The Effect of Local Therapy on Breast Cancer Mortality: Is There an Age-Interaction?

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Abstract There are no randomized trials comparing local therapy versus no therapy in patients with primary breast cancer, as such trials would be deemed unethical. Thus, the impact of local therapy on breast cancer mortality is poorly understood. However, an overview of clinical trials comparing various permutations in the local therapy of breast cancer suggests that inadequate local therapy increases the risk of local recurrences, and thereby increases breast cancer mortality. Yet, age-interactions are commonly reported in studies that have examined the etiology, prognosis, and treatment of breast cancer, and might be associated with the effect of local therapy as well. Moreover, the effect of local therapy on breast cancer mortality might be time-dependent. In cohorts of women with high-risk tumors (predominantly younger women) local therapy may adversely (but only transiently) perturb the natural history of breast cancer. In contrast, such an effect is not evident in cohorts of women with low-risk tumors (predominantly older women). For both groups of patients, local therapy appears to ultimately have a beneficial effect in reducing breast cancer mortality, but in patients with low-risk tumors the benefit is immediate, while in patients with high-risk tumors it is delayed. Evidence for such an age-interaction is derived from comparison of the breast cancer hazard curves in women with high-risk and low-risk tumors, and analysis of the mammography screening trials. Neo-adjuvant systemic therapy may eventually prove useful in modulating the effects of local therapy.

Keywords Breast cancer · Local therapy · Age interactions

The impact of local therapy on breast cancer mortality is poorly understood. Indeed, there are no randomized trials comparing local therapy versus no therapy, as such trials would be deemed unethical. However, there are numerous trials comparing permutations in the local therapy of breast cancer (i.e., more versus less radical surgery, surgery with radiotherapy versus surgery without radiotherapy, etc.). An overview of these trials indicates that inadequate local therapy increases the risk of local recurrences and death, with every 4 local recurrences resulting in one additional breast cancer death over a 15-year period [1]. Thus, optimal local therapy is essential for good long-term prognosis. Yet, breast cancer is a heterogeneous disease, and age-interactions (differences in the etiology, prognosis, and treatment effects of breast cancer according to age) are commonly reported [2]. Thus, one might ponder if an age-interaction is associated with the effect of local therapy on breast cancer mortality. Moreover, the effects of breast cancer local therapy might be time-dependent, as appears to be the case with the effects of adjuvant systemic therapy [3].

Age-Interactions in Breast Cancer Studies

Age-interactions are frequently reported in breast cancer studies, and a few of these should be highlighted. Primary breast cancers with composite high-risk profiles (>2 cm in size, axillary lymph node positive, high histologic grade, estrogen receptor-negative) are predominantly evident in younger women, while primary breast cancers with composite low-risk profiles (≤ 2 cm in size, axillary lymph node negative, low histologic grade, estrogen receptor-positive), are more common in older women [4]. Adjuvant chemotherapy appears to be more beneficial in premenopausal women, when compared to older women [5]. An unplanned subgroup analysis of the NSABP-18 trial suggests that neo-adjuvant chemotherapy decreases breast cancer mortality in pre-menopausal women and increases

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mortality in post-menopausal women [6]. Moreover, nulliparity, obesity, and the use of oral contraceptives have all been shown to decrease the risk of breast cancers in younger women, but increase risk in older women [7]. There is also evidence that the administration of fenretinide reduces the risk of developing breast cancer in pre-menopausal women, but increases the risk in older women [8].

These examples also demonstrate that age-interactions are either “quantitative” or “qualitative” [7]. A quantitative age-interaction exists when the size, but not direction, of the effect varies among patients of different age groups (i.e., a risk factor has a greater effect on one age group than another). In contrast, a qualitative age-interaction exists when the direction of the effect is reversed (a risk factor is associated with an increased risk in one age group, and a decreased risk in another). In this article, I provide evidence that a quantitative age-interaction may also exist with respect to the effect of local therapy on breast cancer mortality.

A careful review of population-based studies and the mammography screening trials suggests that the impact of local therapy may differ between breast cancer patients having tumors with composite high-risk profiles and those having tumors with composite low-risk profiles (i.e., between younger and older patients, respectively). Specifically, local therapy may transiently perturb the natural history of breast cancer in younger women (who have a higher proportion of tumors with composite high-risk profiles), while such a transient, adverse effect is much less evident in older women (who have a higher proportion of tumors with composite low-risk profiles). In the long-term, local therapy has a beneficial effect for both groups of patients. However, for older women, the benefit is immediate, while for younger women, the benefit is delayed. Although it is not possible to directly test this hypothesis (as it would require randomized trials comparing local therapy versus no therapy), evidence derived from population-based studies and the mammography screening trials seem to support it. This hypothesis may provide impetus for the design of additional neo-adjuvant systemic therapy trials in the future.

Population-Based Studies

Population-based studies suggest that breast cancer is a mixture of at least two main phenotypes which differ according to tumor characteristics and age at onset [9]. Patients having breast cancers with either the entire composite of low-risk or high-risk profiles can be identified in SEER, a large U.S. population-based registry [10]. The age frequency distribution curve for patients having tumors with composite high-risk profiles is unimodal, with an early-onset peak at age 48 years and for those patients with composite low-risk profile tumors, the curve is also unimodal, but with a late-onset peak

at age 72 years (Fig. 1). The shapes of the combined curve suggest that breast cancer is a bimodal disease, and that high-risk tumors occur predominantly in younger women, while low-risk tumors occur more commonly in older women. Of course, not all patients present with breast cancers having either the entire composite of low or high-risk profiles. Mixtures often occur, creating a spectrum of diseases with high-risk and low-risk cancers weighted at each end of the age distribution.

Survival curves depict the proportion of patients who are alive at any given time, and the slope is much steeper for women with high-risk tumors (indicating a worse prognosis). Although survival curves are frequently used to report outcomes in cohorts of breast cancer patients, the hazard curves provide far better insights into the time-dependent effects of local therapy [11]. The hazard rate is defined as the rate of failure (recurrence or death) in the next instant of time among the remaining “at risk” individuals. Hazard curves depict how the risk of recurrence or death changes over time after breast cancer diagnosis, and also the magnitude of that risk. The rate of failure (recurrence or death) is indicated on the y-axis and time intervals on the x-axis.

The hazard curve for patients with high-risk, early-onset breast cancer can also be plotted using the SEER database (Fig. 2). These curves indicate that the risk of death is highest approximately 2 years after initial diagnosis, at which time it peaks at 11 % per year and then declines [3]. Interestingly, the interval from initial diagnosis to this peak in the hazard curve remains constant even if we diagnose high-risk breast cancers earlier (smaller tumors) or later (larger tumors), suggesting that the hazard peak is inextricably linked to events occurring at the time of diagnosis (local therapy) [11].

It has been suggested that local therapy may result in the seeding of tumor cells or, alternatively, bestow autonomy on

Fig. 1 **a** Composite high risk profiles included only those cases among women with tumors >2.0 cm + axillary LN positive + high histologic grade + ER negative expression. **b** Composite low-risk profiles included only those breast cancer cases among women with tumors ≤2.0 cm + axillary LN negative + low histologic grade + ER positive expression. Adapted from: Breast Cancer Res Treat. 2005; 90:127–37

Fig. 2 Composite high-risk profiles included only those cases among women with tumors >2.0 cm + axillary LN positive + high histologic grade + ER negative expression. Composite low-risk profiles included only those breast cancer cases among women with tumors ≤2.0 cm + axillary LN negative + low histologic grade + ER positive expression. Adapted from: Breast Cancer Res Treat. 2005; 90:127-37

micrometastasis already present, thereby transiently increasing the risk of recurrences and producing the peak in the hazard curve [12, 13]. Thus, the fixed position of the hazard peak following the diagnosis and treatment of breast cancer could be interpreted to mean that local therapy adversely (but only transiently) perturbs the natural history of the disease. Yet, patients with composite low-risk profile tumors lack the 2-year peak in the hazard curve. For these patients, the risk of death following initial diagnosis and treatment remains fairly constant at about 1.5 % to 2 % per year [14].

The hazard curves derived from the SEER database also reflect the use of adjuvant systemic therapy in the population, but this alone could not account for such dramatic differences in the hazard peak between high-risk and low-risk patients. Randomized trials have shown that the magnitude of the benefit of adjuvant systemic therapies could not alone explain the magnitude of the difference in the peaks of the hazard curves [5]. One might therefore speculate that much of this difference must be due to the effects of local therapy, which appear to differ between patients with high-risk tumors and those with low-risk tumors (predominantly younger and older women, respectively). As discussed below, the mammography screening trials lend further support to this hypothesis.

Mammography Screening

Most of the mammography screening trials were undertaken before the era of adjuvant systemic therapy and, in essence, compared early local therapy (for women with screen-detected breast cancers) against delayed local therapy (for women with tumors detected clinically). Meta-analyses of these trials show that screening reduces breast cancer mortality by about 20 % in women over the age of 50 at the start of the trials, and this benefit becomes evident after 7–

9 years of follow-up [15]. In contrast, among women aged 40–49, there is a paradoxical increase in breast cancer mortality in the screened group during the first 6–8 years of follow-up [16]. Thereafter, screening reduces breast cancer mortality by about 15 %, but this benefit emerges only after 12–14 years of follow-up [17]. Thus, screening seems to have an immediate benefit in older women, and a delayed benefit in younger women [18]. The reason for this paradox has never been fully understood, and has generated intense controversy throughout the medical community.

If we consider the hazard curves previously discussed, we can now perhaps better understand the paradoxical results of the mammography screening trials. As noted previously, women aged 40–49 have a higher proportion of breast cancers with composite high-risk profiles than do those over the age of 50. Thus, the paradoxical increase in breast cancer mortality among younger women during the early years of follow-up in the screening trials might be attributed to the excess hazard of death (the hazard peak) due to the earlier detection and treatment of a reservoir of high-risk cancers. The more protracted peak in mortality (at 6–8 years) rather than the 2-year peak previously reported in other cohorts of younger breast cancer patients, might simply be attributed to the fact that it took several years to accrue women into the mammography screening trials. Eventually, the benefit of mammography screening in younger women became evident, several years after the hazard peak.

Among women over the age of 50 enrolled in the screening trials, there is no paradoxical increase in breast cancer mortality during the early years of follow-up, and the benefit of screening is evident at 7–9 years. This observation is consistent with the fact that older women are more likely to have tumors with composite low-risk profiles, which lack the peak in the hazard curve.

In the United States, the widespread use of mammography screening was initiated around 1980 and soon after, breast cancer mortality rates among African-Americans and Caucasians diverged [13]. Indeed, U.S. population-based statistics indicate that, prior to about 1980, breast cancer mortality rates between these racial groups had been nearly identical. When compared to Caucasians, African-American women have a higher proportion of high-risk, early-onset tumors. Thus, the initiation of mammography screening around 1980 may have transiently increased breast cancer mortality rates among African Americans. In recent years, this racial disparity has narrowed, and it may now largely be attributed to differences in access to healthcare and the widespread use of endocrine agents in patients with ER-positive tumors (African-Americans are less likely to present with ER-positive tumors, and therefore less likely to benefit from recent innovations in endocrine therapy).

Future Directions

In this commentary, I have outlined evidence suggesting that a transient excess in mortality might be associated with the local therapy of high-risk breast cancers, which are more common in younger women. This hypothesis is based upon a comparison of the hazard curves in patients with composite high-risk tumors and those with composite low-risk tumors (predominantly younger and older women, respectively), and analysis of the mammography screening trials. If this hypothesis proves to be correct, then it may have far reaching implications in the design of new treatment approaches for the management of primary breast cancer.

Thus, in the future, neo-adjuvant systemic therapy might be utilized to modulate the effects of breast cancer local therapy. Several retrospective studies seem to suggest that surgery undertaken during the luteal phase of the menstrual cycle (in the presence of circulating progesterone) results in better disease free and overall survival than surgery during the follicular phase (in the presence of circulating unopposed estrogen) [19–21]. Recently, Dr. Rajendra Badwe and his colleagues at the Tata Memorial Hospital in Mumbai, India, undertook a randomized controlled trial whereby women with primary breast cancer were randomized to receive either neo-adjuvant progesterone therapy or placebo [22]. This trial showed that there was no overall benefit to neo-adjuvant progesterone therapy. However, a planned subgroup analysis demonstrated that patients with node-positive disease do indeed benefit from neo-adjuvant progesterone therapy, suggesting that it may benefit patients with high-risk breast cancers. The results of this study are therefore consistent with our hypothesis, and suggest that neo-adjuvant systemic therapy directed at patients with high-risk breast cancers (generally younger patients), may prove beneficial in reducing breast cancer mortality. Thus, treatments aimed at blunting the hazard peak associated with high-risk tumors may ultimately pave the way for ushering in a new era in the management of primary breast cancer.

During the last 30 years there have been dramatic innovations in the systemic treatment of breast cancer, and interest in local therapy has waned. Since 1990, breast cancer mortality rates have declined by about 25 %, largely due to the widespread use of novel adjuvant systemic therapies [23]. Yet, there is clearly a need for a renewed interest in the local therapy of breast cancer. A better understanding of the time-dependent effects of local therapy, and the ability to modulate those effects may ultimately have an enormous benefit in reducing the burden of breast cancer mortality worldwide.

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