



Older breast cancer undertreatment: unconscious bias to undertreat – potential role for the international geriatric radiotherapy group?

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Abstract: The prevalence of breast cancer increases with age. Older breast cancer patients often present with locally advanced disease at presentation because mammography, which diagnosed early stage disease, is not recommended after the age of 75. In addition, they are often undertreated even when they are physically fit and have non-metastatic disease. As a result, survival is often poor. Physicians bias may be a factor in their undertreatment and lack of representation in prospective clinical trials. Physicians should be educated that chronological age is not a contraindication to curative treatment for older breast cancer patients. As a research group devoted to older cancer patients, women, and minorities, the International Geriatric Radiotherapy Group (IGRG) plans to conduct prospective trials to assess biomarkers for frailty, the controversial issue of mammography for older breast cancer patients, and the incorporation of frailty index for curative breast cancer treatment. The data obtained may help to decrease physician bias and to establish future guidelines for older breast cancer patients treatment.

Keywords: Elderly; breast cancer; undertreatment; discrimination

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Introduction

The prevalence of breast cancer increases with age. It is estimated that 67% of breast cancer will develop in women 65 years and older (1). Older breast cancer tumor biology is often slow growing with a good molecular profile including the expression of estrogen (ER) and progesterone (PR) receptors (2). Thus, if diagnosed early and if treated properly, older breast cancer patients should have comparable or better survival compared to

younger patients with a more aggressive tumor biology (3). However, most studies on older breast cancer patients reported a poorer outcome compared to younger patients (4-6). The management of older breast cancer patient is complex. Older patients tend to have multiple co-morbidity with advanced age which may preclude curative treatment or may have contributed to their poor survival (7-9). On the other hand, physically fit individuals who have localized disease may have a poor survival if they are not treated

properly and/or cancer diagnosis is delayed until the disease is locally advanced or metastatic. Undertreatment of older patients with breast cancer has been reported in many studies and may have contributed to their low survival rates (10-17). Omission of surgery, sentinel lymph node dissection, radiotherapy, and adjuvant chemotherapy are frequently reported among older breast cancer patients (14-17). Physicians attitude in the management of older breast cancer patients which may be perceived as discrimination has been implicated as one of the potential cause for their substandard treatment (18,19).

Thus, an understanding of the factors which may influence physicians management of older breast cancer patients may potentially improve their care and may provide guidelines to help the clinicians involved in their care. As an international research group devoted to the care of older people, minorities and women with cancer, the International Geriatric Radiotherapy Group (IGRG) (<http://www.igr.org>) may play a potential role to solve those issues.

The role of mammogram in older cancer patients

Screening mammography has been effective to diagnose breast cancer at an early stage in women 50 years old or older and reduce cancer mortality (20). However, current recommendations set the upper age limit for screening mammogram as 75 years old (21-23). Because of the lack of randomized studies, the benefits of screening mammogram in patients older than 75 remain unproven. However, preliminary studies suggested that as the frequency of screening mammogram decreased among older patients, the prevalence of clinically palpable breast cancer increased significantly, leading to a higher risk of cancer death (24).

In addition, among older women who were diagnosed with cancer through mammography, the ones who had frequent sequential mammograms had a better prognosis because their cancer were diagnosed at an early stage (25). The benefits of frequent sequential mammography among patients 75 years old or older were also corroborated in another study as patients who had mammography performed within a shorter interval had a better survival compared to the ones with a longer period (26). In that study, patients who had mammograms performed at a longer interval presented with locally advanced disease at diagnosis and their tumor were biologically more aggressive. Other studies also corroborated the survival benefit of performing frequent mammography in older patients (27-29). In addition to improved life expectancy, mammography for older patients may also be cost-effective (30).

Unfortunately, it is difficult to make a definite conclusion on the benefits of mammography in older cancer patients since none of those studies were randomized. As most randomized studies specifically excluded the inclusion of older cancer patients, there may be a systemic bias among physicians who designed those studies (31).

Surgery for older breast cancer patients

Surgery remains the corner stone for older breast cancer with localized disease. For selected patients, postoperative mortality was low and survival rates similar to younger patients (3,32). A recent review of the Surveillance, Epidemiology, and End Results (SEER) database of 13,007 breast cancer patients older than 80 years demonstrated better survival and cancer specific survival among patients undergoing surgery compared to the ones with no surgery (33). Another study corroborated the survival advantage of having surgery in that patient population (34). Thus, physically fit breast cancer patients with localized disease should undergo surgery regardless of their chronological age. However, surgical omission for older breast cancer patients remains prevalent. As an illustration, among 23,961 patients with breast cancer older than 70 years and diagnosed at an early stage, 46.1% had endocrine therapy instead of surgery (35). Their survival was significantly decreased compared to the ones who underwent surgery (35).

Omission of surgery ranged from 2.5–24.2% and 4.6–50.8% for stage I and stage III disease respectively for breast cancer patients 70 years old or older (36).

Non-surgical treatment increased with patient age and was worst in patients 80 years or older (37). Among older breast cancer patients who did undergo surgery, axillary lymph node dissection were frequently not performed leading to under staging and undertreatment (13,38). Chronological age and presence of multiple comorbidities were often cited as the rationale for incomplete axillary staging (39). Surgery undertreatment was further compounded by the lack of adjuvant radiotherapy and/or chemotherapy in breast cancer patients 70 years or older resulting in poor survival for those patients (40).

Radiotherapy for older cancer patients

The advent of modern radiotherapy technique allows completion of a short treatment course within one to four weeks for older cancer patients with minimal morbidity (41-48). Excellent loco-regional and survival with acceptable

complications were reported. In addition, in selected patients, accelerated partial breast irradiation (APBI) offered the convenience of finishing treatment within a week, thus, minimizing the challenge of daily transportation if the patients were to undergo a conventional six weeks course of radiotherapy (48). As a result, it is very difficult to justify the omission of radiotherapy after breast conservation surgery or total mastectomy if radiotherapy is indicated.

In reality, radiotherapy is routinely denied to older breast cancer patients following surgery regardless of the stage (40,49-68). The percentage of patients not receiving radiotherapy after surgery increased with patient age. Patients who were 80 years old or older were most affected. The percentage of patients who did not receive radiotherapy after breast conservative surgery (BCS) in that age group ranged from 26% to 89% (40,49,63,64,66). Overall, administration of radiotherapy was associated with a lower rate loco-regional recurrence, and a decreased risk of salvage mastectomy for early stage breast cancer. In selected groups of patients, a survival advantage was also reported among the patients who received radiotherapy (40,49,50,55,57,59,67). The survival benefit was most pronounced among patients ER and PR negative tumors, metaplastic and large tumors (49,55,59,68).

There are several possible reasons for the omission of radiotherapy following BCS. One of them is the Cancer and Leukemia Group B (CALGB) 9,343 report of the lack of survival benefit among older breast cancer women with small, ER and PR positive tumors who underwent adjuvant radiotherapy following BCS compared to the ones receiving Tamoxifen alone (69).

In another study, the most common reason cited for omission of radiotherapy was physician recommendation against its administration (53). However in that study, comorbidity factors did not influence physicians decisions but chronological age was the deciding factor (53).

Corroborating physician bias, Downs-Canner *et al.* (63) reported that patient estimated risk of death in 10 years was not a factor in physicians' decision about delivering radiotherapy to older patients with small ER, PR positive tumors after BCS (63). In fact, there was a wide variation among institutions about the decision whether or not to omit radiotherapy for older patients whose tumors fulfill those criteria (56). Omitting radiotherapy for selected older patients remains a controversial issue among cancer physicians because of the high rate of long-term recurrence among patients receiving Tamoxifen only. Hughes *et al.* (70) reported a 10-year local recurrence rate of 9% and 2%

among patients who had Tamoxifen only and postoperative irradiation as a follow-up of CALGB 9343. The patients who recurred had to undergo salvage mastectomy which may affect their quality of life. Taken together, those studies suggested that physicians decision to omit radiotherapy following BCS were subjective and not based on objective parameters such as frailty index which may impact patient long-term survival (71).

Chemotherapy for older breast cancer patients

Even though the data is sparse, preliminary studies suggested that physically fit older breast cancer patients tolerated chemotherapy quite well. In a survey of 1,280 non-metastatic breast cancer patients 65 years old or older, 76% were considered robust (71). Compared to frail patients, they were able to tolerate chemotherapy and hormone therapy better and had better cancer-specific survival (71). In another study, patients who were 70 years old or older had similar disease free survival compared to younger patients when they underwent adjuvant chemotherapy after surgery for breast cancer despite a higher disease burden and a higher prevalence of co-morbidity (72). Other studies also corroborated the survival advantage of older fit breast cancer patients who received adjuvant chemotherapy (73-75). The benefit of chemotherapy was most pronounced among patients at higher risk of recurrences such as large tumors, axillary lymph nodes involvement and hormonal negative breast cancer (76). Thus, older fit women with breast cancer should receive chemotherapy when indicated to decrease recurrence risk and to improve their survival odds.

Omission of chemotherapy because of chronological age is a worldwide phenomenon. In the Netherlands and Ireland for example, only 6% and 24% of patients 65 years old or older received chemotherapy respectively for stage I-III breast cancer (77). In Japan, the corresponding figures were 36% and 15% for the age group 65-75 and over 75 years old respectively (54). In Germany, non-adherence to chemotherapy also increased with age as only one out of 42 patients 80 years old or older received chemotherapy (40). In the United States (US), among 5,081 women 66 years old and older who had ER and PR negative breast cancer, only 34% received chemotherapy (78). Administration of chemotherapy was associated with a 15% in reduction of breast cancer mortality for those patients (78). Similar omission of chemotherapy and subsequent reduction of survival rate with advanced chronological age was also

reported among breast cancer patients in Georgia (79). Thus, older breast cancer patients face challenge regardless of the geographic location.

Physicians attitude toward older breast cancer patients

Age bias has been recognized as one of the cause of underutilization of BCS in older breast cancer patients. In a survey of medical and surgical residents, modified radical mastectomy (MRM) was recommended for 38% of patients older than 59 years old compared to 11% for patients less than 31 years old even though the residents were instructed that MRM and BCS had similar outcome before the survey (80). As a result, it is not surprising that BCS rates decreased significantly with chronological age across the United States (81). This age bias is also reflected nationally through the underrepresentation of older breast cancer patients in clinical trials. For example, only 9% of patients were 65 years or older in 164 Southwest Oncology group breast cancer trials between 1993 and 1996 (82). This age based disparity was still persistent in breast cancer clinical trials between 2000 and 2002 (83). At the last update in 2016, according to the US Food and Drug Administration (FDA), only 4% of women with breast cancer older than 75 was recruited in US clinical trials (84). Thus, unless clinicians make a conscious effort to design and recruit older women in breast cancer clinical trials, those patients will continue to be undertreated because of the lack of data.

One of the possible cause for under representation of older breast cancer patients in clinical trials is the physician belief that older patients may be unable to tolerate treatment in addition to the lack of data to guide optimal treatment. Foster *et al.* (18) reported the survey of 200 medical oncologists who were given two scenarios of two patients of stage IIA breast cancer with excellent performance status but different age. Ninety three percent of those surveyed recommended adjuvant chemotherapy for the 63 years old patient. However, only 66% would recommend similar therapy if the patient was 75 years old even in the absence of comorbidity. Another survey of medical oncologists about treatment recommendation for breast cancer patients also corroborated the omission of chemotherapy based on patient chronological age (19). Morrow *et al.* (85) also reported that physicians belief was most likely the cause for omission of surgery for older breast cancer patients. There were two groups of older breast cancer patients with almost identical disease stage

and comorbidity factors, in two different cancer treatment units. The physicians who recommended surgery more frequently in one unit instead of endocrine therapy believed that their patients could tolerate anesthesia and the surgical procedure (85). Thus, physicians education may be the key to change their attitude toward older patients with breast cancer.

Potential role of the International Geriatric Radiotherapy Group to minimize bias and to improve the care of older breast cancer patients

As an international organization of over 1,000 institutions in 123 countries devoted to the care of older cancer patients, minorities, and women, the IGRG is well positioned to address the issue of bias and discrimination against older cancer patients. Following our workshop in Barcelona in 2018 and the University of Umea presentation in 2019, we identified critical issues affecting the care of older cancer patients and proposed potential solutions (86). For instance, the upper age limit for screening mammography needs to be revised for early diagnosis of breast cancer for older patients. New biomarkers for frailty such as urinary 8-oxo-7, 8-dihydroguanosine (8-oxoGsn) needs to be investigated to assess patient physiologic age (87). Future prospective studies for older breast cancer patients should be conducted by a team of physicians and scientists who are familiar with the care of older cancer patients. Co-morbidity factors and frailty index should be incorporated in those studies such as physiological age instead of chronological age is the main determinant for curative treatment. The data obtained will demonstrate and allay the fear of physicians that physically fit older breast cancer patients tolerate curative treatment as well as younger patients. In a review of the role of physicians bias toward making improper treatment decision, acknowledging bias may be the first step to decrease undertreatment of older breast cancer patients and to improve their empathy for this segment of the patient population (88).

Conclusions

Older breast cancer patients face discrimination because of their chronological age. Current policy of cancer screening does not encourage mammography after the age of 75. Older breast cancer patients are frequently excluded from current clinical prospective trials and are undertreated subsequently leading to a poor survival. Physicians bias may play a role in the undertreatment of this patient population.

Physicians need to be educated that chronological age is not a contraindication to curative treatment. The IGRG plans to conduct prospective studies in the future to improve the quality of care of older breast cancer patients.

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