



Adrian Deckbar. *Sun Window*. Giclée, 26" × 41". Courtesy of the Hanson Gallery, New Orleans, Louisiana.

*A geriatric assessment in patients over age 70 will facilitate optimal breast cancer management.*

# Management of Breast Cancer in the Older Woman

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**Background:** *Approximately half of all breast cancer cases occur after age 65. Several aspects for the treatment of early breast cancer may be influenced by patient age, including postoperative irradiation after partial mastectomy, axillary lymphadenectomy, primary medical treatment of early breast cancer, and adjuvant chemotherapy.*

**Methods:** *The authors review the literature regarding age-specific issues in the management of breast cancer, and they report their own experience in treating older women with breast cancer.*

**Results:** *In terms of survival and disease-free survival, tamoxifen alone in primary breast cancer is inferior to surgical treatment followed by adjuvant tamoxifen. Tamoxifen alone should be reserved for patients with absolute contraindications to mastectomy. Adjuvant chemotherapy is beneficial to women with hormone receptor-poor tumors. In those with hormone receptor-rich tumors, adjuvant chemotherapy is beneficial for HER2-positive tumors, and the regimen should contain an anthracycline.*

**Conclusions:** *Although the risk of local recurrence after partial mastectomy declines with increasing age, the decision to forego radiation therapy is individualized based on risk of recurrence and on patient desires and resources. The advent of lymph node mapping obviates the need for lymphadenectomy in most patients. The benefits and risks of adjuvant chemotherapy should be individually assessed according to tumor stage, life expectancy, comorbidity, and expected tolerance of treatment.*

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## Introduction

Currently, 48% of breast cancer cases occur in women aged 65 and older, and more than 30% occur in those over age 70.<sup>1,2</sup> The prevalence and incidence of breast cancer in older women may increase by 30% over the next decade if the expansion of the older population continues at the present rate.<sup>2</sup> This article explores age-specific issues of the management of breast cancer in older women, reviews the assessment

of the older person, and discusses the influence of age on the biology of breast cancer and on general aspects of cancer treatment.

## Clinical Definition of Age

Aging is associated with a progressive decline in the functional reserve of multiple organ systems, an increase in prevalence of functional dependence, comorbidity, and memory disorders, and a decline in economic resources and social support.<sup>3,4</sup> These changes influence treatment-related decision making for older individuals because they imply a decrease in life expectancy and tolerance of cancer treatment.<sup>5</sup> Though universal, these changes occur earlier in some people and later in others. Even within the same person, various functions and domains are affected at different rates. This diversity among the older population is poorly reflected in chronological age and thus should be considered when determining optimal treatment approaches for this age group.<sup>5</sup>

A multidimensional comprehensive geriatric assessment (CGA) provides the most reliable information regarding life expectancy, treatment tolerance, social support requirements, and unsuspected conditions (eg, dementia, depression, comorbidity) that may interfere with cancer treatment.<sup>6</sup> Some form of assessment should be performed for all patients aged 70 and

older because age-related changes occur more rapidly in this age group.<sup>3,4</sup> The technical aspects of the CGA are described elsewhere,<sup>5,6</sup> but the basic components of the CGA are presented in Table 1. This article highlights the value of the CGA in the older population in avoiding institutionalization and hospital readmission, maintaining independence, preventing falls, preventing delirium in hospitalized patients, and detecting new and unsuspected problems in 76% of elderly persons living at home.<sup>5,7</sup>

The value of the CGA in the management of the older person with cancer includes:

- Assessment of comorbidity, which may cause older individuals to be susceptible to the complications of chemotherapy. Treatment may reverse or improve many of these conditions.
- Assessment of socio-economic conditions that may prevent compliance with chemotherapy or increase the risk of complications, including access to care and function and independence of the caregiver.
- Assessment of functional dependence that may affect the tolerance of complications from cytotoxic agents.
- Recognition of frailty, a condition in which most functional reserve is exhausted and the aim of treatment is palliation.
- Assessment of emotional and cognitive conditions, such as depression and memory disorders, that may interfere with comprehension and acceptance of treatment plans.
- Some gross estimate of life-expectancy.
- Use of a common language among health care professionals in evaluating the older patient. This common language is necessary for comparisons of the outcome of treatment in different practices and for quality assurance.

Based on the CGA, Hamerman<sup>8</sup> proposed four stages of aging, each implying different survival and functional reserve (Table 2). These stages — primary, intermediate, secondary (frailty), and tertiary (near death) — may be used as a frame of reference for treatment-related decisions.

We recommend that all patients aged 70 and older be subjected to some form of CGA because the prevalence of age-related problems increases after that age.<sup>7,9</sup> Ideally, every older individual should have a pri-

Table 1. — Elements of a Comprehensive Geriatric Assessment

Parameter Assessed	Elements of the Assessment
Function	Performance status Activities of daily living (ADL) Instrumental activities of daily living (IADL)
Comorbidity	Number of comorbid conditions Severity of comorbid conditions (comorbidity index)
Socio-economic conditions	Living conditions Presence and adequacy of a caregiver
Cognition	Folstein mini-mental state evaluation Other tests
Emotional conditions	Geriatric depression scale (GDS)
Pharmacy	Number of medications Appropriateness of medications Risk of drug interactions
Nutrition	Mini-nutritional assessment (MNA)
Geriatric syndromes	Dementia Delirium Depression Falls Neglect and abuse Spontaneous bone fractures

Table 2. — Clinical Definition and Therapeutic Implications of Aging

Stage	Clinical Description	Therapeutic Implications
Primary	No functional dependence No comorbidity Mortality rate at 2 years 8-12%	No limitations in the use of antineoplastic treatment
Intermediate	Dependence in one or more IADLs Significant but not life-threatening comorbidity May have mild memory disorder or depression Mortality rate at 2 years 16-25%	In the use of chemotherapy it is important to: - reduce the initial treatment dose - assure adequate home care - try to rehabilitate the patient to maximal function
Secondary or frailty	Dependence in one or more ADLs Presence of one or more geriatric syndromes Three or more comorbid conditions or presence of comorbidity that significantly influences daily function Mortality rate at 2 years >40%	The condition is irreversible and the main goal of treatment is palliation
Tertiary or near death	Life-expectancy <3 months	Palliation and end of life care

mary care provider responsible for coordinating the patient's care and performing periodic assessments, but any physician or physician-extender part of the oncology team should be able to conduct a CGA. Mindful of the time constrictions of today's practices, we propose that at least an abbreviated screening version of the CGA be adopted,<sup>7,10</sup> with the full assessment being given only to those patients who screen positive in one or more domains.

## General Principles of Cancer Treatment in Older Individuals

Notwithstanding the diversity of the geriatric population, a number of general principles relating to the management of the older patient can be established according to the general aspects of aging. The principles concerning cancer chemotherapy are summarized in the proposed guidelines of the National Cancer Center Network (NCCN)<sup>7</sup> (Table 3).

The glomerular filtration rate (GFR) is the function that most consistently declines with aging.<sup>4,8</sup> In a study of older patients with breast cancer,<sup>11</sup> dose

adjustment of cyclophosphamide and methotrexate was associated with decreased toxicity without compromise of the antineoplastic activity. Two points are noted: (1) A number of drugs (eg, anthracyclines) whose parent compounds are eliminated nonrenally produce active metabolites that are largely excreted through the kidneys,<sup>12</sup> and (2) in the absence of toxicity after the first administration of treatment, escalating the dose of the drugs may be recommended. Given the complexity of human pharmacokinetics and the potential for alternative venues of drug elimination, the area under the curve (AUC) cannot be accurately predicted based on renal function and should be addressed to avoid undertreating the patient.

The risk and severity of myelodepression for moderately intense chemotherapy increase with age.<sup>12,13</sup> In patients aged 70 and older treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combinations of chemotherapy, the risk of severe myelotoxicity has been consistently in excess of 50%, and the risk of mortality varies between 5% and 30%.<sup>14,15</sup> Hemopoietic growth factors have proven to be effective in reducing this complication by 50% or more.<sup>14,15</sup>

Low hemoglobin levels represent an independent risk factor for myelotoxicity.<sup>15</sup> In addition, anemia may be associated with functional dependence and cardiovascular and cerebrovascular complications.<sup>15</sup>

The NCCN guidelines did not address the issue of drug selection. Given the rapid development of cytotoxic drugs of low toxicity potential (eg, low-dose taxanes, capecitabine, navelbine, gemcitabine) and drugs that target the tumor while sparing normal tissue,<sup>16</sup> it is important to recognize that many choices are now available for older women with breast cancer.

Table 3. — NCCN Guidelines for the Management of the Older Cancer Patient With Antineoplastic Chemotherapy

1. All patients aged 70 and older should undergo some form of geriatric assessment.
2. Drugs whose parent compounds or whose active and toxic metabolites are excreted from the kidneys should have the dose adjusted to the glomerular filtration rate (GFR).
3. The prophylactic use of hemopoietic growth factors is recommended for patients aged 70 and older receiving chemotherapy with dose intensity comparable to CHOP.
4. Hemoglobin levels should be maintained >12 g/dL.

## Aging and Biology of Breast Cancer

In general, the behavior of breast cancer appears more indolent with advancing patient age. In older women, the risk of local recurrence of breast cancer after partial mastectomy declines<sup>17,20</sup> and the prevalence of nonvisceral metastases increases.<sup>21</sup> Two mechanisms may be involved in this change of biology (Table 4): a “seed” effect and a “soil” effect, in which the seed is the neoplastic cell and the soil is the older tumor host. It is not surprising to find less aggressive “seeds” in older women than in their younger counterparts. A concentration of more indolent tumors may be expected in older individuals as these tumors develop more slowly and are more likely to become manifest in older individuals.<sup>22</sup> It may be surprising that immunosenescence results in a more indolent tumor growth, as intuitively the immune system should protect the organism from diseases, including cancer. Paradoxically, at least two studies demonstrated that the rate of tumor growth increased with the degree of mononuclear cell infiltration.<sup>23,24</sup> Presumably, mononuclear cells secrete a cytokine that stimulates tumor growth.

While the prevalence of indolent breast cancer increases with the age of the patient, it would be a mistake to assume that all older women have an indolent neoplasm. While it is true that 80% of the cancers occurring in women aged 70 and older are rich in hormone receptors, the converse that 20% of these women have aggressive, hormone-receptor-poor tumors is also true. The treatment should be directed by the aggressiveness of individual neoplasms rather than by the age of the patient.

## Age-Related Management Issues

Patient age may affect all areas of cancer management, including postoperative radiation after partial

Table 4. — Mechanisms by Which the Behavior of Breast Cancer May Become More Indolent in the Older Woman

Seed effect	<p>Increased prevalence of hormone receptor-rich tumors and decreased prevalence of poorly differentiated tumors<sup>21</sup></p> <p>Decreased proliferation rate<sup>22</sup></p> <p>Decreased incidence of lymph node metastases<sup>23</sup></p>
Soil effect	<p>Decreased circulating levels of sexual hormones and growth hormone<sup>24</sup></p> <p>Immunosenescence<sup>21,25</sup></p> <p>Increased concentration of inflammatory cytokines that may inhibit tumor growth<sup>26</sup></p> <p>Decreased neoangiogenesis<sup>27</sup></p>

mastectomy, axillary dissection, the primary treatment of localized breast cancer with tamoxifen, chemotherapy and hormonal therapy in the adjuvant treatment of breast cancer, and the management of the frail patient with metastatic disease.

### Breast Irradiation After Partial Mastectomy

Toxicity does not appear to be an age-related issue. Wyckoff et al<sup>25</sup> reported that women aged 65 and older tolerated breast irradiation as well as younger women did, but the assessment of benefit is more complex.

Several authors found that the rate of local recurrence following partial mastectomy declined with patient age, either with or without radiation therapy.<sup>17-20</sup> Of special interest, Veronesi and colleagues<sup>17</sup> compared prospectively the local recurrence rate of breast cancer after partial mastectomy with and without radiation therapy. They found that the local recurrence rate decreased dramatically after age 55 from 19% to 3% in the absence of postoperative irradiation. According to a common European practice, only patients with tumor diameters less than 2.5 cm were enrolled in this trial and the surgical procedure was in all cases a quadrantectomy. Thus, the conclusions of the trial may not be valid for women with larger tumors or women undergoing a lesser procedure. However, in a United States study, Morrow et al<sup>27</sup> specifically addressed the issue of age and found that the incidence of local recurrences in the absence of radiation therapy in a population of 90 women with a median age of 67 years, T1 tumor (<1 cm in diameter), and negative lymph nodes was 16% after a median follow-up of 16 months.

Since the local recurrence rate of breast cancer declines with age and postoperative irradiation may not be necessary in older women, the decision to forego the inconvenience and cost of radiation therapy must be based on individual assessment of risk and benefits by the patient with the assistance of her clinicians.

Three ongoing prospective studies explored the need of postoperative irradiation after partial mastectomy.<sup>27</sup> The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 compared the local recurrence rate in women of any age with a tumor <1 cm largest diameter treated postoperatively with either breast irradiation and placebo, breast irradiation and tamoxifen, or tamoxifen only. The Cancer and Leukemia Group B (CALGB) 9343 study included women >70 years of age with a tumor size <4 cm and clinically negative nodes and compared postoperative irradiation and tamoxifen with tamoxifen alone. The European Organization for Research and Treatment of

Cancer (EORTC) 10932 study involved women aged >50 with an invasive tumor <2 cm histologic grade I, minimal or absent DCIS component and negative axillary lymph nodes and compared postoperative treatment with irradiation alone or observation. The initial results of the NSABP B-21 study were reported in 2000 and showed that the combination of tamoxifen and radiation therapy was superior to either treatment modality used alone in preventing recurrences both systemically and in the ipsilateral breast.<sup>28</sup>

### *Lymph Node Dissection*

The need for lymph node dissection in older women was questioned when tamoxifen first appeared as an effective form of adjuvant treatment for postmenopausal women. As all patients were destined to receive tamoxifen, the staging of the axilla appeared unnecessary. Two series of women aged 70 and older who were prospectively treated with lumpectomy and no lymph node dissection have been reported, one from Tufts Medical Center<sup>29</sup> the other from the Istituto Nazionale dei Tumori in Milan, Italy.<sup>30</sup> In both reports, more than 80% of the women were disease free at 5 years. The principal drawback with this approach is the lack of information related to axillary involvement, which is vital in determining prognosis, the need for adjuvant chemotherapy, and the risk of locoregional recurrence.<sup>31</sup> The widespread acceptance of the less-morbid lymph node mapping technique in the management of early-stage breast cancer has probably rendered this issue obsolete.<sup>32</sup>

### *Primary Management of Localized Breast Cancer*

Two randomized studies explored primary treatment of localized breast cancer with tamoxifen alone in women aged 70 and older. The 1984 Breast Cancer Campaign Trial (BCCT)<sup>33</sup> compared the use of tamoxifen alone vs partial mastectomy followed by adjuvant tamoxifen in 347 women. More recently, a combined British and Italian study,<sup>34</sup> under the direction of the Group for Research on Endocrine Therapy in the Elderly (GRETA), explored the same issue. After 12 years of follow-up in the BCCT trial and 7 in the British/Italian study, both reported that the breast cancer-related mortality increased for patients who had not received initial surgical treatment. In the present context, these studies have limited relevance since partial and even total mastectomy can be performed under local anesthesia with negligible morbidity<sup>30</sup> and it is recognized that tamoxifen use may be associated with serious cerebrovascular and thromboembolic complications. These studies should be viewed in the historical context in which they were generated, when avoiding

surgery in older patients was a major goal for the management of breast cancer.

## *Systemic Adjuvant Treatment of Breast Cancer*

### *A. Hormonal*

The Early Breast Cancer Trialists' Collaborative Group meta-analysis<sup>35</sup> demonstrates an overall reduction of 25% in recurrence rate and 16% in mortality rate for postmenopausal women treated with tamoxifen for 2 years or longer regardless of whether axillary lymph nodes were involved by cancer. Because the majority of these trials had an upper age limit for enrollment, it is not clear whether the results may be applied to the oldest old. This meta-analysis found that at least 2 years of treatment are necessary for improving patient survival and that 5 years of treatment are superior to 2 years. The benefits of extending treatment beyond 5 years are not established. The NSABP B-14 trial<sup>36</sup> compared 5 and 10 years of tamoxifen in women with hormone receptor-rich tumors and uninvolved lymph nodes and failed to show any advantage for the more prolonged treatment period.

Ongoing clinical trials are exploring the value of prolonging tamoxifen administration beyond 5 years. The Scottish Cancer Trials Breast Group<sup>37</sup> is comparing 5 vs 10 years of tamoxifen in women with uninvolved lymph nodes. The Eastern Cooperative Oncology Group (ECOG) E4181<sup>38</sup> is comparing 5 years of tamoxifen treatment vs lifetime treatment in breast cancer patients with involved axillary lymph nodes. In this relatively small study of patients at high risk of recurrence, prolonging tamoxifen treatment beyond 5 years was associated with reduced tumor recurrence rate. In general, it is reasonable to limit the treatment duration of tamoxifen to 5 years until the results of these trials are available.

Several new options are now available for the endocrine adjuvant treatment of breast cancer. Toremifene, a selective estrogen-receptor modulator, reached the US market in 1998. The effectiveness and toxicity profiles are similar to those of tamoxifen. In the adjuvant setting, tamoxifen and toremifene were compared in a Finnish trial.<sup>39</sup> Toremifene had a small, nonsignificant benefit over tamoxifen in recurrence and survival rates for women with hormone receptor-rich cancer and in the risk of cerebrovascular accidents and endometrial cancer. The pure antiestrogen Faslodex and the new aromatase inhibitors have proved to be effective in metastatic disease resistant to tamoxifen and consequently may result more effective as adjuvant treatment, but their use may be associated with increased risk of osteoporosis.<sup>40</sup>

Table 5. — Age-Related Reduction in Recurrence and Mortality With Tamoxifen and Chemotherapy\*

Age Group	Tamoxifen		Chemotherapy	
	Recurrence	Mortality	Recurrence	Mortality
<50	45% ± 8%	32% ± 10%	37% ± 7%	27% ± 8%
50-59	37% ± 6%	11% ± 8%	22% ± 4%	14% ± 4%
60-69	54% ± 5%	33% ± 6%	18% ± 4%	8% ± 4%
70+	54% ± 13%	26% ± 4%	-	-

\* Data from the Early Breast Cancer Trialists' Cooperative Group meta-analysis.<sup>41</sup>

## B. Chemotherapy

Three issues related to adjuvant chemotherapy are (1) what is the value of chemotherapy in older women, (2) what drugs are effective in older women, and (3) which conditions warrant adjuvant chemotherapy.

The Early Breast Cancer Trialists' Cooperative Group explored the activity of adjuvant chemotherapy in a meta-analysis (Table 5).<sup>41</sup> The benefits of adjuvant chemotherapy in terms of survival and freedom from progression declined with the patient age, and no benefits were seen in patients aged 70 and older. The oldest group of patients, however, represented less than 4% of the total postmenopausal population, which is too small to draw firm conclusions. Since age did not appear to affect the benefits of adjuvant hormonal therapy, one cannot attribute competitive causes of death as an explanation of these findings. Two possible and not mutually exclusive explanations include inadequate dosage<sup>42</sup> and reduced effectiveness.<sup>43</sup>

The examination of individual clinical trials of adjuvant chemotherapy in postmenopausal women helps to identify the most effective agents and the conditions that warrant adjuvant treatment (Tables 6 and 7).<sup>44-60</sup>

Only one study,<sup>50</sup> which was conducted in Italy, failed to demonstrate the advantages of an anthracycline in the adjuvant treatment of postmenopausal women. In fact, Boccardo et al<sup>49</sup> found that a combination of cyclophosphamide, fluorouracil, methotrexate, and epirubicin (CFME) resulted in poorer disease-free and overall survival than tamoxifen alone or CFME plus tamoxifen (CFMET). Rather than denying the benefits of chemotherapy, however, this study supports the impression that tumors rich in hormone receptors are less sensitive to chemotherapy than are tumors poor in hormone receptors. The lack of benefits of chemotherapy in combination with tamoxifen may be explained to some extent by the design of the treatment program, with epirubicin being given after six courses of CMF, ie,

the design contradicted the principle of “best drug first.” It is also possible that the significant toxicity of chemotherapy prevented the use of effective dose/intensity of the drugs.

The results with CMF-like combinations of chemotherapy in the presence of lymph node involvement are less clear. In the NSABP B-07 study,<sup>44</sup> first published in 1977, patients were divided by age (under 50 and 50 and over) rather than by menopausal status. Probably only a limited number were older than 60 years of age. It is possible that the benefits seen in this study concerned mainly old premenopausal women (women who went through menopause in their 50s). Southwest Oncology Group (SWOG) investigators conducted two subsequent studies in postmenopausal women. In the first study,<sup>52</sup> women were randomized to receive melphalan for 2 years or CMFVP for 1 year. The combination appeared superior to single-agent melphalan in terms of disease-free and overall survival. In the second study,<sup>53</sup> which included only women with tumors rich in hormone receptors, investigators compared tamoxifen and CMFVP plus tamoxifen and found that the chemotherapy did not enhance the benefits of tamoxifen. A reasonable conclusion is that this type of chemotherapy may be beneficial to women with hormone receptor-poor tumors but has no appreciable effects in those with hormone receptor-rich tumors. The International Breast Cancer Study Group investigators conducted a large study<sup>57</sup> of CMF in postmenopausal women and showed that the benefits in terms of overall survival declined with advancing patient age and disappeared after age 65.

The Milan study of patients with node-negative tumors<sup>43</sup> reported an improvement of survival for postmenopausal women with negative lymph nodes, but this study had two major flaws: a small number of patients and inadequate patient selection. The only adverse prognostic factor was absence of estrogen receptors, with no consideration for nuclear grade, tumor size, and more recently identified prognostic factors (eg, tumor cell proliferation, *c-erbB-2* concentration, and neovascularization). A recent update of the NSABP B-13 study<sup>61,62</sup> indicates a small advantage in overall survival for postmenopausal women with node-negative tumors who received adjuvant chemotherapy with methotrexate and fluorouracil. An intergroup study<sup>63</sup> reported improved disease-free survival but not overall survival with CMF. It is possible that no difference in survival has emerged yet due to the low number of cancer-related deaths expected in the control group from this patient population with a relatively good prognosis. The NSABP B-20 study<sup>64</sup> also reported a minimal benefit of CMF plus tamoxifen over tamoxifen alone in women with hormone receptor-rich

Table 6. — Selected Trials of Adjuvant Chemotherapy in Postmenopausal Women

Trial	Number of Patients	Upper Age	Patient Characteristics	Regimens	Disease-Free Survival Gain	Survival Gain
NSABP B-07 <sup>44</sup>	1,863	70	+LN	p vs pF	32%	27%
NCCTG <sup>45</sup>	234	75	+LN	CFP vs CFPT vs O	18%	-
ECOG <sup>46</sup>	265	65	+LN	CFMP vs CFMPT vs O	ER+ : - ER- : 18%	-
ECOG <sup>46</sup>	962	80	+LN	CFMPT × 12 vs CFMPT × 4	-	-
NSABP B-11 <sup>47</sup>	281	59	+LN -PR	pF vs pAF	7%	6%
NSABPB-12 <sup>48</sup>	758	70	+LN +PR	pFT vs pAFT	-	-
NSABP B-16 <sup>49</sup>	1,245	70	+LN +PR	T vs ACT	17%	10%
GROCTA <sup>50</sup>	267	65	+LN +ER	T vs CMFE vs CMFET	-25%	-12%
GBSG <sup>51</sup>	546	70	+LN	CMF × 3 vs CMF × 6 ± T	-	-
SWOG <sup>52</sup>	214	NS	+LN -ER	P vs MFVP	14%	12%
SWOG <sup>53</sup>	966	87	+LN +ER	CMFVPT vs T	-	-
CALGB <sup>48</sup>	723	65	+LN	CAh vs CAi vs CA	18%	8%
Milan <sup>54</sup>	188	65	>3 +LN	A→CMF vs A/CMF	30%	12%
GABGG <sup>55</sup>	456	65	Low risk High risk	T vs CMF AC vs ACT	-23% 21%	- 10%
Canada <sup>56</sup>	705	Not stated	+LN +ER or PR	T vs CMFT	-	-
Ludwig III <sup>57</sup>	463	Not stated	+LN ±HR	O vs pT vs CMFpT	20%	8%
IBCSG Trial VII <sup>57</sup>	608	Any age	+LN	T vs CMFT	Age 52-65: 13% Age >65: -	- -
ICCG <sup>58</sup>	604	75	+LN	E vs ET	28%	11%
FASG <sup>59</sup>	565	75	1-3 +LN -HR >3 +LN any ER	FEC 50* vs FEC 100*	22%	18%
IGT 0100 <sup>60</sup>	1,470	80	+LN +HR	CAFT vs CAF→T vs T	24%	12%

\* 50 and 100 refers to epirubicin mg/m<sup>2</sup> - = no difference CALGB = Cancer and Leukemia Group B ECOG = Eastern Cooperative Oncology Group FASG = French Adjuvant Study Group GABGG = Gynecological Adjuvant Study Group Germany GBSG = German Breast Cancer Study Group GROCTA = Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group IBCSG = International Breast Cancer Study Group ICCG = International Cooperative Breast Cancer Group IGT = Intergroup Trial NCCTG = North Central Cancer Treatment Group NSABP = National Surgical Adjuvant Breast and Bowel Project SWOG = Southwest Oncology Group

A = Adriamycin (doxorubicin) C = cyclophosphamide E = epirubicin F = fluorouracil M = methotrexate O = observation P = prednisone p = melphalan T = tamoxifen V = vincristine h = high-dose intensity i = intermediate-dose intensity l = low-dose intensity → = followed by / = alternating with

Table 7. — Randomized Clinical Trials of Adjuvant Chemotherapy in Postmenopausal Node Negative Women

Study	Number of Patients	Upper Age	Characteristics	Regimen	Outcome	
					DFS	Survival
Milan Node (-) <sup>43</sup>	90	65	-LN; -ER	CMF vs O	40%	28%
NSABP B-13 <sup>61,62</sup>	280	60	-LN; -ER	O vs M → F	17%	14%
Intergroup <sup>63</sup>	153	70	-LN	O vs CMFP	12%	-
NSABP B-20 <sup>64</sup>	2,306	75	-LN; +HR	T vs MFT vs CMFT	25-50%	15-20%

NSABP = National Surgical Adjuvant Breast and Bowel Project  
 → = sequential  
 ER = estrogen receptor  
 HR = hormone receptors  
 C = cyclophosphamide  
 F = fluorouracil  
 M = methotrexate  
 O = observation  
 P = prednisone  
 T = tamoxifen

lymph node-negative tumors, and these benefits were mostly limited to premenopausal or younger postmenopausal women. A recent meta-analysis involving 2,368 postmenopausal patients showed that CMF improved by 5.5% the disease-free survival with no effect on overall survival.<sup>65</sup>

A paradox emerges from the analysis of these trials: women with hormone-receptor poor tumors may benefit from the less-toxic CMF-like chemotherapy, whereas women with receptor-rich tumors appear to benefit from adjuvant chemotherapy only when an anthracycline is included. A possible explanation to this paradox was provided by the analysis of the HER2/neu status of patients involved in the SWOG Phase III Intergroup Trial (SWOG-8814, INT-0100).<sup>60</sup> Postmenopausal women with involved lymph nodes and high hormone receptor concentrations were randomized to receive tamoxifen alone or tamoxifen with cyclophosphamide, doxorubicin, and fluorouracil (CAF). For tumors with low HER2/neu concentrations, chemotherapy did not provide any sizable advantage. For those rich in HER2/neu, however, chemotherapy improved disease-free survival by almost 50% at 4 years. An anthracycline-containing chemotherapy is preferable in patients with high concentrations of HER2/neu.<sup>66</sup>

An important consideration related to these trials of postmenopausal women concerns the underrepresentation of women over 70 years of age. Women in this age group were included in only a few trials and always in a proportion much lower than the prevalence of cancer in that age group.

The question of which older women may benefit from adjuvant chemotherapy was addressed in a deci-

sion analysis.<sup>67</sup> Assuming the majority of patients would accept adjuvant chemotherapy for a 1% gain in cure rate or survival, the authors calculated the threshold for the risk of relapse from breast cancer above which adjuvant chemotherapy would be beneficial. They found that the threshold varied with the age, functional status, and health status of the patient. For a 70-year-old woman in average health, adjuvant chemotherapy would be beneficial for her survival if her risk of relapse is 10% or higher and for an 80-year-old, when it is 21% or higher. On the other hand, the influence of age on the benefit in relapse is low.

### *Management of the Frail Patient*

With the expansion of the older population, the number of frail elderly and frail elderly with cancer is expected to rise. According to a conservative estimate, approximately 400,000 frail elderly in the United States are affected by some form of cancer at any given time.<sup>16,68</sup> As already noted, frailty is not equivalent to near death — the average life expectancy of a frail person is in excess of 2 years.<sup>16</sup> Many frail cancer patients have breast cancer with bone metastases that are not life threatening but require active symptom palliation. The use of opioids is complicated by delirium, constipation, and nausea, and these side effects may become so disturbing that an older patient may prefer to tolerate pain rather than the symptoms related to pain management.<sup>69</sup> However, recent drug developments offer options to the frail cancer patients. In addition to the use of bisphosphonates for bone metastases, new anti-tumor agents including capecitabine, low weekly doses of taxanes, liposome-encapsulated doxorubicin, navelbine, and gemcitabine may be beneficial to these individuals while producing minimal toxicity.

## Conclusions

Because breast cancer is a common and generally chronic disease, it is an excellent model to study age-specific issues in the management of cancer. These issues include (1) more indolent clinical course of breast cancer in older women due to more indolent intrinsic disease and lesser support of tumor growth by the older tumor host, (2) advisability of radiation therapy after partial mastectomy since the risk of local recurrence declines with the increasing age of the patient; the balance of risk and benefits includes a personal evaluation of the patient with the help of her primary care provider, (3) the need for lymph node dissection (the advent of lymph node mapping has rendered this issue obsolete), and (4) primary medical treatment of local breast cancer; two large randomized studies showed that this form of treatment provides inferior results to respect to surgery.

In older women with breast cancer, the optimal duration of adjuvant treatment with tamoxifen is probably 5 years. Ongoing studies are exploring other hormonal approaches or more prolonged treatment in the presence of lymph node metastases. Anthracycline-containing combination chemotherapy appears to be beneficial in women with hormone receptor-rich tumors when HER2/neu is overexpressed. A decision analysis may help in selecting older women who will benefit from adjuvant chemotherapy. Frail patients may benefit from "gentle" chemotherapy for palliation of metastatic disease.

We propose the following recommendations related to the management of breast cancer in the older woman:

- Radiation therapy following partial mastectomy is desirable in all cases in which the tumor is larger than 1 cm in diameter. However, watchful waiting is reasonable in patients with limited life expectancy or in those for whom traveling for radiation therapy may cause severe inconvenience.
- Older women should undergo lymph node mapping and have axillary dissection only when the sentinel lymph node is involved by breast cancer.
- Adjuvant treatment with tamoxifen is indicated in women with hormone receptor-positive tumors if no contraindications are present. The optimal treatment duration is 5 years. In women with a history of thromboembolic disease, treatment with an aromatase inhibitor is a reasonable alternative.
- Adjuvant chemotherapy, preferably including an

anthracycline, is beneficial in older women who have substantial risk of dying of breast cancer. The risk threshold for which adjuvant chemotherapy is indicated increases with age. Ideally, adjuvant chemotherapy should include an anthracycline, especially in patients with HER2/neu-positive tumors.

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