Frailty in Patients with Breast Cancer

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Abstract

Clinical guidelines emphasize that breast cancer treatment should be based on clinical need and patient fitness, rather than age. For example, the guidelines for early breast cancer issued by the UK National Institute for Health and Care Excellence (NICE) recommends that women "irrespective of age, are offered surgery, radiotherapy and appropriate systemic therapy, unless significant comorbidity precludes it". However, various UK-based population level studies report considerable variation in the breast cancer treatments received by older women (often defined as age 70 years or older) in comparison to younger women. The higher burden of comorbid conditions among older women may also be a significant contributing factor, with various studies showing lower rates of surgery and other therapies among women with more comorbid conditions. However, these factors only explain some of the reported variation in treatment patterns between younger and older women. One-third of all breast cancers diagnosed are in women aged 70 years or over, so addressing this variation is important for population health. The impact of ageing on health is complex and ageing can influence functional ability, physiology, and social wellbeing to different degrees. Chronological age is increasingly viewed as a poor descriptor of the ageing process. More recently, there is a much greater desire to determine 'biological age'. Geriatric associations have, for a while, recommended that a measure of frailty be used to report on ageing and its complex sequelae

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Introduction:

Breast cancer is currently one of the most prevalently diagnosed cancers and the 5th cause of cancer-related deaths with an estimated number of 2.3 million new cases worldwide according to the GLOBOCAN 2020 data. Deaths due to breast cancer are more prevalently reported (an incidence rate approximately 88% higher) in transitioning countries (Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean) compared to the transitioned ones (Australia/New Zealand, Western Europe, Northern America, and Northern Europe) **(1).**

Besides being the most common, breast cancer is also the leading cause of cancer death in women worldwide. Globally, breast cancer was responsible for 684,996 deaths [95% UI, 675,493–694,633] at an age-adjusted rate of 13.6/100,000. Although incidence rates were the highest in developed regions, the countries in Asia and Africa shared 63% of total deaths in 2020. Most women who develop breast cancer in a high-income country will survive; the opposite is true for women in most low-income and many middle-income countries **(2).**

Several modifiable and non-modifiable risk factors are involved in the occurrence of breast cancer including obesity, physical inactivity, hormonal treatments, and genetic or familial predisposition. However, age is undoubtedly the predominant breast cancer risk factor **(3)**

In the last fifteen years, breast cancer incidence and mortality have generally decreased. This improvement may be attributed to the progress of medical care, notably earlier screening and diagnosis, and more effective treatments, including targeted therapies. There is evidence that this decrease in incidence and mortality has been less significant or has even increased in elderly women **(4).**

Population aging is a major concern. It is estimated that between 2000 and 2050 the population of women aged over 80 will have more than tripled in developed countries. Elderly women are rarely included in national breast cancer screening programs, the upper age limit varying from 65 years in Hungary to 74 years in France, Italy, Sweden, Japan, Israel, and the Netherlands. In the United States, recommendations are that breast cancer screening should be continued if life expectancy is at least 10 years, without age limit **(5).**

The common dogma is that cancer in the elderly spreads slowly and is less aggressive and that the leading cause of mortality in this population is related to co-morbidities. However, epidemiology studies indicate that it is not true until the age of 85 **(6).**

Basics of breast cancer histopathology

The main method for identifying breast cancer is histopathological examination of tissue samples from breast tumors. The majority of breast cancers (BCs) (70–80%) are classed as invasive carcinoma of no particular type (NST) according to the most recent, fourth World Health Organization (WHO) classification of breast tumors, making this the diagnosis by default (invasive breast carcinoma NST, formerly termed invasive ductal carcinoma, IDC) **(6).**

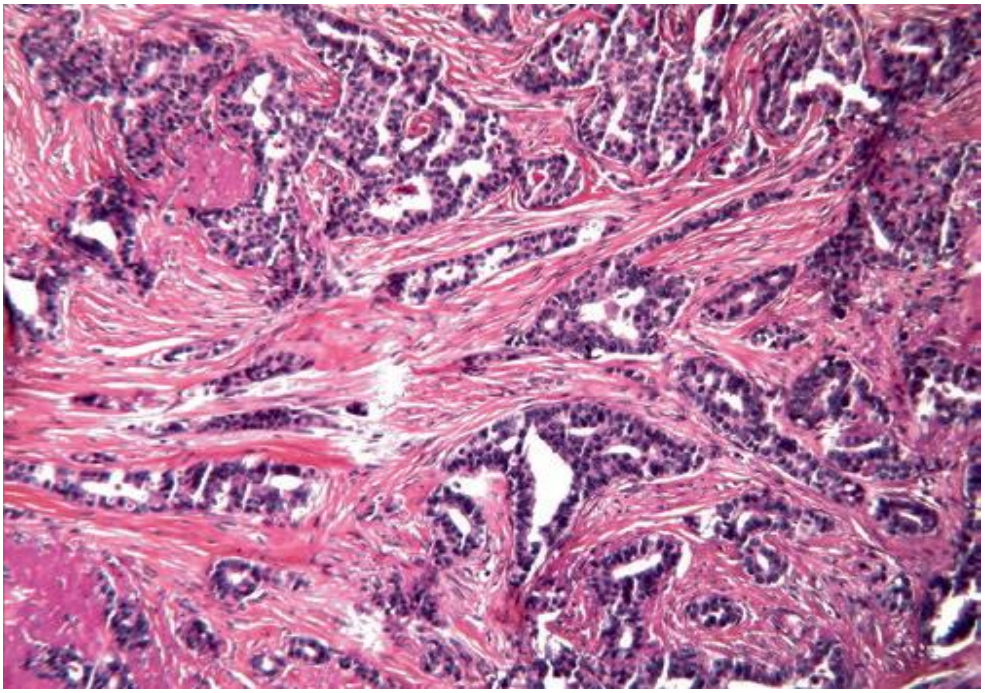

Figure 1: Invasive breast cancer of no special type (7)

Treatment for Breast Cancer

Neoadjuvant chemotherapy

NAC was initially utilized as a way of rendering locally advanced, inoperable breast cancer respectable. More recently, NAC has been used in operable tumors to downstage disease in the breast and axilla with the intention of facilitating breast conservation and, in some instances, avoiding ALND. The oncologic safety and equivalent survival outcomes of NAC have been studied in several randomized trials **(8).**

A meta-analysis of patients treated with NAC versus surgery followed by chemotherapy has shown no differences in survival or LRR with NAC and a 17% decrease in the mastectomy rate in patients receiving NAC. Seventeen percent is a minimal estimate since many of the women enrolled in these studies were candidates for Breast-conserving therapy (BCT) at presentation and thus could not benefit from NAC. NAC is most likely to allow BCT in the woman with a unicentric cancer which is large relative to the size of her breast and in those with HER2 positive or triple negative breast cancers **(9).**

Accurate evaluation of response to therapy and the feasibility of BCT can be problematic. MRI is more accurate than mammography or ultrasound in predicting the extent of residual disease, but a normal MRI does not exclude the presence of scattered foci of viable carcinoma which may preclude BCT. Mammography is complimentary to MRI in evaluating suitability for BCT post-NAC as calcifications present at diagnosis infrequently resolve with NAC. Calcifications may also become apparent after neoadjuvant therapy when breast densities related to the tumor have resolved or secondary to tumor cell death **(10).**

Loss of enhancement on MRI does not reliably indicate that calcifications are benign or due to dead cancer cells, and excision of any residual palpable masses or radiographic abnormalities is the standard. Of note, the entire volume originally occupied by the tumor does not need to be removed in the lumpectomy specimen and a pathologic complete response is not a requirement for successful BCT post-NAC **(11).**

Lumpectomy should include any residual clinical or imaging abnormalities, or, in the case of a clinical and radiographic complete response, removal of the marker at the tumor site and a generous sample of surrounding breast tissue **(8).**

Administration of NAC significantly reduces the rate of axillary metastases in clinically node-negative women and performance of sentinel lymph node biopsy after NAC is standard in this population. More effective systemic regimens have led to increased rates of pathologic complete response in both the breast and axilla after NAC **(12).**

Adjuvant radiation in breast-conserving therapy

It is important to determine preoperatively whether the patient is a candidate for adjuvant radiation. Prior chest wall irradiation, pregnancy at the time of diagnosis, and the presence of a connective tissue/collagen vascular disorder may be contraindications to radiation treatment. Patients with a history of mantle radiation delivered for Hodgkin's lymphoma may be ineligible for adjuvant radiation if the radiation threshold dose has been exceeded during prior therapy **(13).**

Delivery of radiation is contraindicated during all trimesters of pregnancy. However, in a woman presenting with invasive breast cancer in the second or third trimester, a lumpectomy can be performed, and adjuvant chemotherapy administered followed by breast irradiation in the postpartum period **(14)**

In cases where breast cancer is diagnosed in the first trimester without an indication for adjuvant chemotherapy, mastectomy is the preferred procedure. Connective tissue/collagen vascular disorders including scleroderma, Sjogren's syndrome, systemic lupus erythematosus, and dermatomyositis/polymyositis are considered relative contraindications to the delivery of breast irradiation due to small retrospective studies suggesting an increased incidence of acute and late radiation toxicities in these patients **(15).**

Except for scleroderma, matched case control studies have not consistently demonstrated an increase in risk; however, these were very small retrospective studies in which patients with severe disease were likely not selected for radiation. Preoperative consultation with a radiation oncologist is warranted in these patients **(16).**

whole breast irradiation (WBI) is given following lumpectomy to eliminate residual microscopic disease that may remain in the breast even when negative margins are obtained. in pathologic studies of mastectomy specimens in 282 patients with clinical and mammographically unifocal

breast cancers, found additional tumor foci within 2 cm of the index tumor in 20% of cases and > 2 cm from the index cancer in 43% of cases. The delivery of adjuvant radiation following lumpectomy decreases local failure rates by about 50% and increases breast cancer-specific survival **(17).**

Breast-conserving therapy

BCT involves excision of the tumor (lumpectomy) followed by adjuvant whole breast irradiation (WBI). In order to perform BCT, it must be possible to excise the tumor to negative margins with an acceptable cosmetic outcome, the patient must be able to receive radiotherapy, and the breast must be suitable for follow-up to allow prompt detection of local recurrence **(13) .**

The contraindications to BCT arise logically from these requirements. Contraindications to BCT include the presence of diffuse suspicious or malignant appearing calcifications, disease that cannot be resected to negative margins with a satisfactory cosmetic result, and the presence of contraindications to delivery of radiation such as prior treatment of the breast field or active scleroderma. A negative margin is defined as "no ink on the tumor" **(16).**

More widely clear margins do not improve local control in invasive breast cancer and are not required for BCT. If negative margins can be achieved with an acceptable cosmetic outcome, then lumpectomy can be performed irrespective of tumor size. In women with large tumors relative to breast size, neoadjuvant chemotherapy (NAC) can be used to downstage the tumor. Young age, aggressive tumor subtype (HER2 positive and triple negative), and lobular histology are not contraindications to BCT **(8).**

In patients with BRCA1/2 mutations, bilateral mastectomy is a consideration, as the risk of a new primary breast cancer development can range from 26-40% over the 20 years following diagnosis depending upon age of onset of the initial cancer, performance of oophorectomy, and use of endocrine therapy. Despite this higher risk, a BRCA mutation is not an absolute contraindication to breast conservation, and patient preference must also be considered **(18).**

Physical examination, mammography, and diagnostic ultrasound are the imaging modalities in standard use to select patients for BCT. In a population-based study of 1,984 women with ductal carcinoma in situ and stage I and II invasive cancers, 88% of those attempting BCT successfully had the procedure. This is probably an underestimate of the number of women eligible for BCT since many were converted to mastectomy without an attempt at re-excision. The use of magnetic resonance imaging (MRI) in the preoperative setting is controversial **(19).**

MRI is more sensitive than mammography or ultrasound, detecting additional disease in 16% of patients in a meta-analysis. It was hoped that MRI would improve selection of lumpectomy candidates and decrease rates of reoperation. However, multiple studies of preoperative MRI have demonstrated an increase in both ipsilateral mastectomy for the index tumor and contralateral

prophylactic mastectomy rates without an accompanying reduction in reoperation and recurrence rates (20).

Mastectomy

In patients undergoing mastectomy, total mastectomy (simple mastectomy), skin-sparing mastectomy, and nipple areolar-sparing mastectomy are options for most patients. Total mastectomy removes the breast parenchyma, nipple areolar complex, and excess skin from the chest wall, leaving only enough skin to close the incision. It is generally used when the patient will not undergo immediate reconstruction (19).

The skin-sparing mastectomy was developed to facilitate immediate reconstruction, and removes the breast parenchyma and nipple areolar complex, leaving the skin as a natural envelope for placement of the tissue expander/implant or autologous flap. Multiple studies have confirmed the oncologic safety of the skin-sparing mastectomy, with local recurrence rates of approximately 6%, comparable to those observed for the traditional simple mastectomy (21).

The nipple areolar-sparing mastectomy preserves the nipple areolar complex in addition to the skin envelope and was initially used mainly in the prophylactic setting and is now increasingly used in patients with invasive carcinoma. Local recurrence rates of 2-5% are reported, with median follow-up ranging from 2-5 years. Most of these data represent single-institution retrospective series with limited follow-up, and until long-term oncologic safety has been established, patients should be carefully selected for this procedure (22).

Although eligibility criteria vary by institution, we suggest limiting this procedure to patients with tumors < 3 cm and at a distance of at least 1 cm from the nipple which do not have extensive calcifications suggesting an extensive intraductal component (23).

Frailty in Patients with Breast Cancer

Clinical guidelines emphasize that breast cancer treatment should be based on clinical need and patient fitness, rather than age. For example, the guidelines for early breast cancer issued by the UK National Institute for Health and Care Excellence (NICE) recommends that women "irrespective of age, are offered surgery, radiotherapy and appropriate systemic therapy, unless significant comorbidity precludes it". However, various UK-based population level studies report considerable variation in the breast cancer treatments received by older women (often defined as age 70 years or older) in comparison to younger women (24).

Older women are less likely to receive surgery for operable breast cancer. Among those older women who do receive surgery, this is more likely to be a mastectomy than breast conserving surgery (BCS), and of those women having BCS, they are less likely to have adjuvant radiotherapy. Older women are also less likely to receive chemotherapy. There are various possible reasons for these reported differences in treatment provision. On average, older women tend to have larger

tumours at diagnosis, which is partly a consequence of being older than the inclusion ages (usually 50-70 years) of women in national breast screening programmes (25).

The higher burden of comorbid conditions among older women may also be a significant contributing factor, with various studies showing lower rates of surgery and other therapies among women with more comorbid conditions. However, these factors only explain some of the reported variation in treatment patterns between younger and older women. One-third of all breast cancers diagnosed are in women aged 70 years or over, so addressing this variation is important for population health (26).

The impact of ageing on health is complex and ageing can influence functional ability, physiology, and social wellbeing to different degrees. Chronological age is increasingly viewed as a poor descriptor of the ageing process. More recently, there is a much greater desire to determine 'biological age'. Geriatric associations have, for a while, recommended that a measure of frailty be used to report on ageing and its complex sequelae (27).

This approach has been progressively adopted by other specialties, perhaps most evidently in relation to the management of hip fractures. However, there has been slow implementation of this recommendation in breast cancer care pathways, not least because it has not proven straightforward to incorporate the assessment of frailty into routine clinical practice (28).

What is frailty?

Frailty describes how a person becomes increasingly vulnerable to poor health because of an age-related decline in the reserve of multiple physiological systems. Frailty is closely associated with comorbidity and disability, but each one constitutes an independent concept of ageing (29).

Frailty can also be present without concurrent disability or comorbidity, and it is not exclusive to a specific chronological age cut-off . Consequently, although measures of comorbidity and functional status are useful in stratifying patients with different clinical needs and health care outcomes, frailty adds another dimension in capturing the characteristics of an ageing population. Specifically, because frailty is a dynamic manifestation of disease or injury and an increased vulnerability to stressors, it is potentially reversible with early identification and appropriate interventions (30).

There is no single, agreed conceptual model of frailty. There are currently two dominant concepts: the ‘phenotype’ model and the ‘cumulative deficit’ model. The ‘phenotype’ model was developed by Fried et al. and is based on the theory of frailty as a biological syndrome and a “cycle associated with declining energetics and reserves”. It is based on five pre-defined physical frailty elements: weight loss, exhaustion, low physical activity, slowness, and weakness. The classification of a person as: ‘not frail’, ‘pre-frail’ and ‘frail’, is based on their combined performance in these five elements (31).

In the 'cumulative deficit' model, frailty is considered as an accumulation of deficits across a number of domains. These deficits are related to, but not specific to, the ageing process, and include both subjective (observed during a clinical examination) and objective (e.g., biochemical tests, presence of a disease) facets of adverse health and functional status. This model is the basis for several objective frailty assessments, with the original frailty index developed for the Canadian Study of Health and Ageing (CSHA) by Rockwood and colleagues **(32).**

The CSHA frailty index consists of 92 deficits, with the index expressed as a proportion of the number of deficits present divided by the total number possible. The index threshold for classification of frailty was based on the average value of individuals with the same chronological age. Newer frailty indices, such as the Hospital Frailty Risk Score, based on the 'cumulative deficit' model, have explored the inclusion of further deficits to measure frailty. It is a feature of this model of frailty, that these newer measures calculated using different deficits, are still able to identify an increasing burden of frailty among older people and demonstrate poorer health outcomes among those who are frail **(33).**

Both concepts of frailty have been successfully operationalized as frailty assessments for use in populations that include community residents, primary care patients and hospital in-patients. In the clinical setting, the information on five specific elements of frailty (such as grip strength) provided by assessments based on the phenotype model are valuable in identifying potentially reversible aspects of frailty **(34).**

In contrast, the individual deficits within a frailty index are not of value by themselves and provide little insight into how to clinically respond to health problems at a patient level. At population level however, describing frailty as an accumulation of deficits is informative. Given that this model is less prescriptive in its construction of frailty, it underpins the majority of the frailty assessments used in large, primary care and administrative hospital datasets **(35).**

The conceptual basis of frailty and how frailty is best assessed is an ongoing area of research. This is necessary to ensure that the operationalisation of these frailty concepts into assessments is clinically applicable towards the identification and management of frailty in any population. In parallel, it is equally important to initiate the integration of frailty assessments into clinical practice **(22).**

This should be irrespective of disease cohort, with the aim of improving objectivity on the influence of a patient's ageing on clinical decisions **(21).**

Tools for identifying frailty in patients with breast cancer.

In the era of multi-modal breast cancer treatment, decisions about a patient's treatment are made at various time points throughout their care pathway. In the initial stages, identifying an older patient's frailty status can inform clinical decision making, thus guidelines increasingly recommend the use of formal frailty tools. Reliance on subjective 'end-of-the-bed' opinions of patient frailty is

increasingly undesirable, especially given the dynamic and potentially reversible nature of frailty. For example, the perception of frailty in a patient can vary depending on setting (e.g., emergency in-patient vs. out-patient), the time of day or patient mood **(24).**

There are a variety of approaches to assessing frailty, and one widely recommended tool by geriatric professional bodies is the Comprehensive Geriatric Assessment (CGA). This provides a "clinical management strategy which will give a framework for the delivery of interventions which will address relevant and appropriate issues for an individual patient", without prescribing specific methods for assessing these specific CGA domains However, the CGA typically requires expertise from a geriatric medicine specialist and has been estimated by Girones et al. to take between 30 and 40 min to complete **(36).**

The CGA has been used to assess the burden of frailty among breast cancer patients in several studies. These frailty assessments were performed for a range of purposes including the assessment of fitness for primary surgery and the prediction of adverse treatment outcomes. Irrespective of the purpose of the CGA, patients with increasing age were more likely to be described as unfit or frail, and had poorer survival and breast cancer treatment outcomes. Two prospective studies evaluated whether routine CGA altered breast cancer treatment decisions and reported different findings. In the **Table :1(36).**

Table 1: Frailty domains assessed in the Comprehensive Geriatric Assessment (CGA) (36)

Multi-dimensional CGA assessment components:
Physical symptoms
Mental health symptoms
Level of function in daily activity: for personal care and life activities
Social support network (formal e.g. carers, and informal e.g. family and friends)
Living environment (including ability to use local facilities and technological support)
Level of participation and individual concerns
Compensatory mechanisms and resourcefulness which is used by the individual in response to frailty

study by **Okonji et al. (37)**, women defined as unfit, or frail were less likely to undergo surgery or receive adjuvant chemotherapy. In contrast, **Barthel emy et al. (38)** reported that the CGA results did not in- fluence multi-disciplinary team (MDT) decisions on adjuvant chemotherap.

Frailty and surgical treatment planning in early breast cancer

Surgery is the standard of care for patients with early invasive breast cancer unless significant burden of poor fitness precludes it. Elective breast surgery carries a comparably low risk of mortality, and the impact of chronological age and comorbidity burden on post-operative complications is negligible. Specifically, it is only in the presence of poor functional status and cognitive impairment that multiple comorbidities are associated with post-operative mortality and functional decline **(39).**

Despite this, studies repeatedly report a lower rate of surgical resection for older patients with breast cancer, based on age and comorbidity profile. This is particularly the case in patients with estrogen receptor (ER-) positive disease for which primary endocrine therapy (PET) is available as an 'alternative' treatment, despite the inferiority of PET on disease-free survival **(40).**

The Pre-operative Assessment of Cancer in the Elderly (PACE) was developed to measure the functional reserve of older cancer patients with the aim of "reducing unacceptable denial of potentially curative surgery". PACE incorporates the CGA and surgical risk assessments. Early results from the PACE study provide insight on how information from a multi-domain frailty assessment may influence surgical treatment decisions and short term post-operative outcomes **(41).**

For example, patients with poor scores had higher rates of 30-day surgical complications. However, only 47% (of the 460 patients) in the study cohort had breast cancer, and the results were not reported by cancer type. This limits the extrapolation of PACE to guide surgical decisions for patients with breast cancer **(42).**

There are advocates for omitting extensive axillary surgery for older patients with early-stage invasive breast cancer, to minimize morbidity without compromising oncological outcomes. Large longitudinal population-based studies have shown that this perspective is increasingly adopted, with fewer older patients undergoing comprehensive axillary staging over time **(41).**

Whether frailty assessments can provide information to guide decisions on axillary management independent of decisions on primary breast surgery for older patients, is unclear. Few studies specifically address this question, though a multi-center prospective study using the CGA reported that frailty was not strongly associated with non-receipt of axillary surgery among women who were having primary breast surgery **(40).**

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