Management of Breast Cancer in Older Women

Malcolm Reed
Riccardo A. Audisio
Editors

Second Edition

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

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Foreword

The treatment of breast cancer in older women continues to evolve. In the last few years, there has been a greater understanding of the biology of breast cancer and our ability to subtype and the evaluation of genetic signatures. This has led to predictive models which have led to more personalized care. It is always becoming increasingly recognized that many older women have a poor prognosis, particularly those with triple-negative disease. There needs to be a focus on drug regimens for this high-risk group. Unfortunately, older patients continue to be underrepresented in clinical trials. Therefore, clinicians still need to extrapolate data from large trials in which older patients were a small fraction. Also, these clinical trial patients tend to have a better performance and functional status. They do not represent the average patient seen in practice. These patients have more comorbidity and increased polypharmacy and are more likely to have geriatric syndromes. Therefore, clinicians need to understand some basic principles of geriatrics and apply it to their patients to help guide therapy. Predictive models of toxicity and survival have been developed and validated to assist the physician. Clinical trials and geriatric data sets need to be developed to provide information for the patients' unique needs. This textbook will be a valuable addition to the practicing oncologist. It covers a wide range of issues to help care for the older breast cancer patient. It covers screening, diagnosis, and initial evaluation. The appropriate surgical and drug therapy and the prevention of long-term complications of treatment, such as skeletal events, are also discussed. It is hoped that this textbook can stimulate the type of evaluation that the older patient requires.

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Introduction from a Breast Cancer Survivor

In 2001, I was a healthy single mother and project manager for a major international IT company, life was busy, and I had no concerns about the future. All that changed when I found a lump under my arm and subsequent investigations confirmed breast cancer. I was fortunate to be able to undergo treatment at the internationally renowned MD Anderson Cancer Center in Houston, Texas, where I had a lumpectomy and lymph node clearance, followed by chemotherapy and hormone therapy. After much thought and consideration, I subsequently opted for a bilateral mastectomy and breast reconstruction. I subsequently developed lymphedema, and I welcome the rapid reduction in the number of axillary clearances undertaken for breast cancer as this problem is a particular burden for older women. I am also delighted to see the topic of breast reconstruction covered in detail in this textbook as my experiences as a Europa Donna Patient Advocate have led me to observe that many older women miss out on this option as there is a perception that it is not something they would wish to explore.

My work with Europa Donna has been a truly life-enhancing experience, and by 2008, I found myself on the executive board working at a pan-European level, representing Europa Donna at ECCO as a patient advisor committee member also attending clinical trial protocol development meetings and many other activities culminating in the launch of the European Cancer Patient's Bill of Rights at the European Parliament in Strasbourg on World Cancer Day in 2014!

I am passionate about the assessment of the quality of life in older patients and contributed to a crucial SIOG publication, which highlights the importance and reviews the methods involved in accessing the quality of life in older patients [1].

This textbook addresses many important issues facing older women diagnosed with breast cancer and the clinicians who care for them. The textbook highlights the failure to include this group of women in the clinical trials on which treatment guidelines are based, and as we face a major shift in the demographics in both developed and developing countries, there is a rapidly increasing need for an evidence-based guideline to support the treatment of breast cancer in older women who may have multiple comorbidities and frailty. In this way, we can ensure that older women benefit from the many exciting therapeutic advances, which will continue to appear in the coming years.

Mrs. Sema Erdem,
Europadonna Treasurer,
Turkey

Reference

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Contents

Clinical Epidemiology and the Impact of Co-morbidity on Survival

1

Adri C. Voogd, Marieke J. Louwman, and Jan Willem W. Coebergh

Abstract

Breast cancer will increasingly affect the lives of older women, especially in developed countries. In the last three decades, women of all age groups have experienced the benefits of a lowering mortality rate though earlier diagnosis and effective treatment. These benefits have been counteracted by the rising incidence, resulting from higher levels of exposure to risk factors and possibly also from the increased detection of occult, non lethal invasive breast cancers. At the same time, demographics are characterized by a large increase in the elderly population, which will become even more pronounced during the next decades. The most remarkable increase in the absolute number of newly diagnosed breast cancer patients and long-term survivors (at risk for recurrent disease or second breast cancers) will thus exhibit among the higher age groups, the prevalence doubling from 3.5% in 2000 to 7% in 2015 in the Netherlands (Poll-Franse et al., SignaleringscommissieKanker. Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. KWF Kankerbestrijding, Amsterdam, 2004). Being confronted with these rising numbers of patients or anticipating them, many doctors and clinical researchers have taken a special interest in the study of breast cancer in older women (Bouchardy et al., J Clin Oncol 25(14):1858–1869, 2007), as is reflected by the increasing number of papers with a special focus on this group.

Keywords

Epidemiology · Co-morbidity · Survival

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1.1 Breast Cancer in the Elderly: A Changing Picture

Breast cancer will increasingly affect the lives of older women, especially in developed countries. In the last three decades, women of all age groups have experienced the benefits of a lowering mortality rate though earlier diagnosis and effective treatment. These benefits have been counteracted by the rising incidence, resulting from higher levels of exposure to risk factors and possibly also from the increased detection of occult, non lethal invasive breast cancers. At the same time, demographics are characterized by a large increase in the elderly population, which will become even more pronounced during the next decades. The most remarkable increase in the absolute number of newly diagnosed breast cancer patients and long-term survivors (at risk for recurrent disease or second breast cancers) will thus exhibit among the higher age groups, the prevalence doubling from 3.5% in 2000 to 7% in 2015 in the Netherlands [27]. Being confronted with these rising numbers of patients or anticipating them, many doctors and clinical researchers have taken a special interest in the study of breast cancer in older women [5], as is reflected by the increasing number of papers with a special focus on this group.

As part of a recent review of the literature on the clinical epidemiology of breast cancer in the elderly, 22 population-based studies were identified in PubMed, describing age-related differences in detection, staging, treatment, and prognosis of breast cancer [21]. The main conclusions of this review with respect to older breast cancer patients were as follows:

- A relatively large proportion of (7–16%) remained unstaged.
- The proportion with advanced disease (stage III & IV) was clearly higher among elderly patients compared to younger ones.
- The treatment was generally less aggressive than for younger patients.
- Although more patients have received chemotherapy since the early 1990s, its use is still very moderate among the elderly.
- Older patients were less likely to receive radiotherapy than younger patients, illustrating the preference for mastectomy without radiotherapy, instead of breast-conserving treatment (consisting of lumpectomy with axillary dissection (AD) and radiotherapy).
- Disease-specific (or relative) survival was generally lower compared to younger patients.
- Co-morbidity was present more often and was also related to (sub-optimal) treatment.

This chapter expands on the findings of this review by presenting the most recent trends in incidence, treatment, and prognosis of breast cancer in older women based on a variety of registries and provides explanations for these trends. These trends will be illustrated in depth by the data of the Eindhoven Cancer Registry, because of its unique clinical data on co-morbidity, and by European data. Population-based data show actual variations in patterns of detection, staging, and treatment by age and thus offer a scope for improvement of care and for feeding guidelines and future, randomized clinical trials. However, because of the limitations to perform

randomized studies in the elderly, other research strategies also need to be explored for information synthesis, as will be done in this chapter.

1.2 Recent Trends in Epidemiology and Treatment of Breast Cancer in the Elderly

1.2.1 Diagnosis

Already in the 1970s and early 1980s there was a clear tendency toward earlier diagnosis of breast cancer, especially in the younger age groups, as illustrated by the Eindhoven Cancer Registry data [7]. The percentage of tumors measuring ≤2 cm rose from more than 20% to almost 45%. The steadily increasing use of early detection and screening strategies since the mid-1970s, in combination with the rising public awareness of breast cancer, are the most likely explanations for this favorable trend. However, since the mid-eighties no further improvement has been observed in the stage distribution for patients aged <50 years. For patients aged 50–69 years, the stage distribution continued to improve as a result of the introduction of mass mammographic screening, with particularly high attendance rates (85%) [1]. A similar improvement was observed for women aged 70–79 years, following the extension of the upper age limit of the screening program to 75 years in 1998. Recent data show that the stage distribution of patients aged 70–79 years is now almost similar to younger age groups (Fig. 1.1). Women of 80 years and older, however, remained at a higher risk of being diagnosed with more advanced disease.

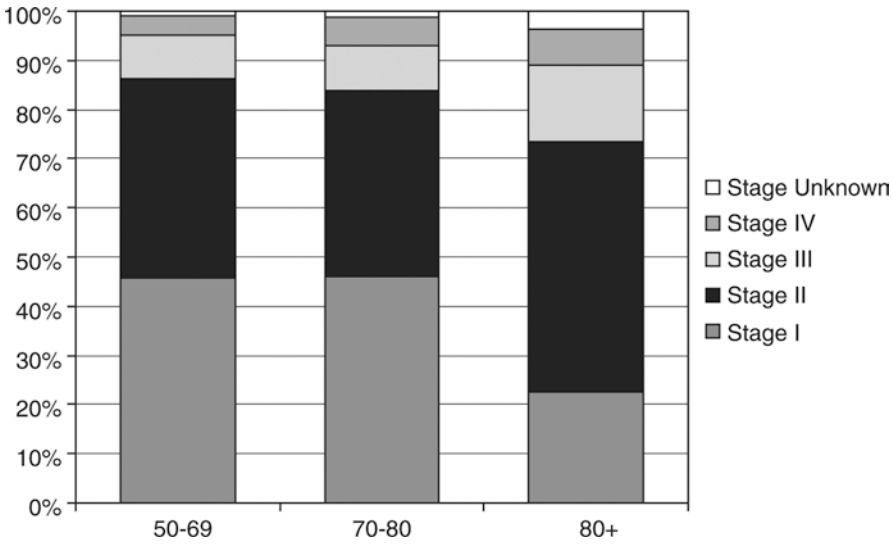

Fig. 1.1 Stage distribution among patients with invasive breast cancer aged 50 years or older, according to age group. Period of diagnosis 2000–2005. (Source: Eindhoven Cancer Registry)

The detection of small nonpalpable lesions by screening has boosted the development and introduction of less invasive staging procedures, such as large core needle biopsy, and localization procedures [10]. Although not invited for the screening program, women aged 75+ years will certainly have benefited from these developments as well.

1.2.2 Prognosis

Relative survival is the preferred way to describe the prognosis of older (breast) cancer patients, because it takes into account the risk of dying from other causes than the disease of interest. An alternative method is to calculate disease-specific survival. However, obtaining reliable information on the cause of death carries the risk of misclassification, especially when the patient has more than one tumor. Getting an adequate diagnosis or retrieving the cause of death especially may be more difficult for older patients, especially in the presence of comorbidity. Fourteen percent of the newly diagnosed patients at age 70–79 and 22% older than age 80 suffered from ≥2 concomitant serious conditions. Such patients are more likely to be admitted to nursing homes and thus disappear from the view of the treating physician or general practitioner. International comparisons of cancer survival estimates, such as in the EUROCARE studies, may also be complicated by the proportion of cases registered purely from death certificate information (DCO cases). A recent analysis of the impact of incomplete ascertainment of cancer cases and the presence of DCO cases concluded that these phenomena should be taken into account when comparing survival estimates between different populations [29] especially for older patients, as incompleteness and DCO registration is associated with increasing age [28].

Relative survival of breast cancer patients of patients aged 40–75 years is largely similar, as is indicated by recent data of the Eindhoven Cancer Registry (Fig. 1.2). A somewhat lower relative survival rate was observed for patients of 75 years or older. These results are confirmed by data from EUROCARE, including data from more than 400,000 patients diagnosed in 20 European countries during 1995–1999. According to these European data, 5-year relative survival percentages were 82, 85, 83, 79, and 71%, respectively, for patients aged 15–44, 45–54, 55–64, 65–74, and 75 years or older. The slightly worse relative survival of older patients could be explained by their poorer stage distribution, under-treatment or by a combination of both factors. However, when looking at the tumor characteristics, there also appears to be an association between increasing age at diagnosis and the presence of more favorable biologic characteristics of the tumor.

In spite of the larger tumor size, older patients have tumors showing a higher expression of steroid receptors, a lower proliferation rate, more diploid cells, more normal p53, and less frequent expression of the HER2/neu receptor [8,

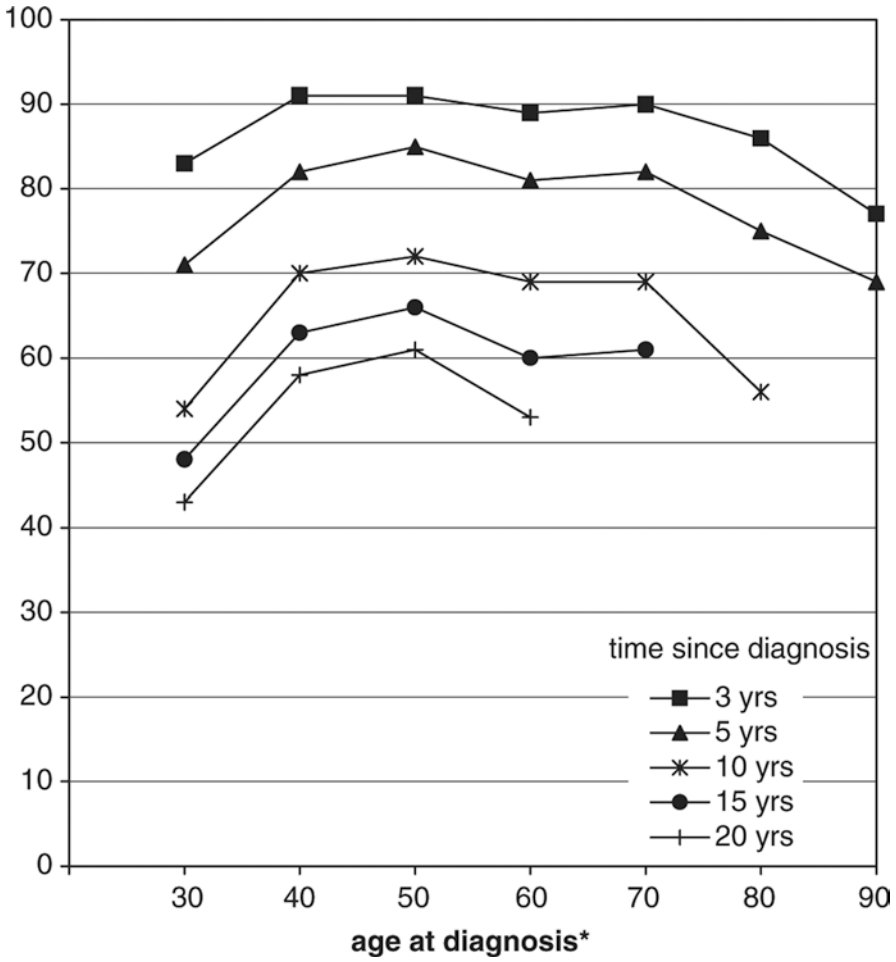

Fig. 1.2 Relative survival of breast cancer patients diagnosed between 1990 and 2002 in south-eastern Netherlands, according to age at diagnosis (*midpoint of 10-year age interval) and time since diagnosis

25]. The prognostic impact of the poorer stage distribution among older women thus seems to be counterbalanced by more favorable tumor biology. Moreover, slower growing tumors can remain undetected for long. Just like for the other age groups, there probably is much variability in aggressiveness of disease in older women, stressing the need for a better understanding of the tumor biology to improve prognostication and choice of therapy [22]. Large-scale genome analysis may help to define the prognostic profile of a tumor and identify molecular subtypes as a basis for potential therapeutic targets, specifically for the elderly [2].

1.2.3 Treatment

Like their younger counterparts, older breast cancer patients have benefited from the development and introduction of less invasive staging and treatment procedures, and new drugs. Still, age continues to play an important role in the use of these and other procedures, which are considered standard care for younger women. For example, data from the Netherlands Cancer Registry indicate that there was not much difference between patients younger than 70 and those aged 70–79 years with respect to the use of breast-conserving surgery (BCS) and radiotherapy following BCS [30]. However, the picture was completely different for women of 80 years and older, who constituted 8% of the total patient group. In the Eindhoven Cancer Registry age appeared to be a stronger predictor for the use surgery or the administration of radiotherapy following BCS than co-morbidity [34] (Fig. 1.3). In fact, after BCS, patients aged 80 years or older were 10 times less likely to receive radiotherapy than those of 50–64 years of age (OR 0.1; 95% CI 0.1–0.2). Factors, such as the distance to radiotherapy facilities, and the protracted radiotherapy course, frailty, limited social support, and psychological and economic factors and patients' or family's preference are mentioned as explanatory factors in this respect.

The same age-related pattern was observed with respect to axillary lymph node staging. In 1997, just before the introduction of sentinel node biopsy (SNB) in the southeast Netherlands, 23% of the women of 70–80 years did not undergo an axillary staging procedure (i.e., AD), compared to 42% of the patients of 80 years or more (Fig. 1.4). Considering the limited morbidity associated with SNB and the valuable prognostic information resulting from it, one would expect the introduction of this procedure to lead to a substantial decrease in the proportion of elderly patients not undergoing axillary staging. This was only true for women of 70–79 years, where this proportion decreased to 13%. In 2005, only 33% of patients

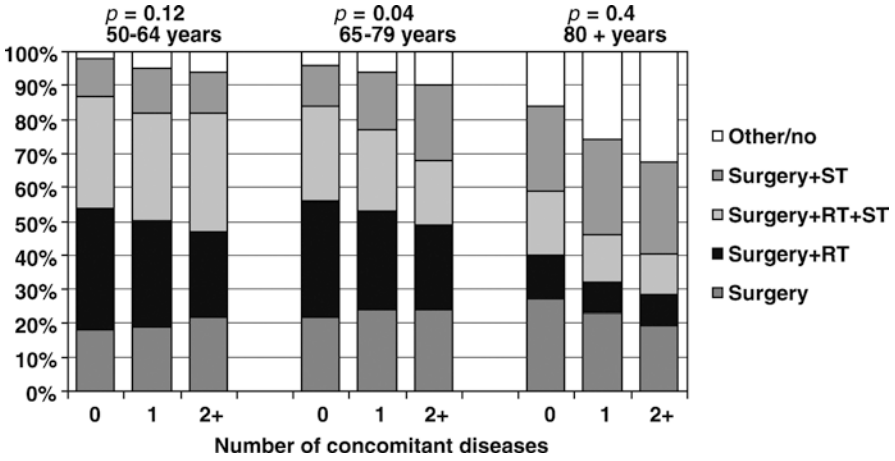

Fig. 1.3 Primary treatment of patients with invasive breast cancer from 1995 to 2002, according to age and concomitant disease. RT: radiotherapy. (Source: Eindhoven Cancer Registry)

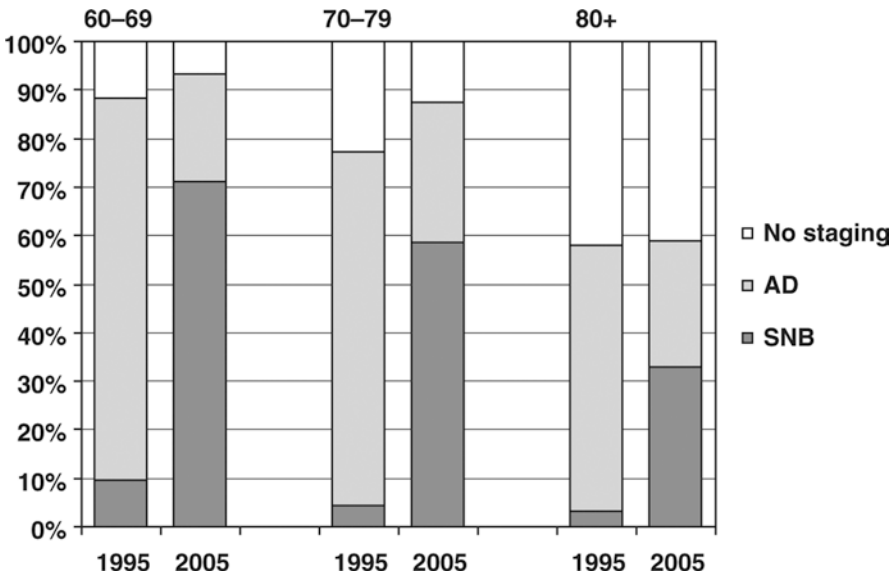

Fig. 1.4 The proportion of patients undergoing axillary dissection (AD), sentinel node biopsy (SNB), or no axillary staging procedure in 1995 and 2005, according to age group. (Source: Eindhoven Cancer Registry)

80 years and older underwent a sentinel node procedure and 41% still did not undergo axillary staging.

Age also plays an important role in the decision to use chemotherapy. Like data from many other studies, data from the Eindhoven Cancer registry showed that in 2006 the use of chemotherapy, alone or in combination with hormonal therapy, decreased with increasing age. Of the patients aged 50–69 years with positive axillary lymph nodes, almost 60% received chemotherapy, whereas of the patients 70 years and older, less than 2% received chemotherapy (Fig. 1.5) [33]. Much higher proportions have been observed in other countries such as Italy, where a recent multicenter observational cohort study, covering the period 2000–2002 reported the use of chemotherapy in 45% of all patients aged 70–75 years and 17% for those older than 75 years [26]. This international variation is almost certainly the consequence of a different interpretation of the available evidence for the benefit of chemotherapy for older patients.

The previous data illustrate that special efforts should be put in studying the safety of less aggravating treatment plans, such as intra-operative radiotherapy and cytotoxic drugs with a more favorable toxicity profile, as well as the implementation of such alternatives in daily practice. In effect, omitting axillary staging, limited use of breast-conserving surgery and omitting postoperative radiotherapy have remained rather common practices among elderly patients, especially in those of 80 years and older; these differences are only partly explained by the presence of concurrent diseases in these patients, but rather seem to imply that older age tends to be confused with chronic illness. Similar deviations from practice guidelines in the elderly

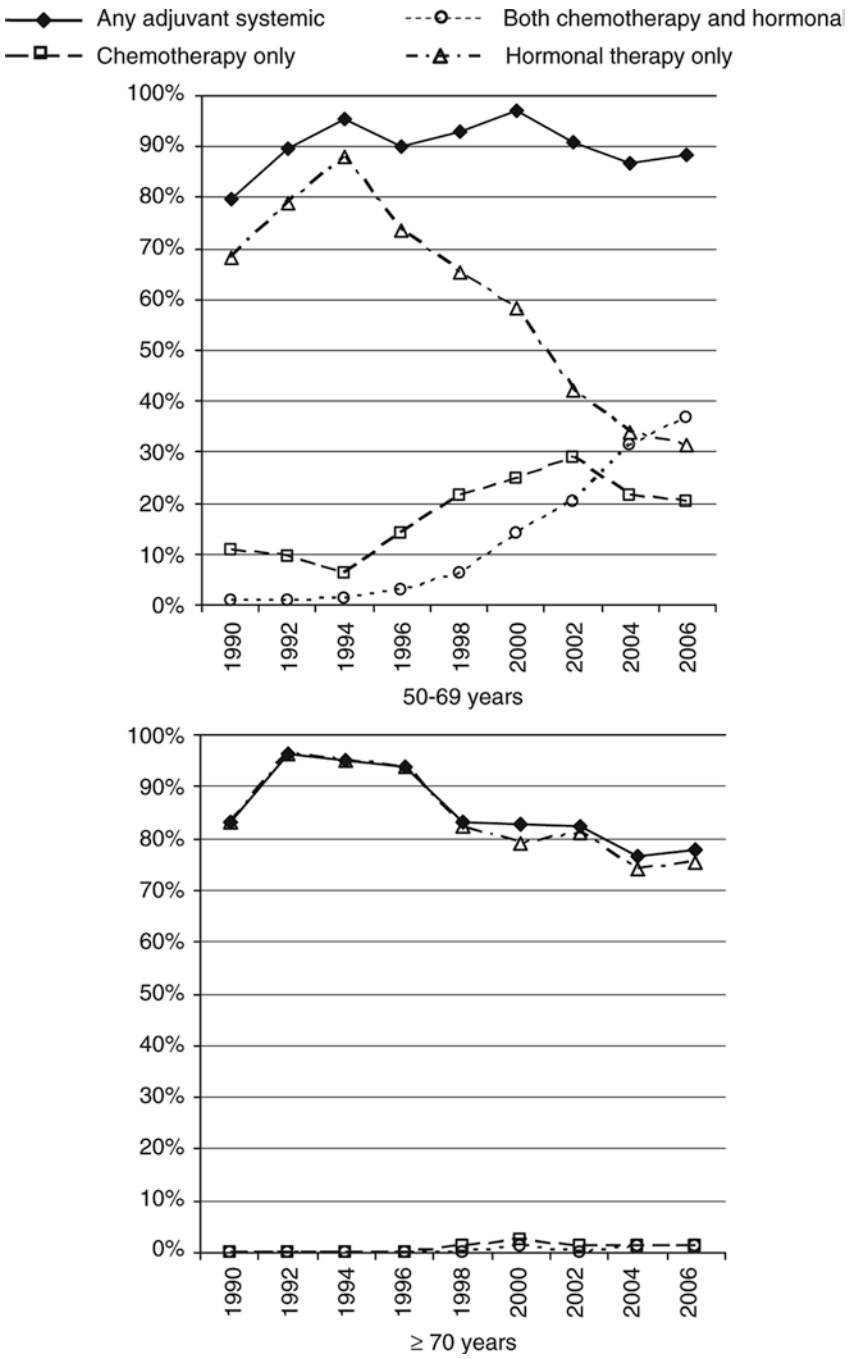

Fig. 1.5 Proportion of women with early stage node-positive breast cancer receiving adjuvant systemic treatment, by age and year of diagnosis

have been observed in other studies [14, 16], but still little is known about the possible reasons.

1.3 Current Dilemmas and Directions for Future Research

Clinical trials are credited for a large proportion of the improvements in cancer therapy. The major thread for the implementation and reproducibility of trial results is the selective uptake of older patients in randomized controlled trials because of co-morbidity, lack of understanding of the consent procedure, and deficient social support. If still desirable, trials testing less aggressive and less arduous treatment strategies and aiming at the majority of the elderly will be much more likely to succeed in entering a sufficient number of patients and providing widely applicable results than trials designed exclusively for patients without functional limitations [31].

There is evidence that selection of patients may explain differences in outcome between randomized patients and patients not entering a trial [4]. However, little evidence exists for effective strategies for trial enrolment among elderly cancer patients [12, 20]. To enable valid generalization of trial results, a thorough administration of the total number of eligible patients in each participating center is needed, as well as the reasons why patients were not entered into the trial.

In modern trials, comparing loco-regional or systemic treatments, explicit age limits are no longer in use. However, many of the elderly are not considered eligible because of co-morbidity or other factors which hamper time-consuming informed consent procedures, intensive treatment, and follow-up prescribed by the trial protocol. In some cases, overall results of trials show a beneficial effect for the total group, but the effect appears to increase or decrease with age. Although 96% of recent breast cancer randomized clinical trials report age, only 28% present evaluation of outcomes by age. However, subgroup analyses often do not solve the problem, as most of the trials are not powered for analyses according to age group, leading to small numbers in the different age strata, especially for the elderly. This explains why difficulties remain when applying results from important trials but even meta-analyses to older patients. Examples are the use of chemotherapy, especially anthracycline-containing regimens, for estrogen-receptor-negative breast cancer [6], the use of a radiotherapy boost following breast-conserving treatment of invasive breast cancer [3] and the use of radiotherapy following lumpectomy for ductal carcinoma in situ [18]. These issues may be solved by trials with a primary focus on the elderly. To guarantee sufficient uptake in such trials, broad inclusion criteria are needed, allowing patients with different levels of disease severity and a wide range of coexisting illnesses to be randomized. Such trials are also desirable to study interventions with a more acceptable toxicity profile and a smaller burden on patients' daily life, such as intra-operative radiotherapy.

In the absence of evidence-based guidelines and/or while waiting for the results from randomized clinical trials to come, decision-making should be guided by risk–benefit analysis for each individual patient, taking into account tumor

characteristics as well as patient-related factors. Nowadays, physicians have a host of validated and standardized instruments at their disposal to determine individual heterogeneity at the tumor level, ranging from the TNM classification system to the measurement of tumor grade, steroid receptor status, HER2/neu receptor, and different proliferation markers. Currently, this arsenal is being extended by genetic assays, which allow the distinction between high- and low-risk tumors at the molecular level. In contrast to younger patients, individual variation among older patients is not mainly a question of differences in disease characteristics, but is also considerable at other levels. Substantial interindividual variation exists with respect to physical and mental health, social network, and patients' expectations. In the elderly, these factors are at least of equal importance as the disease characteristics in providing tailored treatment, and therefore more effort should be put into the development and validation of instruments to measure them.

The difficulty of developing and performing randomized controlled trials for the elderly and the uncertainties about the applicability of the results to general practice leave ample room for descriptive studies [17] based on data of cancer registries or hospital-based registries (Table 1.1). Collecting standard data on tumor stage, disease characteristics (i.e., grade, steroid receptor status), and staging procedures and treatment (i.e., surgery, radiotherapy and adjuvant systemic treatment) will be sufficient to monitor adherence to guidelines or the implementation of new guidelines. It should be noted here that large staging and treatment variations between hospitals should not always be interpreted as a proof of inadequate care, but may also point at absence of guidelines, lack of precision in the indications for treatment, or lack of consensus because of insufficient evidence for the recommendations given in the guidelines.

Adding co-morbid conditions to a population- or hospital-based cancer registry will help to find explanations for noncompliance with guidelines. Moreover, such cancer registries could be of help by collecting follow-up data to give an impression of treatment outcome. Loco-regional control of disease may be such a parameter, but also the assessment of quality of life, treatment-related complications, and healthcare utilization at certain points during follow-up in a random sample of the patients should be relatively easy to organize by a cancer registry.

The following examples illustrate how such data may be used to fill the gaps in knowledge and provide us the evidence to improve the decision-making process.

- A recent prospective study by Marinello et al. shows how observational studies can help to define a subgroup of elderly patients in which chemotherapy is well-tolerated by using information on co-morbidity and performance status [24]: Of 110 consecutive patients older than 70 years of age with lung, colon, or breast cancer, only one-third were found to have completed the scheduled chemotherapy regimen and 66% experienced adverse events as early death (n = 14) and grade III and IV toxicity (n = 40). Several predictors of treatment failure were identified, such as advanced stage of disease, toxicity of treatment, co-morbidity score, and Karnofsky performance status.

Table 1.1 Research strategies to understand and improve care for elderly cancer patients

Strategy	Strengths	Limitations
Randomized controlled trials	Controlled conditions of the trial provide strong conclusive evidence of cause-and-effect relationships. With good preparation and involvement large and quick recruitment should be feasible.	Implementation and reproducibility because of selective uptake of older patients (related to co-morbidity, lack of understanding of the consent procedure, and deficient social support)
Descriptive studies (cancer registry or hospital-based registry)	Collecting standard data on tumor stage, disease characteristics, and treatment will be sufficient to monitor adherence to guidelines or the implementation of new guidelines. Adding co-morbid conditions to the database will help to find explanations for noncompliance with guidelines. Collection of follow-up data will give an impression of outcome (such as loco-regional control, treatment-related complications, and healthcare utilization) Sampling frame for quality-of-life studies.	Documentation of data for the very elderly patients is as good as practice delivers and that is likely to be variable. Completeness and quality of the data are dependent on the continuous accuracy and discipline of (many) doctors to document information in their clinical files. These limitations with respect to completeness and quality of the data might hamper comparability across institutions and over time.
Qualitatively oriented (identification and accurate documentation of the critical steps preceding diagnosis and treatment for each individual patient)	Patterns in the structure or organization of breast cancer care, underlying suboptimal diagnosis and treatment and unfavorable treatment outcomes, can be recognized, which would otherwise have remained undetected. Enables evaluation of new concepts, such as the role of shared decision-making and assessment of patient and doctor preferences.	Documentation for a considerable period of time is needed. Completeness and quality of the data are dependent on the willingness and discipline of (many) doctors and other healthcare workers to provide extra information on their way of working.

- A study by Smith et al. shows how data on life expectancy and a co-morbidity score may be used to calculate the number of patients needing radiotherapy to prevent second breast cancer events (Table 1.2) [32]. This "number needed to treat (NNT)" is a useful tool to weigh the benefits of a breast-cancer-specific intervention against the (short-term) harms and competing risk of dying from other causes in each individual patient [15].

Table 1.2 Number needed to irradiate (Nnt) to prevent one second breast cancer event[a] [32]

Age group (years)	Co-morbidity score	No. in study	8-year survival (%) (95% CI)	Adjusted NNT (95% CI)
70–74	0	2188	84 (83–89)	21 (16–31)
	1	540	72 (68–76)	24 (18–36)
	2–9	226	47 (40–55)	37 (28–55)
80–84	0	1096	51 (57–64)	29 (22–43)
	1	388	47 (40–53)	38 (28–56)
	2–9	218	29 (21–36)	61 (46–90)

[a]Combined outcome of second ipsilateral breast cancer reported and/or subsequent mastectomy
Adapted from Smith et al. [32]

- Doyle et al. used tumor data from the Surveillance, Epidemiology and End-Results (SEER) program and linked them with Medicare files to estimate the risk of cardiomyopathy, congestive heart failure, and heart disease following the use of chemotherapy among women aged 65 years or older, taking into account the presence of heart disease at baseline [9]. Their conclusion was that chemotherapy, especially with anthracyclines, is associated with a substantially increased risk of cardiomyopathy.

But cancer-registry-based studies also have their limitations (Table 1.1). Documentation of data for the very elderly patients is as good as practice delivers and that is likely to be variable. Completeness and quality of the data is dependent on the accuracy and discipline of doctors to document information in their clinical files. Electronic patient records with predefined data fields may increase the completeness of the data and may be used by the cancer registry to link with other relevant clinical data and follow-up data. But even these extra efforts to increase the accuracy and the completeness of the data might be insufficient to visualize and analyze the complexity of the decision-making process.

A more qualitatively oriented strategy would be to analyze the decision-making process in each individual patient by an accurate documentation of the steps preceding diagnosis and treatment (Table 1.1). For example, which clinical information was available when a medical decision was made and what information was taken into account? Which disciplines were involved in the decision-making process? In combination with a structured evaluation and discussion of the data, this method may result in recognizing patterns in the structure or organization of breast cancer care underlying suboptimal care and unfavorable treatment outcomes and which would otherwise have remained undetected. Such a strategy may also be useful to evaluate the potential contribution of comprehensive geriatric assessment [13] and of new concepts such as shared decision-making [22] with assessment of patients' and doctor preferences [11, 19, 23] to the improvement of quality of care in older patients.

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Mammographic Breast Screening in Older Women

2

Lynda Wyld and Rosalind Given-Wilson

Abstract

Breast screening with mammography is widely available in developed countries and is credited with substantial improvements in breast cancer survival rates over the past 30 years. Screening was implemented based on a number of randomised and non-randomised trials, which published promising results in the 1980s, suggesting a reduction in disease stage at diagnosis and a consequent survival benefit. Most of the early trials included women up to the age of 65 with only 2 of the trials including women up to age 70 or 75 (Swedish two Counties and Malmo 1). Very long follow up is now available on these trials and the data confirms survival benefit for all trial age ranges with the exception of the 70–75 age range where the number of participants is too small to provide statistical significance. However, since these initial publications, the issue of screening has become controversial following publication in 2001 by Olsen and Gotzsche of a Cochrane review, wherein the majority of the trials (and all of the trials finding in favour of screening) were considered too methodologically flawed (biased) for inclusion in the analysis. The only trial judged to be of adequate methodological design was the Canadian Trial, the only trial to find against screening benefit. The review was updated in 2013 and has a somewhat more moderate view, allowing a 15% survival benefit but still concludes that

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screening benefit is less than originally hypothesised and causes substantial harms through over-diagnosis. The initial publication triggered a vigorous academic and public debate, and many disputed the review's findings. The article triggered a critical re-evaluation of screening in many countries including the USA, UK and Switzerland. Primary amongst the concerns raised about the harms of screening is that of over-diagnosis and over-treatment which are accepted to be clinically important but the extent disputed. Over-diagnosis occurs when cancers are found on screening which would not otherwise have been detected during a woman's lifetime. This is more likely to occur with screening in older women. The impact of overtreatment may be significant as treatment may include mastectomy, axillary clearance, radiotherapy (which may increase cardiac mortality (RR1.3, CI 1.15–1.45) and lung cancer risk, especially in smokers) and chemotherapy (neutropenic sepsis, which may affect up to 19% of older women, neuropathy and rarely death). It also highlighted the other potential harms of screening such as anxiety and health service costs and raised concerns about truly informed consent and information provision. These issues are all highly relevant to older women considering screening, potentially more so than younger women. This is due to the reduced life expectancy and increased co-morbidity rates in older women and the generally less aggressive biology of breast cancer in older age groups. All of these potentially dilute survival benefit and increase the risks associated with over-diagnosis and over-treatment.

To determine the effect of screening in older women, the UK NHS Breast Screening programme is running a large cluster randomised trial called the Age Extension Trial (AgeX) in the majority of English breast screening units. In 50% of batches of women invited for screening the upper age limit has been extended to 73 and in the other 50% the normal 70 year upper age limit is applied but women age 47–50 are invited as AgeX is also examining the effect of an extra screen for younger women. Data will not be available until the mid 2020s but it is hoped that the study will clarify the benefits and risks of screening in women between age 70 and 73. This still leaves an evidence gap for ages beyond this, especially if it finds screening remains beneficial. The study has raised some concerns about the ethics of a large population based trial for a variety of reasons. These include the announcement that the UK government had decided to extend the age range anyway, potentially disadvantaging women in areas not randomised to extension. Funding for the full extension had, however, not been found so the trial was a pragmatic way to use the funding available to gather evidence for screening women above and below the current age limits. Concerns have also been raised that women are not individually consented although this is in keeping with the cluster randomised design which has full research ethics approval.

This chapter will review these issues.

Keywords
Breast cancer · screening · older age · mammography

2.1 Mammographic Breast Screening

The National Health Service Breast Screening Programme (NHSBSP) was established in 1987 following publication of the Forrest Report [1]. This initially offered mammographic breast screening for all UK women between ages 50 and 64, based on evidence from a number of large screening trials from the USA [2], UK [3], Sweden [4] and Canada [5], (Table 2.1). Subsequently the upper age was extended to 70 with roll out of this change complete in 2009. There were three reasons cited for the initial upper age cut off at 65: other cause mortality, lower attendance rates with increasing age and breast cancer running a less aggressive course in older women. Whilst these factors are still relevant, a new issue must be considered: female life expectancy has now increased from 75 years in 1987 to 83 in 2017 (UK Office for National Statistics, 2017). Consequently it is relevant to review the upper age limit as screening benefit is linked to predicted life expectancy.

Data from the initial screening trials, now with very mature follow up, suggested initially that screening was associated with a reduction in breast cancer specific mortality of between 30% and 40% [11]. However subsequent reanalysis of these trials suggests somewhat lower rates of mortality reduction [12] and a greater appreciation of the risks as well as potential benefits. The independent breast screening review [12] reviewed the available evidence and concluded that for women age 50–69 regular mammographic screening provided a relative reduction of 20% in breast cancer mortality balanced by three over-diagnosed cancers for every life saved. They also stated that there was insufficient evidence to assess risks and benefits of screening over age 70 and supported continuation of the AgeX trial to provide evidence.

The UK NHS BSP has now been running for 30 years and its data suggest an improvement in survival for screened women in-line with the predictions of the trials. Five year survival for UK screen detected breast cancer is 97.4%, compared to

Table 2.1 Review of large mammographic breast screening trials

Trial name	Age range	Number patients	Mammographic frequency	Follow-up, years	Relative risk death	Confidence interval, (95%)	Ref.
Health Insurance Plan	40–64	60,995	1 yearly	18	0.78	0.61–1.0	[2]
Edinburgh Trial	45–64	44,268	2 yearly	14	0.79	0.60–1.02	[6]
Canadian	50–59	39,405	1 yearly	13	1.02	0.78–1.33	[7]
Finnish National	50–64	158,755	2 yearly	4	0.76	0.53–1.09	[8]
Swedish Malmo	45–70	42,283	2 yearly	19.2	0.81	0.66–1.00	[9]
Swedish 2 Counties	40–74	133,065	2–3 yearly	20	0.68	0.59–0.8	[10]

77.6% for symptomatic cancer [13], although much of this striking difference will be due to lead time bias which must be corrected for when assessing the impact of screening.

Screening with two view digital mammography in England is offered 3 yearly. Images are double read. Women whose mammograms show possible abnormalities are recalled to the screening unit for further assessment. Assessment involves clinical examination, further imaging with mammography, tomography, ultrasound and image guided needle biopsy. Women found to have cancer are referred for treatment. Technical improvements since the introduction of screening in England in 1987 include digital mammography, double reading, and core needle biopsy. There has been an associated increase in the rate of cancers detected, in 2016 this was 8.4 per 1000 screens for the programme overall [14]. Cancer detection and length of survival may increase as further new technologies, such as tomosynthesis, which is likely to be used increasingly for screening, become more widely available [15].

In the UK at present, the NHSBSP invites women between 50 and 70 for 3 yearly mammography, women age 70–73 who are randomised into the AgeX trial are invited and over age 70, women may self-refer. Rates of self-referral are low in older women but increasing as there are now very few older women who are too old to have ever been offered screening and routine screening invitation now extends past 70 years. In addition older women are now generally fitter and have a higher life expectancy than when screening programmes were established. Figure 2.1 shows rates of self-referral in the UK for older women which clearly shows an upwards trend for those who are now beyond the age of routine invitation. Attendance rates in women over the age of 70 are generally good, with NHS BSP data showing that uptake is highest in women age 65–70 at 73% compared to 69.5 in 50–52 year olds and 69.6 in women of 70–74. The latter may reflect the fact that screening extension is not complete in this age group due to the AgeX trial.

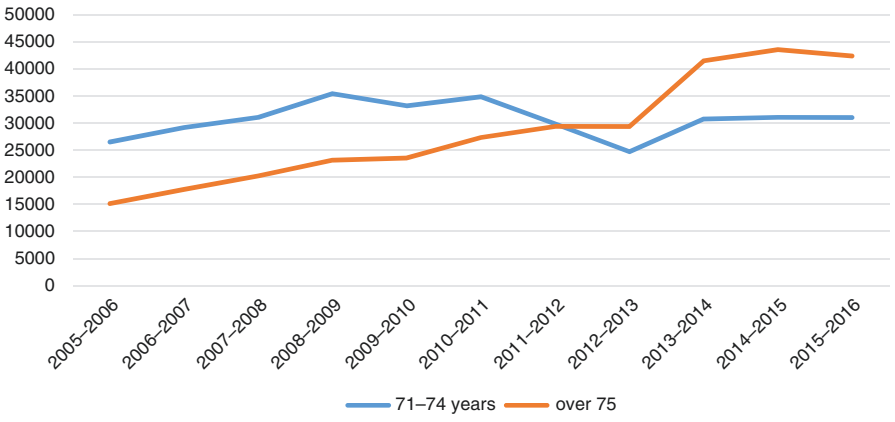

Fig. 2.1 Rates of self referral for NHS Breast Screening by year and age group. (NHS BSP data 2017)

2.2 Attitudes of Older Women to Breast Screening

In the UK, uptake rates for the over 70s are improving as screening age extension occurs but many older women are still not aware that they are eligible for screening [16]. In addition, many are not aware that they are eligible to self-refer, or how to access self-referral if they wished to. However, when asked, 95% of older women are keen to continue to have mammograms and would prefer to see invitations extended indefinitely [16]. In addition, older women intending to continue to have screening are very resistent to dissuasion by their doctors, showing that many women have a very strongly positive view of its benefits [17] although knowledge of the potential harms of screening is also an issue for these women with only 3% expressing concerns about the risks of mammography [16].

Knowledge about breast cancer is poor in older women [18, 19], with low levels of knowledge about breast cancer symptoms and their own level of risk of developing the disease. In this context the value of routine screening may be enhanced in this age group as older women tend to present with later disease stage as they rarely self-examine [20].

Many older women believe they are less susceptible than younger women to developing breast cancer [16, 21], an impression fostered by the fact that they are no longer invited for screening once they are over the screening cut off age. There may also be a perception that other health issues assume more importance and there is a widely held belief that mammography is not helpful if there are no cancer symptoms, which denotes a lack of understanding of the principles of screening [21].

Some women may be deterred from attending by a number of concerns (Table 2.2), but the most common is the perception that screening must no longer be needed because they are no longer invited.

Some work has been done to educate older women in the symptoms of breast cancer which was effective at raising awareness but this has failed to impact on screening self-referral rates [22].

Table 2.2 Reasons for screening non-attendance in women over the age of 70 years based on a questionnaire survey of 382 UK women over age 70 years

Reasons given for non-attendance to breast screening >70 years	*n* (%)
Not invited for screening so thought not necessary (*n* = 382)	199 (52.1)
Did not know I could refer myself (*n* = 382)	134 (35.1)
Felt mammograms not needed at my age (*n* = 382)	72 (18.8)
Other health problems seem more important (*n* = 383)	66 (17.2)
I did not want any more mammograms (*n* = 382)	47 (12.3)
I forgot about it (*n* = 382)	35 (9.2)
Mammograms painful/unpleasant (*n* = 382)	17 (4.5)
Worried about getting to screening centre (*n* = 382)	15 (3.9)
Worried about the risks of having mammograms (*n* = 382)	3 (0.8)

Reproduced with permission from Collins et al. 2010 [16]

2.3 Is Mammography Effective in Older Women?

There are several potential reasons why mammographic screening in older women may appear to have increased efficacy relative to younger women. The cancer detection rate is much higher in this group than in younger age cohorts, increasing from 6.2 per 1000 women screened in the 45–49 year age group to 14.6 per 1000 in the over 70 group (Fig. 2.2, UK NHS Breast Screening Programme data 2017). This reflects both the age related increase in cancer incidence and the increased sensitivity of mammography in older women due to reduced breast density. What is not clear is whether screening enhances survival in this age group and the rate of associated harms. There are several key differences between age groups that may limit the impact of screening (reviewed in detail below). Life expectancy is reduced due to age and coexistent comorbidities, the cancers diagnosed tend to be less biologically aggressive (more likely to be ER positive and Her-2 negative) [24]. This means that a longer lead-time must be factored into analysis and this is difficult to define [25].

There is a lack of direct RCT trial data for older women who were excluded from most of the large screening trials (see Table 2.1). There is therefore little direct

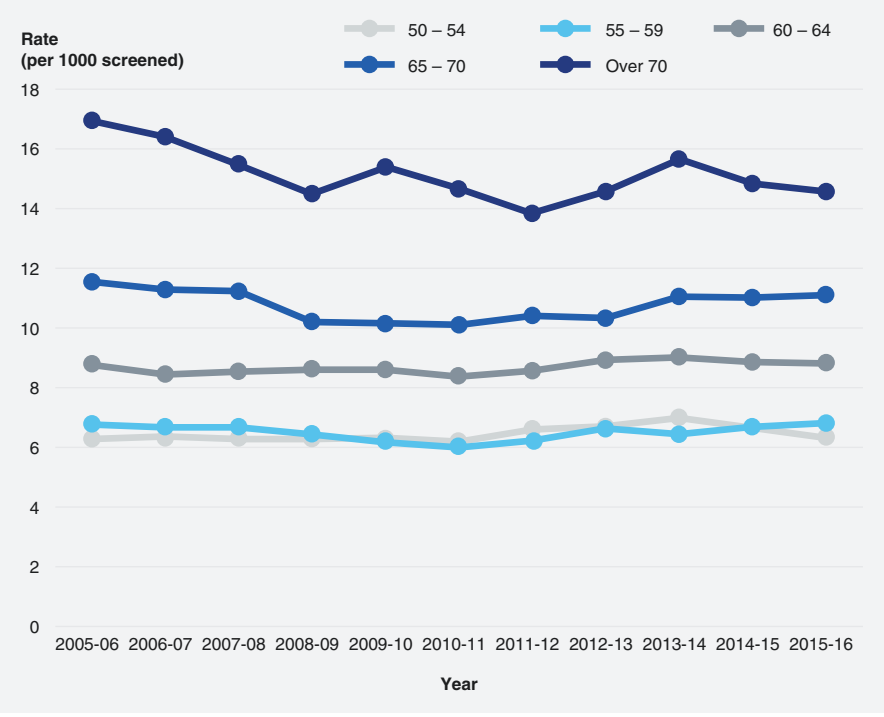

Fig. 2.2 UK NHS breast screening programme cancer detection rates per age group screened between 2005 and 2016. (Rate per 1000 women screened) [23]

Table 2.3 Comparison of prognostic factors between screened and symptomatic cancers by age group [26]

		Age range, (Years)		
Prognostic factor	Method of presentation	<50 (%)	50–64 (%)	65+ (%)
Nodal disease present, (% of cases where known)	Screen detected	20	29.2	21.2
	Symptomatic	46.6	41.3	40.6
Nottingham Prognostic Index, Excellent Prognostic group	Screen detected	33	26.7	26.9
	Symptomatic	6.7	9.6	8.3
Mastectomy rate	Screen detected	33	27.2	26.5
	Symptomatic	45.9	45.3	56.1

evidence of benefit and different forms of evidence must be sought. These include: extrapolation of the randomised controlled trial (RCT) data from younger cohorts (subject to numerous assumptions), uncontrolled case series and cohort studies (subject to allocation bias), the use of surrogate markers, (i.e. stage reduction at diagnosis as a surrogate of improved prognosis, reduced incidence of metastatic disease as a surrogate of mortality) and modelling data.

Screening does result in the diagnosis of earlier stage cancers in older women (Table 2.3) implying that screen detected breast cancers *should* be associated with an improved prognosis in older women. However some would argue that screen detected cancers have a good prognosis because screening detects good prognosis cancers whereas aggressive cancers are more likely to present in the screening interval. There are also other confounding factors which may undermine the impacts of these surrogate outcome measures so they do not translate into improved survival (see below). Detection of good prognosis cancers may indicate increased over diagnosis as less aggressive tumours may not have presented clinically. They may also be associated with overtreatment.

2.4 Evidence for Screening Efficacy in Older Women

2.4.1 Randomised Controlled Trials

RCTs provide the strongest type of evidence for screening as they avoid biases such as lead time, length and selection. Most of the large RCTs performed in the 70s and 80s recruited women up to age 64 or 70, with only 2 of the trials recruiting up to age 74, (Swedish 2 Counties Trial and the Swedish Malmo Trial), and none beyond this age [9]. In a joint analysis of the Swedish studies there was insufficient power to determine whether there was a survival advantage for the cohort of screened women between age 70 and 74 [9]. Thus there is insufficient evidence from previous RCTs to assess the effects of screening in women over 70. The results of the AgeX trial, which is very large and uses current mammographic technology should contribute useful evidence but data are not expected till the mid 2020's.

2.4.2 Cohort Studies

There have been retrospective cohort studies of older women who have had screening versus those who have not. Cohort studies are subject to bias including lead time bias, length bias and selection bias. The evidence they provide is less robust than RCTs. One US study examined the risk of death from breast cancer and the incidence of stage 1 or 2 disease in regular users or non-users of mammography in 3 age cohorts: 67–74, 75–85 and over 85. They found that in the 2 youngest age cohorts the risk of breast cancer death was significantly increased in non users, (RR 3.69, CI 2.58–5.27 for the 75–84 group, RR 3.18, CI 2.27–4.46 67–74 age group [27]). A significant difference persisted even after allowing for a 1.25 year lead time bias, (this was based on the lead time for the 70–74 year age group found in the Swedish 2 Counties Trial, although some suggest that a longer lead time bias is appropriate in older women due to less aggressive disease biology [28],). The trial also used a modified Charlson Index of co-morbidity [29] to correct for co-morbidity variance between cohorts and found the results continued to show a survival advantage. Another cohort study showed a survival advantage for screened versus non-screened women in an age cohort from 68–83 years [30]. They found a relative survival rate of 0.8 in favour of screening, although this was not significant, (CI 0.53–1.22), and no subgroup analysis by age group was possible due to the small sample size.

A Dutch retrospective study based on the National Cancer Registry of women between 70 and 75 examined the impact of screening age extension and found an increase in the rate of diagnosis of early stage cancers and a decrease in advanced cancer but concluded that over-diagnosis may have limited the impact of these findings [31].

A further retrospective cohort study found a direct survival benefit for older screened women versus non-screened [32]. There was a significantly improved relative survival in all age sub-groups over 70, (70–74, RR survival 1.0 screened versus 0.66 non- screened, $P < 0.001$, 75–79, 1.0 versus 0.54, $P < 0.001$, 80–84, 0.89 versus 0.76, $P < 0.039$, >85, 1.0 versus 0.39, $P < 0.007$). However, on testing their data for selection bias (women in poor health not being referred for screening) they found this had occurred in the 75–79 year age group, but not other age groups, although the accuracy of such assessments on retrospective data is open to question. The data were not corrected for lead or length time bias, which may also have had an influence.

Data from existing screening programmes have also been reported and demonstrate that screening in the 70–75 year age group is associated with a reduction in breast cancer specific mortality of 29.5% compared to a cohort of women prior to the introduction of screening into this age group, (1986–1997 versus 1997–2003) [33]. These data may be flawed as there may have been other treatment differences to account for some of the change between these 2 treatment periods, (less use of tamoxifen and less use of chemotherapy and less effective chemotherapy regimes for example).

2.4.3 Surrogate Markers

Surrogate marker studies are again subject to possible bias and are less robust than RCTs. Studies that have used surrogate markers of survival have found that older women (66–79 years) who have regular breast screening have a lower relative risk of having metastatic disease at diagnosis of 0.57 compared to their non-screened counterparts, (CI 0.45–.072) and a higher relative risk of 3.3 of having localised breast cancer (CI 3.1–3.5) [34]. A recent (2015–16) UK audit of symptomatic cancers demonstrated that screening results in a lower average Nottingham Prognostic Index for older women with screened versus symptomatic cancers [23]. The rate of node positivity is almost halved, as is the mastectomy rate. A recent French study found that screening in women over 75 years did reduce stage at diagnosis with the rate of node positivity falling from 35% to 8.8%, an improved rate of breast conservation (74% screened versus 26% non-screened) and an improved disease free survival [35].

2.4.4 Modelling Studies

As data from RCTs in this age group are very limited and few good quality cohort studies are available, many researchers have used modelling techniques to estimate the potential benefit from screening to older age groups. All of these studies have indicated that the relative benefit of screening older women, compared to screening in the 50–69 year age group, decreases with increasing age [36]. For example, Mandelblatt and colleagues [37] found that the relative benefit was 83% for the 70–74 cohort, 61% for the 75–79 group, 45% for 80–84 and only 32% for the over 85 s. Other workers have drawn similar conclusions [38, 39]. In terms of advising on the upper age cut off, some suggest that there is still likely to be cost effective benefit up to at least age 80 years, but the increase in negative effects means the relative cost efficacy is lower in this older age group [25].

More recently a model was developed using UK registry data to explore the threshold for cost effective screening and suggested that this would be at age 78 [40] and clearly showed both a reduction in life years gained and a reduction in QALY (quality adjusted life years) gain as the upper age limit increases by 3 year increments beyond 70. An Australian group recently assessed the impact of screening extension to age 74 compared to 69 and found that there would be 1/1000 women screened fewer deaths from breast cancer, 78/1000 false positives, 28/1000 breast cancer diagnoses of which 8 would be over-diagnoses [41]. Finally a US group developed a series of models with stratification for health status and found this approach was beneficial in selecting patients who may benefit from screening over the age of 70 [42].

2.5 Why Is Screening Potentially Different in Older Women?

There are a number of reasons why it is not appropriate to simply extrapolate RCT trial data on screening efficacy to older women.

2.5.1 Mammographic Sensitivity

Screening in older women will detect more cancers per 10,000 mammograms than in younger women due to a higher incidence of cancer and a greater mammographic sensitivity with age [43–45]. A US study reported a cancer detection rate of 9.2/1000 mammograms in women over 65 versus 5.7/1000 in women between 50 and 64 [46]. The sensitivity of mammograms varies from 68% in 40–44 year olds to 83% in 80–89 year olds [46], with similar figures reported by other authors [45]. A large US study found an inverse correlation between breast density (which has an inverse correlation with sensitivity) and age with dense breasts found in 74, 57, 44 and 36% of mammograms in women in age cohorts of 40–49, 50–59, 60–69 and over 70 respectively [43].

2.5.2 Competing Risks of Death

For a woman to benefit from earlier detection of breast cancer she must survive for long enough to see this benefit. Life expectancy is related to age, with the average 70 year old having a life expectancy of 15 years, the average 80 year old, 7 years. However the elderly are very heterogeneous and co-morbid disease has a major impact on life expectancy. The incidence of co-morbidity increases with age. Once a woman is over the age of 80, even if she has breast cancer, she has a greater chance of dying of non-breast cancer causes. For example, 73% of deaths in breast cancer patients in the 50–54 year age group are due to breast cancer, compared to only 29% of deaths in the over 85 age group [24]. A large study of older women with breast cancer showed that those with 3 or more co-morbid diseases had a 20 times higher rate of non-breast cancer death which was independent of the stage of the breast cancer and therefore earlier diagnosis for these women conferred no survival advantage [47]. In the screening setting, regardless of age, screening no longer confers a survival advantage in women with severe co-morbid disease and the influence of moderate co-morbid disease lessens the impact of screening on survival in an age dependant manner [32].

Cognitive impairment is also very common in older women, with a prevalence of 50% at age 85. This includes a wide spectrum of severities, varying from mild impairment which will have little influence on life expectancy but may compromise a women's ability to weigh up the pro's and cons of screening and make an informed choice, to the severely impaired where life expectancy will be markedly reduced [48].

In the frail elderly much harm may be done by screening women inappropriately. One study offered mammographic screening to 216 women who were nursing home candidates with an average age of 81 years, 91% of whom had dependency in at least one activity of daily living and 49% had some degree of cognitive impairment [49]. Of these 216 women 18% were recalled and two thirds of these recalls were for false positives, which required further tests (further imaging, biopsy or surgery).

Four women were diagnosed with cancer and were treated but 2 of these died within 15 months of unrelated diseases, one of whom had had a severe wound infection post operatively and had chronic wound pain. Only 2 of the patients with treated cancers might have derived some benefit, (0.9% of the total cohort). Of the women who were recalled, almost half had documented anxiety or depression as a result of the process.

As a result of these competing causes of death the effect of any cancer directed interventions are diluted and benefit more difficult to prove. In addition it has been suggested that there is little value in screening women with a predicted life expectancy of less than 5 years as for most screening interventions, cancer specific survival curves don't start to diverge until at least 5 years after the start of screening [50]. The maximal effect of most screening interventions is not seen until 10 years after screening commences [9].

From a health economics perspective, which is important in the assessment of any mass screening intervention, the usual means of assessing cost efficacy is to determine the number of life years gained per unit cost. Consequently in this older population where life expectancy is much lower, the gain in life years per unit cost will inevitably be lower.

Because older women differ in their likely benefit from screening according to their life expectancy, some authors have explored alternate strategies for selection based either on breast cancer risk or on life expectancy. Although absolute age and life expectancy are linked, a more refined prediction can be achieved by use of scoring systems which take into account co-morbid disease, functional status, dementia or a combination of all of these factors [51]. Kerlikowske and colleagues [52], used a modelling technique to examine what the cost to benefit ratio of screening all women to age 79 would be compared to use of a selection technique for identification of high breast cancer risk, (high bone mineral density was taken as a marker for increased risk). They found that whilst screening of all women to 79 had some benefit, this was enhanced if only the higher risk cohort were offered screening. They also suggested that screening up to age 79 would only result in a gain in life expectancy of 7 h per woman screened, compared to 48 h if screening was stopped at age 69.

2.5.3 Over Diagnosis of Cancer

Breast screening results in the over diagnosis of cancer, that is, it identifies a higher rate of cancer than the non-screened population, implying that these additional cancers would never have caused problems during the women's lifetime. This effect is likely to be more significant in older women due to their reduced life expectancy and therefore the treatment related costs, side effects and detrimental effects on quality of life of these clinically insignificant cancers must be taken into account in performing the cost benefit analysis. Estimate of the rate of over-diagnosis vary widely between sources, from zero [53] to 59% [54–57]. The UK

Marmot review, based on a detailed meta-analysis suggested between 11% and 19% of breast cancers are over-diagnosed in the screened age range [12]. The rate is higher in older women as shown by a US study looking at obligate over-diagnosis (i.e. women who have had screen detected cancer but died of other causes). This study found the over diagnosis rate was only 1% in women aged 40, to 22% in women over the age of 80 [58].

In addition, there is a 3.5 times greater incidence of diagnosis of in situ disease in women aged 66–79 who have screening versus those who do not [34]. For women with a short life expectancy, and especially those with small areas of low grade ductal carcinoma in situ, (DCIS), it is unlikely that this disease would ever become significant or symptomatic in the patient's life-time.

The risk of DCIS progressing to invasive disease is dependent on the size and grade. Whilst large areas of high grade disease have a risk of progression if untreated of 75% over 4 years [59], small low grade disease has a progression rate of only 40% at 30 years [60]. Not surprisingly, the incidence of DCIS falls sharply once screening stops [61]. Trial are underway globally (LORD [62] and LORIS [63] for example) to evaluate whether low risk areas of DCIS may be managed by observation only an issue which may be of greater relevance to the older women diagnosed with low risk DCIS.

The age dependency of over-diagnosis is demonstrated by a modelling study using UK registry data clearly showing that whilst the rate of cancer diagnosis increased with age, the proportion of over-diagnosed cancers increases as a proportion (Fig. 2.3, reproduced with permission from [40]).

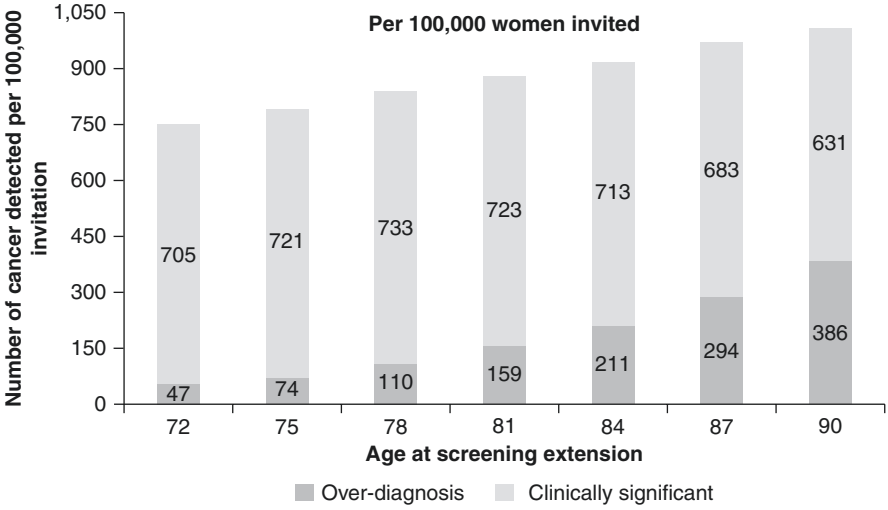

Fig. 2.3 Predicted number of breast cancer cases detected and overdiagnosis per 100,000 women invited in each age group to screening compared to the previous screening strategy. (Reproduced with permission [40])

2.5.4 Different Disease Biology with Age

Breast cancer in older women tends to express different markers of disease aggression than that in younger women with higher levels of ER expression, lower rates of HER 2 receptor expression, lower tumour grade, and lower markers of proliferation [24, 64, 65]. As a result the lead time bias that should be factored into screening studies to allow for the pre-symptomatic period gained through screening may need to be longer in older women. This has not always been considered in studies of screening in the elderly.

2.5.5 Cost

Most of the data indicates that there is still cost effective benefit to be had at all ages [36, 37, 40, 66, 67], although the benefit are smaller in the older age groups and the cost per life saved is much greater [40, 68]. For example, Mandelblatt [37] studied women in 5 age cohorts over age 65, and factored in 3 different levels of co-morbidity, (average health, mild hypertension or congestive cardiac failure). They found the cost per year of life saved was $23,212 for a women in the 65–69 year age group, $27,983 in the 70–74 year age group and $73,000 for a women of over 85 years, (all in the average health category). Factoring in poor health status made these costs even greater. More recently Rafia and colleagues showed cost effective benefit according to NHS QALY thresholds only persisted up to age 78 or 80 [40].

There are several reasons for this increased cost. The number of life years gained will be less due to the reduced life expectancy of this age group and competing causes of death, the increased rate of clinically insignificant cancers and the increased cost of treatment for older women who may require longer inpatient stays and suffer increased side effects from surgery and anaesthesia [69].

Data on quality adjusted life year costs relating to screening older women are very difficult to obtain due to a lack of studies, although Mandelblatt and colleagues [37] found in their modelling study that adverse quality of life effects in the oldest (85+) and least healthy (congestive cardiac failure) cohort in their model probably outweighed the small gain in survival.

Another issue to be considered in screening older women is that the actual process of screening may be more costly, with frailer women taking more time to screen and requiring more assistance. Up to age 69, this does not appear to be a major factor [70], but as the age range is extended, more difficulties may be encountered. Another issue of relevance to this age group is that of the accessibility and practicalities of screening. In the over 70 age group additional time must be allowed as the process takes longer in 29% of women and 15% needed a relative to assist with explanation. The time required is normally 6 min but this may increase to 15 min in some cases (for example, performing the examination whilst seated, difficulties due to kyphosis, access issues and cognition

difficulties [71]. This will have significant impact on the cost efficacy of screening in this age group.

2.6 Risks of Screening in Older Women

Breast screening is associated with risks which include psychological distress, unnecessary biopsies, (both percutaneous and surgical) and the slight risk posed by the radiation exposure itself. The radiation dose of the mammogram may contribute to the development of some cancers, although the risk of such low dose radiation exposure is extremely low, (often quoted as 2 additional radiation induced breast cancers per million mammograms), and the risk is lower in postmenopausal women [72]. A single mammogram exposure of 2 mGy may cause 4.5 cases of breast cancer per million women screened in 40–49 year olds and 1.5 per million in 50–59 year olds [73]. For the older group of women, the radiation risk is smaller still and may be negligible for women over 70 due to their reduced life expectancy, the increased sensitivity of mammograms which may require lower radiation doses to achieve good quality films and reduced breast sensitivity to radiation due to lower rates of breast epithelial proliferation in the post menopausal state [74]. However the diagnostic dose of the mammogram is not the only radiation exposure risk attached to breast screening. Women diagnosed with either invasive or in situ disease may be offered therapeutic radiotherapy and this is associated with potential harms with increased risks of cardiac deaths (1% for smokers versus 0.3% for non smokers) and lung cancer (4% for smokers versus 0.3% for non smokers) [75]. In the context of low risk DCIS or cancer, especially in an older smoker, the beneficial effect of adjuvant radiotherapy may be cancelled out by these risks.

For those diagnosed with cancer, screening may have an adverse effect on quality of life. There may be reduced initial quality of life caused by earlier awareness, (prolonged knowledge of disease, knowledge of disease that would never have become symptomatic), reduced body image due to cosmetic impacts of breast surgery, adverse impacts of axillary surgery (chronic pain, stiffness, lymphoedema), adverse impacts of adjuvant antioestrogens and chemotherapy. All of these are potentially avoidable in the estimated 11–19% of women whose cancer is overdiagnosed according to the UK Marmot report [12].

2.7 Who Should Be Screened and What Selection Criteria Could Be Used

There is evidence that the benefits of screening probably extend beyond the age of 70. But does this effect extend to all women and at what age does efficacy cease? Some work has been done to show that cost effectiveness only extends up to age

75, whilst others suggest that the age cut off should be at age 79 [76], with screening beyond this age only for women in the top 25% of life expectancy for age. This is based on a presumption that screening only benefits people with a life expectancy of over 5 [77] or 10 years [78]. The life expectancy of a 79 year old will be 10 years for 75% of women, compared to only 25% of women of 85 and over [76]. It is therefore apparent that the health status of the individual will have a significant effect. McPherson and colleagues [32], studied women of 65–101 years and found that at all ages, women with no co-morbidity or mild to moderate co-morbidity, screening was of some benefit, even for women over 80. They found that only when a woman had severe co-morbid disease did screening lose its efficacy.

However, restricting mammography to fit women over 70 would pose substantial logistical problems related to the fitness level at which to set the cut off. Who should determine this and most importantly, what do older women think of this type of selection process? In the USA where physician recommendation is a strong predictor of screening uptake, selection of appropriate older women tends to favour fitter older women and age itself is an independent negative predictor of referral, with older women less likely to be advised to attend [79]. There are also a significant number of inappropriate referrals, suggesting a lack of understanding of those likely to benefit from screening. Nursing home residency and dementia have a negative impact on the likelihood of referral, but chronic medical problems do not [80]. In another US study, more than 50% of women having mammograms at age 80 or over were in the worst quartile of health status, suggesting that they would be unlikely to benefit from screening [81]. A further study in the US found that women with greater levels of co-morbid disease were more likely to be advised to have screening, a fact ascribed to increased levels of physician contact in those with other health problems [82]. In short, decision making by US physicians, the main determinant of screening uptake in a voluntary system is poor with both over and under screening occurring. A recent study in Israel of women aged 65–79 found that 56% of women with a life expectancy estimated to be less than 10 years still attend for screening despite evidence that this is no longer beneficial [83].

In the UK, women over 70 self-select for screening. If physicians find this decision difficult, how can patients be expected to make the correct decision?

There are validated methods of assessing patient fitness and use of these to predict life expectancy. These models are becoming more sophisticated as computerised models are developed. It has been suggested that rather than basing the offer of screening on co-morbidity per se, or age cut-offs, it should be based on a women having a predicted life expectancy of over 5–10 years. There are now large data-sets which link co-morbidity and age with life expectancy and prediction accuracy is improving, such as e-Prognosis (http://cancerscreening.eprognosis.org/). However undertaking such an exercise on a case by case basis for a mass screening service is not feasible. The e-Prognosis website does now offer

individualised risk assessment for whether screening may benefit an individual older woman based on her age and fitness which may be helpful when older women wish to discuss screening with the doctors. An age cut off is likely to be the only solution with the threshold set at an age where cost effective benefit is likely for the majority of women, with a tailored approach for women over this threshold based on patient preference and physician advice. This system is in place in several health systems around the world with small variations in details. It would seem sensible to issue guidelines to clinicians to enable them to decide whom to refer for screening and to channel screening requests in women over age 79 through family physicians.

The current system of screening for the over 70's on request in the UK, may already provide some filter to ensure that fitter women attend for screening, but uptake is low. Women in better health may be more concerned with health maintenance and their physicians may be more likely to advise them to attend for screening when they attend for routine health checks.

It appears that practice relating to who should undergo screening is converging internationally. In the USA, there is no upper age limit, but screening is advised for all women with an estimated life expectancy of greater than 10 years [84]. In practice, this places the onus for decision making on the physician and such estimates can be difficult. In addition a recent study found that 70–86% of US primary care physicians recommend screening to women over the age of 80 [85]. In Europe, practice varies between countries but most screen to age 69 or 75, (Table 2.4). The International Society for Geriatric Oncology (SIOG) recommends screening be available up to age 70 with individual decisions about screening for women aged 70–75 years based on patient preference, physiological age and life expectancy [86].

2.8 Summary

Screening women over age 70 is controversial. It may be beneficial to healthy older women, but is likely to do more harm than good to those with a life expectancy of less than 5 years. Further evidence, such as the AgeX trial result, is needed to inform national programmes. National screening programmes must also consider the cost to benefit ratio of screening older women, and whilst there may still be a benefit to be had screening up to age 80, costs for population screening become prohibitive beyond this age. Older women need balanced and comprehensible information about harms and benefits to allow them to make informed individual screening decisions. Screening should be targeted at those older women who are more likely to benefit by education of the patients and their health care providers. This will optimise benefits and costs and minimise harms.

Table 2.4 Summary of national screening practices in western countries (updated for 2018)

Country	Age range offered screening	Periodicity	National programme	Comments
UK	50–69 (47–73 in Age Ex study), 3 yearly for all groups	3 yearly	Yes	Screening on request after age 70 (73)
USA (American Cancer Society) [84]	40–54 annually, 55+ biennially No upper age limit but continue as long as expected to survive 10 years	1–2 yearly	No	No upper age limit: recommended to screen until life expectancy less than 10 years
Sweden	40–55, 18 monthly 56–74, 24 monthly	18–24 monthly	Yes	On request if over 74
Finland	50–69	2 yearly	Local providers	For over 70s no formal screening but may be accessed by private clinics and family physicians
Hungary	45–65	2 yearly	Yes	No provision for older women
Australia	50–74	2 yearly	Yes	40–50 and over 74 s can elect to attend if wished free of charge
Iceland	40–69	2 yearly	Yes	Over 70s may attend 2 yearly if wished outside of programme
Italy	50–70	2 yearly	No, regional	On demand if over 70
Netherlands	50–75	2	Yes	No screening for over 75 s.
Canada	50–69	2	Yes	
France	50–74	2	Yes	
Austria	45–70	2	Yes	Opt in between 40 and 45 and over 70. Sonography 40–55
Portugal	50–69	2	Yes, national coordination of 3 Regional bodies	No provision for over 70s
Switzerland	50–75	2	Locally by Canton but not all offer	Optional if over 75
Greece	>40, no upper limit	40–50, two yearly >50 annual	No	No upper limit
Slovenia	50–70	2 yearly	National	Opt in if over 70
Spain	50–69	2 yearly	National	No provision
Turkey	40–69	2 yearly	National	On request if over 70

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Clinical Assessment: Comprehensive Geriatric Assessment

3

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Abstract

As people age, the differences in health status between individuals become larger. For this reason, there is no universally accepted cutoff for defining an "older" adult. Chronological age itself is less important than biological events in driving the aging process within an individual. However, the use of chronological age is a practical way of defining a target population. In geriatric oncology, 70 years is the most commonly used cutoff for defining patients as older adults. The majority of age-related changes lead to reduced function, but the heterogeneity of the aging process has practical consequences for the assessment of older patients with breast cancer: patients need individualized assessments to determine their *biological or functional* age. Biological age is believed to reflect a person's remaining life expectancy and functional reserves, and will influence treatment decisions and predict treatment tolerance. There is no simple way to assess biological age, and one the best clinical tools available to date is a comprehensive geriatric assessment (CGA).

Keywords

Frailty · Comprehensive geriatric assessment · Functional status · Cognitive impairment · Preoperative assessment

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3.1 Introduction

As people age, the differences in health status between individuals become larger. For this reason, there is no universally accepted cutoff for defining an "older" adult. Chronological age itself is less important than biological events in driving the aging process within an individual. However, the use of chronological age is a practical way of defining a target population. In geriatric oncology, 70 years is the most commonly used cutoff for defining patients as older adults. The majority of age-related changes lead to reduced function, but the heterogeneity of the aging process has practical consequences for the assessment of older patients with breast cancer: patients need individualized assessments to determine their *biological or functional* age. Biological age is believed to reflect a person's remaining life expectancy and functional reserves, and will influence treatment decisions and predict treatment tolerance. There is no simple way to assess biological age, and one the best clinical tools available to date is a comprehensive geriatric assessment (CGA).

3.2 Comprehensive Geriatric Assessment

A CGA is a "a multi-dimensional, interdisciplinary, diagnostic process to identify care needs, plan care, and improve outcomes of frail older people [1]". An assessment of older patients that does not include a treatment plan is simply called a *geriatric assessment* (GA). Although there is no standardized version of a CGA, there is general agreement within the literature of the components that comprise a CGA. Areas where older adults often present with health challenges are systematically assessed. The general composition of a CGA thus involves functional status, mobility, comorbidity, polypharmacy, cognitive function, nutritional status, emotional status, and social support. There are several advantages of doing a CGA in an individual patient with breast cancer: (1) Estimation of remaining life expectancy, (2) identifying remediable problems, (3) prediction of treatment tolerance, and (4) establishing a pre-treatment baseline. There is literature available on how to implement CGA in your clinical practice [2].

3.3 CGA in Patients with Breast Cancer

A number of studies looking at the impact of GA in older patients with breast cancer have been performed. Falandry and colleagues performed a survey among 101 physicians in France in order to understand the decision-making process in patients with breast cancer who were older than 70 years [3]. The authors found that the main decision criteria were performance status, comorbidities, and renal function. In the adjuvant setting, the physicians were mainly concerned about life expectancy. Quality of life was the main concern in the metastatic setting. Of the 631 patients whose medical records were assessed as part of the study, 41% had been evaluated by a geriatrician. This study shows that geriatric covariates are becoming increasingly important in the

decision-making process. Okonji and colleagues studied the use of CGA in 326 older women with early beast cancer [4]. A pre-treatment CGA consisting of eight assessment tools was performed, and patients were defined as fit if they had a normal score in seven out of eight tools. In the total cohort with a mean age of 77 years, 44% were reported as fit, while only 12% of patients older than 84 years were fit. They found that all women >69 years who were deemed fit by CGA underwent primary surgery. However, nearly 50% of fit women with high-risk disease did not receive adjuvant chemotherapy, indicating under-treatment. Hamaker and colleagues studied the association between baseline CGA and toxicity in older patients with metastatic breast cancer treated with first-line palliative chemotherapy [5]. In their sample of 73 patients, 71% had one or more geriatric conditions. Grade 3–4 chemotherapy-related toxicity was experienced by 80% of patients with three or more geriatric conditions, 56% of patients with two geriatric conditions, and 19% of patients without geriatric conditions ($p = 0.001$). Thus, it seems that a CGA could be a useful addition to the decision-making process in older women with breast cancer.

3.4 Screening for Frailty and the Need of CGA

A common objection to performing a GA is that the process is too time-consuming [6]. A minimum requirement for clinicians treating older adults with breast cancer is to identify patients who are frail. Frailty is defined as an increased vulnerability towards negative outcomes such as treatment toxicity, postoperative complications, functional decline, nursing home admission, and mortality. There are several frailty screening tools available, and the most widely used tool in geriatric oncology is the geriatric-8 (G8) [7]. Frailty screening tools are recommended in order to select which patients are in need of a complete CGA.

3.5 Elements of the Comprehensive Geriatric assessment

3.5.1 Functional Status and Physical Performance

Functional status is often divided into basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Basic ADL-functions constitute basic self-care abilities such as feeding, transferring from bed to chair and bathing/showering. Requiring assistance in ADL implies that a person needs help from a caregiver on a daily basis in order to survive. IADL describes more advanced activities, such as doing laundry, managing money and driving, and provides an estimate of the person's ability to live an independent life. Functional status is not a stable variable, and there is subsequently a need for repeated measurements. In the context of a planned surgical procedure, knowledge of functional status prior to the operation provides a useful benchmark for planning post-operative rehabilitation. Functional status is an important predictor of 1-year mortality in older hospitalized patients [8].

Physical performance measures are objective tests of physical function where the patients perform one or more standardized tasks, such as a gait speed test. Gait speed is obtained by having the patient walk four or five meters at a comfortable pace while timed by the tester. Number of meters walked is divided by seconds to complete the task, and gait speed is reported in meters per second. Normal gait speed for healthy women between 70 and 79 and ≥80 years are 1.13 m/s and 0.94 m/s, respectively. For healthy men in corresponding age groups, the numbers are 1.26 m/s and 0.97 m/s. A gait speed of less than 0.8 m/s is generally considered slow, and is predictive of poor clinical outcomes such as disability, falls and institutionalization [9]. The timed up and go test (TUG) is a physical performance test that includes gait, balance and mobility. The patient sits in an armchair, gets up from the chair, walks three meters (10 feet) at usual pace, turns 180°, walks back and sits down again. The result is measured in seconds needed to complete this task.

Oncologists have traditionally assessed physical function in cancer patients by performance status. Examples of scales that have been used include The Eastern Cooperative Oncology Group performance status (ECOG PS) or the Karnofsky Index of Performance Status. Such measurements are simple and well-established, and are feasible also in geriatric patients. However, in a clinical study of 363 cancer patients with mean age 72 years, impairments in ADLs or IADLs were identified in a considerable number of patients with ECOG PS <2 [10], indicating that an evaluation of dependency in ADLs is also needed in the routine patient assessment of older adults.

3.5.2 Comorbidity and Polypharmacy

Comorbidity is defined as the presence of one or more disorders in addition to the cancer disease. Comorbidity impacts on a patient's life expectancy as well as tolerance to cancer therapy. An assessment of overall comorbidity burden is necessary to address the following questions: Is the patient's remaining life-expectancy more likely to be limited by the cancer or another comorbid medical condition [11]? Will the comorbid condition(s) affect treatment tolerance? Are there interactions between the comorbid medical conditions and the cancer disease? The severity of comorbidity is associated with survival in cancer patients, independent of cancer stage [12]. Comorbidity has the greatest prognostic impact among groups with the highest survival rate, and least impact in groups with the lowest survival rate [13]. There are different comorbidity indices that can be used to quantify comorbidity, and examples are the Charlson's comorbidity index [14] and the Cumulative Illness Rating Scale [15].

Comorbidity is often accompanied by polypharmacy. In older patients with cancer, the prevalence of polypharmacy ranges from 32% to 51%, depending on how polypharmacy is defined. A common way to define polypharmacy is the use of five or more medications, but popypharamcy can also be defined as use of unnecessary medications [16]. If there are valid indications for using multiple medications, polypharmacy can be justified. In clinical practice, it is recommended to follow

standardized steps for deprescribing when polypharmacy is suspected. This should be done in collaboration with a geriatrician/internist, the general practitioner, and the patient. The first step is to establish the patient's treatment goals and life expectancy.

3.5.3 Cognitive Function and Dementia

The prevalence of cognitive impairment and dementia increases with age, with as many as 40% of people over the age of 90 having a dementia diagnosis, and an additional 10–15% suffering from cognitive impairment. In cancer survivors, it has been estimated that up to 75% have some form of cognitive impairment [17]. Patients with cognitive impairment have trouble remembering, learning new things, concentrating and making decisions that affect their everyday life. Dementia is a progressive illness, for which there is no treatment, and that leads to death [18]. In cancer patients, cognitive performance may be affected by fatigue, symptoms, depression, and pain. Cognitive problems are frequently not recognized, and formal testing may be required. A commonly used screening instrument is the mini-Cog [19]. Cognitive impairment will affect every step of the treatment trajectory for cancer patients. Before treatment, an assessment of cognitive function is necessary for establishing decision-making capacity, estimating the risk of delirium (acute confusional state) during treatment, and evaluating compliance. It is also useful to establish a baseline before the start of treatment. Cognitive impairment and dementia are prognostic factors for mortality [20]. Cognition after cancer therapy is also relevant for patients with breast cancer as chemotherapy may affect memory, executive function and information processing speed in women with breast cancer; the chemobrain phenomenon [21].

3.5.4 Nutritional Status

Nutritional status is part of a CGA because nutritional problems are frequent in older patients, and weight loss of 4–5% is associated with an increased risk of mortality and treatment complications [22]. Furthermore, nutritional problems provides an opportunity for optimization before surgery or during chemotherapy. The most frequently used scale to measure nutritional status in older adults with cancer is the Mini Nutritional Assessment [23].

3.5.5 Emotional Status

The risk of depression increases with increasing age, and depression frequently coexists with anxiety. A diagnosis of depression is associated with functional decline, increased need for informal caregiving, and increased use of health care resources. Patients with cancer face challenges due to the life-threatening nature of the diagnosis, related symptomatology, and the need for aggressive treatment [24].

Table 3.1 Frailty screening and geriatric assessment

Element	Tool (example)	Score	Interpretation
Frailty screening	Geriatric-8 [7]	0–17	<15, geriatric assessment recommended
Functional status	Barthel's ADL index [26] Nottingham Extended ADL index [27]	0–20 0–66	Higher score indicates better functioning
Objective performance measures	Gait speed [9] Timed Up and Go [28] No of falls in past 6 months	Speed in m/s No of sec	<0.8 m/s slow walker >19 s slow >1 investigate further
Comorbidity	Charlson's comorbidity index [14]	0–9	Higher score indicates more comorbidity
Polypharmacy	No. of medications		>4: further assessment recommended
Cognitive function	Mini-Cog™ [19] MMSE [29]	0–5 0–30	<3 indicates cognitive impairment <24, cognitive impairment
Nutritional status	Mini Nutritional Assessment [23]	0–30	<23.5, risk of malnutrtition/malnutrition
Emotional status	Geriatric depression scale – short form [25]	0–15	>5 indicates depression

Abbreviations: *ADL* Activities of Daily Living, *MMSE* Mini Mental State Evaluation

Furthermore, depression may interfere with the motivation to receive treatment for cancer. The geriatric depression scale is useful to screen for depression as part of a CGA [25].

Examples of tools used for frailty screening and GA are presented in Table 3.1.

3.6 Summary

Older adults with breast cancer vary in their degree of fitness and will differ with regards to life expectancy and treatment tolerance. A CGA may aid the decision-making process in individual patients by (1) estimation of remaining life expectancy, (2) identifying remediable problems, (3) prediction of treatment tolerance, and (4) establishing a pre-treatment baseline. A CGA may be preceded by a frailty screening. Elements comprising a CGA are functional status, mobility, comorbidity, polypharmacy, cognitive function, nutritional status, emotional status, and social support.

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Multi-disciplinary Geriatric Oncology Clinics

4

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Abstract

The incidence of breast cancer rises with older age, but evidence from the literature, and from audits of current UK practice, suggests that older women with breast cancer may not receive optimal therapy. We present evidence to support the use of comprehensive geriatric assessment of frail patients with breast cancer, to ensure optimisation of co-morbidity management and to facilitate optimal cancer therapy. Assessment should include evaluation of dependence in activities of daily living and cognitive function, which correlate with life expectancy. We present experience from two clinics in the United Kingdom, which were established to improve the management of breast cancer in the older patient, and highlight key recommendations from the National Audit of Breast Cancer in Older People and on-going research.

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Breast Cancer · Comprehensive geriatric assessment · Frailty · Geriatric · Old age

4.1 Introduction

The incidence of breast cancer increases with older age [1], such that women aged 70 or more constitute 30% of all breast cancer cases. Despite this, only a few clinical trials have included older patients [2], and very few include those patients with frailty syndromes, resulting in a lack of evidence on which to base guidelines for this population. A Cochrane review from 2007 looked at randomised clinical trials of primary endocrine therapy, with or without surgery [3]. This review demonstrated equivalent overall survival but better local control with surgery. Fennessy et al. conducted one of these randomised controlled trials, with 12-year follow-up, comparing Tamoxifen alone versus surgery plus Tamoxifen in women aged 70 or older with early breast cancer. Their results showed survival curves diverging after 3 years [4]. This implies that a subset of patients living 3 years or more after diagnosis may obtain a survival benefit from local treatment. Conversely, frail patients may experience adverse effects from treatment, including surgery, with minimal or no improvement in quality of life or survival.

In 2012 the multidisciplinary Société Internationale d'Oncologie Gériatrique (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) task force recommended that primary endocrine therapy should only be offered to elderly individuals with ER-positive tumours who have a short estimated life expectancy (<2–3 years), who are considered unfit for surgery after optimisation of medical conditions, or who refuse surgery [5]. However, life expectancy is difficult to estimate, and needs broad and deep consideration for prediction, as older cancer patients are highly heterogeneous. Stotter and colleagues showed a useful correlation between scores from the assessment of functional and cognitive status, and life expectancy. In their audit, no significant association was found between age at assessment with breast cancer and life expectancy [6].

Comprehensive geriatric assessment (CGA) is a multidimensional, interdisciplinary assessment to determine the medical status, and the psychological, cognitive and functional capabilities of elderly patients, in order to develop a coordinated and integrated plan for their treatment and follow-up [7]. It includes several domains and for each domain there may be more than one instrument or formal tool of assessment. There are a number of different versions of CGA, which have been used in different health-care settings and adapted for disease-specific management programs. CGA can be used to evaluate a patient's physiological reserve and thereby may help breast surgeons to manage the cancer patient more safely and effectively. It can also be used to help with the design of a cancer treatment plan by evaluating the vulnerability of elderly patients from various perspectives, and several consensus guidelines now recommend its routine use [8, 9].

4.2 Background

The first geriatric oncology clinics were established in Europe in the 1990s at the Léon Bérard Cancer Centre in Lyon, France, and at the Aviano Cancer Centre in Italy. Since 2000, following the global trend that began then in Europe, specialised geriatric oncology clinics, with multidisciplinary teams and specialist features tailored to older patients' needs, have also been set up in many North American cancer centres [10].

An increasingly ageing world population has driven a global interest in geriatric oncology and led to the creation of the International Society of Geriatric Oncology (SIOG), based in Switzerland, which has now more than 1000 members in 40 countries. Promoting the advancement of geriatric oncology clinics is part of SIOG's mission. Between 2009 and 2010, SIOG asked its national representatives to identify the top 10 global priorities in developing the field of geriatric oncology. Key outcomes of this were the recommendation for establishing interdisciplinary geriatric oncology clinics, especially in academic institutions and comprehensive cancer centres, and the need to integrate geriatric evaluation (including co-morbidities) into oncology decision-making and guidelines. Since then, the number of such clinics has increased, especially in France where it has also been spurred by the French National Cancer Institute's funding of clinics in every main region [10].

In 2007 in Paris an institutional collaboration between the oncology team of the University General Hospital (Pitié Salpêtrière) and the geriatric team at the Charles Foix Geriatric Hospital led to the creation of an onco-geriatric multidisciplinary clinic. An account of their first 2 years' experience has been published [11]. From January 2007 to November 2008, 161 patients with multiple different cancers (median age 82.4 years, range 73–97) were seen at geriatric oncology consultations. Geriatric assessment found severe co-morbidities (grade 3 or 4 in CIRS-G scale) in 75 patients, dependence for at least one activity of daily living (ADL) in 52, cognitive impairment in 42, malnutrition in 104, and depression in 39. In only 29 patients were there no alterations to the treatment plans made before geriatric assessment. Cancer treatment was changed in 79 patients (49%), including delayed therapy in 5, less intensive therapy in 29, and - importantly - more intensive therapy in 45. Patients for whom the final decision was delayed or who underwent less intensive therapy had significantly more severe co-morbidities and dependence for at least one ADL. This study showed that comprehensive geriatric evaluation significantly influenced treatment decisions in these older cancer patients.

Similar results were shown in a study carried out at the Institute Curie Cancer Centre in Paris. Between June 2004 and May 2005, 105 patients (70 years or older) were referred for geriatric oncology consultation there. Functional and nutritional status, mood, mobility, co-morbidity, medication, social support and place of residence were assessed. Oncology data and treatment decisions were recorded before and after this consultation. Patient characteristics included a median age of 79 years and a predominance of women with breast cancer. Nearly 15% presented with severe under-nourishment. Indicators of depression were found in 53% of cases. One third of patients had two or more chronic diseases and 74% took three or more

medications. Of the 93 patients for whom a cancer treatment plan was documented prior to CGA, this plan was modified in 39% of cases after the assessment. The authors concluded that a geriatric oncology consultation often led to a modification of the cancer treatment plan, and they suggested further studies to confirm whether these modifications improve the outcome of older patients [12].

In September 2010, to provide better cancer care for older patients, the Thomas Jefferson University's Kimmel Cancer Center (United States) developed the Senior Adult Oncology Center (SAOC). This centre provides a multidisciplinary evaluation for oncological patients; each patient being evaluated by medical oncology, geriatric medicine, pharmacy, social work and nutrition services during an approximately two-hour visit. At the conclusion of the session, the team met to review each case and formulated a comprehensive treatment plan that incorporated the expertise from each discipline. In 2013, data collected on the first 211 patients seen at SAOC, from 2010 to 2012, were published. The average age of patients seen was 80.7 years (range 61–95). The common cancer diagnoses seen were breast (23%), colorectal (17%), and lung (16%), followed by haematological malignancies (12%). In this study, 24% of patients were determined to be fit, 47% vulnerable, and 29% frail. Furthermore, 21% of patients determined to be frail by CGA had received a performance status score of 0–1 by the oncologist, supporting the need for geriatric input in elderly cancer patients [13].

4.3 Current UK Experience: The National Audit of Breast Cancer in Older Patients

The National Audit of Breast Cancer in Older Patients (NABCOP) was established in 2016 to evaluate the quality of breast cancer care services offered in England and Wales to patients aged over 70 years, in comparison to younger patients (aged 50–70 years). The audit was established in light of perceived differences in the delivery of care between older and younger patients, and in the variability of services offered to older patients on a national level. It seemed that performance status, cancer severity, and level of comorbidity could not explain all the variation in diagnosis and management of breast cancer between older and younger women, and older women tended to be less involved in the decisions regarding treatment options for their breast cancer. This on-going audit covers three main categories of breast cancer: ductal in situ carcinoma (DCIS), early invasive disease and advanced disease. It has so far examined three key areas of breast cancer care: methods of diagnosis, staging and treatment planning, and treatments received. The 2018 NABCOP report (https://www.nabcop.org.uk), covering care between January 2014 and December 2016, will be summarised to provide the current United Kingdom picture on breast cancer services for older women, to highlight areas in which variation is seen within these services, and to provide recommendations for improving breast cancer care in older women.

The latest report highlights that the incidence of breast cancer rises with older age, with 400 cases per 100, 000 in the 65 to 69 age group, increasing to 470 cases

per 100, 000 in the 80–84 years age group. Whilst women aged over 70 are more likely to have larger tumours and axillary node metastasis, they have a similar proportion of higher grade and oestrogen receptor (ER)/human epidermal growth factor receptor 2 (HER2) positive tumours compared to younger women. However, there are fewer cases of DCIS amongst women aged over 85 years (5% vs. 14%), probably due to the greater availability of screening to the younger cohort. More women aged over 70 years have higher numbers of comorbid conditions and poorer World Health Organisation (WHO) performance status, indicating a more complex patient group.

With respect to initial assessment, the route to diagnosis varies significantly between NHS hospital Trusts, with fewer women aged over 70 years being referred from screening, and approximately 60% referred from primary care compared to about 30% in the younger cohort.

In general, it is strongly advocated that all women presenting with a suspected cancer should undergo an integrated clinical assessment, with imaging and biopsy at the initial visit (so-called 'triple assessment'). There is no difference in rates of triple assessment between younger and older women, although there is some uncertainty here because of significant incompleteness in data reporting. However, there is no evident difference in access to a breast cancer specialist nurse between age groups, and overall access is high at 85%.

Median time from diagnosis to initial treatment was similar between older and younger groups (4.9 vs. 4.7 weeks), and this was consistent across NHS Trusts. However, the number of women undergoing surgical intervention for early invasive cancer fell with increasing age (96% aged 50–59 years to 19% aged 90+). As expected, rates of surgical intervention were lower amongst women aged over 70 years with a poorer performance status, though the reduction in surgical intervention was disproportionately greater than that seen for patients aged 50–69 years with poor performance status. Whilst it might be acceptable for suitable older women (with ER positive tumours) who have poor performance status to be offered primary endocrine therapy alone, this would only be appropriate for those with a life expectancy of less than 2–3 years despite optimisation of medical comorbidity, or for reasons of patient choice. Therefore, poor performance status alone cannot account for the disproportionate decline in surgical intervention in older compared to younger women. However, incomplete recording and low accuracy of data on tumour characteristics and performance status has hampered identification of the reasons underlying this disparity in primary surgical intervention. In addition, hospital stay was longer in older women (25% staying ≥2 nights vs. 16% in the younger age group), with greater variation between Trusts in older women. Of course, this variability may be due to differences in case-mix (co-morbidity and performance status), as well as local barriers to discharge.

Rates of sentinel node biopsy at the time of primary surgery were high and comparable for both age groups, however greater variation amongst Trusts was seen in the over 70-year age group, though this may, in part, reflect that NICE guidance on diagnosis and treatment of early and locally advanced breast cancer

has not been updated since 2009. Following a positive sentinel node biopsy, women were offered axillary node dissection +/− radiotherapy, and rates of such treatment were comparable between younger and older age groups (98.2 vs. 95.2%), but again highly variable across NHS trusts, with some applying axillary node removal more selectively, particularly in the older patient cohort. Adjuvant radiotherapy is recommended after breast-conserving surgery for early invasive carcinoma and DCIS, but there is a decrease in the proportion of women receiving this with increasing age (89% aged 50–69 years vs. 72% aged 80–89 years). Adjuvant radiotherapy after mastectomy is only recommended for invasive disease with a moderate-to-high risk of recurrence. Again, adjuvant radiotherapy rates for all primary breast surgery decrease with age, with significant variation in practice for the >70-year-old cohort across NHS Trusts. There was limited information on the use of neo-adjuvant and adjuvant chemotherapy in the current NABCOP report. However, fewer older women receive either forms of chemotherapy, irrespective of oestrogen and HER2-receptor status of the tumours. This may reflect the changing risk:benefit ratio, where benefits tend to be greater in a younger cohort, and risks greater for older women receiving chemotherapy, because of their poorer health status.

The NABCOP report acknowledges a number of limitations. In particular, the audit currently only monitors NHS Trusts and does not account for work undertaken in the private sector. However, at present, private sector services are not mandated to submit audit data. Patients with recurrent disease are also not currently included in the audit, but it is anticipated that these data will become available for future audits. Future directions for the audit will include other important aspects of breast cancer management, such as palliative care, bone health management, and routes to diagnosis. In addition, there are plans to link with other data-sets, including the National Cancer Patient Experience Survey.

The NABCOP made a number of key recommendations. First, there is a need for improvement in data recording and completeness, particularly for tumour size and staging, oestrogen and HER2 receptor status, and patient performance status. Secondly, a better understanding of the reasons underlying reduced and variable primary surgery practices for older women is required, particularly in relation to performance status. Thirdly, there is a need to ensure that all women be offered adjuvant radiotherapy post-operatively where indicated, irrespective of age, and that age alone should not determine the use of neo/adjuvant chemotherapy, which should be guided by the oestrogen and HER2-receptor tumour status and patient fitness. Nonetheless, there were a number of areas of clinical practice in which high performance was identified, with consistency across age groups. These were: triple assessment at first visit, access to a specialist nurse, time from diagnosis to treatment, and rates of sentinel node biopsy. Overall, the NABCOP has been able to identify key areas of disparity in breast cancer care for older women, and has the potential to make recommendations for the care of older women with breast cancer and encourage significant future improvements.

The next sections will present two models of UK Geriatric Breast Oncology Clinics, established by the authors.

4.4 United Kingdom Examples of Geriatric Breast Oncology Clinics: Leicester

In the United Kingdom, the University Hospitals of Leicester NHS Trust set up a geriatric-oncology clinic, aimed at improving the treatment of breast cancer in frail patients. It was started in 2005 and is now well-established. Patients were referred to the clinic if they were identified by their initial clinician as potentially unfit for, or had declined, standard treatment for early breast cancer. There was no lower age limit imposed on referred patients, since when the clinic was started the aim was to move away from ageism and the established practice of offering primary endocrine therapy to women aged over 70 years, regardless of their level of physical and mental fitness. At the time the clinic was set up, there was little known about what would or would not prove useful in routine clinical practice. Therefore, detailed data collection was initiated, and in the early years, at their first visit to the clinic, all patients were assessed by a breast surgeon, breast care nurse, anaesthetist and a geriatrician. The team then got together to discuss their findings, put together proposals for treatment, and the surgeon presented these to the patient and any companions.

The Leicester group audited the first 3 years of clinic activity in which over 250 patients were seen. Of these, 152 had newly-diagnosed early breast cancer; 108 were offered surgery and 103 accepted it. Compared to the years preceding the setting up of the clinic, more Leicester breast cancer patients had surgery. The authors suggested two main reasons for the increase. First, the detailed multidisciplinary assessment allowed confident communication of risks and benefits to the patient, who then felt more positive about the treatment and more able to accept it. Secondly, the successful treatment of patients seen in clinic caused a change in approach among other breast surgeons in the Unit who then recognised that 'fit' patients should be offered standard treatment, accepting that primary endocrine therapy should be for the patients who were really frail [14], not simply those aged over 70.

The Leicester team analysed data from patients who had CGA and developed a risk score to estimate three-year survival in individual older breast cancer patients, to support decision-making [5]. The risk score was derived using logistic regression, with death by 3 years *versus* alive as the dependent variable. All components of their CGA such as co-morbidity score, American Society of Anesthesiologists grade (ASA), Barthel Index of Activities of Daily Living (BI), Geriatric Depression Scale (GDS), instrumental Activities of Daily Living (iADL) and Mini Mental State Examination (MMSE) were included in the model used to derive the risk score. Four components of the assessment proved strongly associated with survival (MMSE, BI and iADL scores, and ASA grade). Age itself was not. The derived CGA risk score gave an adequate level of discrimination with an area under the receiver operating characteristic curve of 0.75 (95% confidence intervals 0.67 to 0.82; Hosmer-Lemeshow statistic $\chi^2 = 0.79$, $p = 0.448$).

The team concluded the following: 'Detailed assessment can allow prediction of survival probability in frail elderly patients. Good scores indicate good survival prospects and a likely benefit from surgery; poor scores are associated with reduced survival, although with wide variation. CGA is recommended before making

decisions on best treatment.' Good life expectancy also supports recommendations for adjuvant treatments. The practice in this Leicester clinic evolved in the light of these findings.

4.5 United Kingdom Examples of Geriatric Breast Oncology Clinics: Brighton

The Brighton geriatric-breast surgery clinic is a specialist tertiary service that aims to improve the treatment of breast cancer in older frail patients. This clinic was set up in 2015 in response to a confluence of several factors, including: local clinical need, local interest, expertise availability and the success and experience of the Leicester clinic and the Brighton and Sussex University Hospital "Silver clinic", a multidisciplinary clinic for older patients with HIV. The team consists of a breast surgeon, a geriatrician and a cancer nurse specialist (CNS) available as required. In addition, there are parallel medical oncology clinics so that if a patient needs oncology input they can be reviewed on the same day. Clinic sessions are held every 2 weeks. On average, six patients are seen in a clinic, with 45-minute appointment slots for new referrals and 30-minute slots for follow-up appointments. Patients can be referred from both breast cancer symptomatic and screening services if their initial clinician identifies them as potentially unfit for, or they decline, standard treatment for breast cancer.

All the patients referred to this clinic are assessed by a breast surgeon and a geriatrician together. During their first visit the breast surgeon performs a breast examination and reviews imaging, biopsy results and any staging investigation results. The geriatrician holistically assesses the patient, focusing in particular on certain domains of CGA such as management of co-morbidities, functional status, polypharmacy, cognitive function, mood and social support. The geriatrician uses a simplified abbreviated CGA, in preference to the labour intensive, time-consuming (up to 3 hours) full CGA. The simplified CGA (see Table 4.1) is problem-directed, focusing on key domains that are important to address or optimise or are vital to the decision-making process regarding cancer management. It is therefore pragmatic and practical to apply in a routine clinic setting. Following joint assessment, the clinicians formulate a management plan that is then discussed with the patient. Any appropriate investigation, or other specialty referral, and necessary changes in medical management, are initiated to optimise patient fitness for treatment. For patients that are immediately or later listed for surgery, an anaesthetic review is booked as a separate appointment.

In an evaluation of the first 2 years of this service, 104 new referrals were seen from April 2015 to June 2017, age range 67–98 years. Overall cancer management was changed in nearly 40% of patients, with approximately half (48/104, 46%) requiring intervention to resolve issues identified by focused geriatric assessment. First, optimisation of medical management was frequently required, particularly for cardiovascular disease (congestive cardiac failure, valvular heart disease, ischaemic heart disease, cardiac arrhythmias, hypertension), anaemia, and the "geriatric syndromes"

Table 4.1 Brighton geriatric assessment data[a]

Social support	Family 63 (61%) Friends/neighbours 8 (8%) None 33 (32%)
Residential status	Own home 58 (56%) Warden controlled flat 5 (5%) Care home 26 (25%) Not recorded 15 (14%)
Mobility	Independently 45 (43%) With walking aid 38 (37%) Wheelchair bound 21 (20%)
History of falls	Yes 23 (22%) No 71 (68%) Not recorded 10 (10%)
Functional status (ADLs)	Katz score 6 65/104 (63%) Katz score 3–5 9/104 (9%) Katz score 0–2 25/104 (24%) Not recorded 5/104 (5%)
Co-morbidities: Satariano index (score 0–7)	SIC 0–2 79/104 (76%) SIC 3–7 25/104 (24%)
Medications	Less than 5 33/104 (32%) 5 or more 63/104 (61%) Not available 8/104 (8%)

[a]These data are based on a population of n = 104

[16], i.e. falls, immobility, incontinence and dementia. This included medication changes in 26% (27/104) of patients, often addressing polypharmacy and related side effects (e.g. confusion secondary to antimuscarinic therapy, drug-induced parkinsonism, renal impairment and over-sedation), as well as optimising pain control. Specialty referral was made in 16% (17/104), including to a Rapid Assessment Clinic for Older People to facilitate a full comprehensive geriatric assessment (n = 6); community specialist services, such as heart failure and dementia teams (n = 3), and to a rapid response community team to assess home safety (n = 2). Other specialist referrals were to cardiology, neurology, physiotherapy for gait and strength training, dietetics, and the memory assessment service – to formally diagnose and appropriately manage patients with suspected or new diagnoses of cognitive impairment. The experiences of the Brighton Geriatric Breast Oncology Clinic are similar to those published by Extermann and colleagues [9, 15]. Their pilot study enrolled 15 early breast cancer patients, aged 70 and older. This group reported a mean of six new issues, not apparent following oncological work-up, identified by geriatric assessment. In their study, 36% of patients had a revised treatment plan, with 55%, having non-oncological interventions implemented to address issues that could influence the course of cancer treatment. Similar results were shown by Girre and colleagues [12], with a geriatric oncology consultation leading to a modification of the cancer treatment plan in 39% of cases. Their clinic was not set up exclusively for breast cancer patients who needed geriatric input, though there was a predominance of women with breast cancer among the patients referred.

A unique aspect of the Brighton Geriatric Breast Oncology Clinic has been study of Patient Reported Outcome Measures (PROMs). A total of 49 consecutive patients attending the clinic received a PROMS questionnaire (see Table 4.2), 40 (84%) being returned. The questionnaire did not ask for the patient's name, to encourage honest responses. It contained 12 multiple-choice items that addressed: waiting time, continuity of care, length of the medical visit, interpersonal manner, information and fulfillment of expectations. Responses were scored in categories, and the questionnaire also included one open-ended question regarding suggestions for improvements to the clinic. Overall, women were supportive of the Clinic, and of the involvement in their care of a specialist in geriatric medicine. All the patients who completed the questionnaire felt well cared for, and they would recommend the clinic to a friend in the same situation. Most aspects of the clinic were viewed positively; 90% of patients reported that the interpersonal manner of the physicians and nurses was "very good", 98% considered that their questions were "completely" answered, 95% had a "high" or "very high" level of fulfillment of their expectations for the medical visit, all patients felt they had sufficient time for their medical appointment. In particular, patients felt the assessment was thorough, with extra time given to discuss their issues, and this was additionally noted by several comments in the free text section. However, the allocation of as much time as was needed may, in part, explain the only negative responses to the questionnaire. More than half of the patients had to wait 30 minutes or longer; 37% rating their waiting time "too long" or "far too long". In addition, over half of the patients (5/9) completing the free text section made specific comments on the long waiting time, even if two patients acknowledged that this was probably due to the thoroughness of the care provided.

Another important factor identified from the PROMS study was the importance of continuity of care for this population' the majority of patients (32/40) meeting the same physician at successive appointments, with 22% and 59% rating this as "quite important" or "very important", respectively. The importance of continuity has been documented in previous studies [17, 18]. For patients in primary care, continuity has been shown to be the main priority when it comes to serious health problems [19]. Bergenmar and colleagues reported that the negative aspects expressed by patients concerning lack of continuity included feelings of being treated as a "medical condition", being weary of having to repeat their story and concerns, and having to take on too many responsibilities to keep things in mind regarding their medical treatment [20]. A special effort has been made to ensure continuity of care for the patients seen in the Brighton Geriatric Breast Oncology Clinic.

Table 4.2 Patient reported outcome measures in a Geriatric Breast Cancer Clinic

Item	Patients response
For how long after your scheduled appointment did you have to wait to meet your physician?	
<15 minutes	12
15–30 minutes	5
30–45 minutes	8
45–60 minutes	10
>60 minutes	6
How did you consider your waiting time?	
Far too long	8
Too long	7
Acceptable	22
I did not have to wait	4
Did you meet the same physician as you did at your previous appointment?	
Yes	32
No	4
This is the first visit	5
How important is it to you to meet the same physician at every appointment?	
Not important at all	4
Of some importance	4
Quite important	9
Very important	24
For how long did you meet your physician at the medical appointment?	
</5 minutes	0
5–15 minutes	3
15–30 minutes	19
>30 minutes	14
Did you get sufficiently time for your medical appointment?	
Yes	41
No, it was little too short	0
No, it was far too short	0
No, it was too long	0
How did you consider the physician's interpersonal manner?	
Very good	38
Good	3
Neither good, nor bad	0
Bad	0
Very bad	0
How did you consider the nurse's interpersonal manner?	
Very good	38
Good	3
Neither good, nor bad	0
Bad	0
Very bad	0

(continued)

Table 4.2 (continued)

Item	Patients response
Did you get answers to your questions?	
Completely	40
Partly	0
Hardly	0
Not at all	0
I did not have any questions	1
To what extent were your expectations on your medical visit fulfilled?	
Very high	28
High	11
Neither high, nor low	2
Low	0
Very low	0
I did not have any expectations	0
Did you feel well cared for at the clinic?	
Yes, absolutely	41
Yes, to some extent	0
Hardly	0
Not at all	0
Would you recommend the clinic at the oncology department to a friend in your situation?	
Never	0
Probably not	0
Maybe	0
Yes	41

4.6 Next Steps: The Bridging the Age Gap Study

Overall, we are confident that the establishment of multi-disciplinary geriatric oncology clinics for breast cancer patients can improve the care of older women with breast cancer, as illustrated by the two models described, as evidenced in the most recent NABCOP report, and with learning from other branches of geriatric oncology. However, there remains an on-going need for research to improve breast cancer outcomes in older women. The Bridging the Age Gap study is a research programme, which aims to improve outcomes in breast cancer care for older women by generating a high quality evidence base for breast cancer treatment in the older population. Such high quality evidence is still lacking, resulting in fewer older women being offered primary surgery (the treatment of choice, except in those with reduced life expectancy), and instead given primary endocrine therapy (PET). The Bridging the Age Gap research programme focusses on three main priority areas:

- Identification of patient and tumour characteristics that can predict when PET will be effective treatment for an oestrogen receptor positive cancer;
- Development of a scoring system that encompasses comorbidity, functional status, age, and tumour characteristics to predict when treatment with PET or surgery is most appropriate;
- Development of an on-line algorithm, for both the clinician and the patient, to support decision-making about breast cancer treatment.

The decision-making support tools seek to address two primary areas where decision-making is currently difficult in breast cancer care in older women. First, decision-making around primary surgery or PET for oestrogen receptor positive cancers in frail older women. Secondly, decision-making around the use of adjuvant chemotherapy for high-risk cancers in the fitter older population. Three interventions are currently under investigation to support shared decision-making in breast cancer care using a decision support tool: an on-line tool, an option grid and a booklet. These tools are being used to decide between two major treatment options: (i) PET and surgery in eligible older women; and (ii) chemotherapy and no chemotherapy. Evaluation of these tools is on-going, to determine clinician opinion, and up-take rates and use in clinical consultations. On completion of the development of the decision-support tools, a cluster randomised trial will be undertaken to evaluate the efficacy of these tools in clinical practice, and the impact on breast cancer care outcomes and quality of life for older people.

The results of this research programme will help address much of the short-fall in evidence-based decision-making for breast cancer treatment in older women, and move towards a more personalised model of care delivery in breast cancer. This will be achieved through the identification of patient and tumour-specific characteristics that can predict those in whom surgery will be of greatest benefit, with acceptable risk. Furthermore, the evaluation of patient decision support tools that help involve the patient in the decision-making process, offering a collaborative approach, taking into account the patient's individual beliefs and choices, and suitable for implementation in a multidisciplinary geriatric oncology service for breast cancer. The results of this study will address many of the limitations outlined in the NABCOP audit, and provide a clear evidence-base on which to form decisions around breast cancer care in older women.

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Primary Endocrine Therapy

5

Jenna Morgan and Lynda Wyld

Abstract

Use of endocrine therapy alone for the treatment of operable breast cancer, (primary endocrine therapy or PET) was first described in the 1980s and is a strategy adopted to varying degrees by different countries. It is a good option for the very frail or unfit older women with ER positive breast cancer. Selection for its use must take into account the probable life expectancy of the woman because secondary antioestrogen resistance develops after a median of 2–3 years. The biology of the tumour has a strong influence on response rates and aromatase inhibitors perform better than tamoxifen in this setting. Primary endocrine therapy is well tolerated and may avoid unnecessary morbidity for some women if selected appropriately. At present there are no evidence based selection guidelines but it is hoped these will be published soon once the Age Gap trial reports.

Keywords

Surgery · Primary endocrine therapy · Outcomes · Risk assessment

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5.1 Introduction

It has been known for over 100 years that removing the ovaries will result in breast cancer regression in some cases. The true underpinning biology of this phenomena was not understood until the 1960s when oestrogen receptors (ER) were identified on breast epithelial cells [1].

Tamoxifen was developed by Arthur Walpole, in 1962, initially being developed as a contraceptive. It was rapidly adopted into the armamentarium of breast cancer therapy, initially in the 1970s in the advanced [2] and later, in the 1980s, in the adjuvant setting [3].

In 1982, Preece and colleagues suggested that for older women surgery might be avoided completely by use of tamoxifen as sole therapy for operable breast cancer [4]. Five year follow up of a cohort of 113 older women, of whom 76% showed an initial clinical response, found that in 62% of cases tamoxifen alone did not control disease until death or latest follow up and they advocated PET only be used as a short term measure or in the very frail [5]. This would permit selective avoidance of surgery in frailer older women at a time when anaesthesia and surgery risks were greater than they are today. In the subsequent decade several randomised trials (RCTs) were conducted which showed that when compared to surgery, tamoxifen PET was associated with no overall survival disadvantage on 5 year follow up on meta-analysis, but there was a reduction in progression or recurrence free survival [6] (Fig. 5.1).

At the time that these studies were performed testing for the presence of oestrogen receptors on tumours was not routinely performed and therefore 15–20% of the enrolled women will have been effectively taking placebo, which may have skewed the results in favour of surgery.

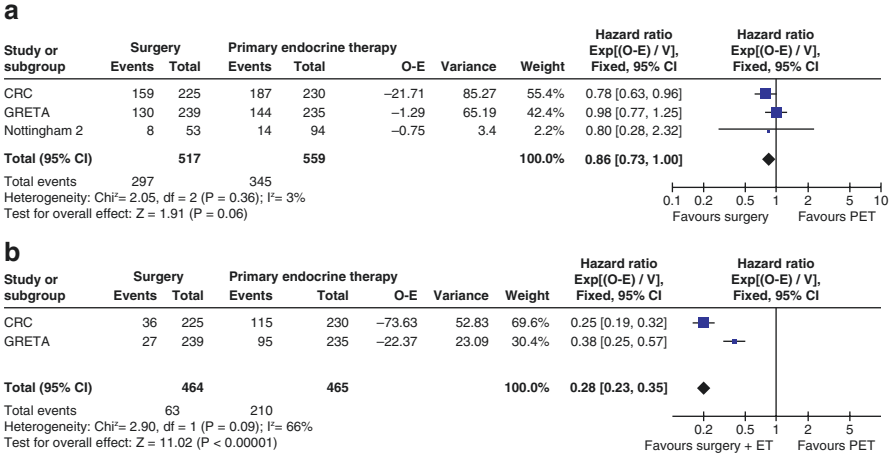

Fig. 5.1 (**a**) Forest plots comparing overall survival after surgery (plus adjuvant endocrine therapy) versus primary endocrine therapy. (Both reproduced with permission from Morgan et al. [6]). (**b**) Forest plots comparing local disease control after surgery (plus adjuvant endocrine therapy) versus primary endocrine therapy

The data in these studies changed practice in some countries and there was a shift away from surgery for women over 70 with early breast cancer. In the UK, up to 40% of older women were treated with PET in some series [7, 8]. A decade after this shift, when longer term follow up of these trials was published [9], clinicians began to realise that fitter older women were disadvantaged by PET. The CRC trial found a hazard ratio (after 13 years of follow up) for overall survival of 1.29 (1.04–1.59) and breast cancer specific survival of 1.68 (1.15–2.49) for older women who had surgery. For those treated with PET, a change of management was often required, with 40% requiring subsequent surgery and others requiring a change of antioestrogen. A more sophisticated approach was required based on assessment of the biology of the tumour, the age and fitness of the patient and giving the woman a role in making the decision herself based on her personal priorities.

Unfortunately, a more sophisticated approach is not yet a reality and rates of non-surgical treatment are still high [10]. There are presently no age and fitness stratified evidence-based guidelines about who may benefit from surgery and who may safely avoid it.

Predicting life expectancy is not an exact science and is not part of routine clinical practice for surgeons as it requires a lengthy assessment, which time constraints in many Units preclude, even if the technical expertise is present.

The following sections review various aspects of PET in present day practice.

5.2 Variation in Use of Primary Endocrine Therapy

Use of primary endocrine therapy is heterogeneous between countries, breast units and surgeons. Derks and colleagues compared rates of non-surgical therapy and found a rate of 28% in the UK, (the highest) versus 9% in Poland [11]. In the USA it is rarely, if ever, used [12]. It has been suggested that this may be one of the reasons for the inferior outcomes seen in older women with breast cancer in the UK [11]. There is also wide variation in the use of PET within the UK with rates of surgery varying between 50% and 90% (Fig. 5.3) [10]. This variance persists after case mix adjustment (for deprivation, age and fitness levels, Fig. 5.2) and likely represents variation in surgeon preference [13]. This is despite current guidelines from several national and international bodies. The National Institute of Health and Care Excellence (NICE) states that PET should only be used if "significant comorbidity precludes surgery" [14]. The International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) recommend that PET should only be offered to patients with a "short estimated life expectancy (<2–3 years), who are considered unfit for surgery or who refuse surgery" [15].

Some units operate on almost every older woman, even those with very poor life expectancy, whereas others offer PET to older women regardless of their level of fitness (Fig. 5.2).

Similarly rates of PET vary between surgeons with some operating on almost all women and others the reverse [13]. Thresholds for offering surgery vary between surgeons as shown by the results of scenario based research where widely different

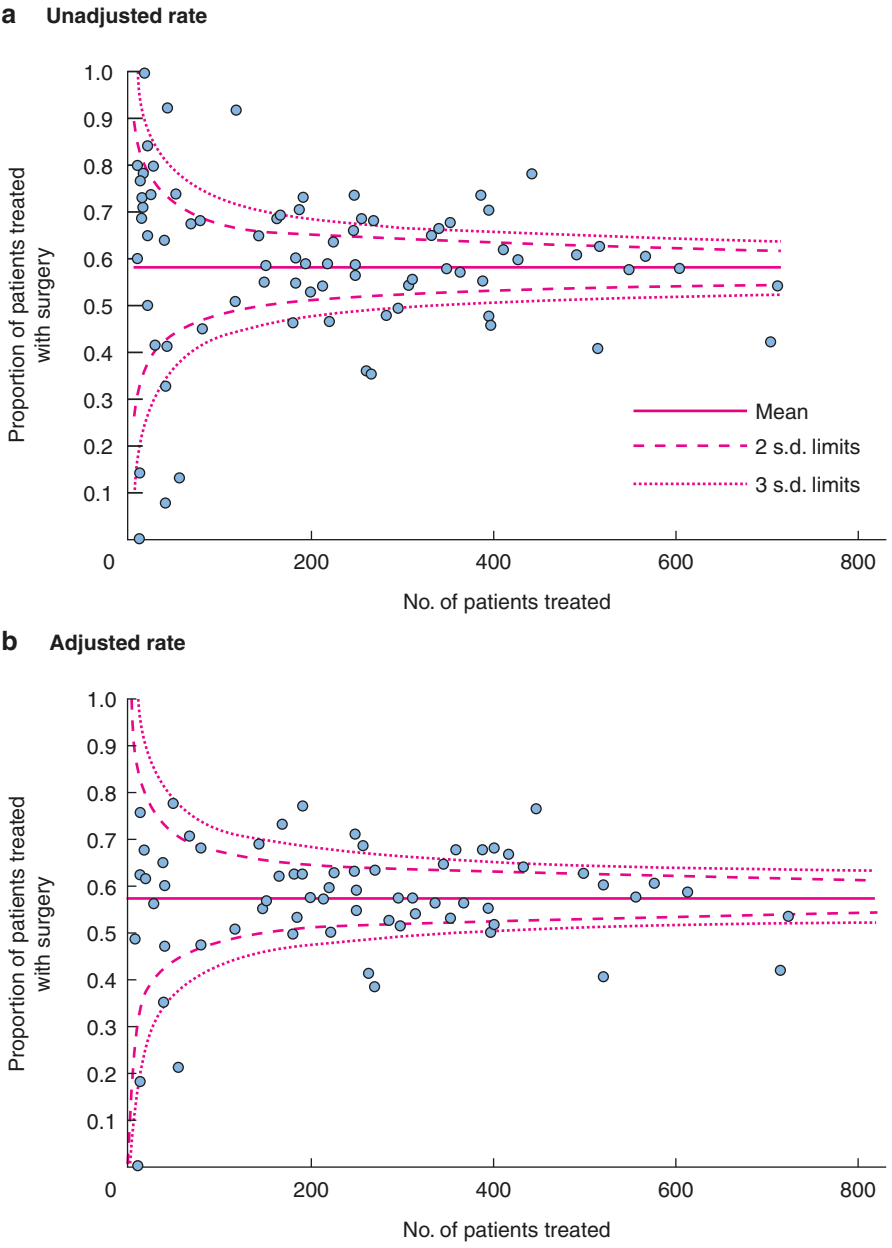

Fig. 5.2 Funnel plots showing case mix adjusted (**a**) and unadjusted (**b**) rates of surgery for older women with ER+ cancer based on UK registry data analysis. (Reproduced with permission from Morgan et al. [13]). Factors adjusted for were age, comorbidity, deprivation quintile, method of cancer detection, tumour size, stage, grade and nodal status

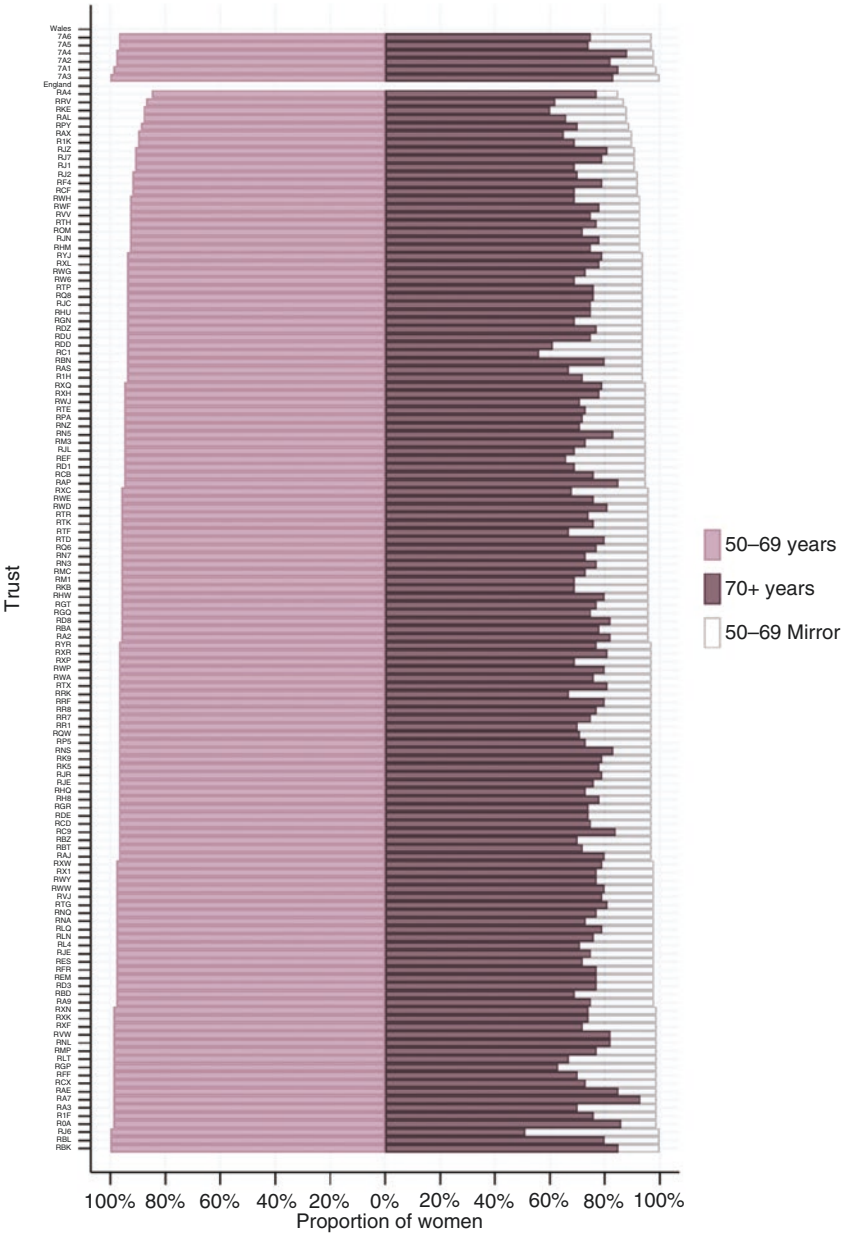

Fig. 5.3 Risk adjusted proportion of women receiving primary surgical treatment for early invasive breast cancer by diagnosing treatment centre and age at diagnosis. (Reproduced with permission from [10]). **Note:** Figure ordered by country of diagnosis and then Organisation-specific proportions receiving primary surgical treatment in women aged 50–69 years at diagnosis. The "50–69 Mirror" bars are the reflection of the proportions for the 50–69 age group over the proportions for the 70+ age group, to aid comparison

preferences have been demonstrated between surgeons for any given set of age/fitness/frailty characteristics of a patient [16, 17]. It is thought that inappropriately low rates of surgery may contribute to inferior breast cancer outcomes in older women [11] (Fig. 5.3).

5.3 Clinical Response to Primary Endocrine Therapy

Primary endocrine therapy does not usually result in rapid tumour regression as is typical of neoadjuvant chemotherapy. In most cases, whilst tumour softening may be seen at 6 weeks, tumour shrinkage is unlikely to be apparent until 3–6 months and the response may continue to improve for 9–12 months or more until maximal response is achieved. Responses are usually graded as either complete response (CR), partial response (PR), static disease (SD) or progressive disease (PD). A combined measure of response, the clinical benefit rate, is the sum of CR, PR and SD. The breakdown of response achieved in PET in reported studies is shown in Table 5.1 (modified from Morgan et al. [18]).

Assessment of response may be by clinical measurement or by imaging, depending on unit protocol and the ease of clinical assessment of a particular tumour. It is important that the same method is always used at each visit as there is variation between US, mammographic and clinical measurements. In modern practice, PET is only offered to women with ER positive tumours. De novo disease progression is indicative of primary antioestrogen resistance. Over the longer term, initially responsive disease acquires secondary resistance, the rate of which varies according to the length of follow up. Failure rates (both primary and secondary) vary between studies, with rates reported between 37% and 84% in studies with median follow up durations of 76 and 70 months respectively [22, 28].

Table 5.1 Summary of percentage tumour response from clinical trials of Tamoxifen or aromatase inhibitor PET in older patients. (Clinical benefit rate is CR + PR + SD). All tumours confirmed as ER+ in these studies

Study	Number of patients	PET Type	Clinical benefit rate	Complete response (CR)	Partial response (PR)	Static disease (SD)	Progressive disease	Median duration of follow up months (range)
[19]	59	Tam	54	24	22	8	34	>6
[20]	62	Tam/AI	60	–	–	–	–	20(2–150)
[21]	84	Tam	100	8	18	74	0	24(6–72)
[22]	70	Tam	77	–	–	–	–	70(9–119)
[23]	104	AI	82	23	40	18	18	56(4–106)
[24]	616	Tam/AI	84	26	30	29	16	41(1–202)
[25]	91	Tam/AI	76	17	45	16	16	18(2–70)
[26]	56	AI	100	11	77	13	0	51(19–78)
[27]	56	AI	100	25	52	23	0	12

Modified from Morgan et al. [18]

Clinical factors which predict a good quality and long duration of response include a small initial tumour size and a good early clinical response. Women with static disease at their 3–6 month assessment are less likely to have good long-term disease control than women with complete, or partial response, with initial complete response being associated with a 50 month response duration, partial response 18 months and static disease 21 months [5].

There is a correlation between early stage disease and good response, with one study reporting a 100% clinical benefit rate for stage 1 disease, 83% for stage 2 disease and 66% for stage 3 disease [5]. Other studies have shown similar findings, with only a 53% response rate in T4 tumours compared to an 80–86% response in T2 and T3 disease [29].

The time taken to reach a best response is quite variable, ranging from 3 to 37 months, with a median of 9 months [5]. In fact for women who have an initial complete response, up to 90–100% will still be controlled at 5 years in some studies [5, 30]. Others studies have shown less favourable results, with only 42% of complete responders in remission at 47 months, but the range of response duration was from 5–96 months in this study, which included a high (47%) proportion of T4 tumours [29].

In terms of the long-term rate of local control, most studies report that local disease progression, requiring a change of management, occurs in between 32 and 62 percent of women. One trial with very long follow up (12 years) (Fennessy et al. [9]), found a failure of local control rate of 53.4%, with the median time for failure to occur at 1.69 years (range 1.43–1.82 years). This was substantially worse than women in the surgical arm of the trial, where local failure occurred in only 15.6% of women. Most of these local failures were treated with surgery (64%), with 29% having a change of hormonal therapy or radiotherapy (19%). As with most of the studies of PET, these data have to be viewed in the knowledge that they do not mirror current PET practice, as approximately 20% of all patients will have had ER negative cancers, and will have thus progressed on PET inevitably and effectively had a delay in starting any effective therapy for a significant period. Secondly, in view of the knowledge accrued from these studies, most (but not all) clinicians would reserve PET for older and frailer women (unlike most of the trials, which recruited women aged over 70 regardless of their health status).

5.3.1 Biological Predictors of Response

Prediction of endocrine responsive breast cancer is increasingly complex although most of our understanding comes from neoadjuvant endocrine therapy where down staging prior to planned surgery is the aim, rather than in the PET setting in the frail elderly. There is now a greater understanding of the molecular biology of primary and secondary endocrine resistance and increasingly sophisticated tools to predict response. The subject is complex as most tumours are genetically heterogeneous at diagnosis. Matters are further complicated by tumour evolution during treatment which may select out certain resistant clones, new mutations may occur and gene

expression may be altered [31]. Simple loss of expression of the ER is an uncommon mechanism of antioestrogen resistance which is more commonly caused by changes in the down-stream regulatory pathways such as the PI3K/mTOR signalling pathway or cell cycle regulatory mechanisms [32]. Therefore, use of alternate antioestrogens, potentially combined with other agents to target specifically these downstream pathways, has potential to overcome resistance.

In current clinical practice two biomarkers are usually used in the prediction of response: the ER and Her-2 receptors. Tumours which have higher ER scores are more likely to respond well and for a long duration than ER poor tumours and may do as well with surgery as with PET in some series [24] and conversely HER-2 positive tumours are more likely to develop antioestrogen resistance, especially to tamoxifen.

However more sophisticated predictive biomarkers are available or under development in the adjuvant, neoadjuvant or advanced setting. None of these technologies have been evaluated in the PET setting with the exception of tissue biopsy after treatment. These may be classified as multigene arrays or treatment response markers (based on either rebiopsy of the tumour after treatment or monitoring of circulating tumour cells or DNA on blood samples).

In the neoadjuvant setting use of one multigene array, Oncotype DX®, in women on exemestane for 6 months before surgery found that a low recurrence score correlated with a higher chance of clinical response and conservation surgery (90 versus 47%) [33] raising the prospect that this might add value in decision making about PET as an option. The recent POETIC study undertook whole exome sequencing of ER positive breast cancers and found that a high mutational load and the TP53 mutation were both associated with poor antioestrogen response [34]. Other tissue biomarkers including a 4-gene signature [35] and apoptosis markers are also potentially valuable.

Tissue re-biopsy after treatment has started is an effective way to predict treatment response and the best-known marker for PET is Ki67, a marker of proliferation. If this falls at 2 weeks then the tumour is more likely to have a good sustained response [36]. The need for a further invasive biopsy in frail older women makes these methods less valuable.

Currently there is much interest in the use of ‘liquid biopsies’ to assess circulating tumour cells or cell free tumour DNA [37, 38]. Again, there has been no application of these technologies in the older age group PET setting but they have potential to avoid re biopsy in the event of progression to allow a more tailored approach to change of management with reduced morbidity. These technologies are being evaluated in managing advanced breast cancer progression where decisions about multiple lines of complex chemotherapy and targeted biologicals may be guided by such tools.

5.3.2 Antioestrogen Drugs for Use in PET

As can be seen from Table 5.1 above, rates of response to antioestrogens are generally high, although complete response is not common. There is a trend for aromatase inhibitors to yield higher clinical benefit rates than tamoxifen which is in

keeping with published studies of use of AIs compared to tamoxifen in other clinical settings such as adjuvant [39], and neoadjuvant [40, 41]. Therefore unless specifically contraindicated, AIs should be used in preference to tamoxifen as first line endocrine therapy for PET.

5.3.2.1 Tamoxifen Versus Aromatase Inhibitors

Comparison of letrozole with tamoxifen in the neo-adjuvant setting in 337 postmenopausal women demonstrated a significantly higher clinical response rate in the letrozole group (55% versus 36%, $P < 0.001$) at follow-up of 4 months [40]. Of interest was the fact that letrozole was superior to tamoxifen regardless of the level of ER positivity, even inducing response in only weakly ER positive tumours, where tamoxifen was ineffective.

Another neo-adjuvant Letrozole study demonstrated that Letrozole was effective in reducing the size of large primary cancers considered unsuitable for breast conserving surgery. This study found that whilst in most women the best response had been achieved by 4 months of therapy, further benefit was seen at up to 8 months with letrozole which was the maximum period of neo-adjuvant therapy [42]. They found a 62% reduction in tumour volume at 4 months and 70% at 8 months.

Similarly, anastrozole is superior to tamoxifen in the neo-adjuvant setting and has been studied in 2 trials: IMPACT and PROACT. In the IMPACT study (IMmediate Pre-operative Arimidex, Tamoxifen or Combined with Tamoxifen), 330 women with a median age of over 70, found a significantly higher rate of breast conservation with anastrozole compared to tamoxifen when used for only 3 months prior to surgery (46 versus 22%) [43].

The PROACT study compared 12 weeks of pre-operative anastrozole or tamoxifen (PRe-Operative Arimidex Compared to Tamoxifen, [44]), in women with large operable or potentially operable breast cancer. Anastrozole resulted in increased rates of breast conservation versus tamoxifen (43 versus 31%, $P < 0.04$), and numerically superior clinical response rates (36 versus 26%).

Exemestane has also been used in the neoadjuvant setting and has a similar efficacy to anastrozole [45].

5.3.2.2 Fulvestrant

Fulvestrant is a pure ER receptor antagonist which is licenced for use in the advanced breast cancer setting where it has been shown to have superior efficacy to anastrozole (if used at the correct 500 mg dose) [46, 47]. It has not been studied in the PET setting and is rarely used clinically due to costs and the fact that it must be given by injection.

5.3.2.3 Agents for the Future

There has been huge development in targeted biological agents for use in breast cancer and although none of these are being trialled in the PET setting there may be roles for them in the future in second or third line therapy where surgery is not an option. Drugs such as bisphosphonates may have a role as an adjunct to PET both to reduce

the osteopenic side effects of AIs but also, recent evidence suggests they may have a small survival impact in women with post-menopausal breast cancer [48].

Other agents with high efficacy rates in ER positive breast cancer are the CD4/6 kinase inhibitors palbociclib and ribociclib which are co prescribed with aromatase inhibitors and enhance response rates significantly in the metastatic setting [49] and show high efficacy rates in the neoadjuvant setting [50]. There is little experience with these agents in older patients however and none in the PET setting.

5.4 Patient Selection for Primary Endocrine Therapy

Several studies have explored the selection criteria for PET in the older breast cancer population. In the UK, 45% of PET patients were high risk for general anaesthesia due to co-morbidity; in 8.5% of cases they were offered PET on the basis of extreme old age (over 85 years); in 10.6%, they were significantly cognitively impaired and in 36% of cases they were offered a choice of PET or surgery and chose PET [7]. Another UK study that examined the use of PET quoted a figure of 32% for patients being selected due to unfitness for surgery [25]. Functional status and chronological age are more likely to predict the use of PET than co-morbidity [8]. Similar figures were quoted by Hooper and colleagues [51] in their Irish cohort, with 62% offered PET based on the presence of significant co-morbidity (including dementia), 14% based on age and 11% based on patient preference. In the Netherlands Hamaker and colleagues found that co-morbidity accounted for only 6% of the decision to omit surgery and overall health status for only 5% in their study [52] with 32% being due to patient request. This is in contrast with results from the UK, where Rai and colleagues [53] found only 4% of patients treated without early surgery were due to patient choice and Lavelle and colleagues [54] who stated that lower rates of surgery were unlikely to be due to patients actively opting out of surgery.

The assessment of older patients for surgical fitness is complex and time consuming and detailed assessment is out-with the scope of many breast units both in terms of time and geriatric expertise availability. One study [55] reported on the use of comprehensive geriatric assessment (CGA) in a joint clinic with geriatrician input into the decision making process for older women. They found that CGA permitted relatively accurate prediction of 3-year survival and that good survival scores were indicative of benefit from surgery.

Stratified analysis of outcomes from surgery or PET do show that surgical benefit is more likely to be seen in fitter, younger women as shown in the study by Ward and colleagues. This examined UK registry data and stratified by age subgroup and comorbidity rates and found that as both age and comorbidity levels rise, differential breast cancer specific survival narrows significantly (Fig. 5.4) [56].

Age has a marked impact on rates of surgery. The recent National Audit of Breast Cancer in the Older Patient (NABCOP) UK National audit shows clearly that rates of surgery decline markedly with age and this is consistent with several published studies that have identified a reduction in surgery rates with increasing age for older patients with operable breast cancer [57–59]. Life-expectancy is considered

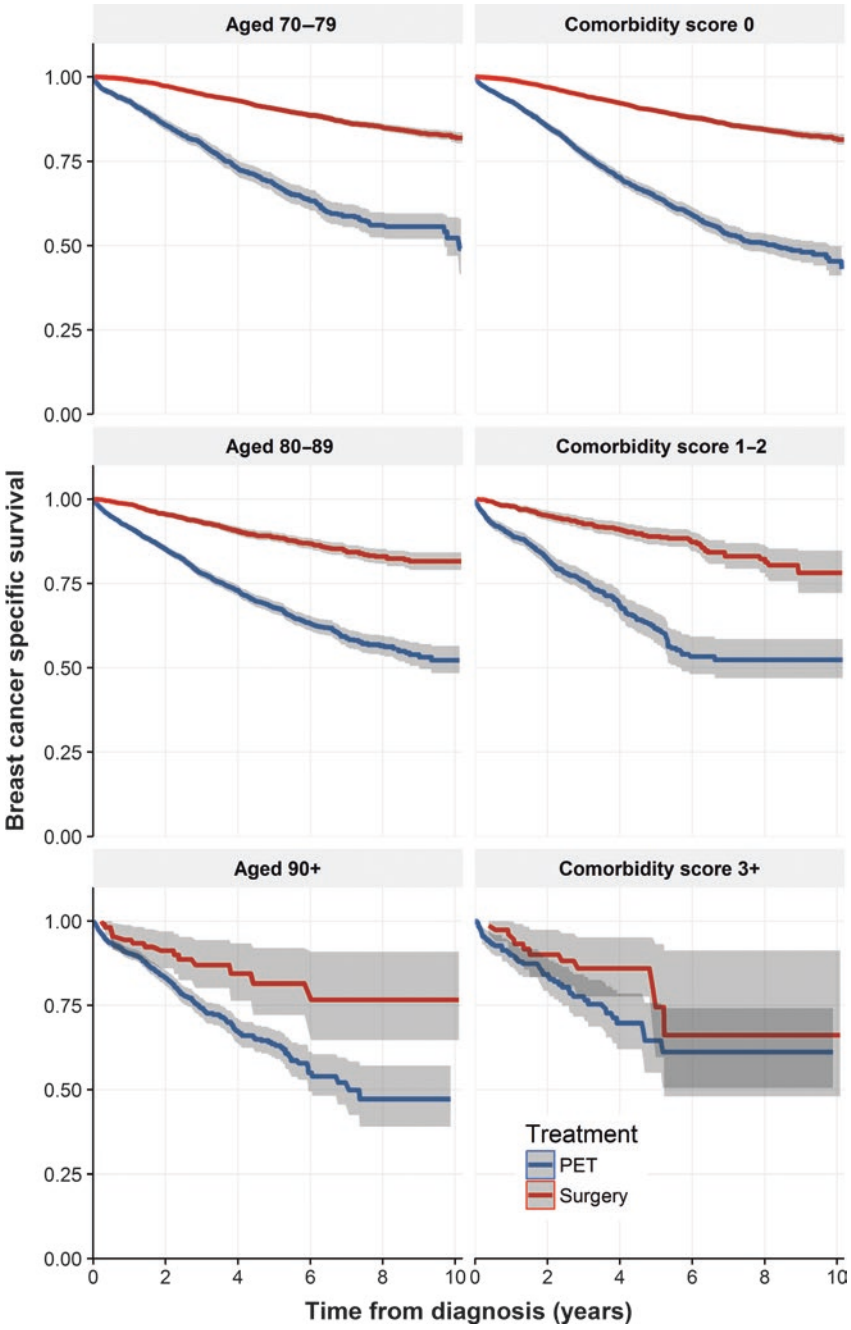

Fig. 5.4 Breast cancer specific survival (BCSS) by age group (left) and by comorbidity score (right) for surgery and PET treatment of UK cancer registry data (2002–2012). These curves demonstrate that BCSS remains inferior for patients receiving PET despite older age or increasing numbers of co-morbidities. (Reproduced with permission from [56])

relatively important in how clinicians determine treatment options [60], and chronological age is often used by clinicians as a surrogate marker of life expectancy alongside other factors, such as comorbidity and frailty, however a recent UK questionnaire study found that surgeons are poor at gauging life-expectancy of older patients, with a tendency to under-estimate it [17].

Several UK based observational studies have shown a clear association between use of surgery and the number of comorbidities. Lavelle and colleagues [61] in a registry cohort of over 65 s, found rates of surgery of 73, 66 and 49% according to comorbidity scores of 0, 1 or >2.

Some specific comorbidities have been examined for their impact on breast cancer treatment selection and outcomes. Dementia is the most notable of these.

Significant cognitive impairment affects up to 10% of people over the age of 65, and is more prevalent in women where the rate increases to 20% for women aged between 85 and 89 years of age [62]. As a result, dementia is a common comorbidity in older breast cancer patients and is associated with a significant reduction in life expectancy and is a leading cause of death for women in the UK [63]. Dementia may preclude surgery under local anaesthesia and cognitive and functional ability may worsen following general anaesthesia [64], so for patients with ER+ breast cancer and dementia, PET may be an effective alternative. In fact there are studies that have examined the use of PET in small cohorts of elderly patients which have suggested that the presence of dementia may have been a contributing factor in treatment decision making in some patients [30, 51, 65–67]. Studies from the USA have shown that women with dementia are less likely to receive standard treatment such as surgery for their breast cancer [68, 69]. However, a survey of clinicians showed that opinion was divided regarding the best treatment approach in elderly breast cancer patients with dementia. There are currently no UK guidelines for the treatment of operable breast cancer in this complex group of patients, which may reflect this lack of consensus

5.4.1 Psychological Response and Quality of Life

There has been little formal study of the quality of life impact of surgery versus PET in this age group. Only one of the historic randomised trials compared QoL outcomes between women having surgery or PET using the general health questionnaire, which is a generic tool and not very sensitive for detecting the impacts of breast cancer treatment [70]. Whilst this study showed a small difference in QoL when measured during early follow up, by 2 years, any differences had disappeared. This is somewhat surprising considering the proven negative impacts of breast surgery on quality of life. One would expect that breast cancer surgery would have a detrimental effect on at least short term QoL as has been shown in a number of studies where breast cancer specific instruments have been used.

Breast cancer surgery has detrimental effects on QoL, with adverse effects at 1 month post-operatively (fatigue, loss of function and pain). These effects may persist for a long time, with up to 45% still complaining of fatigue and 15% still struggling with household chores, at 12 months [71]. In addition chronic wound pain may

affect 75% of women following breast cancer surgery, regardless of type (50% mild, 25% moderate), which may impact on QoL. In 35% of breast cancer patients the pain is of neuropathic origin, and therefore relatively difficult to control [72].

In contrast for women on PET, there may be additional concerns about treatment failure or recurrence sometimes due to the continued presence of the palpable lump: fear of cancer progression or recurrence affects quality of life [73].

Lavelle and colleagues looked at a range of quality of life measures after breast cancer diagnosis and found that scores were worse in women who went on to have PET but did not assess QoL after treatment and deduced that this may have been a factor in treatment decision making [54]

A very small study comparing QoL in older women treated with or without surgery showed no significant differences at 6 weeks or 6 months between groups but was underpowered and therefore no valid conclusions could be drawn from this [74].

More recently the Age Gap study has undertaken a more rigorous approach to QoL impacts, using a range of validated QoL tools (the generic cancer EORTC QLQ C30, the breast specific EORTC BR23 and the elderly specific EORTC ELD14) at baseline and at intervals up to 2 years with adequate study power to detect differential responses. The results are complex to interpret as the study is a pragmatic observational study and therefore baseline characteristics vary between women having surgery and those having PET. When this variance is adjusted for using propensity score matching and variation in baseline QoL there is a significant disadvantage to surgery in many of the QoL domains in a matched cohort of frail older women, which persists in some domains out to 2 years [75]. As can be seen in the limited data reproduced below (Fig. 5.5), global QoL falls from 72 to 61 between pre-treatment baseline and 6 months in surgically treated women, compared to a fall of only 68 to 64 in the PET group ($P < 0.05$). Similarly, in the physical function domain there is a fall of 11 points compared to only

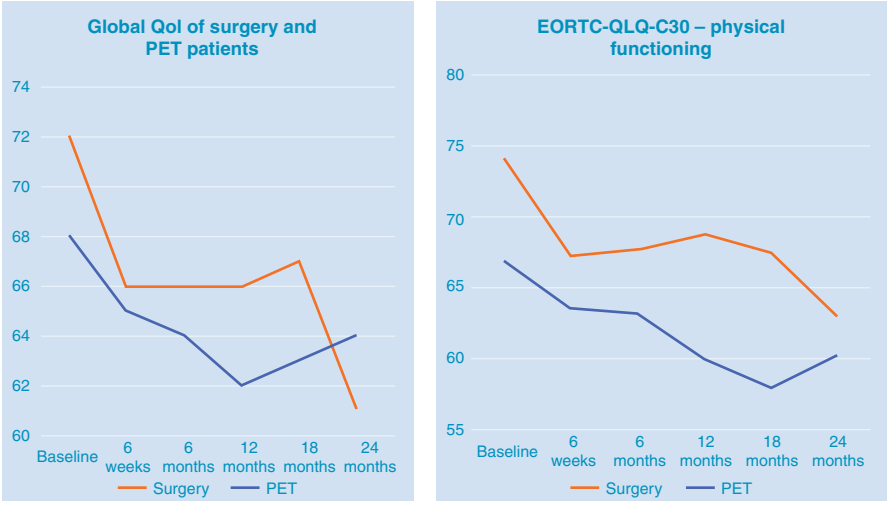

Fig. 5.5 Quality of life outcomes from baseline to 2 years follow up of propsensity score matched cohorts of women treated with surgery (red) or PET (blue) [75]

a 7 point decrease in PET patients. In several other domains significant falls in QoL were seen for surgery to be greater than for PET and in no domain was surgery superior. This is not surprising due to the impacts of surgery (chronic pain, disfigurement, arm and shoulder symptoms) and the lack of resilience to the effect of anaesthesia in this group of frailer women.

The psychological impact of PET has been studied in older women using qualitative methodology and potential concerns about anxiety relating to the continued presence of the tumour are not realised as women felt reassured that they were able to feel the lump shrinking. In general many women who chose PET did so because of a wish to avoid surgery and anaesthesia, a wish to reduce the burden on their carers and family, a pragmatic sense of acceptance of their likely limited life expectancy and ability to tolerate such treatment [76]. Detailed interviews with women who had previously had PET or surgery in this older age group have shown that older women tolerate both therapies very well [76]. Women on PET are unconcerned by the persistence of a palpable lump in the breast. In fact, the reverse is true and most are reassured that they can feel the lump themselves and know that the endocrine therapy is still working. Older women find PET a simple and attractive option, despite awareness that the treatment may not control their disease indefinitely. They are concerned that there be as little disruption to their normal daily life as possible. Surgery mandates a hospital visit about which many older women have anxieties. Surgery for some older women will take the form of a mastectomy and for many, the loss of a breast is a source of distress. Many older women are concerned about the risks of surgery and anaesthesia. Of those women who do have surgery however, many find the experience tolerable.

5.4.2 Survival Outcomes

Whilst the historic randomised trials have not shown significant overall survival advantage to surgery on meta analysis (Fig. 5.1), subgroup analysis of a cohort of women between 70 and 75 did show improved survival [77]. Very long follow up has shown improved survival in some studies.

The RCTs referenced above do not represent modern real world practice as they recruited women of any level of fitness over age 70 and, in most cases, only frailer, older women are offered PET today. Observation data of UK practice and outcomes from cohort studies and registry analysis has confirmed the perception that breast cancer specific survival is superior in women having surgery, although stratification by age and fitness suggests that the oldest old and those with significant health issues derive no benefit (Fig. 5.4).

5.4.3 Patient Decision Making

Older women differ slightly in their desire for involvement in medical decision-making and tend to be slightly more passive in their approach. However this is not always the case and there is great variability in this. At present there are no bespoke,

age appropriate decision support tools for older women faced with this choice and most counselling is supported using booklets designed to support use of adjuvant antioesrogens and primary surgery with no resources to fully explain the nature of PET, the risks of potential benefits. A large UK study has recently developed a range of decision support tools specifically for this task, tailored to the informational needs and preferences of older women [78, 79]. These comprise a booklet and an online tool that can calculate survival rates at 2 and 5 years with either choice and which is responsive to age, fitness, frailty and disease biology. The output from this tool can be printed in a user-friendly format to be used in counselling older women. The tools are at present being evaluated in a cluster RCT nationally and will be published in 2019 [80].

5.4.4 Clinician Involvement

Clinicians vary in their attitudes to offering PET and the relative weights they place on patient and disease attributes when making these decisions. A recent survey of MDTs by the RCS as part of the National Audit of Breast Cancer in Older People (NABCOP) gave MDTs a set of patient scenarios and asked whether PET or surgery would be preferred. The results showed that whilst the majority of clinicians had similar views, some scenarios clearly divided opinion and in all scenarios there was a significant minority holding counter views, all of which shows the heterogeneity of opinion in this area. A survey of 244 UK healthcare professionals also demonstrated how opinions differ regarding the use of PET, especially in those patients with dementia. There was a general consensus that patient preference was the most important factor when considering treatment options, yet only around a quarter would offer it as a choice in patients with ER positive disease [60] .

A more rigorous example of scenario based evaluation of breast clinicians showed that decisions were significantly affected by age, dementia, frailty and fitness [16]. Again, whilst the majority of individuals selected treatment in accordance with current guidelines relating to the presence of significant comorbidity, in some scenarios, opinion was divided and age did appear to be an independent factor that was considered when making a treatment decision.

Hamaker and colleagues have also suggested that variation in treatment may reflect underlying clinician preference influencing communication of treatment options [52]. An interview study of older breast cancer patients demonstrated that the most influential factor affecting older women's breast cancer treatment decisions was the surgeon's recommendation [81].

5.5 Summary

Primary endocrine therapy for women with primary, operable breast cancer should be reserved for women with moderately or strongly ER positive tumours and who have a predicted life expectancy of less than 5 years (that is women of over 85 or

those over 75 with significant co-morbid disease). Close monitoring during the first year of therapy should aim to identify those who have a complete or partial response who may be predicted to have a long duration of local disease control. For those with static or progressive disease, early consideration should be given to surgery, either under local or general anaesthesia as these tumours are unlikely to have a long duration of disease control. For frailer women or those who refuse surgery on progression, second line endocrine therapy may be offered (switching between Tamoxifen and an AI or *vice versa*), although the duration of response may be less than with the primary agent used. Radiotherapy may also be a good second line option.

In terms of the choice of endocrine therapy, there is good evidence that aromatase inhibitors should be preferred unless specifically contraindicated, but bone density will need to be monitored and treated. In terms of which AI to use, the strongest evidence of efficacy relative to Tamoxifen is for Letrozole, but all AIs have been demonstrated to be effective in the short-term neo-adjuvant setting.

Older women who are thought suitable for a choice of PET or surgery should be offered a role in the decision making process. Both surgery and PET are generally well tolerated although QoL outcomes may be slightly worse with surgery, but the trade off is the slightly enhanced oncological outcomes with surgery. This trade off should be discussed with patients so they may set their own priorities.

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General and Local Anesthetics

6

Irwin Foo and Faisal Jafar

Abstract

Anesthetising the older surgical patient present its own unique challenges. Heterogeneity is the most consistent feature of this age group and preoperative assessment and optimisation must take into account the varying comorbidities, extent of physiological ageing, frailty and the size of surgery which will determine patient outcome. Breast surgery can be undertaken either with local, regional or general anaesthesia and the choice of technique is individualised for each patient based on the risk benefit of each technique. Changes in pharmacokinetics and pharmacodynamics in this age group alters the drug responses of anaesthetic drugs and anatomical and neuronal changes influence the ability in performing regional blocks and the response to local anaesthesia. Anesthetic drugs which are short-acting, predictable and independent of organ metabolism are most suitable for this patient cohort and the use of ultrasound to aid placement of local anesthetic blocks has improved success rates and minimised complications.

Whichever technique is chosen, careful intraoperative monitoring including the use of advanced monitoring for example processed electroencephalogram will minimise haemodynamic instability and reduce postoperative complications. Postoperative pain is best managed with multimodal analgesia and strategies to reduce the impact of postoperative cognitive impairment implemented. Lastly, the older patient requires greater vigilance throughout the perioperative period as their reduced capacity for adaptation means they decompensate and develop complications more readily.

Keywords

Anesthesia risk · Local anesthesia · Regional anesthesia · General anesthesia · Postoperative complications

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6.1 Introduction

The number of older patients presenting for breast surgery is increasing due to advances in both surgical and anesthetic techniques, patient expectations and improved outcomes. However, anesthetising older patients presents its own challenges and impact on every aspect of care from the preoperative period to well beyond the post anaesthetic care unit.

Aging is an all-encompassing multifactorial process that results in reduced capacity for adaptation and a gradual decrease in physiological reserve of the different organ systems. However, there is considerable physiological heterogeneity in the rate and extent of ageing in each individual which is determined by both genetic and environmental factors. Apart from variable physiological ageing impacting on organ function, the number of comorbidities also increase with age. A recent UK population study showed that by the age of 50, half of the population had acquired at least one comorbidity and by the age of 65, multimorbidity was present in 65% of the population [1] (Fig. 6.1). Furthermore, in the last decade, frailty in older surgical patients has emerged as an independent risk factor for postoperative outcomes. This is in addition and independent from comorbidities [2]. Therefore, the response to surgical stress is often unpredictable.

There is a strong correlation between advancing age and postoperative complications [3]. These complications which can occur in up to 25% of older surgical patients can ultimately lead to adverse outcomes such as disability, loss of

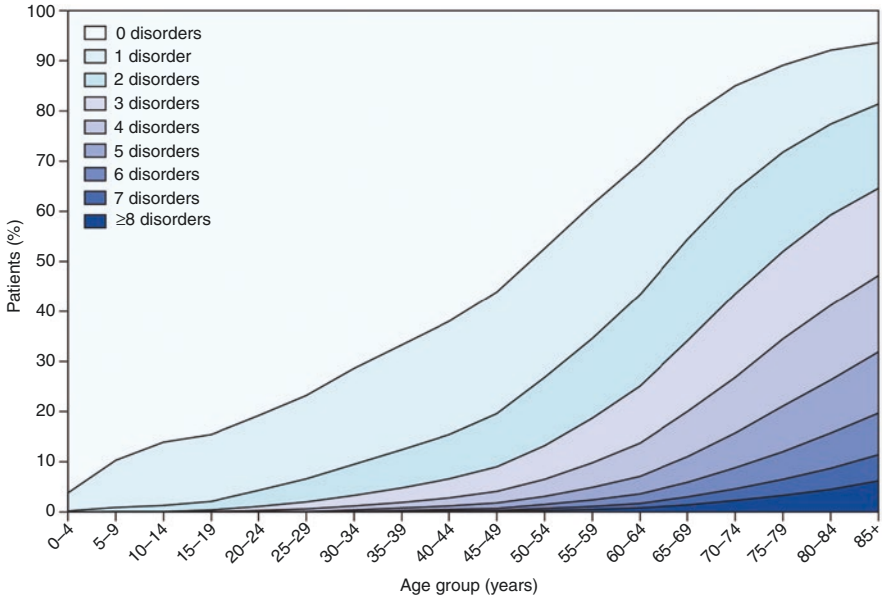

Fig. 6.1 Number of chronic disorders by age-group. (Reproduced from Barnett et al. [1])

independence, diminished quality of life and mortality. From an anesthetic viewpoint, careful preoperative assessment and optimization, choosing the correct anesthetic technique and careful administration of drugs can help minimize the impact of postoperative complications e.g. delirium and chest infections.

6.2 Preoperative Assessment and the Risk of Anesthesia in the Elderly

The purpose of preoperative assessment includes identifying potential anesthetic difficulties e.g. difficult tracheal intubation, identifying existing medical conditions and potential for optimization, assessment of individual organ functional reserve and planning the most suitable anesthetic technique. This will enable risk assessment and stratification informing doctors, patients and their relatives/carers about the risks and benefits of the intended surgery. With this age group, proactive identification and optimization of modifiable risk factors such as anaemia and poor nutrition can improve the likelihood of a good outcome after surgery.

The American Society of Anesthesiologists (ASA) grading system (Table 6.1) has been shown to be a good predictor of risk of death following surgery in older patients [4]. It is based solely on co-existing preoperative disease and its severity. Conditions most indicative of a higher risk of morbidity and mortality postoperatively are ischaemic heart disease, hypertension, diabetes, chronic respiratory disease and impaired renal function. However, it does not take into account the presence of frailty, a geriatric syndrome which can be regarded as a decreased physiological reserve across multiple organ systems. As a consequence of frailty, there is a diminished capacity to withstand external stressors such as surgery with the consequences of increased postoperative complications, prolonged hospital stay, institutionalization and death. Combining the ASA grading system with frailty assessment has been demonstrated to be a better predictor of adverse outcomes in older patients [5].

Therefore, the risk and outcome of anesthesia and surgery in the older patient is an interplay between physiological ageing, comorbidities, frailty and the extent of surgery. It is important to emphasize that age per se is not considered a major factor in predicting the risk of anesthesia and surgery. Each of these factors require careful consideration when assessing an older patient for surgery and the choice of anesthetic technique is determined by the risk benefit of each technique once all these factors are considered.

For practicing clinicians, a risk prediction tool is useful to quantify the risk of anesthesia and surgery and to allow meaningful discussion with the patient and also to plan management. Although there are no specific tools for breast surgery, there are several validated tools which are useful in this respect. The preoperative assessment of cancer in the elderly tool (PACE) which incorporates instruments such as the Comprehensive Geriatric Assessment and ASA grading have been found to be useful in evaluating fitness in this patient cohort [6] but may impractical in the often time pressured preoperative clinic. Other tools which are simpler and used for rapid risk assessment are the

Table 6.1 ASA physical status classification system (October, 2014)

ASA PS classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥ 40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purpose	

Adapted from Doyle and Garmon [53]

Surgical Outcome Risk Tool which calculates risk based on type and severity of surgical procedure, ASA status, urgency of surgery, presence of cancer and the age of patient, and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) surgical risk calculator, which predicts various perioperative risks based on patient's physiology and type of surgery [7, 8].

6.3 Pharmacokinetics and Pharmacodynamics in the Elderly

Although heterogeneity is a key feature of the older patient, there are some generalisations that can be made regarding the influence on aging on drug pharmacokinetics and pharmacodynamics [9]. After a drug bolus, a higher than expected initial plasma drug concentration is seen due to a reduction in blood volume by

Table 6.2 Recommendations for dosage adjustment consequence of altered pharmacokinetics and pharmacodynamics in the elderly

Medication	Dose adjustment
Local anesthetics	Slight to modest reduction in dose per segment
Inhalational agents	6% reduction per decade after age of 40 years
Thiopentone	Modest reduction in dose
Propofol	30–50% reduction in bolus dose and infusion rate
Benzodiazepines	50–75% reduction in dose
Non depolarizing muscle relaxants	Bolus dose is unchanged but about 30% reduction in repeat doses depending upon the agent
Opioids	30–50% reduction in bolus and repeat doses

as much as 20–30% in the older population. Older people tend to maintain higher blood concentration of drugs due to many factors which include changes in volume of distribution, reduced protein binding, changes in the proportions of body water and fat, slower drug metabolism due to loss of hepatic function and reduced renal excretion. The resulting effect is that the time required for the elimination of drugs is prolonged and this is especially true for lipid-soluble drugs such as benzodiazepines. Furthermore because of the reduction in plasma protein binding of drugs with age (especially albumin), the free active portion which is able to cross membranes, including the blood brain barrier is proportionately greater compared with younger people and this is responsible for a greater pharmacological effect when the same dose is given. Older patients require lower doses of anesthetic drugs related to changes in pharmacodynamics (concentration-response changes). A reduction of the number and function of neurons, alterations in synaptic transmission, and reduction of the number of receptor sites may also contribute to the increased sensitivity to anesthetic drugs both centrally and peripherally (Table 6.2).

Due to the factors above, many of the drugs used in anesthesia have a greater initial effect and a more prolonged effect in the older surgical patient and the adage ‘start low, go slow’ is aptly appropriate for this age group. Careful drug titration is necessary in view of the interaction of coexisting disease and physiological changes in this surgical cohort.

6.4 Anesthetic Technique for Breast Cancer Surgery

The selection of anesthetic technique in breast surgery is based on the patient’s clinical condition, surgical requirements and the anesthetist’s experience. The goals of anesthetic management are to maintain haemodynamic stability, provide good analgesia, prevention of postoperative complications or exacebations of pre-existing comorbid conditions and at the same time provide good surgical conditions. These goals can be met by either local anesthesia, general or regional anesthesia.

6.5 Local Anesthesia

Minor breast surgery and simple mastectomy can be performed using local anesthetic with or without sedation. Local anesthesia provides many advantages over general anesthesia in older patients. The patient's physiology is minimally affected and therefore more suited for patients with severe frailty and/or with multiple comorbidities. In addition, it can be performed in the day case setting in the majority of cases, is less costly and provides faster recovery time. However, more invasive procedures such as axillary lymph node dissection, or oncoplastic procedures and reconstruction are difficult to perform by using local anesthesia alone and there is potential for systemic toxicity with increased doses that may be required for such procedures.

6.6 General Anesthesia

General anesthesia provides reliable and effective anesthesia for major surgery or when local anesthesia is deemed unsuitable because of patient choice, patients with cognitive impairment or who are unable to lie still or flat for the duration of the proposed procedure. Fortunately, as breast surgery is mainly superficial surgery and is not usually associated with major fluid shifts, general anesthesia is well tolerated even in elderly patients with significant co-morbidities. However, as already discussed earlier, adjustments to anesthetic drug dosages are required and older patients require careful intraoperative monitoring to maintain haemodynamic stability.

Apart from the routine monitoring used in all patients undergoing anesthesia (e.g. ECG, non- invasive blood pressure, pulse oximetry, end-tidal CO_2), this group of patients may benefit from additional monitoring e.g. intra-arterial blood pressure monitoring and depth of anaesthesia monitors. The benefits of an arterial line is to allow beat-to-beat monitoring which allows intraoperative hypotension to be detected earlier especially in between non- invasive blood pressure measurements. Even a mean blood pressure less than 50 mmHg for 5 minutes is associated with a 2.4 increased risk of myocardial infarction and acute kidney injury [10]. It is recommended that the mean arterial blood pressure should be greater than 65 mmHg intraoperatively to reduce the risk of adverse outcomes. Monitoring depth of anaesthesia using either the Bispectral Index Monitor (BIS) or the Entropy Monitor can reduce the amount of anaesthetic required therefore preventing a relative overdose in older patients as the doses needed to induce and maintain general anaesthesia decrease with increasing age [11]. Therefore, excessive hypotension is avoided. Furthermore, the use of the BIS monitor has been demonstrated to reduce the incidence of postoperative delirium by up to 30% [12].

Anesthetic drugs commonly used for general anesthesia are discussed below detailing the changes seen with the older patient compared with younger adults.

6.6.1 Inhalation Agents

Anesthetic sensitivity of the central nervous system (CNS) to inhalational agents is defined in terms of the minimal alveolar concentration or MAC. As age increases, the sensitivity of the CNS to these agents increase and therefore MAC value decreases. It is estimated that MAC value decreases by 6% for each decade after the age of 40 [13]. Therefore, older patients require lower dose of inhalational agents to produce the same level of anesthesia compared to their younger counterparts.

The other important property of inhalational agents to consider is their onset and offset times in this age group. This is determined by a complex set of factors which is beyond the scope of this chapter. However, one important factor is the blood gas partition coefficient of the agent. Inhalational agents with poor solubility have rapid onset and offset and therefore offer advantages in day case surgery in this population due to rapid recovery times. Newer agents such as desflurane produce rapid awakening from anesthesia compared to isoflurane or propofol intravenous anesthesia [14].

Unfortunately, all the inhalational agents depress the cardiovascular system to some degree and promote hypotension which may not be well tolerated in the older and frailer patients. This can be circumvented by careful titration of these agents and the judicious use of fluids and vasopressors to counteract the hypotension.

6.6.2 Intravenous Agents

Intravenous agents are used to rapidly induce general anesthesia. Anesthesia is then maintained with inhalational agents or by continuous infusion of ultrashort acting intravenous agents such as Propofol.

Both pharmacodynamics and pharmacokinetics of Propofol and other intravenous agents are significantly altered in the elderly. There is a decrease in the initial volume of distribution and subsequent clearance of Propofol [15]. In addition, free fraction of the drug is increased due to a fall in albumin levels [16]. This results in higher than normal plasma concentration both after a bolus dose and with continuous infusion. Onset of induction however is delayed in the elderly due to prolonged arm to brain circulation time, slow brain uptake and blood-brain equilibrium. Up regulation of $GABA_A$ receptors results in increased CNS sensitivity to Propofol and other GABA-ergic agents [17]. Propofol induced hypotension is exaggerated and peak hypotensive response is delayed when compared to younger patients [18]. Therefore, Propofol bolus and subsequent infusion should be reduced by 30–50% in the elderly. This is also the case with a bolus dose of Etomidate which is sometimes used in this age group due to its cardiovascular stability.

Propofol can also be used as part of total intravenous anesthesia (TIVA) using computer controlled infusion pumps in a process called target control infusion (TCI). TIVA provides many advantages compared to traditional IV induction and inhalational maintenance anesthesia e.g. rapid recovery times and less post-operative

nausea and vomiting. The original Marsh model did not incorporate age in the dose calculation and therefore produces undesirably high plasma concentration in the elderly but the subsequent Schneider model considers both lean body mass and the patient's age for its calculation of the bolus and maintenance doses so is more appropriate for this population [19]. Dose titration is further enhanced by the use of anesthesia depth monitors (BIS or Entropy) to guide infusion rates.

Thiopentone induction dose requirements are reduced in the elderly mainly due to changes in its pharmacokinetics [20]. Awakening from a single bolus dose is not delayed but if subsequent boluses or infusion is given then the drug accumulates. Thiopentone pharmacodynamics remains largely unaltered in the elderly. The response to ketamine in the elderly is also altered due to age related changes in NMDA receptors in the brain making them more sensitive to the drug but with prolonged effects due to reduced clearance.

6.6.3 Opioids

All opioids have the potential to cause sedation, respiratory depression, nausea and vomiting, delayed gastric emptying, constipation and urinary retention. Their long-term use can produce tolerance and physical dependence. Immunosuppression is another potential issue which can occur even with short term use. There is great interest in exploring the potential effects of opioid induced immunosuppression and cancer recurrence rates, however current evidence on this issue remains inconclusive [21].

Nociceptive response is altered in elderly patients because of neuronal degradation, demyelination and changes in synaptic transmission [22]. Increased potency of opioids is demonstrated with EEG studies due to alterations in pharmacodynamics [23]. Therefore, dose reduction is required for most opioids. Pharmacokinetics of individual opioids varies significantly. For example, the initial volume of distribution (Vd) and hepatic metabolism of Sufentanil is decreased and therefore lower loading and maintenance doses are required [24]. In contrast, the pharmacokinetics of Fentanyl and Alfentanil are unchanged compared with younger patients, however, a dose reduction of about 50% is still required to compensate for alterations in pharmacodynamics [25, 26]. Morphine clearance is also reduced by 50% resulting in its prolonged duration of action in this age group. Therefore, a dose reduction and an increase in the dosing interval is recommended.

Remifentanil, a potent, ultra-short-acting synthetic opioid is used increasingly in intraoperative practice because of its predictable onset and offset of action. This is due to its metabolism via ester hydrolysis in the plasma and is unaffected by organ function. Thus it has a fixed context sensitive half-life and recovery is as fast as in younger patients. However in the elderly, there is an approximately 30% reduction in Vd which necessitates a reduction in the bolus and maintenance doses by up to 50%. There is also a 20% reduction in plasma-effect site equilibrium time which results in the onset of peak action being delayed by 2–3 minutes after a bolus dose compared to younger patients [27].

6.6.4 Muscle Relaxants

Older patients often have less skeletal muscle mass because of disuse atrophy and this is accompanied by the upregulation of neuromuscular junction receptors. The net result of this is an unaltered pharmacodynamic response to neuromuscular blocking agents (NMBA) and therefore the initial loading dose should be based on the patient's actual body weight. As aging is accompanied by alterations in hepatic and renal blood flow, the maintenance doses of NMBA may need to be reduced.

The competitive NMBAs are divided into two groups depending on their molecular structure. The aminosteroid compounds (e.g. Vecuronium and Rocuronium) are dependent on hepatic and renal blood flow for their clearance and therefore, their maintenance doses should be reduced by 30% and the time to clinical recovery may be prolonged. The benzylisoquinolinium compounds (Atracurium and Cis-Atracurium) are less dependent on organ blood flow and metabolism as in addition to organ based mechanisms, they have an alternative metabolic pathway, Hoffman degradation which is dependent on temperature and plasma pH only. About 50% of Atracurium clearance depends on hepatic metabolism, therefore, a modest increase in its terminal half-life is seen in elderly patients. In contrast, as more than 80% of Cis-Atracurium is metabolised via Hoffman degradation, its terminal half-life is unchanged and therefore the time to clinical recovery is similar in both young and old patients [28]. However, it is recommended that when NMBAs are used in this age group that the degree of muscle paralysis is monitored by peripheral nerve stimulators and repeat doses guided by their response.

Succinylcholine, a non-competitive NMBA which is used occasionally to secure the patient's airway promptly in cases of severe gastro-esophageal reflux may demonstrate a reduction in metabolism due to a decrease in plasma cholinesterase activity with age but this has not been shown to be of any clinical significance.

6.6.5 Benzodiazepines

The sensitivity of the CNS to benzodiazepines increases with age therefore a dose reduction is required in the older patient [29]. In addition, the duration of action of most benzodiazepines in this age group is increased as a result of reduced renal and hepatic elimination. Benzodiazepines are best avoided in the elderly due to the increased risk of precipitating delirium and cognitive dysfunction in the postoperative period.

6.7 Regional Anesthesia

Regional anesthesia offers many advantages for breast surgery. It can be used to provide anesthesia for surgery on its own but it is more often used in addition to general anesthesia to provide intraoperative and postoperative analgesia. The incidence of both postoperative nausea and vomiting (PONV) and sedation are reduced due to its opioid sparing effects. In addition to providing superior quality acute pain

control, the incidence and severity of persistent post surgical pain (PPSP) is also reduced [30].

Some of the regional blocks that are useful in breast surgery are:

1. Thoracic Epidural block
2. Paravertebral block
3. Pectoral blocks (PECS) and its variations.

6.7.1 Age-Related Changes Relevant to Regional Anesthesia

Neuronal sensitivity to local anesthetic is increased in the elderly due to neuronal loss, demyelination of neurons, reduction in conduction velocity and changes in synaptic transmission. The duration of peripheral nerve block is therefore increased by 2.5 times [31] and the duration of motor neurone block is also prolonged.

There are several changes in spinal anatomy with increasing age. Spine height decreases due to atrophy of the intervertebral discs and osteoporosis, and flexibility of spinal ligaments is also reduced as a consequence of connective tissue ossification [32]. These changes increase the technical difficulty in performing central neuraxial blocks. The epidural space which is a cylindrical space between the dura mater and the ligaments and periosteum lining the vertebral canal, extends from the foramen magnum superiorly to the sacral hiatus inferiorly. This space is used to deposit local anesthetic agents which extend up and down the vertebral canal bathing the spinal nerves which traverse this space. With age, the epidural compliance increases and the resistance decreases due to a reduction in epidural fat. However, this is counteracted by intervertebral foramen sclerosis which prevents escape of epidurally administered local anesthetics. These changes result in a rapid onset of epidural block, greater spread of the local anesthetic agents and a much more prolonged duration of action in older patients. Peripheral nerves are also affected by age due to a reduction in myelinated nerve fibres. This results in a decrease in the conduction velocity especially of the motor nerves and may be a factor in the increased duration of action seen after peripheral nerve blocks in older patients.

Local anesthetics show a biphasic absorption from the epidural space. There is an initial rapid decline in local anesthetic concentration followed by a gradual and slower decline [33]. However, the overall transfer rate of local anesthetic from epidural or subarachnoid space to blood is unchanged. There is also a decrease in the clearance of amide local anesthetics from the plasma due to a reduction in hepatic metabolism in the older patient, so there is a potential risk of toxicity which increases with repeated boluses in this age group compared with younger patients.

6.7.2 Thoracic Epidural Anesthesia

Thoracic epidural anesthesia (TEA) is used mainly in breast surgery as an adjunct to general anesthesia (combined regional and general anesthesia) as it

provides good analgesia in both the intraoperative and postoperative period. However, in selected patients who are able to lie flat for a few hours and who are not severely cognitively impaired, awake surgery with TEA is feasible. With a catheter placed into the epidural space, a continuous infusion of local anesthetics can be used to extend the analgesia for a few days. Apart from excellent acute pain control, it also reduces the risk of persistent post surgical pain (PPSP) and subsequent chronic pain development [30]. In addition, when the epidural anesthesia involves the cardiac segments (T1–T4), myocardial function is improved due to a reduction in systemic vascular resistance and a relative bradycardia as a consequence of the sympathetic nerve blockade. The left ventricular supply demand ratio is optimized and the perioperative stress response is also attenuated. The reduction in systemic vascular resistance also provides a relatively blood free surgical field. Other advantages include a reduction in the incidence of postoperative nausea and vomiting (PONV) and postoperative sedation due to opioid sparing effects which helps with early mobilization.

The level of placement of the epidural catheter is important to ensure optimum pain control. For a mastectomy, the required dermatomes to be blocked are from T2–T7 and the epidural can be placed anywhere between T2 and T4. However, if an axillary lymph node dissection is part of the procedure, an extended block to C5 is required and can be achieved by using a larger volume of local anesthetics to extend the block. Performing an epidural in an older patient may be technically challenging due to difficulty in positioning the patient and also anatomical changes such as kyphoscoliosis which may distort the intervertebral space for epidural placement.

There are also potential disadvantages in the use of thoracic epidural anesthesia in the older patient. Blockade of cardio-accelerator fibres (T1–T4) produces hypotension and bradycardia, which are exaggerated in this age group due to limited compensatory mechanisms and cardiac reserve. The incidence is also higher because of increased sensitivity of nerve fibres and greater spread of local anesthetics in the epidural space. To prevent hypotension, a combination of vasopressor therapy and fluid administration is usually required.

Pneumothorax, accidental nerve damage, epidural haematoma and post dural puncture headache are also potential risks. Sympathetic blockade related vasodilation is associated with significant heat loss and hypothermia which is proportional to the height of the epidural block. Core temperature decreases rapidly in older patients because of a decrease in subcutaneous fat and a lower basal metabolic rate compared to younger patients. Measures to prevent or limit the temperature decrease intraoperatively such as the use of forced air warmers is of great importance as hypothermia itself has many negative consequences for example increased bleeding tendency, myocardial ischaemia due to increased oxygen demand as a result of shivering and postoperative wound infections [34]. Postoperative rewarming to normal core temperature is also prolonged so active rewarming may be required in the postoperative care unit to decrease the risk of complications.

6.7.2.1 Paravertebral Block

Thoracic paravertebral block is a well established technique in providing anaesthesia and analgesia during breast surgery [35]. It entails the injection of local anesthetic adjacent to the thoracic vertebrae close to where the spinal nerves emerge from the intervertebral foramina. It provides a quality of anesthesia and analgesia that is comparable to an epidural block. It blocks both somatic and sympathetic nerve fibres, but unlike an epidural block, it does not produce any hypotension due to its unilateral action.

Paravertebral block can be performed with either the traditional landmark technique or preferably under ultrasound guidance to locate the paravertebral space and needle advancement in real time. Use of ultrasound improves the success rate whilst minimising risk [36]. A single injection technique can be used if the incision crosses one or two dermatomes only whereas more extensive surgery requires multiple injections to cover adjacent dermatomes. In addition, the duration of analgesia can be extended by inserting a nerve block catheter into the paravertebral space and running a continuous infusion of local anesthetics for up to 5 days postoperatively.

The overall risk of complications is in the region of 6–10%; with the risk of vascular puncture at 6.8% and bilateral block approaching 10%. Major complications such as extensive epidural or intrathecal spread (1%), accidental pleural puncture (0.8%), and pneumothorax (0.5%) occur rarely after a paravertebral block [37]. The other disadvantage of paravertebral block is that it does not provide anesthesia or analgesia to the axilla. Therefore, local infiltration of the axilla is required if surgery includes axillary dissection. No specific studies have been performed to investigate the effect of age on the clinical profile of paravertebral blocks.

6.7.2.2 Pectoral Blocks (PECS)

Recently, Blanco demonstrated successful regional analgesic techniques for breast surgery by infiltration of local anesthetic in the thoracic muscle planes. PECS-1 block is performed by injecting 10–20 ml of local anesthetic between pectoralis minor and major muscle using ultrasound. It blocks the medial and lateral pectoral nerves, and provides adequate analgesia for breast surgeries that do not require axillary dissection [38]. PECS-2 block requires a further 20 ml injection of local anesthetic (in addition to PECS-1) between the serratus anterior muscle and pectoralis minor muscle at the 4th rib in order to provide analgesia to the axilla. It blocks the intercostobrachial nerve, medial brachial cutaneous nerve, long thoracic nerve and anterior collateral branches of the intercostal nerves [39]. A third variant of this block is called the serratus plane block, which is performed between latissimus dorsi (LD) and serratus anterior(SA) muscle at the 5th intercostal space in the mid axillary line. This provides analgesia for LD flap surgery [40].

PECS blocks are simple, easy to learn techniques for breast surgery and are safer than PVD or thoracic epidurals. However, the density of the block is not equivalent to an epidural or paravertebral block so they are mostly used as adjuncts to general anesthesia. Furthermore, for bilateral surgeries, careful attention should be paid to the doses used to avoid LA toxicity.

6.8 Postoperative Pain Management

Postoperative pain management after breast surgery can be challenging in older patients due to the presence of coexisting diseases, concurrent medication usage, diminished physiological reserves and age related alterations in pharmacodynamics and pharmacokinetics. In addition, the assessment and measurement of pain may be difficult due to pre-existing or postoperative cognitive dysfunction. Apart from the extent of surgery, factors such as anxiety, pre-existing chronic pain conditions, poor prior surgical experience and exposure to radio or chemotherapy may influence the severity of postoperative pain [41]. Patients after breast surgery are also at risk of developing persistent postsurgical pain and poor pain control not only delays patient's discharge home but can also lead to poor patient satisfaction scores and unplanned admissions.

Postoperative pain is best managed with multimodal analgesia in order to achieve optimal pain control and minimise analgesic medication adverse effects. Surgical procedures such as wide local excision are generally not associated with significant postoperative pain and therefore can be managed easily with local anesthetic infiltration, paracetamol and weak opioids, whereas more extensive surgeries including mastectomy may require the addition of stronger opioids. Nonsteroidal anti-inflammatory drugs should be used with caution in older patients due to the higher incidence of gastrointestinal, renal and cardiovascular adverse effects in this age group.

Pain during the immediate postoperative period should be managed with small intravenous doses of strong opioids e.g. morphine or oxycodone. However, most patients resume oral intake soon after surgery and therefore subsequent analgesia can be given through the oral route with satisfactory results. Oxycodone may be preferable over morphine for oral administration due to its higher bioavailability, reduced inter-individual variability in absorption, less active metabolites and lower emetogenic potential.

Patient controlled analgesia (PCA) is useful in managing postoperative pain that is associated with more extensive procedures. It is safe, effective, associated with less opioid consumption and with comparable pain relief and high patient satisfaction scores [42]. However, adjustment of opioid bolus dose and interval is required in the extreme old and frail patients because of age related alterations in pharmacodynamics and pharmacokinetics.

The use of local and regional anesthetic techniques for postoperative pain control has several advantages in older patients due to their opioid sparing effects e.g. less sedation and respiratory depression. The duration of analgesia can be extended by using extended release local anesthetic preparations or by wound catheter and elastomeric pump to deliver LA over several days. There is also interest in adjuvant medications to modulate the pain response. Clonidine, ketamine and intravenous lidocaine are some of the drugs that has shown benefits in reducing acute and chronic pain after breast surgery [43].

6.9 Postoperative Nausea and Vomiting

Breast surgery is one of the few surgeries that is associated with a relatively high incidence of post-operative nausea and vomiting (PONV) with some studies quoting incidence of anywhere between 25% and 80%. This may be related to several PONV risk factors in this cohort e.g. female gender, anxiety, use of radiotherapy or chemotherapy and use of opioids. Fortunately, increasing age provides some degree of protection against PONV. The risk can be further minimised by using combination antiemetics (5HT-3 antagonists e.g. ondansetron and dexamethasone), adequate hydration, total intravenous anesthesia and the avoidance of excessive opioids. Although combination antiemetics is more effective than monotherapy after breast surgery [44], it is best to avoid antiemetics with anticholinergic activity in the elderly e.g. cyclizine and hyoscine as the risk of postoperative delirium may be increased.

6.10 Postoperative Cognitive Function

Older patients are more susceptible to postoperative cognitive dysfunction compared to their younger counterparts [45]. It is becoming recognized that cognitive deterioration post surgery may be associated with increased mortality and permanent disability [46].

Postoperative delirium is a non-specific cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake schedule. It has an acute onset, most commonly presenting within the first few days after surgery and the duration and severity is variable. Many patients with delirium may already be showing symptoms in the recovery room [47]. The incidence varies from 25–60% in elderly patients depending on the surgical population studied with fractured neck of femur patients having the highest risk. Although it tends not to persist beyond 1 week, there is evidence to link it with longer term cognitive (risk factor for postoperative cognitive dysfunction (POCD) and dementia) and non-cognitive morbidity (increased postoperative complications e.g. respiratory infections, increased risk of institutionalisation and hospital length of stay) as well as a reduced quality of life.

Intraoperative strategies such as the avoidance of deleriogenic medications e.g. benzodiazepines, prevention of blood pressure fluctuations, the use of depth of anaesthesia monitors e.g. BIS and adequate multimodal pain control may reduce the postoperative incidence [48]. Unfortunately, regional anaesthesia and analgesia have not shown any benefit in respect of postoperative delirium [49]. Early detection of postoperative delirium is part of the solution as increased age favours the hypoactive presentation (35%) which is easily missed on the ward and may be simply be mistaken as sleepiness unlike the hyperactive (agitated and combative) form which is rarely missed. Early diagnosis of delirium is important to trigger focused and effective treatment therefore, patients should not leave the recovery room

without being screened for delirium using either the Confusion Assessment Method (CAM) or the Nursing Delirium Screening Tool (Nu-DESC).

Postoperative cognitive dysfunction (POCD) on the other hand, presents later than delirium (weeks to months) and is more subtle and does not affect the level of consciousness. It tends to affect a wide variety of cognitive domains e.g. memory, information processing and executive functioning. Typically, patients complain of deterioration of memory and concentration, and poor ability to carry out complex tasks or to multitask. There is no universally accepted definition unlike delirium and can only be detected with neuropsychological testing before and after surgery. Approximately 25% of elderly patients exhibited POCD 1 week after non-cardiac surgery and 10% at 3 months [50]. However, by 1 year, the majority have recovered but despite recovery, POCD has negative consequences e.g. impairment of activities of daily living, premature loss from the workforce and increased mortality [46]. The most important risk factors for POCD are increasing age, low level of education, postoperative complications, type of surgical procedure and duration of anesthesia.

Two strategies that have been found to be able to decrease the impact of POCD are fast track techniques which focus on early mobilisation, multimodal opioid-sparing analgesia and early discharge and the use of intraoperative bispectral index (BIS) monitoring where values were maintained at a specified range and cerebral oxygen saturation monitoring [51, 52].

6.11 Conclusion

Aging is a process that results in reduced capacity for adaptation and a gradual decrease in physiological reserve which affects most organs. Not only is there variability in decline of function and reserve between patients but there is also variability between organs within the same patient. Such heterogenicity is the hallmark of this patient population and added to this is the increased number of comorbidities and frailty. This translates to the older patient being less able to withstand the stress of surgery and therefore, more susceptible to postoperative complications and adverse outcomes. The role of the anaesthetist is to assess, optimise and to select an anaesthetic technique which will minimise complications and to facilitate a good postoperative outcome.

An understanding of the physiology of aging and how it impacts on the pharmacokinetics and pharmacodynamics of the various anaesthetic drugs used is paramount to ensure optimal anaesthetic management. Safe regional anaesthesia in the older patient requires less local anaesthetics and the use of ultrasound for placement of blocks have improved safety and success rates of the blocks used in breast surgery. Advanced monitoring such as the use of anaesthetic depth monitors is emerging as useful to reduce the impact of postoperative cognitive issues such as delirium and POCD. Lastly, the older patient deserves greater vigilance throughout the perioperative period as their reduced capacity for adaptation means they decompensate and develop complications more rapidly than their younger counterparts.

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The Surgical Management of Breast Cancer in Elderly Women

7

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Abstract

One third of all women diagnosed with breast cancer are over 70 years of age, equating to some 13,000 women in the UK annually. As the UK population ages, this number will increase. Whilst many of these older women will be fit for standard therapies, increasing age, frailty, and co-morbidity levels may render some women unfit for certain treatments. This chapter will deal with the role of surgery in these women. It has long been recognized that older women do not receive the same surgical and adjuvant treatments as younger women and the evidence base for treating older women with breast cancer is weak due to the historic exclusion of these women from research studies. This Chapter summarises the current evidence for the surgical management of older womed with breat cancer and suggests strategies to deliver treatment based on available evidence and in conjunction with patients and those close to them.

Keywords

Surgery · Axillary treatment · Comorbidity

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7.1 Introduction

One third of all women diagnosed with breast cancer are over 70 years of age, equating to some 13,000 women in the UK annually. As the UK population ages, this number will increase. Whilst many of these older women will be fit for standard therapies, increasing age, frailty, and co-morbidity levels may render some women unfit for certain treatments. This chapter will deal with the role of surgery in these women. It has long been recognized that older women do not receive the same surgical and adjuvant treatments as younger women [7, 8, 31, 68, 70, 75, 77, 105]. Chemotherapy is frequently omitted omitted, surgery may be omitted or minimized to be less onerous, (in particular axillary staging is less likely to be performed) and radiotherapy may be omitted after surgery. Rates of surgery vary widely between units and country [27, 74]. How these changes impact on local and systemic disease control has been largely studied in the context of observational studies with few good-quality randomized clinical trials having been performed. Rates of local control are inferior when surgery is omitted and there is some suggestion that systemic disease control rates are impaired in the elderly generally, although this is based on few good quality studies [11, 101]. This is a difficult area to research as survival in this age group is heavily influenced by competing causes of death and the very heterogeneous nature of the population in terms of basal health status. Previous studies have demonstrated that surgery, supported by modern anesthetic techniques (general, regional, and local), is well-tolerated, precluding fewer women [78, 103]. However, there are still women for whom extreme age, co-morbidity, and frailty render surgery more hazardous. This chapter will examine the evidence for the role of surgery in older women and suggest alternative strategies for those in whom the risks are raised. The evidence base for these modified strategies is poor, due to a lack of good-quality primary research in this age group and the inherent difficulties in studying disease processes, patient-related variance, and treatment variance in such a heterogeneous patient group.

7.2 Tumor Biology and Stage at Presentation

There are differences in tumor biology, which may make it acceptable to moderate the treatment of breast cancer in older women. The biology of the disease is less aggressive with higher rates of estrogen receptor positivity, reduced rates of HER-2 receptor expression, and a higher rate of favorable histological subtypes such as tubular and mucinous cancers [26, 28, 96]. These features suggest a less aggressive disease course, a longer time to recurrence, and reduced rates of recurrence. However, these beneficial biological features may be offset by a later stage of presentation in the elderly, [77]. There is a slightly higher rate of locally advanced and metastatic disease, and the size of the primary cancer is larger. This is likely to be due to a combination of two factors: a lack of screening in the elderly and a lower level of breast awareness and self-examination [22]. It is therefore not clear how

these factors interact when examining outcome data and this complicates attempts at extrapolation of outcomes from studies in younger women.

7.3 Impact of Breast Cancer on Survival in Older Women

Increasing age is inevitably associated with a reduction in life expectancy partly due to the normal physiological decline in organ function (senescence) and the increasing incidence of co-morbid diseases. Consequently, overall survival for women with breast cancer is markedly influenced by age, with 73% of women aged 50–54 with breast cancer dying of the disease compared to only 29% of women of 85 and over [28]. There are a number of computer-based algorithms that allow estimation of this interaction (http://www.cancermath.net/ and e-prognosis (Suemoto Index) Suemoto et al. [95]), but currently none of the available tools allows for detailed assessment of co-morbidity. As a result of this, breast cancer is proportionately less of a threat to an older woman's life than to a younger woman's, which is one of the justifications for the modified treatment regimes frequently employed. For younger women, surgery is the mainstay of treatment, and until the 1980s was also the standard treatment for all but the frailest elderly [57, 61]. In the 1980s, the concept of primary endocrine therapy (PET) with Tamoxifen was first suggested by researchers in Edinburgh [83]. This approach rapidly gained popularity as several trials demonstrated that there was no survival disadvantage to omission of surgery in women over the age of 70 and the concept that breast cancer was a systemic disease held sway. Whilst local control rates were inferior, even long-term follow-up showed little detriment in overall survival with only one of the trials showing a slight but significant improvement in survival with surgery, although meta-analysis of all studies demonstrated only a small, nonsignificant trend for improved survival with surgery [53]. The role of PET is discussed in more detail elsewhere in this book.

Breast cancer-specific mortality in this age group is difficult to determine from the literature. This is due to the fact that outcomes are rarely adjusted to reflect patient co-morbidity, there is widespread disease understaging in older women as many either have no surgery or limited surgery (often excluding axillary staging), and lastly, overall treatment is often substandard when compared to younger patients. All of these factors result in inaccurate or misleading comparisons with younger women's outcomes. Progress in this area can only be made either by the conduct of randomized controlled trials in this age group or detailed observational studies which accurately stratify patient outcomes according to age, disease stage, and health status.

7.4 Age and Surgical Treatment

Aging has significant effects on normal physiological processes (senescence) independent of any associated disease processes. For example, cardiac reserve is reduced due to a reduction in the number of myocytes, a reduction in the number of

pacemaker cells, and a reduction in the maximal heart rate with age. Renal reserve is similarly reduced with a halving in the number of nephrons and in renal blood flow by age 70. As a result, tolerance to dehydration and fluid overload are poor. Cognitive function is also reduced, as is balance and coordination, all of which delay recovery or impair tolerance to anesthesia and surgery [4, 84].

However, despite this the operative mortality associated with surgery for breast cancer is negligible (0–0.3%) in most series [78]. This reflects the fact that breast surgery is body-surface surgery and causes very little hemodynamic or pulmonary-function disturbance. In addition, most of the surgical procedures are of fairly short duration and patients are ambulatory immediately afterwards. In many cases, the surgery can also be performed under local or regional anesthesia, further reducing the risks. Morbidity is generally low, although lymphedema, chronic wound pain, and the psychological morbidity associated with the loss of a breast may cause some women considerable distress and should not be underestimated.

In addition to the above-mentioned senescent organ impairment, co-morbid diseases are increasingly common with age and may significantly impact on life expectancy and treatment tolerance [92]. For example, the prevalence of angina in 45–55 year olds is less than 1%, compared to almost 5% in people of 75 and over. Similarly, the risk of significant cardiac arrhythmia increases from 0.6% to 4.2% between the ages 45 and 75. Rates of dementia increase from 0.9% to 40% between the ages of 65 and 90 years. These conditions impact significantly on both life expectancy and on the risks associated with anesthesia. As the number of co-morbid conditions increase, the relative risk of death from breast cancer is reduced [91]. As mentioned above there are some computer-based algorithms that allow prediction of life expectancy and relative risk of death from breast cancer with age and co-morbidity. However the widely used on line tool, adjuvant online has been shown to be inaccurate in older women [25]. These are simple and easy to use and access but perhaps oversimplify the situation when making decisions about whether surgery is appropriate [23]. Simply using the crude number of co-morbid conditions should not be considered as the only criteria for denying a surgical option as the nature and severity of each co-morbidity may have a widely varying impact [87]. A number of more complex and specific scoring systems have been developed to predict life expectancy and guide treatment decision-making in the elderly with cancer. One of the first to be developed was the Charlson Index, which considers both the number and severity of a defined selection of co-morbid diseases and can predict mortality with modest accuracy [19]. More recently, the Comprehensive Geriatric Assessment and the multidimensional assessment for cancer in the elderly (MACE) have been developed and validated. These include a detailed assessment of co-morbidity, functional status, cognitive function, and depression scores [34, 50]. Measures of global functional ability have also been shown to be independently useful in predicting life expectancy. For example, the activities of daily living (ADL), the instrumental activities of daily living (IADL) and the mini mental state examination (MMSE) scores have all been shown to have prognostic value [6, 43, 59, 82, 89].

Some of these tools are relatively time-consuming to administer and may require specialist interpretation. For this reason it has been proposed to utilize quick

screening tools during clinical practice in order to provide a thorough assessment and identify frailty [81].

7.4.1 Surgical Treatment and Disease Control in Older Women with Breast Cancer

Until the 1980s when primary endocrine therapy was first proposed, all but the frailest elderly were treated with surgery for their breast cancer. A number of large series of surgical outcomes demonstrated that this was associated with a low morbidity and mortality. Primary endocrine therapy is similarly associated with a low mortality and morbidity with little to choose between the two strategies in older women based on comparative RCT data comparing the two [53]. Seven randomized trials were performed. All these studies recruited women over the age of 70 with operable breast cancer who were fit for surgery under general anesthesia. Endocrine treatment was with tamoxifen although most of the studies did not assess the estrogen receptor status of the tumors as this was not widely accessible technology at the time. Three studies [37, 44, 90] compared surgery without adjuvant tamoxifen to tamoxifen alone. Four studies [15, 36, 75, 104] compared surgery with adjuvant tamoxifen to tamoxifen alone. Surgery included mastectomy or wide local excision with or without radiotherapy combined with axillary clearance or staging in most of the trials.

These studies demonstrated that endocrine therapy alone is inferior to surgery with adjuvant endocrine therapy for the local control of breast cancer in this group of patients. However, meta-analysis demonstrated no significant difference in overall survival between the two treatments. One of the trials showed a small but significant survival advantage for surgery at 13 years follow-up, with survival curves diverging after 3 years [36]. Despite the lack of clear evidence of survival benefit for surgery, the clear advantage in local disease control suggests that PET should be reserved for women with a poor premorbid state likely to reduce life expectancy to 2–5 years [18]. According to current NICE guidelines [79] patients with operable breast cancer should be treated with surgery, and not PET, 'irrespective of age' unless comorbidities preclude this. The 2012 multidisciplinary Société Internationale d'Oncologie Gériatrique (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) task force recommended that primary endocrine therapy should only be offered to elderly individuals with ER-positive tumours who have a short estimated life expectancy (<2–3 years), who are considered unfit for surgery after optimisation of medical conditions or who refuse surgery [10].

Comparison of quality of life between these two treatment strategies has been poorly assessed in the trials with only one undertaking any assessment of this. This comparison showed that surgery was associated with impaired outcomes in the short term, (3 months), and that there is no difference at longer follow-up, (2 years). It is worth noting, however, that the tool used for this assessment was not a breast-cancer-specific QoL tool and it is likely to have been insufficiently sensitive to detect many of the life-domain issues that may be influenced by these treatments [2,

40, 49, 66, 85]. Data from Bridging the Age Gap Study will provide important information on QoL and different treatment strategies, as one of its objectives is to determine QoL outcomes in older women undergoing surgery, chemotherapy or PET for breast cancer and correlate outcomes with age, comorbidity and frailty.

Another area of concern for the use of PET is the risk that some patients will not adhere to their endocrine medication, which will be less of a problem if this medication is an adjuvant to surgery rather than the primary treatment. This may be a particular problem for patients on multiple medications as is commonly the case in the older population. There is good data in the geriatric literature that adherence to medication, especially for women on multiple medications, is poor in this age group. Compliance with antioestrogens generally is also poor in all age groups.

Furthermore, patients on primary endocrine therapy may be called back more frequently for clinical review than patients who undergo surgery – this may have a negative impact on quality of life, although conversely patients may appreciate the close clinical review and the knowledge that the tumor is reducing in size [58, 88].

However, recent audits demonstrate the continued use of primary endocrine therapy in a substantial proportion of older, less fit patients with breast cancer in the UK [13, 68, 103, 105] with 93% of UK surgeons using this option for some patients [106]. These studies, demonstrating the continued use of primary endocrine therapy in a substantial proportion of older women, are at variance with the results of a survey of UK breast surgeons, 98% of who state that age alone is not relevant in offering surgery for the treatment of breast cancer. However, 34% of respondents acknowledged that the patient's biological age is a significant factor although less than half utilize any form of assessment of fitness with only a very small minority using tools such as comprehensive geriatric assessment [5]. There is also a wide variation in rates of nonsurgical treatments amongst UK surgeons, as demonstrated by the BCCOM audit, which found rates varying from 11% to 40% in women aged 70 and older treated without surgery [9]. More recently the 2017 Annual Report from the National Audit of Breast Cancer in Older Patients (NABCOP) highlighted a weakness of the current clinical guidelines and the lack of specific guidance on the management of breast cancer in older women with significant regional variations in treatment patterns unlikely to be entirely explained by differences in the type and stage of breast cancers across England and Wales [76]. These findings demonstrate that while surgeons in the UK are open to treating older patients with standard approaches, including surgery, they frequently fail to do so; this is predominantly due to concerns about the patient's fitness and overall life expectancy, as well as lack of familiarity with screening tools for frailty. The above mentioned 2017 NABCOP Audit demonstrated a significant variation in the methods and tools used to make formal assessments of how older patients' general health is affected by comorbidities, cognitive function and frailty and it showed that multidisciplinary teams caring for the older patient are rarely involved in the formal management of older breast cancer patients. The Audit's recommendations to breast units within NHS trusts included the development and implementation of local protocols to improve the formal assessment of older patients' health in order to guide decision making about treatment.

Less information is available on the rates of omission of surgery in other countries but several publications indicate similar trends in other European countries [62, 70]. Little is known about patient attitudes and choices in relation to these different options. A small qualitative UK study demonstrated that this group of patients generally do not show strong preferences and tend to defer decisions about treatments to their physicians with overall high levels of satisfaction with either surgery or primary endocrine therapy [58]. Similarly, Burton et al. [14] found that, while older women appreciated being offered a choice of PET or surgery, many wanted direction from their healthcare professionals to recommend or support a treatment choice. These studies highlight the need to engage older women with breast cancer in discussions with their physicians about their treatment options and the need for an appropriate decision making support system.

Until evidence from clinical trials is available the appropriate management of older patients with breast cancer should include adequate surgery and appropriate adjuvant therapies in all patients. In the subset of patients with a predicted limited life expectancy, due to extreme age or poor functional status, the surgical and adjuvant treatments may be modified or in some cases omitted.

7.5 Surgery to the Breast

There are two main surgical approaches to the treatment of primary breast cancer: mastectomy or wide local excision plus radiotherapy. In recent years several studies have shown the superiority of breast conserving surgery plus radiotherapy over mastectomy inearly breast cancer in terms of breast cancerspecific survival and overall survival even when adjusting for stage [24, 54, 98]. In addition recent publications focusing on women with triplenegative breast cancer indicate that BCS plus RT is at least as good as mastectomy in terms of survival outcomes [107]. The importance of local control on long-term overall survival outcomes has been highlighted by the overview analysis of the Early Breast Cancer Trialists' Collaborative Group. This demonstrated the importance of adequate local treatment in the management of primary operable breast cancer. They demonstrated that for both mastectomy and wide local excision treated patients, radiotherapy reduced the risk of local recurrence. Of great interest was their finding that there was a small but significant survival advantage at 15 years for patients treated with radiotherapy in addition to breast conserving surgery or mastectomy. The benefit in the mastectomy group was predominantly seen in patients with axillary node involvement whereas the survival benefit for patients treated by breast conservation was independent of nodal status. The EBCTCG concluded that "in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided." The implication of this for older women with breast cancer is that adequate local control of disease is important and may have a significant impact on survival in women with a life expectancy of between 10 and 15 years. Therefore, for a fit woman of 70 years with a predicted life expectancy of 15 years, treatment should follow standard guidelines based on

evidence from trials recruiting younger women. However, in women of more advanced age, frailty or with associated co-morbidity where life expectancy may be restricted to less than 5 years it is reasonable to consider alternative approaches. The PRIME II trial, along with the Cancer and Leukemia Group B (CALGB) 9343 trial, are major, practice-changing studies regarding the role of radiotherapy in low-risk elderly patients treated with breast-conserving surgery. These trials provide high-quality evidence that in selected women who are older and have biologically favorable disease, it may be possible to modify treatment, if this is something that patients would prefer. Both studies have similar local recurrence rates for cohorts treated with or without whole-breast radiotherapy (PRIME II 5-year rate of 4.1% with no whole-breast radiation therapy vs 1.3% with whole-breast radiation therapy; CALGB 9343 10-year rate of 10% with no whole-breast radiation therapy vs 2% with whole-breast radiation therapy). Though these differences in local recurrence between the arms of each study were statistically significant, the addition of whole-breast radiotherapy did not result in differences in axillary relapse, distant metastasis, or breast cancer–specific survival. The majority of deaths in both the PRIME II and CALGB trials were non breast cancer related events [56, 67].

For any age group of women, the "absolute" indications for mastectomy include inflammatory breast cancer and failure of breast conserving surgery. In addition, for some women mastectomy may be mandated by a relatively large primary tumor in relation to overall breast size, and in patients with an extensive in situ component to their invasive cancer. A further important indication for mastectomy is patient preference. Large primary tumors (UICC TNM stage T3) are no longer an absolute controindication for mastectomy due to the increasing utilization of neoadjuvant therapy to enable tumor shrinkage and allow BCS and thank to the introduction of oncoplastic surgical techniques that allow resection of larger breast volumes without compromising the cosmetic outcome. There is also a growing acceptance of BCS for multicentric (different quadrants) and multifocal (same breast quadrant) disease. A retrospective study from Gentilini et al. [45] shows that in selected patients with MF/MC breast cancer, breast conserving surgery is not associated with poor local disease control and can be considered whenever acceptable cosmetic results can be achieved. While in Europe there is a trend towards more BCS [33], in the USA mastectomy rates are rising likely due to controlateral risk reducing surgery [51]. The 2007 BCCOM Report demonstrated that a proportion of patients with small tumors, suitable for breast conservation surgery prefer mastectomy if given a choice. In older women, primary tumor size is slightly larger than average, which may be one reason for the increased mastectomy rate and older women may be less concerned about the impact of mastectomy on body image and perhaps more anxious about the time and inconvenience that radiotherapy may entail. However, the loss of the breast is still a major cause of psychological distress for many older women. Surgeon and healthcare professional factors may also be important in guiding decision-making about choice of surgery for older women.

Another factor to consider in choice of surgery is whether it necessitates general anesthesia. Some frailer older women may be averse to general anesthesia and for some they may face increased risks of morbidity. Wide local excision is often

possible under local anesthetic, whereas for a larger-breasted woman mastectomy under local anesthetic may not be feasible due to the possibility of toxicity levels of the amount of local anesthetic required for adequate anesthesia. However, a series of cases of mastectomy under LA did demonstrate that LA mastectomy was feasible and rarely necessitated the use of harmful levels of local anesthetics [80]; however, there are no data on patient tolerance of the procedure or the pain associated with it. A more recent study by Kitowski et al. [65] shows that the benefits of LA or regional anaesthesia include excellent pain control as well as low rates of postoperative nausea and vomiting. Isotope and/or blue dye guided sentinel node biopsy is possible under LA but axillary clearance is not amenable to LA.

For those patients whose tumors are too large for breast conservation or where the tumor is locally advanced and the tumor is ER positive, primary endocrine therapy may be utilized to downstage the tumor. In this neo-adjuvant setting, Letrozole has increased efficacy compared to Tamoxifen, (55 vs. 36% response rate) [32]. Although, there are no data to support the use of neo-adjuvant chemotherapy in this patient group, it may be theoretically possible to use this technique for women with larger ER negative tumors and those with Her-2 positive tumours but caution must be exercised in patient selection as toxicity levels are increased in this age group, especially with doxorubicin-based regimes where cardiac and other toxicities may be more significant. The NeoSphere study [46] showed that, following only four cycles of neoadjuvant treatment, pertuzumab and trastuzumab plus docetaxel resulted in complete pathological response in significantly more women than for those treated with trastuzumab plus docetaxel alone. Importantly, the combination of pertuzumab with trastuzumab and docetaxel did not result in any additional cardiac toxicity. NeoSphere also examined a chemotherapy-free regimen of pertuzumab and trastuzumab that resulted in pathological complete responses in a proportion of women and a favourable safety profile. However median age was 50 years old (range 28–77) for the pertuzumab and trastuzumab plus docetaxel group and 49 years old (range 22–80) for the pertuzumab and trastuzumab. Furthermore in the published data there is no mention of how many patients were aged 70 years or older.

7.6 Surgery to the Axilla

Traditionally staging and treatment of the axilla has been undertaken for two reasons. Firstly, where there is clear clinical or biopsy proven nodal disease, axillary clearance is indicated to prevent local progression and its attendant morbidity (pain, lymphedema, brachial plexus compression). In the last two decades routine axillary clearance has been superseded by less invasive approaches such as sentinel lymph node biopsy [39, 71, 99] utilizing the injection of a radioisotope-labeled colloid and/or blue dye into the breast prior to surgery to localize the sentinel nodes/s In many ways the SLNB approach is ideally suited to older patients where the potential morbidity associated with more radical axillary surgery may have a greater impact on arm function. It is interesting to note, however, that axillary morbidity

following both, standard axillary management or SLNB, is lower in older women than younger women [39]. More recently the need for completion axillary clearance or radiotherapy in patients with a positive SLNB has been challenged by the results of the ACOSOG Z011 trial which demonstrated no benefit from further treatment in patients with limited nodal involvement undergoing breast conserving surgery, adjuvant systemic therapy and breast radiotherapy [47]. Whilst there were some concerns in relation to this study such as the inclusion of patients with micrometastases, the possible inclusion of the lower axilla in radiotherapy fields the recently published ten year follow up data confirm no additional benefit for further axillary treatment in terms of survival in this study [48]. Given that the average age of patients was 54 years in Z011 it seems likely that the findings would be even more relevant for an older potentially frail population with competing comorbidities and reduced life expectancy.

Similar results have been shown by the AMAROS [30] and OTOASOR [93] trials. These studies compared completion of axillary dissection to axillary irradiation in patients with positive sentinel node biopsy [97]. There was no difference in axillary recurrence rate but axillary radiotherapy resulted in significantly less morbidity.

Apart from potentially enhancing local disease control, determining the extent of axillary nodal disease was considered important for estimating prognosis and selecting appropriate adjuvant therapies. Older women are much less likely to be offered adjuvant chemotherapy and therefore some would suggest axillary staging is less important. A randomized controlled trial with 15 years follow-up looked at the omission of axillary surgery in older (65–80 years) breast cancer patients with clinically and radiographic T1 N0 disease [72]. After 15 years of follow-up, distant metastasis rate, overall survival, breast cancer mortality, in the axillary surgery and no axillary surgery groups were similar. The incidence of axillary recurrence in the no axillary dissection arm was 6%. The authors conclude that older patients with early breast cancer and a clinically clear axilla treated by conservative surgery, postoperative radiotherapy, and adjuvant endocrine treatment do not benefit from axillary surgery. However, all the women in the trial were treated with adjuvant radiotherapy. When axillary positivity will help determine whether a woman is advised to have adjuvant chest wall or supra-clavicular fossa radiotherapy axillary staging should be considered, unless the patient is judged too frail to benefit from this treatment. Chagpar et al. [16] looked to determine factors associated with lymph node metastasis among hormone sensitive breast cancer patients, aged 70 years or older, and to develop and validate a clinical rule to predict the risk of lymph node metastasis in this population. Patient age, tumor size, and lymphovascular invasion were found to be significant and the authors concluded that some elderly breast cancer patients at low likelihood of lymph node metastasis might be spared lymph node evaluation.

Taking these studies together it may be reasonable to omit SLNB in older patients with clinically (and ultrasonographically) normal axillae particularly if comorbid conditions indicate a potentially restricted likliehood of survival [12]. However approxiamately 15% of patients aged $\geq$70 will present with affected nodes and where biopsy proven disease is confirmed treatment with surgical clearance or

radiotherapy is appropriate particularly for those patients who are also likely to be considered suitable candidates for adjuvant systemic chemotherapy [17].

A recent study [29] looked at patterns of axillary surgery in 68,205 women aged ≥65 years with clinically node-negative, stage I-II breast cancer treated between 2012 and 2013, identified using the National Cancer Data Base. Overall, 91.2% had axillary surgery.

The standard of care for women with clinically node negative breast cancer remains axillary staging with sentinel node biopsy and further studies on how to tailor node assessment in older patients are warranted particularly for those with lower-risk disease.

7.7 Alternative Approaches in Patients with Restricted Life Expectancy

An increasing number of women will present with breast cancer who are frail due to very advanced age or co-morbidity and for whom life expectancy will be predicted to be short. Treatment tolerance for all but the simplest interventions will be reduced. For these women, their breast cancer is unlikely to have a major impact on life expectancy, which will be largely determined by their general health status. Similarly, the treatment of their cancer will have little impact and surgery may be an unnecessary imposition, especially if local control can be achieved with endocrine therapy. However, surgical treatment may still be appropriate in such patients to avoid the development of distressing symptoms, such as pain, ulceration, and bleeding due to local disease progression if the disease is estrogen receptor negative. Surgery may be performed under local, regional, or a carefully tailored general anesthetic. Axillary surgery may be omitted in the clinically uninvolved axilla or axillary clearance under a regional block or axillary radiotherapy offered for those with clinical axillary disease. In general terms, even in frail elderly patients, general anesthesia is a safe option with a mortality of less than 1%, although the morbidity may be higher. In cases where CGA demostrtaes a short life expectancy (less than 3 years) or significant risk of perioperative morbidity or mortality a a formal anesthetic assessment should be performed prior to surgery by an experienced anesthetist who will recommend the most appropriate approach. This is discussed elsewhere in this textbook (Chap. 6).

A number of minimally invasive procedures have been proposed, i.e., percutaneous tumor excision, radio-frequency ablation, focused US ablation, interstitial laser ablation, and cryotherapy. These techniques are suggested to be associated with improved cosmetic results, reduced psychological morbidity, and short hospital stay [41]. They require a clearly defined lesion visible on imaging (typically ultrasound scan) with one centimeter or more clearance from the overlying skin. These techniques which include thermal ablation, radiofrequency ablation and cryoablation therapy have not been evaluated in the older/frail patient population and must be considered experimental at this stage and only utilized in a clinical trial setting. These techniques have recently been reviewed by Mauri [73]. They require a close

interaction with the X-ray department and might be suitable for frail individuals; although, they should be regarded as investigational until more data are available [52, 60, 94, 100].

For those frail elderly women with ER positive disease, primary endocrine therapy may be all that is required to control their disease for the remainder of their life. Disease control rates are high in the short to medium term and in some cases complete tumor resolution may occur. This is discussed in more detail elsewhere in this text.

7.8 Complications of Surgery

Breast cancer surgery is generally regarded as low-risk body-surface surgery and is associated with a very low mortality rate even amongst the elderly. However, morbidity rates can be quite high and include scar formation, wound pain, seroma formation, hematoma, infection, and skin necrosis following mastectomy. Axillary surgery is also associated with complications, including seroma and hematoma, infection, paraesthesia and neuropathic pain, mammary edema, shoulder stiffness, and rarely damage to the long thoracic nerve resulting in "winging" of scapula. The most significant complication of axillary node clearance is lymphedema which may occur in up to 38% of patients following a full axillary clearance [64]. Sentinel node biopsy and axillary sampling techniques are less likely to be associated with these complications but may still occur [39]. The incidence of these complications following surgery is not significantly increased by patient age or co-morbidity [55] and in particular the morbidity of axillary surgery may be lower in older women than in younger.

In addition to the physical morbidity of breast cancer surgery, there is also considerable psychological morbidity, especially for those women who undergo mastectomy. There is evidence that physical appearance is less significant in older than in younger women [38, 42, 63].

Uniquely in this older population we have some data of the impact of surgery vs. no surgery in those women who have primary hormonal therapy. Whilst there is no difference in the long-term psychological outcomes between these two treatments, surgery has negative effects at 3 months postoperatively which disappear by 2 years [35].

Little is known about the occurrence of postoperative delirium. This is a relatively frequent complication of general anesthesia in the elderly but is rarely studied. The detection of delirium and the early implementation of adequate management can resolve the condition in over 50% cases [21]. Postoperative delirium independently associates to postoperative morbidity, mortality, length of hospital stay, and costs. An early discharge of elderly women to their usual environment may play a significant role to their psychiatric well-being. It is important to notice how the detection of depression at the diagnosis of cancer is linked to a longer hospital stay; this reinforces the value of utilizing the Comprehensive Geriatric Assessment instruments which also assesses depression. A recent systematic review and

meta-analisys of forty-one studies and over 9000 patients, identified protective and modifiable prognostic factors, including smoking, frailty, and psychotropic medication use, which should be further studied to develop interventions aimed at mitigating potential harm of post operative delirium [102].

7.9 Breast Reconstruction and Oncoplastic Surgical Techniques

Over the last 20 years there has been a substantial increase in the rates of breast reconstruction following mastectomy. This has been associated with an increase in the range of approaches available for breast conservation such as therapeutic mammoplasty and breast reshaping by volume displacement known as oncoplastic surgical approaches [20]. These new techniques have had a substantial impact in the management of women with breast cancer but to date the evidence indicates that older women, particularly those over the age of 70 years of age, are not benefiting from breast reconstruction or oncoplastic approaches despite guidelines indicating how these techniques should be widely available [3]. There are a number of potential reasons for this, including patient and health care professional factors, or the assumption that older patients may consider the physical impact of the surgical treatment of breast cancer less important than younger patients and have fewer concerns about their body image [42]. However, body integrity is an important issue for some patients and some case series describe excellent results of breast reconstruction in older women. These report the results of techniques using autologous flaps although in general simple implant-based approaches tend to be utilized more frequently in older women [1, 69]. In addition to patient factors the extremely low utilization of breast reconstruction in women over the age of 75 may indicate that surgeons also have reservations despite the lack of an evidence base. There is no doubt that reconstructive techniques, particularly those utilizing autologous myocutaneous flaps are more major surgical procedures which can be associated with an increased risk of side effects and complications such as flap necrosis. Studies in younger women indicate that these complications are more prevalent in patients with associated co-morbidity and it is this factor which is likely to be influencing surgeons and resulting in a failure to offer these options in the older population of women with breast cancer. Patients are also aware of these concerns and this may contribute to their decision not to seek breast reconstruction [86]. The UK National Mastectomy and Reconstruction audit has provided comprehensive data on this topic. It describes patterns of treatment, and the clinical and patient-reported quality of life outcomes associated with these types of procedure. Overall, 21% of the 16,485 women who had mastectomy between 1 January 2008 and 31 March 2009 underwent immediate reconstruction. Women who had a mastectomy only tended to be older and frailer. None of the women aged 80 years or older had reconstruction (immediate or delayed). Two percent of the women who had immediate reconstruction and three percent of the women who had a delayed procedure were aged 70–79 years old. The main reasons for clinicians not offering reconstruction were

patient age and comorbidity, and the need for adjuvant treatments. For women aged less than 60 years, roughly 60% of mastectomy patients were offered immediate reconstruction. For women aged between 60 and 69 years, the proportion fell to around 50%, and tailed off rapidly between the ages of 70 and 80 years. However, the proportion of women offered immediate reconstruction varied considerably between Cancer Networks, for both women under 70 years and 70 years or over. The variation was not explained by differences in patient comorbidity or tumour characteristics [27].

7.10 A Surgical Strategy for Older Patients with Breast Cancer

Wherever feasible in women with an expectation of a reasonable life expectancy and where treatments are likely to be well-tolerated, older patients should be treated with standard surgical procedures applicable to younger patients. This should include the choice of breast conservation or mastectomy where appropriate and breast reconstruction or oncoplastic procedures should be included in the options available. The choice of surgical treatment should be decided in consultation with the patient after appropriate information has been made available. The axillary nodal status should be assessed in all suitable patients and nodal metastases should be confirmed by preoperative biopsy or sentinel lymph node biopsy techniques before proceeding to full axillary node clearance or radiotherapy for those patients with nodal disease.

In the subset of patients with an impaired life expectancy due to extreme age or frailty alternative approaches may be considered. These patients should be managed in consultation with specialist geriatricians and anesthetists in addition to surgeons and oncologists. Appropriate assessment tools such as CGA should be utilized and patient preferences carefully sought – this topic is discussed elsewhere in this text (Chaps. 4, 5, and 6).

Patients with ER positive tumors may opt for surgery or primary endocrine therapy. In this group of frailer patients' surgery may be performed under local or regional anesthesia if not fit for general anesthesia.

The difficult task with these patients is to avoid the onset of distressing symptoms while offering the largest chances of cure; a slight increase in overall survival does not justify any treatment modality that might significantly impair the patient's well-being. It is therefore essential to include patient preferences in the decision-making process and to undertake procedures which combine the minimum risk with the maximum achievable benefit in terms of avoiding morbidity either as a result of the surgical procedure or due to disease progression. In patients with proven axillary node disease complete clearance should be considered; radiotherapy to the axilla is an alternative for frail patients and primary endocrine therapy might be considered when the patient is not fit enough for a prolonged course of radiotherapy. In patients with a clinically node-negative axilla, a sentinel lymph node biopsy may be

employed or axillary surgery omitted altogether, particularly for patients with estrogen receptor positive disease.

7.11 Summary

Older women are a very heterogeneous group in terms of their health status and likely treatment tolerances. For the frailer woman, for whom breast cancer may pose a reduced threat to life, and its treatment be associated with increased risk, tailored strategies to surgery may be needed. In some women surgery may be minimized or even avoided without detriment to breast cancer outcomes. The advice of specialist geriatricians and anesthetists will ensure treatment is optimized in each case.

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Breast Reconstruction Surgery in Older Women

8

Anne Shrestha and Lynda Wyld

Abstract

Post-mastectomy breast reconstruction and oncoplastic conservation surgery have developed rapidly over the past 2 decades as new techniques have been developed and disseminated. Immediate and delayed breast reconstruction (IBR and DBR) techniques have proliferated with a range of new techniques including skin and nipple sparing mastectomy, numerous new autologous flaps (DIEP, TUG, TDAP, LICAP), enhanced sophistication in our use of implants and adjuncts to implant use such as a wide range of acellular dermal matrices (ADMs) and lipomodelling.

Advanced oncoplastic techniques for breast conservation surgery have resulted in expanding indications for breast conservation leading to enhanced aesthetic outcomes even in challenging conservation cases. Surgeons have a better evidence base for safe application of these techniques from a surgical and oncological perspective although currently there are very few well designed randomised studies to support the majority of these procedures. As these techniques have evolved, the surgical community in some countries has embraced these developments with increasing availability of training to enhance the implementation of novel techniques. As a result of these developments rates of post mastectomy breast reconstruction have risen sharply in the UK from 7% in 1997 to 23% in 2013 (Jeevan et al., Br J Surg. 103:1147–56, 2016). However, these complex surgeries are still performed only rarely in older women. This is due to a combination of factors including surgeon reticence (due to concerns about surgical morbidity) and possibly reduced interest from older women who may be less concerned with cosmetic issues or wish to avoid complex surgery themselves. This chapter will give a brief overview of some of the new techniques and then

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explore the use of complex reconstructive and oncoplastic surgery for breast cancer in older women. It will cover the uptake and indications, trends, outcomes (cosmetic, morbidity, mortality, oncology outcomes and quality of life) and technical considerations.

Keywords
Older women · Breast reconstruction · Oncoplastic · Breast cancer · Surgery · Quality of life

8.1 Breast Reconstruction and Oncoplastic Conservation Surgery

Breast reconstruction (BR) has become a realistic consideration for the majority of women facing mastectomy, either as an immediate procedure (immediate breast reconstruction (IBR)) or subsequent to mastectomy and oncology treatments (delayed breast reconstruction (DBR)) [1]. A number of studies have demonstrated a significant increase in self-esteem, body image and quality of life (QoL) after BR in both younger and older breast cancer survivors [2, 3].

The techniques for breast reconstruction vary in complexity from the simple placement of an implant under the pectoral muscle or a sheet of ADM to a free autologous flap procedure such as a Deep Inferior Epigastric Perforator (DIEP) flap. Similarly, there are a large number of different therapeutic mammoplasty techniques (volume displacement oncoplasty), which may be used depending on tumour location in the breast and the breast size and shape (Fig. 8.1) [4]. Oncoplastic breast conservation may also be achieved by partial breast volume replacement using a range of local pedicled flaps or lipomodelling.

Selection of technique is complicated, varying according the wishes and expectations of the patient for symmetry, breast volume and degree of ptosis and whether the patient has any suitable donor sites for harvesting an autologous flap. There are significant potential technical differences between older and younger patients (Table 8.1), which may influence the choice of post mastectomy reconstruction or whether therapeutic mammoplasty is offered. Older women tend to have significantly more breast ptosis than younger women, significantly more fatty breasts and often have a higher body mass index. The skin is often thinner and lacks elasticity and is therefore less likely to adapt to a new underlying breast volume and shape. In addition, rates of co morbidity, polypharmacy and senescent organ degeneration are higher, which may increase the risks of surgery and anaesthesia.

Most studies suggest that older women are less likely to be offered autologous flap-based reconstruction than implant-based reconstructions (IBR), due to concerns over fitness for lengthy anaesthesia despite the fact that their breast shape, size and consistency are better matched by autologous rather than implant-based techniques.

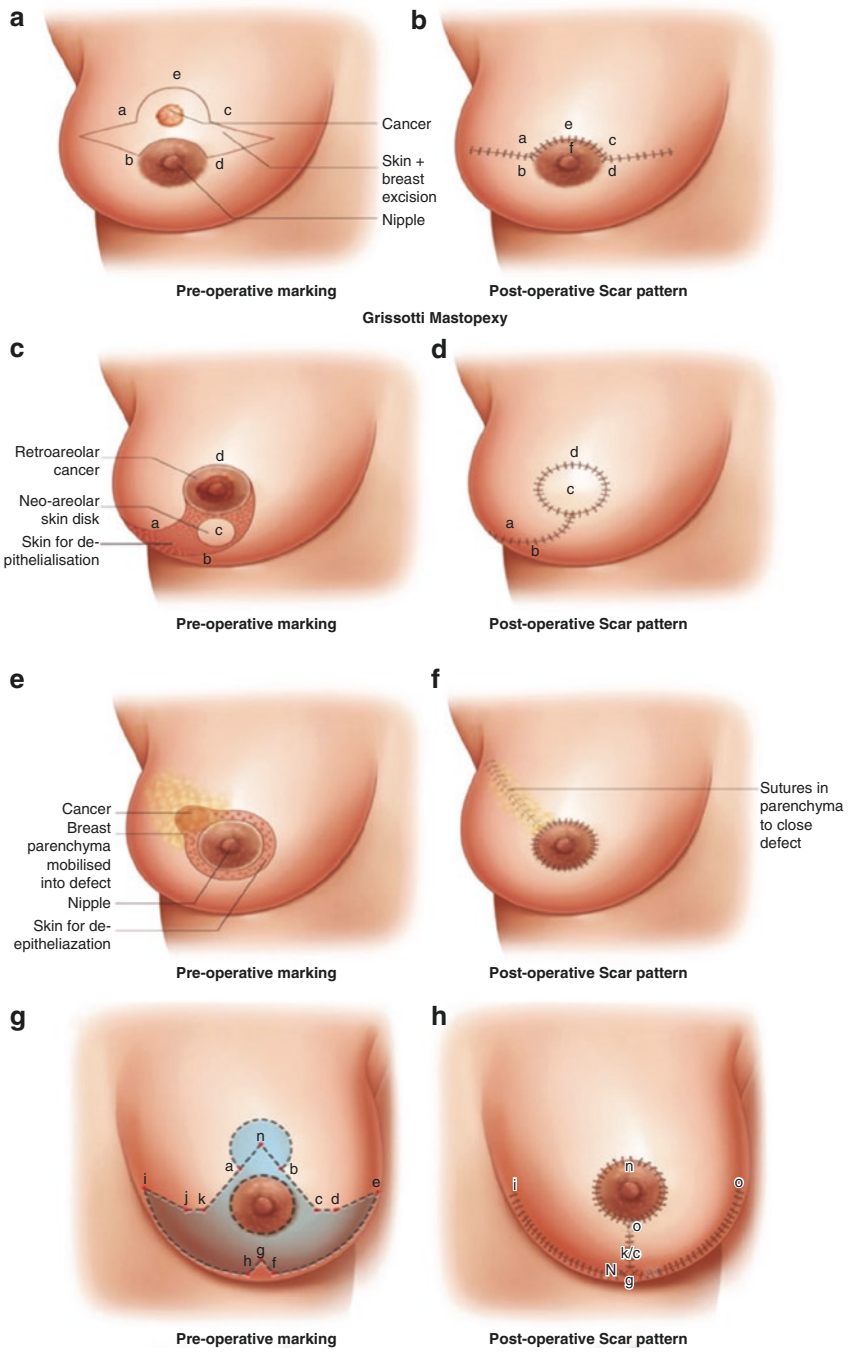

Fig. 8.1 Summary of some of the most common therapeutic mammoplasty techniques showing preoperative mark up and post-operative scar appearance. Batwing (**a**, **b**), Grissotti (**c**, **d**), Donut (**e**, **f**) and Wise Pattern (**g**, **h**)

Table 8.1 Characteristics of older age that may impact on choice of reconstruction technique

Characteristic	Impact on choice of mastectomy reconstruction	Impact on oncoplastic conservation
Greater breast ptosis (droop)	Achieving significantly ptotic reconstructed breasts is challenging and easier using autologous techniques than implants. In very ptotic breasts symmetrisation is likely to be needed. Some reconstructive techniques depend on ptosis, for example the dermal sling and the goldilocks procedure	Ptosis correction is an integral part of many therapeutic mammoplasty techniques, which capitalise on skin laxity to reshape the breast. Symmetrisation of the contralateral breast may be required
Fatty, low density breast tissue	Breast texture is very soft and unlikely to be matched by implants but may be matched by autologous fatty tissue	Level 1 oncoplastic techniques where extensive mobilisation of parenchymal flaps is required may result in fat necrosis and should be avoided in fatty breasts. Less good recipient site for lipo-aspirates from fat grafting with higher risk of fat necrosis
Lack of skin elasticity	Skin envelope after skin sparing mastectomy must closely 'fit' the new breast mound to avoid 'pseudoptosis' or skin wrinkling	
Diabetes, hypertension, arteriopathy	Increased risk of wound healing problems, infection and implant loss. Increased risk of autologous flap failure	Increased risk of wound healing problems, nipple necrosis and fat necrosis
Increased co-morbities	Higher risk of prolonged anaesthesia especially in free flap surgery	Higher risk of prolonged anaesthesia in lengthy therapeutic mammoplasty surgery
Sarcopenia (age related loss of skeletal muscle mass)	Pectoral muscle may be very thin and fragile which may compromise its use in implant-based techniques using a submuscular pocket. This may preclude the use of a fully submuscular technique, may compromise a partially subpectoral technique (for example with an ADM to support the lower implant pole) and make use of a fully prepectoral ADM advisable.	
Atrophic adipose tissue at donor sites	Less volume for autologous flaps	Less volume available for harvesting fat for lipomodelling

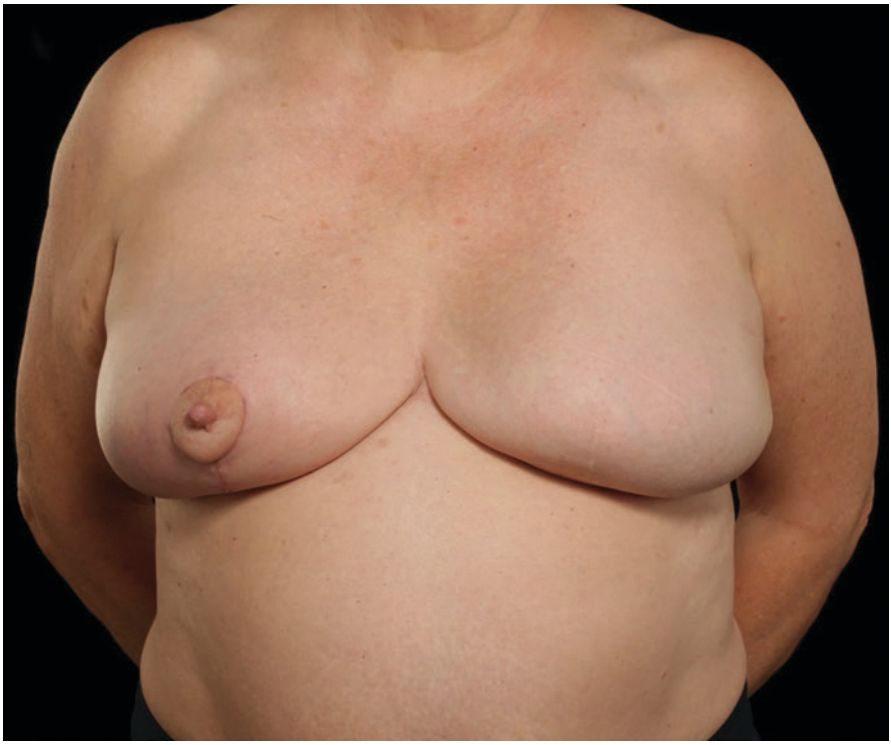

Fig. 8.2 Photograph of a left skin sparing mastectomy and dermal sling plus implant reconstruction in an older (age 71) woman plus a right symmetrisation reduction (reproduced with consent)

A technique that is very valuable in older women with ptotic breasts, especially if they desire less ptotic breasts, is the dermal sling technique which uses the skin laxity to create a well-padded implant pocket whilst simultaneously substantially tightening the skin envelope [5] (Fig. 8.2).

8.1.1 Utilisation Rates of Complex Reconstructive and Oncoplastic Techniques in Older Women

Although guidelines suggest BR should be offered to all women without age restriction, real world practice shows a clear age-related trend for lower reconstruction rates with increasing age. Data from the National Mastectomy and Breast Reconstruction Audit (NMBRA) in 2010 showed that older women are significantly less likely to undergo reconstructive surgery (Fig. 8.3) [6]. This trend is in contrast to various national and international guidelines. The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) recommend that patients >70 years should be offered the same surgery as younger patients [7]. This recommendation was reinforced by the UK Association

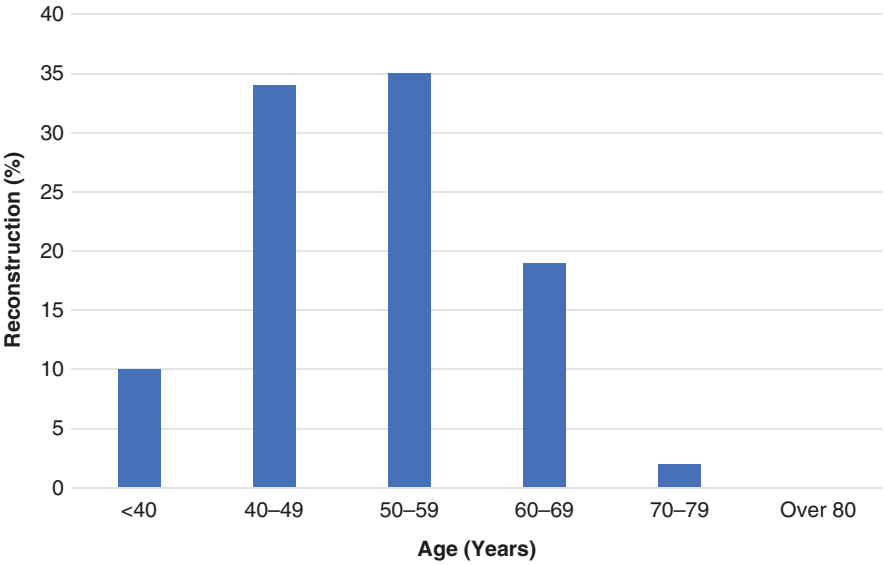

Fig. 8.3 UK data adapted from the National Mastectomy and Breast Reconstruction Audit (2010) [6]

of Breast Surgeons in 2012 [8]. The National Institute for Health and Care Excellence (NICE) published breast cancer guidelines also stating that reconstructive surgery should be discussed and offered to all patients with early breast cancer undergoing mastectomy, should patients' fitness not be a contraindication [9].

The reasons for this age-related variance in reconstruction rates are complex and may not necessarily indicate age bias on the part of health professionals. Breast reconstruction surgery is always more complex than simple mastectomy, even for the simpler, implant-based techniques and as multimorbidity rates increase with age, fitness for more complex surgery is likely to be reduced in older women. Standard breast surgery has a very low mortality rate in older women ranging from 0–2% [10] however there are very few data about rates of morbidity and mortality in older women.

Breast reconstruction rates in older patients vary between individual clinicians, breast units and geographically and published rates range from <5% to 85% [11]. The reasons behind the generally low uptake of BR are poorly understood. Older age is an independent risk factor for non-guideline compliant treatment for breast cancer across all domains of therapy [12]. Kamali and colleagues reported that immediate breast reconstruction (IBR) rates decreased significantly with age, and stated that older patients were less likely to opt for BR [13]. These findings are further supported by the UK National Mastectomy and Breast Reconstruction Audit (2009), which showed that 45% of women aged >70 were offered BR but only 8% accepted and 18% of those above 80 were offered BR and only 2% accepted [14]. De Lorenzi and colleagues reported that although all women aged 65 and above in their study were offered BR, only 17% proceeded to breast reconstruction surgery

[15]. Jeevan and associates studied the proportion of breast cancer patients undergoing mastectomy who were offered IR and noted that only 25.6% of those above the age of 70 were offered IR [16]. In a study by Mays and colleagues, <1% of women over 70 underwent reconstructive surgery [17]. The likelihood of older women receiving IR is increased in larger hospitals or those with dedicated oncoplastic services [18].

The reconstruction decision-making process is more complex in an older patient. Clinicians generally hold preconceptions about older womens' attitudes regarding their body image, believing that they are less likely to be concerned about having reconstructive surgery than younger patients [19]. Older women are more likely to accept their disease pragmatically and often wish to avoid optional extensive surgery, which they understand may carry increased risks for them. Clinicians may be concerned that operating on an older patient may lead to increased morbidity and mortality due to co-morbidities, senescent deterioration in organ function, frailty and polypharmacy, all of which are more common in older women. Unfortunately, there is a lack of information in the literature about breast reconstruction in older women; they are under-represented in many studies or excluded altogether on the basis of 'old age' with the cut off commonly at age 60 or 65 years. When older women are included, the group usually only forms a small proportion of the study. Hence, there are limited results regarding outcomes and use of available techniques in this cohort of patients. Studies involving older patients, have largely been retrospective in design and involved case series or surveys. Ultimately, the only acceptable reason for not providing equivalent treatment for older patients would be if they were at high risk of surgical morbidity or to respect patient autonomy.

8.2 Assessment of the Older Patient for Reconstructive Surgery

Understanding the patients' expectations regarding their breast cancer treatment is critical in ensuring a shared decision making approach to their management. There should be a consultation dedicated to discussing reconstruction in detail after the initial diagnosis has been communicated with a suitable amount of time for the patient to adapt to the diagnosis. A study reviewing breast cancer treatment on patients above the age of 70 by Fenlon and colleagues demonstrated that breast reconstruction was discussed only rarely despite all women stating that they would like to have the option [20]. Older patients who were not initially provided with information regarding reconstruction, wished they had been counselled before their mastectomy [21]. The failure of clinicians to discuss this topic with older patients may represent a degree of age bias amongst clinicians, potentially due to perceptions about individual women's preferences or clinician and patient concerns about the (possible) medical risks.

There is a tendency by clinicians to underestimate a patient's predicted life expectancy and overestimate the potential rate of complications. Older women in

good health often have a good predicted life expectancy and breast cancer survival rates are generally high due to the often favourable biology in this age group. Survival rates at 4.2 years for women aged 65 and over who underwent reconstruction with implants or transverse rectus abdominus myocutaneous flaps (TRAM) was 91% and 88% respectively [22]. Chronological age is not always a good indicator of a patients' physical health and more importance should be placed on the patient's physiological age. Prediction of 10-year survival according to age and co-morbidities can be done using a range of tools such as the Modified Charlson Co-morbidity Index (MCCI) and range of validated online calculators such as the Schonberg Index [23, 24].

With age, there is an increased likelihood of co-morbidities and polypharmacy, and therefore a higher risk of surgical complications. Nevertheless, age alone is not associated with increased post-operative risks [25]. Morbidity can be minimised with careful preoperative assessments. Various scoring tools have been developed to ensure a more objective approach when assessing the suitability of a patient. The Comprehensive Geriatric Assessment (CGA) consists of multiple components not only looking at the mental and physical component of the patient's health but functional and social aspects too, allowing for a more holistic assessment of the patient [23]. This allows for accurate risk assessment before reconstructive surgery is offered and which technique may be most appropriate (see above).

8.3 Types of Breast Reconstruction in the Older Breast Cancer Patient

Studies involving breast reconstruction in older women remain limited. As a result, there is minimal guidance for surgeons regarding the approach to take when offering it. Oncoplastic breast-conserving surgery in the elderly has been reported very rarely in the literature. A retrospective study of women aged 65 and above found 14/63 had oncoplastic breast conserving surgery. Six had bilateral procedures (2 bilateral cancers and 4 for symmetrisation). Two of these patients then proceeded onto having a mastectomy. Overall, outcome were good and oncologically safe [15].

Autologous fat grafting or lipomodelling has now become an integral part in the management of breast deformities after reconstruction. Studies of lipofilling specifically in older women with breast cancer are limited but one study in 137 women (median age 64.8 range 60–78) showed older women were more likely to have atrophic adipose tissue and fatty breasts, which may reduce graft viability and lead to higher rates of complications. However, the authors concluded that lipomodelling is a feasible option to correct defects in older breast cancer patients following breast conservation [26].

Immediate breast reconstruction at the time of mastectomy has become increasingly popular [16]. Compared to a delayed approach, IBR offers the potential for fewer operations, decreased costs and less discomfort and inconvenience for the patient. In the case of older patients, this may be the preferred approach, as patients

are potentially less likely to request reconstructive surgery later and may suffer a decline in fitness with time.

As noted above there are technical considerations when planning the type of reconstruction in an older woman (Table 8.1). Not surprisingly, reconstruction type varies by patient age. In a comparative study of breast cancer patients aged >65 versus younger patients, Girotto and colleagues, noted that 79% of older women underwent immediate reconstruction with 50% having implant reconstruction. Older patients were less likely to have autologous breast reconstruction compared to younger patients. The rate of nipple areolar complex reconstruction was also lower in the older age group [27]. Lipa and colleagues reported increased rates of autologous reconstruction in patients >65; 40.5% of their patients had a TRAM flap, 28.6% an LD flap, and 31% underwent implant based surgery [22]. Bezuhly and colleagues reported that patient above the age of 70 who opted for BR were more likely to receive a combined reconstruction with both a flap and implant, such as a latissimus dorsi procedure [28]. In general, the trend seems to be that older patients are more likely to receive implant based reconstruction than autologous (summarised in Table 8.2). This could be due to concerns about prolonged anaesthetic time as well as the increased morbidity associated with the donor site and worries about the quality of the vascular supply to the flap in an age group where atherosclerosis may be more prevalent. There have been studies reporting free flap usage in reconstruction in older women, however, the numbers remain low [3, 29, 30] and as can be seen old age is classified as 60 or 65 in most series which in a geriatric context is now not regarded as old in Western populations.

8.4 Complications of Breast Reconstruction

Older women are more likely to have comorbidities than younger women and also have senescent organ deterioration such as reduced renal, cardiac and respiratory reserve and may also have sarcopenia, arthritis and loss of independence [37]. They tend to be less resilient to surgery and anaesthesia and may suffer an irreversible loss of functional level after major interventions [33, 38, 39]. Rates of diabetes, hypertension and atherosclerosis are all more common, all of which may increase the risks of flap perfusion failure and necrosis [35]. Polypharmacy is also common, with many being on regular medication, some of which, for example anticoagulants, may increase the risk of post-operative bleeding. Matsumoto and colleagues noted that women over 60 years of age had significantly higher rates of hypertension and diabetes and there were higher rates of American Society of Anaesthesiologists (ASA) grades 2 or above in the older age group. The older cohort of patients were 1.6 times more likely to develop complications post BR than the younger group [35]. Similar findings were reported regarding higher rates of comorbidities and ASA grades in the older group of patients undergoing BR by Selber and associates [30].

Despite this complications associated with breast reconstruction in the older age group in reported studies remain similar to younger breast cancer patients. Several

Table 8.2 Evaluation of studies involving breast reconstruction in older breast cancer patients

Author	Sample size (% of older patient) age classified as old	Age groups (mean age)	Types of reconstruction undertaken by study cohort	
			Older cohort	Younger cohort
Santonsa [31]	1531 (15%)	≤45 (NS) 45–60 (NS) ≥60 (NS)	Implant based – 70.1% Autologous – 29.9%	Implant based – 69% Autologous – 31%
Song [32]	1809 (3%) ≥65	>65 (48.9) ≥65 (67.4)	Autologous – 100%	Autologous (100%)
Laporta [33]	993 (20%) ≥60	<50 (42.6) 50–59 (53.5) 60–69 (64.1) ≥70 (71.4)	Implant based – 34.6% Autologous +/− implant – 65.4%	Implant based – 36.1% Autologous +/− implant – 63.9%
Mays [17]	54,831 (<1%) ≥70	>70 (NS) ≥70 (NS)	NS	NS
Ludolph [34]	179 (21.7%) ≥60	>60 (NS) ≥60 (NS)	Autologous – 100% (DIEP – 18%, TRAM – 82%)	Autologous 100% (ms-TRAM – 64%, DIEP – 36%)
Kamali [13]	4450 (100%) ≥60	60–65 (NS) 65–70 (NS) 70–75 (NS) 75–80 (NS) ≥80 (NS)	Implant based – 76.8% Autologous – 17.4% Combined – 5.8%	–
Matsumoto [35]	560 (16.8%) ≥60	>60 (NS) ≥60 (NS)	Autologous – 37.2% Implant based – 38.3% Combined – 24.5%	Autologous – 25.6% Implant based – 50.6% Combined – 23.8%
Girotto [27]	316 (8%) ≥65	>65 (47.4) ≥65 (69.3)	Implant based – 50% Autologous – 50%	Implant based – 33% Autologous – 67%
Bezuhly [28]	54,660 (28%) ≥70	<50 (NS) 50–69 (NS) ≥70 (NS)	Implant based – 26.8% Autologous – 31.8%	Implant based – 22.7% Autologous – 43.3%

(continued)

Table 8.2 (continued)

Author	Sample size (% of older patient) age classified as old	Age groups (mean age)	Types of reconstruction undertaken by study cohort	
			Older cohort	Younger cohort
Lipa [22]	84 (100%) ≥65	≥65 (69.2)	Implant based – 31% Autologous – 69% (LD – 29%, TRAM – 40%)	–
Butz [3]	40,769 (37%) (10.8% of older patients had BR)) ≥65	>65 (50) ≥65 (69)	Implant based – 83.5% Autologous – 16.5% (LD – 7.9%, TRAM – 6%, Free Flap – 2.6%)	Implant based – 78.7% Autologous – 21.3% (LD – 6.1%, TRAM – 10.5%, Free Flap – 4.7%)
Gibreel [36]	364,767 (35%) (3.6% of older patients had BR) ≥65	>65 (NS) ≥65 (NS)	NS	NS

NS not stated

studies have compared outcomes following either autologous or implant-based surgery in older patients compared the younger group of reconstruction recipients. August and associates stated that implant reconstructions were performed more often than autologous BR in their series of older women, however, they found that there was no significant difference in complications between the two types of reconstruction in older patients as well as when compared to younger breast cancer patients undergoing BR [40]. Lipa and colleagues reported significantly higher rates of complications for patients undergoing implant reconstruction (77%) compared to those who underwent autologous procedures (LD 42%, TRAM 35%). The majority of the complications in the implant group were minor and self-limiting such as seroma formation, however, there was a 42% (n = 11) rate of implant removal in their mean follow up period of 4 years, with 4 being removed in the early post-operative period [22].

A retrospective analysis by Kamali and colleagues with a sample size of 4450 breast cancer patients aged >60, looked into IBR and associated complications. The majority of the reconstructions were implant based (77%), followed by autologous (17%) and combined (6%). In this study, higher complication rates were associated with autologous reconstructions in the 30-day post-operative period, with significant differences noted in rates of bleeding, infections and thromboembolic complications, when compared to implant and combined reconstructions [13]. In a study by Chang and co-workers involving free-flap BR, the complication rate was 26.2% for those aged 60–69 (n = 103) and 42.6% for those 70 and older (n = 19). The older age group suffered from a higher percentage of fat necrosis and thrombosis although this was not statistically significant in comparison to other age groups, probably due to the small sample size. They also reported no difference in the complication rates when comparing with patients below the age of 60 [29]. This is further emphasised

by Matsumoto, reporting no significant difference of complications between those who were below and above 60 potentially reflecting careful patient selection in all age groups [35].

In a study carried out by Butz and associates with a sample size of 40,769 breast cancer patients of which 1624 were above the age of 65 undergoing BR, there was no significant difference in complications between those aged >65 or <65 who underwent implant reconstruction. Older patients undergoing autologous reconstruction were more likely to have venous thromboembolism compared to younger women and surprisingly, the median length of hospital stay was lower in the older age group [3].

Gibreel and colleagues, found that women who did not undergo BR had a higher number of co-morbidities than those who did with 18.4% of those who had BR having more than one co-morbidity compared to only 9.8% of those below the age of 65 years. Thirty-day readmission rate was higher in the older age group and the overall length of hospital stay was longer [36].

Knackstedt and colleagues reviewed their practise of direct to implant BR in women >65. Nineteen patients underwent direct to implant procedures compared to 88 patients who had expander/implant reconstruction. The direct implant group had a higher median age of 73.5 years compared to 69.2 years in those who had expander/implant BR. Interestingly, no significant difference was noted in rates of seroma formation, haematoma, necrosis or reconstructive failures at 30 days and 1 year. Also, the length of stay was lower in those who had direct to implant reconstruction reconstructions [41].

Laporta and collegues, reported that the rate of fat necrosis, flap loss, infection, and mean length of stay were very similar in older and younger cohorts but rates of implant loss were higher in those >70 [33]. Selber and colleagues' study of free flap reconstruction in older patients found that reconstructive operative time was the same regardless of age but that older patients were more likely to require blood transfusion. However overall, the complication rates remained similar between those above and below 65 years of age.

With regards to a study of 137 older breast cancer patients of age 60 and above, having lipomodelling to revise defects, Chirappapha and colleagues did not observe any complications at the donor site; 12% experienced lipomodelling associated complications, with 5% of the patient suffering from liponecrosis, 1% (2 patients) had cellulitis, both were managed conservatively, and 1% had liponecrosis with abscess. Thirty-three percent of the patients did undergo further lipomodelling [26].

Overall, the larger studies indicate that BR is well tolerated in the older age group of breast cancer patients. However, it is likely that older women selected for BR are likely to be a group of selected and highly motivated older women. Implant reconstruction is associated with overall less complications compared to autologous and complications rates between the younger and older age groups are very similar indicating that older women should not be discouraged from having BR. It is worth noting that there are controversies and inconsistencies regarding what age is actually considered old. Studies have reported older or elderly ranging from 50 to 70 years of age. In the study by Matsumoto, age was stratified by 2 methods; the

World health Organisation (WHO) categorisation of young (<44 years), middle-age (45–59 years) and elderly/extremely old (>60) and the Brazilian National Elderly Policy (NEP) defines old as those >60 years of age [35]. This is appropriate in a global and developing world context where average life expectancy rates remain low. However, in the developed world, where life expectancy rates usually exceed 80 years, and where most complex reconstructive surgery is performed, true old age is probably not present until age 70. Studies involving patients >70 years of age remain rare in this subject area and the median age of many studies are more reasonably described in a western context as late middle age/young-old (60–65/70).

It is also worth noting that none of these studies have reported in detail on the fitness level of the women included in these studies which varies widely in older age cohorts. It is likely that most of the women included in these series will have been heavily selected to ensure fitness with few having significant co-morbidities.

The UK Age Gap study has compared fitness levels of older women who undergo mastectomy or mastectomy and reconstruction and showed that age, comorbidity and frailty levels varied substantially between these groups showing how selective surgeons are in offering these complex procedures (unpublished data Fig. 8.4).

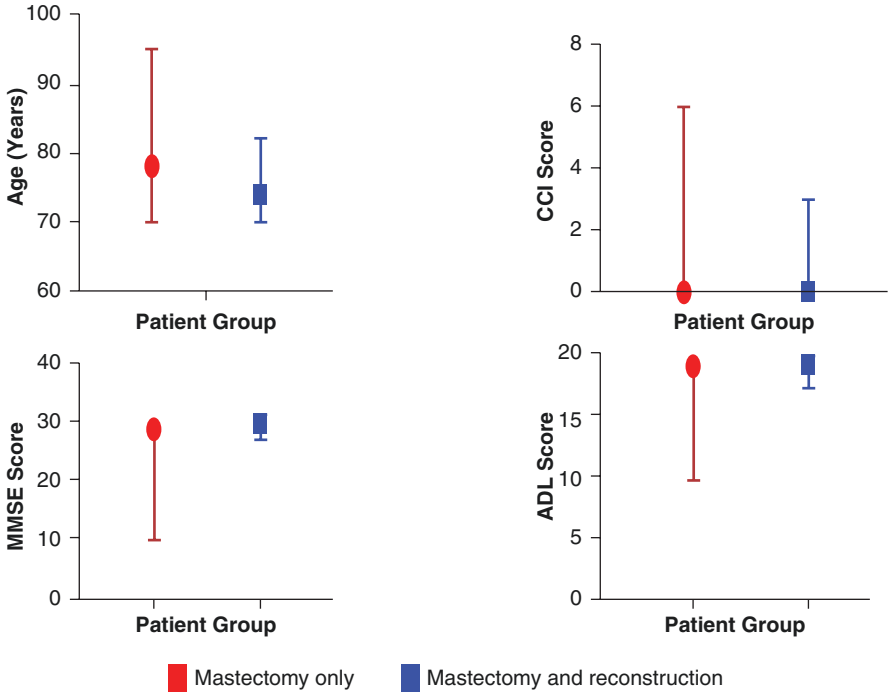

Fig. 8.4 Comparison of age, fitness (CCI charlson comorbidity index), frailty (Activities of Daily Living (ADL) score), cognition (Mini-Mental State Examination (MMSE) score) in a cohort of 900 older women undergoing mastectomy versus 33 undergoing mastectomy and reconstruction in the UK between 2013 and 2018

8.5 Quality of Life and Patient Satisfaction

Long after the diagnosis of breast cancer, many women face a variety of emotional challenges, especially regarding the perception of their bodies. Quality of life (QoL) is now considered an important end point in cancer treatment and body image and self-esteem play an important role in maintaining a good QoL. In a survey by Smith and colleagues, it was noted that 18% of the patients >70 who underwent mastectomy would have preferred to have had breast conservative surgery (BCS) instead, and 40% would have liked to have tried primary endocrine treatment (PET) to shrink the tumour so BCS could have been an option, implying that having breasts is still important to older women. Smith also reported that 55% of those who underwent mastectomy and 37% who had BCS stated that they had concerns that having mastectomy would lead to low self-esteem or depression [42]. Figueiredo and colleagues reported that older breast cancer patients who had undergone BCS had better body image at 2 years post treatment compared to those who had a mastectomy. Body image was felt to be an important factor in their treatment decision by 31% and those patients who undergo mastectomy are more likely to have body image issues as well as mental health issues than patients having BCS [43]. Breast reconstruction is therefore particularly important in ensuring that confidence in this age group is maintained.

In a study by Sisco and associates looking at QoL post-mastectomy reconstruction in older women (>65), they concluded that those who underwent reconstruction had a better body image and breast-related psychosocial health compared to those who opted not to have any reconstructive surgery. It was also noted that the outcomes were similar to those seen in younger women [44]. Girotto and colleagues also reported that when using the Short Form-36 (SF-36) QoL tool, patients who had underdone BR scored higher than those who just had mastectomy and these patients also scored higher in the mental health domain compared to the younger patients who underwent BR [27]. Maruccia and associates reported one-stage breast reconstruction in older patients helps preserve QoL in older patients and patient satisfaction using a visual analogue scale (VAS) was excellent [45]. Song and colleagues also reported high satisfaction regarding their reconstructive outcomes when measured with the BREAST-Q tool, and this is also reflected by the study by Ludolph and colleagues [32, 34].

Bowman and colleagues performed a survey with 75 BR patients aged 60–77 to ascertain their QoL and overall patient satisfaction. The study found that 70% of the women reported they were happy with their results, reporting them as good or excellent. Almost all (90%) felt that all breast cancer patients should be offered reconstructive surgery regardless of their age and a discussion about BR should take place for all breast cancer patients [21].

Santosa and colleagues stated that older women generally reported improved satisfaction and psychosocial well-being after BR and also when compared to those below 60 years of age. It was noted that older women with implant reconstruction had lower physical well-being after the procedure, in contrast to the

those who had autologous reconstruction where physical well-being actually improved. Interestingly, at 2 years follow-up, older patients who had undergone implant reconstruction were more likely to have better sexual well-being than the younger age group. They were however, less satisfied with the results of their reconstruction than those <60 years of age. The older patients who had autologous reconstruction surgery expressed more satisfaction with the outcome than those who had IMBR surgery [31].

8.6 Conclusion

Cancer care is now becoming increasingly patient centred. Older women form a heterogeneous group of patients where physical fitness, psycho-social dynamics and expectations about treatment should all be considered. For older women who undergo breast reconstruction the psychological and quality of life impacts are clearly better than for women who have no reconstruction. Physical complications of the surgery maybe slightly higher, especially after autologous reconstructions in what is almost certainly a highly selected group of fitter, highly motivated women. Mortality rates are so low as to be unreliable to report. As median life expectancy in the western world continue to climb, surgeons should be open minded about discussing reconstruction with older women, especially those in good health and move away from a preconception that older women are not interested, are too high risk for these types of procedures and have poor outcomes.

Better quality data about outcomes in the over 70 age group are urgently needed.

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Adjuvant Endocrine Therapy

9

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Abstract

The risk of subsequent development of distant metastases from early breast cancer (BC) underpins the rationale for offering treatment in the adjuvant setting. Current guidelines recommend that patients with hormone receptor-positive disease be offered adjuvant endocrine therapy (ET). Oestrogen receptor (ER)-positivity progressively increases with age, with more than 80% of BCs being ER-positive in patients aged 65 and older. As such, given that the majority of early BC cases in the elderly would be considered theoretically eligible for ET, the evidence regarding its use in the adjuvant setting is of particular interest for this cohort. Recent large randomised controlled trials and meta-analyses have provided data regarding the type, duration and sequencing of ET in postmenopausal women, which can assist clinicians in their recommendations to elderly patients. This chapter will summarise the findings of these seminal trials, and their applicability to the elderly subpopulation will be discussed.

Keywords

Adjuvant · Endocrine therapy · Elderly · Hormone receptor positive · Aromatase inhibitor · Tamoxifen · SERD

A major concern associated with early breast cancer (BC) is the subsequent development of distant metastasis. Adjuvant treatment is given with the intent to reduce the risk of eventual tumour relapse and death, with adjuvant endocrine therapy (ET)

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being offered to patients with oestrogen-receptor (ER) and/or progesterone-receptor (PgR)-positive disease. The current St Gallen guidelines recommend that adjuvant ET should be offered to patients with highly endocrine-responsive tumours (high expression of both ER and PgR in a majority of tumour cells) as well as to patients with incompletely endocrine-responsive BC (low expression of ER and/or PgR) [10]. Given that ER-positive disease progressively increases with aging, with less than 20% of BC cases being ER-negative in patients aged 65 or older, the majority of elderly patients are therefore candidates for adjuvant ET.

9.1 Tamoxifen: Efficacy and Safety Data

Tamoxifen, a selective ER modulator, has historically been the most commonly used hormonal therapy for endocrine sensitive early BC. The administration of 5 years of tamoxifen versus no treatment almost halves the annual recurrence rate (recurrence rate ratio 0.59 [SE 0·03]), and reduces BC mortality rate by a third (death rate ratio 0.69 [SE 0·04]). This translates to an absolute 15-year gain of 11.8 and 9.2% in terms of recurrence and BC mortality, respectively [16]. This benefit is observed, irrespective of patient age.

In terms of adverse events, 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. The risk of uterine cancer is strongly correlated with age [17]. With respect to the impact of age on the risk of thromboembolic events among tamoxifen users, Ragaz et al. calculated that the relative risk of mortality for thromboembolic events was 1.5 at the age of 50, with a dramatic increase to 17.5% by the age of 80 [36]. However, in that specific age group, the risk of thromboembolic-related mortality was outweighed by a protective cardiac effect bestowed by tamoxifen. There is evidence that the risk of thromboembolic events is related to the duration of the treatment, which was shown by another group to double from 2 to 5 years [38].

9.2 Aromatase Inhibitors

The introduction of aromatase inhibitors (AIs) to clinical practice has challenged the role of tamoxifen in post-menopausal women. Adjuvant AI trials can be grouped according to the modality of introduction of an AI in the adjuvant treatment regimen, as follows: (1) Upfront therapy trials, in which there is a head-to-head comparison between tamoxifen and an AI, or direct comparison between two or more AIs; (2) switching trials, in which 5 years of therapy with tamoxifen or an AI is compared with tamoxifen for 2–3 years followed by AI for an overall duration of 5 years; (3) extended adjuvant trials, evaluating the potential benefits of various ET regimens/combinations for durations beyond 5 years. The study design and results of published trials are summarised in Table 9.1.

Table 9.1 Trials evaluating the role of aromatase inhibitors (AIs) in the adjuvant setting

Study (No. patients)	Study design		Follow-up months	Endpoints					
Up-front trials									
ATAC [11] (n = 6241)	5 y A		120	DFS	HR 0.91; $p = 0.04$	TDR	HR 0.87; $p = 0.03$	OS	HR 0.97; $p = 0.6$
	5 y T			TTR	HR 0.84; $p = 0.001$				
BIG 1–98 [37] (n = 4922)	5 y L		104	DFS	HR 0.86; $p = 0.007$	DRFI	HR 0.86; $p = 0.047$	OS	HR 0.87; $p = 0.048$
	5 y T			BCFI	HR 0.86; $p = 0.03$				
FATA-GIM3 [13] (n = 1847)	5y L		60	DFS	NS			OS	NS
	5 y A								
	5 y E								
FACE [39] (n = 4136)	5y L		65	DFS	HR 0.93; p = 0.32	TDM	HR 0.94; p = 0.99	OS	HR 0.98; p = 0.79
	5 y A								
				DDFS	HR 0.96; p = 0.62				
Switching trials comparing 5 y T versus 2–3 y T → AI									
Intergroup Exemestane Study (IES) [33] (n = 4724)	2–3y T	2–3y E	120	DFS	HR 0.85; $p = 0.002$	BCEFS	HR 0.86; p = 0.03	OS	HR 0.89; $p = 0.08$
	2–3y T	2–3y T		EFS	HR 0.81; p < 0.001				
ABCSG8/Italian tamoxifen anastrozole (ITA)/ ARN095 [27] (n = 4600)	2–3y T	2–3y A	128	DFS	HR 0.59; p < 0.0001	EFS	HR 0.55; p < 0.0001	OS	HR 0.71; $p = 0.04$
	2–3y T	2–3y T		DRFS	HR 0.61; p = 0.002				

(continued)

Table 9.1 (continued)

Study (No. patients)	Study design		Follow-up months	Endpoints					
Switching trials comparing 5 y IA versus 2–3 y T → AI									
FATA-GIM 3 [13] (n = 3697)	5 y AI	2 y T	60	DFS	HR 0.0.89; p = 0.23			OS	HR 0.72; p = 0.052
		3 y AI							
TEAM [12] (n = 6120)	5 y E	2–3 y T	118	DFS	HR 0.96; p = 0.39	DRFI	HR 0.91 p = 0.15	OS	HR 0.98 p = 0.74
		2–3 y E							
Extended adjuvant therapy									
MA 17 [19] (n = 5187)	5y T	5 y L	30	DFS	HR 0.58; $p < 0.001$	DDFS	HR 0.60; p < 0.002	OS	HR 0.82; p = 0.3
	5y T	placebo							
MA.17R [22] (n = 1918)	10y AI	5y L	75	DFS	HR 0.66; p = 0.01			OS	HR 0.97, p = 0.83
	4.5–6 yr. ET	placebo							
ABCSG 6a [26] (n = 856)	5y T ± AG	3 y A	62.3	DFS	HR 0.62; $p = 0.031$			OS	NS
	5y T ± AG	NT							
NSABP B-33 [31] (n = 1598)	5y T	5y E	30	DFS	HR 0.68; $p = 0.07$	RFS	HR 0.44; $p = 0.004$	OS	NS
	5y T	placebo							
DATA [42] (n = 1860)	2–3 y T	2–3 y T	50	DFS	HR = 0.79; p = 0.066			OS	HR 0.91, p = 0.6
	3 y A	6 y A							
IDEAL (Blok et al. 2017) (n = 1824)	ET 5y	ET 5y	79	DFS	HR = 0.96; p = 0.7			OS	HR 1.08; p = 0.59
	2.5 y L	5 y L							

NSABP-B42 [32] (n = 3966)	ET 5y	ET 5y	83	DFS	HR = 0.85; p = 0.048 (NS)			OS	HR = 1.15, p = 0.22
	L 5y	P 5y							
ABSCG −16 [23] (n = 3484)	ET 5y	ET 5y	105	DFS	HR = 1.007, p = 0.925			OS	HR 1.007, p = 0.947
	A 2y	A 5y							
SOLE (Colleoni et al., 2017) (n = 4851)	4–6 y ET	4–6y ET	60	DFS	HR = 1.08 p = 0.31	DDFS	HR 0.88p = 0.25	OS	HR = 0.85, p = 0.16
	5y L	5y IL							

AI aromatase inhibitor, *A* anastrozole, *T* tamoxifen, *L* letrozole, *IL* intermittent letrozole, *E* exemestane, *NS* not significant, *NT* no treatment, *HR* hazard ratio, *ET* endocrine therapy, *y* years, *AG* aminoglutethimide, *BCEFS* breast cancer event-free survival, *BCFI* breast cancer-free interval, *EFS* event-free survival, *DFS* disease-free survival, *DRFI* distant recurrence-free interval, *DRFS* distant recurrence-free survival, *TDR* time to distant recurrence, *OS* overall survival, *TTR* time to recurrence, *DDFS* distant disease-free survival, *TDM* time to distant metastasis, *RFS* relapse-free survival. Modified from Biganzoli et al. [1], with permission

9.2.1 Efficacy Data

9.2.1.1 Upfront Trials (Tam Versus AI Comparison)

The Arimidex & Alone or in Combination (ATAC) trial randomised a total of 9366 postmenopausal patients to receive adjuvant tamoxifen or anastrozole alone, or a combination of tamoxifen plus anastrozole for 5 years [41]. The most recent analysis, conducted after a median follow-up of 120 months, anastrozole monotherapy appeared superior to tamoxifen alone [11]. In the hormone receptor-positive subgroup, anastrozole was favoured in terms of PFS, TTR and TDR, but no OS advantage was seen.

The Breast International Group (BIG) 1–98 study was a randomised, phase 3, double-blind trial that compared 5 years of treatment with four possible adjuvant ET regimens: (1) letrozole, (2) letrozole followed by tamoxifen, (3) tamoxifen, or (4) tamoxifen followed by letrozole. A total of 4922 patients were randomised in the upfront comparison of the tamoxifen versus letrozole arms [4]. Patient median age was 61 years (range: 38–90). After a median follow-up of 8.1 years, an advantage in favour of letrozole monotherapy over tamoxifen was seen in terms of DFS, TTR and TDR, whilst also gaining an advantage in terms of OS which was not observed in earlier published analyses (HR 0.79; 95% CI 0.69–0.90) [37]. Adjusted analyses using inverse probability of censoring weighting modelling, designed to adjust for the selective crossover that occurred after initial trial results were reported, produced a statistically significant 18% reduction in the hazard of an OS event with letrozole over tamoxifen [6].

9.2.1.2 Switching Trials

In the intergroup exemestane study (IES) 4724 postmenopausal women with ER-positive or ER-unknown BC, who were disease-free on 2–3 years of tamoxifen, were randomly assigned to switch to exemestane or continue tamoxifen for the remainder of 5 years of treatment [8]. Patients' median age was 64 years. At a median follow-up of 55.7 months, patients who switched to exemestane demonstrated a DFS and TDR advantage. Adjustment for potential confounders related to baseline and treatment characteristics did not substantially affect the estimates of treatment effect (DFS adjusted 0.75 [0.65–0.86, $p = 0.0001$]). Final analysis after a median of 120 months follow up revealed a reduction in BC related events with an absolute difference between exemestane and tamoxifen of 4% (95% CI 1.2–6.7) favouring exemestane [33]. This difference persisted in multivariate analyses taking into account nodal status, prior endocrine therapy and prior chemotherapy.

Three clinical trials: the Arimidex-Nolvadex (ARNO 95), the Austrian Breast and Colorectal Cancer Study Group (ABCSG 8), and the Italian tamoxifen anastrozole (ITA) studies, randomised postmenopausal women to receive anastrozole after 2–3 years of tamoxifen or to continue to take tamoxifen up to 5 years of treatment. It should be noted that while the ITA and ARNO 95 are two classical switching trials, in ABCSG 8 patients were randomised from the outset with a pure sequencing strategy. A meta-analysis of these three clinical trials, amounting to a total of 4600 eligible patients, was published in 2006. Median patient age

was 63 years. After a median follow-up of 30 months, a significant reduction in the DFS hazard rate and in the risk of death was observed in patients treated with anastrozole [27]. The advantage in terms of OS in favour of incorporating an AI was confirmed in a separate analysis of the ARNO trial. Among 979 patients aged ≤75 years, at a median follow-up of 30.1 months, switching to anastrozole resulted in a statistically significant improvement in DFS, with a 34% reduction in the relative risk of disease recurrence or death (HR 0.66, $p = 0.049$) and in OS, with a 47% improvement (HR 0.53, $p = 0.45$), compared with patients who continued with tamoxifen [28]. After adjustment for potential prognostic factors including age, switching to adjuvant anastrozole still resulted in a statistically significant improvement in DFS and OS.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial randomised patients to receive either 5 years of exemestane monotherapy, or a sequential regimen of tamoxifen followed by exemestane for 5 years in total. This protocol was amended in 2004 after the publication of the IES trial, with all those assigned to tamoxifen being switched to exemestane after 2.5–3 years of initial tamoxifen therapy. After 5 years of median follow up, no difference was observed between the two groups in terms of DFS, OS or relapse-free survival [43]. Ten-year outcomes continued this trend overall, and planned analyses failed to identify any clinicopathological subgroup (including age) who benefited more from either treatment [12].

FATA-GIM3 assigned 3697 patients to one of six treatment strategies: anastrozole, exemestane or letrozole upfront for 5 years, or tamoxifen for 2 years, followed by a switch to one of the three aforementioned AIs for the subsequent 3 years [13]. Approximately 28% in each arm were aged 70 or more. After a median follow up of 60 months, 5 years of upfront therapy with an AI was not shown to be superior to the switch strategy, with a DFS of 89.8% (95% CI, 88.2–91.2) and 88.5% (95% CI, 86.7–90.0), respectively.

9.2.1.3 Data from EBCTCG

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has undertaken meta-analyses of randomised trials which evaluated the following strategies: (1) upfront tamoxifen versus upfront AI; (2) upfront tamoxifen versus tamoxifen followed with a switch to an AI; or (3) upfront AI versus tamoxifen followed with a switch to an AI. Reporting in 2009 [14] and again in 2015 [17], the group most recently demonstrated that when comparing 5 years of an AI against 5 years of tamoxifen, the recurrence rate ratios favoured AIs in the first 4 years of treatment, but not significantly thereafter. These rates differed little according to age, with a recurrence risk reduction rate ratio of 0.60 (CI 0.48–0.76) in patients aged 70 or more. Proportional overall recurrence rates were reduced by approximately 30% in this setting. The 10-year BC mortality rates were reduced by about 15% in favour of AI therapy. Ultimately, these analyses illustrate the overall advantage of AIs over tamoxifen, which underlines the importance of including an AI backbone in the adjuvant treatment regime at some stage (either upfront or sequentially) in postmenopausal women.

9.2.1.4 Which AI to Choose?

Three large trials have demonstrated that there are no observable differences between the AIs. MA.27 was the first trial to compare adjuvant steroidal and non-steroidal aromatase inhibitors in postmenopausal women [20]. This open-label phase 3 trial enrolled 7576 women (median age, 64 years; approximately 28% in each arm were aged 70 or above) to receive 5 years of either exemestane or anastrozole. After a median follow up of 4.1 years, neither were found to be superior in terms of BC outcomes by two-sided test. Planned multivariate analyses revealed no significant treatment-factor interactions, however, a worse event-free survival rate was observed in women aged 70 or older (HR 1.89; 95% CI, 1.35–2.66; $p < 0.001$).

The FACE study compared 5 years of letrozole versus anastrozole in a postmenopausal population with node-positive early disease [39]. Approximately 40% of enrolled patients were aged 65 or older, with a median age of 62 in each arm. Letrozole did not demonstrate superior efficacy over anastrozole in either PFS or OS. Similarly, FATA-GIM3 demonstrated no differences between the three AIs in terms of efficacy [13]. The five-year DFS was 90.0% (95% CI, 87.9–91.7) for anastrozole, 88.0% (95% CI, 85.8–89.9) for exemestane and 89.4% (95% CI, 87.3–91.1) for letrozole.

9.2.1.5 Extended Adjuvant Trials

A recent meta-analysis of 88 trials involving 62,923 women who were disease-free after receiving a total of 5 years of prescribed adjuvant ET has underlined the significance of late recurrence after cessation of treatment at the five-year mark [35]. Recurrences continued to occur throughout the study period from 5 to 20 years, correlating strongly with the original tumour and nodal stage and histological grade. In patients with T1, node negative disease, the risk of distant recurrence was 13%, rising to 20% in those with 1–3 involved nodes, and up to 34% in those with 4–9 nodes. The absolute risk of distant recurrence in those with T1 N0 low grade disease was 10%, 13% for moderate grade, and 17% for high grade status. Given this significant rate of recurrence, even in patients with small primary cancers and no nodal involvement, endocrine therapy extension beyond 5 years is of particular interest.

The NCIC CTG MA.17 study targeted women who had completed approximately 5 years of adjuvant tamoxifen [18]. A total of 5187 patients were randomised to receive (double-blind) either letrozole or placebo for 5 years. Patients median age was 62 years, with 25% aged ≥70 years. The study was interrupted and unblinded after the first interim analysis due to the clear advantage in terms of DFS with letrozole. At a median follow-up of 30 months, extended therapy with letrozole resulted in prolonged DFS and DDFS [19]. A subgroup analysis also showed an OS advantage among node-positive patients (HR 0.61; $p = 0.04$). After the unblinding, patients in the placebo arm were offered letrozole. An intention-to-treat analysis performed after a median follow up of 54 month demonstrated that patients originally randomised to receive letrozole outperformed patients originally randomised to placebo in terms of DFS (4y DFS HR = 0.64; $p = 0.00002$) and DDFS (4y DDFS HR = 0.76; $p = 0.041$), despite 73% of the patients on placebo crossed to letrozole after unblinding [24].

The National Surgical Adjuvant Breast and Bowel Project B-33 trial aimed to randomise 3000 patients who were disease-free after 5 years of tamoxifen to 5 years of exemestane or 5 years of placebo [31]. Due to the results of MA.17, the study was discontinued with 1598 randomised, at which point treatment assignment was unblinded, and exemestane was offered to patients in the placebo arm. Seventy-two percent of the patients in the exemestane group chose to continue exemestane while 44% of the patients on placebo switched to exemestane. With 30 months of median follow-up, original exemestane assignment resulted in a borderline statistically significant improvement in 4-year DFS, and a statistically significant improvement in 4-year RFS.

In the ABCSG-6a study, 456 women who had received, in the context of trial ABCSG6, either 5 years of tamoxifen or tamoxifen plus aminoglutethimide for a 2 -year period followed by 3 years of tamoxifen alone, were re-randomised to switch to anastrozole or no treatment for a further 3 years [26]. Patients' median age was 61.8 years. At a median follow-up of 60 months, significantly fewer patients in the AI group experienced disease recurrence compared with the no-treatment group.

The DATA trial assigned women to receive either 3 or 6 years of anastrozole after having previously received 2–3 years of tamoxifen therapy [42]. One thousand eight hundred sixty patients were enrolled, with a median age of 57 years for each arm. Just over 40% of patients were aged 60 or over. Overall, the 5-year DFS was 83.1% for the 6-year arm, and 79.4% in the 3-year arm (HR 0.79, 95% CI 0.62–1.02, p = 0.066). A subgroup analysis of patients aged 60 or more similarly revealed no benefit for extended therapy (HR 0.85, 95% CI 0.61–1.19, p = 0.63). IDEAL, another trial conducted by the same group, randomised patients to receive either 2.5 or 5 years of letrozole after an initial 5 years of any adjuvant endocrine therapy [2]. A total of 1824 women were enrolled, with a median follow up of 6.6 years. Just under a quarter were aged between 65–75 in each arm, with a small representation of patients over 75 (6.8% and 8.4% in the 2- and 5-year groups, respectively). Overall, no superiority was found for 5 years versus 2.5 years of extended therapy in terms of DFS, OS or distant recurrence free interval. In patients aged 65–75, PFS HR was 0.69 (95% CI 0.45–1.08), and 0.98 in patients aged more than 75 years (95% CI 0.53–1.81) (p = 0.82).

NSABP B42 randomised 3966 patients to receive either letrozole or placebo for 5 years, after having first completed 5 years of adjuvant endocrine therapy (either AI monotherapy, or tamoxifen followed by a switch to an AI) [32]. After a median follow up of 6.9 years, extended AI therapy resulted in a non-significant 15% reduction in the risk of a disease-free survival event, but did not improve OS. A statistically significant 29% reduction in the risk of BC recurrence or cancer in the contralateral breast was noted, as was a 28% reduction in the cumulative risk of disease recurrence.

Results from the ABCSG-16 trial suggest that truncation of the extension period of endocrine therapy may yield sufficient clinical benefits, whilst simultaneously avoiding associated side-effects [23]. Three thousand four hundred eighty-four women were randomised to receive either 2 or 5 years of extended adjuvant endocrine therapy (anastrozole 1 mg/day), after having completed 5 years of prior

tamoxifen or AIs. The median age was 64. After a median follow up of 105 months, 22% in each group had recorded DFS events. There was no significant difference between the two groups in terms of DFS, OS, time to secondary carcinoma or time to contralateral BC. There was, however, a greater rate of bone fractures in the five-year arm (6% versus 4%; HR, 1.405, 95% CI 1.03–1.91, p = 0.029).

One thousand nine hundred eighteen women were enrolled in MA.17R, which randomised patients to receive either placebo or letrozole for 5 years, following the completion of 4.5–6 years of initial adjuvant endocrine therapy which included an AI [22]. The majority of enrolled patients (79.3%) had received tamoxifen prior to an AI during the period of initial therapy. The median age was 65.1 years. At a median follow up of 6.3 years, the 5-year DFS rate was 95% with letrozole, versus 91% with placebo (HR 0.66; p = 0.01). However, the rate of overall survival was not higher in the letrozole arm (93% versus 94% respectively; HR 0.97; p = 0.83). It is important to note that the definition of DFS in this study did not included events of death. When all causes of death were included, there was only a 2% absolute benefit in terms of DFS (p = 0.06). In the context of elderly patients, this is of particular interest, as competing causes of death may reduce the benefit of a given treatment in an older population.

SOLE enrolled postmenopausal women with node positive early disease who had already received 4–6 years of adjuvant ET to receive either continuous or intermittent letrozole for a subsequent duration of 5 years [7]. Four thousand eight hundred fifty-one women comprised the intention-to-treat population, with a median age in both arms of 60. Intermittent dosing did not result in lower toxicity rates or improved efficacy (DFS of 85.8% for intermittent therapy, and 85.8% for continuous; HR, 1.08, 95% CI 0.93–1.26, p = 0.31). As such, continuous dosing of ET remains the standard approach.

Briefly, the above-discussed trials and metanalyses largely showed that AIs are superior to tamoxifen in reducing the risk of tumour relapse. The approach of either upfront AIs, or a switching regimen (whilst not superior to monotherapy), are both reasonable strategy choices, and can be made according to disease risk factors and patient co-morbidities, treatment tolerance and personal preference. Whilst extending the duration of ET beyond 5 years may be of benefit in preventing late recurrence, there is a paucity of evidence specifically derived from the elderly subpopulation. Furthermore, competing potential causes for mortality and morbidity and the added risk of cumulative side-effects and resultant compliance issues should be weighed up when considering an extended approach in the elderly.

9.3 From the "Postmenopausal" to the Elderly Population

Can the results from seminal trials observed in a general "postmenopausal" population be extrapolated to older women? Results from adjuvant trials that reported subgroup analyses of DFS in terms of age are presented in Table 9.2. Only for two studies detailed analyses have been conducted focused on the older population.

Table 9.2 Per age subgroup analysis for disease-free survival in adjuvant trials

Study	Follow-up	Age group	n	HR	95% CI	p
ATAC	100 months	<65	5137	0.76	0.63–0.91	NR
		65+	4229	0.77	0.63–0.93	NR
BIG 1–98	51 months	<65	3127	0.82	0.67–0.99	0.04
		65+	1795	0.82	0.67–1.01	0.06
IES	120 months	<60	1523	0.82	0.63–1.06	NR
		60–69	2021	0.70	0.56–0.87	NR
		70+	1180	0.81	0.63–1.04	NR
ABCSG8/ARN095	28 months	<60	1265	0.63	0.40–1.00	0.05
		60+	1959	0.58	0.39–0.87	0.007
MA.17	4-year outcome	<60	2152	0.46	0.30–0.70	0.0004
		60–69	1694	0.68	0.44–1.04	0.078
		70+	1323	0.67	0.41–1.11	0.12
ABCSG 6a	62.3 months	<60	147	0.60	0.21–1.72	0.336
		60+	705	0.63	0.39–1.03	0.064
NSABP B-33	4-year outcome	<60	777	0.53	NR	0.06
		60+	785	0.80	NR	0.43
TEAM	9.8 years	<50	211	1.02	0.57–1.83	NR
		50–59	1874	0.84	0.70–1.01	NR
		60–69	2373	0.95	0.81–1.11	NR
		70+	1662	1.04	0.90–1.20	NR
MA.27	4.1 years	≤59	5417	NR	NR	NR
		≥70	2159	1.89	1.35–2.66	<0.001
DATA	50 months	<60	971	0.75	0.52–1.10	NR
		≥60	689	0.85	0.61–1.19	NR

Modified from Biganzoli et al. [1], with permission
NR not reported

Crivellari et al. explored potential differences in efficacy in elderly women receiving adjuvant tamoxifen or letrozole in the BIG 1–98 trial [9]. The report included 4922 patients with a median follow-up of 40.4 months. Subpopulation treatment effect pattern plot (STEPP) analysis was used to examine the patterns of differences in DFS according to age. The authors found that letrozole was superior to tamoxifen across the age spectrum and was not significantly influenced by age (interaction of age and treatment, $p = 0.84$): leading to the assumption, as has already been shown for tamoxifen, that older patients derive the same benefit from AI as younger patients.

Regarding the extended adjuvant strategy, per age subgroup analysis data for DFS are summarised in Table 9.2. In particular, Muss and colleagues divided patients randomized in MA.17 in three age-groups: younger than 60 (<60), 61–69, and 70 years old and older (70+) [34]. There was no significant difference in DFS (4-year outcome = 92.4, 91.4, and 92.5% for women aged <60, 60–69, and 70+, respectively) and DDFS (4-year outcome = 96.0, 94.3, and 95.0% for women aged <60, 60–69, and 70+, respectively) between the three age groups. As expected, OS

was significantly different between the three age groups due to an increased risk of non-BC-related death with increasing age (4-year outcome = 97.4, 96.2, and 90.6% for women aged <60, 60–69, and 70+, respectively). The results were unchanged after adjusting for other potential prognostic factors such as letrozole or placebo treatment, duration of prior tamoxifen, nodal status, and prior chemotherapy. Significant letrozole-associated improvements in both DFS and DDFS was observed only in women younger than 60 years. However, the interaction between age and treatment was not statistically significant for neither DFS, DDFS or OS ($P = 0.36$, 0.77, and 0.98 for DFS, DDFS, and OS, respectively), indicating no evidence of a heterogeneous effect of letrozole among age groups. MA.17 showed an OS advantage for all node-positive patients. In this age-directed subset analysis, only node-positive patients aged 70+ had significant improvement in OS, which may be considered when recommending extended therapy in patients with high risk disease. Conversely, when considering extended therapy in a population with comparatively low-risk features, in the context of the findings of ABCSG-16, a shorter duration of extension may be considered in order to reduce the likelihood of associated side-effects.

9.4 Side Effects

Aging is associated with an increased incidence and prevalence of co-morbidities. The presence of co-morbidities often influences the choice between tamoxifen and AIs in an aged population, therefore an awareness of safety issues is of significant importance. The long-term safety profile of tamoxifen is well-known, with a greater association with endometrial cancer and thromboembolic events when compared to AIs. Conversely, AIs are classically associated with a higher risk of musculoskeletal disorders. Among these AI-specific side effects, osteopenia, osteoporosis, bone fracture, and cardiac events are particularly worrisome for older patients.

Therapy with AIs is generally associated with a significant increase in clinical fracture. Data from IES and BIG 1–98 suggest that there is no significant effect of age on the risk of fracture [5, 9]. The 10-year analysis of the entire ATAC population confirmed that although the incidence of fractures was greater in the anastrozole group during treatment (OR 1.33, 95% CI 1.15–1.55, p = 0.0001), following treatment completion, the incidence of fractures was similar between the two groups (OR 0.98, 95% CI 0.74–1.30, p = 0.9) [11]. Hip fractures were found to be similar in incidence between both groups throughout the study period, whereas spinal fractures were more prevalent in the anastrozole group (OR 1.49, 95% CI 1.01–2.22). A separate update on the bone mineral density (BMD) of patients from ATAC at 7 years demonstrated anastrozole-related bone loss did not persist beyond the cessation of study treatment [15]. The 10-year update of IES reported no significant difference in fracture incidence during the

post-treatment period between the exemestane and tamoxifen groups (9.3% and 8.0%, respectively; p = 0.14) [33].

On-treatment toxic bone effects were more frequent in patients receiving extended letrozole treatment compared to placebo in the MA17.R trial, an effect that did not persist beyond discontinuation of trial regimen [22]. The difference observed on treatment did not appear to be influenced by the intercurrent use of bone-protecting agents, which were utilised in similar percentages in both groups.

MA.27B, a sub-study of the MA.27 trial, recruited two groups of women: those with bone mineral density t-scores of −2.0 or more, and those with t-scores less than −2.0 [21]. Both groups received orally supplemented calcium and vitamin D, and those with t-scores of less than −2.0 also received bisphosphonate therapy. The primary endpoints were the changes in BMD in lumbar spine and hip at 2 years. In the group of women with baseline t-scores of less than −2.0, the mean change in lumbar and hip BMD after 2 years did not differ significantly between those who received exemestane, compared to those who received anastrozole, leading the authors to conclude that aromatase inhibitors may be considered in patients with t-scores less than −2.0.

The 2015 EBCTCG meta-analysis of trials comparing aromatase inhibitors to tamoxifen in early breast cancer revealed the incidence of bone fractures was increased in patients allocated to AI regimens; an effect that was observed beyond 5 years. The 5-year fracture risk for the AI group was 8.2%, versus 5.5% in the tamoxifen group (absolute excess 2.7%, 95% CI 1.7–3.7) [17].

Cardiovascular events

A higher incidence of cardiovascular events (CV) with AIs has been reported in some adjuvant trials. In the ATAC trial, apart from a statistically non-significant difference in angina, the occurrence of other ischemic CV events was similar between tamoxifen and anastrozole [40]. At 10-year follow up, 2.9% of the anastrozole group, and 3.0% of the tamoxifen group had died of cardiovascular causes. Similarly, 1.1% and 1.2% died from cerebrovascular disease, respectively [11].

Although the overall incidence of cardiac adverse events did not differ significantly between the two treatments in BIG 1–98, a trend towards higher grade (3–5) cardiac events on letrozole compared with tamoxifen was seen [4], most notably, double the incidence of cardiac deaths was reported with letrozole versus tamoxifen. Looking at the overall incidence of cardiac events, Crivellari et al. found that after adjusting for risk factors, a significant difference favouring tamoxifen was observed in the older age cohort (65–74 years), but not in the elderly cohort (≥75 years) [9]. Regarding ischemic heart events, after adjusting for risk factors, a significant difference in time to first grade 3–5 ischemic heart event favouring tamoxifen was observed in the older age cohort (65–74 years), but not in the younger (<65 years), or elderly (≥75 years) cohorts. On the basis of Cox model analysis, history of hypertension represented a statistically significant risk factor for both cardiac and ischemic heart events. Perhaps unsurprisingly, prior cardiac and

ischemic heart events were risk factors for future on-treatment cardiac and ischemic heart events, respectively.

In the IES trial, there was a trend towards a higher incidence in myocardial infarctions (MI) on exemestane, however, the effects of treatment on the risk of MI seemed largely restricted to patients with a history of hypertension. Seventy-one percent of patients on exemestane who experienced MI had hypertension at baseline, compared with 32% of the corresponding patients on tamoxifen [8].

Of particular interest are the data from MA.17, in which AI was compared with placebo. No difference in terms of CV events was reported in this trial, suggesting that the cardioprotective effect of tamoxifen may be the principal factor accounting for the difference in cardiac toxicity observed in all those adjuvant trial that compare an AI to tamoxifen. Indeed, this hypothesis appears to be validated by a recent meta-analysis of 19 randomised controlled trials (n = 62,345) concerning cardiotoxicity of AIs and tamoxifen in post-menopausal women with breast cancer [30]. Risk of cardiovascular events were increased by 19% in the setting of adjuvant AI therapy, compared to tamoxifen (relative risk, 1.19, 95% CI, 1.07–1.34). Compared to placebo in the extended adjuvant setting, AIs did not confer an analogous increased risk. Conversely, tamoxifen decreased risk by 33% when compared to placebo or no-treatment (relative risk, 0.67, 95% CI, 0.45–0.98), leading the authors to conclude that this cardioprotective effect completely accounts for the increase in risk observed in trials that compare tamoxifen to AIs.

9.5 Compliance

Adverse effects on quality of life caused by ET can lead to non-compliance and therefore a reduction in potential treatment efficacy. As such, due diligence by clinicians with regards to early detection and effective supportive treatment of treatment-associated toxicities is of paramount importance. Poor compliance and early cessation of letrozole (largely due to side effects) were both found in the BIG 1–98 trial to be associated with reduced DFS [3]. Reduced adherence was greater in patients older than 70 (HR, 1.478, 95% CI, 1.196–1.826, $p < 0.001$). One institutional retrospective analysis of ET-related side-effects reported by breast cancer patients aged over 65 years revealed 22.7% experienced hot flushes, and 16.2% had arthralgia [25]. Just over 20% discontinued treatment prematurely due to side effects, and of those, 38.6% cited arthralgia as the main cause (OR = 5.37, 95% CI, 2.33–12.39, $p = 0.0001$).

9.6 Treatment Options for Elderly Patients

A fundamental issue is whether ET is necessary in all elderly patients with hormone-receptor-positive early BC. 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 both ipsi- and

contralateral BC relapse, the patient's life expectancy, and treatment-related adverse events. Older patients who have small (<1 cm) node-negative tumours, or who have serious co-morbidity with an estimated survival less than 10 years are unlikely to derive any survival benefit from tamoxifen or other endocrine treatments. No adjuvant treatment could be considered a viable option in these patients.

In elderly patients considered appropriate for adjuvant ET, it is appropriate to follow the same approach as for younger post-menopausal patients. In the absence of any absolute contraindications, an AI should be considered as a part of the five-year treatment strategy, whether upfront or as a part of a switching regimen, especially so in those patients whose disease had characteristics consistent with a high risk of relapse. A patient-profile-based approach should be considered to maximise the therapeutic index of the treatment. From the safety point of view, when ET is considered for a new patient, all risk factors for cardiovascular disease and osteoporosis should be evaluated. As such, in the setting of co-morbidities such as osteoporosis with pre-existing bone fractures or a significant cardiac history, a switching strategy may be preferred.

Data supporting extended adjuvant treatment with an AI bases its rationale on evidence of a relatively constant risk of tumour relapse for ER-positive tumours over time. Individualised estimates of the risk of relapse and death after 5 years of tamoxifen based on standard pathologic prognostic markers suggest that extended adjuvant treatment could be avoided in women at low-risk of relapse [29]. A subgroup analysis of the MA.17 trial showed that this "prolonged" approach is effective in healthy 70+ women with high-risk breast cancer [34]. In patients who receive 5 years of initial upfront AI therapy, it must be noted that extended therapy has been shown in trials to bestow arguably marginal benefits in DFS, with a paucity of data with regards to OS advantage. The overall issue of extended therapy may be less relevant in the elderly population, as many will succumb to co-morbid conditions or advanced age before any survival benefit attributable to extended therapy is reached. Relapsed or metastatic disease may be salvaged by the same ET agents as are used in the adjuvant setting. As such, the decision as to whether to extend initial ET in the adjuvant setting in order to obtain a prolonged DFS, or to offer a more conventional 5-year approach, reserving the hypothetical option of salvaging relapsed disease with ET at a later date, should be balanced according to patient preference, tolerance of treatment, and competing co-morbid conditions.

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Adjuvant Systemic Therapy

10

Nicolò Matteo Luca Battisti and Alistair Ring

Abstract

Breast cancer is prevalent in older women. In this population, a different disease biology, competing comorbidities, a shorter life expectancy and concerns about patient fitness make decision-making for early-stage breast cancer particularly challenging in the context of a lack of age-specific evidence. As a result, older breast cancer patients are offered adjuvant systemic therapy less frequently.

However, the use of adjuvant chemotherapy is supported by retrospective evidence showing an overall reduction in mortality compared to patients who are not offered any treatment and similar benefits derived from more aggressive forms of chemotherapy compared to their younger counterparts, despite a worse overall survival owing to comorbidities. Prospective data are lacking but suggest improved outcomes for high risk older patients in the absence of survival benefit. Nonetheless, more gentle forms of chemotherapy did not appear beneficial and the preferred therapeutic regimen for older women is still uncertain.

Older patients derive from Trastuzumab the same benefit as younger women. Nevertheless, data are again limited since only a small proportion of older women were enrolled in the pivotal trials testing Trastuzumab. Retrospective studies confirmed that Trastuzumab is safe and well tolerated and prospective studies demonstrated that anthracycline-free regimens are an appealing option for older HER2-positive breast cancer patients.

Acute and long-term chemotherapy-related toxicities are more frequent in older breast cancer patients, who are generally subject to increased mortality and haematological adverse events. Cardiac toxicity is also a frequent concern when anthracyclines are used, while neurotoxicity is associated with the use of taxanes. The potential impact on cognitive status and function and an increased risk

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of acute myeloid leukaemia have also been described. Despite Trastuzumab is safe in this population, careful monitoring should also be considered for older patients on anti-HER2 treatment, especially regarding the increased risk of cardiotoxicity.

The prevalence of low-risk disease biological features, the incidence of frailty and functional limitations and the impact of comorbidities on life expectancy should always guide therapeutic decisions, which may also benefit from the use of risk and chemotherapy toxicity prediction tools and of molecular profiling. The use of screening tools and a comprehensive geriatric assessment may also detect problems that are usually underestimated by routine evaluation.

Keywords
Breast cancer · Older · Adjuvant systemic therapy

10.1 Introduction

Age is a risk factor for breast cancer. In the United Kingdom, between 2013 and 2015, 25% of new diagnoses of breast cancer were made in people aged 75 and older with age-specific incidence rates rising steadily with age [1]. Furthermore nearly half of all breast cancer-related deaths occur in women aged 75 and older.

When making treatment plans with older patients with breast cancer it is vital to take into account differences in disease biology, competing comorbidities, life expectancy, general health and functional status. This is particularly the case when considering adjuvant systemic therapy, where the benefits of treatment may be relatively modest and the inconvenience and toxicity of treatment may be substantial [2]. Unfortunately clinical decision-making is further complicated by a limited evidence base in older patients. This is because older patients have historically been underrepresented in clinical trials [3], and whilst there have been some recent trends suggesting an improvement [4], there remain limited robust data on which to make age-specific treatment recommendations. What we do know from observational studies is that adjuvant chemotherapy use is relatively uncommon in older patients with early breast cancer. The AcheW study examined the treatment of 803 women aged 70 or over with early breast cancer and demonstrated that only 8% of the whole population received adjuvant or neoadjuvant chemotherapy [5]. Even when analysing those 309 patients with high risk disease, only 30% were offered chemotherapy and 17% went on to receive it. The most common reasons for not offering chemotherapy to older women included the fact that other treatments were deemed more appropriate and that the related benefit was deemed minor, along with increasing comorbidities and frailty. In a more recent prospective study, nearly half of women aged 70 and older deemed fit by Comprehensive Geriatric Assessment (CGA) and with high-risk disease did not receive adjuvant chemotherapy, suggesting potential under-treatment [6].

This chapter describes the evidence supporting the use of adjuvant systemic therapy (chemotherapy and anti-HER2 therapy) in older women with breast cancer. This evidence should be viewed in the light of the low rates of treatment in older patients described above, and provides an opportunity to examine whether more proactive treatment might enable improved outcomes in this patient population.

10.2 Rationale for the Use of Adjuvant Systemic Therapy

10.2.1 Chemotherapy

Retrospective and prospective data support the use of adjuvant chemotherapy in older breast cancer patients. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated a survival advantage from polychemotherapy for patients up to the age of 69 years. For patients aged 70 or older, the proportional reductions in risk of recurrence were similar to those seen in younger postmenopausal women, but (in contrast to the younger age group) were no longer statistically significant [5]. However, only 4.1% of over 150,000 patients included (in the trials examined) were aged 70 and older and this underpowered the analysis. A retrospective series of 5081 patients aged over 65 from the Surveillance, Epidemiology and End Results (SEER) database with hormone receptor-negative early stage breast cancer confirmed a 15% reduction in mortality for women treated with adjuvant chemotherapy, [7] despite the fact that patients aged 70 and older were less likely to receive chemotherapy. Similarly, a SEER database analysis of 41,390 stage I–III patients over 65 confirmed reduced rates of chemotherapy treatment in women aged 75 and older but a survival benefit in patients with oestrogen-receptor (ER)-negative node-positive breast cancer when chemotherapy was given [3]. The study failed to identify any benefit in ER-positive and in ER-negative, node-negative patients.

These retrospective analyses focus on trials or clinical practice comparing patients who do or do not receive chemotherapy. However, in subset analyses of studies where different adjuvant chemotherapy regimens are compared it is also possible to see the same incremental benefits from treatment in older and younger patients, lending support to the notion that adjuvant chemotherapy can be effective in older patients. A combined report of the Cancer and Leukemia Group B (CALGB) 7581, 8082, 8541 and 9344 trials in 6487 node-positive patients (8% aged 65 and older) documented that both younger and older patients derived benefit from more aggressive forms of chemotherapy and similar benefits in recurrence risk and mortality compared to standard treatment at the time [4]. However, *overall* survival was worse in patients aged over 65 due to deaths from other causes. Similarly a US Oncology Trial 9735 showed that non-anthracycline containing chemotherapy regimens like docetaxel and cyclophosphamide (TC) provide similar improved efficacy to doxorubicin and cyclophosphamide (AC) in older as well as younger patients [8]. These findings are of particular interest for older patients who may have pre-existing cardiovascular problems, and therefore where anthracyclines should be avoided.

In contrast to the retrospective data and subset analyses described above, prospective data specifically addressing the benefits of adjuvant chemotherapy in older breast cancer patients are limited. The French Adjuvant Study Group 08 trial (FASG 08) enrolled 388 patients aged over 65 in a study comparing Tamoxifen and Epirubicin-based chemotherapy with endocrine therapy alone. The study demonstrated a reduction in the risk of relapse for node-positive patients, which was more pronounced in patients with ER negative disease but there was no overall survival benefit [9].

The ICE (Ibandronate with or without Capecitabine in Elderly Patients) study, examined whether oral capecitabine chemotherapy could reduce the risks of relapse in older women with early breast cancer. A comparison was made between ibandronate (with endocrine therapy where indicated) and the same treatments with capecitabine chemotherapy. This study randomised 1358 patients and there were no differences in disease-free or overall survival [10] FASG08 and ICE are the only two studies which have prospectively directly addressed the absolute benefits of adjuvant chemotherapy in older women with early breast cancer by comparing chemotherapy with no chemotherapy arms. Other studies have attempted to address the same question but have but closed early due to poor recruitment [11].

In parallel a number of prospective clinical trials have taken as a premise that adjuvant chemotherapy is of benefit in older women with high-risk breast cancer and have compared different chemotherapy regimens [9]. The CALGB 49907 study enrolled women aged 65 or older with invasive T1-T4 breast cancer of any nodal and hormone receptor status. Women were randomised to receive standard chemotherapy (6 cycles of cyclophosphamide, methotrexate, and fluorouracil [CMF] or 4 cycles of doxorubicin/cyclophosphamide [AC], according to physician choice) or 6 cycles of oral capecitabine [12]. Accrual stopped at 633 patients, at which point 61% of patients were aged 70 years or over. After a median follow up of 2 years, patients randomised to capecitabine were 2.4 times more likely to experience a relapse-free survival event (95% CI, 1.5–3.8; adjusted $p = 0.0003$) and 2.1 times more likely to die (95% CI, 1.2–3.7; $p = 0.02$) than those receiving standard chemotherapy. This trial, therefore failed to demonstrate a benefit from adjuvant capecitabine compared with standard adjuvant chemotherapy in older women. Recently, the ELDA study failed to detect any differences in disease-free survival and risk of death in 302 patients aged 65–79 randomized to CMF or weekly Docetaxel [13]; moreover, quality of life was worse in the taxane arm. It is unknown whether how either of these arms would compare with an anthracycline containing treatment (such as AC, used in 56% of those in the control arm of CALGB 49907). Non-pegylated liposomal doxorubicin along with cyclophosphamide and followed by weekly Paclitaxel has also been tested in a small cohort of high-risk patients aged 65 and older with low rates of cardiac complications. However, in the absence of a control or reference arm it is difficult to draw conclusions as to the efficacy of this regimen, compared with the other regimens tested in this population [14].

Overall it would seem reasonable to conclude from the retrospective and (limited) prospective data that there is a benefit to adjuvant chemotherapy in older

women with higher risk (node-positive and ER-negative) breast cancer. However, there is no definite preferred regimen based on efficacy data alone.

10.2.2 Anti-HER2 Therapy

Limited data are available on the role of adjuvant Trastuzumab in the older population. Only 16.2% of patients were aged 60 years and older in the HERA trial that defined the standard of care of 1 year of postoperative Trastuzumab for early-stage, HER2-positive breast cancer [15]. Nonetheless, a 47% relative risk reduction has been observed in older patients receiving chemotherapy and Trastuzumab compared to those treated with chemotherapy alone in a large meta-analysis [16]. Therefore, all patients (regardless of age) with HER2-positive breast cancer should be considered for Trastuzumab in combination with chemotherapy in the absence of cardiac (or chemotherapy-related) contraindications [17, 18].

A retrospective series of 2028 patients demonstrated that most older individuals (81.7%) are able to complete a one-year course of adjuvant Trastuzumab, although increasing age and comorbidities were associated with earlier discontinuation rates [19]. Older patients with low risk disease also derive benefit with excellent disease control and low rates of cardiac events, as shown in a recent retrospective series of patients with small (less than 2 cm), node-negative tumours [20]. Nonetheless, a shorter duration may also be an option in older individuals in order to reduce cardiac risks. The PHARE trial failed to document non-inferiority of 6 versus 12 months of Trastuzumab at 3.5 years of follow-up, although more cardiac events were seen in the standard-of-care arm [21]. The SOLD study also failed to show non-inferiority of 9 weeks of Trastuzumab compared to the current standard [22]; however, the absolute differences in disease-free and overall survival were small and more detailed age subgroup analyses are certainly needed.

The use of an anthracycline-free regimen may be an important option in elderly individuals with low- and intermediate-risk of relapse or with comorbidities potentially increasing the chances of cardiotoxicity. An open-label phase II study demonstrated that patients up to the age of 75 on a combination of TC and Trastuzumab obtained excellent disease-free and overall survival rates at 2 years (respectively, 97.8% and 99.2%) and a 6% rate of cardiac dysfunction which was usually reversible [23]. Docetaxel plus Carboplatin and Trastuzumab (TCH) is also able to provide similar outcomes compared to anthracycline-taxane regimens with less cardiac toxicity; however, it has been tested only in patients aged less than 70 years [24, 25]. Weekly paclitaxel and Trastuzumab is a well-tolerated regimen. This has been studied in a single-arm phase II trial with an encouragingly high disease-free survival rate of 98.7% at 3 years in node-negative disease, although only 10% of patients were aged 70 years or more [26]. At 7 years, disease-free survival has recently been confirmed as 93.3% with a breast cancer-specific survival of 98.6% and an overall survival of 95.0% [27]. This regimen is generally well-tolerated and makes an attractive option for older patients with HER2 positive breast cancer.

Currently, no clinical trial data are available to support treatment with Trastuzumab alone (without chemotherapy) in the adjuvant setting. However, when chemotherapy is not appropriate Trastuzumab monotherapy may be reasonable, especially if given alongside endocrine therapy in case of hormone receptor-positive disease. This use of Trastuzumab is outside of the EU Marketing authorisation, however in observational studies Trastuzumab alone is associated with a relapse-free survival rate of 84% at 3 years and 80% at 5 years and an overall survival rate of 93% and 87%, respectively [28].

Evidence regarding Pertuzumab in older patients is even more limited in the setting of early-stage breast cancer. Patients up to the age of 80 have been treated in the pivotal studies that defined Pertuzumab as standard of care in the neoadjuvant setting, but the age-specific details have not been reported [29]. In the adjuvant setting, 13.1% of patients treated with Pertuzumab in the APHINITY study were aged 65 and older but again age subgroups analyses are not available [30].

Overall, older patients appear to derive similar benefits from adjuvant Trastuzumab as younger patients, and this treatment should be considered in older patients with HER2 positive breast cancer where there are no cardiac (or chemotherapy) contraindications.

10.3 Toxicities of Adjuvant Systemic Therapy in Elderly Breast Cancer Patients

10.3.1 Chemotherapy

Older patients have increased risk of adjuvant chemotherapy-related toxicities. Individuals over the age of 65 were found to experience higher mortality rates compared to their younger counterparts whilst receiving CMF in a meta-analysis of the International Breast Cancer Study Group (IBCSG) trials (1.28% above the age of 65 versus 0.26% in age 51–64 and 0.08% below the age of 50) [31]. Likewise, a meta-analysis of 3 CALGB studies showed increased risk of toxic death associated with adjuvant chemotherapy across three age groups (1.5%, 0.4% and 0.19% for patients aged over 65, 51–64 and less than 50, respectively) [32].

The increase in treatment-related mortality observed in older patients is likely to reflect in part an increased rate of haematological toxicity. Age is associated with reduced bone marrow reserve and increased risk of haematological toxicity whilst undergoing chemotherapy. The incidence of chemotherapy-induced neutropenia increases with age in early-stage breast cancer patients treated with anthracyclines in the absence of any pharmacokinetic differences [33]. Therefore, age is considered as a risk factor for the development of febrile neutropenia and early consideration of granulocyte colony stimulating factors (G-CSF) is warranted in this population [34, 35]. In the CALGB analysis described above, older patients had a higher incidence of grade 4 hematologic toxicities, treatment discontinuation and mortality from acute myeloid leukaemia or myelodysplastic syndromes [32]. In the IBCSG VII study, patients aged above 65 experienced higher rates of hematologic

toxicity and mucositis on CMF and were less likely to receive the initially planned dose intensity, [36]. Leukopenia, neutropenia, nausea, cardiac toxicity and thrombophlebitis were more frequent and severe on CMF in patients over 65 also in another institutional series [37]. More recently, the sequential combination of anthracyclines and taxanes has been found to increase the risk of hematologic and non-hematologic toxicities with increasing age but nonetheless could still be feasible in older patients in a pooled analysis of four trials [38].

Cardiac toxicity is well documented on anthracycline-based chemotherapy [39]. In a SEER-Medicare database study on 43,338 women aged 66–80 treated with stage I–III breast cancer and no history of heart problems, the congestive heart failure rates at 5 and 10 years were found to be 19% and 38% respectively on anthracyclines, 18% and 33% respectively without an anthracyclines and 15% and 29% respectively without chemotherapy [40]. Aside from age, black ethnicity, hypertension, diabetes and coronary artery disease are also all associated with increased cardiac risk, which may only become apparent 10 years following treatment. Therefore, careful consideration should be made before offering older patients anthracycline-based chemotherapy. This should include: a thorough cardiac assessment, consideration of whether there are anthracycline regimens with lower cardiac toxicity [41, 42] or whether a taxane only regimens might be appropriate.

The use of taxanes is associated with a predominantly sensory neuropathy. Paclitaxel appears to be more neurotoxic than Docetaxel, with an overall incidence of neuropathy of 60% versus 15% respectively [43]. In an analysis of Southwest Oncology Group (SWOG) studies in participants aged 65 or older, age and history of diabetes were independent predictors of the development of peripheral neuropathy, which was more frequent with Paclitaxel rather than with Docetaxel [44]. Older age was also a risk factor for long-term peripheral neuropathy in the NRG Oncology/NSABP B-30 study [45]. Other potential risk factors are concomitant use of a platinum, obesity and lower activity level. When combined with other age-related phenomena (such as loss of muscle mass and deteriorating visual acuity) neuropathy can be a significant concern both in terms of quality of life and risk of falls.

Cognitive impairment is another area of concern for cancer patients [46]. Age is a risk factor for cognitive decline and older adults are more prone to cognitive adverse effects of cancer and its treatment [47]. However, 11–41% of elderly patients have cognitive issues before receiving adjuvant treatment for breast cancer [48, 49]. A prospective study in 123 older patients receiving adjuvant chemotherapy for breast cancer demonstrated an objective cognitive decline in 49% of them, affecting especially the working memory [50]. This may be a significant concern in older patients contemplating chemotherapy. However a key, unanswered question, is to what extent this improves over time?

The functional impact of chemotherapy was found to be mild to moderate in older patients treated with chemotherapy when measured by questionnaires such as Lawton's Instrumental Activities of Daily Living (IADL) [51]. One component of this, muscle weakness, is as frequent as other haematologic and non-haematologic side effects and independent of fatigue [52]. Chemotherapy was also associated with an increased risk of functional adverse events in various age groups in a

retrospective cohort of 44,626 patients from the SEER-Medicare database, especially over the first 3 months after completion of chemotherapy and persisting though follow-up [53]. Nevertheless, elderly breast cancer survivors who received chemotherapy have demonstrated similar long-term physical performance compared to those not treated with cytotoxics despite reporting slightly lower physical function [54]. This may reflect selection bias, in that those selected to receive chemotherapy had better baseline performance. Nonetheless, those who received chemotherapy do at least maintain physical performance to a similar extent to survivors treated with endocrine therapy.

Cytotoxics also increase the risk of developing secondary acute myeloid leukaemia (AML) in older adults. In an observational analysis from the SEER-Medicare dataset, 10,130 patients treated with chemotherapy and aged 66 and older had an increased risk of AML (HR 1.53, 95% CI 1.14–2.06) compared to those not treated with chemotherapy [55]. More recently, an analysis of patients enrolled in four adjuvant Alliance for Clinical Trials in Oncology trials documented rates of AML or myelodysplastic syndrome (MDS) of 0.8 and 1.0% in patients aged over 65 and over 70 compared to 0.4% below the age of 65. There was an increased risk for patients older than 65 (HR 3.13, 95% CI 1.18–8.33) and receiving anthracyclines (HR 5.16, 95% CI 1.47–18.19) [56].

There are therefore both short and long-term adverse effects of chemotherapy for older women contemplating adjuvant chemotherapy. These factors need to be discussed in an informed discussion with the patient regarding her benefits and risks of treatment.

10.3.2 Anti-HER2 Therapy

Anti-HER2 therapy is associated with a five-fold higher risk for congestive heart failure (CHF) and a two-fold higher risk of decline in left ventricular ejection fraction (LVEF) [57, 58]. Nonetheless, the overall incidence of cardiac toxicity is low (1–4%) in prospective studies in the overall population and it is reversible with appropriate medical treatment, especially if detected early [25, 59–62].

A combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 studies in 3351 patients demonstrated an absolute increase of serious cardiac adverse events of 3.3% and 2.9% respectively in the two trials [63, 64]; however, only 16% of patients were aged 60 and older. In the NSABP B-31 study, older age and a LVEF measured at 50–54% were significant predictors of cardiac heart failure [65]. Likewise, in the NCCTG N9831 patients above 50, with a LVEF lower than 55% and on antihypertensives were found to have a higher risk of cardiac complications [66]. A large SEER-Medicare retrospective analysis was conducted in 9535 patients aged 66 and older who were treated with chemotherapy for stage I-III breast cancer, with 23.1% also receiving Trastuzumab. This analysis identified higher rates of congestive heart failure compared to those reported in clinical trials (29.4% with Trastuzumab versus 18.9% without Trastuzumab). Cardiac comorbidities

(including coronary artery disease and hypertension) and older age were identified as risk factors [67]. Furthermore, a small retrospective series of patients aged 70 and older suggests that a previous history of cardiac events and diabetes correlates with an increased incidence of cardiotoxicity on Trastuzumab [68]. Despite this, most older patients are able to complete 1 year of adjuvant Trastuzumab. In a SEER-Medicare retrospective series of 2028 women aged 66 and older, 81.7% were able to complete 1 year of Trastuzumab, with lower odds of treatment completion for older patients and those with comorbidities. There was however 3.6% rate of hospitalization for cardiac events [19]. Adequate cardiac monitoring is therefore key in this population, although it was found to be suboptimal in 64.0% of 2203 women from a recent retrospective study and physician characteristics played a crucial role in limiting its adequacy [69]. Moreover, a recent analysis of 1077 patients above 65 from the SEER-Medicare database demonstrated similar rates of adverse events and hospitalizations and 5-year breast cancer-specific and overall survival in women treated with doxorubicin, cyclophosphamide, paclitaxel, and Trastuzumab (ACTH) versus docetaxel, carboplatin, and Trastuzumab (TCH), although the former group was less likely to complete Trastuzumab [70]. It is therefore clearly possible to treat older patients safely with contemporary Trastuzumab-containing treatment regimens, although close attention should be paid to cardiac monitoring protocols.

10.4 Factors Affecting Treatment Decisions in Older Patients

As discussed, above, older women with early stage breast cancer derive similar benefits from adjuvant chemotherapy as their younger counterparts, although potentially with greater toxicity [4]. Therefore if an older woman presents with high risk breast cancer, then, just as for younger women, adjuvant chemotherapy should be considered.

However breast cancer often presents with more indolent features in older age [71] and these include increased expression of hormone receptors [72], lower rates of human epidermal growth factor receptor 2 (HER2) overexpression [73] and increased frequency of other low-risk pathological features [74]. Therefore, many older patients, may not fall within a high risk profile (based on histopathological features), and chemotherapy may not be indicated, irrespective of age. Where the risk profile is suggestive of a high risk of recurrence, this has to be viewed in the context of a patient's age. This is because advanced age correlates more frequently with reduced functional reserve and resistance to stressors and with a higher prevalence of comorbid medical conditions, social issues, cognitive impairment and frailty, [75]. As a result of these factors, breast cancer is often not the cause of death in older women with early breast cancer and recommendations should always be formulated within the context of predicted life expectancy. Online tools may help estimating life expectancy although their use has not been validated in cancer patients [76]. Interestingly, breast cancer increases the risk of death in stage II older patients but not in stage I patients, where cardiovascular disease remains the most common cause of mortality [77].

Life expectancy is almost halved by the presence of concurrent health conditions in breast cancer patients [78] and comorbidities are an independent predictor of decreased life expectancy and survival [79]. Conditions affecting the functional status increase overall and breast cancer-related mortality especially if they are chronic and expected to deteriorate (e.g., dementia, chronic obstructive pulmonary disease and diabetes mellitus with end-organ damage) [80]. Therefore, comorbidities should always be evaluated at baseline for older breast cancer patients that may impact on their tolerance to chemotherapy and useful tools include the Charlson Comorbidity Index Score [81], the Cumulative Index Rating Scale-Geriatric (CIRS-G) [82] and the physical health section of the Older American Resources and Services (OARS) [83].

Functional status limitations are also independently associated with decreased life expectancy in breast cancer patients and increased risk of death from all causes and competing causes [84]. Frailty involves decreased reserve and resistance to stress impacting several physiologic systems and increasing susceptibility to adverse outcomes [85]. A standard definition includes weight loss, slow walking speed and decreased physical activity, which increases the likelihood of hospitalizations and decreases overall survival of older breast cancer patients [86].

A number of tools are available to support decision-making. Adjuvant! Online estimates cancer recurrence and survival based on individual and disease-specific characteristics, including comorbidities [87]. However, it was found to overestimate 10-year recurrence risk when comorbidity was set as "average for age" across a group of older breast cancer patients, while this was accurately predicted (along with an underestimation of overall survival) when the level was assigned by an expert panel in a Dutch study [88]. Adjuvant! Online should be used with caution since it was derived by cohorts not including a large proportion of older patients. On the other hand, NHS PREDICT [89] included 32% of patients aged 65 and older in its development: it incorporates mode of detection, HER2 status, and Ki67 and provides overall survival estimates at 5 and 10 years [90]. This model was found to accurately predict 5 year overall survival and to significantly overestimate it at 10 years [91]. The main limitations of this model are the lack of input of information regarding comorbidities and the absence of breast cancer-specific mortality and recurrence.

A two-step approach involving a screening tool for geriatric problems followed by a CGA based on screening results is helpful to develop a coordinated plan regarding adjuvant systemic therapy for older breast cancer patients. A variety of screening tools can identify either fit or frail patients in whom treatment decisions can be readily made, whilst vulnerable patients require a CGA which may identify potentially correctable problems where interventions are available [92]. As discussed in Chap. 4, CGA has been utilized in the assessment of elderly cancer patients [93] and found to influence treatment decisions [94, 95].

The identification and validation of gene-expression profiles has recently been a major improvement in the management of early stage breast cancer and their use is supported by the American Society of Clinical Oncology [96]. The Oncotype Dx 21-gene recurrence score (RS) is the best-validated prognostic

assay and may identify patients, including older individuals, who are most and least likely to derive benefit from adjuvant chemotherapy [97, 98]; its use is currently indicated for women with node-negative, ER-positive, HER2-negative disease, and increasing evidence supports its use also in node-positive patients [99, 100]. Interestingly, high breast cancer-specific mortality has been documented in patients aged 70 and older with either no 21-gene assay done or a RS of 18 and higher but not with a RS lower than 18 in a large population-based observational study of 184,190 individuals [101].

It is therefore vital that older women with early breast cancer undergo a thorough assessment of both their risk of recurrence (including molecular profiling) and risk of death from competing causes in order to optimise decisions regarding adjuvant therapies.

10.5 Toxicity Prediction

Several scales have been demonstrated to predict chemotherapy-related adverse events and guide treatment planning [102, 103]. Moreover, models based on geriatric variables have been prospectively developed to predict chemotherapy toxicity.

The Chemotherapy Risk Assessment Scale for High age (CRASH) score was developed and validated at the Moffitt Cancer Center to predict the risk of chemotherapy-related haematological and non-haematological toxicities in older individuals [104]. This score integrates both patient and chemotherapy risk. Patient risk is based on clinical and laboratory data and information derived from the CGA. Chemotherapy risk is a mathematical score (called Chemotox) derived from the average of the two highest-frequency grade 4 hematologic and grade 3 and more non-hematologic toxicities using data from published clinical trials.

Haematological toxicity was found to correlate with the IADL score, lactate dehydrogenase level, diastolic blood pressure and the Chemotox score. Non-haematological toxicity was predicted by ECOG Performance Status, Mini–Mental State Examination, Mini Nutritional Assessment and the Chemotox (Table 10.1).

Another model has been developed by the Cancer and Aging Research Group (CARG) at the City of Hope to identify patients at increased risk of severe or fatal toxicity from chemotherapy [105]. It was developed in an observational study included 500 older patients with cancer (not limited to breast cancer). The model includes age above 71, a primary cancer involving the gastrointestinal or genitourinary tract, the administration of full-dose chemotherapy without dose reduction, the use of multi-agent chemotherapy regimens, anaemia, a low creatinine clearance (less than 34 mL/min), fair or worse hearing (self-reported), more than one fall in the previous 6 months, inability to independently take medications (or requiring some help), limited ambulatory ability and decreased social activity due to physical or emotional limitations. Each factor is assigned one to three risk points. The model has been validated in an independent cohort and shown to correlate with a 30% incidence of grade 3–5 toxicities in the low risk group, 52% in the intermediate risk group and 83% in the high risk group [106].

Table 10.1 The chemotherapy risk assessment scale for high-age patients (CRASH) score [104]

		Points		
Predictors		0	1	2
Hematologic score	Diastolic blood pressure	≤72	>72	
	IADL	26–29	10–25	
	LDH	0–459		>459
	Chemotox	0–0.44	0.45–0.57	>0.57
Non-haematologic score	ECOG PS	0	1–2	3–4
	MMS	30		<30
	MNA	28–30		<28
	Chemotox	0–0.44	0.45–0.57	>0.57

	CRASH score (points / % of patients with severe toxicity)			
Sample	Heme subscore	Non-Heme subscore	Combined score	Risk category
Derivation (n = 347)	0–1: 7% 2–3: 23% 4–5: 54% Greater than 5: 100%	0–2: 33% 3–4: 46% 5–6: 67% Greater than 6: 93%	0–3: 50% 4–6: 58% 7–9: 77% Greater than 9: 79%	Low Int-Low Int-High High
Validation	0–1: 12% 2–3: 35% 4–5: 45% Greater than 5: 50%	0–2: 42% 3–4: 59% 5–6: 66% Greater than 6: 100%	0–3: 61% 4–6: 72% 7–9: 77% Greater than 9: 100%	

Based on these findings, the evaluation of functional and nutritional status along with the well-known clinical and laboratory parameters is now recognized as crucial for decision-making. As such this has been included by the European Organisation for Research and Treatment of Cancer (EORTC) group as a minimum data set for the baseline assessment and screening of elderly cancer patients in their future trials [107].

10.6 Ongoing Research

The current evidence base supporting the use of adjuvant systemic therapy in older breast cancer patients relies largely upon data extrapolated from trials conducted in younger women and a small number of prospective and retrospective studies performed in older individuals. However it is hoped that a number of ongoing prospective studies focusing specifically on older patients will enhance this evidence base over the next few years. Currently ongoing or anticipated trials are listed in Table 10.2.

Table 10.2 Active trials recruiting focusing on chemotherapy for elderly early-stage breast cancer patients on ClinicalTrials.gov [108]

Trial	Anticipated accrual	Cooperative group/sponsor	Description	Identifier
A Breast Cancer Treatment Decision Aid for Women Aged 70 and Older	312 patients	Dana-Farber Cancer Institute	Evaluate a decision aid to help women aged 70 and older decide on treatment for their breast cancer	NCT02823262
Cognition in Older Breast Cancer Survivors: Treatment Exposure, APOE and Smoking History	540 patients	Memorial Sloan Kettering Cancer Center	Assess cognition in older women who are survivors of breast cancer and either did or did not receive chemotherapy are affected by treatment, compared to older women who have never had cancer	NCT02122107
Trastuzumab in Treating Older Women With Early-Stage Breast Cancer	56 patients	Cynthia Owusu, MD, Case Comprehensive Cancer Center/ National Cancer Institute (NCI)	Study the side effects of Trastuzumab and its efficacy in older women with early-stage breast cancer.	NCT00796978
Liposomal Doxorubicin Compared With Observation or Cyclophosphamide and Methotrexate in Treating Older Women Who Have Undergone Surgery for Breast Cancer (CASA)	77 patients	International Breast Cancer Study Group	Compare the breast cancer-free interval in elderly women with resectable, hormone receptor-negative breast cancer treated with pegylated doxorubicin hydrochloride liposome (PDL) vs observation or PDL vs cyclophosphamide and methotrexate.	NCT00296010

(continued)

Table 10.2 (continued)

Trial	Anticipated accrual	Cooperative group/sponsor	Description	Identifier
ATOP Trial: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer	200 patients	Academic and Community Cancer Research United/ National Cancer Institute (NCI)	Evaluate the efficacy of Trastuzumab emtansine works in older patients with human epidermal growth factor receptor 2 (HER2)-positive stage I-III breast cancer.	NCT02414646
Adjuvant Therapy in Older Versus Younger Women With Breast Cancer: Longitudinal Impact of Adjuvant Chemotherapy on Functional Status, Comorbidity and Quality of Life	200 patients	City of Hope Medical Center/ National Institute on Aging (NIA)	Describe longitudinal trajectory of physical functional status and quality of life and determine if the patient assessment measure predicts morbidity in adult breast cancer patients from prior to adjuvant chemotherapy to 6 months after end of treatment. Assess potential biomarkers for physiologic age, including Advanced Glycation Endproducts (AGEs) and markers for oxidative stress and inflammation	NCT01030250
Adjuvant Systemic Treatment for (ER)-Positive HER2-negative Breast Carcinoma in Women Over 70 According to Genomic Grade (GG): Chemotherapy + Endocrine Treatment Versus Endocrine Treatment (ASTER 70s)	2000 patients	UNICANCER	Evaluate the benefit of adjuvant chemotherapy on overall survival for elderly patients with breast cancer, in a sub group with a high risk of relapse according to Genomic Grade test.	NCT01564056

(continued)

Table 10.2 (continued)

Trial	Anticipated accrual	Cooperative group/sponsor	Description	Identifier
An Open Label Phase II Trial to Investigate the Cardiac Effects of Pegylated Liposomal Doxorubicine (Caelyx) in Elderly Breast Cancer Patients With New Imaging and Biochemical Techniques.	16 participants	Universitaire Ziekenhuizen Leuven	Evaluate the cardiac effects of liposomal doxorubicin n elderly patients (65y or older) with early breast cancer who are candidate for adjuvant chemotherapy with new non-invasive techniques, i.e. strain rate imaging, classical echocardiography, and special blood tests measuring troponin I and BNP.	NCT00284336
Gene Polymorphisms and Gene Products as Biological Markers of Aging and Correlation With Clinical Geriatric Assessment, Tolerance of Chemotherapy and Outcome in Elderly Breast Cancer Patients (EBS)	110 patients	Universitaire Ziekenhuizen Leuven	Evaluate the biology of aging in breast cancer patients, and study the impact of chemotherapy on aging related blood biomarkers.	NCT00849758
Bridging the Age Gap in Breast Cancer	3200 patients	University of Sheffield	Developing a predictive tool to tailor treatment options for older women according to breast cancer factors and their fitness/ frailty Developing a Decision Support Instrument (DESI) to assist older women making informed decisions about their preferred treatment	N/A

10.7 Conclusions

Adjuvant systemic therapy can be safe and beneficial for many older patients with early-stage breast cancer at high risk of recurrence. However, decision-making is challenging as it involves complex considerations regarding disease biology, comorbidities, life expectancy and patient fitness. The decision-making process is further complicated by the limited evidence base for this specific group of patients. However, several ongoing trials now aim to fill this gap of knowledge. In addition to the information gained from these trials, further insight into the molecular pathogenesis of breast cancer in older women is warranted in order to identify patients more likely to benefit from chemotherapy. Irrespective of the outcomes of these studies, it is clear even today, that a thorough assessment of global health status, including geriatric assessment domains and along with patients' preferences, are central to determining the risks and benefits of treatment.

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Adjuvant Radiotherapy

11

Ian Kunkler

Abstract

There is a dearth of level 1 (randomised controlled trial) evidence on adjuvant radiotherapy confined to older patients but it is slowly accumulating and influencing guidelines and practice. There are wide international variations in the application of adjuvant radiotherapy after breast conserving surgery and mastectomy in this age group. There are conflicting data on the effect of age on risk of local recurrence. Local recurrence rates have been falling in older patients treated by breast conserving therapy, reflecting the impact of screening, closer attention to surgical margins, better systemic therapy and radiotherapy. Recent trials support the use of hypofractionation and selected forms of partial breast irradiation. Breast boost is recommended in higher risk patients after breast conserving surgery. There is growing support for selective omission of postoperative radiotherapy in 'low risk' older patients. Trials of biomarker- assisted selection of such subgroups are ongoing. There is no level 1 evidence on postmastectomy radiotherapy (PMRT) confined to older patients. PMRT remains standard for patients with 4 or more positive nodes. For patients with 1–3 involved nodes, the role of PMRT remains controversial.

Keywords

Breast cancer · Adjuvant radiotherapy, radiation, older · Elderly

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11.1 Introduction

Breast cancer represents a rising health care challenge in older women. In most European countries, the incidence of breast cancer in women =/>70 years has risen steadily [1]. The aim of adjuvant radiotherapy is to maximise local control and breast cancer survival while minimising toxicity. However the receipt of radiotherapy internationally varies widely in older women [2, 3]. Where life expectancy is diminishing in older patients and comorbidities abound, there is added importance in minimising radiation induced toxicity and maintaining quality of life. In this balance must be weighed the evidence that older patients have a lower absolute risk of recurrence compared to younger women [4]. However older patients are more likely to be undertreated based on perceived risk of treatment induced toxicity [5].

Evidence based on trials confined to older patients remains limited, in part due to the historical exclusion of patients =/>70 years. Consequently clinicians often extrapolate from findings in trials of younger patients, limiting the strength of evidence to support practice. As life expectancy diminishes, the question arises as to whether treatment should be 'deescalated' and adjusted to the remaining years of life or maintain the normal intensity of treatment applied in younger patients [6]. However de-escalating radiotherapy is controversial. There are strong advocates [7] of selective omission of radiotherapy after breast conserving surgery (BCS) in 'low risk' older patients, while others strongly advocate maintenance of standard radiotherapy treatment policies [8].

In this article priority has been given to level 1 evidence in relation to adjuvant radiotherapy, specifically in older patients. There are grounds for optimism with the lifting of an age limit in contemporary trials and the application of advanced radiotherapy techniques which should reduce treatment induced loco-regional morbidity and mortality. Modern radiotherapy techniques have reduced the risks of adverse effects of radiotherapy. However, there remain risks particularly of cardiac radiotoxicity [9] and carcinogenesis [10]. The increased risk of radiation induced heart disease is proportional to the mean dose to the heart [9, 11]. The absolute risk of radiation induced cardiotoxicity increases significantly in women with pre-existing cardiac risk factors [9] (more common in older women) and the group likely to include those with the lowest risk of local recurrence. There is a small but statistically significant risk of inducing lung cancer [10].

There are conflicting data on the effect of age on ipsilateral breast tumour recurrence (IBTR). IBTR has been reported in some trials to increase with age [12] or no effect is seen [13, 14]. A Dutch cohort study of 1922 patients =/>65 years with pT1-T2/pN0-2 treated by BCS and postoperative radiotherapy (median age 70 years) showed 5 and 10 year loco-regional recurrence rates of 2% and 3% respectively. Patients with low risk tumours (T1, grade 1 or 2, node negative, ER positive) had a lower risk of distant metastases (HR 0.26) and superior overall survival (HR 0.65) compared to higher risk (grade 3 and/or node positive) patients [15]. Changes in surgical practice in particular the widespread adoption of sentinel node biopsy to stage the axilla with considerably less morbidity than axillary node clearance are widening the application of axillary irradiation for older as well

younger patients. Greater attention to achieving clear surgical margins and more effective systemic therapy are contributing with radiotherapy to lower loco-regional recurrence rates reported in recent randomised trials and cohort studies [16]. Prognosis and treatment decisions, originally partially based on axillary node status are increasingly based on disease burden, biological tumour type and multigene assays. Research in gene assays of radiosensitivity has generally lagged behind equivalents for predicting response to systemic therapy. However encouraging results have been reported for the Radiotype DX molecular signature validated in independent patient cohorts treated by breast conserving therapy and postoperative whole breast irradiation [17].

11.2 Local Recurrence and Mortality

The sequential 5 year meta-analyses of the overall effects of radiotherapy after breast conserving surgery and mastectomy in RCTs by the Oxford Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have contributed enormously to our understanding of benefits and risk of adjuvant radiotherapy. The first Oxford overview [18] suggested that adjuvant radiotherapy improved loco-regional control but did not influence long term survival. It emerged that approximately a 2% reduction in breast cancer survival at 20 years was counterbalanced by an equivalent increase in deaths from vascular disease, predominantly cardiovascular [19]. This reflected the impact of older radiotherapy techniques (eg orthovoltage) where dose to the heart was excessive. Of note the adverse effects of radiotherapy on the heart were seen 10 or more years after treatment, emphasising the need for long term follow up of patients of any age. The evidence that adjuvant radiotherapy reduced breast cancer mortality as well as loco-regional recurrence was shown in landmark trials in which 'high risk' pre [20, 21] or postmenopausal patients [22] receiving systemic therapy in Danish and Canadian clinical trials were randomised to comprehensive loco-regional irradiation after mastectomy or no further treatment. The Danish trials had employed a direct electron field with limited penetration over the chest wall overlying the heart. There was no increase in late radiation induced cardiovascular morbidity or mortality [23].

The EBCTCG meta-analysis of adjuvant radiotherapy [27] concluded that, in the hypothetical absence of other causes of death, one breast cancer death would be avoided over 15 years for every four local recurrences avoided ('4 to 1 ratio'). This equates to a 20% reduction in risk of local recurrence translating into a 5% reduction in 15 year breast cancer mortality. These findings are consistent with Hellman's observations [24] that 'breast cancer is a heterogeneous disease – a spectrum ranging from a disease that remains local throughout its course to a disease which is systemic when first detectable'. This represented a shift in thinking from considering breast cancer as a systemic disease There may be situations in which residual inadequately treated loco-regional disease gives rise to distant metastases. However the '4 to 1' ratio between local regional recurrence at 5 years and survival at 15 years proved not to be statistically sound. Time to loco-regional recurrence is not well

defined because of competing risks of local and distant disease and the known systemic effect of radiotherapy [25]. A local recurrence may either have limited impact for the individual patient or be the genesis of life threatening metastatic disease. However in either situation local recurrence causes substantial anxiety to the patient and impairs quality of life.

While the causal link between loco-regional control and breast cancer mortality is well established, the biological explanation is not. It may be that sterilisation of breast cancer within the primary site prevents dissemination to distant sites. Alternatively it may reduce the burden of breast cancer cells on which systemic therapy has to exert its effects. More recently it has been documented that local radiotherapy may have an abscopal effect, exerting an immune anti-cancer effect at distant sites. It has been hypothesised [26] that this might explain in part the beneficial effect of radiotherapy on breast cancer mortality observed in the recent EBCTCG overviews.

11.3 Postoperative Radiotherapy After Breast Conserving Therapy

Postoperative radiotherapy remains the standard of care for most older patients after BCS with clear margins [1]. However the evidence is accumulating to support the selective omission of radiotherapy in low risk patients. Consensus around what constitutes sufficiently 'low risk' to avoid radiotherapy is not universal. This may be in part because clinico-pathological factors such as age, tumour size, grade, lymphovascular invasion and axillary node status do not sufficiently characterise 'low risk' and that features of tumour biology (oestrogen, progesterone, HER2 and Ki67 status) are important adjuncts to properly define low risk.

The Oxford overview [27] showed that adjuvant radiotherapy roughly halves the risk of first recurrence (predominantly loco-regional) irrespective of overall risk of recurrence. However the absolute reduction in risk of first recurrence in older (=/>60 years) is relatively small. In pN0 disease the first recurrences are mainly loco-regional in patients allocated to surgery alone (22.8%) compared to surgery combined with radiotherapy (7.3%). For this group of patients rates of metastatic disease with or without radiotherapy were similar (8.2% vs 8.3%). Patients with pN0 disease were categorized according to factors such as age, ER status, tumour grade, extent of surgery and use of tamoxifen in three groups based on the reduction in risk of 10 year first recurrence with RT. High risk was >20%,intermediate (10–20%) and low risk (<10%). There was a 7.8% reduction (95% CI 3.1–12.5) in 15 year breast cancer mortality for patients who had =/>20% reduction in first recurrence. For patients in the intermediate risk group the risk reduction was only 1.1% (95% CI 7.5.7.7).Thus radiotherapy in the lower and intermediate risk categories had negligible impact on breast cancer mortality and implies that there is a group of patients from whom postoperative radiotherapy could be reasonably omitted. For such patients most loco-regional recurrences could be managed surgically.

11.4 Omission of Postoperative Radiotherapy After Breast Conserving Surgery

The omission of postoperative radiotherapy after surgery has remained a controversial issue. There is limited level 1 evidence but it is accumulating and tilting consensus among breast cancer specialists towards omission in subgroups of 'low risk' older patients. However there are variations in guidelines in what constitutes 'low risk'. Matters are complicated by factors independent of radiotherapy such as better attention to surgical margins and more effective systemic therapy (eg aromatase inhibitors and taxanes) have contributed to lower loco-regional contemporary 5 year local recurrences rates (now around 2%) [16] compared to 5% a decade or more ago with surgery and radiotherapy. At the same time the morbidity of radiotherapy has declined with 3D treatment CT planning, diminishing the dose to critical structures such as the heart.

There are three randomised trials which have assessed the impact of the omission of radiotherapy in lower risk patients. The earliest was the CALGB 9343 trial which randomised 636 T1, N0, ER positive patients, =/>70 years to BCS and tamoxifen +/− postoperative radiotherapy (50 Gy in 25 daily fractions over 5 weeks).There was a 3% reduction in loco-regional recurrence in the irradiated group at 5 years (1% vs 4% [p = 0.001]) [28] and a 7% reduction at 10 years (2% vs 9%) [29]. There was no compromise in 5 or 10 year overall survival from the omission of radiotherapy.

On the basis of the 5 year results the National Comprehensive Cancer Network (NCCN) guidelines were amended in 2005 to state: 'Breast irradiation may be omitted in those 70 years or older with estrogen receptor positive, clinically node-negative T1 tumors who receive adjuvant hormonal therapy' [30]. However in the USA (similarly to the rest of North America, Europe and Australasia, there was limited impact of these results. A study of over 12,000 patients from SEER-Medicare data in the United States of a cohort of patients who met the eligibility for the CALGB 9343 study (70 years or older, stage 1, treated with BCS and oestrogen receptor positive) showed little reduction in the use of radiotherapy [31]. It only dropped from 79% to 75%.This probably reflected a conservative view among surgeons, oncologists and probably patients concerned about the omission of radiotherapy and the risks of recurrence. In addition it is possible that the medical community may be less influenced by a study withholding treatment than one adding a new treatment [32]. However the study did not report on the use of hormonal therapy during the period of the study so it was not known whether patients were taking an anti-estrogen or not.

The PRIME 2 trial [33] randomised 1326 women =/>65 years with T 1–T2 (up to 3 cm), pN0, M0 breast cancer treated with BCS and clear (minimum 1 mm) margins, appropriate endocrine therapy for 5 years to no further treatment or to whole breast irradiation (40–50Gy in 15–25 daily fractions).

There was a small but statistically significant reduction in local recurrence from RT at 5 years (4.1% vs 1.3%, p = 0.002) (Fig. 11.1). There was no compromise in overall survival from omission of RT. Of note, while patients with grade 3 tumours were eligible for the trial as long as they did not have associated

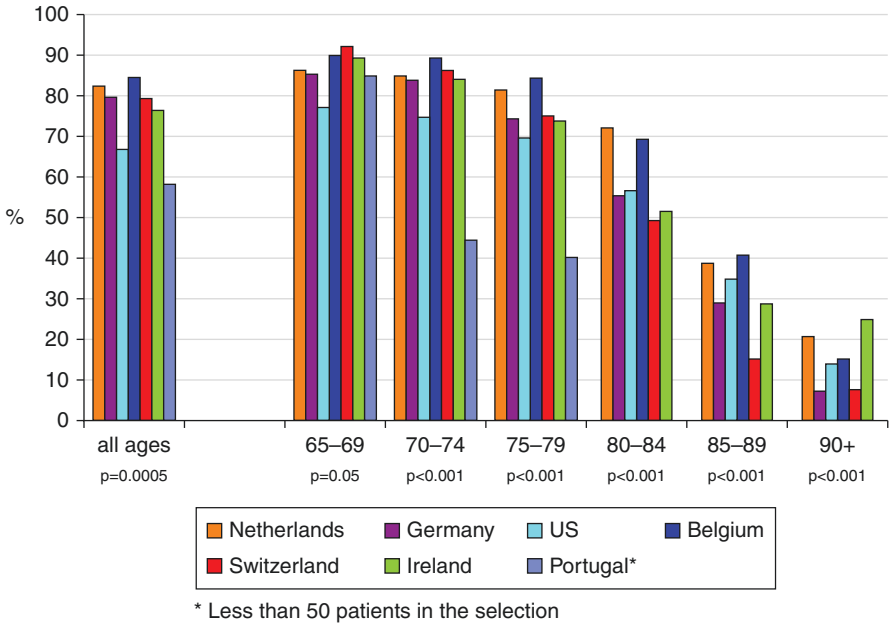

Fig. 11.1 Time to actuarial ipsilateral breast tumour recurrence [33]

lymphovascular invasion, the numbers included were small, only 36 patients (3%). Higher grade tumours [34] as well as those with positive margins [35] and axillary involvement are known to be associated with a higher risk of local recurrence. Within the subgroup of patients with grade 3 tumours unirradiated patients had a higher risk of local recurrence, three (13%) of 23 patients, compared to those in the irradiated arm (none of 13). The numbers are small and therefore should be interpreted with caution. However the authors were confident that the findings of the trial were applicable to patients with grade 1–2, T1–T2 tumours up to 3 cm but were cautious about their generalisability to grade 3 cancers.

In a hypothesis generating unplanned subgroup analysis local recurrence at 5 years according to hormone receptor status, the risk of ipsilateral breast tumour recurrence was lower in hormone receptor rich patients than in the whole population [33]. In the non-irradiated group the 20 (3%) of 593 patients relapsed locally compared with 5 patients (<1%) of 601 patients in the irradiated group 5-years ipsilateral breast tumour recurrence was 3.3% (95% CI 1.7–4.8) and 1.2% (95% CI 0.1–2.2) respectively [p = 0.002]. In oestrogen receptor poor patients six (9%) of 65 women had a local recurrence in the non irradiated group compared to none of 55 women in the irradiated group ipsilateral breast tumour recurrence at 5 years was 10.3% [95% CI 2.5–18.2] and 0% respectively; (p = 0.026). However the numbers are small and should be interpreted with caution. These observations would have to be confirmed prospectively. The authors considered that

omission of radiotherapy was a reasonable option for selected older women. The accompanying editorial endorsed this recommendation [7].However the findings could be interpreted differently. It can be argued that the fitness of a 70 year old woman varies significantly. A 70 year old woman in good health is very likely to live live more than 10 years and would have a 10% of relapse if irradiation was omitted compared to 2% if it was given. The probable benefit to patients is influenced by the patient's general health and comorbidities. Using adjuvantonline! data, a 73 year old woman in poor health with a 2.1–3 cm, ER positive, grade 3 with 1–3 involved nodes would only have a 3% absolute increase in 10 year survival compared to a fit 40 year old women [36]. The latter authors acknowledge that adjuvantonline! has limitations, pointing to a recent Dutch study demonstrating that in patients 65 years or older, it does not accurately predict recurrence or survival [37]. However the absolute differences in local recurrence with or without irradiation in the CALGB 9343 and PRIME 2 trials are small and it is possible that many older patients with good prognosis cancer, if asked, might prefer to omit adjuvant irradiation on the basis of a very small increased risk of local recurrence [36] However radiation is generally well tolerated, as demonstrated in the PRIME 1 trial [38, 39] with a low risk of morbidity with modern radiation delivery systems [40].

Account must also be taken of the inconvenience to patients and their families of several weeks of postoperative radiotherapy and the substantial costs of treatment, particularly where radiotherapy resources are limited. In the PRIME 1 trial it was concluded that radiotherapy was only cost effective if at least a 5.5% increase in local recurrence occurred after omitting radiotherapy, at the £30,000 threshold [38]. However one should be cautious in extrapolating from the PRIME 1 to the PRIME 2 trial since no formal economic assessment was made in the latter.

The opposite line of argument can be taken [41] that a fit 70 year old women with a life expectancy in excess of 10 years has a 1 in 10 risk of a local recurrence if radiotherapy is omitted compared to 1 in 50 risk if irradiation is given based on updated follow up of the CALGB 9343 trial [29].Such patients might prefer emerging and shorter and more convenient hypofractionated dose fractionation regimes to the omission of radiotherapy [42]. Shorter, hypofractionated dose fractionation schedules (15/16 daily fractions) for breast cancer reduce both the length of the treatment and breast toxicity compared to the standard 50 Gy in 2 Gy fractions over 5 weeks [43, 44].

The interpretation of the CALGB 9343 follow up results will depend on whether the glass is seen as half full or half empty. A five fold increase in risk of local recurrence is not likely to be perceived as small [8]. The latter authors argue that radiotherapy is a local treatment whose principal function is to sterilise tumour cells within the irradiated breast so local recurrence should trump overall survival as the most important clinical endpoint. Furthermore overall survival is a late event which is influenced by other factors apart from local control. Local recurrence is linked to mortality so if sufficient time elapses, mortality will be increased even for a slowly growing cancer. The psychological

impact of local recurrence should not be underestimated either [8]. Finally in a holistic approach to older patients, the values, priorities, preference and competing morbidities of the individual patient need to be weighed by the physician [40]. A recent survey of the information needs for making decision on radiotherapy in older women with breast cancer [45] showed that they rated benefits highest followed by side effects. The wide variation in information needs suggests that decision aid tools are needed to support older patients in considering treatment options.

11.5 Guidelines on the Omission of Adjuvant Radiotherapy After Breast Conserving Surgery

Guidelines on adjuvant radiotherapy after BCS in older patients have gradually evolved, reflecting the accumulated evidence from clinical trials comparing BCS with or without postoperative radiotherapy. In 2013 the Scottish Intercollegiate Guidelines Network advocated postoperative radiotherapy for all patients following BCS irrespective of age [46]. A similar recommendation was made by the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) [1] demonstrating resistance to the omission of RT, even in low-risk cases [47].There is no international consensus in guidelines on the omission of postoperative radiotherapy. In part this may reflect the view that in most studies clinico-pathological factors alone have not been able to identify a truely low risk group of older patients [48]. However the cumulative evidence from randomised trials of omission of radiotherapy in selected patients is gradually changing. Provisional guidelines of the National Institute of Care and Clinical Excellence [49] recommending that omitting radiotherapy can be considered for women who

- have had BCS for invasive breast cancer with clear margins **and**
- have a very low absolute risk of local recurrence (defined as women aged 65 years or older with tumours that are T1, NO, ER positive, HER2 negative and grade 1 and 2)
- **and** are willing to take adjuvant endocrine therapy for a minimum of 5 years.

11.6 Biomarker Aided Selection of Patients for the Omission of Postoperative Radiotherapy after Breast Conserving Surgery

Efforts are being made to refine the selection of a genuinely low risk group of older patient from whom RT can be safely omitted by supplementing clinico-pathological factors with biomarkers. Tumour biology, namely ER positivity, which seems to play an important factor in influencing risk of recurrence [50]. While the risk of

local recurrence in breast cancer is influenced by local treatment, systemic therapy and tumour biology, tumour biology may be the key factor [40].

Molecular subtype may be a useful criterion for selecting patients for radiotherapy. A report on a small subset of patients demonstrated that molecular subtype was the only significant predictor for local recurrence after breast conserving surgery [51].This approach is exemplified by the PRIME TIME prospective cohort study [52].In this UK study 2400 patients are being recruited =/>60 years with T1, pN0, M0, hormone receptor positive, HER2 negative breast cancer. Patients are divided by a combination of clinico-pathological factors (eg age, grade etc) and biomarker panel (IHC + C) into a very low risk group with a 10 year risk of metastases of <5% to treatment with tamoxifen alone after breast conserving surgery. All patients with a higher risk are treated by postoperative radiotherapy in addition to adjuvant endocrine therapy. Biomarkers are also under investigation in the Canadian LUMINA study (NCT01791829).In the United States the PRECISION trial is using genomic profiling by Prosigma to identify 'low risk' women aged 50–75 years with ER+, PgR+, HER2 negative, grade 1–2 tumours to endocrine therapy alone after breast conserving surgery in a single arm study [53].

11.7 Should Older Patients Receive a Boost Dose of Irradiation to the Site of Excision Following Breast Conserving Surgery and Postoperative Radiotherapy?

Level 1 evidence on the role of boost irradiation after breast conserving surgery and postoperative radiotherapy is available from the EORTC boost trial. This recruited over 5000 patients treated by breast conserving surgery, whole breast irradiation with 50 Gy in 25 daily fractions over 5 weeks. Patients were randomised to a boost of 16Gy in 8 daily fractions or no boost [54]. For patients =/>60 years with clear margins, a tumour bed boost resulted in a 3.5% gain in local control at a median follow of 10.8 years. However the benefit in this age group was lost after 20 years of follow up [55].

In a central pathology review of 1616 patients from the EORTC boost trial (about one third of the original patients in the trial) the cumulative incidence of IBTR at 20 years was 11% (95% CI 8%–15%) in patients 50 years or older [56]. High grade tumours relapsed more frequently in the early period of follow up but the effect diminished over time. For the whole group, the cumulative incidence of IBTR never attained a plateau, and the beneficial effect of the boost increased over time [57]. The delivery of a boost benefitted most patients under the age of 50 years (+/− a DCIS component), those with high-grade tumours or oestrogen receptor negative tumours. A boost did not significantly benefit older patients with low-grade, estrogen receptor– positive tumours. For older patients a boost would therefore be advised in patients with grade 3 or ER negative tumours and omitted in those with low grade ER positive tumours.

11.8 Is There a Role for Partial Breast Irradiation After Breast Conserving Surgery?

There has been considerable interest in evaluating the role of accelerated partial breast irradiation (APBI) techniques, limiting the region of highest dosage to the region in and around the site of the primary tumour excision site with the convenience of shorter overall treatment times. Accelerated partial breast irradiation could be an alternative to whole breast irradiation, but also to the omission of radiotherapy. A number of different ABPI techniques based on postoperative approaches: brachytherapy or external beam or intraoperative irradiation using low energy photons or electrons. Of the four randomised trials of ABPI published, none is confined to older patients.

A Cochrane analysis [58] of 7586 of the 8955 women enrolled in seven RCTs showed inferior recurrence free survival in women receiving partial breast irradiation/accelerated partial breast irradiation compared to WBRT (HR 1.62 [95% CI 1.11–2.35]). Cosmesis appeared inferior with PBI/ABPI (OR 1.51 [95% CI 1.17–1.95]). Overall survival did not differ (HR 0.90 [95% CI 0.74–1.09]). Late radiation toxicity was worse with PBI/ABPI (OR 6.58 [95% CI 3.08–14.06]). The recently published IMPORT LOW non inferiority trial in women 50 years or older with pT1–T2 tumours (3 cm or less) with 0–3 involved nodes randomised patients after breast conserving surgery to receive 40 Gy whole-breast radiotherapy (control), 36 Gy whole-breast radiotherapy and 40 Gy to the partial breast (reduced-dose group), or 40 Gy to the partial breast only (partial-breast group) in 15 daily treatment fractions [59]. The authors showed non-inferiority of partial-breast and reduced-dose irradiation compared with the standard WBRT in terms of local relapse and equivalent or less late normal-tissue toxicity. No specific analysis was made for older patients. The authors comment that the discrepancy between the results of the IMPORT-LOW trial and the Cochrane Analysis might be explained by the limited number of contemporary partial-breast radiotherapy trials described in the Cochrane report [58]. Four other phase 2 trials evaluating partial-breast radiotherapy are yet to publish 5-year results (NSABP/RTOG NCT00103181, RAPID NCT00282035, SHARE NCT01247233, and IRMA NCT01803958). The simplicity of the IMPORT-LOW partial breast technique is readily applicable to older patients and should have worldwide impact.

The RAPID trial (NCT00282035) compared three-dimensional (3D) conformal partial-breast radiotherapy (38·5 Gy in ten fractions over 5 days) at 3 years, with WBRT (42·5 Gy in 16 fractions or 50 Gy in 25 fractions with an optional boost). Cosmesis and late normal-tissue toxicity were inferior in the partial-breast radiotherapy group [60] implying that dose-time effects were the predominant factor over reduced irradiated volume [59]. In a subgroup analysis of 117 women 70 years or older in an Italian phase 3 randomised controlled trials (median follow up 5 years) comparing partial breast irradiation with intensity modulated radiotherapy (IMRT) with whole breast radiotherapy (WBRT) in which 520 women were enrolled, the ipsilateral breast tumor recurrence (IBTR)

rate was 1.9% in both arms [61]. Less acute skin toxicity of any grade was observed in the ABPI group.

The role of intraoperative radiotherapy (IORT) in older patients is unclear. The ELIOT equivalence trial of intraoperative electron beam therapy after breast conserving surgery was not specifically limited to older patients but showed a significantly higher local recurrence rate in the IORT arm at 5 years (4.4%) compared to whole breast irradiation (0.4%) after BCS ($p = 0.0001$); [62].

The design, statistical interpretation and clinical applicability of the non inferiority TARGIT-A trial of intraoperative radiotherapy with a 50kv source [63] have been challenged [64].Patients were randomised to TARGIT or to whole breast radiotherapy (WBRT). For 67% of the patients randomisation took place at lumpectomy (designated "prepathology"). Participants with high-risk features received WBRT after TARGIT. For 33% of participants pathology was available from prior lumpectomy (designated "post-pathology"). The "post-pathology" stratum was predetermined as being low risk and such patients, if randomised to TARGIT, had the lumpectomy wound reopened for IORT. Among the key criticisms the non-inferiority criterion was not met since this requires the upper 90% confidence interval to be below the predetermined threshold of 2.5%. When the correct 5- year local failure rates are used, there was a significant 2% superiority of external beam radiotherapy and a confidence interval which extended beyond 2.5% [64]. A second criticism is that the non inferiority test is not reliable as its correct application necessitates that the 5 year follow up data is available for all the patients in the trials [65]. This was not the case since 5 year data was only available on 20% of the patients. Thirdly, the median follow of the trial was only 2 years 5 months. This is too short to assess the risk of local recurrence or normal tissue toxicity [66] and longer follow up is needed. Finally the trialists claimed that non-breast cancer deaths were increased nearly immediately after external beam irradiation due to an increase in cardiovascular events and radiation induced malignancies. This is extremely implausible given that the minimum latency of death due to radiation induced toxicity is around 10 years [67]. In the TARGIT-A trial the toxicity of WBRT seems to be related to whether patients were randomised before or after access to the definitive pathology results. On subgroup analysis there was a lower rate of non-breast cancer deaths in the "pre-pathology" group with TARGIT. By contrast the non-breast cancer deaths in the "post-pathology" TARGIT stratum did not differ from the WBRT group. This implies that the patients were not appropriately assessed and stratified for co-morbidities. As a consequence the allocation to treatment arms would not be balanced [65].On this basis it is premature to recommend IORT with the TARGIT technique as a standard of care. A prospective phase 2 study of IORT (TARGIT-Elderly) in patients =/>70 years, <3.5 cm, cNO, M0 with early invasive breast cancer is ongoing (NCT01299987). Additional postoperative radiotherapy (46–50Gy) is given to patients with risk factors (eg positive nodes or lymphovascular invasion).

Interstitial multi-catheter brachytherapy for Accelerated Partial Breast Irradiation (APBI) after BCS has been well validated (WBI) [68]. It delivers a high dose

accurately to a well defined breast target volume, minimising exposure of adjacent organs at risk, yielding excellent local control with a good quality of life [69] and low incidence of toxicity. APBI using multi-catheter brachytherapy is the only method of breast irradiation with a duration of only 4–5 days with level 1 evidence showing it to be an alternative to WBI after breast conserving surgery (BCS) for low-risk breast cancer patients. Between 2004 and 2009, 551 patients received WBRT and tumour bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. At 5-year follow-up, the cumulative incidence of local recurrence was 1.44% (95% CI 0.51–2.38) with APBI and 0.92% (0.12–1.73) with WBRT (difference 0.52%, 95% CI −0.72 to 1.75; p = 0.42). The risk of severe (grade 3) fibrosis at 5 years was 0.2% with WBRT and 0% with APBI (p = 0.46). Adjuvant APBI using multicatheter brachytherapy after BCS in patients was found not to be inferior to WBRT in terms of 5-year local control, disease-free survival, and overall survival. This is a well conducted trial with adequate follow up.

Selection of older patients for highly fractionated, partial or no irradiation following breast conserving surgery based on patient and tumour profiles will require testing in RCTs taking cognizance of the patient's biological age and tumour biology [70].

11.9 Is There a Role for Preoperative Radiotherapy in Breast Conserving Therapy?

Preoperative (neoadjuvant) therapy is theoretically attractive since radiation can be targeted at the intact tumour and with accelerated partial breast irradiation, overall treatment times can be short (around 2 weeks). In the past preoperative radiotherapy was studied and not found to be advantageous. However advances in radiotherapy technology (IMRT, accelerated PBI, simultaneous boost and image guided RT) have reawakened interest (see Ref. [71] for review). Neoadjuvant radiotherapy remains investigational with no long term data on local control but some limited data on toxicity. A Dutch trial reported its interim analysis of local morbidity data [72] of the first 70 patients in the trial (recruitment target 120).The trial recruited women >60 years with invasive, unifocal (<3 cm on MRI), non lobular, adenocarcinoma of the breast and negative sentinel node biopsy. Patients received preoperative accelerated partial breast irradiation (40Gy in 10 fractions over 2 weeks). A wide excision was carried out 6 weeks after radiotherapy. At a median follow up of 23 months (3–44 months), the postoperative infection rate was 11%. The global cosmetic outcome was good to excellent in 77% at 6 months to 100% at 3 years. A US Phase 1 dose escalation study [73] of preoperative partial breast irradiation with a single fraction (15, 18 or 21 Gy) in 32 women 55 years or older with clinically node negative ER and/or PR positive, HER2 negative T1 invasive breast cancer or low/intermediate grade in situ disease (<2 cm) reported no dose limiting toxicity. Dose dependent changes in cell density, vascular permeability and gene expression regulating immunity and cell death were observed in response to RT.

11.10 Postmastectomy Irradiation

Postmastectomy irradiation still continues to be underutilised, in recent studies of older patients. In a series of 178 octogenarian women diagnosed with early breast cancer between 2001 and 2010 and 'high-risk' features, the overall use of more aggressive loco-regional and systemic therapies was low [74].

There is no published level 1 evidence relating to postmastectomy radiotherapy in older patients and practice is extrapolated from clinical trials in younger patients. Postmastectomy radiotherapy remains the standard of care for patients with patients with 4 or more involved nodes and for T3, NI and T4 tumours. The role of postmastectomy radiotherapy in patients with 1–3 involved nodes remains controversial. The 2014 Oxford overview shows a survival advantage at 15 years both in the 4 or more positive node group and the 1–3 involved node group [75] and this has influenced some clinicians to irradiate patients with 1–3 involved nodes. The BIG 2.04 MRC/EORTC SUPREMO trial [76] has recruited over 1600 patients with 1–3 involved nodes or node negative with other risk factors. There was no upper age limit for the trial which is expected to report around 2023. International guidelines for postmastectomy radiotherapy vary. The recent St Gallen consensus guidelines [77] recommend PMRT for all patients with 4 or more involved axillary nodes and/or pT3 tumours. For pN1 patients with lower risk factors, they advise that the use of PMRT is balanced against of toxicity including the increased risk of complications following breast reconstruction. The North American guidelines consider that there is clear evidence that PMRT reduced loco-regional failure, any recurrence and mortality for patients with T1–2, NI disease [78]. The 2018 guidelines of the National Institute for Care and Clinical Excellence have been revised. They now recommend postmastectomy radiotherapy for all patients with axillary macrometastases [49] based on the result of the EBCTCG 2014 meta-analysis of postmastectomy radiotherapy [71]. Whether the loco-regional and survival rates in the SUPREMO trial will mirror those in the EBCTCG meta-analysis remains to be seen.

In conclusion, there is limited level 1 evidence of adjuvant radiotherapy confined to older patients. Where it is lacking, extrapolation from RCTs in younger patients is required. Breast conserving surgery and postoperative radiotherapy remains the standard of care for most older fit patients with early breast cancer. There is a growing body of level 1 evidence supporting the omission of postoperative radiotherapy in low risk older patients. Studies of the role of biomarkers to assist in identifying truly 'low risk' patients are ongoing. Hypofractionated radiotherapy (15/16 fractions) has become standard care. A boost dose to the tumour bed following WBRT should be considered in higher risk patients. Partial breast irradiation with IMRT and postoperative brachytherapy are more recent additions to the evidence base. The role of preoperative radiotherapy remains investigational. Postmastectomy radiotherapy should be considered for higher risk patients.

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Prevention and Treatment of Skeletal Complications

12

Robert Coleman

Abstract

Considerable advances in breast cancer care over recent decades have led to improved survival across all age groups. However, this increases the clinical relevance of long-term consequences of anti-cancer treatments, with effects on bone health of particular relevance to the older population of women with breast cancer. The risk of cancer treatment induced bone loss should be considered by clinicians and recent international management guidelines followed. Bone targeting agents, supplemented by calcium and vitamin D supplementation alongside modifications in life-style, can prevent osteoporosis and fractures. Use of bisphosphonates in the adjuvant setting also reduces breast cancer recurrences and deaths in older women.

Bone metastases are common in advanced breast cancer and may cause major morbidity including fractures, pain, nerve compression and hypercalcaemia. Diagnosis may be more difficult in the elderly due to overlapping clinical and imaging features with osteoporotic and degenerative bone diseases. Through optimum multidisciplinary management and use of both systemic treatments to treat the underlying cancer and bone-targeted treatments such as potent bisphosphonates or denosumab to improve the structural integrity of bone, the experience of advanced cancer patients has been transformed with a major reduction in skeletal complications, less bone pain and improved quality of life.

Keywords

Bone loss · Osteoporosis · Bone metastasis · Skeletal complications · Bisphosphonates · Denosumab

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12.1 Introduction

Due to a combination of earlier diagnosis and improved loco-regional and systemic adjuvant treatments, the management of early breast cancer has become increasingly successful, leading to current 10-year breast cancer survival rates of around 85%. Nevertheless, breast cancer remains a leading cause of cancer death in women and the median age of those who die of the disease is 68 years. Since the number of elderly women is rapidly rising, the number of breast cancers and their associated complications, including bone metastases and the adverse on bone of systemic therapies on bone, will inevitably increase.

12.2 Early Breast Cancer

Approximately 75% of all breast cancers and >85% of those in the older population are hormone receptor positive, and these patients are usually managed in the adjuvant setting with targeted hormonal agents and, if indicated due to adverse pathological features, cytotoxic chemotherapy. These treatments are not without side effects, and of particular relevance to the older woman is the impact of treatments on skeletal health.

Bone loss occurs naturally with increasing age, with 1 in 3 women over the age of 50 years sustaining a fragility fracture of the wrist, hip or vertebrae. Osteoporosis is defined by the World Health Organisation as a bone mineral density (BMD) result that is 2.5 standard deviations or more below that expected for young healthy women (T-score of ≤ -2.5 SD). A T-score of ≥ -1.0 is considered to reflect normal bone mineral density and a T-score between -1.0 and -2.5 classified as osteopenic [1]. Fragility fractures increase with decreasing T-score; however, an analysis of nearly 150,000 healthy post-menopausal women found that 82% of fractures occurred in non-osteoporotic women (T-score > -2.5) with 52% of fractures occurring in women with osteopenia (T-score -1.0 to -2.5) indicating that fracture risk is not just dependent on BMD [2]. In light of this, the WHO working group identified risk factors for fracture in addition to BMD; these include increasing age, female sex, smoking, personal history of fracture over the age of 50 years, a parental history of hip fracture, a low body mass index (BMI) of <20 mg/m^2, consumption of >3 units of alcohol per day, corticosteroid use and other diseases such as rheumatoid arthritis [3]. Older woman undergoing treatment for breast cancer are thus inherently at moderate to high risk of fracture onto which is added any adverse effects of treatment.

Importantly, an osteoporotic hip fracture is associated with a 20% risk of dying within 12 months [4] and this risk may be increased with the potential toxicities associated with breast cancer treatment. Hence, it is imperative for clinicians treating elderly women with breast cancer to be aware of the adverse effects of treatments on bone health and to act appropriately to protect and treat the skeleton.

12.2.1 Current Adjuvant Treatment of Early Breast Cancer

Aromatase inhibitors are now the cornerstone of hormonal therapy in post-menopausal women and, due to better efficacy, have largely superseded tamoxifen in this treatment setting. Large randomised trials have shown superiority of the aromatase inhibitors over tamoxifen in the adjuvant treatment of breast cancer in terms of disease-free survival, cancer recurrence and a number of important toxicities such as thrombo-embolic and endometrial complications. However, the aromatase inhibitors are not without side effects.

Older women, although post-menopausal with no ovarian production of oestrogens, still have low levels of circulating oestrogen resulting from the conversion of androgens to oestrogen by the enzyme aromatase in peripheral tissues; this is important for bone health as oestrogen inhibits osteoclastic resorption of bone and induces osteoclast apoptosis. Aromatase inhibition by either the non-steroidal reversible inhibitors (anastrozole and letrozole) or by the steroidal, irreversible inhibitor (exemestane) reduces circulating postmenopausal oestrogen to nearly undetectable levels. Therefore, such low levels of oestrogen induced by the aromatase inhibitors can be expected to accelerate bone loss in the elderly and have a negative impact on skeletal health.

Many older women with hormone receptor positive early breast cancer now receive an aromatase inhibitor as part of their management. This is usually recommended for 5 years but, in women at high risk for late recurrence, the duration of treatment may be extended for up to 10 years. An aromatase inhibitor is also the treatment of choice for elderly women receiving primary endocrine therapy instead of surgery where it is continued indefinitely or until progression. In most countries now, only women with hormone-receptor positive breast cancers who are unable to tolerate an aromatase inhibitor, are treated with tamoxifen alone [5].

12.2.2 Aromatase Inhibitor Induced Bone Loss

All aromatase inhibitors will induce bone loss. As part of the ‘Arimidex, Tamoxifen alone, or in Combination’ (ATAC) trial, a bone sub-study evaluated 308 women who were investigated for the comparative effects of anastrazole or tamoxifen on bone [6]. Lumbar spine and total hip BMD were assessed by dual energy X-ray absorptiometry (DXA) scan at base line, and at 1, 2 5 and 7 years. In anastrozole treated patients, there was a loss of BMD at 5 years of 6.08% at the lumbar spine, and 7.24% at the hip, compared to the tamoxifen-treated patients who had an increase in BMD of 2.77% (lumbar spine) and 0.74% (total hip). However, whilst anastrozole was associated with an accelerated loss of bone, this never resulted in a woman with a normal BMD at baseline becoming osteoporotic with a T score of ≤ -2.5. Fracture rates were significantly increased during treatment with anastrazole with an annual fracture rate in the anastrozole group of 2.93% compared to 1.9% in the tamoxifen group. Whilst on treatment, an incidence rate ratio of 1.55 [1.31–1.83], ($p < 0.0001$) was seen [7]. However, fracture rates between the groups

were not different following discontinuation of treatment and anastrazole treated patients had, on average, an increase in BMD at the lumbar spine and no further loss at the hip during years 5–7, suggesting that aromatase inhibitor bone loss is, at least partially, reversible [8].

The National Cancer Institute of Canada Clinical Trials Group MA-17 study investigated the benefit of letrozole versus placebo, after 5 years standard treatment with tamoxifen. The trial included over 5000 women and confirmed that the addition of letrozole, after 5 years of adjuvant therapy with tamoxifen, was associated with significantly improved disease-free survival (DFS) in postmenopausal women [9]. However adverse effects on bone were more frequent in the letrozole group with a significantly greater incidence of (newly) diagnosed osteoporosis than in the placebo group (8.1% versus 6%, respectively, $p = 0.003$), and a non-significant increase in fractures (5.3% versus 4.6%, $p = 0.25$). The MA-17 trial also had a bone sub-protocol that evaluated serial BMD changes in a subset of 226 women. As in the ATAC study, the letrozole-treated patients had a significant decrease in BMD, both at the hip ($p = 0.044$), and lumbar spine ($p = 0.008$) [10].

In the Intergroup Exemestane Study (IES), postmenopausal women completing 2–3 years of adjuvant tamoxifen were randomised to continue the treatment until the fifth year or switch to exemestane [11]. Exemestane is a steroidal aromatase inhibitor and possesses weak androgenic activity. As such exemestane was anticipated to have fewer adverse effects on bone than the non-steroidal AIs letrozole and anastrozole. However, this appears not to be the case. In the IES study, those treated with exemestane experienced a greater decrease in BMD and, in the intention to treat population, a higher annual fracture incidence (7.0%) was seen compared with those who continued to take tamoxifen (4.9%). Bone effects associated with use of non-steroidal and steroidal AIs thus appear to be similar [12]. Indeed, in the Letrozole, Exemestane, and Anastrozole Pharmacodynamics (LEAP) study in post-menopausal women, there were no detectable differences between letrozole, anastrozole, and exemestane on biochemical markers of bone metabolism [13] and it is now accepted that the effects of aromatase inhibitors on bone loss and fractures are a class effect and influenced more by other risk factors including age than the specific agent used. In the BIG 1–98 trial that compared letrozole to tamoxifen the influence of age on treatment efficacy and adverse events was assessed; age categories were: ‘younger’ post-menopausal patients (<65 years, n = 3127), ‘older’ patients (65–74 years, n = 1500), and ‘elderly’ patients (>75 years, n = 295) [14]. As with the overall trial results, letrozole significantly improved disease-free survival, and, importantly for considering the use of aromatase inhibitors in the elderly, this was not adversely affected by age. In the elderly (>75 years) group, whilst those receiving letrozole had a significantly greater number of grade 3–5 adverse events, compared to tamoxifen, fracture rates within the letrozole group did not differ by age. This observation differs from an analysis of the ATAC study in which 3 age groups (<60 years, 60–70 years, and >70 years) were assessed for risk of fracture associated with aromatase inhibitor use; the incidence of fracture increased over time and with increasing age, with the over 70 years age group being the most at risk [15].

The randomized controlled trials evaluating an aromatase inhibitor had stringent inclusion and exclusion criteria that may not reflect the unselected population seen in routine clinical practice. Furthermore, fracture ascertainment was through adverse event reporting and not a major endpoint of the trials. As a result the 1–2% per year fracture rate on treatment reported by the trials is probably an under-estimate [16]. The real-world fracture risk has been investigated in a number of case-control studies, prescription based analyses and single center observational studies. In a recent placebo-controlled trial for which fracture incidence was the primary endpoint, the fracture incidence in women with breast cancer on an aromatase inhibitor was found to be around 18–20% after 5 years follow-up suggesting that in clinical practice, about one in five women on an aromatase inhibitor without a bone protective agent will sustain a fracture [17].

Investigators have also evaluated CYP19A1 (aromatase) gene polymorphisms to see if these are associated with a higher susceptibility to aromatase inhibitor induced bone loss. It has been reported that G to A substitution at Val80 in the exon 3 (rs700518) is associated with significant BMD decrease at LS and hip at 12 months [18]. More recently, a significant correlation between another polymorphism (rs4646, GG genotype) and osteoporosis during treatment with an aromatase inhibitor was described [19].

12.2.3 Evaluation and Management of Bone Health in the Older Woman with Breast Cancer

Elderly women are at risk of osteoporosis from age alone, regardless of whether they have other risk factors, such as those imposed by breast cancer treatments, co-existing conditions or medication causing bone loss [20]. For this reason various screening tools have been set up for assessment of osteoporotic fracture risk, which can be applied to elderly women seen in the breast cancer clinic, regardless of whether DXA scan is available. The EPISEM database combined two prospective multicenter population-based cohorts, EPIDOS and SEMOF. EPIDOS (EPIDemiology of OSteoporosis), a cohort of 7598 French women ≥75 year. of age and SEMOF (Swiss Evaluation of the Methods of measurement of Osteoporotic Fracture risk), a cohort of Swiss women ≥70 years of age [21]. The populations were followed prospectively for clinical risk factors that could be used to determine hip fracture risk and which, when combined with quantitative ultrasound (QUS) measurement of the stiffness index of the heel, could estimate a 10 year probability of osteoporotic hip fracture. Clinical risk factors in elderly women that predicted future hip fracture included low BMI, previous history of fracture, an impaired chair test, diabetes, current cigarette smoking and history of recent fall. Combining a clinical risk factor score with the stiffness index score enhanced the predictive value of QUS or clinical risk factors alone, and was not dependent on DXA scanning.

Another screening tool for osteoporotic fracture risk assessment is the FRAX™, developed by the World Health Organisation Collaborating Centre for Metabolic

Bone Diseases [22]. Like the EPISEM database, this on-line tool gives a 10-year probability of fracture risk. FRAX™ also takes country of origin of patient into account and uses clinical risk factors, identified from previous meta-analyses (age, sex, BMI, previous history of fracture, a parental history of fracture, rheumatoid arthritis, use of glucocorticoids, current smoking, alcohol >3 units/day, and other secondary causes of osteoporosis) either alone or combined with BMD if a DXA scan result is available, to give a 10-year fracture risk. Assessment is done on-line at www.shef.ac.uk/FRAX/. The tool does not advise on treatments, which should be based on clinical judgement, but is a very useful adjunct in the clinic when faced with an elderly women who is about to start an aromatase inhibitor, especially if DXA is either not available or may take some time to perform.

12.2.4 Management of Aromatase Inhibitor Induced Bone Loss

All patients beginning an aromatase inhibitor should be advised to exercise moderately (resistance and weight-bearing exercise) [20, 23]. Although weight-bearing exercise has beneficial effects on BMD, fracture risk reduction has not been demonstrated. In addition, to maintain good bone health, the International Osteoporosis Foundation recommends a daily intake of 1200 mg calcium and 800–1000 IU vitamin D for postmenopausal women (guidelines available at www.iofbonehealth.org). Elderly women, or those with reduced physical activity and sunlight exposure, may need higher levels of these nutrients and for these individuals at high risk for fracture, the measurement of 25-OH Vitamin D levels is recommended and high dose vitamin D supplementation (100,000 IU weekly) given if deficient as daily supplements at the usual dose would take many months to bring deficient levels up to normal. For other postmenopausal women receiving an aromatase inhibitor, a dose of to 2000 IU of vitamin D every day is recommended to maintain replete levels. Although it is important to ensure adequate vitamin D intake for a range of health benefits, such supplements are not sufficient to prevent fractures; a meta-analysis of the use of Vitamin D +/− calcium supplementation in women with breast cancer showed no significant reduction in fracture risk [24].

For patients initiating an aromatase inhibitor and not receiving a bisphosphonate for disease recurrence prevention, a BMD measurement is advised. DXA scanning of the hip and lumbar spine is the preferred imaging technique, as it is generally available, sensitive and accurate. Other techniques, such as quantitative computed tomography, quantitative ultrasound, high-resolution magnetic resonance imaging and ultrasound transmission velocity densitometry, are not currently used routinely, but may have scope for the future.

Current guidelines for preventing bone loss in postmenopausal and older women with breast cancer suggest that patients having adjuvant endocrine treatment should be managed according to risk of fracture [20, 23]. Patients with a T-score of greater than −2 and no additional risk factors are advised to exercise and receive calcium and vitamin D, with risks and BMD monitored every 1–2 years. If the T-score is less than −2, or there are two or more risk factors (T-score < −1.5, age >65 years, low

BMI (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use of >6 months, and current or recent history of smoking), patients should receive the same advice and supplements plus a bisphosphonate (zoledronic acid, alendronate, risedronate or ibandronate) or denosumab. Figure 12.1 provides a management algorithm to illustrate this.

However, following on from the results of adjuvant bisphosphonate trials and, notably the EBCTCG meta-analysis [25], which compared outcomes in >18,000 women who were allocated adjuvant bisphosphonates of any type or duration versus those who were not, guidelines for prevention are evolving [26–28]. The improvements in both DFS and overall survival (OS) in early breast cancer in older patients with low levels of reproductive hormones are now clear. There is thus now a case for giving anti-resorptive therapy to all patients being treated with an aromatase inhibitor, independent of BMD; this should be a bisphosphonate (zoledronic acid, or daily oral clodronate or ibandronate) for those at moderate to high risk of disease recurrence and denosumab for those at low risk for recurrence where risk of fracture is the greater concern. Furthermore, given the steeply increased risk of hip fractures after the age of 70–75, prevention of bone loss with a bisphosphosphonate or denosumab should probably be recommended for all patients aged over 75 [20].

Older women are also at greater risk for having secondary osteoporosis, and should be investigated for this by measuring full blood count, erythrocyte sedimentation rate, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, transaminases), serum urea and creatinine, endomysial antibodies, and serum thyroid stimulating hormone. This will screen for conditions such as hyperparathyroidism, hyperthyroidism, chronic renal failure, and chronic liver failure, which may be overlooked or not clinically apparent in the elderly.

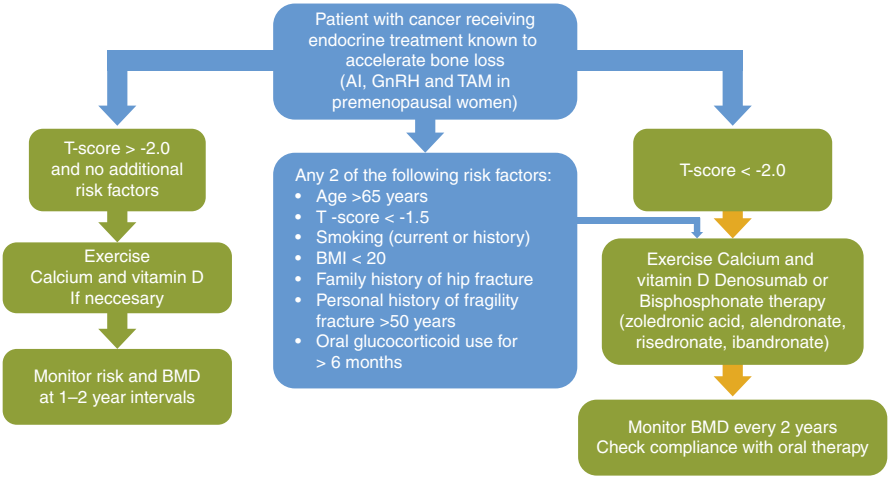

Fig. 12.1 Recommended algorithm for managing bone health in women receiving aromatase inhibitor therapy for breast cancer

12.2.4.1 Bone Targeted Agents for the Treatment of Aromatase Inhibitor-Induced Bone Loss

The effects of both bisphosphonates and denosumab on bone loss in postmenopausal women receiving aromatase inhibitors have been studied in multiple randomized clinical trials (Table 12.1). These studies have used dosing regimens that are similar, but not necessarily identical to those used for the treatment of age related osteoporosis.

Intravenous (IV) Bisphosphonates

The data supporting IV bisphosphonate therapy to prevent aromatase inhibitor bone loss in postmenopausal women with early breast cancer come predominantly from four independent studies with a total of more than 2700 postmenopausal women with early breast cancer. The three companion Zometa®-Femara® Adjuvant Synergy Trials (Z-FAST, ZO-FAST, E-ZO-FAST) compared the efficacy of zoledronic acid (4 mg IV every 6 months) given in conjunction with an aromatase inhibitor (immediate group), or after a BMD decrease to a T-score < −2.0 at any site or a non-traumatic fracture (delayed group) [29, 30, 32]. The final 61-month update from Z-FAST showed that delaying zoledronate resulted in losses in BMD at lumbar spine and total hip (−2.42% and −4.12%, respectively; P ≤0.0003 for both vs. baseline) [30]. However, patients who immediately initiated zoledronic acid continued to gain BMD at the lumbar spine and total hip (P ≤0.0003 for both vs. baseline). Similar positive results were seen for the 60-month analysis of the ZO-FAST study [29] and the E-ZOFAST trial [32]. Supporting data come from the N03CC (ALLIANCE) trial in which women who received immediate zoledronic acid had significantly increased mean BMD at both the lumbar spine (3.66% at 12 months and 4.94% at 24 months) and total hip (1.02% at 12 months and 1.22% at 24 months) compared with baseline (P <0.001) for all comparisons [31].

None of these studies were designed to show a significant difference in fracture incidence between the treatment arms. Nevertheless, despite the absence of fracture data, the BMD data from these four well-designed trials demonstrate that zoledronic acid (4 mg every 6 months) at initiation of aromatase inhibitor therapy can effectively prevent the associated bone loss. Data from trials in postmenopausal osteoporosis would suggest that bisphosphonates confer a relative risk reduction (RRR) of 45% for vertebral fractures and approximately 16% RRR for non-vertebral fractures. No specific information is provided on the effects in older women but there is no reason to anticipate that the response to zoledronic acid would be significantly influenced by age.

Oral Bisphosphonates

Several randomized clinical trials have investigated the efficacy of oral bisphosphonates for preventing aromatase inhibitor bone loss. These include SABRE [33], IBIS II [36] and ARBI [37] amongst others for risedronate, ARIBON [39] for oral ibandronate and BATMAN [40] for alendronate. The numbers of patients included in each study is somewhat less than for the zoledronic acid studies and thus, unlike for other forms of osteoporosis, the evidence for efficacy of oral bisphosphonates in this

Table 12.1 Major trials of anti-resorptive agents for the prevention of aromatase anhibitor bone loss

Anti-resorptive agent (Trial)	N	BMD data, N[a]	Dose	Treatment duration	Follow-up, months	Mean BMD increase from baseline, %		
							LS	TH
IV bisphosphonates								
Zoledronic acid (ZO-FAST) [29]	1065	264	4 mg q6mo	5 yr	60		4.3	1.6
Zoledronic acid (Z-FAST) [30]	602	602	4 mg q6mo	5 yr	61		6.2	2.6
Zoledronic acid (N03CC) [31]	558	395	4 mg q6mo	5 yr	24		4.9	1.2
Zoledronic acid (E-ZO-FAST) [32]	527	527	4 mg q6mo	5 yr	36		6.0	NR
Oral bisphosphonates								
Risedronate (SABRE) [33]	154	111	35 mg/wk	2 yr	24		2.2	1.8
Risedronate (REBeCCa) [34]	87	87	35 mg/wk	2 yr	24		0.4	0.9
Risedronate (REBeCCa2) [35]	109	102	35 mg/wk	2 yr	24		2.3	0.6
Risedronate (IBIS II- osteopenic) [36]	245	127	35 mg/wk	5 yr	60		−0.4	−2.5
Risedronate (IBIS II- osteoporotic) [36]	73	41	35 mg/wk	5 yr	60		0.3	−0.7
Risedronate (ARBI) [37]	213	132	35 mg/wk	2 yr	24		5.7	1.6
Risedronate (French study) [38]	118	11	35 mg/wk	1 yr	12		4.1	1.8
Ibandronate (ARIBON) [39]	131	50	150 mg/mo	5 yr	60		5.0	1.2
Alendronate (BATMAN) [40]	303	303	70 mg/wk	3 yr	36	Osteoporotic	15.6	5.6
						Osteopaenic	6.3	6.3
Rank ligand inhibition								
Denosumab (HALT-BC) [41]	252	252	60 mg q6mo	2 yr	24		6.2[b]	3.7[b]
Denosumab (ABCSG-18) [17]	3420	3420	60 mg q 6mo	3 yr	36		10.2	7.9

Fracture reduction: OR 0.53 (CI 0.333–0.85, p = 0.009)

Abbreviations: *AI* aromatase inhibitor, *AIBL* aromatase inhibitor-associated bone loss, *BMD* bone mineral density, *LS* lumbar spine, *mo* months, *NR* not reported, *TH* total hip, *yr* years

[a]Number of patients randomized to bisphosphonate and evaluable for BMD at the reported timepoint

[b]Estimates based on published graph.

specific setting is less robust. Additionally, indirect cross trial comparisons suggest the increases in BMD are somewhat less with oral regimens than with zoledronic acid or (as shown below) denosumab. Again, none of the trials with oral agents were designed to assess reliably the impact of oral bisphosphonates on fracture risk.

Oral bisphosphonates are generally well tolerated. However, the rigid dosing requirements for oral bisphosphonates, with fasting before and after dosing and the need to remain upright after dosing are associated with some inconvenience for patients. Moreover, patients' compliance and persistence with oral therapies is suboptimal [42]. Insights from the osteoporosis setting show poor long-term adherence to treatment. In one study, less than 20% of patients receiving a daily bisphosphonate and only 30% on a weekly regimen achieved clinically relevant persistence levels over 1 year [43]. Because of the strong association between treatment adherence and clinical outcome, strategies to improve patients' compliance and persistence with oral bisphosphonate therapy are necessary to ensure benefit from these agents in the aromatase inhibitor bone loss setting.

Denosumab

The Adjuvant Denosumab in Breast Cancer Trial (ABCSG-18) is the only study to have fracture incidence as the primary endpoint and was adequately powered to investigate the effect on fracture risk [17]. The trial compared adjuvant denosumab (60 mg by subcutaneous injection given twice a year) with placebo (both with calcium and Vitamin D supplements) in 3425 postmenopausal women receiving adjuvant aromatase inhibitor treatment. Postmenopausal women with hormone receptor positive breast cancer treated with denosumab had a significant risk reduction of any clinical fracture (hazard ratio [HR] 0.50 [95% CI 0.39–0·65], p <0.0001). Denosumab treatment furthermore significantly decreased the number of incident vertebral fractures and worsening of prevalent vertebral fractures over 36 months (odds ratio 0.54 [95% CI 0.34–0·84], p = 0.007). The fracture risk reduction appeared to be irrespective of age and baseline BMD.

12.2.5 Disease Modifying Effects of Bone Targeted Treatments

The potential benefits of bone-targeted treatments on the clinical course of breast cancer in terms of prevention of recurrence and death from breast cancer have been an area of intense study over the past 20 years. Individual trials provided varying results that suggested benefits were restricted to women who had low levels of reproductive hormones due to either natural age related menopause or ovarian function suppression. This hypothesis was confirmed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of individual patient data from >18,000 breast cancer patients included in randomized trials of adjuvant bisphosphonates. The meta-analysis showed that adjuvant bisphosphonates (intravenous zoledronic acid, oral clodronate and oral ibandronate) only reduced breast cancer recurrences and breast cancer deaths in postmenopausal women [25]. Overall, across all age and menopausal groups, despite a reduction in bone

metastases, adjuvant use of a bisphosphonate had no significant effect on breast cancer recurrence (rate ratio 0.94) and the effect on breast cancer mortality, though statistically significant, was small (RR = 0.91). However, in postmenopausal women or those receiving ovarian suppression with goserelin, clinically important benefits were seen with improvements in overall breast cancer recurrence (RR = 0.86), distant recurrence at any site (RR = 0.82), bone recurrence (RR = 0.72) and breast cancer-specific mortality (RR = 0.82). This equates to prevention of more that 1 in 6 breast cancer deaths at 10 years. Several international guidelines now recommend the use of adjuvant bisphosphonates in postmenopausal early breast cancer [23, 26–28], especially for those at moderate to high for recurrence (Fig. 12.2).

The disease modifying effects of denosumab have also been assessed but this agent, at least when given in the intensive schedule selected in the adjuvant DCARE study, has no effect on disease recurrence in either pre- or postmenopausal women

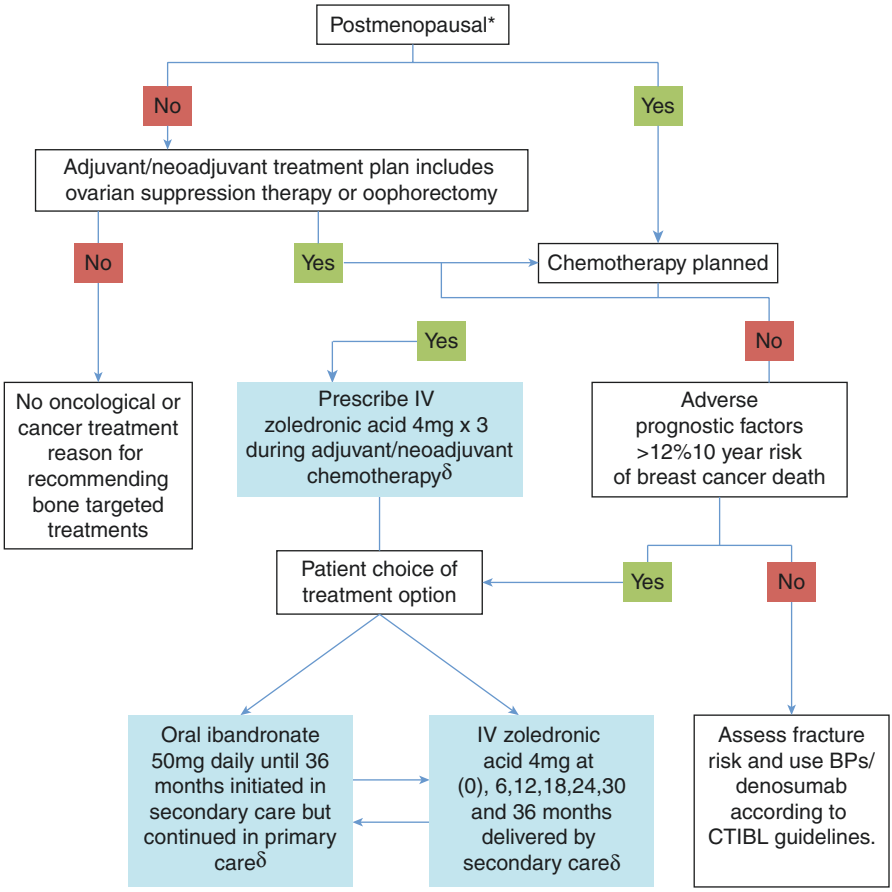

Fig. 12.2 Algorithm for selecting adjuvant bisphosphonate treatment to improve disease outcomes as the priority rather than fracture prevention

[44]. The osteoporosis schedule of denosumab may have some beneficial effects on the underlying disease but no survival benefits have been seen and the agent is only recommended for fracture prevention.

Bisphosphonates do not currently have regulatory approval for the prevention of breast cancer recurrence that may limit the ability to prescribe these agents in some health care settings unless the patient fulfills the criteria for intervention due to bone health concerns and risk of osteoporosis or fracture. However, several international expert panels of oncologists and bone experts have published guidelines and consensus statements recommending the use of adjuvant bisphosphonates in women with breast cancer at intermediate or high risk for disease recurrence due to adverse clinical or biological characteristics such as node positive disease, tumour size >2 cm, grade II/III breast tumor or disease found to be ER negative or HER-2 positive (Fig. 12.2). This means that, where available, women with early breast cancer may be recommended to receive a bisphosphonates irrespective of fracture risk. In this setting, BMD monitoring may not be necessary.

12.2.6 Current Recommendations for Choice of Bone Targeted Agents

Based on current evidence, subcutaneous denosumab (60 mg twice yearly) and intravenous zoledronate (4 mg q6mo) were the preferred agents recommended for prevention and treatment of aromatase inhibitor bone loss in recent guidelines endorsed by a wide range of international osteoporosis societies and the Cancer and Bone Society [28].

If an oral bisphosphonate is preferred, 35 mg risedronate/week is the bisphosphonate with the strongest evidence for prevention of aromatase inhibitor associated bone loss. Alendronate 70 g weekly or ibandronate 150 mg monthly may also be considered. BMD should be monitored and compliance assessed every 1–2 years in all patients receiving oral bisphosphonate therapy. Periodic assessment of bone resorption markers may offer a convenient, non-invasive measure of compliance with therapy. In case of poor compliance or a decline in BMD after 1–2 years of treatment, a switch to denosumab or an intravenous bisphosphonate is recommended. For patients receiving denosumab or intravenous bisphosphonates, BMD monitoring during therapy is much less important as compliance is assured. Repeat assessment of BMD may be performed on an individualized basis and in accordance to local guidelines.

Patients receiving an aromatase inhibitor are at increased risk for fracture for at least the duration of treatment. As a result, guidelines recommend continuing antiresorptive therapy for as long as the patient is receiving the aromatase inhibitor (up to 5–10 years), although there is uncertainty about the need to continue bisphosphonate treatment in years 6–10 for those women on extended therapy. Patients treated with denosumab may need bone protection with a bisphosphonate when the treatment is discontinued to prevent rebound osteolysis and the increased risk of multiple vertebral fractures associated with denosumab withdrawal [45].

12.3 Advanced Breast Cancer

Breast cancer commonly metastasises to the skeleton, representing the most commonly affected organ and the first site of metastases in approximately half of patients developing recurrent disease. Furthermore 65–75% of women with metastatic breast cancer have skeletal involvement [46]. In stark contrast to first relapse at a visceral site, the median survival of patients with first relapse in the skeleton is associated with a more prolonged clinical course, at 2–5 years [46, 47], depending on whether other metastatic sites are involved or not, and so the prevalence of metastatic bone disease from breast cancer is high. Bone metastases are associated with considerable morbidity and thus place significant demands on health care systems.

12.3.1 Causes of Bone Metastases

Bone is a fertile soil for metastatic tumour growth. Disseminated tumour cells, facilitated by growth factors and exosomes released by the primary tumour, can initiate the metastatic process before the diagnosis of breast cancer is made. These circulating tumour cells are attracted to bone surfaces within the bone marrow and are thought to bind to the osteoblastic, vascular and haematopoetic niches within the bone marrow where they may enter a state of tumour dormancy lasting for years before signals, currently uncharacterised, encourage the dormant disseminated tumour cells to leave their quiescent state, start to proliferate and initiate overt metastases both in bone and at other anatomical sites [48]. Late recurrence of the disease is frequent, especially to bone, with disseminated malignant cells seemingly able to evade adjuvant treatments and remain dormant, before re-activating and causing disease relapse many years after diagnosis.

The presence of proliferating tumour cells inside the bone microenvironment has been shown to destroy the normally balanced coupling of osteoclastic bone resorption and osteoclastic bone formation [49]. The release of tumour cell derived factors, such as PTHrP, and a variety of growth factors and cytokines stimulate osteoclastic activity, leading to accelerated bone resorption and the formation of lytic and destructive bone lesions. This mainly occurs through the osteoblastic activation of receptor activator of nuclear factor κβ (kappa beta) ligand (RANKL) and subsequent binding to its receptor, RANK, which is present on osteoclasts [50]. As a result of this accelerated bone resorption, increased levels of bone derived growth factors, such as TGF-β (beta), are released from the bone matrix and in turn stimulate tumour growth. This creates the formation of a self-sustaining vicious cycle of cancer induced bone disease. Inhibition of bone resorption and blockade of these molecular pathways within the vicious cycle have become therapeutic targets and strategies for both treatment and, more recently as described earlier, the prevention of bone metastases.

12.3.2 Diagnosis of Bone Metastases

Bone metastases from breast cancer are most common in the axial skeleton and limb girdles, thought to be as a result of the drainage of blood via the vertebral-venous plexus to these sites. Once established, bone metastases commonly cause pain that may be severe; however, lesions can also be painless and discovered unexpectedly by imaging tests. In older patients, the diagnosis of bone metastases can be problematic, due to the co-existence of more common bone disorders such as degenerative disease, traumatic fractures and osteoporosis. In elderly women with a previous history of breast cancer presenting with back pain, it may be very difficult to ascertain the aetiology as both malignant osteolytic destruction and osteoporotic collapse may have similar clinical and imaging characteristics. The implications for the patient of an advanced breast cancer diagnosis are profound and, consequently, a patient should only be labelled with a diagnosis of metastatic skeletal disease in the presence of confirmatory investigations. To ascertain the correct diagnosis, it is imperative that the clinical presentation and relevant medical history are interpreted alongside appropriate imaging complemented by additional investigations such as tumour and bone biomarkers. The measurement of metabolic bone markers in serum, such as bone alkaline phosphatase (bALP), propeptides of procollagen type 1 (all markers of bone formation), and markers of bone resorption and the breakdown of type I collagen, such as serum C-telopeptide (CTX) and N-telopeptide (NTX) in urine, are only occasionally of value in diagnosis but do provide useful prognostic information on the risk of skeletal morbidity and predict clinical outcomes [51].

12.3.3 Skeletal Morbidity

Breast cancer patients with bone metastases are at significant risk for skeletal morbidity that can be debilitating and result in loss of function and independence as well as reduced survival. Complications include pain that may require narcotic analgesia and/or radiotherapy, hypercalcaemia, pathological fracture and/or the need for orthopaedic intervention, spinal cord or nerve root compression and hypercalcaemia of malignancy. These skeletal complications, also termed skeletal related events (SREs) can significantly reduce a patient's quality of life as well as social and functional independence and, additionally, impact adversely on carers and health care resources. In the pre-bisphosphonate era, almost 70% of women with breast carcinoma and osteolytic bone metastases (of whom approximately one third of patients were >65 years old) had at least one SRE over the course of a 2-year follow-up. The most frequent SRE was pathological fracture, occurring in approximately 50% of patients. On average, patients experienced an average of four skeletal events, including two pathological fractures per year, with an increase in frequency as the disease progressed and therapeutic options declined [52].

12.3.4 Treatment of Bone Metastases in Older Breast Cancer Patients

Bone metastases from breast cancer represent incurable disease but, as the median survival of patients with metastatic disease confined to the skeleton is measurable in years, both symptomatic treatment and prevention of longer-term risks of bone-related events form an essential part of clinical care. The primary goals of treatment are to palliate symptoms and reduce the risk of bone events, thereby maintaining quality of life. Patients require input from a multi-disciplinary team setting that should include involvement not only of medical and radiation oncologists but also radiologists, orthopaedic surgeons, palliative care physicians and specialist nurses.

There are additional considerations in older patients that should also be taken into account. Ageing is associated with a progressive physiological decline in the functional reserve of organ systems e.g. age related decline in glomerular filtration rate and an increased prevalence of co-existing co-morbidities associated with the challenging problem of poly-pharmacy, including the potential concomitant administration of medications such as non-steroidal anti-inflammatory drugs for pain, as well as anti-hypertensive, lipid-lowering and anti-diabetic drugs.

12.3.4.1 Treatment of Bone Pain

Many patients with metastatic skeletal disease experience significant bone pain, which remains a clinically challenging problem to treat rapidly and effectively. The pathophysiology of cancer-induced bone pain is not well understood although animal models have revealed potential mechanisms that may be used as strategies for targeted therapies. Bone pain may be due to a combination of a neuropathic type nerve injury, direct tumour compression or ischaemia and sensitisation of peripheral nociceptors or primary afferent neurons as a result of the release of a variety of growth factors and cytokines, such as prostaglandins, endothelins and TGF-β [53]. Appropriate analgesia should follow the principles of the WHO analgesic ladder starting with non-opioid analgesia including paracetamol and non-steroidal anti-inflammatory drugs and followed by weak and ultimately, for some, increasing doses of strong opioids. Analgesics are the first line of treatment supplemented, as appropriate, by the addition of adjuvant analgesics including glutamate inhibitors and NMDA antagonists.

Beyond analgesics, treatment for metastatic skeletal disease includes external beam radiotherapy, radioisotopes, surgical stabilisation and systemic therapies including endocrine treatment, chemotherapy and bone targeted agents. The choice of therapy often depends on whether the symptomatic disease is focal or widespread and on the presence or not of visceral metastases. The clinical course may be characterised by periods of disease response or stability, interspersed by progressive disease, at which point changes in therapy are warranted in an attempt to regain disease control. However, ultimately resistance to all anticancer treatments emerges.

- **Radiation therapy**

External beam radiotherapy is a highly effective and relatively simple treatment for metastatic bone pain, with up to 80% of patients having some pain relief and approximately one-third experiencing complete pain relief [54]. Numerous published studies have reported similar efficacy in terms of pain relief between single and multiple fractions in the management of painful bone metastases. A meta-analysis showed no significant difference in rates of pain relief and duration of palliation among different dose and fractionation schedules of localised radiotherapy ranging from 8 Gy in a single fraction to 40 Gy in 15 fractions; overall response rates of 73% were seen with both the single and multi-fractionation arms [55]. There appears to be a higher need for re-treatment rate with the use of single large fractions, but many patients prefer the convenience of a single fraction radiotherapy regimen, especially elderly patients who may have co-morbidities; the single fraction approach is also recommended from a health economic perspective.

Systemically administered radioisotopes such as strontium-89 and samarium-153, although not often used, have been shown to reduce bone pain in patients with widespread painful bone metastases [56] These agents preferentially bind to bone matrix in areas of active bone turnover. Most of the published data relates to studies in hormone-resistant prostate cancer, and as yet, only small studies in breast cancer patients have been reported. Nevertheless, this limited experience has demonstrated improvements in pain and reduction of analgesic use with acceptable adverse event profile. Repeated dosing is possible, and further research in breast cancer patients is certainly warranted with the newer, safer alpha-emitting radiopharmaceuticals such as radium-223.

- **Surgery**

Metastatic destruction of bone causes a reduction in load-bearing capability and the accumulation of resulting microfractures may lead to pathological fracture, most commonly occurring in ribs and vertebrae. Fracture of a long bone or epidural extension of tumour into the spine represent major complications and will often require surgical intervention. The aims of surgery are to relieve pain, provide structural stability, restore mobility and in the case of vertebral metastases, reduce neurological deficit or risk of nerve compression. Increased attention is focused on the prediction of long-bone metastatic sites at risk of fracture, and in these patients, referral to an orthopaedic surgeon should be considered to evaluate the need for prophylactic surgery. Prophylactic internal fixation should be generally followed by radiotherapy to try and prevent failure of the prosthesis as the disease and resultant bone destruction progresses. Spinal instability causes debilitating pain that is mechanical in origin and can be refractory to radiotherapy or systemic therapy. Referral to a spinal surgeon is strongly recommended for consideration of spinal stabilisation. In an appropriately selected patient group, major clinical benefits can result from skilled surgical intervention and age, *per se,* should not be seen as a barrier to surgical management.

Spinal cord or cauda equina compression is always a medical emergency and requires immediate attention and treatment, including high dose steroids and urgent referral for radiotherapy or surgical decompression and spinal stabilisation. Early diagnosis is paramount to successful rehabilitation.

- **Systemic therapy**

Systemic therapy for the treatment of bone metastases from breast cancer can potentially have direct or indirect anti-tumour effects. Endocrine therapy, cytotoxic chemotherapy, and biologically targeted agents aim to directly reduce skeletal tumour burden and the release of tumour cell-derived growth factors and cytokines. Alternatively, bone targeted treatment e.g. bisphosphonates or denosumab, are given to inhibit the effects of tumour cell-derived factors on host bone cells, such as osteoclasts and osteoblast / stromal cells and minimise the risk of SREs.

Endocrine treatment, increasingly supplemented by a target agent such as an inhibitor of the CDK4/6 pathways, is the preferred initial treatment option in the initial management of patients with hormone receptor positive breast cancer and metastases isolated to bone. Median time to progression with modern endocrine treatment combinations is around 2 years [57]. There are few data specific to elderly patients, but a single trial has reported that letrozole, as first-line treatment, is as effective in older post-menopausal women (≥70 years) as in younger post-menopausal women (<70 years) in analyses of time to progression and objective response rate, and was more effective than tamoxifen in both older and younger patients [58].

Chemotherapy is indicated in patients with hormone-insensitive tumours and in those with rapidly progressing life-threatening disease in addition to bone metastases. Women over the age of 70 treated with chemotherapy for metastatic disease gain similar benefits to younger patients, and therefore should not be excluded from chemotherapy treatment on the basis of age alone The addition of trastuzumab with chemotherapy or, especially in an elderly population, endocrine treatment should be considered in all patients with HER2/neu positive disease. Treatment decisions should also always be influenced by the presence of co-morbidities and, most importantly, the wishes of the patient.

The primary aim of palliative chemotherapy is control of symptoms, with pain relief and resumption of functional activity the main goals. In general, responses to treatment are only partial, with a median duration of response of around 12 months. Strict on-treatment review of patients is required to ensure avoidance of over-treatment and to monitor impact on quality of life, toxicity, and the need for dose modification and supportive care. Chemotherapy may be potentially hazardous in those with disease-induced poor bone marrow reserve and the use of haematopoietic growth factors may be required. Recommendations of the International Society of Geriatric Oncology suggest that preference should be given to monotherapy using chemotherapy drugs with safer profiles such as weekly taxane regimens, anthracycline formulations with less cardiotoxicity, and capecitabine, gemcitabine and vinorelbine [59].

- **Bone targeted treatments**

Bone targeted agents, both bisphosphonates and denosumab, as potent inhibitors of osteoclast-mediated bone resorption, have become firmly established in the treatment of breast cancer patients with bone metastases [23] Guidelines suggest that starting bone targeted agents should be considered in patients with breast cancer as soon as bone metastases are confirmed by radiographs, even in absence of symptoms and continued indefinitely throughout the course of the disease as patients transition from one anticancer agent to another [23, 60].

Clinical trials that have investigated the benefits of bisphosphonates in the setting of bone metastases from breast cancer have used a variety of clinical end-points. Endpoints such as assessments of quality of life and pain can be affected by subjective bias and therefore trials have assessed measurement of skeletal-related events (SRE) as a composite end-point. These are defined as events including pathological fracture, spinal cord compression, irradiation of or surgery on bone, and hypercalcaemia of malignancy. Effective treatment that prevent or delay these events would clearly be of clinical importance, impacting positively on quality of life and clinical outcome.

Both intravenous and oral bisphosphonates have shown significant clinical benefit in breast cancer patients with bone metastases and are approved in this treatment setting (Table 12.2). Back in the 1990s, randomised placebo-controlled trials of pamidronate infusions for up to 2 years in addition to chemo- or hormonal therapy in breast cancer patients with at least one lytic bone metastasis demonstrated that bisphosphonates could reduce skeletal morbidity rate by more than one-third, increase the median time to the occurrence of the first SRE by almost 50% and reduce the absolute number of patients having any SRE [64, 65].

Subsequently, more convenient and effective aminobisphosphonates have emerged including zoledronic acid and both intravenous and oral ibandronate [66–69]. A randomised, double-blind, multicentre trial compared the efficacy of zoledronic acid and pamidronate in 1648 patients with breast cancer or multiple myeloma. The proportions of patients with at least one SRE (the primary efficacy end point) were similar in all treatment groups and the pre-established criterion for non-inferiority of zoledronic acid versus pamidronate was met [69]. A multiple-event analysis in the breast cancer subgroup however showed that zoledronic acid (4 mg) reduced the risk of developing a skeletal complication by an additional 20% compared with that achieved by pamidronate (P <0.05) [70]. The short infusion time also offers a more convenient therapy.

Oral ibandronate may be considered for patients who are not able to attend regular hospital care. This agent was compared to intravenous zoledronic acid in a randomised trial of 1404 patients and shown to be not quite as effective in prevention of skeletal morbidity as zoledronic acid. Although similar to zoledronic acid in delaying time to the first event the overall risk of skeletal events (rate ratio for SREs was 1.148, 95% CI: 0.967–1.362) and non-inferiority could not be established [71].

It should also be remembered that the use of oral bisphosphonates is complicated by specific dosing requirements needed to minimise gastrointestinal toxicities and

Table 12.2 Randomised placebo- controlled trials demonstrating the effects of BPs (at currently recommended doses) on skeletal morbidity

BP and formulation	No. of patients	Results
Clodronate 1600 mg/day PO Paterson et al. [61]	173	Significantly reduced combined event rate of all morbid skeletal events: SMR 305 vs. 219 events/100 women years ($p < 0.001$) HR for ≥1 SRE 0.83; NS
Clodronate 1600 mg/day PO Kristensen et al.* [62]	100	Significantly delayed time to first SRE ($p = 0.015$) Reduced fracture incidence ($p = 0.02$) HR for ≥1 SRE 0.69; NS
Clodronate 1600 mg/day PO Tubiana-Hulin et al. [63]	144	Significantly delayed time to first SRE (244 days vs. 180 days, $p = 0.05$) Reduction in pain intensity and use of analgesia HR for ≥1 SRE 0.92; NS
Pamidronate 90 mg, 3–4 weekly IV Hortobagyi et al. [64]	382	Significantly reduced percentage of patients experiencing SRE (65% vs. 46%, $p <0.001$) Significantly delayed time to first SRE (13.1 months vs. 7.0 months, $p = 0.0005$)
Pamidronate 90 mg, 4 weekly IV Theriault et al. [65]	374	Significantly reduced percentage of patients experiencing SRE (67% vs. 56%, $p = 0.027$) Significantly delayed time to first SRE (10.4 months vs. 6.9 months, $p = 0.049$)
Ibandronate 2 or 6 mg, 3–4 weekly IV Body et al. [66]	466	6 mg dose vs. placebo: significantly reduced SMPR** by 20% (1.48 vs. 1.19 periods with events per patient year, $p = 0.004$) 2 mg dose: no significant clinical benefit Significantly delayed time to first SRE (50.6 weeks vs. 33.1 weeks, $p = 0.018$) Reduction in pain intensity and use of analgesia
Ibandronate 50 mg/day PO Body et al. [67]	564	Significantly reduced SMPR** (1.18 vs. 0.95, $p = 0.004$) HR for ≥1 SRE 0.86; $p = 0.08$
Zoledronic acid 4 mg, 4 weekly IV Kohno et al. [68]	228	Significantly reduced percentage of patients experiencing SRE** (50% vs. 30%, $p = 0.003$) Significantly delayed time to first SRE ($p = 0.007$) Reduction of risk of SREs by 41%** in multiple event analysis (RR = 0.59, $p = 0.019$) Significantly improved pain scores compared to placebo

SMR skeletal morbidity rate, * not placebo-controlled, *SMPR* skeletal morbidity period rate (the number of 12 week periods with new bone events, allowing for time on study, **excludes HCM)

to ensure adequate absorption. Oral bisphosphonates are poorly absorbed from the gut and absorption is negatively affected by food intake. Furthermore, oral formulations need to be taken on an empty stomach in the upright position, and patients should continue to fast and remain upright for at least 30 minutes post dosing. These complex instructions for treatment adherence may be particularly challenging for older patients who are likely to be on multiple medications and may have a degree of memory impairment.

The efficacy of denosumab in metastatic breast cancer was clearly demonstrated in a double-blind, phase III randomised trial that included a total of 2049 bisphosphonate-naive patients with bone metastases [72]. Patients were randomly assigned to receive subcutaneous injections of denosumab (120 mg) or intravenous zoledronic acid (4 mg) every 4 weeks, with supplements of calcium and vitamin D. The primary end point was the time to first SRE. Denosumab was statistically superior to zoledronic acid in delaying the first SRE (HR 0.82, 95% CI: 0.71–0.95, $P = 0.01$) and also superior to zoledronic acid in preventing subsequent SREs, reducing the overall risk of SREs over and above that achieved with zoledronic acid by a further 23% (HR = 0.77, 95% CI, 0.66–0.89, $P = 0.001$). Small benefits in pain relief and quality of life in favour of denosumab were also seen.

12.3.5 Prescribing Bone Targeted Agents in the Elderly Patient

There are limited data on the specific use of bone-targeted agents in elderly breast cancer with bone metastases. However, a population-based analysis of the use of intravenous bisphosphonates in older women treated for breast cancer reported that women ≥75 years old were less likely to receive treatment than patients <70 years old [73]. However, following a consideration of life expectancy and potential benefit, their use is recommended with no specific limitations. Clearly, it is important that the treating physician chooses the most appropriate bone targeted agents with the most acceptable toxicity profile, weighed up against the patient's co-morbidities, functional status and concomitant medications. Unfortunately, comparative safety and efficacy data of bone-targeted agents in older patients specifically are lacking. However the choice and implications of administration may be of considerable importance in the elderly patient, and specific considerations in this age group are presented in (Table 12.3).

Elderly patients are at higher risk of developing renal impairment; this may be due to reduced hydration or the use of concomitant nephrotoxic drugs such as non-steroidal anti-inflammatory agents and anti-hypertensives. The use of concomitant nephrotoxic agents with bisphosphonates should be limited if possible. An International Society of Geriatric Oncology task force recommends that in patients being treated with pamidronate or zoledronic acid, creatinine clearance should be monitored in every patient, even when serum creatinine is within the normal range, with evaluation and optimisation of hydration status and review of concomitant medications [20].

In addition, the elderly have an increased incidence of dental problems, and therefore are potentially at higher risk of osteonecrosis of the jaw (ONJ). This complication is characterised by the appearance of exposed bone in the maxillofacial region with failure of healing after 8 weeks. The development of ONJ seems to be related to potency, frequency of administration and duration of treatment and much more likely in patients undergoing a significant dental intervention e.g. extraction. The risk appears to be approximately 1% per year on monthly intravenous

Table 12.3 Current bisphosphonates licensed for treatment of bone metastases in breast cancer (summary table compiled from recommendations of the International society of geriatric oncology of the use of BPs in elderly patients)

BP choice	Formulation	Dose and schedule	Considerations in the elderly patient
Clodronate[a]	Oral	1600 mg daily (single or 2 divided doses) Range: 800–3200 mg	Reduce dose to 800 mg daily in severe renal impairment (<30mls/min) Contraindicated if cr.cl <10mls/min High incidence of gastrointestinal adverse events/difficulty swallowing may limit compliance Avoidance of food for 1 hour before and after medication
Pamidronate	Intravenous infusion over 2 hours	90 mg every 3–4 weeks	Monitor renal function prior to each dose Not recommended if cr. cl <30 ml/min Withhold until renal function returns to within 10% of baseline value Caution when used concurrently with other potential nephrotoxic drugs
Zoledronic acid	Intravenous infusion over 15 minutes	4 mg every 3–4 weeks	Monitor renal function prior to each dose Not recommended if cr. cl <30mls/min Withhold treatment in patients with renal deterioration Caution when used concurrently with other potential nephrotoxic drugs
Ibandronate[a]	Oral or intravenous infusion over 1 hour	Oral: 50 mg daily Intravenous: 6 mg every 3–4 weeks	Renal monitoring at physician's discretion Reduce dose if cr. cl <30mls/min: 2 mg IV every 3–4 weeks or 50 mg PO weekly No dosing restrictions with other potential nephrotoxic drugs Oral formulation to be given upright after overnight fast, before food

[a]Approved in Europe but not USA, *cr. cl* creatinine clearance

bisphosphonate or denosumab therapy. It is strongly recommended that a dentist reviews patients before starting bone-targeted therapy and any pre-existing dental problems treated to reduce the risk of ONJ in the future [74].

There remains uncertainty regarding the most appropriate duration and schedule of treatment, and factors that need to be taken into consideration, particularly in the older patient, include life expectancy, disease extent and the risk of developing a SRE, the logistics and accessibility of treatment for the patient, and treatment cost. Bone targeted therapy should certainly not be stopped following the development of a first skeletal related event whilst on treatment; this should not be considered a failure of treatment, as the trials demonstrate a significant reduction in second and subsequent complications with continued treatment.

Several trials have investigated the schedule of bisphosphonate treatment. Two studies recruiting patients after about a year of monthly treatment to "load" the skeleton (ZOOM and OPTIMIZE) suggested that the efficacy of 3 monthly and monthly administration of ZA is similar [75, 76]. More recently, the CALGB 70604 (Alliance) trial, randomised patients with bone metastases from a range of different primary tumour types (including breast cancer) to zoledronic acid on a monthly or three monthly schedule from the outset of treatment for 2 years. This study demonstrated non-inferiority of less frequent administration; in both arms, 29% of patients developed ≥1 SRE [77]. The proportion of patients with renal dysfunction (2% versus 0.6%) and ONJ (2% vs 1%) were similar for the monthly and three-monthly schedules respectively. There are some concerns about numerically higher numbers of patients requiring surgical intervention for fractures or developing spinal cord compression with administration every 3 months. However, overall, the evidence suggests that three monthly administration of zoledronic acid is reasonable, certainly after a short period of monthly treatment.

12.4 Summary

Older patients represent a significant proportion of the breast cancer population and are unfortunately substantially under-represented in clinical trials. Patients with bone metastases from breast cancer are at significant risk of skeletal morbidity, associated with debilitating consequences complicating the clinical course and contributing to reduced survival. There are important considerations specific to this population, and the optimal management of bone metastases requires an experienced multi-disciplinary input to ensure appropriate and timely diagnosis and the coordination of both local and systemic therapeutic strategies.

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Medical Management of Advanced Disease

13

Hans Wildiers

Abstract

Advanced or metastatic breast cancer is considered incurable, but not untreatable. The goals of treatment in older patients are not different from those in younger patients. For most patients with hormone receptor positive breast cancer, hormonal therapy 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 regimens and agents is dependent on individual patient characteristics, preferences, and drug availability. Targeted treatments are used more and more, and also in older persons they can provide major clinical benefit with acceptable safety profile.

Keywords

Metastatic · Advanced · Systemic therapy · Chemotherapy · Antihormonal therapy · Targeted therapy

13.1 Introduction

About a third of the global breast cancer cases occurs in patients above age 65, and in more developed countries this is more than 40%. Breast cancer can recur many years after the initial diagnosis and treatment, so within the 'metastatic breast cancer' population, the percentage of older women will even be higher.

The terminology of 'advanced disease' is understood in this chapter as being incurable/metastatic disease. In contrast, locally advanced breast cancer has a reasonable chance of cure if it is appropriately treated, but will not be discussed

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here. Although metastatic breast cancer can be treated and is often sensitive to therapy, it is generally not curable. Many treatment options are available for patients with metastatic breast cancer. Since metastatic breast cancer is considered a systemic disease, the role of local therapy such as surgery, radiotherapy or radiofrequency ablation is limited in controlling the global disease, although in selected patients and for symptom control, there can certainly be an indication for local therapy in metastatic breast cancer. Systemic therapy such as hormone therapy and chemotherapy, and more recently, also targeted therapy is in general the treatment of choice since the global disease including micrometastases can be treated and controlled. The main aims in treating older patients, as in younger patients with metastatic breast cancer are to maintain quality of life, minimize symptoms from disease, and prolong survival without causing excessive toxicity. This chapter describes possible treatment options in older breast cancer patients with advanced/metastatic disease.

13.2 Local Therapy

Local therapy can be used with two goals in metastatic disease: to improve outcome by locally treating metastases or the primary tumor, and to improve symptom control.

Local treatment of metastases can be an option in selected patients. Several case reports and small patient series show that progression free survival can be very long, up to many years, when solitary metastases are resected or irradiated [1]. There are no randomized studies, and selection bias was certainly present in these studies. In selected patients, local therapy of limited metastases might lead to a long period of disease control. The chance that this local therapy will cure patients with metastatic breast cancer is very small however, and this information should be clearly explained to patients before starting (sometimes debilitating) local therapy.

Also the role of primary breast tumor resection in patients with metastatic breast cancer has been an issue of controversy. Several randomized trials are ongoing, and an Indian study recently reported no survival benefit by removing the primary tumor after response to front-line chemotherapy [2] while a Turkish study (presented but not yet published) suggested some benefits [3].

A second goal of local therapy is local symptom control. Local therapy can be very effective in local symptom control; antalgic radiotherapy has a high chance of relieving pain when painful bone metastases are present, orthopedic surgery for pathological fractures or bone metastases at risk of fracture can be crucial in maintaining a good quality of life, mastectomy can relieve important wound problems from local breast tumors with cutaneous invasion. Local therapy for symptom relief in metastatic breast cancer should be considered in older patients in the same way as for younger patients.

13.3 Hormone Therapy

Breast tumors are hormone receptor positive in about 80% of patients, and in older patients even higher percentages (up to 90%) have been reported [4]. The selective estrogen receptor modulator (SERM) tamoxifen has been the standard of care for the last decades for hormone-responsive advanced breast cancer due to its favorable safety profile and good efficacy. It is still an acceptable first line therapy if other endocrine therapies are not suitable, but it is generally replaced by aromatase inhibitors which consistently demonstrate an increased median time to progression of about 2–3 months in first line compared to tamoxifen, and are also associated with overall survival benefit in a meta-analysis compared to tamoxifen first line (HR 0.89, 95% CI 0.80–0.99) [5]. Everolimus can be added to exemestane leading to some improvement in progression free survival, but lack of survival benefit and major potential toxicity limit the use of everolimus in older breast cancer patients. Fulvestrant is generally used in second of third line, but the FALCON trial showed that in women with metastatic ER-positive breast cancer who had not received prior hormone therapy, those randomly assigned to fulvestrant 500 mg experienced improved PFS over anastrozole at a median follow-up of 25.0 months (16.6 versus 13.8 months; HR for progression or death 0.80, 95% CI 0.637–0.999) [6]. Subgroup analysis showed an even greater PFS benefit for patients whose disease had not spread to the liver or lungs at baseline in the fulvestrant arm (22.3 versus 13.8 months). Quality of life outcomes were similar between the two groups, with the most common adverse effects being arthralgia (17% versus 10%) and hot flashes (11% versus 10%) for fulvestrant and anastrozole, respectively. The choice between these different antihormonal agents will depend on avoidance of specific side effects, which is more relevant for older than younger women (e.g. no tamoxifen in case of previous thrombosis, prudence with aromatase inhibitors in case of severe osteoporosis, avoidance of intramuscular injections of fulvestrant in case of therapeutic anticoagulation).

The advent of CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) has changed the landscape of antihormonal treatment in metastatic hormone sensitive breast cancer dramatically [7]. In first line therapy, addition of a CDK4/6 inhibitor consistently improved progression free survival by about 12 months, without adding important toxicity. An FDA pooled analysis [8] based on the pivotal first line trials showed very similar benefit in patients ≥70y versus younger patients. But also second line studies showed major benefit by adding a CDK4/6 inhibitor to fulvestrant. One of the major questions at this point is whether all patients should receive a CDK4/6 inhibitor first line, or whether (subgroups of) patients can have an aromatase inhibitor first line, often also with long disease control, and only add the CDK4/6 inhibitor in second line. Adding a CDK4/6 inhibitor first line does not impact Qol adversely, but these drugs are very expensive, and require frequent blood checks, physician visit, and drug interruptions or dose modifications. Certainly

older individuals may prefer to start with a simple antihormonal tablet, and only start the CDK4/6 inhibitor second line. Further research is needed to identify patients who can safely delay the introduction of a CDK4/6 inhibitor until second line. In terms of toxicity, the FDA pooled analysis showed that grade 3–4 adverse events were more frequent in patients ≥70y (82%) compared to women <65y (66%). Also the number of adverse events leading to dose reduction/interruption (77% versus 66%) and adverse events leading to drug discontinuation (17% versus 8%) were higher in older persons. It should also be acknowledged that the toxicity profile of abemaciclib (more diarrhea) is somewhat different from palbociclib and ribociclib (mainly neutropenia). Diarrhea can be debilitating for older patients, and even grade II toxicity can have major impact on quality of life in this group [9]. Most of these studies have not been performed or analyzed specifically for older patients. Only the Monaleesa-2 study [10] published a separate analysis on age effect of ribociclib in first line disease, and found a similar benefit in terms of progression free survival, while toxicity was similar.

In conclusion, aromatase inhibitors are most often used as first line therapy, in patients ≥70y as in postmenopausal patients <70y. Fulvestrant rather than an aromatase inhibitor, is an alternative first line option, if available, for patients that have not received antihormonal therapy before (including in the adjuvant setting). In other situations, fulvestrant is generally used as second line hormonal therapy. Whether the new CDK4/6 inhibitors need to be added to antihormone therapy in first or second line, remains a challenging question, certainly for older persons for whom frequent hospital visits may be debilitating. Tamoxifen is not 'dead', but it often moves to later lines, and its activity after aromatase inhibitor, fulvestrant, and CDK4/6 inhibition is unknown.

13.4 Chemotherapy

Since hormone receptor positive breast cancer is more frequent with older age, hormonal therapy is less toxic than chemotherapy, and a significant proportion of (older) patients can have longer term benefit from hormonal therapy in metastatic setting, blocking the hormone receptor pathway is generally the initial treatment of choice when metastases are diagnosed. However, a smaller proportion of breast tumors (10–20%) are hormone receptor negative. Moreover, all patients with hormone receptor positive tumors will eventually develop resistance to hormonal therapy. In these cases, chemotherapy is in general the most appropriate therapy.

Patient selection is an important issue for older patients. Physicians are sometimes reluctant to use chemotherapy in older patients with metastatic (breast) cancer because of concerns of inducing toxicity without having much benefit. However, one study found that women older than 70 years of age who are treated with chemotherapy for metastatic disease derive similar benefits to their younger counterparts [11]. This case-comparison study of patients with metastatic breast cancer treated in five clinical trials of the Piedmont Oncology Association compared outcome in relation to age. Seventy patients 70 years of age or older were compared with 60 patients

aged 50 through 69 years and 40 patients less than 50 years of age. Women 70 years of age or older who were enrolled in these trials were similar to their younger counterparts in response rates, time to disease progression, survival, and toxicity effects. The authors concluded that women in this age group should not be excluded, based on age alone, from clinical trials involving chemotherapy for advanced breast cancer. For fit patients, it is generally quite obvious that chemotherapy is likely to be beneficial in contrast to frail patients where the disadvantages of chemotherapy will often be greater than the advantages. The most difficult category is the category in between, also called 'vulnerable' patients. A full comprehensive geriatric assessment (discussed elsewhere in this book) is certainly required in this patient category in order to have a better view on the global health situation which may ultimately allow to make a more appropriate decision on the indication of chemotherapy. Models have been developed to predict chemotherapy toxicity that are based upon geriatric assessment [12, 13].

Choosing the most appropriate chemotherapy regimen (product and dosing) for a specific older patient is also a major challenge. It is not really possible to provide strict guidelines on which specific regimen or which order of regimens should be used in sequential situations (first line, second line, third line, etc.). This is quite similar to the situation in metastatic breast cancer in the younger population; some international guidelines [14] are available, but still leave large space for individualization. For older women, more than in younger patients, preference should be given in general to chemotherapeutic agents with safer profiles. The choice of a specific regimen depends on different factors; is there a need for urgent response (might be a reason to take the most active regimens first)? Is it a slow growing disease in a vulnerable patient where toxicity should be avoided in any case (soft oral regimens or even wait and see approach)? Is comorbidity present that excludes specific regimens (e.g. avoid anthracyclines in patients with cardiac failure; or taxanes in those with existing significant neuropathy)? Which drugs are available/reimbursed in the country? Which regimens is the oncologist familiar with? Hamberg reviewed available clinical trials in metastatic breast cancer in older women in 2008 [15], but since then no new reviews have been published. It should be acknowledged that most trials had a small sample size and that it is difficult to generalize the results of these trials to the broader population of older patients, since selection bias was probably highly prevalent, indicated by the fact that the large majority of the population in all these studies had a WHO performance status of 0 or 1, which is not representative for a general older population. Also, age cut-off was 65 or even 60 in most of these studies, and a large part of the so-called older patients were below the age of 70, which is more or less an accepted threshold above which age related problems become more prevalent.

Another issue is that the pharmacology of these drugs might change with increasing age [16]. Physiological changes in bodily functions and physiology are known to occur with age. These changes can have a considerable impact on the pharmacokinetic processes of absorption, distribution, metabolism and excretion and the pharmacodynamic properties of administered drugs. For many drugs with a high therapeutic index, this will be clinically unimportant, but for anticancer drugs,

which usually have a low therapeutic index, these pharmacological changes can lead to dramatic consequences, such as excessive drug concentrations and unacceptable toxicity, or subtherapeutic drug concentrations and ineffective treatment. Despite the increased susceptibility of the elderly to these changes, doses are rarely adapted on the basis of pharmacokinetics and pharmacodynamics, with the exception of changes secondary to altered renal function. Several reviews have been published on the effect of age on the pharmacokinetics and dosing of different chemotherapeutic agents [17]. Also specific guidelines on the impact of renal function on chemotherapy are available for the most used chemotherapeutics [18]. Here below some further information on commonly used regimens in older persons [16].

Concerning anthracyclines, some considerations and recommendations have been suggested when used in older persons. Several strategies to reduce toxicity are available, such as prolonged infusion rate, prophylactic use of white blood cell growth factors, or use of the cardioprotective agent dexrazoxane [16]. Weekly epirubicine is well studied in older patients with metastatic breast cancer. In a phase III study [19], epirubicin was superior for progression free survival compared to gemcitabine in first line treatment, while toxicity was very acceptable. 'Older age' was defined however as age greater or equal to 60 years (median 68 years) so this is not representative of the general older population. Liposomal formulations of doxorubicin have been shown to significantly decrease the risk of cardiotoxicity, while providing comparable antitumor activity. The Dutch group published a (prematurely closed) phase III trial [20] comparing the efficacy and safety of first-line chemotherapy with pegylated liposomal doxorubicin (PLD) versus capecitabine in MBC patients aged ≥65 years. Both PLD and capecitabine demonstrated comparable efficacy and acceptable tolerance as first-line single-agent chemotherapy in older patients with MBC, even in vulnerable patients or patients aged ≥75 years. However, patients aged ≥80 years were unlikely to complete chemotherapy successfully.

The role of taxanes in metastatic older breast cancer patients has recently been reviewed by a SIOG task force [21]. Weekly paclitaxel and three-weekly docetaxel are among the cornerstones of treatment, with generally acceptable toxicity. Pharmacological studies are suggestive of a decreased clearance of unbound paclitaxel in older patients compared to younger patients while clearance of docetaxel seems rather unaffected by age. Three-weekly docetaxel at a dose of 100 mg/m^2 is not appropriate for older persons. Nab-paclitaxel has efficacy comparable with solvent-based taxanes without need for steroid premedication but has been poorly studied in older BC patients. Choice of taxane and regimen in the metastatic setting relies on availability and preferences with regard to schedule, toxicity profile and cost, especially for recently developed formulations.

Capecitabine is an attractive drug for older women because of its side effect profile, while having significant and sometimes prolonged metastatic disease control. It has significant renal excretion, so the dose should be adapted when creatinine clearance falls below 60 ml/min. The registered dose of 1250 mg/m^2 is not realistic for most older patients, and a small randomized phase II study showed antitumoral equivalence with better safety profile when using a dose of 1000 mg/m^2 rather than the higher registered dose [22].

Although not specifically investigated for the older population, metronomic cyclophosphamide (C) and methotrexate (M) [23] in patients with metastatic breast cancer might be a very attractive treatment option, especially in vulnerable/frail patients where any significant toxicity may result in severe morbidity or even mortality.

In summary, there is no proof that high dose chemotherapy or combination of strong chemotherapeutic agents provides significant benefit above using sequential monotherapy regimens in metastatic disease. In older patients, it is acceptable to use less aggressive regimens. The goal of chemotherapy in metastatic breast cancer is to control disease for as long as possible without causing excessive toxicity/harm [16]. Since the aim of chemotherapy in this situation is palliative, quality of life is paramount and significant toxicity is not acceptable. Older patients should be followed more closely than younger patients for toxicity since the incidence of toxicity is higher, and since they have less reserve capacities to deal with toxicities. For instance, when older persons have vomiting or severe diarrhea, they dehydrate much faster and can develop renal failure and related complications, which will result in a downwards vicious circle. In principle, dose reductions in the elderly are not systematically recommended, but should be considered based on pharmacological parameters and altered according to observed toxicity [16, 18]. Close follow-up is essential in this population in particular to avoid overtreatment and debilitating side effects. Specific attention should be paid to supportive care, for example, older patients are more likely to develop neutropenia than younger patients and can benefit more from white blood cell growth factors. Older persons generally have less functional reserve than their younger counterparts and are more vulnerable to treatment side effects. Bisphosphonates or denosumab can also provide symptomatic relieve in patients with bone metastases. This topic is discussed elsewhere in this book.

13.5 HER2 Positive Breast Cancer

Targeted therapies have been a breakthrough in the treatment of (metastatic) breast cancer. Trastuzumab, a monoclonal antibody against the HER-2/neu receptor, increases the response rate of chemotherapy significantly, and combination of taxanes and trastuzumab can achieve response rates about 60–70% in HER-2/neu positive disease. The addition of pertuzumab to trastuzumab and a taxane further improves outcome in the general HER2 positive first line population, and is currently the standard of care. Trastuzumab is generally very well tolerated. The main side effect is cardiac failure. The highest incidence of cardiac failure with trastuzumab has been observed in combination with anthracyclines, and for this reason these two drugs are generally not used together. Age is a documented risk factor for congestive heart failure in patients receiving trastuzumab, but this depends more on pre-existing comorbidities than on age by itself [24], and is reversible after discontinuation of trastuzumab. Pertuzumab is also well-tolerated although diarrhea can sometimes be a disturbing side effect. Taxanes administration is possible in the

majority of older women, but tolerance and acceptance may be more difficult in frail patients. The EORTC 75111 study [25] evaluated dual anti-HER2 treatment without classical chemotherapy in older/frail HER2-positive metastatic breast cancer (MBC) patients. Patients were randomly assigned to metronomic oral cyclophosphamide (M) 50 mg/day + trastuzumab (T) and pertuzumab (P) (TPM), or to TP alone. With 20.7 months of median follow-up, the median PFS was 5.6 months (95% CI 3.6–16.8) versus 12.7 months (95% CI 6.7–24.8) for TP and TPM, respectively. This was a randomized phase II and not phase III study so no formal recommendations can be drawn from it, but TPM showed an interesting 7 months longer median PFS than TP alone in an older/frail HER2+ MBC population, with an acceptable safety profile. TPM, followed by T-DM1 after progression, may delay or even supersede taxane chemotherapy in this population. Hormonal therapy plus anti-HER2 treatment (trastuzumab or lapatinib) can be an alternative with hormone sensitive tumors. Lapatinib may be less effective than trastuzumab and more difficult to use because of side effects and interactions. T-DM1 is the standard for fit trastuzumab and taxane-exposed patients, and also seems active and well tolerated in the older population [25].

13.6 Conclusion

The goals of treating metastatic breast cancer in older patients are not intrinsically different from those in younger patients. For the majority of patients with hormone receptor positive breast cancer, hormonal therapy 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 regimens and agents is dependent on individual patient characteristics, preferences, and drug availability. Major progress has been made in HER2 positive breast, and for older persons, targeted regimens seem to provide major clinical benefit with very acceptable safety profile.

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The Assessment of the Older Woman with Breast Cancer

14

Lodovico Balducci

Abstract

Aging is a complex condition· a process where, similar to a carpet design, multiple threads are inextricably interwoven. The management of the older aged person involves management of complexity, an individualized approach to each patient that may not be accommodated in classical guidelines or pathways.

In this chapter we analyze the decisional process in a complex clinical case to identify the elements on which medical decisions should be based.

Keywords

Older woman · Complexity · Breat cancer · Management

Aging is a complex condition [1]. Complex, from the Latin *Cum Plexere,* to weave together, describes a condition comparable to a carpet design, that results from multiple threads inextricably interwoven. The management of the older aged person involves management of complexity, an individualized approach to each patient that may not be accommodated in classical guidelines or pathways [1, 2].

In this chapter we analyze the decisional process in a complex clinical case to identify the elements on which medical decisions should be based.

Clinical Case. A small right breast nodule was identified by a nurse aid in an 82-year-old woman receiving a bath. A needle biopsy revealed a well differentiated invasive ductal carcinoma rich in hormone receptors and negative for HER. The patient is not interested in surgery and is referred to a medical oncologist.

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Review of system reveals a performance status of three. She is dependent in all IADLs and ADLs. She has been hemiplegic for 10 years due to a right middle cerebral artery vascular accident in the presence of thrombocytosis diagnosed as essential thrombocythemia. She has atrial fibrillation, a kidney stone, and type II diabetes.

Past medical history is positive for colon cancer stage II 5 years earlier treated with laparoscopic surgery.

On Physical Exam she has left hemiplegia, dysarthria, and a nodule 1 cm in diameter in the right breast. Axillary LNs are not palpable.

CBC shows Hemoglobin of 10.1 GM/dl MCV 79 Iron is 7 mg and ferritin 15 mg Several approaches are reasonable in this case (Table 14.1).

All decisions are considered acceptable because most likely the cancer won't reduce the life-expectancy of the patient and the patient may tolerate all forms of treatment included. Noticeably complications of her cancer may include local advanced disease, but observation is still reasonable because one can carefully monitor the growth rate of the tumor and institute treatment later.

After discussing the alternatives with the patient and her daughter it was decided to institute therapy with an aromatase inhibitor and with denosumab to prevent

Table 14.1 Potential Management Choices

Choices	Advantages	Disadvantages
Observation	No therapeutic complications Low cost	Patient's anxiety
Surgery	Elimination mass Pathologic staging	Patient and family don't want surgery Risk of anesthesia and surgical complications No systemic effect Cost
Surgery + adjuvant hormonal therapy	Elimination mass Reduced risk of recurrences	Patient and family don't want surgery Surgical and medical complications Cost
Radiation therapy External beam Brachytherapy Radiosurgery	Elimination mass	Local inflammation Risk of recurrence Cost Not necessary at this point No systemic effects Radiosurgery was considered experimental in this condition
Hormonal therapy Selective estrogen receptors modulators Aromatase inhibitors Faslodex	May eliminate mass and control systemic disease if present	Medical complications Cost
Aromatase inhibitor + CDK4 /6 inhibitor	Better chance of cancer control	Medical complications Cost

osteoporosis. When we proposed observation as the least toxic and least costly approach both patient and daughter became very anxious. They could not conceive the possibility of not treating the cancer.

The exam of this case indicates that the decision to manage cancer in the older aged person is based on risk of cancer related mortality, risk if cancer complications, risk of treatment complications and obviously patient preferences [1]. To answer these questions, it is necessary to estimate the physiologic age of each individuals, which includes life-expectancy and functional reserve, the social context of the patients and the patient's goals.

14.1 Determination of Physiologic Age

The determination of life expectancy and functional reserve (ability to withstand stress) is based on a comprehensive geriatric assessment (Table 14.2). Several models have integrated the results of the CGA in the prediction of mortality and functional dependence. Of these the best validated are the e-prognosis [3, 4], an online approach that allows the use of different models and the Rockwood frailty index in its different formulations [5, 6]. The frailty index is obtained adding up the functional

Table 14.2 Comprehensive Geriatric Assessment (CGA)

Domain	Evaluation
Function	Performance status (PS) Basic activities of daily living (ADL): Continence, ability to dress, to bath, to eat, to transfer, to use the bathroom Instrumental Activities of Daily Living (IADL): ability to use transportations, take medications, manage finances, arrange a meal, go shopping
Geriatric syndromes	Dementia Depression Delirium Falls Dizziness Failure to thrive Neglect and abuse
Social status	Living conditions Availability of a caregiver Validity of the caregiver
Nutritional status	Screen for: Malnutrition Risk of malnutrition
Comorbidity	Number of diseases Seriousness of each disease
Polypharmacy	Number of medications Medication interactions Redundancy
Sensorial function	Hearing Eyesight

and medical deficiency of each individual. Originally it contained almost hundred parameters but in the most recent version the number of parameters has been reduced to 31 [6].

Germane to the this chapter are models that predict the risk of complications of surgical [7] and medical treatment [8, 9] of cancer also based on the geriatric assessment.

As a general rule, dependence in ADLs, or the presence of one or more geriatric syndromes are associated with significantly reduced life-expectancy and functional reserve. The majority of these patients are therefore not candidates for aggressive cytotoxic chemotherapy but may benefit from palliative intervention that include hormonal therapy, CDK4/6 inhibitors and immune checkpoint inhibitors in the case of breast cancer.

It should be underlined that the importance of the CGA goes well beyond the assessment of physiologic age. Indeed, the original role of the CGA was to prevent progressive functional deterioration related to age, by addressing the multidimensional need of an older patients. Prevention of malnutrition, provision of an adequate caregiver, management of depression, compensation for functional disability may improve the outcome of cancer treatment [10].

A number of laboratory tests (Table 14.3) are also available to assess the physiologic age of the patient. As aging may be considered a chronic and progressive inflammation the assessment of the inflammatory status is a reliable predictor of mortality and disability. The inflammatory index was derived from a multivariate analysis of the relation of different circulating cytokines and the risk of mortality [11]. It was validated in two cohort of patients followed over 20 years: The Chianti study and the Baltimore Longitudinal studies.

Table 14.3 Laboratory Tests for the Determination of Physiologic Age

Test	Performance	Advantages and disadvantages
Length of lymphocyte telomere	Peripheral blood	Inadequate for determination of individual physiologic age due to interindividual variability
Inflammatory index	Peripheral blood. Ratio of log of circulating Interleukin 6 and tumor necrosis factor 1 receptor	In two healthy population cohorts predicted risk of mortality and functional dependence May be affected by cancer
Oxidative damage		Not superior to CGA
Genomic clock	Assessment of DNA methylation	Predicts risk of all cause mortality, of disease related mortality and of cancer
P14 INk4a	Peripheral blood and tissues	Correlated with disability and disease. Not validated yet in large patient population
Vitamin D levels	Peripheral blood levels	Inversely correlated with all causes of mortality and disease risks Supplementation of vitamin D3 reduced risk of mortality in three randomized controlled studies

The oxidative damage assessed as derivative of reactive oxygen metabolites (d-ROM) and Total Thiols Levels (TTL) was shown in the cohorts of Check and German patients to predict the risk of mortality [12].

Aging is associated with increased DNA methylation at CpG sites. The degree of methylation is called epigenetic clock and it predicts the risk of overall mortality, of cancer and cognitive decline and of cancer and cardiovascular related mortality [13]. As expected, in 5 cohorts of healthy individuals, the epigenetic clock becomes less and less correlated with chronologic age among the oldest old (90 and over). Presumably people who survive into the oldest ages are also the heathiest and the youngest from a physiologic standpoints.

The accumulation of P16INK4a in aging tissue is associated with decreased organ function and survival. Possibly Increased concentration of this protein in circulating lymphocyte may represent a marker of physiologic age [14, 15].

25-OH vitamin D circulating levels have been associated with a decline of all causes mortality. This has been a consistent result in several cohorts of older individuals [16]. Interestingly at least three randomized controlled studies have demonstrated that supplementation of Vitamin D in older individuals has led to decreased mortality [17]. The mechanism of this association that appears all but certain is at present unknown.

Which biological marker if any may complement the geriatric assessment in providing a more accurate estimate of physiologic age? The question is still open as the knowledge is scarce. It is known that the geriatric assessment is comparable to the assessment of oxidative damage in predicting risk of mortality [12]. In a small number of nonagenarian the frailty Index 31 appeared superior to the genomic clock in predicting mortality [6] . Clearly the issue needs further study. It appears reasonable to recommend that inflammatory index, genomic clock, vitamin D levels and possibly P16Ink4a be included in the evaluation of older individuals undergoing clinical studies.

14.2 Assessment of the Social Context

Clearly the patient we described could not survive alone as she needed help even in the basic ADLs. This dependence mandates a home caregiver. Patients who are dependent in one or more IADLs may survive without a home caregiver but do need a person able to do their shopping, prepare or provide their meals, manage their finances, and take them to the clinic. Even older individuals who are in perfect health and are fully independent should be able to rely on a caregiver when undergoing cancer treatment. Age is indeed associated with increased risk of complications of cytotoxic chemotherapy which may include development of functional dependence [18]. For example an older individual with febrile neutropenic infection may develop delirium or may become unable to drive to the hospital or even to reach the phone to call for help. Fatigue, a common complication of cancer chemotherapy, may lead to deconditioning and functional dependence in the aged [19].

The role of the caregiver goes well beyond compensating for the patient functional deficit and providing timely access to medical care. The caregiver is responsible for emotional support during the ordeal of cancer treatment. In the presence of

multiple family members the caregiver becomes the spoke-person for the family, responsible to maintain the contact with the provider and to mitigate the conflict that inevitably occur within the family. The patient we described had a demented spouse in need of a caregiver for all of his IADLs and three children of which only the daughter lived in the same town as the patient. Fortunately they had the means to hire a live in caregiver, but the responsibility of medical decisions fell on the daughter, who was the patient's health care surrogate.

In general the family caregiver of the older patient is an elderly spouse with health problem of his/her own or a child, most commonly a daughter who must balance the need of an older parent with the demands of her/his profession and of her/his family [20]. For example, in our case, the daughter was a school teacher, married to an executive who traveled frequently out of town and was primarily responsible for the care of her two pre-teen children. This situation is referred to as the "Aeneas syndrome." In the stanze of Raffaello in the Vatican the mythological Trojan hero Aeneas is depicted carrying his father on his shoulders and holding his child by hand while escaping from the fire that destroyed the city [21].

Not surprisingly caregiving is associated with substantial stress that may lead to increased risk of depression and other diseases and increased risk of mortality [22–24]. Caregiving is also costly as the caregiver may lose her/ his employment and may have increased medical expenses, such us need for counseling and psychotherapy.

The provider managing an older patient should address a number of questions (Table 14.4). As already mentioned a patient dependent in ADLs require an in home caregiver and a patient dependent in IADLs needs a caregiver able to perform the activities the patient is unable to execute on his/her own. Even patients who are completely independent may benefit from a person supervising their life. For example older individuals are at risk of malnutrition simply because they don't care to eat alone and malnutrition may lead to increased risk of surgical and medical complications. The patient's need may depend in part from the treatment. Patient undergoing surgery, cytotoxic chemotherapy, or daily radiation may need a caregiver even if they are completely independent at the beginning of the treatment.

All caregivers should be available on a short notice to manage emergencies, should be able to provide transportation, to make medical decisions "in lieu" of the patients and to compensate for a patient functional deficiencies.

Factors of risk for caregiver's decompensation may include age, medical conditions, and competing priorities. While medical conditions may represent the major threat to the health of an older caregiver, competing priorities may represent the main one for a younger caregiver involved in a demanding profession and with a demanding young family [22].

Table 14.4 Questions related to the caregiver

What are the patient functional and medical needs?
Is the patient at risk to become functionally dependent during treatment?
Is a caregiver available?
Is the caregiver adequate?
What are the caregiver's competing priorities?
Is the caregiver at risk?

The caregiver may be the key to successful treatment and may represent the best ally of the provider. It behooves the provider to assess the caregiver and to provide all necessary advise and support.

14.3 Treatment Goals

Though observation represented the safest and least costly treatment, and surgical resection would have been the second best option, we elected to institute hormonal treatment in our patient based on her and her family preferences. Rapid advances in medical care have provided a gamut of opportunities to adapt the treatment to a patient individual goals. So the treatment goals are an integral part of the discussion once that the available treatments have been identified based on life expectancy and functional reserve. Common example may include the choice of adjuvant therapy and the management of life-threatening metastases.

The decision of whether to add adjuvant chemotherapy to hormonal therapy in a person of advanced age and high risk of recurrence is exquisitely personal. It is difficult to assess the benefits let's say of adjuvant chemotherapy in an 80 year old woman with a hormone receptor rich tumor and involvement of the sentinel lymph-node. Risk averse people may decide to take the chemotherapy even if the benefits are marginal. Risk takers may choose to forgo the immediate complications of chemotherapy and accept instead a marginally increased risk of recurrence during the next 5 years. The right treatment is based on individual goals.

A patient with extensive liver metastases that threatens to kill her over the next 6 months and has progressed despite most forms of systemic treatment may choose a relatively peaceful and painless death from liver failure, is she has no businesses left unfinished in her life or alternatively may decide to undergo some forms or loco regional treatment that may delay her death of an additional 6–9 months if she wants to reach an important deadline such as an anniversary or a family celebration.

Notwithstanding treatments that are clearly inappropriate because they are not effective or are too toxic the right treatment for each individual is based on individual goals.

14.4 Late Therapeutic Complications

It is important to remember that age is associated with increased risk of late complications from systemic treatment and we have no reliable instruments to predict these complications [25].

Age over 70 is a risk factor for endometrial cancer and deep vein thrombosis from selective estrogen receptor modulators such as tamoxifen or toremifene. Aromatase inhibitors may increase the risk of osteoporotic bone fractures in older women.

Fatigue is probably the most common long term complications of cytotoxic complication in older patients and fatigue may lead to functional dependence, deconditioning and early mortality. Prevention of fatigue include exercise throughout treatment and maintenance of the hemoglobin above 10 GM/dl.

Peripheral neuropathy from taxanes or platinum derivatives, while reversible in younger individuals may be persistent in the older ones and lead to reduced activity, functional dependence, and deconditioning.

The incidence of chronic cardiomyopathy from anthracyclines and possibly from trastuzumab increases with age, though its effects on function, mortality and quality of life are not very well established.

Finally age is a risk factor for myelodysplasia and acute myelogenous leukemia from cytotoxic chemotherapy. The use of this treatment in older women should be restricted to those in whom chemotherapy effects a substantial reduction of the risk of recurrence, such as at least 5%.

14.5 Conclusions

The management of breast cancer in the older woman is complex and requires a personalixed approach (Fig. 14.1).

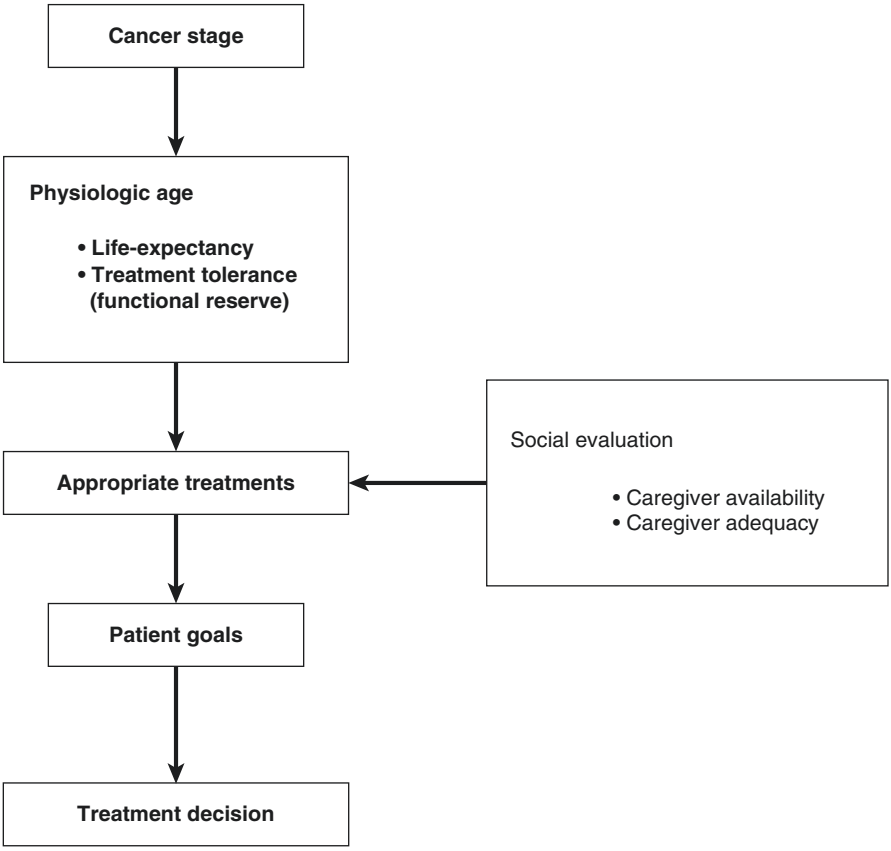

Fig. 14.1 Algorithm for Personalizing Cancer Treatment in the Older Patient

The first step is estimate of functional age, that is of life expectancy and functional reserve. The basic instrument for this is a comprehensive geriatric assessment (CGA). Some laboratory markers of aging such as the inflammatory index, the epigenetic clock, the determination of P16INK4 in circulating lymphocytes and the circulating levels of 25-HO vitamin D may render this estimate even more precise.

The second step is to assess the social situation and in particular the availability of an adequate caregiver.

The choice between reasonable treatments will be finally determined by the patient goals.

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Nurses' Role in Care of Older Women with Breast Cancer

15

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Abstract

Breast cancer is the most common type of cancer in women worldwide World Health Organization (WHO). It is estimated that 568,000 deaths occurred in women from breast cancer in 2016. As women age their risk of breast cancer increases. The lifetime risk of developing breast cancer in women is 1 in 8. However, the older you are, the higher the risk. This means a 30 year old has a 1 in 227 risk of developing cancer as compared to a 70 year old whose risk is 1 in 26. Older adults diagnosed with cancer often have needs that are left unmet. Nurses play essential roles as part of the multi-disciplinary team caring for older women with breast cancer. As often is the case with nurses, they play many unique roles throughout patient's trajectory of care including, but not limited to, providing clinical care, to psychosocial support, to helping patients navigate the system. This chapter will highlight the importance of nurses in providing care for older women with breast cancer through their trajectory of care.

Keywords

Oncology nurse · Nurse navigator · Nurses · Breast cancer · Older women · Breast cancer treatment · Advanced practice nurses

15.1 Introduction

Breast cancer is the most common type of cancer in women worldwide (World Health Organization (WHO) [1]. It is estimated that 568,000 deaths occurred in women from breast cancer in 2016 [2]. As women age their risk of breast cancer

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increases [3]. The lifetime risk of developing breast cancer in women is 1 in 8 [4]. However, the older you are, the higher the risk. This means a 30 year old has a 1 in 227 risk of developing cancer as compared to a 70 year old whose risk is 1 in 26 [4]. Older adults diagnosed with cancer often have needs that are left unmet [5]. Nurses play essential roles as part of the inter-disciplinary team caring for older women with breast cancer [6]. As often is the case with nurses, they play many unique roles throughout patient's trajectory of care including, but not limited to, providing clinical care, to psychosocial support, to helping patients navigate the system [7]. This chapter will highlight the importance of nurses in providing care for older women with breast cancer through their trajectory of care.

15.2 Diagnostic Phase and Psychological Distress

Women may discover a breast abnormality through: breast cancer screening imaging, self-breast exam, or by a clinical exam. The discovered abnormality typically requires further diagnostic imaging, and a biopsy if needed, to reach a final diagnosis. The amount of time from detection of an abnormality to diagnostic work-up to final diagnosis can vary from days to months. This means women may spend a significant amount of time in distress during diagnostic phase [8]. The distress in part is due to the uncertainty [9] and fear of the worst possible outcome. This distress can negatively impact women's ability to receive the required follow-up care [10]. In addition, barriers specific to elderly women's care during the diagnostic phase can also cause distress. The barriers, as described by older breast cancer survivors include: limited knowledge, health co-morbidities, and multiple appointments with health care providers [11].

15.3 Barriers to Care During Diagnostic Phase

Timely and accurate information sharing is significant in the patient's experience during the diagnostic phase. Women who are well informed about the diagnostic process experience less psychological distress [12]. However, women report feeling inadequately prepared and describe dissatisfaction at the amount and/or quality of information received [13]. For example, patients undergoing a biopsy report being: ill-informed about the procedure, why it is required, what is to be expected, or what is involved in post-procedural care [13]. As well, lack of a contact person to reach out to with any concerns or questions acts as a barrier to information sharing while adding to the patient distress [13]. Nurses are well positioned with the knowledge, skill, and judgment to educate and inform patients in turn mitigating some of the patient's stress and anxiety.

Additionally, existing health comorbidities can make follow up diagnostic procedures difficult for older patients [14]. As an example, an older patient may suffer from co-morbidities that affect their mobility, such as arthritis, causing discomfort with positioning for procedures that typically requires one to stay still [14]. It could

be physically challenging for an older women to climb a high examination table, which can cause pain but also put them at risk for falls. Moreover, it could be a frightening experience for women suffering from cognitive disorders, such as dementia, who may not understand what is being done to them [14]. Nurses acting as patient advocates can identify patient specific challenges and limitations and in turn can use this knowledge to accommodate patient needs and define their goals of care.

Lastly, multiple appointments are usually required to reach a diagnosis. Older women may be faced with the practical challenge of getting to the appointments as they may be dependent on family members for transportation. This can cause feelings of guilt from the awareness of burdening their family [11]. In addition, several appointments can cause significant interruption in the life of an older women who has other commitments [11]. As an example, an older woman may be the sole care giver of her spouse making it challenging for her to make it to several appointments. This may lead the women to experience feelings of distress and influence treatment decision making [11].

15.4 Nurses' Role During Diagnostic Phase

Women's experiences during the diagnostic period are believed to influence treatment outcomes once a diagnosis is reached [8]. Thus, it is important that concerns particular to an older patient population are paid attention to, including improving access to care, reducing anxiety and ensuring positive patient experience. Importantly, nurses recognize the importance of holistic care that considers all aspects of patients including their values, belief, culture and care needs. This allows them to identify unique individual patient needs and goals and advocate having them addressed and incorporated in the diagnostic and treatment process.

Nurses practice efficiently during diagnosis stage to expedite the diagnostic process and provide support, education, and navigation. One such example is the nurse practitioners (NPs) working in a rapid diagnostic clinic (RDC) in a large cancer centre in Canada. The RDC's aim is to quickly provide patients with assessment and diagnosis of their breast abnormality to decrease the anxiety associated with waiting. RDCs have been proven to reduce wait time to definitive diagnosis [9]. Its operation requires collaboration of inter-professional healthcare members including nurse practitioner, radiologist, pathologist, surgeons to expedite the diagnostic process. Nurse practitioners play an integral role to its function as they organize the program and serve in various roles as follows. The NPs triage referrals to RDC's in a timely manner allowing patients to be seen expeditiously. They perform patient assessment and facilitate necessary diagnostic work-up, including a biopsy if needed, the same day in a single visit with prompt results. NPs also give the diagnosis to the patient and facilitate referral and appointment with a surgeon for patients diagnosed with breast cancer. This means less time spent worrying and more prompt treatment if needed.

Similarly, specialized oncology nurses, such as nurse navigator, are also essential to help reduce barriers to care, facilitate timely diagnosis, increase patient satisfaction, and lower anxiety in women [15]. A program led by a nurse navigator has been shown to be effective in reducing waiting times to surgical treatment [16]. Nurses in collaboration with inter-disciplinary team focus on assessing individual educational needs helping to address gaps in patient knowledge, clear misconceptions, and decrease anxiety [8]. In addition, it empowers patients to make informed decisions and take ownership of their care.

Elderly patients' are often unaware that breast cancer risk increases with age. Thus, when diagnosed with cancer, the initial reaction is shock [11] and is difficult to understand and accept [17]. An opportunity should be taken during the diagnostic phase to educate elderly on risks of breast cancer with increasing age, especially those in whom index of suspicion for breast cancer is high.

15.5 Surgery

Surgery is often the first treatment patients undergo for breast cancer across various age groups, including older women [18]. Breast surgery is widely considered a low-risk procedure with the mortality rate in older women being 0–0.3% [19]. Despite surgery being common in older women, 17–33% of women with breast cancer over 80 do not undergo surgery [20]. This is for many reasons but older patients often have an increased number of co-morbidities [11] which can impact their surgical plan and recovery [21]. This holds true for patients undergoing surgery for a breast cancer. The nursing role is hugely important during the pre-, peri-, and post-operative period, which will be further highlighted as the patient's surgical journey is discussed in more detail.

15.6 Pre-operative Period

Nurses can play an integral role from the initial consult with the surgeon. They can help to attain a more complete health history, as older patients are more likely to have complex health histories [11]. Moreover, older women may be more comfortable sharing information with a nurse, over their surgeon, due to more historical views of health professionals, their roles within the team, and social constructs [11]. This patient specific information, crucial to the surgical plan, can be extracted by nurses using the right questions and therapeutic techniques. Moreover, polypharmacy being common in older adults [11] the nursing team can be helpful to gather a full medication history or help to flag patients who may benefit from pre-operative consults such as with a pharmacist, anesthesiologist or thrombosis specialist.

Interprofessional breast teams can also consider integrating an abbreviated Comprehensive Geriatric Assessment which nurses are well positioned to integrate into their practice. This provides an in depth assessment of the patient prior to moving forward with treatment, helping to flag patients at high risk for surgical

complications, those who are not good surgical candidates or who are more likely to have a delayed recovery [6]. This assessment would allow the team to reorient the plan with the patient's best interests in mind [6].

Navigating a surgical decision can be challenging for patients undergoing breast surgery since often, with early stage cancers, they can choose between lumpectomy or mastectomy. For older women there are additional considerations, such as are they able to care for a surgical drain post-operatively or will a mobility restriction make it challenging to attend daily radiation treatments. These are the things that nurses can highlight, to the interprofessional team, during the initial consults prior to making a final surgical plan. Discussing breast reconstruction, with older women undergoing mastectomy, should also be consistent and offered when appropriate. Reconstruction is not always discussed with older patients as the surgical team may think it is not relevant because of age or because they assume the patient may not be a candidate [22]. Note that reconstructive rates are much lower in older women than younger women undergoing a mastectomy [22]. This is another opportunity for nurses to advocate for the patient and ensure all options are reviewed especially since breast reconstruction has been shown to increase the quality of life in patients post-mastectomy and that age alone does not increase risk for post-reconstructive complications [22].

Beginning at the initial consult, patient education, led by nurses, is an important element of patient centered care [6]. Nurse led education is important as lack of information has been flagged as a barrier for older women undergoing breast cancer treatments [11]. Older women may have information that is out of date, such as the use of axillary node dissections as standard of care or may be influenced by myths such as surgery causes cancer to spread [11]. Patient education is of utmost importance but takes time and in busy clinics the surgeons may not have time to review in detail all patient's questions or the pre-surgical instructions. At a large cancer centre in Canada the role of the Surgical Nurse Coordinator is important to this process, as they provide much of the initial pre and post-op education. Nurses have also created written resources which are important for patient autonomy and understanding [11]. A nurse lead pre-operative class can also provide another means of educating the older patient as it allows, a multidisciplinary team, consisting of dietician, social worker and physiotherapist, to present the information again in a different way. This engages an interprofessional team which can help meet some of the patients' needs such as for psychosocial support [5].

In addition to the educator role a nurse can play in the pre-operative period, it is also a time many women will organize themselves for recovery, in turn the nursing team is vital in connecting them with community resources. For example, nurses can link the patient with in-home nursing, volunteer drivers, or whatever else they may need in the recovery period. Nurses also play role in easing some patient concerns or fears about surgery which Burton and her team found to be focused primarily on disfigurement, fear of hospitals and impact on their independence [18]. Nurses can help dispel these beliefs through creating an open dialog and shedding light on some of these concerns.

The time between diagnosis and surgery is very stressful for patients [11] even once a surgical plan is in place. Older women are no exception to this and often rely heavily on their friends and families [11]. This presents opportunities where nurses can act as important providers of psychosocial support [6]. Moreover, this is an opportunity for the nurse to act as an advocate and to engage other members of the interprofessional team such as social work or psychiatry if appropriate. Another element to consider in this pre-operative period is costs associated with treatment. For example post-operative bras or other clothing or medications for post-op pain control may be out of pocket costs even in systems with public healthcare. A nurse can step in to offer less costly or free alternatives to the traditional post-surgical bras or link patient's to programs where cost can be covered or reduced. Again nurses can engage the interprofessional team in order to best meet the patient's needs.

15.7 Peri-operative Period

During the peri-operative period nursing again plays a vital role. The risk of delirium [23] and falls post-operatively is higher in older adults [24]. Frontline nurses play an important role in assessing and flagging at risk patients using tools and clinical judgement. The Morse fall Scale [24] for fall risk and Confusion Assessment Method (CAM) [23] for delirium are simple examples of tools nurses use to help with this in clinical practice. Nurses can also monitor for side effect of medications, such as opioids as they can be less well tolerated in order adults [25]. These assessments allow nurses to be proactive and provide early interventions and treatment as needed.

Skin break down is also a concern for older adults undergoing surgery. Nurses make use of Braden Scale or Waterlow Score to flag at risk patients and provide necessary intervention. Nurses are also integral to encouraging early ambulation on the floor after the surgery. This is important for decreasing post-operative complications, such as pressure ulcers and pneumonia [26]. Nurses are able advocate for a longer length of stay when a patient has no in home support or in home nursing care, or they can help to link a client to a convalescence center if appropriate. Nurses at this stage also must re-iterate any post-operative teaching to ensure women know the instructions for self-care once they are home.

15.8 Post-operative Period

Once the patient is discharged home from the hospital nursing again plays multiple roles. If a patient is leaving with a post-surgical drain after surgery, ensuring a plan is in place for drain care, a visiting nurse may see the patient in home or at a local clinic. This provides valuable opportunity for re-enforcing patient teaching to ensure the patient is able to care for her drain independently. This also minimizes the number of hospital visits which is important as older patients [11] who may have

more limited mobility. At a large cancer centre in Canada, the Surgical Nurse Coordinator calls the patient a couple days after surgery to see how they are coping after discharge and assess for post-operative complications. This call also emphasizes previous teaching and reminds patients they have a resource to voice post-operative concerns, which is very important for older patients who may have more difficulty communicating their symptoms or concerns [21].

15.9 Medical Oncology and Radiation Oncology Treatment Considerations

Primary endocrine treatment regimens are offered to women with hormone –receptor positive breast cancers who are unfit for or decline surgery [27]. Adjuvant treatment consists of radiation treatment and systemic therapy. Systemic treatments include endocrine treatment, chemotherapy, as well as targeted therapies. While the majority of elderly women present with more favorable tumor biology that responds to endocrine therapy, there are some who present with larger and more advanced cancers requiring chemotherapy [19, 27, 28]. Systemic treatment may be prescribed in the adjuvant or neoadjuvant setting [29, 30].

In general, older adults are more complex and vulnerable to treatment as they present with: multiple comorbidities, multiple medications, functional limitations and cognitive difficulties [31] and limited support system. Hence, older women require special consideration and careful management of their breast cancer. Although, older women account for a large proportion of breast cancer diagnosis, they are not represented accurately in clinical trails due to existing comorbidities and limited life expectancy [19]. This can impact the delivery of evidence based care [6] resulting in possible risk of both over and under treatment of this population [32]. Typically the chronological age of the patients doesn't reflect the physiological age. Therefore, the goal is to individualize the treatment plan, while considering the risks and benefits. A retrospective chart review at two large Canadian cancer centers identified that woman ≥80 years were treated less aggressively, than their younger counterparts, and found to have less favorable disease free survival and overall survival [20]. Hence, this study emphasized the use of clinical judgement and assessment of tumor biology and patients' comorbidities to formulate treatment decisions.

Evidence shows that older women are often passive while discussing their treatment options with their health care professionals [33] and are less likely to ask for help and guidance, despite wanting the information of the prognosis and treatment outcomes [34]. Nurses are well positioned to address patient needs surrounding decision making. Nurses in collaboration with the health care team provide in-depth education on the benefits and risks of the proposed treatments. This facilitates patient autonomy and a confident informed decision making [34, 35]. The utilization of tools such as Comprehensive Geriatric Assessment as well helps guide treatment decision based on patient's medical, psychological and functional capability/status [36].

15.10 Systemic Treatment

Woman age ≥65 years are less likely to receive the standard treatment for their breast cancer and less likely to receive chemotherapy when compared to younger women [27]. However, studies have shown that patients are willing to accept treatment related toxicity if it increases their survival and they are likely to return to their baseline functioning at the end of therapy [37]. Less aggressive treatment regimens are usually selected for older women due to their complex medical history or fear of possible side effects of treatment [6]. In turn, more often, older woman with hormone receptor positive disease are prescribed endocrine therapy, which are more convenient and often manageable. Nevertheless this can pose challenges due to polypharmacy and compliance to treatment.

It has been shown that nurses are actively involved to improve treatment options, including advocacy for older woman with advanced cancer to receive chemotherapy [38]. In addition, nurses work collaboratively with the health care team, especially with pharmacy team to ensure proper screening of patient's drug profiles, assessing the effect of their comorbid condition and reviewing the drug interactions.

15.11 Radiation Treatment

The benefits of radiation treatment following breast conserving surgery and in specific conditions the benefits of post mastectomy radiation treatment has been well established [39]. However, some studies have also evaluated less aggressive radiation regimens, especially in early breast cancer presentations [40]. Evidence suggests that radiation treatment can be safely omitted in women ≥65 years old with T1N0M0 cancer, treated with breast conserving surgery, with clear resection margins, and endocrine positive tumor [40]. Although with the less aggressive regimens, the local recurrence will be higher in comparison to standard regimen but the low absolute local recurrence risk may justify the consideration of these approaches in an older woman with early breast cancer presentation. Nurses through comprehensive patient assessment, while considering patients' needs and wishes, can collaboratively choose best treatment option surrounding radiation therapy.

15.12 Nurses' Role During Systemic and Radiation Treatment

Patients encounter multiple appointments and consultations with disciplines such as surgical, radiation, and medical oncology. Nurse navigator/coordinators work collaboratively to provide timely access to care, coordination of services and continuity of care [11]. Once the treatment plan has been established, nurses work very closely in providing: education to patients and families in regards to treatment goals, treatment schedules, and possible side effects of therapy [11]. Throughout the patients' cancer treatment, nurses as well play a key role in assessing and

communicating patient's physical and emotional status. They also advocate for additional support such as transportation, extra home care support, referral to dietitian and social work. As previously mentioned cancer treatments and follow-up visits usually require many visits to the cancer center and increases the burden to patients and their families. This especially is true for radiation treatment which typically requires 3–6 weeks of daily treatments in the adjuvant setting [30]. Nurses play an essential role in connecting patients with appropriate resources. Although, patients may refuse additional services such as social support, it is important to provide the education on what they can offer, their benefits, and encourage patients to access them [33].

Nurses take part in educating patients on the possible side effects of radiation, each antineoplastic agent, and the self-care activities for reducing their severity. For example this could be in the form of providing patients with written information and reviewing the materials with them and allowing for questions. It is essential to provide education prior to initiation of therapy and continue throughout the treatment phase. At a large cancer center in Canada, breast nurses work closely with the oncology team seeing new patients in clinic and provide education and information in regards to the proposed treatment (s). These nurse-led education sessions highlight the treatment and side effect management. These side-effects can have negative impact on the patient's quality of life [41]. Providing relevant information regarding treatment, side effects and their management have shown that patients cope better [11].

Chemotherapy and radiation treatments are generally administered in an outpatient setting, requiring patients to manage treatment related symptoms at home. It is essential patients are educated on common symptoms related to their treatment and have ongoing medical support in managing these symptoms [6]. Some cancer centres have nurse led dedicated triage phone line for calls related to symptoms management. It enables effective communication with patients and addresses any concerns they may have regarding a new or worsening symptom, side effects of treatment, or questions regarding their plan of care. Nurses assess patient severity and use evidence based clinical pathways in proposing appropriate interventions. These interventions range from directing patients to manage symptoms at home, to visiting oncologist, to directing them to emergency department. Studies have shown benefits of using phone based symptom management including improved communication with health care professionals, improved symptom management and patients feel reassured their symptoms were being monitored while at home [42, 43].

15.13 Palliative Care

For older women with breast cancer sometimes treatment is not an option related to co-morbidities or they opt not to have or to discontinue treatment. Breast cancer although often treatable this is not always the case. Nurses can advocate for initiating palliative care early on, for women with advanced breast cancers, as it improves

the patient's quality of life, while patients are receiving treatment for their cancer [44]. Facilitating collaboration with the interprofessional team during this phase is also very important [44] and nurses are essential to increasing access to palliative care [45]. Symptom and pain management are keystones of palliative care [44] and frontline nurses are critical in ensuring proper management of these in home, hospital or hospice [45].

15.14 Conclusion

Nurses are essential to providing optimum care for older women with breast cancer [6]. Nursing care is a critical element to consider when planning the care for older women with breast cancer no matter her illness trajectory. Nurses can help expedite the diagnostic process and the anxiety related to their treatments. Nurses act as resources, as a comfort, navigators, educators, leaders and advocates [7] which can diminish some of the stress and challenges older women face throughout their cancer trajectory.

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Research, Clinical Trials and Evidence-Based Medicine for Older Patients with Breast Cancer

16

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Abstract

Evidence-based treatment is the golden standard of current oncology care. Treatment guidelines are developed by gathering, weighing and summarizing all available scientific research, and subsequent treatment recommendations are used to formulate criteria to assess, compare and improve quality of care. Older patients often require tailoring of care, which can conflict with the intrinsic rigidity of guidelines and quality criteria that focus primarily on optimal disease treatment, without taking the heterogeneity of an ageing cancer population into account. Although it is worthwhile to strive for evidence-based treatment in older patients, several important issues in current scientific research and treatment guidelines can limit their applicability to the older patient population. These issues include external validity of clinical trials, trial participation, confounding by indication in observational research and relevant patient-related outcome measures for older patients.

Keywords

Research · Evidence based medicine · Internal and external validity · Clinical trials · Observational studies · Patient-related outcome measures

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Evidence-based treatment is the golden standard of current oncology care. Treatment guidelines are developed by gathering, weighing and summarizing all available scientific research, and subsequent treatment recommendations are used to formulate criteria to assess, compare and improve quality of care. Older patients often require tailoring of care, which can conflict with the intrinsic rigidity of guidelines and quality criteria that focus primarily on optimal disease treatment, without taking the heterogeneity of an ageing cancer population into account. Although it is worthwhile to strive for evidence-based treatment in older patients, several important issues in current scientific research and treatment guidelines can limit their applicability to the older patient population. These issues, which include external validity of clinical trials, trial participation, confounding by indication in observational research and relevant patient-related outcome measures for older patients, are discussed in this chapter.

16.1 Internal Versus External Validity

Internal and external validity are key terms when assessing the quality of a clinical trial. Internal validity is the extent to which the observed effects are true for the study participants [1]. It can be negatively affected by a non-randomized method of treatment allocation, lack of blinding, loss to follow-up and other issues that will not be further discussed in this chapter. One of the best ways to improve the internal validity is by performing a double blind randomized controlled trial (RCT) [1]. An RCT demonstrates what can be achieved with careful observation and under certain restrictions [2]. This is not the same as demonstrating what can be achieved in daily practice, since this is also affected by external validity [3].

External validity is the extent to which the results of a study are a true reflection of what can be expected in the target population, irrespective of the study population [1]. Often, internal and external validity are at conflict: measures taken to improve internal validity, such as patient selection through in- and exclusion criteria, can limit the generalizability of a trial [3].

16.2 Trial Participation of Older Patients

The study population of a clinical trial strongly affects the applicability of trial results for the general population of older patients. To allow for generalisation of trial results, the study population should resemble patients seen in daily clinical practice [4]. Thus, to obtain evidence on cancer treatment for older patients, it is important that these patients participate in clinical trials.

However, in- and exclusion criteria can be overly exclusive of older patients. These patients are often excluded based on age itself or on the basis of comorbidity, which is highly prevalent among older patients [3, 5–8]. In a review of 41 studies of the National Institutes of Health in the United States, 73% of patients with a specific disease did not meet the inclusion criteria and were excluded from trial participation

[9]. In another study that assessed 109 clinical trials from five major medical journals, 20% of all studies excluded patients above a specific age. In addition, nearly half of these studies used criteria that disproportionally excluded older patients [5]. Hence, improving evidence for older patients with breast cancer is only possible if researchers make their trials as inclusive as possible [10].

Even when researchers aim to include older subjects and use adapted in- and exclusion criteria to achieve this goal, patient populations may end up being highly selected [3, 5, 11], and there are often difficulties recruiting and maintaining older patients in research projects. Doctors appear reticent in suggesting a clinical trial to older patients, even if a suitable study is available [12–14]. For example, in a questionnaire, 50% of oncologists reported considering patients above a certain age not suited for clinical trial participation [13]. As a result, in clinical trials focusing on diseases that are not age-specific, only 9% of participants is older than 65 years, and 1% older than 75 years [15]. Interestingly, elderly patients are even underrepresented in studies investigating methodology of research and opportunities for improving trial participation [16].

An important reason for excluding older patients is that comorbidity - as a competing cause of death - and limitations in the ability to tolerate treatment may result in less significant treatment effects compared to a younger, healthier population [17]. Although this could appear to be a valid argument on one hand, it also underlines the importance of trial participation for older patients since this limits the applicability of trial results for the general older population.

16.3 External Validity in (Breast) Cancer Trials

There are few studies assessing the external validity of breast cancer trials. One study compared the participants of the randomized, double-blind TEAM-trial that assessed adjuvant hormonal therapy in postmenopausal breast cancer patients, with unselected breast cancer patients of corresponding age. The study showed that even when the in- and exclusion criteria of the trial were applied to the general population, trial participants had fewer comorbid diseases, a higher socioeconomic status and smaller tumours (all $p < 0.01$). A hazard ratio for mortality of 1.39 was found (95% confidence interval 1.05–1.82, $p = 0.02$) in favour of the trial patients. Thus, the patients in this trial did not adequately reflect the average older breast cancer patients, negatively affecting the external validity of this trial [11].

More data is available from other cancer types. For example, the Dutch CAIRO study assessed the effect of various types of chemotherapy in patients with metastatic colon cancer [4]. The results of this trial were subsequently compared to patients receiving the same treatment, who had not participated in the trial. In this comparison, patients who fulfilled the inclusion criteria but did not participate, achieved similar benefits as trial patients. However, non-eligible non-participants had significantly poorer results, with a hazard ratio for mortality of 1.70 (95% confidence interval 1.33–2.17, $p < 0.01$) [4]. A similar result was seen in a Norwegian

study in patients with metastatic colorectal cancer: trial patients had a 40% longer survival than non-trial patients receiving the same treatment [18].

While much research is done regarding the interval validity of RCTs and systematic reviews, external validity is addressed much less frequently [3]. For example, when assessing new drugs, agencies such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) do not require evidence that a new drug achieves a clinically meaningful effect or that the study population of registration studies is a good reflection of daily clinical practice [3].

Critically evaluating the extent to which the study population is similar to the target population treated in daily practice is only possible if key baseline characteristics of the participants in studies are recorded and reported. For older patients, these should include cognitive and physical function (such as capacity for performing (instrumental) activities of daily living), comorbidities and their treatment, and frailty [16]. The International Society for Geriatric Oncology, The Alliance and the European Organization for Research and Treatment of Cancer therefore recommend that all studies in oncology report baseline characteristics including a detailed age distribution and geriatric parameters [19]. Unfortunately, these data are often not reported. For example, in a systematic review assessing a random sample of 300 RCTs published in 2012, only a minority of studies specifically addressing older patients reported on physical (22% of studies) and mental functioning (14%) of study participants [20]. As a result, it remains unclear to which patients the study results are applicable.

In addition, for practical reasons, secondary publication such as meta-analyses and treatment guidelines require summarizing of study protocols. Along the way, vital information on patient selection is often lost, making a comparison of the trial population with the real-life patient in the consulting room even more difficult [3].

16.4 Validity of Observational Studies

An alternative to clinical trials for improving the evidence in treating older patients with breast cancer is using observational data. However, there is an important limitation of observational research in which two treatments are compared that influences the validity. In observational studies, treatment of patients is allocated by physician's judgement instead of randomization. There are always specific reasons that determine why a patient receives a specific treatment, resulting in the phenomenon of "confounding by indication" in observational studies [21]. For example, older patients with breast cancer who receive chemotherapy are relatively more "fit" and have less geriatric deficits than patients in whom chemotherapy is omitted, as is highly understandable. Thus, poorer outcome could be due to the a priori fitness of patients, rather than the chemotherapy or omission thereof. On the other hand, patients with more aggressive disease often receive more aggressive treatment (for example chemotherapy). Poorer outcome could therefore be the result of tumour characteristics rather than treatment choice. These two examples both result in bias

in observational studies, since differences in outcome could be incorrectly attributed to treatment choice rather than the patient or tumour characteristics that affected treatment choice. Although it is possible to adjust for some of these so-called confounders, there are always many factors that are unmeasured and cannot be adjusted for. Even using the concept of a propensity score, which could be seen as an average of all measured confounders, does not solve the problem of unmeasured (so-called residual) confounders.

A recent systematic review showed that of all observational breast cancer studies in older patients that were published between 2009 and 2013, 71% directly compared two treatments thereby resulting in confounding by indication [22]. Hence, there is a large proportion of studies that is currently performed and published using invalid statistical methods.

In the remaining 29%, some form of instrumental variable was used. This is a methodologically valid alternatives for circumventing confounding by indication. An instrumental variable is a factor that is associated with treatment allocation, but not with the outcome [23]. Examples of instrumental variables can be geographical region, country or time-period [22, 24]. Important conditions that must be met in order to use an instrumental variable, are that it must determine treatment allocation and cannot be associated with the outcome through any other way than through the difference in treatment. Hence, patient populations must be comparable, access to health care systems should be similar, etcetera. It has been shown that by using a (valid) instrumental variable, it is possible to approach the validity that is reached in a randomized clinical trial [25].

As an example, the EURECCA project compares outcome of treatment in European countries using population-based cancer registries [26]. Because of the limited evidence, there are large differences in current treatment strategies within, and between countries, which enables researchers to compare the effects of these differences on long-term outcomes [27, 28].

16.5 Validity of Prognostic Models in Older Patients with Breast Cancer

The issue of external validity is also highly relevant to prognostic models used in breast cancer care. There are many such models available, that can be used to calculate outcomes such as overall survival, breast-cancer survival and recurrence-risk [29]. Some models also incorporate expected benefits of treatment and can be used to counsel patients in clinical decision making. Here, we give an overview of the validity for older patients of the most commonly used prognostic models in breast cancer.

First, there are several clinical prognostic models available in breast cancer. Until it went offline in 2016, the most well-known and frequently used prognostic model in breast cancer is Adjuvant! Online [30]. This model was developed in a large dataset that was extracted from the SEER-database and included patients aged 36 to 69 years that who were diagnosed with breast cancer between 1988 and 1992 [31]. Hence, the model included no patients aged 70 years and older. Although the model

performed well in external validation studies of several populations [32, 33], it was recently shown in a large population-based study in the Netherlands that the model is not reliable in patients aged 65 years and older [34]. In particular, the risk of recurrence was strongly overestimated, most likely due to an underestimation of competing mortality. Also, the unstandardized comorbidity score that is used in Adjuvant! Online strongly influenced its predictions.

Alternatively, the PREDICT-tool predicts 5- and 10-year overall survival in patients with breast cancer. This tool was developed in a British cohort and included almost 1800 women aged 65 years and older [35]. It was recently shown that the tool predicts overall survival much better in older patients with breast cancer than Adjuvant! Online [36]. However, it must be noted that the tool does not incorporate comorbidity and only predicts overall survival outcome, which limits the applicability especially in older patients with a high risk of competing mortality.

Older clinical prediction tools include the Nottingham Prognostic Index, OPTIONS and the BC Nomogram. These models were all validated in external cohorts that included only few patients aged 70 years or older, which limits their external validity. This was shown in a recent systematic review that summarized all these validation studies: subgroups aged 76 years and older, and 66–75 years showed the largest differences in observed and predicted values, especially in the validations from the OPTIONS tool and BC Nomogram [29].

Second, there are several genomic profiles available in breast cancer, of which MammaPrint and Oncotype Dx are the most well-known. MammaPrint was developed in a Dutch cohort and includes patients with breast cancer with a maximum age of 70 years [37]. Validation studies only included very small numbers of patients aged 70 years and older [29, 38]. Oncotype Dx was developed in a cohort that included 300 patients aged 60 years and older, more detailed age distribution is not described. This profile was validated in several external cohorts, in which again only small numbers of older patients were described [29, 39, 40]. The largest validation study included 411 patients aged 70 years and older but did not report specific performance of the genomic profile in this subgroup [41].

Third, geriatric assessment parameters such as physical functioning, cognition and nutritional status have been shown to be highly predictive for toxicity of chemotherapy in older patients with cancer [42]. Two tools have been developed specifically for predicting grade III toxicity or higher in older patients: the CRASH-score (Chemotherapy Risk Assessment Scale for High-Age Patients), which predicts haematological and non-haematological toxicity [43], and the Cancer and Ageing Research Group (CARG) Score, which predicts overall grade III or higher toxicity [44, 45]. These tools are not breast cancer-specific but can aid in the selection of patients who are fit enough to undergo chemotherapy.

Geriatric parameters are also predictive of prognosis (irrespective of cancer-related prognosis) in older patients. Many of the available instruments for estimating survival can be found on the Eprognosis-website, including a range of time scales (6 months to 10 years) and settings (community-dwelling, nursing home, hospital) [46, 47]. However, these have generally not been developed or validated specifically in (older) patients with cancer.

16.6 Patient-Related Outcome Measures

A final issue to address when assessing the value of current evidence for decision making in older breast cancer patients, are patient-related outcome measures. While simple clinical outcomes are often easiest to assess objectively, these may not necessarily be a good reflection of a patient's priorities [3]. Both the FDA and the EMA emphasize the importance of including the patients' perspective when evaluating the outcome of oncologic treatment [48].

Several studies have demonstrated that patients and doctors have different priorities when it comes to treatment outcomes. A study among 350 breast cancer patients demonstrated that they gave higher priority to patient-related outcome measures than to clinical outcomes such as survival [49]. Other studies showed that while doctors focussed more on the physical effects of treatment, patients gave the highest priority to their mental health, emotional well-being, general health and vitality [50, 51]. Older patients were shown to be as willing to receive life-prolonging chemotherapy as younger patients [52], but less accepting of toxicity [53], particularly when this could affect their independence, cognitive functioning or social situation [19, 54, 55].

When weighing various treatment options, information regarding the effect of the treatment on the patient is as important as tumour effect. However, the majority of oncology studies still focus primarily on clinical outcomes such as survival, progression-free survival and toxicity [56, 57]. In an overview of 463 current breast cancer trials listed in the National Institutes of Health clinical trial registry – by far the largest registry in the world – only 20% included any patient-related endpoint, primarily quality of life. Functional status or cognitive functioning were included in less than 5% of studies [58]. In addition, results with regards to quality of life often remain unpublished: in an analysis of 201 phase III trials in poor prognosis malignancies, less than half of studies that assessed quality of life, incorporated these results in trial publications [59]. Studies addressing both quality of life and prolongation of life generally base their overall conclusions on the survival results, even when quality of life results demonstrated an opposite pattern of benefit between treatment arms [60, 61]. Particularly when the primary trial results are negative, the results regarding quality of life appear to be considered irrelevant in terms of selecting from available options. Thus, despite their importance to decision making in older cancer patients, patient-related outcome measures are insufficiently considered in current research.

16.7 Conclusion

The need for tailored care in older cancer patients is increasingly acknowledged. However, making specific treatment recommendations for this patient population in clinical guidelines or based on prognostic models is difficult due to insufficient participation of older patients in clinical trials, affecting external validity. In addition, observational data are often affected by confounding by indication and

Table 16.1 Recommendations for clinical trial design and observational studies in older patients

Subject	Recommendation
Clinical trials	Geriatric assessment to describe population [62] Choose relevant endpoints [51] Consider composite endpoints [51] Use appropriate inclusion criteria (not too stringent) in order to increase enrolment [10] Consider abandoning an upper age limit for trials [10]
Observational studies	Avoid direct comparisons of treatment resulting in confounding by indication [22] Use alternative study designs such as the instrumental variable or studying time trends [22]

outcome measures most relevant to the older population are often not incorporated in research. Table 16.1 summarizes the recommendations from several key (position) papers regarding clinical trial design and observational studies in the older patients with cancer. Without a significant shift in the research agenda and methodology, tailoring of care will remain to be based on expert opinion rather than solid scientific evidence.

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