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Optimal surgical management for high-risk populations

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ABSTRACT

The recognition that breast cancer is a group of genetically distinct diseases with differing responses to treatment and varying patterns of both local and systemic failure has led to many questions regarding optimal therapy for those considered to be high risk. Young patients, patients with triple-negative breast cancer (TNBC), and those who harbor a deleterious mutation in BRCA1 or BRCA2 are frequently considered to be at highest risk of local failure, leading to speculation that more-aggressive surgical treatment is warranted in these patients. For both age and the triple-negative subtype, it appears that the intrinsic biology which imparts inferior outcomes is not overcome with mastectomy; therefore, a recommendation for more extensive surgical therapy among these higher-risk groups is not warranted. For those at inherited risk, a more-aggressive surgical approach may be preferable, however; patient age, ER status, stage of the index lesion, and individual patient preferences should all be considered in the surgical decision-making process.

Introduction

The recognition that breast cancer is a group of genetically distinct diseases with differing responses to treatment and varying patterns of both local and systemic failure has led to many questions regarding optimal therapy for those considered to be high risk. Young patients, patients with triple-negative breast cancer (TNBC), and those who harbor a deleterious mutation in BRCA1 or BRCA2 are frequently considered to be at highest risk of local failure, leading to speculation that more-aggressive surgical treatment is warranted in these patients. In addition, there is considerable overlap among these risk factors whereby up to 40% of women <40 years of age with TNBC will be found to harbor a BRCA mutation, adding to the complexity of surgical decision making. This article will summarize current evidence regarding the choice of local therapy and outcomes in these high-risk populations.

Abbreviations: ACOSOG, American college of surgeons oncology group; BCSS, breast cancer-specific survival; BCT, breast-conserving therapy; CI, confidence interval; CBC, contralateral breast cancer; CPM, contralateral prophylactic mastectomy; DFS, disease-free survival; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; HERA, herceptin adjuvant; IHC, immunohistochemistry; OS, overall survival; RFS, recurrence-free survival; TNBC, triple-negative breast cancer; SEER, surveillance, epidemiology, and end results.

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Breast cancer in young women

It is clear that young breast cancer patients experience higher rates of both local and distant recurrence; they frequently present with more-aggressive clinicopathologic features, including hormone receptor negative and HER2/neu overexpressing disease, and are more likely to be categorized in the high-risk group by molecular subtyping when compared to their older counterparts [1,2]. Given the overlapping risk factors of young age and high-risk features, it is remains unclear whether age itself is an independent prognostic factor.

When considered in the context of the 4 intrinsic molecular subytpes (Luminal A, Luminal B, HER2 enriched, and basal-like), the distribution of the molecular subtypes among women <40 years of age differs from that of women ≥40 years of age, with proportionally fewer luminal cancers, and more HER2 positive and basal-like tumors [3,4]. A recent population-based analysis of 1101 women <50 years of age treated from 1986-1992 and 1945 women treated from 2004-2007, using immunohistochemical surrogates to define the 4 molecular subtypes, demonstrates the effect of patient age within each subtype and the impact of modern adjuvant therapy [5]. Within the hormone receptor positive subgroups, both recurrence-free survival (RFS) and overall survival (OS) improved over time with increasing use of anti-estrogen therapy; however, both outcomes remained inferior for women <40 years of age as compared to those 40–49 years of age (2004–2007: 5-year RFS 79% versus 92%, $p < 0.001$; and 5-year OS 89% versus 95%, $p < 0.001$). In

contrast, for the HER2 enriched subtype, age <40 years was associated with inferior 5-year RFS and OS in the earlier time period (5-year RFS: 39% versus 58%, p = 0.039; OS: 49% versus 66%, p = 0.017), but not in the later years following the introduction of taxanes and trastuzumab into clinical practice (5-year RFS: 81% versus 84%, p = 0.879; 5-year OS: 89% versus 89%, p = 0.879). There was no effect of age observed for either RFS or OS for the triple-negative subtype irrespective of years of treatment, and outcomes for both age groups improved over time. Among women <40 years of age, 5-year RFS improved from 60% to 78% (p = 0.014) and 5-year OS improved from 67% to 82% (p = 0.011).

The observation that young age is a prognostic factor for hormone receptor positive and HER2 positive subtypes, but not TNBC, was also demonstrated in two Korean studies of patients <35 years of age treated prior to the routine availability of trastuzumab [6,7]. However, in the large Herceptin Adjuvant (HERA) trial, age <40 years was not associated with inferior disease-free survival (DFS) or OS among patients treated with chemotherapy plus trastuzumab [8]. Collectively, these findings demonstrate that advances in systemic therapy have contributed to improvements in survival across all subtypes and have eliminated the impact of age in HER2 positive breast cancer, yet a significant disparity still exists for women < 40 years of age with hormone receptor positive breast cancers, likely driven by the luminal B subtype.

Age, local recurrence, and survival

Although earlier studies comparing rates of local recurrence following breast-conserving therapy (BCT) versus mastectomy in young women report conflicting results (reviewed in Pilewskie and King [9]), more recent data demonstrate dramatic improvements in local control among young women over time, and no difference in local recurrence or survival between BCT and mastectomy. A report by van Laar et al. [10] evaluated rates of local recurrence in women ≤40 years of age treated with BCT in the Netherlands between 1988 and 2010. The overall 5-year local recurrence rate was 7.5%; however, when broken down by time period, rates of local recurrence decreased significantly over time, from 9.8% in the earliest time period (1988–1998) to 5.9% (1999–2005), and to 3.3% in the most recent years of the report (2006–2010, p = 0.006). Local recurrence was also significantly impacted by the use of systemic therapy (10-year local recurrence rates with and without systemic therapy were 9.9% and 21.6%, respectively; p < 0.0001), and the improvement in local recurrence over time appeared closely related to the increased use of systemic therapy.

In an early population-based study, Coulombe et al. [11] reported no significant difference in locoregional recurrence based on surgery type (BCT versus modified radical mastectomy) for women 20–39 years of age or 40–49 years of age, and no difference in breast cancer-specific survival (BCSS) in the younger cohort. In those 40–49 years of age, BCSS was superior following BCT, likely due to significant differences in tumor characteristics, and a subgroup analysis among patients considered "ideal candidates" for BCT demonstrated no significant difference in local recurrence or survival between BCT and mastectomy-treated patients in either age cohort. These findings have now been updated and expanded by Cao et al. [12] in a recent report of 965 women 20–39 years of age treated with either BCT (n = 616) or modified radical mastectomy (n = 349) as reported to the British Columbia Breast Cancer Agency [12]. At a median follow-up of 14.4 years there remains no difference in BCSS (76.0% versus 74.1%, p = 0.62), OS (74.2% versus 73.0%, p = 0.75), local RFS (85.4% versus 86.5%, p = 0.95), local regional RFS (82.2% versus 81.6% p = 0.61), or distant RFS (74.4% versus 71.6%, p = 0.40) between the 2 surgical treatment groups. The rate of local recurrence was 15% at 15 years in both treatment groups, and type of local therapy was not a predictor of OS, BCSS, or local regional RFS on multivariable analysis. Similar to the report by van Laar et al. [10], chemotherapy was found to improve locoregional recurrence in both treatment groups.

The effect of local therapy on survival was also studied in 9285 young patients (<50 years of age) from a population-based Danish registry. After adjusting for tumor size, surgical treatment, lymph node status, histologic grade, year of treatment, and protocol allocation, survival was not inferior following BCT in any age group, and was improved following BCT compared to mastectomy in women 45–49 years of age (hazard ratio [HR] for risk of death: age <35 years, 0.87; age 35–39 years, HR 1.02; age 40–44 years, HR 0.80; age 45–49 years, HR 0.66; p < 0.05) [13]. Similarly, after controlling for clinicopathologic factors, none of the previously reported retrospective studies comparing BCT to mastectomy among young women have demonstrated reduced survival in young women treated with BCT [11,14–17].

Thus, while one may postulate that more extensive surgery would mitigate risk factors for local recurrence leading to improved outcomes in young patients, the accumulating evidence suggests that breast cancer biology and appropriate use of systemic therapy, rather than the extent of surgery, is the major determinant of survival outcomes [9].

Age, contralateral breast cancer risk, and contralateral prophylactic mastectomy

The use of contralateral prophylactic mastectomy (CPM) has increased dramatically in the United States. First reported by Tuttle et al. [18], rates of CPM among women with invasive breast cancer increased from 4% to 11% between 1998 and 2003. Subsequent reports from both population-based registries [19,20] and single-institution series [21,22] confirmed the persistence of this trend, and, more recently, Kurian et al. [23] reported that among women <40 years of age, nearly 40% will pursue bilateral mastectomy for the management of unilateral breast cancer.

Factors associated with the receipt of CPM are multifactorial and include both patient factors (age, family history, breast density) and treatment factors (genetic testing, use of preoperative MRI, immediate breast reconstruction), yet the majority of patients choosing CPM are not at elevated risk of contralateral breast cancer [19,20,22,24,25]. BRCA mutation carriers and those with a history of mantle irradiation comprised only 13% of women undergoing CPM in a large series from Memorial Sloan Kettering Cancer Center [22]. Even among the youngest patient cohorts, the risk of contralateral breast cancer with modern adjuvant therapy is low and has decreased over the past decade. In a recent SEER study, the risk of contralateral breast cancer (CBC) for patients <30 years of age was 4.5%, and 12.6% at 10 years for patients with estrogen receptor (ER) positive and ER negative disease, respectively [26]; rates well below that of local and distant recurrence events in women <40 years of age treated with unilateral mastectomy as reported by Cao et al. [12].

Studies specifically addressing the potential survival benefit associated with CPM have generated conflicting results, largely driven by their retrospective nature and inability to account for selection bias [22,27–30]. In a Surveillance, Epidemiology, and End Results (SEER) study of 107,106 women with unilateral breast cancer undergoing mastectomy between 1998 and 2003, 8902 (8.3%) underwent CPM [31]. Notably, in the subset of 4854 women 18–49 years of age with stage I and II ER negative breast cancer, CPM reduced the rate of CBC from 0.9% to 0.16% and, in an adjusted analysis, was associated with a 4.8% improvement in disease-specific survival, yet it remains unclear how a <1% reduction in CBC incidence can result in such a large difference in BCSS. A similar