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Letter to the Editor

The evolving role of pathologic complete response in breast cancer

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Dear Editor,

The concept of pathologic complete response (pCR) has been an enigmatic one, often at the center of much debate and controversy. While most researchers would agree that the absence of residual invasive carcinoma in the breast and axilla is imperative in defining pCR, the impact of residual *in situ* tumor is still debated. The current AJCC 8th Edition defines pCR as the absence of any residual invasive carcinoma in the breast/axilla/lymph vessels. The presence of *in situ* tumor in the absence of invasive carcinoma still constitutes a pCR.[1]

From the early studies onward, pCR showed great promise in its ability to predict outcomes after chemotherapy. This association was strongest in aggressive biology tumors, such as triple-negative and HER2-positive cancers.[2] Researchers surmised that pCR could potentially be a surrogate marker for survival. Based on its ability to improve pCR rates,[3] pertuzumab was the first drug to receive accelerated approval from the Food and Drug Administration in 2013. The corresponding adjuvant trial (APHINITY) demonstrated only a marginal improvement in disease-free survival (94.1% vs. 93.2%, $P = 0.045$) in its early analysis, and further maturing of data is awaited. Along similar lines, addition of lapatinib improved pCR rates significantly; however, in the adjuvant setting, it failed to impact survival outcomes.[4,5] The CTNeoBC meta-analysis[6] funded by the US-FDA confirmed the prognostic value of pCR, especially in aggressive tumor subtypes; however, it could not validate pCR as a surrogate endpoint for survival.

Following this, pCR continued to simmer for a while and found its clinical application in its ability to prognosticate aggressive subtypes. However, the recent turn of events, specifically the CREATE-X[7] and KATHERINE[8] trials, has demonstrated, a hitherto unexplored, predictive capability of pCR. The CREATE-X study suggested a survival benefit with the addition of capecitabine, in women with triple-negative breast cancer, with residual disease post-neoadjuvant chemotherapy (NACT). Likewise, the early analysis of KATHERINE points toward a benefit in invasive disease-free survival with Trastuzumab emtansine over trastuzumab, in HER2-positive breast cancers with residual disease post-NACT. In both these studies, pCR, or more specifically, the lack of it, was used as a marker to tailor adjuvant therapy, with improved outcomes.

Since its inception, the role of pCR is now entering an exciting phase. It may lack the ability to be a surrogate marker for survival on the scale of a clinical trial, but it does remain a crucial marker for prognosis on an individual patient level and is an emerging predictive marker for tailoring adjuvant therapy.

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Conflicts of interest

There are no conflicts of interest.

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