Clinical Update

Personalising Care in the Older Woman with Primary Breast Cancer

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Abstract

The incidence of breast cancer increases with age. Despite this, most research in the field is targeted at younger patients. Age-specific guidelines are not widely referred to and guidelines which allude to the older woman as an individual are based solely on conventional factors. This creates a problem for older women with primary operable breast cancer who are not fit, too frail or do not wish to have surgery. Preliminary studies have shown that older women with breast cancer have distinct biological features compared to their younger counterparts. This means that they are likely to have less aggressive cancers such as those who are oestrogen receptor-positive. Geriatric assessment (GA) has been used in clinical practice to identify patients that are suitable for certain treatments. More research on this group of patients' unique biological features and GA will help tailor personalised care for them.

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Introduction

The 2 main challenges in initial management of primary breast cancer, at diagnosis, are as follows: 1) Which patients with oestrogen receptor (ER)-positive tumours should receive surgery versus primary endocrine therapy (PET)? (Breast cancer in older women tends to be ER-positive and human epidermal growth factor receptor 2-negative.[1] Historically, there is no significant difference in overall survival when comparing surgery to PET in this cohort);[2] and 2) What alternative treatments can be given to ER-negative tumour patients who are not candidates for or do not wish to undergo surgery?

In addition, quality of life (QOL) may be more important to the older individual than curative treatment alone.[3]

The National Institute for Health and Care Excellence in the United Kingdom advises surgery as first-line treatment of primary operable breast cancer.[4] This is echoed in European,[5] American[6] and international[7] guidelines. None of these guidelines are specific to the management of breast cancer in the older woman[8] (they simply refer to "all women"). Currently, the most age-specific guidelines are by the International Society of Geriatric Oncology (SIOG) which has issued a set of recommendations for treatment following a review of all literature on breast cancer. Published in 2007,[9] the guidelines were updated in 2012[10] in collaboration with the European Society of Breast Cancer Specialists. The guidelines state that patients ≥70 years old should be offered the same surgery as younger patients and that PET should only be offered to patients with ER-positive tumours with a life expectancy of 2–3 years despite optimisation of medical conditions. The guidelines recommend employing a geriatrician to aid with the estimation of life expectancy and optimisation of comorbidities.

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While age alone should not be a deterrent to surgery, there is no clear consensus on how to select older patients for the treatments. As such, older women with breast cancer tend to receive suboptimal treatments. They are either undertreated due to lack of clinical attention and/or high-level research evidence, or overtreated due to overzealous adoption of recommendations for younger counterparts, while ignoring the specific needs of the older population.[8,9] With an ageing population, this approach is unsustainable to healthcare.

Therefore, we must seek to provide effective personalised care to the individual older woman with primary breast cancer. Growing evidence is emerging for the use of geriatric assessment (GA) to determine which other factors may contribute to treatment decision-making in the older population. However, which tools should be used and in what context they should be interpreted remain unclear.[11]

In this article, we highlight the current problems with biological features and GA in this cohort, summarise the current literature and outline future steps to achieve personalised care.

How Can We Personalise Care in the Older Woman with Breast Cancer Based on Biology?

The Current Problems with Biology

There are 2 problems with the biology of breast cancer in older women. First, the suitability of an individual patient's breast cancer to receive a specific treatment and second, endocrine treatment options when surgery is not feasible (which is different for patients with ER-positive tumours when compared to those with ER-negative tumours).

There is evidence linking an increase in ER positivity with advanced age—>80% of older women tend to have ER-positive tumours which are considered as a less aggressive phenotype.[1] PET, in the form of aromatase inhibitors such as anastrazole, has become first-line treatment for older women who are deemed not suitable for or who do not want to undergo surgery by choice. Historical data has shown similar survival rates between PET and surgery.[2] More recent data has suggested that surgery has an advantage over PET in terms of local recurrence. However, this is only apparent after 5 years of treatment[12,13] and therefore, largely dependent on age-at-diagnosis to guide treatment decision. This calls for an individualised approach when treating this group of patients while leaning towards the use of PET in patients with a very limited life expectancy.[14]

More problems arise in patients who have ER-negative tumours, of which there is little discussion in the current literature. Primary surgery is still recommended, where possible. One alternative option is primary radiotherapy although this may present problems such as tolerability and side effects. Another option is chemotherapy. However, it is expected that if a patient could not tolerate surgical management, it would be the same for chemotherapy. Historically, some patients with ER-negative tumours have received endocrine therapy regardless of receptor status.[15]

Summary of Current Literature

Syed et al[16] examined a database comprising histological samples and clinical data of 575 older women (≥70 years old) with early primary breast cancer who were treated with surgery and then compared this to a series of disease stage-matched younger patients. Partitional clustering technique analysing a panel of 24 biomarkers based on tissue microarrays (TMAs) identified 6 biological clusters in older patients—5 of which were common in young patients (Fig. 1)[16] and 1 novel cluster (or "category") (low ER, luminal) which was distinctive to the older population (Fig. 2).[16] Overall, older women showed less aggressive tumour biology. The luminal phenotype showed better breast cancer-specific survival (BCSS) (Fig. 3).[16]

This is echoed in the work by Jenkins et al[17] who looked at clinical and gene expression microarray data of 3947 patients with breast cancer. They agree that more favourable subtypes of breast cancer are seen with increasing age (with luminal A tumours having the best outcome in this age group).

Molino et al[18] performed a retrospective analysis of 3814 patients of all ages with operable breast cancer looking at pathological and biological differences between younger and older women. They found that although older women are more likely to have larger and more frequently node-positive tumours, they are biologically less aggressive and have lower proliferative indices.

These unique biological features in older women may help in treatment decision-making for patients considering surgery versus PET. This also highlights the potential scope for new therapeutic targets.

Most recently, cyclin E, a regulator of the cell cycle, has been found to be an exciting potential therapeutic target.[19,20] Preliminary work in the older age group has confirmed that cytoplasmic cyclin E is associated with poor clinical outcome and biomarkers of poor prognostic significance in this population.[21] Therefore, it is possible to identify patients who may benefit from alternative treatment strategies targeting cyclin E.

We have developed a technique in our institution to construct TMAs from core needle biopsy specimens.[22] This has the advantage of obtaining biological information from older women with breast cancer, regardless of whether they have undergone surgery or PET. More work is underway to construct TMAs from a historical series of older women diagnosed with breast cancer. We hope that this will highlight more unique biological features in this age group, which may be potential therapeutic targets.

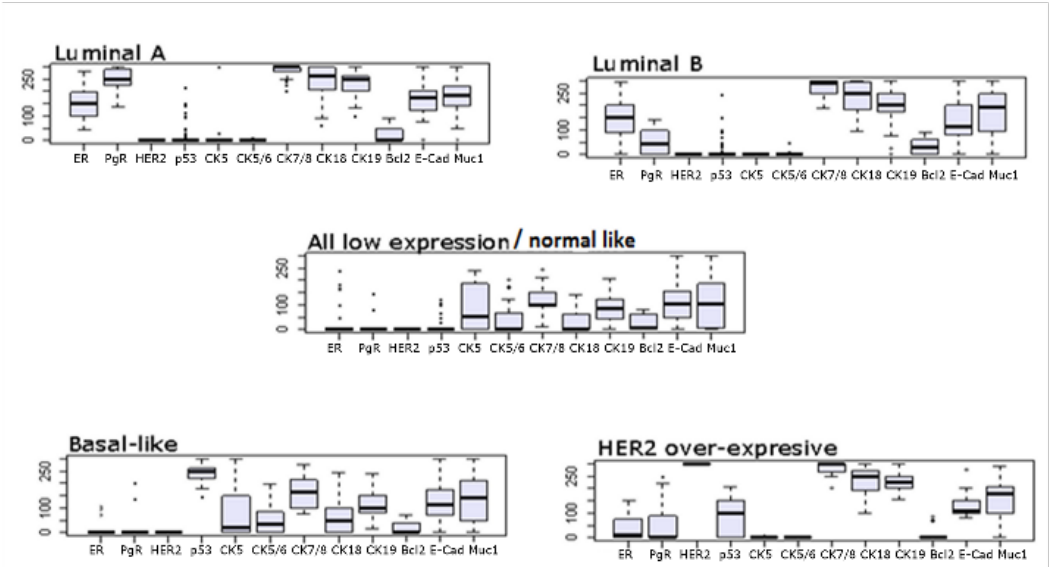

Fig. 1. Biological clusters determined by partitional clustering technique analysis of a panel of biomarkers in the younger and older populations. HER2: Human epidermal growth factor receptor 2. Reprinted with permission from Syed BM, Green AR, Paish EC, Soria D, Garibaldi J, Morgan L, et al. Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. Br J Cancer 2013;108:1042–51.

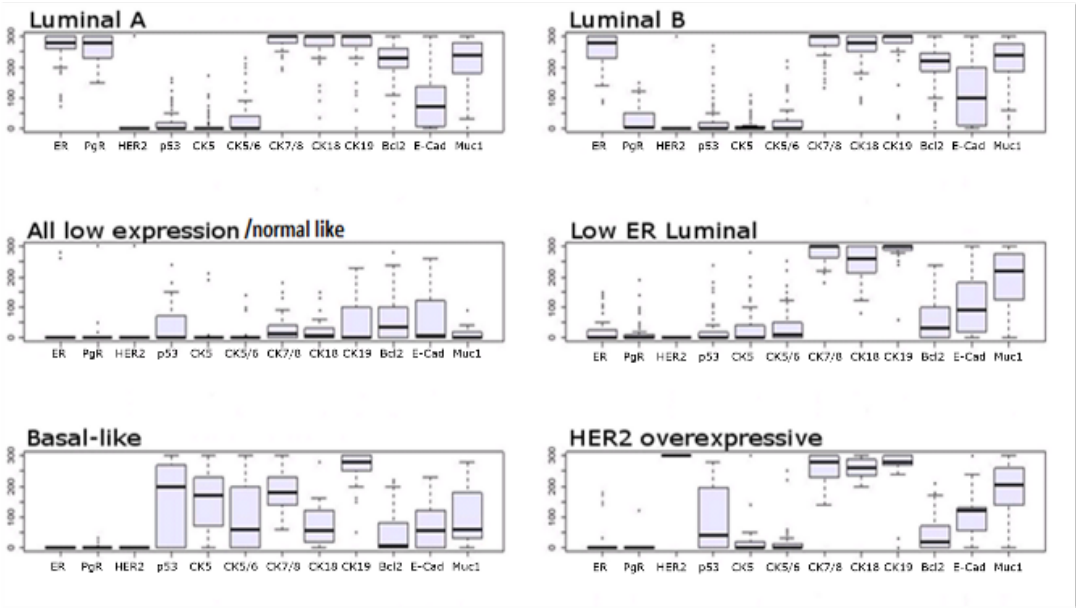

Fig. 2. Biological clusters determined by partitional clustering technique analysis of a panel of biomarkers in the older population. ER: Oestrogen receptor; HER2: Human epidermal growth factor receptor 2. Reprinted with permission from Syed BM, Green AR, Paish EC, Soria D, Garibaldi J, Morgan L, et al. Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. Br J Cancer 2013;108:1042–51.

Future Work to Personalise Care

In future, we expect the development of a tool to analyse an extensive panel of biomarkers for each individual patient, based on their core needle biopsy specimen. This would help to generate a predicted outcome for each potential treatment option, allow consideration of all relevant biomarkers and lead to personalised care.

There are currently a number of gene assay tools that provide prognostic and predictive information tailored for the individual patient to help guide potential therapy such as Oncotype Dx (Genomic Health, Inc.)[23] and MammaPrint test (Agendia, Inc).[24] However, their use is applicable in the adjuvant setting rather than at the time of diagnosis when a personalised decision to operate or to use an alternative treatment that is potentially as effective is needed.

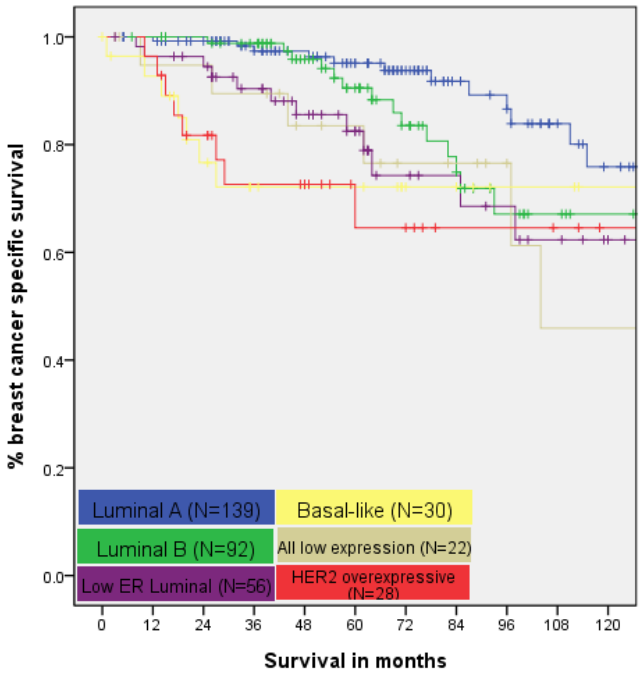

Fig. 3. Breast cancer-specific survival of different biological clusters in the older population. ER: Oestrogen receptor; HER2: Human epidermal growth factor receptor 2. Reprinted with permission from Syed BM, Green AR, Paish EC, Soria D, Garibaldi J, Morgan L, et al. Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. Br J Cancer 2013;108:1042–51.

Although the above research efforts that focus on the biology of breast cancer in the older woman are much needed, we know that in clinical practice, treatment decision-making is much more complex and that there are many other factors which must be considered (for e.g., concurrent comorbidity, QOL, social support and patient's wishes).

How Can We Personalise Care in the Older Woman with Breast Cancer Based on GA?

The Current Problem with GA

While the integration of geriatric care and assessment has long been established in some areas of medicine—for example, trauma and orthopaedic surgery (following hip fractures)[25] and stroke medicine[26]—the field of oncogeriatrics is far behind.[27,28]

Breast cancer surgery carries a much lower morbidity compared to colorectal cancer surgery or other visceral surgeries. Hence, generally speaking, there are few patients who cannot undergo breast surgery.[29] However, there are still issues specific to the older population which must be considered (for e.g., delivery of anaesthesia and tolerance of postoperative complications). The use of GA can help to determine who might benefit from geriatric intervention for other issues which are unique to the older population (for e.g., social support, mood disturbances, concerns with travel arrangements or cultural beliefs).

The SIOG Guidelines published in 2015[30] and 2018[31] state that GA should be performed in the setting of oncology. The domains included in GA vary greatly between studies, but generally consist of assessment of comorbidity and current health issues including medications, measurement of physical function, psychological evaluation and assessment of social support.[11]

Full GA itself is very time-consuming and may be unnecessary in the extremely fit patient with good activity status. Some studies have opted for the use of a frailty screening assessment to decide who should receive full GA,[32–34] but again, which screening tool best serves this purpose remains unclear. Biganzoli et al[32] have suggested that the Vulnerable Elders Survey-13 (VES-13) can be used as a frailty screening tool if the facility does not have resources to conduct a comprehensive GA. A multicentre prospective cohort study[35] has suggested that Geriatric 8 (G8) is superior to VES-13 in many types of cancer including breast. Owusu and Berger[36] suggest that VES-13 and G8 should be used in combination. Furthermore, Russo et al[37] have shown that Senior Adult Oncology Programme-2 is superior to G8 as a screening tool in solid cancers.

There is also discrepancy in the literature on how data from frailty assessment and GA should be utilised in clinical practice,[38] with thoughts varying from treating the most problematic issue only, referral to a specialist geriatrician for more comprehensive testing, or referral to other relevant specialities such as physiotherapy or dietician services.

Although the importance of GA is clear, we need to work towards a uniform GA-positive/-negative screening tool which can feasibly be implemented at diagnosis of breast cancer and interpreted to provide clinically useful information to guide treatment decisions.

Summary of Current Literature

A pilot study performed at our institution had looked specifically at implementation of GA in 47 older women (≥70 years old) with early operable primary breast cancer.[39] Decision of primary treatment followed consultation with the clinical team and was not guided by GA. A validated cancer-specific tool (not breast cancer-specific) was used. GA was conducted within 6 weeks' postdiagnosis. Assessment of QOL was also undertaken. GA determined that older age, greater comorbidities, higher number of daily medications and slower Timed Up and Go test (a measure of physical function) were significantly related to non-surgical treatment. QOL remained stable at 6-months in all patients regardless of treatment. Average time to complete the GA was 32 min (range, 15–65 min) and was conducted by a variety of trained research team members, who were not necessarily clinicians (this pilot study confirmed the feasibility of GA in a research setting). The study has now expanded to include 2 countries. The aim is to definitively

identify the components which should be included in GA in this setting.

Clough-Gorr et al[40] evaluated 660 women aged ≥65 years old who were diagnosed with stage 1–3 primary breast cancer in the United States to examine survival based on cancer-specific GA. The GA was described by 4 domains using 6 measures including sociodemographic, clinical, function and psychosocial. Survival from all-cause and breast cancer-specific mortality were recorded for different groups of subjects with domain deficits as measured by GA. They found that regardless of age and stage of disease, cancer-specific GA predicted 5-and 10-year all-cause and BCSS in older women. Therefore, they concluded that GA may help to guide treatment decision-making and to identify factors requiring intervention.

Future Work to Personalise Care

In future, we expect a breast cancer-specific GA tool that can be implemented in the clinic setting (or preclinic setting of community general practice) for older women with potentially operable breast cancer. There should be clear guidelines on how to use information derived from GA and how to standardise potential interventions.

Summary of Future Perspectives

Breast cancer in the older woman is biologically different than in the younger woman and this should be utilised to help predict outcomes in ER-positive and -negative disease when considering alternative treatments to surgery. Treatment goals in this population may also be different and this must be considered when discussing management options with the patient.

GA is paramount in treatment decision planning. There needs to be consensus on how to implement it and what to do with the results of GA performed in a breast cancer-specific setting.

The same approach (i.e., considering both biological features and GA) is relevant when considering potential adjuvant therapies (especially in patients with ER-negative tumours when the only systemic therapy available is chemotherapy, which often poses challenges due to comorbidities and limited physiological reserves more commonly seen in this population), which is beyond the scope of this article.

The ultimate goal of achieving personalised care in older women with primary breast cancer may involve a combination of biological features and GA considerations in diagnostic and adjuvant settings.

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