

PRIMARY BREAST CANCER IN THE ELDERLY

H. Lavina A. Lickley, MD, PhD

OBJECTIVES: With respect to breast cancer in the elderly, to define "old" in the context of comorbidity and physiologic rather than chronologic age. In addition, after discussion of factors influencing decisions regarding screening, stage at presentation and treatment decisions, to present an approach to the treatment of primary breast cancer in the elderly, taking into account quality of life, expected outcomes and cost-effectiveness.

DATA SOURCES: A review of the medical literature from 1980 to 1996, using the MEDLINE database and 2 relevant studies from The Henrietta Banting Breast Centre Research Programme at Women's College Hospital, Toronto.

STUDY SELECTION: A large number of breast cancer studies that might provide a better understanding of primary breast cancer in the elderly.

DATA SYNTHESIS: The studies reviewed demonstrated that the annual incidence of breast cancer increases with age, along with a longer life expectancy for women. There appears to be a delay in presentation for elderly women with breast cancer, related in part to patient and physician knowledge. Biennial mammography and physical examination are effective in women aged 50 to 74 years, but compliance with screening recommendations decreases with age. Although treatment goals are the same for women of all ages, most treatment decisions are based on studies that seldom include women over 65 years of age. Physicians tend to underestimate life expectancy and older women are less likely to seek information. Breast conserving surgery, partial mastectomy and even axillary dissection can be carried out under local anesthesia with little physiologic disturbance, but unless axillary dissection is required to make a treatment decision, it may be foregone in clinically node-negative elderly women. The role of adjuvant radiotherapy in the elderly is not yet well established; tamoxifen is the usual adjuvant systemic therapy given to older women. For those who are truly infirm, tamoxifen alone can be considered. Studies to date do not clarify whether breast cancer in older women runs a more or less favourable course. However, locoregional recurrence appears to decrease with age. Deaths from competing causes are a confounding issue.

CONCLUSIONS: It is imperative to develop a coherent strategy for the treatment of primary breast cancer in the elderly that takes into account functional status and quality of life. Clinical trials must include older women and there must be good clinical trials designed specifically for older women.

OBJECTIFS : En ce qui concerne le cancer du sein chez les personnes âgées, définir le terme «âgé» dans le contexte de la comorbidité et de l'âge physiologique plutôt que chronologique. En outre, après discussion au sujet des facteurs qui jouent sur les décisions relatives au dépistage, le stade au moment de la présentation et les décisions relatives au traitement, présenter une stratégie de traitement du cancer du sein primaire chez les personnes âgées qui tiennent compte de la qualité de vie, des résultats attendus et de l'efficacité des coûts.

SOURCES DE DONNÉES : Recension des écrits médicaux de 1980 à 1996 dans la base de données MEDLINE et deux études pertinentes du Henrietta Banting Breast Centre Research Programme au Women's College Hospital de Toronto.

From The Henrietta Banting Breast Centre, Women's College Hospital, Toronto, Ont.

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Correspondence to: Dr. H. Lavina A. Lickley, Suite 522, The Henrietta Banting Breast Cancer Centre, Women's College Hospital, 60 Grosvenor St., Toronto ON M5S 1B6

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SÉLECTION D'ÉTUDES : De nombreuses études sur le cancer du sein qui pourraient permettre de mieux comprendre le cancer du sein primaire chez les personnes âgées.

SYNTHÈSE DES DONNÉES : Les études examinées ont démontré que l'incidence annuelle du cancer du sein augmente avec l'âge et avec l'espérance de vie plus longue des femmes. Les femmes âgées atteintes du cancer du sein semblent se présenter en retard, et le retard semble lié en partie aux connaissances de la patiente et à celles du médecin. La mammographie biennale et l'examen médical sont efficaces chez les femmes de 50 à 74 ans, mais l'observation des recommandations relatives au dépistage diminue avec l'âge. Même si les buts du traitement sont les mêmes chez les femmes de tous les âges, la plupart des décisions relatives au traitement sont fondées sur des études qui incluent rarement des femmes de plus de 65 ans. Les médecins ont tendance à sous-estimer l'espérance de vie et les femmes âgées sont moins susceptibles de chercher à se renseigner. Les interventions de conservation du sein, la mastectomie partielle et même la dissection des ganglions axillaires peuvent se faire sous anesthésie locale et entraînent peu de troubles physiologiques, mais si une dissection des ganglions axillaires n'est pas nécessaire pour prendre une décision relative au traitement, on peut y renoncer chez des femmes âgées dont les ganglions sont négatifs sur le plan clinique. Le rôle d'une radiothérapie adjuvante chez les personnes âgées n'est pas encore bien établi et l'on administre habituellement aux femmes âgées du tamoxifène comme traitement général adjuvant. Chez les personnes vraiment invalides, on peut envisager le tamoxifène seulement. Les études réalisées jusqu'à maintenant ne clarifient pas si le cancer du sein chez les femmes âgées a une évolution plus ou moins favorable. La récurrence locorégionale semble toutefois diminuer avec l'âge. Les décès causés par d'autres facteurs sont une cause de confusion.

CONCLUSIONS : Il est impératif d'élaborer une stratégie cohérente de traitement du cancer du sein primaire chez les personnes âgées qui tienne compte du statut fonctionnel et de la qualité de vie. Les études cliniques doivent porter aussi sur les femmes âgées et il faut procéder à de bonnes études cliniques conçues spécifiquement pour elles.

Four concepts concerning breast cancer were derived solely from the cover picture in *Time* magazine or *The New York Times*, we would believe that breast cancer is solely a disease of the young and beautiful. However, data from the Surveillance, Epidemiology and End Results (SEER) study have given us a different and much more accurate perspective: the annual incidence of breast cancer increases with age, thus for a woman aged 65 years breast cancer is 3 times more likely to develop in the coming year than for a woman of 45 years.¹ Thus, between the ages of 30 and 80 years, the annual incidence of breast cancer rises from 1:5900 to 1:290.^{2,3} It has been estimated that by the year 2030, almost two-thirds of the women in whom breast cancer is diagnosed will be 65 years of age or older.⁴

It has been stated⁵ that 18 600 cases of breast cancer will be diagnosed in Canada in 1996, and of these 10 900 (58.6%) will be in women 60 years of age and older, and 3500 (18.8%) in women between 50 and 59 years of age. With respect to the death

rate, it is estimated that 5300 women will die of breast cancer in Canada in 1996; 3700 (69.8%) of these will be 60 years of age or older and 810 (15.3%) will be aged 50 to 59 years. The incidence of breast cancer in Canada has risen steadily over the past decade,⁵ attributed by many to increasing mammographic surveillance. However, a substantial proportion of this increase occurred in women above the age targeted in most breast cancer screening programs. There has been considerable interest in primary breast cancer in the elderly, and a number of investigators have addressed aspects of this problem.⁶⁻¹⁴

People are living longer: in an issue of *Cancer Control* devoted to various aspects of breast cancer in the elderly, the editors pointed out that in 1950 only 8% of the population was over 65 years of age, whereas by the year 2000 approximately 13% of the population would be over 65,³ and that the fastest growing group was the "over 80s." Since age is the single most important risk factor for breast cancer,^{1,2,15} the appropriate management of breast cancer

in the elderly should be a major concern in geriatric medicine.

Over the years there have been several recurring themes with respect to breast cancer in the elderly, and I would like to pose the following questions:

- How do you define old?
- What are the issues relating to comorbidity?
- What factors influence the stage of presentation?
- What are the issues around screening for breast cancer?
- What factors play a role in treatment decisions for patients with primary breast cancer? — principles of management, deciding what constitutes "appropriate" treatment for breast cancer in the elderly, the role of clinical trials in decision-making around the treatment of breast cancer in the elderly, why data are relatively scarce, physician-related factors and patient factors important in treatment decisions.
- What treatment options are there for primary breast cancer in the elderly, including surgery, radiother-

apy and adjuvant systemic therapy?

- What modifications in treatment are appropriate for the truly infirm?
- What are the cost considerations?
- What is the impact of breast cancer on the quality of life of elderly women?
- How fast does breast cancer progress, are outcomes better or worse and are prognostic factors any different in the elderly?

HOW SHOULD WE DEFINE OLD?

Is old age reached at 60, 65, 70, 75, 80 (somewhat trendily referred to as old-old) or even 90 (oldest-old) years of age? Age means different things to different people at different times and in different contexts, so it is inadequate to designate a woman as old solely on the basis of chronologic age. A more useful definition is the biologic or physiologic age, which relates to social, cultural, psychological, mental and functional status.

ASSESSMENT OF COMORBIDITY

In considering age, one must also take into account factors relating to the concept of comorbidity. Overall health must play an important decision-making role for the optimal treatment of older women with primary breast cancer. The whole issue of multiple or comorbid conditions assumes greater significance in older women. Greenfield and colleagues¹⁶ have developed a measure of this, which they have termed a comorbidity index; it rates 11 system categories, including "circulation, respiration, neurological, mental status, urinary, feeding, ambulation, transfer, vision, hearing and speech."¹⁶ Each individual condition is given a value. Complications and how they affect the functional status are also taken into account. These are rated for each category on a 3-point

scale (0 represents no comorbid disease, 1 represents mild, controlled comorbid disease and 2 represents moderate to severe comorbid disease). Of considerable interest was the finding that the 3-year rate for death unrelated to the cancer per se was increased 28-fold in elderly patients with 3 or more comorbid conditions. Caron stated recently¹⁷ that although age influences the ultimate outcome as a result of the gradual decline in physiologic reserve of organ function, the increased presence and severity of concomitant disease appears to have an even greater effect on outcome.

FACTORS INFLUENCING THE STAGE OF PRESENTATION

There appears to be a significant delay in presentation in elderly women, as evidenced by more advanced disease (both regional and metastatic), fewer asymptomatic cases and a longer time between the onset of symptoms and presentation.^{6,18-21} The stage of any cancer at the time of diagnosis not only relates to the biologic characteristics of the tumour and the host but is also influenced by both patient and physician and patient knowledge and behavioural characteristics.²² The elderly may exhibit reduced homeostatic mechanisms and reserve capacity and are more subject to iatrogenic illness. They are also more likely to be widowed, poor or multiply dependent, all of which can have an impact on both detection and response to treatment.

SCREENING FOR BREAST CANCER

It has been well-established that screening asymptomatic women aged 50 to 74 years for breast cancer using mammography and physical examination of the breast prevents deaths from breast cancer.^{21,23,24} However, a consis-

tent observation has been an age-related decline in compliance with screening recommendations.^{25,26} This may relate to factors such as lack of information, poor accessibility, lack of transportation and lack of physician support.²⁷ Mah and Bryant⁶ have shown that knowledge about breast cancer among women decreases with age. Also, problems relating to social support, cultural differences and functional status all have a bearing on whether or not older women are screened.

Organizations have made differing screening recommendations, which can be confusing to women and the professionals who care for them. One pragmatic recommendation is that if the woman is functional with a life expectancy estimated at 3 years or more, screening should be carried out.²⁸ Cost may also be a barrier to screening. It has been estimated that to scan 25% of the female population between the ages of 55 and 75 years would cost \$80 000 to \$90 000 per year of life saved.²⁸

Sterns⁷ has shown that the cancer detection rate actually increases with age for every mode of presentation (mass, nodularity, pain, skin and nipple changes and discharge). Also, breast masses are very likely to be malignant in older women.

Although there is no proof that screening offers secondary prevention in women over 75 years of age, early detection of breast cancer may improve quality of life.

FACTORS INFLUENCING TREATMENT FOR BREAST CANCER

Principles of management

There is a wide range of treatment options, but the basic principles of breast cancer management, such as attempting to control local disease,

preventing metastatic spread and treating symptomatic disease, should be equally applicable to older and younger women.⁴ In deciding on the optimal treatment for breast cancer in the elderly, several questions must be answered: Is the treatment contemplated as effective in older women? Is the toxicity of a treatment different in elderly women from that in younger women? Is the treatment necessary? and Will the woman live long enough to benefit from the treatment?²⁹

What constitutes “appropriate” therapy for breast cancer?

The concept of “appropriate” therapy is an appealing one. The NIH Consensus Conference on the treatment of early stage breast cancer³⁰ concluded that partial mastectomy with levels I and II axillary lymph-node dissection and the addition of adjuvant breast irradiation is the preferred form of treatment for the primary tumour regardless of age, with total mastectomy being reserved for multicentric or relatively large primary tumours. Systemic therapy in the form of tamoxifen or other chemotherapy may be recommended according to circumstances. The recommendations concerning surgery were based on 4 large randomized trials, which compared total mastectomy with breast conservation and postoperative breast irradiation.³¹⁻³⁴ These trials showed no difference in disease-free survival or overall survival, but few of the women involved were older than 65 years. It may well not be valid to extrapolate recommendations derived from studies involving younger women to the elderly.

The role of clinical trials in treatment decisions

To determine how best to treat women with breast cancer, we rely on

the results of properly conducted clinical trials. Unfortunately controlled trials of cancer therapy have failed to involve older women in sufficient numbers,^{29,35,36} perhaps for logistic reasons. It has also been stated that the relative difficulty in obtaining truly informed consent in the elderly can add to the difficulty of carrying out prospective randomized controlled clinical trials.³⁷ Prospective cohort studies may be more feasible in elderly patients. In addition, comorbidity is a confounding factor in assessing outcomes of treatment and is not always easy to take into account. Nonetheless, it was encouraging to find a listing of clinical breast cancer research protocols in which older women took part. Fourteen were for, or included, postmenopausal women and 2 trials were specifically designed for women over 70 years of age.³⁸

Factors relating to physicians that can influence treatment decisions

It is often stated that older women receive less than definitive treatment aimed at potential cancer control.^{16,39-44} It is true that a less aggressive treatment approach seems entirely reasonable for frail patients with recognizable comorbidity.⁴³ However, in 1 study of women over the age of 70 years, all with a low comorbidity index, fewer patients received definitive potentially curative treatments than would have been provided for younger women,¹⁶ suggesting that physicians may treat according to chronologic rather than physiologic age, and this may translate into poorer outcomes.

Physicians tend to spend less time with their elderly patients and are less likely to involve them in decision-making,^{43,45,46} and physical and social disabilities are frequently underes-

timated.⁴⁷ Also, many physicians are not up to date on current life expectancy.^{29,43,48} A woman who is 75 years old has an average life expectancy of 12 years. In a group of physicians polled, approximately 40% estimated life expectancy for a 75-year-old woman to be 4 years or less and 85% underestimated it by at least 2 years.^{43,48} In addition, local customs for treatment can become entrenched. A study was done to assess the distribution of breast conserving therapy in Medicare patients over 65 years of age in the United States.⁴⁹ In many states, breast conserving therapy was carried out in less than 10% of cases, and the highest rate was less than 22%.

Factors relating to the patient and her family that can influence treatment decisions

Some problems are related to the patient herself, who may even be older than the clinician and therefore less likely to seek information and to challenge. She may also tend to act on beliefs accumulated over years.³ The family can play a greater or lesser role in medical decision-making.

TREATMENT OPTIONS FOR PRIMARY BREAST CANCER

With respect to every modality of possible treatment for primary breast cancer in the elderly, there are controversies — regarding the extent of surgery on the breast, whether or not an axillary dissection should be carried out, if radiation to the breast should be given and regarding the role of adjuvant therapy.

Surgical treatment

With respect to surgical treatment, several authors have written over the years about the ability of older women

to withstand even a radical mastectomy,^{35,50} but should this, in itself, constitute a reason for such an aggressive surgical approach? Although, as mentioned before,³⁰ partial mastectomy is the preferred surgical treatment to total mastectomy in most cases, the SEER data from Detroit showed that women over 55 years of age were actually much less likely to have had breast conserving surgery,⁵¹ although when women were 85 years or over, this trend was reversed.^{1,29} There are no data to suggest that older women should not undergo breast conserving surgery, and there is nothing to say that an older woman is not as upset as a younger woman by the sequelae of breast loss. However, the older woman herself may be part of the equation by choosing total mastectomy "just to be sure" or to obviate the need for radiotherapy.

Surgery for breast cancer, particularly partial mastectomy, does not usually result in a major physiologic disturbance, and if a patient poses a high anesthetic risk because of extensive comorbidity, partial mastectomy and even axillary dissection can be carried out under local anesthesia, with excellent sedation and relief of anxiety being achieved by neuroleptic agents.

Axillary dissection can undoubtedly be done, but should it? It provides staging information and, to a minor extent, may contribute to the control of regional disease. If the information will be used in decision-making concerning systemic therapy, then there is a clear indication for axillary dissection. However, the recent trend has been to treat all older women with tamoxifen regardless of nodal status or even estrogen-receptor status. Thus, it seems entirely reasonable to adopt a "wait and see" policy regarding axillary dissection. In the National Surgical Adjuvant Breast Project protocol B-04,⁵² which included women up to

70 years of age, one-third had total mastectomy only. Although 20% demonstrated nodal progression at the 15-year follow-up, there was no survival advantage in carrying out the axillary dissection prophylactically. There is some suggestion that axillary progression is even less common in older women.³⁵

Adjuvant treatment

Radiotherapy

Radiation is the accepted treatment after lumpectomy,^{53,54} but, again, can studies in younger women be extrapolated to the elderly? There is no doubt that radiation can be tolerated,⁵⁵ but there are certainly technical difficulties regarding such mundane matters as transportation that figure more prominently with advancing years.

One randomized study from Milan⁵³ indicated that radiotherapy actually appears to confer less benefit in older women. A definitive answer would be extremely useful. There is a study underway in Toronto that has recently expanded to include the Province of British Columbia. Supported by the Ontario Ministry of Health, the study was initiated by Fyles and associates to assess the need for breast radiotherapy in women 50 years of age and over with node-negative breast cancer (Dr. A.W. Fyles, Radiation Oncology, Princess Margaret Hospital, Toronto: personal communication, 1997). Women with T1 or T2 tumours receive lumpectomy, and attention is paid to achieving resection margins that are pathologically clear of malignant cells. Between the ages of 50 and 65 years, axillary dissection is done to confirm the node-negative status, but for women over 65 years of age, clinical node negativity is accepted. Accepting the hypothesis that tamoxifen alone

can probably serve to keep local recurrence to an acceptable level, the researchers prescribe tamoxifen for 5 years for all women, and they are randomized to receive radiotherapy or no radiotherapy. The target for entry is 900 women and nearly 600 have been randomized to date (Dr. A.W. Fyles: personal communication, 1997).

Adjuvant systemic therapy

With respect to hormonal manipulation, it is true that breast tumours in the elderly are much more likely to be estrogen-receptor positive.^{20,35,56} One randomized, controlled study of surgery, with or without tamoxifen, carried out in 181 women 65 to 85 years of age by Cummings and associates,^{57,58} showed that tamoxifen extends the time to treatment failure by 3 years and reduces recurrences, deaths and second breast cancers. Other studies have noted similar benefits with tamoxifen in postmenopausal women, but usually have only included women up to 70 years of age.⁵⁹⁻⁶³ An overview analysis by the Early Breast Cancer Trialists' Collaborative Group,⁶⁴ showed that tamoxifen caused a small but real improvement in disease-free survival in women 50 years of age and older. There are also potential benefits to women in this age group with respect to cardiovascular disease and osteoporosis.

Chemotherapy is a matter for more deliberation. Again an overview analysis was carried out and showed that chemotherapy, although effective in women under 50 years of age, resulted in only a 10% reduction in the annual odds of death in women aged 60 to 69 years and did not appear to be beneficial in women older than 70 years.⁶⁵ The lack of effectiveness of adding conventional chemotherapy to tamoxifen therapy in postmenopausal women was suggested by the study of

Pritchard and colleagues.⁶⁶ Fisher and associates,⁶⁷ on the other hand, studied women 50 years of age or older and noted a significantly better distant disease-free survival and overall survival for those treated with combination chemotherapy (tamoxifen with adriamycin plus cyclophosphamide or with melphalen plus 5-fluorouracil) as opposed to tamoxifen alone. Although 55% of these women were 60 years of age and older, the results for this group were not separated from those of women less than 60 years of age. In a trial conducted by the Ludwig Breast Cancer Study Group,⁶⁸ a subset of patients 65 years of age and older (node-positive and estrogen-receptor positive) were randomized to receive 1 of the following 3 protocols: (1) cyclophosphamide, methotrexate and 5-fluorouracil plus prednisone plus tamoxifen; (2) prednisone plus tamoxifen or (3) no further treatment. Through 5 years of follow-up, no difference was noted between protocols (1) and (2). Some people have attributed the lack of effect in older women in this study to the fact that older women seldom received anthracycline-based chemotherapy regimens. However, there may be a trend toward less benefit from the adjuvant chemotherapy with advancing years rather than a "cut-off" effect at the time of menopause.

The elderly with extremely poor functional status

Special consideration should be given to the truly infirm. Margolese and Foster⁸ reported a pilot study in which nothing but tamoxifen was given to 30 patients who were infirm or refused surgery. The majority regressed or remained stable. Of importance is the fact that none subsequently suffered from uncontrollable locoregional disease.

Three European randomized trials^{37,69,70} of tamoxifen therapy versus surgery have been carried out in elderly women, and although the results of the studies were not that dissimilar, the conclusions differed. Gazet and associates⁶⁹ reasoned that because tamoxifen was as effective as surgery in many ways, surgery should be reserved for those who do not respond or whose disease progresses. Robertson and colleagues⁷⁰ noted that with surgery, 70% were free of local disease, whereas with tamoxifen therapy alone, only 47% remained free of local disease. Therefore, they concluded that primary treatment should include surgery. It has been said that most elderly patients will accept surgery, as the fear of cancer is greater than that of surgery, and leaving the cancer is equated with inoperability and a painful end. Bates and associates³⁷ on behalf of the Elderly Breast Cancer Working Party showed no difference in survival or quality of life between optimal surgery and tamoxifen therapy, but those treated with tamoxifen alone more frequently had a subsequent change in management — usually surgery for local treatment failure. However, it is clear that for elderly women who are infirm, tamoxifen therapy alone may be the optimal form of management.

COST AND QUALITY-OF-LIFE CONSIDERATIONS

Cost-effectiveness is an important consideration. The costs related to screening have been mentioned. If radiotherapy or axillary dissection prove to be unessential, why generate extra costs or submit the patients to the morbidity inherent in these treatment modalities? Surgery in the form of partial mastectomy usually deals definitively with the primary cancer and may well be less expensive than prolonged

treatment with tamoxifen to which surgery may ultimately have to be added. A partial mastectomy alone may be as efficacious for patients with limited life expectancy and possibly more cost-effective.

Although elderly women can tolerate adjuvant polychemotherapy for breast cancer,⁷¹ the benefit is extremely modest and the costs are relatively high.⁷² The greater morbidity of conventional chemotherapy compared with tamoxifen therapy is also a quality-of-life factor that must be taken into account, particularly in a women with limited life expectancy.

Therapy for metastatic disease is only palliative and quality-of-life issues assume even greater importance in patients with systemic spread of disease. Except in patients with rapidly progressing visceral involvement, endocrine therapy is usually the first approach, even in estrogen-receptor-negative tumours.⁷³ When tamoxifen therapy was compared to conventional chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil) and combination therapy (conventional chemotherapy plus tamoxifen) in postmenopausal women, the response rate to tamoxifen therapy alone was lower, but when the response to subsequent chemotherapy was taken into account, the results were virtually identical in the 3 treatment groups.⁷⁴ In another study of women over 65 years of age,⁷⁵ similar results were seen. Patient preference should be an important factor, for what seems worthwhile to one woman may not be to another with a different value system.

Quality-of-life studies have suggested that adjustment to a diagnosis of breast cancer is no worse in older than in younger women with respect to measurable parameters such as somatization, obsessions/compulsions, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, para-

noid ideation, psychoticism and the Global Severity Index.⁷⁶ Psychologic distress in older women studied correlated positively with life stressors such as financial, family or health problems experienced in the year before diagnosis. Much of the psychologic literature is focussed on the loss of the breast as the central theme,⁷⁷ but a more important consideration is the threat to life and functional status that a diagnosis of breast cancer may represent. Adjuvant treatment and regular follow-up surveillance may be a constant reminder. Also, there are a number of questions concerning the cost-effectiveness of extensive follow-up in patients with breast cancer aside from routine mammography.⁷⁸ On the positive side, the older woman may be less likely to have dependent children and financial problems and has had many life experiences to prepare her to cope with illness. However, a more limited social situation and functional status, and comorbid conditions, may affect quality of life more adversely in the older woman.

PROGNOSTIC FACTORS AND OUTCOME IN RELATION TO AGE

With respect to outcome, it has often been stated that breast cancer in the elderly tends to be more well differentiated^{35,79} and to exhibit a lower growth rate as assessed by the thymidine labelling index or flow cytometry.^{80,81} Tumours in older women are more likely to be estrogen-receptor positive.^{20,35,56}

It has been claimed that older women with stage I or II disease have slightly better survival than younger women.^{35,82} However, this finding is counterbalanced by the fact that older women tend to present with more advanced disease.^{10,18,20,83} The view that breast cancer runs a more favourable course in older than in younger

women has been challenged.^{10,84} In a large Swedish study of 57 068 women whose breast cancer was diagnosed between 1960 and 1978 (98% of total cases in Sweden), in order to get a measure of the breast-cancer-specific death rate, the authors assessed the relative survival rate (the ratio of the observed to the expected rate of survival). They found that there was a decline in the relative survival rate in women 50 years of age and older and also in women under 35 years. This was consistent with findings in another study comparing outcomes in 169 women 35 years of age and younger with 169 women 75 years of age and older.⁸⁵ No significant difference in outcome was noted between these 2 groups.

In The Henrietta Banting Breast Centre at Women's College Hospital in Toronto, we examined a cohort of 196 women 70 years of age and older with primary invasive breast cancer.¹² At 10 years, with a median follow-up of 5.7 years, the disease-specific death rate was 26% and the overall death rate was 54%. Although the single largest cause of death was related to breast cancer, the sum total of deaths from competing causes was even greater. Factors predictive of distant disease and local recurrence in a multivariate analysis included tumour size, number of involved nodes and estrogen-receptor status. In terms of treatment, total mastectomy did not appear to result in better outcome than did partial mastectomy. Radiotherapy did not appear in the best Cox stepwise model. The local recurrence rate without radiotherapy was approximately 12%.

McCready and colleagues^{13,14} have studied the question of local recurrence in what could be termed a "pure" group of 366 patients. Primary treatment consisted of partial mastectomy alone, unadulterated by

radiotherapy or adjuvant systemic treatment. Relapse was significantly less in patients 65 years of age or older. Assessment of prognostic factors (including age, axillary node status, tumour size, estrogen- and progesterone-receptor status, histologic and nuclear grades, vascular and lymphatic invasion and the presence and percentage of in situ carcinoma) was carried out on a cohort of 293 patients treated by partial mastectomy alone and followed up prospectively for a median of 8 years. With use of Cox stepwise multivariate model building, the factors that proved to be important in local recurrence in the whole cohort were determined. Decreased local recurrence was associated with absence of tumour emboli in vascular and lymphatic spaces, increase in age, minimal or no in situ carcinoma and the absence of nodal metastases. Similar findings were reported by Veronesi and colleagues⁵³ who studied 273 women who underwent quadrantectomy alone. Local recurrence was significantly lower in women 50 years of age and older than in the group 50 years of age and younger.

It should be noted that most of the patients in these studies were treated at a time when the use of adjuvant systemic therapy was much less common than it currently is, particularly in the older age groups. Although it is not clear whether breast cancer itself pursues a more or less lethal course in older as opposed to younger patients, there is no doubt about the confounding issue of death from competing causes in older women, which does impact on overall survival.

RECOMMENDED THERAPY

A schema for an approach to the primary treatment of breast cancer in the elderly (70 years and older) de-

rived from studies cited in this review is presented in Table I. In patients who are healthy, with a low comorbidity index (CI), and who have small node-negative tumours, a partial mastectomy is recommended; axillary dissection should be reserved for those who are clinically node-positive. Women with larger tumours should undergo total mastectomy, with axillary dissection if they are clinically node-positive. In patients with several comorbid conditions, partial mastectomy and even axillary dissection or total mastectomy can be carried out, if necessary, under local anesthesia with sedation. Those with extremely poor functional status (multiple and severe comorbid conditions) should be disturbed as little as possible; however, tamoxifen might provide some benefit and is associated with few side effects. Radiation should be given after partial mastectomy to control local disease, although, with increasing infirmity, this may be impractical. It is hoped that the completion of the study to determine the need for breast radiation in addition to tamoxifen therapy in older women with node-negative

breast cancer, will identify at least a subgroup of women in whom radiotherapy is not necessary. In women 70 years of age or older, there is probably little place for adjuvant chemotherapy.

It has been stated,⁸⁶ "In determining individualized therapy for older patients, physicians should weigh the risks and benefits of treatment, evaluate the patient's biologic, psychological, and social systems; assess the quality and quantity of life possible, and base decisions on individual patient information not age."

CONCLUSIONS

It is imperative that we identify coherent strategies for the treatment of primary breast cancer in the elderly, taking into account outcomes that address not only survival time but also the quality of that time gained. Our knowledge on how best to treat the elderly woman with breast cancer should come from clinical trials including older women and from good clinical trials designed specifically to study primary breast cancer in older women.

References

1. Yancik R, Ries LG, Yates JW. Breast cancer in aging women: a population-based study of contrasts in stage, surgery and survival. *Cancer* 1989; 63:976-81.
2. Henderson IC. Risk factors for breast cancer development. *Cancer* 1993;71 (suppl 6):2127-40.
3. Henderson CC, Balducci L. Breast cancer and the older woman: the challenging blend of biology and culture. *Cancer Control* 1994;1:302-3.
4. Stewart JA, Foster RS Jr. Breast cancer and aging. *Semin Oncol* 1989;16: 41-50.
5. *Canadian cancer statistics 1996*. Toronto: National Cancer Institute of Canada; 1991.
6. Mah Z, Bryant H. Age as a factor in breast cancer knowledge, attitude and screening behaviour. *Can Med Assoc J* 1992;146:2167-74.
7. Sterns EE. Age-related breast diagnosis. *Can J Surg* 1992;35:41-5.
8. Margolese RG, Foster RS Jr. Tamoxifen as an alternative to surgical resec-

Table I

Recommendations for Treatment of Primary Breast Cancers in the Elderly

Recommendation	Clinical status	Comorbidity		Extremely poor functional status
		Low	High	
Surgery	Small tumour node -ve	PM	PM under LA	± PM under LA
	node +ve	PM + AD	PM under LA ± AD	None
	Large tumour node -ve	TM	TM under LA	None
	node +ve	TM + AD	TM under LA ± AD	None
Radiotherapy	After PM	BR	± BR	None
Tamoxifen therapy	Estrogen receptor +ve or -ve	T	T	± T
Chemotherapy	Node +ve	± C	None	None

PM = partial mastectomy, AD = axillary dissection, TM = total mastectomy, BR = breast radiation, T = tamoxifen, C = chemotherapy, LA = local anesthesia

- tion for selected geriatric patients with primary breast cancer. *Arch Surg* 1989;124:548-51.
9. Pritchard KI, Meakin JW, Boyd NF, DeBoer G, Paterson AHG, Ambus U, et al. A prospective randomized controlled trial of adjuvant tamoxifen in postmenopausal women with axillary node positive breast cancer. In Jones SE, Salmon SE, editors. *Adjuvant therapy of cancer IV*. Orlando (Fla.): Grune and Stratton; 1984. p. 339-47.
 10. Mueller CB, Ames F, Anderson GD. Breast cancer in 3,558 women: age as a significant determination in the rate of dying and causes of death. *Surgery* 1978;83:123-32.
 11. Devitt JE. The influence of age on the behaviour of carcinoma of the breast. *Can Med Assoc J* 1970;103: 923-6.
 12. Trudeau ME, McCready DR, Allen GE, Lickley LL. Characteristics of recurrence in the elderly subpopulation of the Henrietta Banting Breast Centre Database [abstract]. *Clin Invest Med* 1991;14(Suppl):25.
 13. McCready DR, Chapman J-A, Wall JL, Lickley HLA. Characteristics of local recurrence following lumpectomy for breast cancer. *Cancer Invest* 1994;12:568-73.
 14. McCready DR, Hanna W, Kahn H, Champan J-A, Wall JL, Fish E, et al. Factors associated with local breast recurrence after lumpectomy alone. *Ann Surg Oncol* 1996;3:358-66.
 15. Host H, Lund E. Age as a prognostic factor in breast cancer. *Cancer* 1989;57:2217-21.
 16. Greenfield S, Blanc DM, Eldashoff RM, Ganz PA. Patterns of care related to age of breast cancer patients. *JAMA* 1987;257:2766-70.
 17. Caron JL. Surgery in the elderly: a time for reappraisal [editorial]. *Can J Surg* 1996;39:94-5.
 18. Holmes FF, Hearne E. Cancer stage-to-age relationship: implications for cancer screening in the elderly. *J Am Geriatr Soc* 1991;24:55-7.
 19. Schottenfeld D, Robbins GF. Breast cancer in elderly women. *Geriatrics* 1971;March:121-31.
 20. Cox EB. Breast cancer in the elderly. *Clin Geriatr Med* 1989;3:695-713.
 21. Balducci L, Schapira DV, Cox CE, Greenberg HM, Lyman GH. Breast cancer of the older woman: an annotated review. *J Am Geriatr Soc* 1991;39:1113-23.
 22. LaVecchia C, Franceshi S, Lucchini F, Levi F. International variations and trends in the incidence of breast cancer in older women. *Cancer Control* 1994;1:327-33.
 23. Strax P. Detection of breast cancer. *Cancer* 1990;66:1336-40.
 24. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten- to fourteen-year effect of screening on breast cancer mortality. *J Natl Cancer Inst* 1982; 69:349-55.
 25. Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group at the Swedish National Board of Health and Welfare. *Lancet* 1985;1:829-32.
 26. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, et al. Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988;297:943-8.
 27. Costanza ME, D'Orsi CJ, Greene HL, Gaw VP, Karellas A, Zapka JG. Feasibility of universal screening mammography. Lessons from a community intervention. *Arch Intern Med* 1991;151:1851-6.
 28. Beghe C, Balducci L, Cohen H. Secondary prevention of breast cancer in the older woman: issues related to screening. *Cancer Control* 1994;1: 320-6.
 29. Goodwin JS, Samet JM. Care received by older women diagnosed with breast cancer. *Cancer Control* 1994;1:313-9.
 30. NIH consensus conference. Treatment of early-stage breast cancer [review]. *JAMA* 1991;265:391-5.
 31. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981;305:6-11.
 32. Sarrazin D, Le M, Rouesse J, Concesso G, Petit JY, Lacour J, et al. Conservation treatment versus mastectomy in breast cancer tumors with macroscopic diameter of 20 millimeters or less. The experience of the Institut Gustav-Roussy. *Cancer* 1984; 53:1209-13.
 33. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer [published erratum appears in *N Engl J Med* 1994;330:1467] [see comment]. *N Engl J Med* 1989;320:822-8. Comment in: *N Engl J Med* 1989;321: 689-90.
 34. Veronese U, Banfi A, Del Vecchio M, Saccozzi R, Clemente C, Greco M, et al. Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. *Eur J Cancer Clin Oncol* 1986;22:1085-9.
 35. Foster RS Jr. Management of primary breast cancer in older patients: treatment options. *Cancer Control* 1994; 1:339-43.

36. Goodwin JS, Hunt WC, Humble CG, Key CR, Samet JM. Cancer treatment protocols: Who gets chosen? *Arch Intern Med* 1988;148:2255-60.
37. Bates T, Riley DL, Houghton J, Fallowfield L, Baum M. Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. The Elderly Breast Cancer Working Party. *Br J Surg* 1991;78:591-4.
38. Gross-King M. Clinical research protocols concerning breast cancer in older women. *Cancer Control* 1994;1:386-7.
39. Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. *Cancer* 1993;72:594-601.
40. Allen C, Cox EB, Manton KG, Cohen HJ. Breast cancer in the elderly: current patterns of care. *J Am Geriatr Soc* 1986;34:637-42.
41. Chu J, Diehr P, Feigl P, Glaefke G, Beg C, Glicksman, et al. The effect of age on the care of the women with breast cancer in community hospitals. *J Gerontol* 1987;42:185-90.
42. Silliman RA, Guadagnoli E, Weitberg AB, Mor V. Age as a predictor of diagnostic and initial treatment intensity in newly diagnosed breast cancer patients. *J Gerontol* 1989;44:M46-50.
43. Silliman RA, Balducci L, Goodwin JS, Holmes FF, Leventhal EA. Breast cancer care in old age: what we know, don't know and do [review]. *J Natl Cancer Inst* 1993;85:190-9.
44. Samet J, Hunt WC, Key C, Humble CG, Goodwin JS. Choice of cancer therapy varies with age of patient. *JAMA* 1986;255:3385-90.
45. Keeler EB, Solomon DH, Beck JC, Mendenhall RC, Kane RL. Effect of patient age on duration of medical encounters with physicians. *Med Care* 1982;20:1101-8.
46. Radecki SE, Kane RL, Solomon DH, Mendenhall RC, Beck JC. Do physicians spend less time with older patients? *J Am Geriatr Soc* 1988;36:713-8.
47. Calkins DR, Rubenstein LV, Cleary PD, Davies AR, Jette AM, Fink A, et al. Failure of physicians to recognize functional disability in ambulatory patients [see comment]. *Ann Intern Med* 1991;114:451-4. Comment in: *Ann Intern Med* 1991;115:70.
48. Goodwin JS. Knowledge about aging among physicians. *J Aging Health* 1989;1:234-43.
49. Nattinger AB, Goodwin JS. Geographic and hospital variation in the management of older women with breast cancer. *Cancer Control* 1994;1:334-8.
50. Hunt KE, Fry DE, Bland KI. Breast carcinoma in the elderly patient: an assessment of operative risk, morbidity and mortality. *Am J Surg* 1980;140:339-42.
51. Satariano ER, Swanson GM, Moll PP. Non-clinical factors associated with surgery received for treatment of early-stage breast cancer. *Am J Public Health* 1992;82:195-8.
52. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985;312:674-81.
53. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast [see comments]. *N Engl J Med* 1993;328:1587-91. Comments in: *N Engl J Med* 1993;328:1633-4; *N Engl J Med* 1993;329:1578-9.
54. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985;312:665-73.
55. Wyckoff J, Greenberg H, Sanderson R, Wallach P, Balducci L. Breast irradiation in the older woman: a toxicity study. *J Am Geriatr Soc* 1994;42:150-2.
56. McCarty KS Jr, Silva JS, Cox EB, Leight GS, Wells SA Jr, McCarty KS Sr. Relationship of age and menopausal status to estrogen receptor content in primary carcinoma of the breast. *Ann Surg* 1983;197:123-7.
57. Cummings FJ, Gray R, Davis TE, Tormey DC, Harris JE, Falkson GG, et al. Tamoxifen versus placebo: double-blind adjuvant trial in elderly women with stage II breast cancer. *NCI Monogr* 1986;1:119-23.
58. Cummings FJ, Gray R, Tormey DC, Davis TE, Volk H, Harris J, et al. Adjuvant tamoxifen versus placebo in elderly women with node-positive breast cancer: long-term follow-up and causes of death [see comment]. *J Clin Oncol* 1993;11:29-35. Comment in: *J Clin Oncol* 1993;11:3-4.
59. Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J, et al. Randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor positive tumours. *N Engl J Med* 1989;320:479-84.
60. Fisher B, Brown A, Wolmark N, Redmond C, Wickerham DL, Wittliff J, et al. Prolonging tamoxifen therapy for primary breast cancer. Findings from the National Surgical Adjuvant Breast and Bowel Project clinical trial. *Ann Intern Med* 1987;106:649-54.
61. Bianco AR, De Placido, Gallo C, Pagliarulo C, Marinelli A, Petrella G, et al. Adjuvant therapy with tamoxifen in operable breast cancer. 10-year results of the Naples (GUN) study. *Lancet* 1988;2:1095-9.

62. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organisation. *Lancet* 1985;1:836-40.
63. Adjuvant tamoxifen in the management of operable breast cancer: The Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet* 1987;2:171-5.
64. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. [Part 1]. Early Breast Cancer Trialists' Collaborative Group [review] [see comments]. *Lancet* 1992;339:1-15. Comments in: *Lancet* 1992;339:423; *Lancet* 1992;339:424.
65. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. [Part 2]. Early Breast Cancer Trialists' Collaborative Group [see comments]. *Lancet* 1992;339:71-85. Comments in: *Lancet* 1992;339:423; *Lancet* 1992;339:423-4.
66. Pritchard KI, Paterson AHG, Fine S, Paul N, Pater J, Zee B, et al. A randomized trial of CMF chemotherapy added to tamoxifen as adjuvant therapy in post-menopausal women with node positive, estrogen and/or progesterone receptor positive breast cancer [abstract]. *Proc Am Soc Clin Oncol* 1992;11:60.
67. Fisher B, Redmond C, Legault-Poisson S, Dimitrov NV, Brown AM, Wickerham DL, 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 [see comments]. *J Clin Oncol* 1990;8:1005-18. Comments in: *J Clin Oncol* 1990;8:1922-6; *J Clin Oncol* 1991;9:526-8.
68. Goldhirsch A, Gelber R. Adjuvant treatment for early breast cancer: the Ludwig breast cancer studies. *NCI Monogr* 1986;1:55-70.
69. Gazet J-C, Ford HT, Bland JM, Markopoulos CH, Coombes RC, Dixon RC. Prospective randomized trial of tamoxifen versus surgery in elderly patients with breast cancer. *Lancet* 1988;1:679-81.
70. Robertson JFR, Todd JH, Ellis IO, Elsten WC, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *BMJ* 1988;297:511-4.
71. Begg CB, Carone PP. Clinical trials and drug toxicity in the elderly: the experience of the Eastern Cooperative Oncology Group. *Cancer* 1983;52:1986-92.
72. Desch CE, Hillner BE, Smith TJ, Retchin SM. Should the elderly receive chemotherapy for node-negative breast cancer? A cost-effectiveness analysis examining total and active life expectancy outcome. *J Clin Oncol* 1993;11:777-82.
73. Muss HB. Chemotherapy of breast cancer in the older patient. *Semin Oncol* 1995;22:14-6.
74. A randomized trial in post-menopausal patients with advanced breast cancer comparing endocrine cytotoxic therapy given sequentially or in combination. The Australian and New Zealand Breast Cancer Trials Group, Clinical Oncological Society of Australia. *J Clin Oncol* 1986;4:186-93.
75. Taylor SG 4th, Gelman RS, Falkson G, Cummings FJ. Combination chemotherapy compared to tamoxifen as initial therapy for stage IV breast cancer in elderly women. *Ann Intern Med* 1986;104:455-61.
76. Roberts CS, Cox CE, Reintgen DS. Psychological adjustment to breast cancer by older women. *Cancer Control* 1994;1:367-71.
77. Ganz PA. Breast cancer in older women: quality-of-life considerations. *Cancer Control* 1994;1:372-9.
78. Schapira DV. Cost considerations for elderly women with breast cancer. *Cancer Control* 1994;1:380-2.
79. Peer PG, van Dijck JAA, Hendricks JHC, Holland R, Verbeek ALM. Age-dependent growth rate of primary breast cancer. *Cancer* 1993;71:3547-51.
80. Meyer JS, Hixon B. Advanced stage and early relapse of breast carcinomas associated with high thymidine labelling indices. *Cancer Res* 1979;39:4042-7.
81. Gentili C, Sanfilippo O, Silvestrini R. Cell proliferation and its relationship to clinical features and relapse in breast cancers. *Cancer* 1981;48:974-9.
82. Ries LAG, Henson DE, HARRAS A. Survival from breast cancer according to tumour size and nodal status. *Surg Oncol Clin North Am* 1994;3:35-54.
83. Goodwin JS, Samet JM, Key CR, Humble C, Kutvirt DM, Hunt C. Stage at diagnosis of cancer varies with the age of the patient. *J Am Geriatr Soc* 1986;34:20-6.
84. Adami HO, Malker B, Holmberg L, Persson I, Stevie B. The relation between survival and age at diagnosis in breast cancer. *N Engl J Med* 1986;315:559-63.
85. Rosen PP, Lesser ML, Kinne DW. Breast carcinoma at the extremes of age: a comparison of patients younger than 35 years and older than 75 years. *J Surg Oncol* 1985;28:90-6.
86. Cohen HJ. Geriatric principles of treatment applied to medical oncology: an overview. *Semin Oncol* 1995;22:1-2.