Breast cancer in older people

Breast cancer is the most commonly diagnosed cancer and primary cause of cancer-related death worldwide. The biggest risk factor for developing breast cancer is increasing age[1] and in the UK 50% of breast cancer patients are over 65 years.

Dr Jordan Bowen Specialist Registrar (ST4), Elderly Care Medicine, Royal Berkshire NHS Foundation Trust
Professor Margot Gosney Professor of Elderly Care Medicine, University of Reading and Royal Berkshire NHS Foundation Trust
Email jstbowen@googlemail.com

The widespread introduction of breast screening programmes coupled with significant improvements in the treatment of breast cancer has led to a downturn in breast cancer-related mortality in younger age groups. However, this has not been echoed in the elderly population where evidence suggests the mortality rate has remained static (70–79 age group) or has increased (80+ years),[2,3] although estimating disease-specific mortality rates due to breast cancer in later age is subject to methodological difficulties.[4] Multiple studies demonstrate older patients are less likely to be offered all modalities of treatment[5] and breast cancer has a poorer prognosis when diagnosed in older age.[6]

Over the past decade increasing attention has been paid to the specific management problems of older women with breast cancer.[7] Increasing population life expectancy brings with it the increased likelihood of frail and elderly cancer patients presenting to both oncologists and geriatricians. Unfortunately, older age groups are under-represented in clinical trials and there is consequently a deficiency of evidence to guide clinicians. Recent large prospective studies specifically directed at breast cancer in older women have had to close due to poor recruitment.[4] Moreover, researching breast cancer in older patients is hampered by their heterogeneity. Defining them on the basis of age yields a diverse set of patients ranging from robust to frail to whom the same treatment strategies cannot be generalised.

It has been suggested that examination of databanks, large audits and observational studies may have a hitherto overlooked role in providing necessary data that the failed RCTs have not been able. Meanwhile, steps have been made in defining the altered biology of breast cancer in older age while headway has been made in exploring the practitioner, patient and cultural biases which have contributed to the different treatment of older breast cancer patients.

Epidemiology

In 2008 there were 47693 new cases of breast cancer diagnosed in the UK, 81% of which occurred in women over the age of 50 years with the peak incidence occurring between the ages 60–64 (14%).[8,9] Age-standardised five-year relative survival rate at diagnosis between 2001–2006 in the UK for 60–69 year group was 87%, 70–79 year group was 78% and for 80+ was 64%.[10] The mortality rate in 2008 for patients over 70 years was 161.2 per 100,000, which has been steadily falling since a peak in 1991, although it is still on par with the rate in 1981.[11]

The high likelihood of micro-metastatic disease undetectable at diagnosis makes recurrence in breast cancer a possibility at any stage after treatment and consequently the relative survival rate continues to fall even 20 years after diagnosis. Nonetheless, even in patients over 70 years the predicted 20-year relative survival rate is 59% (based on diagnosis in 2001–2003). This pattern is approximated in other epidemiological data from Europe and the US.[12]

Presentation and management

The majority of older breast cancer patients are symptomatic

at presentation with around 15% presenting via screening or from incidental findings on other imaging modalities.[13,14] Breast tumours presenting in older age are more likely to be larger, more advanced, more likely to involve the axilla and more likely to be metastatic, though this is likely to be due to delayed diagnosis rather than more aggressive biology.[15] Tumour biologic profile is conversely more benign in older age with increased steroid receptor expression (90% of cases), lower proliferative rate, diploidy, normal p53 and reduced expression of unfavourable biochemical markers.[14, 16]

Special considerations in the elderly population

The high survival rate in breast cancer means longevity is frequently measured in years. The implications for treatment in older age groups are that other comorbidities often pose a higher mortality risk than breast cancer. Furthermore, frailty, poor physiological reserve, poor social support, deteriorating cognition and capacity issues can all complicate management decisions for the clinician. Consequently, the key difficulty is predicting the response of elderly patients to treatment modalities without exacerbating their existing comorbidities and without subjecting them to undesirable toxicity devoid of survival or symptomatic benefit.

Existing performance indices correlate poorly with measures of comorbidity load and neither is sufficiently specific in older age groups. The comprehensive geriatric assessment (CGA) has been strongly recommended when assessing older cancer patients,[17] although a minority of oncologists attempt it.[18] It outperforms standard predictive tools, detects problems missed by standard assessment of cancer patients,[19] improves function and decreases hospitalisations though a definitive mortality benefit has not yet been proven.[20]

Nonetheless older patients with breast cancer are more likely to be undertreated with poor adherence to standard guidelines.[21] They are less likely to participate in screening, experience lower diagnostic procedures, are less likely to be treated in specialist centres, are less likely to be offered or to receive adjuvant chemotherapy or radiotherapy and are less likely to be offered surgery or breast conservation treatment. They consequently have a reduced disease-free and overall survival which is not fully accounted for by comorbidity.[6, 22, 23] On the other hand older patients are less likely to self-examine for breast lumps, are less likely to be aware of the increased risk of breast cancer with age,[24] and are less likely to adhere to adjuvant therapy. On subgroup analyses patients with increased comorbidity and patients with dementia are least likely to be offered treatment.[25, 26]

Screening

The UK National Breast Cancer Screening Programme was established in 1988 following the Forrest Report to the government. Triennial screening was initially offered to women aged 50–64, which was extended to included women up to the age of 70 years in 2004. A further extension to include women aged 47–73 has been implemented since 2008 and will be completed by 2012. Patients over 70 years are still encouraged to request further mammography at their local centre at three-yearly intervals though they are not subject to the automatic call/recall service. Some evidence suggests that there may be possible benefits to survival in screening up to the age of 80,[27] possibly because at older ages the sensitivity and specificity of mammography is higher due to reduced breast density. Nonetheless, guidelines recommend tailored decisions for individuals over the age of 75 taking into account the risks of over-diagnosis, benefits of potential treatment and cultural context.[28]

Local/surgical

Primary surgical treatment is the most common treatment offered for early breast cancer in older women.[13] However, a survival benefit has only been demonstrated after 15 years[29] and surgery is only recommended in patients who have a life expectancy greater than five years.[28] Nonetheless, surgical treatment is a low risk operation (0–0.3 mortality). The risk can be mitigated further for the very frail by being performed as day case procedures or under local or regional anaesthetic.[30]

Breast conservation therapy (BCT), commonly as lumpectomy or partial mastectomy, is the recommended standard of care for early breast cancer in all ages while

total mastectomy is recommended for patients with tumours greater than 5cm or multi-quadrant disease.[30] Older women have a better quality of life after BCT when compared with mastectomy.[31] However, older women are more likely to be offered mastectomy in cases where BCT is appropriate[21] and mastectomy is more likely to be inadequate in these cases.[32]

Axillary surgery is important for prognostication and treatment. Axillary node clearance is often avoided in older women due to concerns over the risk of lymphoedema, though evidence suggests any decreased quality of life resolves after six months.[33] Recently sentinel lymph node biopsy (SLNB) has been developed as a safe and accurate method of identifying axillary involvement in older patients, though there is a slightly reduced identification rate with increasing age (97.1% in over-70s versus 98.8% in patients under 70 years).[34] Elderly patients should be encouraged to undergo SLNB if they are clinically node negative or they have tumours less than 2–3cm to help guide further treatment decisions.[28]

Breast reconstruction is performed less frequently in the elderly population. Surgeon preference may be the predominant reason,[30] and though body image may be less concerning for some older patients its importance to others is reflected in the success of some breast reconstruction series in older women.[35]

Radiotherapy

Radiotherapy is offered in the adjuvant setting to reduce local recurrence[36] and can be used to palliate symptoms such as pain, bleeding and soft tissue involvement. The absolute benefit of radiotherapy declines with age but remains significant in all age groups, though any survival benefit is only seen after 15 years.[29] It is well tolerated, there is no significant increase in toxicity at any age and though there is a small reduction in quality of life post-procedure this normalises quickly.[37] For frailer patients there is the possibility of shorter or less demanding schedules. Current recommendations are that radiotherapy should be offered to older women who are expected to live longer than five years requiring locoregional control.[28]

Endocrine

Primary endocrine therapy is administered to women with steroid receptor-positive breast cancer where its high efficacy and tolerability have made it an attractive treatment option in frail elderly patients. Nonetheless primary endocrine therapy alone is inappropriate for older women with operable breast cancer who are considered fit for surgery as it results in reduced median progression-free interval, increased local recurrence and diminished overall survival.[38]

The oestrogen receptor antagonist tamoxifen has been the mainstay of hormonal treatment for 30 years, but the newer third generation aromatase inhibitors—letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin)—have been increasingly shown to be superior. In metastatic cancer there may be value in crossover therapy by following tamoxifen with aromatase inhibitors or vice versa.

Though serious adverse events are uncommon, tamoxifen carries with it the increased risk of thromboembolic events, stroke and endometrial cancer, whereas aromatase inhibitors increase risk of fractures, bone and joint pain, hypercholesterolaemia and cardiac events.[39] Recent evidence suggests that zoledronic acid (Zometa) administered with letrozole is effective in preserving bone mineral density and improves disease-free survival.[40] Reports of a possible association of cognitive impairment with endocrine therapy have not been confirmed by the most recent subanalysis of the IBIS II trial.[41]

Adjuvant endocrine

Adjuvant endocrine therapy is given subsequent to local treatment to minimise recurrence and to reduce the risk of distant disease. The evidence from large phase 3 trials suggests that there are no differential effects of age on the efficacy of adjuvant endocrine therapy.[39] The standard of care has historically been tamoxifen given to receptor positive women for five years after surgery, which reduces recurrence by 41% and death by 34%.[29]

The ATAC trial found adjuvant anastrozole was better tolerated than tamoxifen, improved disease free survival and reduced distant metastases though there was no change in overall suvival.[42] The BIG 1-98 trial demonstrated improved tolerability of adjuvant letrozole and disease-free survival

compared with tamoxifen.[43] The recent MA-17 trial showed improved disease-free survival and distant disease-free survival with letrozole in patients with early breast cancer who had received five years of tamoxifen.[44] The ESTEeM trial was designed to ascertain the role of primary anastrozole therapy in women over 75 years compared with adjuvant anastrozole in operable breast cancer, but unfortunately was closed due to low accrual.

There is still some uncertainty about when to give aromatase inhibitors: immediate therapy, switching after 2–3 years of tamoxifen or extended adjuvant treatment after five years of tamoxifen. Current guidelines suggest that maximal benefit of aromatase inhibitors to elderly patients may be after 2–3 years of tamoxifen.[28]

Chemotherapy

Chemotherapy is predominantly offered in hormone-negative or metastatic disease as well as having a role in aggressive hormone-positive tumours and in the 20% of patients not responsive to endocrine therapy. Chemotherapy is the least studied treatment modality for breast cancer in the elderly population. The ACTION trial was designed to assess the effect of chemotherapy versus no chemotherapy on relapse-free survival in older women with breast cancer. Sadly, despite a robust design and initial enthusiasm it was closed after a year due to poor recruitment.[4] The CASA trial designed to assess adjuvant chemotherapy in women at advanced age similarly had to close due to poor accrual.

Partly because of this paucity of data, older patients are much less likely to be offered adjuvant chemotherapy (6.4% in those over 75 years compared with 35% in patients 50-74 years). The Oxford Overview suggests the absolute benefit diminishes decade by decade[29] though others have shown that adjuvant chemotherapy confers the same reduction in breast cancer-related mortality as younger women.[45] Retrospective analyses suggest there is no apparent age effect on toxicities[46] but clinical trials may underestimate toxicity in older age.[47] Moreover, older patients receiving chemotherapy have a reduced overall survival rate due to non-breast cancer causes and higher treatment-related mortality (0.5–1.5%).[48]

Nonetheless, guidelines recommend healthy older women should be considered for chemotherapy in the same way as younger women. Treatment decisions should not be age-based but should take into account comorbidity, treatment toxicity and an estimation of absolute benefit.[28]

Anthracyclines (doxorubicin/epirubicin) are most effective but carry a significant risk of cardiac toxicity. The risk is higher with increasing age and underlying heart disease (47% heart failure risk in 67–70 age group), and anthracycline therapy mandates regular cardiac monitoring. Taxanes can be added in high risk fit patients or can be used as single chemotherapy in older patients who would previously have been considered too frail, particularly with the advent of reduced weekly regimes. CMF (cyclophosphamide, methotrexate and fluorouracil) is less effective in older women but better tolerated and is an alternative in patients who have an excessively high cardiac risk. The CALG-B trial recently compared oral capecitabine (Xeloda) with standard chemotherapy (CMF or doxorubicin/cyclophosphamide) and concluded that though capecitabine was associated with a better quality of life this ceased after one year, while relapse-free and overall survival was significantly improved by standard chemotherapy.[49]

The HER2/neu receptor monoclonal antibody trastuzumab (Herceptin) is only effective in the 15% of patients over 75 years who are HER2 positive and confers an increased risk of cardiac toxicity. There is little evidence for its use in older groups though it is still recommended in receptor positive older patients who are otherwise fit for chemotherapy.[28]

The narrow therapeutic window of chemotherapeutic agents deters a lot of clinicians who have difficulty in predicting the response of frailer patients and so prefer to avoid chemotherapy altogether. A possible solution developed recently is gene expression profiling.[50] Though still in their infancy, multigene assays may help predict responsiveness and the risk of relapse in elderly patients and thereby better identify patients who stand to benefit from chemotherapy and endocrine therapy.[51]

In metastatic disease the aims of chemotherapy are different and treatment strategies should aim to minimise toxicity by using monotherapy, oral or

Conclusion

The appropriate management of breast cancer in the elderly population is still uncertain. The deficiency of research guiding management in older age groups is slowly being addressed but data are still lacking. The practice of clinicians treating breast cancer in elderly women is varied and is subject to many influences but cannot be said to be underpinned by robust research. Furthermore, it is increasingly apparent that breast cancer in older age behaves differently to that in younger women and it is insufficient to extrapolate treatment decisions based on experience with younger women.

The challenge facing clinicians lies in elucidating any differential biology of breast cancer in older women, clarifying the role of local and systemic therapy for breast cancer in the context of frailty and chronic disease, identifying predictive tools that will guide treatment in older people, and doing so using sound but practicable scientific method.

In the meantime, the management of frail elderly patients with breast cancer is likely to face clinicians with increasing frequency. These patients will be served best by multidisciplinary team management which incorporates an oncologist adept at managing frail elderly patients or a geriatrician familiar with the management of cancer. Together they will be able to deliver the tailored approach to the patient facing them that fully accounts for the complexities of older age and maximises healthful life.

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