatment modalities (%)				
Modified mastectomy	74·5%	75·5%	82%	NS
Radical mastectomy	17%	8%	12%	NS
Axillary dissection	96%	97%	91%	0·011
Sentinel-node dissection	5%	8%	9%	NS
Radiotherapy	84%	89%	80%	0·029
Chemotherapy	61%	42%	12%	<0·0001
Hormonal treatment	61%	74%	73%	NS

NS=not specified.

Table 4: **Male breast cancer clinicopathological features and treatment methods (%) according to age in a French study (n=489 cases)[82]**

Male breast cancer

Male breast cancer represents less than 0·5–1·0% of all breast cancers. Median age at diagnosis is 64 years.[82] In Surveillance, Epidemiology and End Results (SEER) data from 2003–2004, 392 men had invasive disease: 24% aged 70–79 years and 17% aged 80 years or older.[83] Elderly men with breast cancer seem to have similar survival to elderly women with breast cancer. Breast cancer in elderly men is usually self-detected and most are ER-positive.[83] Rates of HER2 overexpression are reported as 12–37%,83 but with the paucity of data, it is difficult to assess the prognostic ability of HER2 status in elderly men. A French study reported clinicopathological features and treatment according to age (table 4).[82]

There are no evidence-based treatment recommendations for elderly men with breast cancer. Clinical trials are difficult because of the rarity of the disease. Recommendations,

including National Comprehensive Cancer Network guidelines, suggest treating men using guidelines for post-menopausal women.[84]
Most men are treated by mastectomy and ALND. Older men are less likely than younger men to receive ALND and chest-wall radiotherapy.[82,83] In men, particularly those with nodal involvement, adjuvant chemotherapy has been shown to improve DFS and overall survival.85 The decision to use chemotherapy should take into consideration comorbidities, which can compromise tolerability. Tamoxifen is the standard adjuvant therapy in men with ER-positive disease, with proven DFS and overall survival benefit.[85] Aromatase inhibitors have not been adequately studied in men. Incomplete suppression of oestrogen production by aromatase inhibitors in healthy men suggests that these drugs alone might be inadequate for men with ER-positive breast cancer and that aromatase inhibitors should be combined with surgical or medical orchidectomy.[86] Case studies describe the use of aromatase inhibitors with or without concurrent luteinising hormone-releasing hormone agonist, but further study is needed. There is no data for trastuzumab in male breast cancer; however, based on the benefit in women, trastuzumab should be offered for HER2-positive disease.

Search strategy and selection criteria

Medline was the primary information source for this task force. A search of PubMed was done for English language articles published from 2007 to June, 2010, for the updated sections, and from 1990 to June, 2010, for the new sections. The search terms used were "breast neoplasms", "aged", "aged 80 and over", "frail elderly", "survival", "geriatric assessment", "mammography", "radiography", "mastectomy", "segmental", "lymph node excision", "sentinel lymph node biopsy", "radiotherapy", "neoadjuvant", "adjuvant", "secondary", "chemotherapy", "tamoxifen", "aromatase inhibitors", "pharmacology", "communication barriers", "communication", "information", and "male". Additional publications considered important by the task force were included. Randomised control trials, meta-analysis, retrospective studies, cohort studies, and reviews were included. Meeting abstracts from key international conferences were also included. The taskforce meeting was held July 1–2, 2010. Recommendations were initially prepared in small working groups and consensus was reached by whole group discussion. Publications and abstracts from key international meetings held between July, 2010, and manuscript finalisation in October, 2011, which were relevant to the topic were included by task-force members during manuscript preparation. Final consensus was reached by email refinements.

Conclusions

No aspect of management of older individuals with breast cancer should be driven by chronological age alone. A multidisciplinary oncological and geriatric approach can optimise management. Patient preference, comorbidities, and potential toxicity should guide management decisions. Patients should be closely monitored, with prompt intervention for toxicity. Several breast-cancer trials in older individuals have closed prematurely because of poor accrual. In some settings, prospective subgroup analyses and observational studies could be practical alternative sources of information to guide management.

Contributors

LB and LM had the idea, and coordinated development of the recommendations. LB, MA, and RA chaired the task-force meeting. Members of the EUSOMA/SIOG specialist task force developed a first draft on specific topics (ACV, BC, and HW for epidemiology and general

characteristics, MG for geriatric evaluation and competing causes of mortality, SC for screening, BC for ductal carcinoma in situ, RA and MR for surgery, BC and IK for radiotherapy, SL and MR for primary endocrine therapy, EB for adjuvant hormonal therapy, HW for adjuvant chemotherapy, LB and CO for metastatic breast cancer, CT for drug safety and compliance, CO for patient preferences and barriers to treatment, BC for male breast cancer). CO, LM, LB, HW, IK, MR, RA, and SL reviewed the manuscript. All authors approved the final recommendations and manuscript.

Conflicts of interest
We declare that we have no conflicts of interest.

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