The Breast xxx (2017) 1–8

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Age, molecular subtypes and local therapy decision-making

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Molecular subtype
Age
Local therapy
Local recurrence

ABSTRACT

The relationship between age and breast cancer subtype is complex: both impact risk of locoregional recurrence (LRR) and survival. Young patients frequently present with aggressive tumors but the increased risk imparted by young age appears to differ among breast cancer subtypes. Dramatic improvements in local control among young women with breast cancer of all tumor subtypes have been observed, likely attributable to improved local therapy strategies, improvements in adjuvant therapies and implementation of subtype-specific targeted therapies. In the light of these improvements in local control, accumulating evidence demonstrates that there is no difference in LRR or survival between breast conserving therapy (BCT) and mastectomy in young patients. An increased risk of LRR in triple-negative cancers is apparent; yet this increased risk of LRR is present following surgical treatment with both BCT and mastectomy and does not significantly differ by age. Also, contralateral breast cancer rates remain low for all age groups and, although the use of contralateral prophylactic mastectomy (CPM) has increased, there is no evidence that CPM improves survival. At the other end of the age spectrum, there is a growing body of evidence demonstrating a favorable interaction between older age and molecular subtype such that many older women with estrogen receptor positive breast cancer may be spared axillary staging and/or radiation therapy without a detrimental impact on survival. Thus for both age and subtype, it appears that the intrinsic biology is the strongest predictor of outcome. Tumor biology, and not age, should be the driver in local therapy decision-making.

1. Introduction

The relationship between age and breast cancer subtype is complex. Both impact risk of locoregional recurrence (LRR) and survival; however, the increased risk imparted by young age appears to differ among breast cancer subtypes, and as more is learned about the heterogeneity of breast cancer, the absolute risk from young age alone will likely continue to lessen. At the other end of the age spectrum, there is a growing body of evidence demonstrating a favorable interaction between older age and molecular subtype such that many older women with estrogen receptor (ER) positive (+) breast cancer may be spared axillary staging and/or adjuvant radiation therapy (RT) without a detrimental impact on survival.

2. Breast cancer in young women

It is well recognized that younger breast cancer patients present with tumors of more aggressive biology, illustrated by more aggressive clinicopathological features (i.e. ER negative (−) or HER2+ tumors of higher grade) [1,2] or assignment to the high-risk group by molecular subtyping [3,4], which is accompanied by a higher risk of LRR and distant recurrence as compared to their older counterparts. Over recent years, it has become evident that tumor biology, indicated by molecular subtypes, largely overshadows the influence of young age with regard to breast cancer outcome.

The distribution of the four distinct molecular subtypes (luminal A, luminal B, HER2 and basal-like) differs between younger (<40 years) and older patients (≥40 years of age) with a decreasing incidence of more aggressive molecular subtypes with increasing age [5,6]. Younger patients are more likely to be diagnosed with HER2-enriched and basal-like tumors and less likely to be diagnosed with luminal tumors as compared to older patients. In addition, among patients with hormone receptor (HR) positive (+)/HER2- disease by immunohistochemistry (IHC) there are proportionally less true luminal cancers in young women [3]. In parallel with advances in systemic treatment, LRR and breast cancer mortality rates in young breast cancer patients continue to decline [7] and this decline is seen among all tumor subtypes [8,9]. In

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http://dx.doi.org/10.1016/j.breast.2017.06.032
0960-9776/

addition, there is a growing body of evidence that young age is no longer associated with inferior outcomes in HER2+ disease [10,11] or triple-negative breast cancer (TNBC) [12], yet remains an important prognostic factor in HR+ disease [13,14].

2.1. Young age, molecular subtype and locoregional recurrence

The dramatic improvement in local and regional control among young women with breast cancer is illustrated by two recent population-based studies from the Netherlands. Van Laar et al. [7] reported an overall 5-year local recurrence (LR) rate of 7.5% among 1143 women aged ≤40 years with early stage breast cancer (pT1-2/cT1-2, N0-2, M0) treated with breast conserving therapy (BCT) between 1988 and 2010; however when evaluated over time, 5-year LR risk decreased dramatically from 9.8% for patients treated between 1988 and 1998 to 3.3% for patients treated in later years (2006–2010). Aalders et al. [8] confirmed this trend in decreasing risk of LRR in a cohort of 1000 Dutch women <35 years of age surgically treated for primary invasive breast cancer between 2003 and 2008. The overall 5-year rate of LR and regional recurrence (RR) were 3.5% and 3.7% respectively, yet these rates varied significantly by tumor subtype in patients treated prior to the introduction of trastuzumab. When analyzed for the period after the introduction of trastuzumab these observed differences were no longer significant: <2% of patients with HR+ disease, regardless of HER2-status, 5.6% of patients with HR-/HER2+ disease and 4.5% of patients with TNBC suffered a LR at 5-years of follow-up ($p = 0.24$).

Table 1 summarizes the studies evaluating the association between LR risk, age and tumor subtype [6,8,9,15,16]. Although most studies demonstrate that, younger age remains independently associated with increased LR risk even after correction for tumor biology, LR risk in young patients treated with either mastectomy or BCT appear to be acceptably low. Arvold et al. [9] assessed the association between age, tumor biology and LR risk in 1434 consecutive patients treated with BCT at two centers between 1997 and 2006. On multivariate analyses, including adjustment for tumor subtype, increasing age remained independently associated with decreased risk of LR (HR 0.97/year increase, 95% CI 0.94–0.99, $p = 0.01$). However, at a median follow-up of 85 months the overall cumulative incidence of LR was 2.1% and was acceptably low in all age quartiles: 5.0% for patients 23–46 years; 2.2% 47–54 years; 0.9% 55–63 years and 0.6% 64–88 years. Luminal type tumors were associated with the lowest risk of LR and HER2 or TNBC with a higher crude LR risk in all age quartiles. In the youngest patients a LR risk of 4.7%, 8.1%, 3.0%, 13.3% and 10.2% was observed for luminal A, luminal B, luminal-HER2, HER2 and TNBC, respectively. In an updated and expanded analysis of this dataset, now including 2233 consecutive patients who underwent BCT between 1998 and 2007, Braunstein et al. [15] reported a crude overall LR rate of 3.1% at a median follow-up of 106 months and the 8-year risk of LR was 1.8%, 5.5%, 2.2%, 11.7% and 9.8% for patients with luminal A, luminal B, luminal-HER2, HER2 and TNBC, respectively. In the youngest patients (23–46 years of age, n = 504) 10-year LR Kaplan Meier estimates were 6.3%, 9.3%, 3.5%, 29.3% and 9.3% for luminal A, luminal B, luminal-HER2, HER2 and TNBC patients, respectively. Luminal B subtype (vs. luminal A; HR 2.64, $p = 0.001$), HER2 subtype (HR 5.42, $p < 0.01$) and TNBC (HR 4.33, $p < 0.01$) were independently associated with increased LR risk on multivariable analysis. Younger age ≤50 years (HR 0.56 for patients >50 year, $p = 0.01$) and increasing number of positive nodes (HR 1.06 per involved node, $p = 0.004$) were also independently associated with increased LR risk [15]. It is important to note that none of the patients included in these studies received anti-HER2 therapy. In the more recent population-based study by Aalders et al., where all HER2+ patients treated after 2005 received trastuzumab, 5-year LR risk was <6% among all tumor subtypes and type of surgery was not associated with risk of LR [8].

Similarly low LR rates among all tumor subtypes were observed among 1994 patients ≤50 years of age treated with mastectomy without post-operative RT in a multi-institutional cohort study by Truong et al. [16]. After a median follow-up of 4.3 years the crude LR risk was 1.3%, 2.3%, 4.6%, 5.6% and 2.2% for luminal A, luminal B, luminal-HER2, HER2 or basal-type, respectively. Approximately half of the HER2+ patients included in this study received anti-HER2 therapy. On multivariable analysis age was not independently associated with LRR risk, factors that conferred a higher LRR risk were tumor >2 cm (HR 2.57, 95% CI 1.23–5.35), lobular histology (HR 3.48, 95% CI 1.51–8.02) and close/positive surgical margins (HR 3.42, 95% CI 1.36–8.55).

2.2. Surgical decision making in younger patients

Earlier studies comparing LR rates following BCT versus mastectomy in young women demonstrated conflicting results (extensively reviewed in Pilewskie and King) [17]; however, more recent studies demonstrate excellent LR rates after BCT in young patients with comparable LR rates and survival between BCT and mastectomy [18–23].

Using data from two large tumor registries in Utah, Frandsen et al. [24] demonstrated significant improvements in LR over time for young women (<40 years) treated with BCT or mastectomy and among patients treated in the modern era (after 2000), 5- and 10-year LR rates, relapse free survival (RFS) and overall survival (OS) were equivalent following BCT or mastectomy. Five-year LR rates for patients <40 years of age treated with BCT before and after 2000, were reported as 10.9% and 3.9% respectively ($p < 0.05$) and similar 5-year LR rates were observed for patients who underwent mastectomy (9.4% and 4.8% for patients treated before and after 2000 $p < 0.05$, respectively). In addition, there was no significant difference in 10-year LR, RFS or OS between BCT and mastectomy in patients treated after 2000 (10-year LR 6.1% vs. 7.9%, $p = 0.57$; RFS 85.1% vs.74.8%, $p = 0.14$; OS 85.1% vs. 79.7%, $p = 0.52$, respectively) [24]. The impact of local therapy on breast cancer specific survival (BCSS) was also evaluated in a report from the Surveillance, Epidemiology and End Results (SEER) database which included 7665 women aged <40 years diagnosed with stage I or II invasive breast cancer treated between 1998 and 2003 [25]. At a median follow-up of 111 months there was no difference in BCSS observed between patients treated with BCT or mastectomy, 10-year BCSS 87.7% vs. 85.2%, $p = 0.01$, respectively.

In a recent multicenter prospective cohort study including 3000 women 18–40 years of age treated between 2000 and 2008 in the United Kingdom [26], LR risk varied over time with similar LR rates for BCT and mastectomy at 18 months (1.0% vs. 1.0%, $p = 0.35$) but higher rates for BCT at 5 and 10-years (5.3% vs. 2.6%, $p < 0.01$ and 11.7% vs. 4.9%, $p < 0.01$, respectively). After adjustment for potential confounders BCT remained associated with increased risk for LR (5-year HR 5.00, 95% CI 3.57–23.69, $p < 0.01$ and 10-year HR 6.06, 95% CI 1.29–28.40, $p = 0.02$ for BCT vs. mastectomy); however, there was no significant difference in 10-year distant disease free survival (DDFS) or OS by surgery type (HR 0.82, 95% CI 0.64–1.05, $p = 0.115$ and HR 0.79, 95% CI 0.61–1.03, $p = 0.081$, for DDFS and OS, respectively) [26]. Although the increased risk of LR overtime following BCT in this study cannot be ignored it should also be noted that BRCA mutation status in this cohort remains to be analyzed. Lastly, in a recent meta-analysis, which included data on 22,598 patients ≤40 years with stage I or II breast cancer from five population-based studies and a pooled study of two clinical trials, mastectomy was not associated with an improved OS or DDFS

Please cite this article in press as: Kuijer A, King TA, Age, molecular subtypes and local therapy decision-making, The Breast (2017), http://dx.doi.org/10.1016/j.breast.2017.06.032