Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology

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Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality in women worldwide. Elderly individuals make up a large part of the breast cancer population, and there are important specific considerations for this population. The International Society of Geriatric Oncology created a task force to assess the available evidence on breast cancer in elderly individuals, and to provide evidence-based recommendations for the diagnosis and treatment of breast cancer in such individuals. A review of the published work was done with the results of a search on Medline for English-language articles published between 1990 and 2007 and of abstracts from key international conferences. Recommendations are given on the topics of screening, surgery, radiotherapy, (neo)adjuvant hormone treatment and chemotherapy, and metastatic disease. Since large randomised trials in elderly patients with breast cancer are scarce, there is little level I evidence for the treatment of such patients. The available evidence was reviewed and synthesised to provide consensus recommendations regarding the care of breast cancer in older adults.

Introduction

Worldwide, nearly a third of breast cancer cases occurs in patients over the age of 65 years (figure 1), and in more developed countries this proportion rises to more than 40%.[1] Despite a growing level of interest by researchers with regard to this age group, no internationally agreed recommendations currently exist specifically for the management of breast cancer in elderly patients. To a large degree this is due to a paucity of evidence-based clinical trial data for older patients with breast cancer. Indeed, many breast cancer clinical trials have tended to exclude elderly individuals, mainly either on the basis of age alone, comorbidity, or both. The International Society of Geriatric Oncology (SIOG) created a taskforce to review the published literature and to provide evidence-based recommendations for the diagnosis and treatment of breast cancer in elderly individuals. This report outlines these recommendations and identifies areas in which the existing evidence is weak and where level I evidence is needed to underpin best practice.

Incidence and general characteristics

Breast cancer is the most common cancer in women in the world,[2] with 1·15 million new cases per year, of which 361 000 (27·3% of all cancers in women) are in Europe and 230 000 (31·3%) in North America.[3] Breast cancer is the leading cause of cancer mortality in women worldwide: in 2002, 411 000 women died of the disease. The crude incidence of breast cancer in North America is 141·9 per 100 000 women a year, and breast cancer-related mortality is 29·8 per 100 000 women.[1] By contrast, incidence is 130·0 per 100 000 women a year and mortality 41·0 per 100 000 women in northern and western Europe.[2] For those aged 65 years and older, crude incidence rates are 432·7 per 100 000 women in North America and 295·0 per 100 000 in northern and western Europe;

corresponding breast cancer mortality figures are 121·2 and 135·0 per 100 000 women, respectively.[1] Similar incidence and mortality figures are found in South America (Argentina and Uruguay), New Zealand, and Australia, and in central and eastern Europe (Czech Republic).[1] Figure 2 shows the age-specific incidence and mortality of breast cancer in developed and developing countries.

Figure 1: **Breast cancer has a high incidence in elderly women**

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Review

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See **Online** for webappendix

Advanced age at diagnosis of breast cancer is associated with more favourable tumour biology as indicated by increased hormone sensitivity, attenuated ERBB2 overexpression, and lower grades and proliferative indices (see references 1–9 in webappendix).[4] However, elderly patients are more likely to present with larger and more advanced tumours, and recent reports suggest that the involvement of lymph nodes increases with age.[5] Furthermore, there seem to be no major differences in outcomes in stage-matched patients as age increases.[6] Nevertheless, elderly patients are less likely to be treated according to accepted treatment guidelines,[7–9] and undertreatment can, as a consequence, have a strong negative effect on survival.[10–12] The explanation for these age-related differences in approach to treatment is complex and includes physician and patient bias, the views of relatives and caregivers, psychosocial issues, cost, and proximity to the oncology or radiotherapy centre.

Despite the fact that breast cancer occurs mainly in elderly patients, this population is substantially under-represented in clinical trials. Age is a significant predictor of whether older patients with breast cancer are offered entry into clinical trials,[13–15] when in fact older patients are just as likely as younger patients to participate if given the opportunity.[14]

Collaboration with geriatricians and comprehensive geriatric assessment are of paramount importance in detecting unaddressed problems, improving functional

status and possibly survival in elderly patients with cancer.[16] Because comorbidities and functional status significantly affect prognosis and treatment choice,[17–19] thorough consideration must be given to the overall health of elderly patients. A sizeable proportion of patients older than 70 years with operable breast cancer dies of non-cancer-related causes.[12,20] Age alone, however, should not be a barrier to treatment.

Screening for breast cancer in elderly individuals

Population-based mammography screening is generally regarded to be effective for women aged 50–70 years.[21,22] The picture is less clear for women over 70 years: some studies show no association between screening and reduced breast cancer mortality for those aged 70–74 years,[23] whereas other retrospective and modelling studies suggest a potential survival benefit even in patients over 80 years of age.[24] The Dutch experience with population-based mammography screening of patients up to 75 years is encouraging.[25]

Biologically, it is not likely that mammography screening is less effective in women older than 70 years. The accuracy of mammography (ie, sensitivity and specificity) for detecting cancers even increases with advancing age because of the increase in radiolucency of breast tissue. However, the benefits of screening needs to be weighed against the presence of other concurrent medical conditions that would limit the patient's life expectancy or limit the patient's ability to tolerate cancer treatment, and against the possibility of overdiagnosis, or the detection of lesions that would not affect a woman's lifespan.[26]

There might be cultural differences in the approach to breast cancer screening. Europe has a preference for centrally organised screening programmes with personal invitations on a population-based level. 50–70 years is generally accepted as the most appropriate target group. Within this context, the term elderly is taken to include patients aged 70 years and older, and recommendations for mammography beyond the target group age would not easily be given by a physician without a specific (medical) indication. In North America (especially the USA), breast screening is more commonly done on an individual basis rather than being population based, and the decision to do screening mammography in patients above age 70 might depend on the clinical situation. The American Geriatrics Society[27,28] recommends that screening should be individualised rather than setting guidelines by age. They recommend setting no upper age limit as long as estimated life expectancy is 4 years or more; the American Cancer Society advises to continue breast cancer screening as long as the individual is in good health and a candidate for treatment.[29]

Recommendations

There are no strong data supporting or opposing the systematic use of mammography in women over 70 years
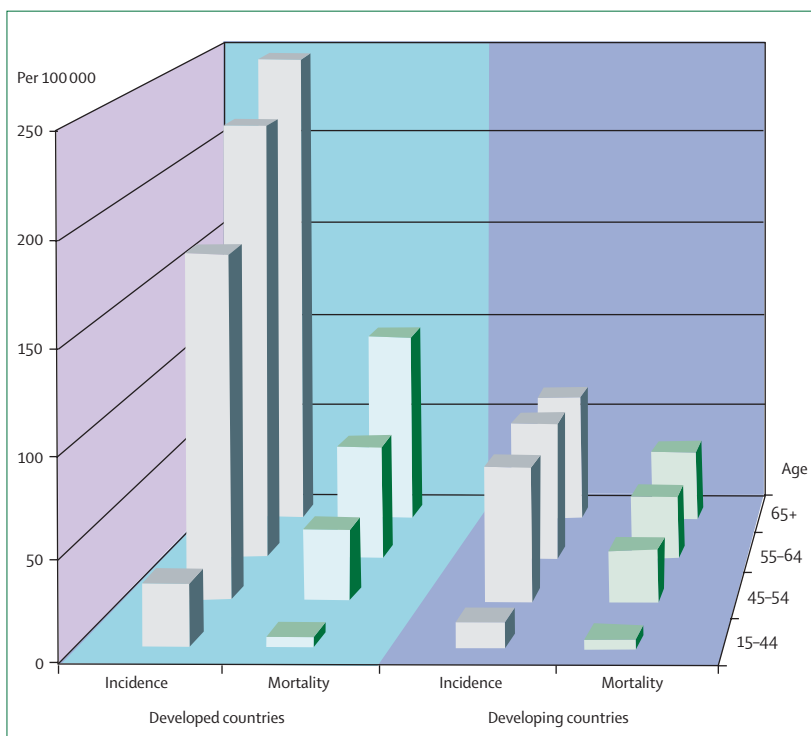

Figure 2: Age-specific incidence and mortality of breast cancer per 100 000 women in developed and developing countries[1]

of age. Cultural differences in the approach to breast cancer screening should be taken into account. In well-organised, population-based breast cancer screening programmes, mammography screening up to the age of 75 years could be appropriate. In individual patients, the decision should be individualised to take into account the risks and benefits of screening, patient preference, physiological age, and life expectancy.

Treatment of early stage breast cancer

Multidisciplinary treatment planning should be used to integrate local and systemic therapies as well as their sequence.

Surgery

Several treatment guidelines and practice standards have been developed for the surgical management of patients with breast cancer (see references 10–15 in webappendix). For the elderly population, breast cancer surgery-related mortality is low, ranging from 0 to 0·3%.[5,30,31] Alternatives to conventional surgery include outpatient surgery[32] or surgery under local anaesthesia,[33] which are preferably undertaken when family support is present.

Past assumptions that elderly patients should receive less aggressive forms of breast cancer treatment and about reduced life expectancy have meant that hormonal treatment alone without surgery has been considered a reasonable treatment option for elderly women with breast cancer with limited life expectancy, mainly in frail patients or the very old (eg, ≥80 years).[34] The effect of omitting surgery on overall survival is not clear and differs in different studies (table 1).[35–40] Four of these trials compared tamoxifen monotherapy with surgery alone.[35–37,39] The surgery alone arm is currently regarded as suboptimum in terms of treatment since no adjuvant hormone treatment was given. The Group for Research on Endocrine Therapy in the Elderly (GRETA) trial used a more informative design where surgery and adjuvant tamoxifen[38] showed a non-significant benefit in overall survival compared with tamoxifen alone, despite a long follow-up. More importantly, a significantly higher proportion of patients treated with tamoxifen alone experienced local relapse for which subsequent salvage breast cancer surgery would have been done. Another study showed an increase in breast cancer mortality in the group who did not have surgery; 455 women aged 70 years or more with operable breast cancer were randomised to surgery and tamoxifen or tamoxifen alone.[40] There was an increase in breast cancer mortality with no surgery (hazard ratio 1·68, 95% CI 1·15–2·47) and in overall mortality (1·29, 1·04–1·59). A Cochrane meta-analysis has confirmed that primary hormonal treatment with tamoxifen is inferior to surgery (with or without hormonal treatment) for the local control and progression-free survival of breast cancer in medically fit older women.[41] However, surgery does not result in significantly better overall survival.[41]

Patients, n	Follow-up, months	Treatment	Overall survival	Local recurrence	Ref
164	120	Tamoxifen	39·0%	57·0%	35
		Surgery	27·0%*	9·0%†	
135	24	Tamoxifen	85·0%	44·0%	36
		Surgery	74·6%*	24·6%‡	
200	72	Tamoxifen	67·0%	56·0%	37
		Surgery	72·0%*	44·0%*	
474	80	Tamoxifen	38·7%	47·2%	38
		Surgery and tamoxifen	45·6%*	11·0%†	
171	41	Tamoxifen	68·0%	27·0%	39
		Surgery	72·0%*	6·0%†	
455	151	Tamoxifen	28·8%	50·0%	40
		Surgery and tamoxifen	37·7%†	16·0%†	

*No significant difference between tamoxifen versus surgery and tamoxifen or surgery alone. †Significant difference between tamoxifen versus surgery and tamoxifen or surgery alone. ‡Significance not reported.

Table 1: Effect of omitting surgery on overall survival and local recurrence in elderly women with breast cancer

Neoadjuvant treatment with aromatase inhibitors has shown better response rates than has tamoxifen in postmenopausal patients with breast cancer.[42–44] There are no specific data comparing aromatase inhibitors alone with surgery combined with an aromatase inhibitor in elderly patients. This approach warrants further investigation, preferably in older patients who have a limited life expectancy and where the omission of surgery is unlikely to affect breast cancer specific mortality.

Breast conservation treatment

Breast conservation treatment, consisting of breast-conserving surgery (lumpectomy or partial mastectomy) and postoperative radiotherapy, is now recommended as the standard of care for patients of all ages with early disease (see references 16 and 17 in webappendix). Large randomised studies have clearly shown that breast conservation treatment has similar efficacy to mastectomy. Differences in disease-free survival or overall survival were similar between the two approaches, although a significant increase in local recurrences was seen in the breast conservation treatment groups, especially in younger patients. Most elderly women with primary breast cancer are candidates for breast conservation treatment. However, available data suggest that older patients are less likely to receive such treatment.[11,45] The conclusions of large randomised trials of breast conservation treatment versus mastectomy are not easily applied to elderly patients because women over the age of 70 years were excluded from these trials. However, smaller studies involving patients aged 70 years or older have documented that breast conservation treatment, in comparison with mastectomy, is associated with better quality-of-life[46] and is preferred by most elderly patients,[47] compared with mastectomy.

The association between a microscopically close or positive resection margin and the subsequent risk of breast tumour recurrence after conservative surgery and radiotherapy is controversial. Many retrospective studies have reported a significantly increased rate of breast tumour recurrence in those who received radiotherapy with positive microscopic resection margins compared with those with negative margins (see references 18–24 in webappendix). This association has also been reported in three prospective randomised trials that analysed the microscopic margin status and subsequent risk of breast tumour recurrence in patients undergoing conservative surgery and radiotherapy.[48–50] Several factors have been associated with a low risk for breast tumour recurrence in patients with positive margins. In some series, a positive margin that is characterised as focal has been associated with a lower risk of breast tumour recurrence when compared with more extensively involved margins.[51–53] These patients have been considered candidates for conservative surgery and radiotherapy, especially in the absence of an associated extensive intraductal component.[54] In the European Organisation for Research and Treatment of Cancer (EORTC) trial, the effect of positive margins on local recurrence was highly significant in woman under 50 years of age;[55] however, its significance disappeared in the older patients. As in younger patients, an attempt should be made to achieve negative surgical margins. If not achieved, the management of close or positive margins needs to be addressed by the multidisciplinary meeting. Depending on patient's age, comorbid conditions, or life expectancy, surgical re-excision could be discussed as well as additional radiotherapy in the tumour bed (boost). However, radiotherapy should not be considered as a substitute for adequate surgery with negative margins.

Total mastectomy

As in younger patients, total mastectomy remains a surgical option for patients who prefer it over breast conservation treatment, and for those who decline or are not fit for postoperative breast radiotherapy. Mastectomy is also indicated in patients with large primary lesions or tumours that cannot be approached by breast conservation treatment (eg, multicentric disease or even large unifocal tumours). Mastectomy is also indicated as salvage treatment after breast tumour recurrence after breast conservation treatment or when cosmetic results of breast conservation are likely to be poor.

Axillary surgery

Axillary lymph node dissection should be done in patients with clinical evidence of the involvement of axillary lymph nodes. However, for those without clinical lymph node involvement, the indication for upfront axillary lymph node dissection has been less clear for the elderly population, and such surgery has recently become largely redundant for this subgroup because of the possibility of a sentinel lymph node procedure. Before the sentinel lymph node procedure, older patients with breast cancer were less likely to undergo axillary lymph node dissection than were younger patients for several reasons.[12,56] First, although generally considered a safe procedure, axillary lymph node dissection can be associated with postoperative numbness, paraesthesia, pain, and muscle weakness, which could contribute to a subsequent reduction in quality of life.[57,58] One study, however, has shown that older patients experience fewer axillary lymph node dissection-related arm symptoms than do younger patients.[59] Second, axillary lymph node dissection is considered a staging rather than a therapeutic procedure for breast cancer, and is used to determine pathological nodal involvement and, therefore, to dictate need for adjuvant treatment. However, axillary lymph node dissection does not usually affect systemic treatment choice in elderly, clinically node-negative patients with tumours that are oestrogen-receptor-positive or small. Third, several studies have shown no difference in outcome in older patients with small tumours without palpable lymph nodes when axillary lymph node dissection was omitted.[60–64] In elderly patients in whom the results of an axillary lymph node dissection will not affect adjuvant chemotherapy decisions, including those with small tumours and low risk of nodal involvement, it might be appropriate to omit axillary lymph node dissection. In such cases, other factors such as quality of life and perception of body image should be weighed and discussed with the patient.

In recent years, biopsy of sentinel lymph nodes, a minimally invasive, highly sensitive and reproducible technique, has been introduced as an alternative to axillary lymph node dissection.[65] Sentinel lymph node biopsy has been shown to be a safe and accurate method of predicting axillary status in patients with breast cancer (see references 25–28 in webappendix) including those aged 70 years or more.[5,66] Sentinel lymph node biopsy could negate the requirement for axillary lymph node dissection and the resulting over-treatment of many patients.[67,68] Sentinel lymph node biopsy is now widely considered as an acceptable treatment option in patients of all ages with tumour size less than 2–3 cm and no clinical evidence of axillary involvement.[69] Elderly patients with breast cancer are ideal candidates for biopsy of sentinel lymph nodes and should be encouraged to undergo this procedure. Findings from such biopsies in older patients with breast cancer could significantly affect subsequent treatment decisions, including adjuvant systemic treatment. Controversy exists regarding the need for complementary axillary lymph node dissection after a positive sentinel lymph node is found, especially when the axilla was explored during surgery. The risk of macroscopic disease is limited and

microscopic disease will probably not be used for choosing adjuvant treatments, such as chemotherapy. Van Zee and colleagues[70] have published a nomogram to predict the risk of subsequent nodal metastasis on the basis of the results of the sentinel lymph node biopsy and tumour characteristics. This nomogram was developed in patients of all ages but could be particularly useful when deciding whether to do an axillary lymph node dissection in older patients.

Recommendations

Surgery should not be denied to patients with breast cancer who are older than 70 years of age and should not differ from procedures offered to younger patients, unless patient preference dictates. Axillary lymph node dissection should be used when there is clinical suspicion of axillary lymph node involvement or high-risk tumours, since adjuvant treatment could depend on the pathological results of the axillary lymph node dissection. Biopsy of sentinel lymph nodes is a safe alternative to axillary lymph node dissection in patients with clinically node negative tumours. Elderly patients with tumour size of less than 2–3 cm and no clinical evidence of axillary involvement should be offered a sentinel lymph node biopsy. Controversy exists with regard to the need for an axillary lymph node dissection after a positive sentinel lymph node biopsy.

Radiotherapy

Tolerability is not a limiting factor for radiotherapy in older patients. Huguenin and colleagues[71] showed no important toxicity in women over the age of 75 years. Similarly, Whyckoff and colleagues[72] compared a group of women aged 65–78 years with a younger group and showed no higher toxicity in women aged 65 years or older. We will discuss radiotherapy after breast-conserving surgery and postmastectomy.

After breast-conserving surgery

Postoperative radiotherapy after breast-conserving surgery combined with appropriate systemic treatment has been shown to achieve reduction in absolute risk of 5-year local recurrence from 25·9% to 7·3% (p<0·0001), and a reduction in 15-year absolute breast cancer mortality risk from 35·9% to 30·5% (p=0·0002).[73] A slight but noticeable increase in non-breast cancer mortality in women who received radiotherapy (mainly heart disease and lung cancer) was probably related to the use of older suboptimum radiotherapy regimens and technique. Despite these benefits, elderly patients continue to receive radiotherapy less frequently after breast-conserving surgery than younger patients.[7,56]

A number of randomised trials, usually limited to an upper age limit of 70 years, show a significant reduction in risk of local recurrence from postoperative breast irradiation, but no effect on overall survival. Some trials have found age to be a factor that predicts for a lower

	5-year local recurrence risk, %		5-year absolute risk reduction, %
	Breast-conserving surgery	Breast-conserving surgery plus radiotherapy	
<50 years	33	11	22*
≥70 years	13	3	11

*p=0·00002 vs women aged ≥70 years.

Table 2: Effects of age and radiotherapy on local recurrence in patients who underwent breast-conserving surgery[73]

	Boost, %	No boost, %	p
Total population (N=5318)	6·2	10·2	<0·001
Aged >60 years (n=1732)	3·8	7·3	0·008

Table 3: 10-year actuarial local recurrence with and without supplementary radiotherapy in patients who underwent breast-conserving surgery for early breast cancer[89]

risk of local recurrence after whole breast irradiation compared with conservative surgery alone.[50,74–79] Several studies have specifically assessed the benefits of radiotherapy in elderly patients. All large studies have shown a decrease in the relative rate of breast tumour recurrence. However, the absolute incidence of relapse as well as the absolute benefit from radiotherapy tended to be low, and data on overall survival was generally absent, with the exception of one trial.[80] Some have concluded that radiotherapy could be avoided in low-risk older patients,[81,82] whereas others have suggested it could offer benefits in terms of slight reductions in local relapse rates[80,83] and improvements in overall survival. The Early Breast Cancer Trialists' Group overview, involving about 42 000 women with breast cancer, showed that the 5-year risk of local recurrence after breast-conserving surgery was higher in women aged under 50 years (33%) compared with those aged over 70 years (13% of 3459 in this age group).[73] The absolute effects of radiotherapy after breast-conserving surgery on local recurrence (mainly in the conserved breast) were also greater for women aged under 50 years than in older women (5-year risk reductions of 22% vs 11%, respectively), although the risk reduction was still significant in older women (table 2). Postoperative breast irradiation should therefore be considered in all patients undergoing breast-conserving surgery, irrespective of age. For women aged over 70 years with a low risk of recurrence (eg, small tumours ≤2cm, clear margins, axillary node-negative, hormone-receptor positive with plans to receive endocrine treatment), the absolute reductions in local recurrence tend to be slight and mortality is usually associated with non-breast-cancer-related conditions. The Cancer and Leukemia Group B (CALG-B) trial, in which women aged 70 years or older with T1,N0,M0 oestrogen-receptor-positive breast cancer were randomly assigned after breast-conserving surgery to tamoxifen alone or to breast radiotherapy and tamoxifen showed only a 3% reduction in breast tumour

recurrence at 5 years (1% *vs* 4%, p<0·001).[81] The use of radiotherapy in such patients should therefore depend on a multidimensional assessment including the absolute benefit of radiotherapy, comorbidity, life expectancy, and patient preference.[47] Shorter courses of radiotherapy, such as hypofractionation, are under investigation.[84–86] There are trials in progress to assess the omission of breast radiotherapy in lower risk older patients.

A supplementary dose (boost) of radiation to the excision site after breast-conserving surgery with clear margins and 50 Gy of whole breast radiation improved 5-year local recurrence (4·3% *vs* 7·3% compared with no boost).[87] Although the absolute benefits decreased with age, the relative effect of reducing the local recurrence by nearly half remains similar in all age groups.[88] The 10-year reduction in risk of local recurrence in patients over the age of 60 years was 3·5% (7·3% *vs* 3·8%; p=0·008) in favour of a boost (table 3).[89] Partial breast irradiation confined to the area around the primary tumour is being explored in prospective trials and has the potential advantage of much shorter overall treatment time.

Postmastectomy radiotherapy

There is limited level I evidence on the effects of postmastectomy radiotherapy in older patients. The largest trial[90] was restricted to patients younger than 70 years. By contrast with radiotherapy after breast-conserving surgery, the absolute effects of post-mastectomy radiotherapy on the 5-year risk of local recurrence (mainly in the chest wall or lymph nodes) have been shown to be independent of age.[73] In this meta-analysis of women who had a mastectomy, axillary clearance, and node-positive disease, reductions in recurrence averaged about 18% in all age groups; however, few women aged over 70 years were included in the trials assessed. A retrospective analysis from the US Surveillance Epidemiology and End Results (SEER) Medicare data from 1992 to 1999 identified 11 594 women aged 70 years or older who had undergone mastectomy for invasive breast cancer.[91] At a median follow-up of 6·2 years, postmastectomy radiotherapy was associated with a significant improvement in survival (hazard ratio 0·85, 95% CI 0·75–0·97, p=0·02) in high-risk patients but not in patients at low or intermediate risk. In a much smaller retrospective cohort of 233 women aged 70 years or over with T3 tumours or with four or more involved nodes referred to the Canadian British Columbia Cancer Agency[92] between 1989 and 1997, the risks of recurrence were significantly lower in women treated by postmastectomy radiotherapy compared with surgery alone (16% *vs* 28%, p=0·03) at a median follow-up of 5·5 years. On multi-variate analysis, high-grade histology and omission of postmastectomy radiotherapy predicted local recurrence. Increasing numbers of involved nodes were

associated with impaired survival and increased risk of distant metastases. In such retrospective series there is probably a selection bias in favour of offering post-mastectomy radiotherapy to fitter patients with higher risk disease.

In principle, patients should be offered postmastectomy chest wall radiotherapy if they have four or more involved nodes, a T3 or T4 tumour, or positive resection section margins.[93] This recommendation is based on the findings of a randomised controlled trial[94] that showed a reduction in locoregional failure and a 10% 10-year survival advantage in high-risk postmenopausal patients who received comprehensive locoregional radiotherapy plus tamoxifen versus tamoxifen alone. The survival advantage only emerged after 5 years. Therefore, in older patients with a life expectancy of less than 5 years, decisions regarding the use of adjuvant radiotherapy should be based on considerations of locoregional control. For patients with T1/T2 tumours with one to three positive nodes, consensus guidelines of the American Society of Clinical Oncology,[93,95] the American Society for Thera-peutic Radiology,[95] and the National Institutes of Health[96] indicate that there is insufficient evidence to recommend routine postmastectomy radiotherapy. Additionally, for node-negative patients with other risk factors (eg, grade 3 histology or lymphovascular invasion), the role of adjuvant radiotherapy is uncertain. For both of these groups the role of adjuvant postmastectomy irradiation is currently being explored by the UK Medical Research Council/EORTC 22052-10051 SUPREMO trial, for which there is no upper age limit of eligibility.

Recommendations

Radiotherapy after breast-conserving surgery and adjuvant systemic treatment decreases the risk of local relapse and should be considered in all elderly patients with breast cancer. The absolute benefit on local relapse might be small in elderly patients with low-risk tumours, but a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) shows no differences in proportional reductions in local recurrence risk by age.[73] The effect of radiotherapy on mortality caused by breast cancer or by any other cause is less clear and further stratification is not available. That radiotherapy will improve overall survival—which is much more affected by comorbidity, ageing, or the occurrence of distant meta-stases than local relapse—is unlikely. A decision to offer radiotherapy will need to take into account patient health and functional status, risks of mortality from comorbidities (particularly cardiac and vascular), and the risks of local recurrence.

In principle, postmastectomy chest-wall irradiation is indicated if patients have four or more involved nodes or a T3 or T4 tumour. In older patients with a life expectancy of less than 5 years, a decision of whether to implement adjuvant radiotherapy should be based on considerations of locoregional control alone. Limited

data are available to support the use of systematic postmastectomy chest-wall radiotherapy in patients with one to three positive nodes or who are node-negative with other risk factors.

Additional doses of radiation to the tumour bed should be considered in older patients after breast-conserving treatment and systemic treatment to decrease risk of local relapse.

Adjuvant hormone treatment

A primary issue is whether or not hormone treatment is necessary in all elderly patients with hormone-receptor-positive early breast cancer. For women with minimum-risk disease, treatment decisions should be based on a risk–benefit analysis that takes into account the low relapse rate within the first 10 years, the potential reduction in ipsilateral and contralateral breast cancer relapse, the patient's life expectancy, and treatment-related adverse events. Patients with oestrogen-receptor-negative and progesterone-receptor-negative tumours should not receive hormone treatment.

Data show that there are no age-related differences in the efficacy of tamoxifen. A meta-analysis by the EBCTCG showed that for hormone-receptor-positive breast cancer, treatment with 5 years of adjuvant tamoxifen reduces the yearly death rate due to breast cancer by 31%, independent of age, compared with no hormonal treatment (figure 3).[97] Another study showed that adjuvant tamoxifen significantly improved 15-year overall survival by 21% compared with no adjuvant hormone treatment in women aged 66–80 years.[98] Most large phase III trials investigating the role of aromatase inhibitors versus tamoxifen (sequentially or head-to-head) have also shown no differential effect of age on the relative efficacies of endocrine treatment (see references 29–35 in webappendix). A specific age-related subanalysis of the MA17 trial showed a significant benefit in the subgroup of women aged under 60 years only.[99] This benefit lost significance above this threshold, possibly because of non-breast cancer deaths, which stresses the competing issues of life expectancy estimation and control of side-effects, even if overall, the absolute benefits of letrozole after 5 years of tamoxifen were similar in the different age groups.[99]

As with younger patients, the choice of adjuvant hormone treatment in older patients should be determined by the risk of relapse, tumour biology, and potential adverse events. Several large randomised studies have compared the efficacy and tolerability of aromatase inhibitors and tamoxifen in the treatment of early breast cancer (see references 29–35 in webappendix). In these studies, aromatase inhibitors were better than tamoxifen in terms of disease-free survival, although there was little difference in rates of overall survival. Except for the ABCSG8-ARNO trial, there was no upper age limit, and the median age was between 61 and 64 years.
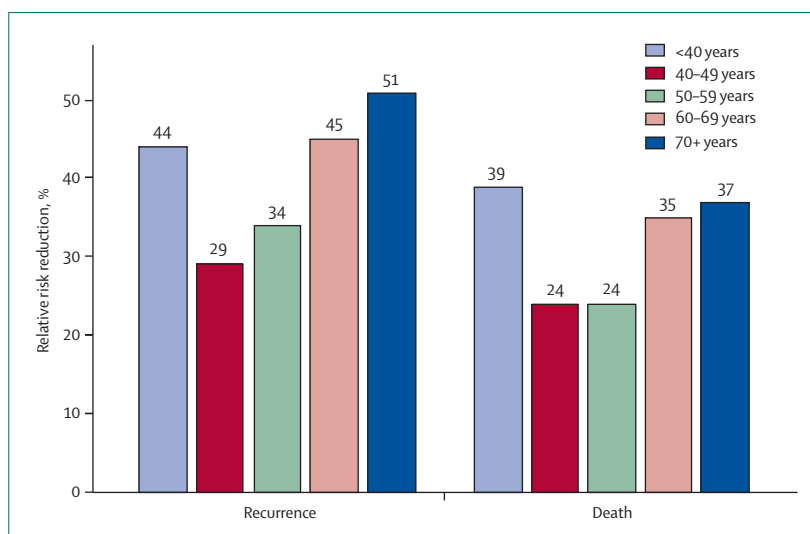

Figure 3: **Relative recurrence and mortality reduction per age group with adjuvant tamoxifen compared with no hormonal treatment**[97]

In terms of tolerability, treatment with tamoxifen is associated with an increased risk of endometrial cancer and thromboembolic events such as deep venous thrombosis, pulmonary embolism, and cerebrovascular accidents. However, the small increase in mortality from endometrial cancer and thromboembolic episodes is much smaller than the mortality reduction as a result of deaths avoided from contralateral breast cancer and cardiovascular events in patients between 50 and 80 years of age.[100] Of note, ageing has been shown to be related to alterations in the metabolism of tamoxifen, resulting in higher levels of tamoxifen and its metabolites in elderly women, but whether this leads to altered efficacy or side-effects is unknown.[101] A lower dose of tamoxifen might prove to be as useful and potentially less toxic than standard doses, as suggested by several biological surrogate endpoints studied in a small randomised trial.[102] This area deserves further investigation.

Aromatase inhibitors are more likely to cause muscle and osteoarticular pain, osteoporosis, and bone fractures than tamoxifen, a consideration in elderly patients who have lower bone mineral density than younger patients. The optimum use of bisphosphonates to prevent bone loss in patients receiving aromatase inhibitors is currently under investigation.[103] The oral bisphosphonates are most commonly used for the treatment of osteoporosis; however, preliminary data suggest that zoledronic acid given intravenously every 6 months is also effective in preventing bone loss.[104] As a general rule, the lack of analysis of the safety profile of aromatase inhibitors according to age is regrettable and common, even in the largest trial of such compounds.[105] There is evidence from the Breast International Group 1-98 trial that the risk of cardiovascular events is slightly raised with aromatase inhibitors compared with tamoxifen. However, since this
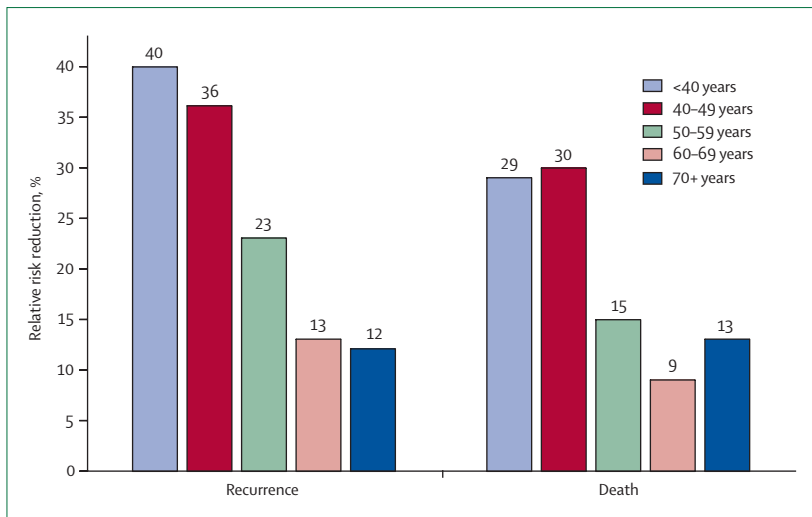
Figure 4: Relative recurrence and mortality reduction per age group with adjuvant polychemotherapy compared with no chemotherapy[97]

evidence has not been reported in other trials comparing an aromatase inhibitor with tamoxifen, nor in the MA17 trial that compared an aromatase inhibitor with placebo after tamoxifen-based adjuvant treatment, we could speculate that this is not a class-related side-effect.

Cognitive impairment has also been described in association with adjuvant hormonal treatment,[106,107] but the data are controversial[108] and insufficient to confirm this association or to compare the relative effect of aromatase inhibitors versus tamoxifen on cognitive function.

Tamoxifen should be started after chemotherapy is completed. For aromatase inhibitors, there are no data on timing related to chemotherapy, but it seems acceptable to use the same approach as that for tamoxifen.

Recommendations
Elderly patients with hormone-sensitive breast tumours benefit from adjuvant hormone treatment. There is no evidence of age-related differences in the efficacy of tamoxifen and aromatase inhibitors. Aromatase inhibitors are slightly more effective than tamoxifen, but elderly patients are more vulnerable to some adverse events, and safety should be an important factor in choosing between tamoxifen and aromatase inhibitors. Older patients who are candidates for endocrine treatment should be offered initial treatment with aromatase inhibitors or tamoxifen. For those initially treated with tamoxifen, consideration should be given to changing to an aromatase inhibitor after 2–3 years of tamoxifen treatment.

Adjuvant chemotherapy
An EBCTCG meta-analysis of randomised trials done before 1995 showed substantial benefits of adjuvant chemotherapy in postmenopausal women in all age groups, compared with no chemotherapy.[97] The gain was larger in those aged under 50 years of age compared with those over 50 years (figure 4). The gain for patients above age 70 years was in the same range as for those between 50 and 70 years, but was not significant due to smaller numbers.

In general, patients with hormone-receptor-negative tumours derived a greater absolute survival benefit compared with patients with hormone-sensitive tumours. Two independent studies using the SEER database[109,110] have shown that adjuvant chemotherapy improves overall survival in elderly patients with oestrogen-receptor-negative tumors and that the benefit was similar for women above and below the age of 70 years. In one of the studies,[109] the benefit was restricted to patients with lymph-node-positive breast cancer. However, the absolute benefit depends on individual patient health and on other tumour parameters, such as lymph-node status, tumour size and grade, and ERBB2 overexpression, and considerable uncertainty remains regarding the subgroups of older women most likely to benefit.

For hormone-sensitive tumours, the benefits of chemotherapy are reduced and less obvious in elderly individuals. Anthracycline-containing regimens have clearly shown improvements in both survival and relapse rate in node-positive postmenopausal patients under the age of 70 years, compared with no anthrocyclines.[111,112] However, whether this benefit also holds true for highly hormone-sensitive low-grade or intermediate grade tumours is not clear.[113] In a large retrospective review of four randomised trials with tumours that were lymph-node positive, but which could be positive or negative for oestrogen receptor, older and younger women derived similar reductions in breast cancer mortality and recurrence from regimens containing more chemotherapy.[114] Only one phase III trial specifically designed for elderly patients (≥65 years of age) has been published.[114,115] In this study, weekly flat doses of epirubicin plus tamoxifen improved disease-free survival compared with tamoxifen alone, but did not improve overall survival. The benefit of adjuvant chemotherapy in addition to hormone treatment in hormone-sensitive breast cancer is likely to be higher in tumours that are not clearly hormone sensitive (eg, low levels of hormone receptors, absence of oestrogen or progesterone receptors, high grade), although no conclusive data are available.

With regard to choice of chemotherapy, healthy older patients can receive the same regimens as their younger counterparts, but care is warranted because elderly patients experience greater toxicity,[116] with up to 1·5% of patients having treatment-related deaths in the CALG-B retrospective analysis.[114] At the 2-yearly breast-cancer conference in St Gallen, Switzerland, in 2005, it was recommended that four cycles of an anthracycline-containing regimen or six cycles of cyclophosphamide, methotrexate, and fluorouraci (CMF) were

adequate treatment for patients with hormone-responsive tumours.[117] For patients with disease unresponsive to hormones, or those in which the hormone response is uncertain, anthracycline-containing regimens with or without taxanes were favoured. However, these recommendations referred to the general population, and the panellists acknowledged that special consider-ations could apply to elderly women. Anthra-cycline-containing regimens have been shown to have better efficacy than CMF, and this effect was not age dependent.[97,117] The potential toxicity induced by taxanes added concurrently or sequentially to anthracyclines is likely to challenge the benefit expected from chemo-therapy. Therefore, these combinations should be confined to biologically aggressive tumours in fit elderly women. Taxane-based regimens could also replace anthracyclines, rather than being added. Although not specifically aimed at elderly patients, a recent study showed that docetaxel in combination with cyclo-phosphamide was better in terms of disease-free survival compared with four cycles of doxo-rubicin-cyclophosphamide.[118] The combination of doce-taxel and cyclophosphamide might be a reasonable alternative for high-risk patients, certainly for those at cardiac risk for anthracyclines.

Adjuvant chemotherapy is an option for elderly patients. However safety concerns should be considered. The use of anthracycline-containing regimens has been associated with a 47% 10-year cardiac failure rate for women aged 66–70 years compared with 33% for CMF recipients and 28% for controls who received no adjuvant chemotherapy.[119] By contrast, CMF has been shown to be less effective and is also poorly tolerated in older women,[120,121] compared with mortality of 1·28% among 545 women aged 65 years or older in the International Breast Cancer Study Group trials.[122] Treatment-related mortality of 1·5% with chemotherapy has also been reported in patients aged 65 years or older in four CALG-B trials,[114] and must be considered when choosing adjuvant chemotherapy. Therefore, in the absence of cardiac contraindications, four courses of anthracycline-containing regimens should be con-sidered in the elderly. Docetaxel and cyclophosphamide might be an alternative, certainly in patients at cardiac risk.[118] Anthracycline-containing regimens and CMF have threshold doses below which efficacy becomes inferior. Thus dose reductions should be avoided in a curative setting. Studies into the use of adapted chemotherapy regimens with limited toxicity for elderly patients are ongoing. Healthy elderly patients with node-positive breast cancer and estimated survival of 10 years or more should be considered for more aggressive chemotherapy regimens that include anthracyclines and taxanes.

Treatment with adjuvant trastuzumab, concurrent with taxanes or after chemotherapy for a total duration of 1 year, improves outcome significantly in ERBB2-positive patients.[123,124] Despite a significant effect on disease-free survival, irrespective of age group, in the Herceptin Adjuvant (HERA) trial, few patients aged 70 years or over have been included in these large trials and oncologists should remain cautious regarding to adjuvant trastu-zumab use in elderly patients. In all these studies, patients with cardiac comorbidity were excluded and, in the National Surgical Adjuvant Breast and Bowel Project B31 study, age over 50 years was an independent predictor of trastuzumab-associated congestive heart failure.[125] Cardiac adverse events are more a concern in older patients who are at higher risk of cardiovascular disease. Healthy elderly patients without cardiac disease and with ERBB2-positive tumours should be considered for trastuzumab treatment. Close cardiac monitoring is essential for older patients receiving trastuzumab in the adjuvant setting.

There are no conclusive data to confirm that colony-stimulating factors confer a survival benefit to elderly patients with breast cancer who are undergoing chemotherapy, despite the known benefits of colony-stimulating factors in reducing febrile neutro-penia, which many elderly patients are at high risk of developing. EORTC and American Society of Clinical Oncology (ASCO) guidelines recommend the use of prophylactic colony-stimulating factors if the expected rate of febrile neutropenia is 20% or higher. They do not advise the systematic prophylactic use of colony-stimulating factors in all elderly patients with breast cancer receiving chemotherapy with a lower than 20% risk of febrile neutropenia, but state that age by itself (≥65 years) can be a risk factor for febrile neutropenia that needs to be taken into consideration in the decision on use of prophylactic colony-stimulating factors.[126,127] Recently, some safety concerns emerged concerning the use of colony-stimulating factors, since the risk of developing leukaemia might increase,[128] but these concerns were not confirmed by another study.[129]

Recommendations

Treatment with adjuvant chemotherapy should not be an age-based decision, but, instead, should take into account individual patients' estimated absolute benefit, life expectancy, treatment tolerance, and preference. Older patients with node-positive, hormone-negative breast tumours potentially derive the largest benefit in survival gain. Although not specifically validated in the elderly population (≥70 years), decision aides such as Adjuvant! Online can be used to help weigh the risks and benefits of adjuvant treatment together with the patient.

In the absence of cardiac contraindications, four courses of an anthracycline-containing regimen are usually preferred over CMF in elderly patients with breast cancer. Taxanes could be added to anthracyclines in high-risk fit elderly women. Docetaxel and cyclo-phosphamide or CMF can replace anthracyclines in

patients at cardiac risk. In the absence of cardiac contraindications, adjuvant trastuzumab should be offered to older patients with ERBB2-positive breast cancer when chemotherapy is indicated, but cardiac monitoring is essential.

Metastatic breast cancer

Metastatic breast cancer is treatable but not curable. Therefore, the main aims in treating elderly patients, like younger patients, with metastatic breast cancer are to maintain quality of life, minimise symptoms from disease, and prolong survival without causing excessive toxicity. Older women are more likely than younger women to be diagnosed at a more advanced stage of breast cancer due to a lack of screening or delays in management.[56,130] In selected patients with low tumour burden and metastases (especially bone metastases only), primary tumour removal can improve survival.[131,132]

Hormone treatment

Hormone treatment should be the treatment of choice for women with oestrogen-receptor-positive or progesterone-receptor-positive tumours without life-threatening disease. The superiority of aromatase inhibitors as first-line treatment over tamoxifen has been shown in the postmenopausal population,[133,134] but whether the same is true beyond the age of 70 years is suggested only in a single trial with letrozole.[135] Since the benefit of aromatase inhibitors over tamoxifen is mainly in terms

of disease-free survival and not overall survival, tamoxifen can be a valuable alternative to aromatase inhibitors if adverse events or cost are a concern. Patients who initially respond to hormone treatment or who have prolonged stable disease can have significant benefit from a subsequent line of non-cross-resistant hormone treatment (eg, tamoxifen when an aromatase inhibitor has been used or vice-versa, or exemestane when anastrozole or letrozole are used or vice-versa). Treatment options include tamoxifen, an aromatase inhibitor, a pure antioestrogen such as fulvestrant, a non-cross-resistant aromatase inhibitor (steroidal aromatase inhibitor when a non-steroidal aromatase inhibitor has been used, or vice versa), progestins, or high-dose oestrogens. There is no evidence for the use of other forms of hormone treatment in elderly patients with breast cancer with metastatic disease, compared with younger postmenopausal patients.

Chemotherapy

Women older than 70 years of age who are treated with chemotherapy for metastatic disease derive similar benefits to their younger counterparts.[136] Older patients should not be excluded from receiving chemotherapy for advanced breast cancer. The use of chemotherapy should be considered in hormone-receptor-negative or hormone refractory patients. If oestrogen or progesterone receptor status is not available or not fully reliable, one course of hormone treatment might be an option, particularly in asymptomatic patients, those without life-threatening metastases, or those who have had a prolonged interval between primary tumour and metastatic disease.

Preference should be given to chemotherapeutic drugs with safer profiles, such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine, and vinorelbine. These drugs are often used in elderly patients with adapted doses compared with younger patients, based on pharmacokinetic or pharmacodynamic (toxicity) alterations in this population, but level I evidence on these specific dosing schedules is generally lacking.[137–142] Monotherapy is generally favoured over combination chemotherapy since the latter is generally associated with increased toxicity and little, if any, survival gain compared with the sequential use of single drugs. Choice of chemotherapy drugs and regimens is dependent on individual patient characteristics and drug availability or reimbursement by the health system. Since chemotherapy in this situation is only palliative, the quality of life is paramount and significant toxicity is generally not acceptable. In principle, dose reductions in elderly patients are not systematically recommended, but should be considered based on pharmacological parameters and altered according to observed toxicity.[137,138,143] Strict follow-up is essential in this population in particular to avoid overtreatment and debilitating side-effects. Chemotherapy

regimens with a risk of febrile neutropenia of more than 20% should be delivered with upfront growth factor support,[126,127] but alternative drugs (eg, liposomal anthracyclines) or regimens with less myelosuppression, such as weekly dosing of anthracyclines and taxanes, are available and do not require prophylactic administration of colony-stimulating factors. Particular attention should be paid to supportive care, since older patients are more likely to develop neutropenia than are younger patients,[144] and generally have less functional reserve than their younger counterparts.

Bisphosphonates provide a supportive, albeit expensive and non-life-prolonging, benefit to many patients with bone metastases. Starting bisphosphonates in women who have bone destruction on imaging but who have normal plain radiographs is considered reasonable treatment.[145] The safety of long-term administration of bisphosphonates in elderly patients with cancer has also been established.[146]

Targeted treatments

Targeted treatments have been shown to be useful in the treatment of breast cancer. In ERBB2-positive patients, trastuzumab should be used in conjunction with chemotherapy. Age is a documented risk factor for congestive heart failure in patients receiving trastuzumab, but depends probably more on pre-existing comorbidities than on age by itself.[147]

In a study of patients of all ages, the addition of bevacizumab to paclitaxel as first-line treatment for metastatic breast cancer showed an improvement in response and disease-free survival.[148] There are few data specific to the risks and benefits of bevacizumab in older patients with breast cancer; however, a pooled analysis of patients with all types of cancer from five randomised trials showed that patients over the age of 65 years are at increased risk of arterial thromboembolic events, particularly when bevacizumab is given in combination with chemotherapy.[149]

Recommendations

The goals of treating metastatic breast cancer in older patients are not different from those in younger patients. For most patients with hormone-receptor-positive breast cancer, hormonal treatment should be the first choice. The use of chemotherapy should be considered in patients with hormone-receptor-negative, hormone-refractory, or life-threatening disease. Choice of chemotherapy drugs and regimens is dependent on individual patient characteristics, preferences, and drug availability.

Conclusions

Elderly patients comprise a large part of the breast cancer population, and there are important specific considerations for this population. Our recommendations for the treatment of breast cancer in such individuals are based on evidence and consensus. However, most of the available data rely on retrospective studies or subanalyses from general population studies, and there is a further need to develop prospective clinical trials for this older population of patients with breast cancer.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. Cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon: IARCPress GLOBOCAN, 2004.
2. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973–1997. *Int J Epidemiol* 2005; **34:** 405–12.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55:** 74–108.
4. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst* 2000; **92:** 550–56.
5. Gennari R, Curigliano G, Rotmensz N, et al. Breast carcinoma in elderly women—features of disease presentation, choice of local and systemic treatments compared with younger postmenopausal patients. *Cancer* 2004; **101:** 1302–10.
6. Singh R, Hellman S, Heimann R. The natural history of breast carcinoma in the elderly—implications for screening and treatment. *Cancer* 2004; **100:** 1807–13.
7. Ballard-Barbash R, Potosky AL, Harlan LC, Nayfield SG, Kessler LG. Factors associated with surgical and radiation therapy for early stage breast cancer in older women. *J Natl Cancer Inst* 1996; **88:** 716–26.
8. Joslyn SA. Radiation therapy and patient age in the survival from early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 1999; **44:** 821–26.
9. Tyldesley S, Zhang-Salomons J, Groome PA, et al. Association between age and the utilization of radiotherapy in Ontario. *Int J Radiat Oncol Biol Phys* 2000; **47:** 469–80.
10. Bouchardy C, Rapiti E, Fioretta G, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol* 2003; **21:** 3580–87.
11. Giordano SH, Hortobagyi GN, Kau SWC, Theriault RL, Bondy ML. Breast cancer treatment guidelines in older women. *J Clin Oncol* 2005; **23:** 783–91.
12. Yancik R, Wesley MN, Ries LAG, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA* 2001; **285:** 885–92.
13. Goodwin JS, Hunt WC, Humble CG, Key CR, Samet JM. Cancer treatment protocols. Who gets chosen? *Arch Intern Med* 1988; **148:** 2258–60.
14. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol* 2003; **21:** 2268–75.
15. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23:** 3112–24.
16. Extermann M, Aapro M, Bernabei RB, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol* 2005; **55:** 241–52.
17. Louwman WJ, Janssen-Heijnen MLG, Houterman S, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *Eur J Cancer* 2005; **41:** 779–85.

18 Walter LC, Covinsky KE. Cancer screening in elderly patients—a framework for individualized decision making. *JAMA* 2001; **285:** 2750–56.

19 Satariano WA. Aging, comorbidity, and breast cancer survival: an epidemiologic view. *Adv Exp Med Biol* 1993; **330:** 1–11.

20 Pierga JY, Girre V, Laurence V, et al. Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. *Breast* 2004; **13:** 369–75.

21 Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; **137:** 347–60.

22 Vainio H, Bianchini F: Breast cancer screening. IARC handbooks of cancer prevention, volume 7. Lyon: IARC Press, 2002.

23 Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002; **359:** 909–19.

24 Galit W, Green MS, Lital KB. Routine screening mammography in women older than 74 years: a review of the available data. *Maturitas* 2007; **57:** 109–19.

25 Fracheboud J, Groenewoud JH, Boer R, et al. Seventy-five years is an appropriate upper age limit for population-based mammography screening. *Int J Cancer* 2006; **118:** 2020–25.

26 Walter LC, Lewis CL, Barton MB. Screening for colorectal, breast, and cervical cancer in the elderly: a review of the evidence. *Am J Med* 2005; **118:** 1078–86.

27 AGS Ethics Committee. AGS position paper: health screening decisions for older adults. http://www.americangeriatrics.org/products/poitionpapers/stopscreeningPF.shtml (accessed Dec 24, 2004).

28 AGS Clinical Practice Committee. American Geriatrics Society (AGS) position statement: breast cancer screening in older women. http://www.americangeriatrics.org/staging/products/poitionpapers/brstcncrPF.shtml (accessed Dec 24, 2004).

29 Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2004. *CA Cancer J Clin* 2004; **54:** 41–52.

30 Gennari R, Rotmensz N, Perego E, dos SG, Veronesi U. Sentinel node biopsy in elderly breast cancer patients. *Surg Oncol* 2004; **13:** 193–96.

31 Audisio RA. The surgical risk of elderly patients with cancer. *Surg Oncol* 2004; **13:** 169–73.

32 Tan LR, Guenther JM: Outpatient definitive breast cancer surgery. *Am Surg* 1997; **63:** 865–67.

33 Najarian MM, Johnson JM, Landercasper J, Havlik P, Lambert PJ, McCarthy D. Paravertebral block: an alternative to general anesthesia in breast cancer surgery. *Am Surg* 2003; **69:** 213–18.

34 Rai S, Stotter A. Management of elderly patients with breast cancer: the time for surgery. *Anz J Surg* 2005; **75:** 863–65.

35 Fentiman IS, Christiaens MR, Paridaens R, et al. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. *Eur J Cancer* 2003; **39:** 309–16.

36 Robertson JFR, Todd JH, Ellis IO, Elston CW, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *BMJ* 1988; **297:** 511–14.

37 Gazet JC, Ford HT, Coombes RC, et al. Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *Eur J Surg Oncol* 1994; **20:** 207–14.

38 Mustacchi G, Ceccherini R, Milani S, et al. Tamoxifen alone versus adjuvant tamoxifen or operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. *Ann Oncol* 2003; **14:** 414–20.

39 van Dalsen AD, de Vries JE. Treatment of breast cancer in elderly patients. *J Surg Oncol* 1995; **60:** 80–82.

40 Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer. *Br J Surg* 2004; **91:** 699–704.

41 Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev 2006; **1:** CD004272.

42 Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005; **23:** 5108–16.

43 Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neo-adjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001; **19:** 3808–16.

44 Buzdar AU. 'Arimidex' (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer-efficacy overview. *J Steroid Biochem Mol Biol* 2003; **86:** 399–403.

45 Hurria A, Leung D, Trainor K, Borgen P, Norton L, Hudis C. Factors influencing treatment patterns of breast cancer patients age 75 and older. *Crit Rev Oncol Hematol* 2003; **46:** 121–26.

46 De Haes JCJM, Curran D, Aaronson NK, Fentiman IS. Quality of life in breast cancer patients aged over 70 years, participating in the EORTC 10850 randomised clinical trial. *Eur J Cancer* 2003; **39:** 945–51.

47 Sandison AJP, Gold DM, Wright P, Jones PA. Breast conservation or mastectomy: treatment choice of women aged 70 years and older. *Br J Surg* 1996; **83:** 994–96.

48 Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N Engl J Med* 1996; **334:** 1356–61.

49 Vandongen JA, Bartelink H, Fentiman IS, et al. Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer—Eortc Trial-10801, breast conservation compared with mastectomy in TNM stage-I and stage-II breast cancer. *Eur J Cancer* 1992; **28A:** 801–05.

50 Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast—long-term results of 3 randomized trials on 1,973 patients. *Eur J Cancer* 1995; **31A:** 1574–79.

51 DiBiase SJ, Komarnicky LT, Schwartz GF, Xie Y, Mansfield CM. The number of positive margins influences the outcome of women treated with breast preservation for early stage breast carcinoma. *Cancer* 1998; **82:** 2212–20.

52 Park CC, Mitsumori M, Nixon A, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol* 2000; **18:** 1668–75.

53 Smitt MC, Nowels KW, Zdeblick MJ, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. *Cancer* 1995; **76:** 259–67.

54 Gage I, Schnitt SJ, Nixon AJ, et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 1996; **78:** 1921–28.

55 Jones HA, Antonini N, Hart G, et al. Significance of margins of excision on breast cancer recurrence (on behalf of the EORTC Radiotherapy, Breast Cancer Groups). *Eur J Cancer* 2004; **2:** (abstr 316).

56 Litvak DA, Arora R. Treatment of elderly, breast cancer patients in a community hospital setting. *Arch Surg* 2006; **141:** 985–90.

57 Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. *J Clin Oncol* 1999; **17:** 143–49.

58 Mandelblatt JS, Edge SB, Meropol NJ, et al. Predictors of long-term outcomes in older breast cancer survivors: perceptions versus patterns of care. *J Clin Oncol* 2003; **21:** 855–63.

59 Yap KPL, McCready DR, Narod S, Manchul LA, Trudeau M, Fyles A. Factors influencing arm and axillary symptoms after treatment for node negative breast carcinoma. *Cancer* 2003; **97:** 1369–75.

60 Martelli G, Miceli R, De Palo G, et al. Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilla? *Cancer* 2003; **97:** 1156–63.

61 Martelli G, Boracchi P, De Palo M, et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer—results after 5 years of follow-up. *Ann Surg* 2005; **242:** 1–6.

62 Truong PT, Bernstein V, Wai E, Chua B, Speers C, Olivotto IA. Age-related variations in the use of axillary dissection: a survival analysis of 8038 women with T1-ST2 breast cancer. *Int J Radiat Oncol Biol Phys* 2002; **54:** 794–803.

63 Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; **349:** 546–53.

64 Holmberg SB, Crivellari D, Zahrieh D, et al. A randomized trial comparing axillary clearance versus no axillary clearance in older patients (=60 years) with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *Proc Am Soc Clin Oncol* 2004; **22:** (abstr 505).

65 Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. *N Engl J Med* 1998; **339:** 941–46.

66 McMahon LE, Gray RJ, Pockaj BA. Is breast cancer sentinel lymph node mapping valuable for patients in their seventies and beyond? *Am J Surg* 2005; **190:** 366–70.

67 Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 1999; **17:** 460–69.

68 Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. *Ann Oncol* 2005; **16:** 383–88.

69 Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; **23:** 7703–20.

70 Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol* 2003; **10:** 1140–51.

71 Huguenin P, Glanzmann C, Lutolf UM. Acute toxicity of curative radiotherapy in elderly patients. *Strahlenther Onkol* 1996; **172:** 658–63.

72 Wyckoff J, Greenberg H, Sanderson R, Wallach P, Balducci L. Breast irradiation in the older woman: a toxicity study. *J Am Geriatr Soc* 1994; **42:** 150–52.

73 Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

74 The Uppsala-Orebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Natl Cancer Inst* 1990; **82:** 277–82.

75 Clark RM, Mcculloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 1992; **84:** 683–89.

76 Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996; **88:** 1659–64.

77 Liljegren G, Holmberg L, Adami HO, et al. Sector resection with or without postoperative radiotherapy for stage-I breast cancer—5-year results of a randomized trial. *J Natl Cancer Inst* 1994; **86:** 717–22.

78 Liljegren G, Holmberg L, Bergh J, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999; **17:** 2326–33.

79 Veronesi U, Luini A, Delvecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993; **328:** 1587–91.

80 Truong PT, Bernstein V, Lesperance M, Speers CH, Olivotto NA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. *Am J Surg* 2006; **191:** 749–55.

81 Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004; **351:** 971–77.

82 Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 2001; **12:** 997–1003.

83 Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst* 2006; **98:** 681–90.

84 Courdi A, Ortholan C, Hannoun-Levi JM, et al. Long-term results of hypofractionated radiotherapy and hormonal therapy without surgery for breast cancer in elderly patients. *Radiother Oncol* 2006; **79:** 156–61.

85 Munshi A, Budrukkar A. Hypofractionated radiation therapy in breast cancer: a revolutionary breakthrough or a long way to go? *J Clin Oncol* 2007; **25:** 458–59.

86 Ortholan C, Hannoun-Levi JM, Ferrero JM, Largillier R, Courdi A. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. *Int J Radiat Oncol Biol Phys* 2005; **61:** 154–62.

87 Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; **345:** 1378–87.

88 Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007; **82:** 265–71.

89 Bartelink H, Horiot JC, Poortmans P, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 years results of the EORTC trial 22881-10882. *Breast Cancer Res Treat* 2006; **100:** S8.

90 Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353:** 1641–48.

91 Smith BD, Haffty BG, Hurria A, Galusha DH, Gross CP. Postmastectomy radiation and survival in older women with breast cancer. *J Clin Oncol* 2006; **24:** 4901–07.

92 Lee JC, Truong PT, Kader HA, Speers CH, Olivotto IA. Postmastectomy radiotherapy reduces locoregional recurrence in elderly women with high-risk breast cancer. *Clin Oncol (R Coll Radiol)* 2005; **17:** 623–29.

93 Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1539–69.

94 Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353:** 1641–48.

95 Harris JR, Halpin-Murphy P, McNeese M, Mendenhall NP, Morrow M, Robert NJ. Consensus statement on postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **44:** 989–90.

96 National Institutes of Health Consensus Development Conference statement: adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst Monogr* 2001; **30:** 5–15.

97 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365:** 1687–717.

98 Crivellari D, Price K, Gelber RD, et al. Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV. *J Clin Oncol* 2003; **21:** 4517–23.

99 Muss HB, Tu D, Ingle JN, et al. The benefits of letrozole in postmenopausal women with early stage breast cancer who have had five years of tamoxifen are independent of age. 29th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 14–17, 2006. Abstract 102.

100 Ragaz J, Coldman A. Survival impact of adjuvant tamoxifen on competing causes of mortality in breast cancer survivors, with analysis of mortality from contralateral breast cancer, cardiovascular events, endometrial cancer, and thromboembolic episodes. *J Clin Oncol* 1998; **16:** 2018–24.

101 Sheth HR, Lord G, Tkaczuk K, et al. Aging may be associated with concentrations of tamoxifen and its metabolites in breast cancer patients. *J Womens Health (Larchmt)* 2003; **12:** 799–808.

102 Decensi A, Robertson C, Viale G, et al. A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. *J Natl Cancer Inst* 2003; **95**: 779–90.

103 Aapro M. Improving bone health in patients with early breast cancer by adding bisphosphonates to letrozole: the Z-ZO-E-ZO-FAST program. *Breast* 2006; **15**: S30–40.

104 Brufsky A, Dong M, Lund K, et al. Twenty-four month follow-up of the effect of zoledronic acid (ZA) on aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (LET). 29th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 14–17, 2006. Abstract 5060.

105 Buzdar A, Howell A, Cuzick J, et al. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; **7**: 633–43.

106 Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. *Psycho-Oncol* 2004; **13**: 61–66.

107 Bender CM, Sereika SM, Ryan CM, et al. Memory impairments with anastrozole versus tamoxifen therapy in women with early stage breast cancer. 28th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 8–11, 2005. Abstract 6074.

108 Jenkins V, Atkins L, Ambroisine L, Fleissig A, Fallowfield L, Howell A. Preliminary results from the IBIS II (prevention) cognitive sub-protocol. 29th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 14–17, 2006. Abstract 6074.

109 Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J Clin Oncol* 2006; **24**: 2750–56.

110 Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. *J Clin Oncol* 2006; **24**: 2757–64.

111 Fisher B, Redmond C, Legaultpoisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast-cancer patients aged 50 years and older with tumors responsive to tamoxifen—results from the National Surgical Adjuvant Breast and Bowel Project-B-16. *J Clin Oncol* 1990; **8**: 1005–18.

112 Albain KS. Adjuvant chemotherapy for lymph node-negative, estrogen receptor-negative breast cancer: a tale of three trials. *J Natl Cancer Inst* 2004; **96**: 1801–04.

113 Albain K, Barlow W, O'Malley F, et al. Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen (ER) and/or progesterone (PgR) receptor-positive breast cancer: mature outcomes and new biologic correlates on phase III intergroup trial 0100 (SWOG-8814). 27th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 8–11, 2004. Abstract 37.

114 Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005; **293**: 1073–81.

115 Fargeot P, Bonneterre J, Roche H, et al. Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. *J Clin Oncol* 2004; **22**: 4622–30.

116 Du XL, Osborne C, Goodwin JS. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. *J Clin Oncol* 2002; **20**: 4636–42.

117 Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005; **16**: 1569–83.

118 Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006; **24**: 5381–87.

119 Giordano SH. Congestive heart failure (CHF) in older women treated with anthracycline (A) chemotherapy (C). *Am Soc Proc Clin Oncol* 2006; **24**: (abstr 521).

120 Crivellari D, Bonetti M, Castiglione-Gertsch M, et al. Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. *J Clin Oncol* 2000; **18**: 1412–22.

121 De Maio E, Gravina A, Pacilio C, et al. Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. *BMC Cancer* 2005; **5**: 30.

122 Colleoni M, Price KN, Castiglione-Gertsch M, Gelber RD, Coates AS, Goldhirsch A. Mortality during adjuvant treatment of early breast cancer with cyclophosphamide, methotrexate, and fluorouracil. *Lancet* 1999; **354**: 130–31.

123 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353**: 1659–72.

124 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353**: 1673–84.

125 Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23**: 7811–19.

126 Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006; **42**: 2433–53.

127 Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24**: 3187–205.

128 Touw IP, Bontenbal M. Granulocyte colony-stimulating factor: key (f)actor or innocent bystander in the development of secondary myeloid malignancy? *J Natl Cancer Inst* 2007; **99**: 183–86.

129 Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. *J Clin Oncol* 2007; **25**: 3871–76.

130 Freyer G, Braud AC, Chaibi P, et al. Dealing with metastatic breast cancer in elderly women: results from a French study on a large cohort carried out by the 'Observatory on Elderly Patients'. *Ann Oncol* 2006; **17**: 211–16.

131 Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery* 2002; **132**: 620–26.

132 Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006; **24**: 2743–49.

133 Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; **21**: 2101–09.

134 Milla-Santos A, Milla L, Portella J, et al. Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer—a prospective, randomized, phase III study. *Am J Clin Oncol* 2003; **26**: 317–22.

135 Mouridsen H, Chaudri-Ross HA. Efficacy of first-line letrozole versus tamoxifen as a function of age in postmenopausal women with advanced breast cancer. *Oncologist* 2004; **9**: 497–506.

136 Christman K, Muss HB, Case LD, Stanley V. Chemotherapy of metastatic breast cancer in the elderly—the Piedmont Oncology Association experience. *JAMA* 1992; **268**: 57–62.

137 Lichtman SM, Wildiers H, Chatelut E, et al. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.

138 Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer* 2007; **43**: 14–34.

139 Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol* 2005; **23:** 2155–61.

140 Del Mastro L, Perrone F, Repetto L, et al. Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: a phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer). *Ann Oncol* 2005; **16:** 253–58.

141 Feher O, Vodvarka P, Jassem J, et al. First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: a multicenter, randomized, phase III study. *Ann Oncol* 2005; **16:** 899–908.

142 ten Tije AJ, Verweij J, Carducci MA, et al. Prospective evaluation of the pharmacokinetics and toxicity profile of docetaxel in the elderly. *J Clin Oncol* 2005; **23:** 1070–77.

143 Wildiers H, Highley MS, de Bruijn EA, van Oosterom AT. Pharmacology of anticancer drugs in the elderly population. *Clin Pharmacokinetics* 2003, **42:** 1213–42.

144 Dees EC, O'Reilly S, Goodman SN, et al. A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer. *Cancer Invest* 2000; **18:** 521–29.

145 Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003; **21:** 4042–57.

146 Tralongo P, Repetto L, Di Mari A, et al. Safety of long-term administration of bisphosphonates in elderly cancer patients. *Oncology* 2004; **67:** 112–16.

147 Giuliani R, Minisini AM, Paesmans M, et al. Is age a risk factor of congestive heart failure (CHF) in patients receiving trastuzumab (H)? Results from two Belgian compassionate use programs in metastatic breast cancer (MBC) patients (pts). *Proc Am Soc Clin Oncol* 2004; **22:** (abstr 838).

148 Miller KD, Wang M, Gralow J, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). 28th San Antonio Breast Cancer Symposium; San Antonio, TX, USA; Dec 14–17, 2005. Abstract 3.

149 Skillings JR, Johnson DH, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizurnab (BV) with chemotherapy. *J Clin Oncol* 2005; **23:** 196S.