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Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis

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Abstract

Purpose—While various studies have highlighted the prognostic significance of pathological complete response (pCR) after neoadjuvant chemotherapy (NAT), the impact of additional adjuvant therapy after pCR is not known.

Experimental Design—PubMed was searched for studies with NAT for breast cancer and individual patient-level data was extracted for analysis using plot digitizer software. Hazard ratios (HRs), with 95% probability intervals (PIs), measuring the association between pCR and overall survival (OS) or event-free survival (EFS), were estimated using Bayesian piecewise-exponential proportional hazards hierarchical models including pCR as predictor.

Results—Overall, 52 of 3209 publications met inclusion criteria, totaling 27,895 patients. Patients with a pCR after NAT had significantly better EFS (HR 0.31, 95% PI: 0.24–0.39), particularly for triple negative (HR 0.18, 95% PI: 0.10–0.31) and HER2+ (HR 0.32, 95% PI: 0.21–0.47) disease. Similarly, pCR after NAT was also associated with improved survival (HR 0.22, 95% PI: 0.15–0.30). The association of pCR with improved EFS was similar among patients who received subsequent adjuvant chemotherapy (HR 0.36, 95% PI: 0.19–0.67) and those without adjuvant chemotherapy (HR 0.36, 95% PI: 0.27–0.54), with no significant difference between the two groups (p = 0.60).

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Interpretation—Achieving pCR following NAT is associated with significantly better EFS and OS, particularly for triple negative and HER2+ breast cancer. The similar outcomes with or without adjuvant chemotherapy in patients who attain pCR likely reflects tumor biology and systemic clearance of micrometastatic disease, highlighting the potential of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response.

Introduction

Neoadjuvant chemotherapy (NAT) is increasingly being utilized as the frontline therapy for the management of high-risk localized breast cancer. Studies have demonstrated no difference in survival between adjuvant or neoadjuvant setting.[1,2] NAT for breast cancer is an established therapeutic option for selected high-risk, locally advanced or unresectable breast cancers, or to improve eligibility for breast conserving surgery (BCS).[2] Because the primary tumor remains intact during therapy, the neoadjuvant treatment strategy allows for monitoring of treatment response and discontinuing of therapy in the event of disease progression.

From a research perspective, the neoadjuvant setting has become recognized as a human *in vivo* system to evaluate predictive biomarkers, surrogate endpoints, and the efficacy of therapies including novel agents.[3] The neoadjuvant therapy model provides a potential efficient trial design to explore the efficacy of novel therapies utilizing pathological complete response (pCR) as a surrogate marker for disease free-survival and overall survival.[3]

Yet, the prognostic significance of pCR after neoadjuvant chemotherapy remains somewhat controversial. While pCR demonstrates sensitivity to agents received in the neoadjuvant setting, true demonstration of treatment efficacy is dependent on its ability to predict long-term outcomes of recurrence and death, and this issue has not been completely settled in the literature. In a pooled analysis of 12 clinical trials by Cortazar et al., the authors demonstrated that pCR is associated with improved event-free survival (EFS), but the association between the magnitude of treatment-induced pCR change and corresponding improvement in EFS could not be established (i.e. delta pCR and delta EFS).[4] Similarly, a meta-regression of 29 randomized prospective studies of NAT demonstrated pCR to be a strong prognostic factor, but the magnitude of relationship between pCR and EFS varied by type of NAT.[5] However, most neoadjuvant trials are powered to detect a difference in pCR among regimens, and likewise are not powered for long-term outcomes. Furthermore, these studies did not evaluate the impact of pCR on the utility of adjuvant therapy, which could potentially influence the clinical outcomes in patients with localized breast cancer. Additionally, clinical subtype of breast cancer is an important factor to consider given differences in tumor biology as well as targeted therapy usage. The association of pCR with improved long-term outcomes is recognized for human epidermal growth factor receptor-2 positive (HER2+) breast cancer and triple negative (TN) breast cancer (TNBC),[6] but is less understood for hormone receptor-positive (HR+)/HER2- breast cancer, where pCR is less common and adjuvant endocrine therapy is the mainstay of systemic therapy.

The objective of this study was to conduct a comprehensive meta-analysis of studies on neoadjuvant chemotherapy for localized breast cancer using extracted patient level data to ascertain the potential association between pCR and subsequent breast cancer recurrence as well as survival, with careful consideration of tumor subtype, and the relationship between pCR and adjuvant treatment in modulating clinical outcomes.

Materials and Methods

Identification of Studies

Based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[7] a librarian-led systematic search restricted to English of PubMed was initially performed in September 2016 to identify potentially eligible studies. Meeting abstracts were excluded. The search strategy keywords included “breast cancer,” “neoadjuvant therapy,” “preoperative therapy,” “pathologic complete response,” “survival”, and “recurrence.” The detailed search strategy (eAppendix 1) and the flow diagram detailing study selection (eFigure 1) are available in the Supplement. We also reviewed reference lists of eligible studies, manuscripts citing the selected studies, and relevant reviews to identify additional publications. If it was determined that more than one publication reported on the same trial or patient cohort, the outcomes from the most recent publication were included.

Eligibility Criteria

Inclusion criteria were clinical trials, prospective cohort studies, or retrospective cohort studies that reported pCR results after neoadjuvant chemotherapy as well as breast cancer recurrence and/or survival stratified by the presence or absence of pCR, with a total sample size of 25 patients or greater. Publications were included regardless of neoadjuvant regimen received. Studies including any neoplasm other than female breast cancer were excluded, as well as studies analyzing unresectable or metastatic breast cancer. Endocrine-therapy based neoadjuvant studies and neoadjuvant studies with radiation were also excluded. Studies were excluded from sub-analyses based on receptor subtypes if HER2 status was unknown. Furthermore, only those publications where individual patient level data was extractable either in the form of Kaplan Meier curves with event data and/or survival estimates (e.g. median survival, and/or another landmark event such as 5 year survival with event data) were included.

Data Extraction

For each selected manuscript, the following information was recorded by two independent reviewers: primary author name, year of publication, sample size, duration of follow-up, definition of pCR, patient and tumor characteristics, neoadjuvant regimen, adjuvant regimen if applicable, number of patients achieving a pCR, and number of outcome events by pCR status. When available, outcomes based on the major breast cancer subtypes were extracted. We obtained the individual patient data (IPD) used in our analysis from the selected manuscripts by one of two methods. If available, method one used the Kaplan-Meier (KM) curves (extracted from the manuscript using the DigitizeIt (c) software)[8] to reconstruct the IPD data via the method of Guyot et al.[9] Alternatively, if KM curves were not available, method two used either a measure of median survival or a landmark event, and assumed an

exponential distribution to impute the IPD from the metric. Identical methods to recover the IPD data were used for both the pCR and non-pCR groups within each study to reduce bias.

Evaluation of Bias

A broad inclusion criterion was utilized as detailed above. All manuscripts were peer-reviewed publications and abstracts were therefore not included. Studies were allowable regardless of industry sponsorship. Demographic information on the study population and treatment details for each included manuscript was extracted and is presented in Table 1 and the Supplement (eTable1) for comparison. A broad global population was represented.

End Points

The primary clinical outcomes were breast cancer recurrence and overall survival. Results were examined in the overall study population and in sub-analyses based on tumor subtype and treatment characteristics. Overall survival (OS) results were used to determine survival. A variety of end points were used among the manuscripts to describe breast cancer recurrence, including event-free survival (EFS), progression-free survival, recurrence-free survival, relapse-free survival, disease-free survival, and distant disease-free survival. These end points were treated as equivalent for the aggregate analyses and EFS is used throughout this article as a representative term, as done in previous meta-analyses.[6] Endpoints with local recurrence only were excluded. The number of patients with and without a pCR (both breast and lymph nodes) in each manuscript was extracted. Allowable definitions of pCR were *ypT0 ypN0* (no invasive or noninvasive residual in breast or nodes) and *ypT0/is ypN0* (no invasive residual in breast or nodes; noninvasive breast residuals allowed), as suggested by FDA guidelines.[10] If results were available for both of the allowable pCR definitions, *ypT0/is ypN0* was utilized. Studies only listing pCR breast (with no information on lymph nodes) were excluded as well as studies utilizing the Sataloff criteria for pathologic tumor status given this definition allows minimal residual disease in the breast.[11] Studies were considered to have used adjuvant chemotherapy if the majority (≥90%) of patients received adjuvant chemotherapy, and studies were considered to have not used adjuvant chemotherapy if the minority (<10%) of patients received adjuvant chemotherapy.

Statistical Methods

Hazard ratios (HRs) measuring the association between pCR and OS or EFS, were estimated using Bayesian piece-wise exponential proportional hazards hierarchical models (considering dispersed prior distributions) using pCR as a predictor, together with their 95% probability intervals (95% PIs, the Bayesian equivalent of a confidence interval). A piece-wise exponential model assumes the hazard of an event to be constant within pre-specified time intervals.[12] Following Broglio et al., in our analyses we assumed that the hazard of OS or recurrence remained constant within each of 22 intervals of follow-up, the first 2 spanning 6 months and the remaining each spanning 12.[6] Random effects were considered when pooling data across multiple studies to account for heterogeneity. More details, including specification of the prior distributions and the computational strategy adopted to fit the model, are provided in the Supplement (eAppendix 2). In addition, to explore the effect of pCR on OS or EFS in selected subgroups, we performed several stratified analyses using the model described above.

Results

A total of 3,209 citations with associated abstracts were reviewed. Of these, a total of 166 were selected for full review. From these, 107 were excluded for not meeting eligibility criteria and 12 were excluded because individual patient level data could not be extracted using the described methods. An additional 5 manuscripts were identified through reviewing reference lists of eligible studies, manuscripts citing the selected studies, and relevant reviews. Ultimately, 52 studies met the criteria for inclusion (Figure 1).[4,14–63]

Study Characteristics

The selected studies were published from 1999 to 2016. The study sample size available for analysis ranged from 27 to 11,955, and featured a broad global patient population, including Europe, the United States, Mexico, Kuwait, Saudi Arabia, China, Japan, and Korea. Summary details on the selected studies are shown in eTable1 in the Supplement and a detailed list of each study is shown in Table 1. Further details on each individual study and the associated patient population can be found in the Supplement (eTable 2). The CTNeoBC FDA meta-analysis,[4] a pooled analysis of 12 randomized control trials (RCTs), was treated as a single study for this analysis given most of its studies did not make extractable IPD publicly available. The 52 studies included in our analysis represent 27,895 total evaluable patients, with 14,254 (51.1%) from RCTs, 1,709 patients (6.1%) from non-randomized clinical trials, and 11,932 patients (42.8%) from retrospective cohort studies. The overall pCR rate based on all 52 studies was 21.1% (range: 10.1–74.2%), with the highest rates of pCR seen in HER2+ tumors at 36.4% (range: 17.5–74.2%) and TN tumors at 32.6% (range: 20.3–62.2%), with HR+/HER2- tumors the lowest at 9.3% (range: 5.5–31.3%).

Event-free survival and overall survival

Overall, patients who had pCR, as compared to absence of pCR, had significantly better EFS (HR 0.31, 95% PI: 0.24–0.39, n = 26,378) as outlined in Figure 2A. Similarly, patients who had pCR, as compared to absence of pCR, had significantly better overall survival (HR 0.22, 95% PI: 0.15–0.30, n = 23,329) as outlined in Figure 2B.

Trial data vs. retrospective data

The association of pCR with significantly improved EFS remained when only clinical trials were considered (HR 0.30, 95% PI: 0.20–0.46, n = 15,873; eFigure 1). Similarly, when only clinical trials were considered, the association of pCR with significantly improved OS was also observed (HR 0.31, 95% PI: 0.14–0.68, n = 14,431, eFigure 2).

Role of duration of follow-up

The median follow-up time among all studies was 48 months (range 21.3 – 107) for EFS and 49.9 months (range 31.2 – 118) for OS. Among the subset of studies with 5 years or more of follow-up, the association of pCR with improved EFS (HR 0.45, 95% PI: 0.26–0.76, n = 15,449) remained (eFigure 3).

Clinical outcomes among major breast cancer subtypes

We evaluated the association between pCR and clinical outcomes by three major clinical subtypes of breast cancer (BC). The association of pCR with better EFS was statistically significant in patients with TNBC (HR 0.18, 95% PI: 0.10–0.31; n = 2,039), HER2+ BC (HR 0.31, 95% PI: 0.21–0.50; n = 5,711), and trended towards significance for HR+ BC (HR 0.15, 95% PI: 0.02–1.10; n = 3,385) as outlined in eFigures 4A–C. Similarly, the association of pCR with significantly improved survival was seen in TN BC (HR 0.20, 95% PI: 0.07–0.41, n = 778) and HER2+ BC (HR 0.13, 95% PI: 0.04–0.35, n = 1,654) as outlined in eFigures 5A–B. A significant relationship between pCR and improved survival was also noted in HR+ BC (HR 0.0003, 95% PI: $2.70E^{-11}$–0.81, n = 1,872) as outlined in eFigure 5C, but wide probability intervals were observed.

In addition, we constructed model-based survival curves to evaluate the temporal relationship between pCR and EFS, overall and by breast cancer subtypes. As demonstrated in Figure 3A–D, patients who had a pCR achieved a 5-year EFS of 88% (95% PI: 85% −91%) while those without pCR had a 5-year EFS of 67% (95% PI: 63%−71%). Among patients with TNBC, patients with pCR had a 5-year EFS of 90% (95% PI: 81%−95%) while those without pCR had a 5-year EFS of 57% (95% PI: 41%−70%). For HER2+ subgroup, patients with pCR had a 5-year EFS of 86% (95% PI: 74%−94%), while those without pCR had a 5-year EFS of 63% (95% PI: 43%−78%). Among HR+ subgroup, those with pCR had a 5-year EFS of 97% (95% PI: 87%−100%), while those without a pCR had a 5-year EFS of 88% (95% PI: 75%−95%). Similar results were observed for OS. As demonstrated in eFigure 6A–D, patients who experienced pCR achieved a 5-year OS of 94% (95% PI: 90%−96%), while those without a pCR achieved a 5-year OS of 75% (95% PI: 65%−82%). Among TN patients with pCR the 5-year OS was 84% (95% PI: 60%−97%), while those without pCR had a 5-year OS of 47% (95% PI: 13%−77%). For HER2+ patients, those who experienced pCR achieved a 5-year OS of 95% (95% PI: 89%−99%), while those without a pCR achieved a 5-year OS of 76% (95% PI: 63%−88%). Among HR+ patients, those who experienced pCR achieved a 5-year OS of 98% (95% PI: 86%−100%), while those without a pCR achieved a 5-year OS of 82% (95% PI: 3%−97%).

Among HER2+ patients, we also evaluated the role of neoadjuvant and adjuvant anti-HER2 therapy. For HER2+ patients receiving neoadjuvant anti-HER2 therapy, those with pCR had improved EFS compared to those with RD (HR 0.33, 95% PI: 0.19–0.61, n = 4,636), as seen in eFigure 7A. Similarly, among patients who did not receive neoadjuvant ani-HER2 therapies, those with pCR experienced improved outcomes compared to those with RD (HR 0.19, 95% PI 0.03–0.83, n = 213) as demonstrated in eFigure 7B. In the adjuvant setting, patients receiving adjuvant anit-HER2 therapy who had a pCR experienced superior EFS compared to those with RD (HR 0.38, 95% PI 0.21–0.68, n = 1,962), as seen in eFigure 8A. For HER2+ patients who did not receive adjuvant anti-HER2 therapy, EFS was greater in the pCR group compared to the RD group (HR 0.12, 95% PI 0 – 1.66, n = 133), though sample size was limited and results were not significant (eFigure 8B).

Role of adjuvant cytotoxic chemotherapy

We then evaluated the association between pCR and clinical outcomes by adjuvant chemotherapy usage. Among patients who received additional cytotoxic chemotherapy in the adjuvant setting, pCR remained associated with significantly improved EFS (HR 0.36, 95% PI: 0.19–0.67, n = 1,601), as seen in Figure 4A–B and eFigure 9A. Similarly, among patients who *did not* receive cytotoxic chemotherapy in the adjuvant setting, pCR remained associated with significantly improved EFS (HR 0.36, 95% PI: 0.27–0.54, n = 18,462), as outlined in Figure 4A–B and eFigure 9A. Similar results were observed in terms of overall survival (eFigure 10A–B). As evident from model-based survival curves (Figure 4A), patients who had pCR and received adjuvant chemotherapy achieved a 5-year EFS of 86% (95% PI: 74%−93%), which was similar to the 5-year EFS of 88% (95% PI: 81%−92%) among those who had pCR but received no adjuvant chemotherapy. In statistical comparison of pCR with EFS among the adjuvant chemotherapy group versus the no adjuvant chemotherapy group, no significant difference was seen between the two groups using a paired T-test (difference in log-HR: 0.02, 95% PI: −0.75–0.73; p = 0.60).

Discussion

To our knowledge, this study, including a total of 52 studies representing 27,895 patients, is the largest meta-analysis exploring the significance of pCR following NAT. This is the first study to specifically explore the role of adjuvant cytotoxic chemotherapy following pCR after neoadjuvant treatment, and we notably found this did not further improve outcomes. The results of this comprehensive meta-analysis overall suggest pCR is a strong surrogate endpoint for TNBC and HER2+ breast cancer. Our results are consistent with other smaller studies and support the FDA's decision to use pCR rate as a surrogate marker of efficacy from neoadjuvant treatment, particularly for TNBC and HER2+ BC.[10, 65,66,67]

The study results have major implications for the field. Advances in adjuvant treatment have significantly improved breast cancer outcomes. However, as the bar is progressively set higher it becomes more difficult to demonstrate therapeutic improvement in the adjuvant setting, with long follow-up required to see the number of events needed from a statistical standpoint. Between the expense of such trials, the large number of patients needed, and the need to assess therapies more efficiently in the era of targeted therapy, large adjuvant trials are becoming increasingly recognized as impractical in breast cancer.[13] The neoadjuvant setting has therefore become recognized as an efficient model for drug development and is utilized by the FDA.[3,13] I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) 2, a multicenter, randomized, phase 2 trial with multiple arms and pCR as the primary endpoint, utilizes an adaptive strategy for matching targeted therapies for breast cancer with the patients most likely to benefit from them.[68] One of the major strengths of the I-SPY2 approach is its ability to triage promising new therapies and novel combinations in a relatively short time frame.[69] Our results support this approach, and continued exploration of novel neoadjuvant clinical trial designs is needed to advance the field. The rapidly evolving field of blood-based biomarkers may also change the interpretation of pCR in the future through the identification of minimal residual disease with circulating tumor DNA, offering a number of avenues for novel trial design.[70]

The potential role of adjuvant therapy after neoadjuvant therapy in influencing the relationship between pCR and survival was carefully considered in our study. Our results demonstrate the survival benefit is maintained whether adjuvant chemotherapy was received, with a similar magnitude, though it should be noted that this was not a randomized trial between adjuvant chemotherapy (versus not) and there could be inherent differences between the two groups. Nevertheless, the results are based on adequately-powered meta-analysis of multiple studies and represent the best evidence to date. The finding possibly reflects tumor biology wherein tumors sensitive to NAT in breast and lymph nodes are also typically sensitive to the therapy in micrometastatic sites. Presence of complete response in breast and axilla is likely associated with response in micrometastatic sites, minimizing the magnitude of benefit from additional adjuvant therapy. Given the potential toxicity associated with chemotherapy, one could potentially consider abbreviating adjuvant chemotherapy in patients who attain pCR in both breast and axilla after NAT. However, these findings are hypothesis generating and further research is needed before it can be incorporated in clinical practice. For example, the ongoing DAPHNe study (NCT03716180) and the planned HER2Compass trial will evaluate omitting adjuvant cytotoxic chemotherapy for HER2+ patients who achieve a pCR after neoadjuvant paclitaxel, trastuzumab, and pertuzumab. Conversely, there are a number of studies exploring additional adjuvant therapies for TNBC patients with residual disease following neoadjuvant chemotherapy, and the use of adjuvant capecitabine for such patients has become a favored approach based on the improved overall survival results observed in the CREATE-X trial.[71] However, it must be recognized that the strongest data for use of pCR as a surrogate exists for neoadjuvant cytotoxic therapies and the anti-HER2 antibodies trastuzumab and pertuzumab. More research, such as that being done in I-SPY2, is needed to understand the prognostic significance of pCR following the use of neoadjuvant targeted therapies and immunotherapy agents.

The results for TNBC and HER2+ breast cancer demonstrating significant improvement in long-term outcomes with achievement of pCR supports clinical trials triaging novel therapies for further development based on pCR. For HER2+ breast cancer, neoadjuvant trials are now exploring regimens featuring HER2-directed agents only based on pCR as primary endpoint.[72] In TNBC, the addition of a platinum agent to anthracyline/taxane-based treatment has been shown to increase pCR rates, but at the expense of greater toxicity.[73–75] While trials studying the addition of neoadjuvant platinum among TNBC patients have had divergent long-term outcomes, these trials were not powered for survival.[76,77]

Major strengths of the present study are its large size and the inclusion of both trial and cohort studies, representing a more realistic experience and providing external validity. Additionally, results were highly significant despite the inclusion of a variety of neoadjuvant regimens, suggesting the path taken to attain a pCR may not be critical. Although trial-level analyses, which allow comparison of different treatments, have not validated pCR as a surrogate endpoint for improved long-term outcomes,[4,5] it is important to note that most neoadjuvant trials are powered for pCR and not for measures of long-term outcomes. Further research into this question is needed and will benefit from improved access to direct patient-level data in publications on this topic. Predictive data regarding pCR as a surrogate

endpoint could be more thoroughly assessed if more publications included a breakdown of the long-term data by pCR status and treatment arm.

This meta-analysis has several potential limitations. First, the analysis is subject to variable reporting and study specific outcome definitions used across studies. For example, a variety of end points were used to represent breast cancer recurrence. Some of these endpoints include local recurrences, which are potentially curable, while other utilized endpoints focused on distant events only. Endpoints with local recurrence only were excluded. The definition of hormone receptor-positivity also varied among some studies and over the years in which the studies were undertaken. The definition of pCR also varied at times between studies, and we included *ypT0 ypN0* and *ypT0/is ypN0* as allowable definitions. However, each study's definition for pCR and long-term outcomes were consistently used for both the pCR and the non-pCR groups, minimizing bias. Some meta-analyses on this topic have included studies which only considered pCR in the breast and/or allowed minimal residual disease in the breast, which we were careful to exclude given these definitions do not confer the same survival advantage.[78] Second, there was heterogeneity in the type of neoadjuvant therapies employed and the study results are broadly based on neoadjuvant chemotherapy in general rather than a specific therapeutic regimen. Third, a number of analyses of interest, such as exploring the relationship between molecular breast cancer subtypes and pCR with corresponding long-term outcomes, could not be performed based on the data available. Among HR+ tumors, pCR rates are higher and the relationship with long-term outcomes is stronger among grade 3 tumors compared to lower grade tumors.[4] A pooled analysis by the German Breast Group based on 6,377 patients receiving neoadjuvant anthracycline-taxane-based chemotherapy in seven randomized trials suggested pCR is a suitable surrogate end point of recurrence for patients with luminal B/HER2-negative, HER2-positive (nonluminal), and triple negative disease, but not for those with luminal B/HER2-positive or luminal A tumors.[78] While luminal A versus B classification could not be evaluated in this study, our results support these findings, with the greatest absolute benefit of pCR being observed in HER2+ and TN tumors. However, a trend towards significance for HR+ tumors was observed, likely driven by higher grade and/or luminal B subtypes, where the recurrence risk tends to be earlier while late recurrences are more often seen with luminal A tumors. Fourth, for HR+ breast cancer an alternative surrogate endpoint such as the residual cancer burden (RCB) index may be more appropriate as pCR rates are low, but was not evaluated in this study to maintain homogeneity in assessment of the primary endpoint (pCR in breast and nodes).[79] Finally, the median follow-up time for the study overall was only 4 years, which is short for the natural history of certain subtypes of breast cancer (HR+), but one would have expected the bias to be toward the null if recurrence events did not lead to mortality in a shorter time frame.

In conclusion, the study results comprehensively demonstrate that pCR after neoadjuvant chemotherapy is associated with significantly better EFS and overall survival. This study highlights the impact of adjuvant therapy in modulating relationship between pCR and outcomes and provides guidance for clinical trials evaluating neoadjuvant therapies for patients with localized breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Laura M. Spring reports consulting fees from Novartis, Lumicell, Puma Technology, travel support from Merk and Tesaro, and institutional research funding from Tesaro and Merck.

Brian M. Alexander reports consulting fees from Bristol-Myers Squibb, Precision Health Economics, and Schlesinger Associates and employment with Foundation Medicine, Inc.

Beverly Moy reports her spouse is a consultant for MOTUS GI.

Steven J. Isakoff reports consulting or advisory roles with Abbvie, PharmaMar, Genentech/Roche, Myriad Genetics, Hengrui Therapeutics, Puma Technology, and Immunomedics, institutional research funding from Genentech, PharmaMar, Abbvie, OncoPep, Merck, and AstraZeneca/MedImmune, and travel support from PharmaMar

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References

1. Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis. J Natl Cancer Inst 2005; 97: 188–94. [PubMed: 15687361]
2. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26: 778–85. [PubMed: 18258986]
3. Bardia A, Baselga J. Neoadjuvant therapy as a platform for drug development and approval in breast cancer. Clin Cancer Res 2013; 19: 6360–70. [PubMed: 24298066]
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet 2014; 384: 164–72.
5. Berruti A, Amoroso V, Gallo F, et al. Pathologic Complete Response As a Potential Surrogate for the Clinical Outcome in Patients With Breast Cancer After Neoadjuvant Therapy: A Meta-Regression of 29 Randomized Prospective Studies. J Clin Oncol 2014; 32: 3883–91. [PubMed: 25349292]
6. Broglio KR, Quintana M, Foster M, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. JAMA Oncol 2016; 2: 751–60. [PubMed: 26914222]
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg Lond Engl 2010; 8: 336–41.
8. DigitizeIt - Plot Digitizer Software. Digitize graphs, charts and math data. https://www.digitizeit.de/ (accessed Aug 1, 2018).
9. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012; 12: 9. [PubMed: 22297116]

10. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm305501.pdf (accessed July 12, 2018).
11. Penault-Llorca F, Abrial C, Raoelfils I, et al. Comparison of the prognostic significance of Chevallier and Sataloff's pathologic classifications after neoadjuvant chemotherapy of operable breast cancer. Hum Pathol 2008; 39: 1221–8. [PubMed: 18547616]
12. Crowther MJ, Riley RD, Staessen JA, Wang J, Gueyffier F, Lambert PC. Individual patient data meta-analysis of survival data using Poisson regression models. BMC Med Res Methodol 2012; 12 DOI:10.1186/1471-2288-12-34. [PubMed: 22333319]
13. Berry DA, Hudis CA. Neoadjuvant therapy in breast cancer as a basis for drug approval. JAMA Oncol 2015; 1: 875–6. [PubMed: 26181139]
14. Kuerer HM, Newman LA, Smith TL, et al. Clinical Course of Breast Cancer Patients With Complete Pathologic Primary Tumor and Axillary Lymph Node Response to Doxorubicin-Based Neoadjuvant Chemotherapy. J Clin Oncol 1999; 17: 460–460. [PubMed: 10080586]
15. Chollet P, Amat S, Cure H, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. Br J Cancer 2002; 86: 1041–6. [PubMed: 11953845]
16. Diéras V, Fumoleau P, Romieu G, et al. Randomized Parallel Study of Doxorubicin Plus Paclitaxel and Doxorubicin Plus Cyclophosphamide As Neoadjuvant Treatment of Patients With Breast Cancer. J Clin Oncol 2004; 22: 4958–65. [PubMed: 15611510]
17. Lee YJ, Doliny P, Gomez-Fernandez C, Powell J, Reis I, Hurley J. Docetaxel and cisplatin as primary chemotherapy for treatment of locally advanced breast cancers. Clin Breast Cancer 2004; 5: 371–6. [PubMed: 15585076]
18. Ring AE, Smith IE, Ashley S, Fulford LG, Lakhani SR. Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. Br J Cancer 2004; 91: 2012–7. [PubMed: 15558072]
19. Abrial SC, Penault-Llorca F, Delva R, et al. High prognostic significance of residual disease after neoadjuvant chemotherapy: a retrospective study in 710 patients with operable breast cancer. Breast Cancer Res Treat 2005; 94: 255–63. [PubMed: 16267618]
20. Guarneri V, Broglio K, Kau S-W, et al. Prognostic Value of Pathologic Complete Response After Primary Chemotherapy in Relation to Hormone Receptor Status and Other Factors. J Clin Oncol 2006; 24: 1037–44. [PubMed: 16505422]
21. Hurley J, Doliny P, Reis I, et al. Docetaxel, Cisplatin, and Trastuzumab As Primary Systemic Therapy for Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced Breast Cancer. J Clin Oncol 2006; 24: 1831–8. [PubMed: 16549824]
22. Andre F, Mazouni C, Liedtke C, et al. HER2 expression and efficacy of preoperative paclitaxel/FAC chemotherapy in breast cancer. Breast Cancer Res Treat 2007; 108: 183–90. [PubMed: 17468948]
23. Liedtke C, Mazouni C, Hess KR, et al. Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer. J Clin Oncol 2008; 26: 1275–81. [PubMed: 18250347]
24. Eralp Y, Smith TL, Altundağ K, et al. Clinical features associated with a favorable outcome following neoadjuvant chemotherapy in women with localized breast cancer aged 35 years or younger. J Cancer Res Clin Oncol 2008; 135: 141–8. [PubMed: 18581139]
25. Frasci G, Comella P, Rinaldo M, et al. Preoperative weekly cisplatin–epirubicin–paclitaxel with G-CSF support in triple-negative large operable breast cancer. Ann Oncol 2009; 20: 1185–92. [PubMed: 19218307]
26. Al-Tweigeri TA, Ajarim DS, Alsayed AA, et al. Prospective phase II study of neoadjuvant doxorubicin followed by cisplatin/docetaxel in locally advanced breast cancer. Med Oncol 2009; 27: 571–7. [PubMed: 19526202]

27. Chang HR, Glaspy J, Allison MA, et al. Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. Cancer 2010; 116: 4227–37. [PubMed: 20549829]

28. Chen XS, Wu JY, Huang O, et al. Molecular subtype can predict the response and outcome of Chinese locally advanced breast cancer patients treated with preoperative therapy. Oncol Rep 2010; 23: 1213–20. [PubMed: 20372832]

29. Jinno H, Sakata M, Hayashida T, et al. A phase II trial of capecitabine and docetaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide (FEC) as preoperative treatment in women with stage II/III breast cancer. Ann Oncol 2010; 21: 1262–6. [PubMed: 19854722]

30. Kim SI, Sohn J, Koo JS, Park SH, Park HS, Park BW. Molecular subtypes and tumor response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. Oncology 2010; 79: 324–30. [PubMed: 21430399]

31. Arun B, Bayraktar S, Liu DD, et al. Response to Neoadjuvant Systemic Therapy for Breast Cancer in BRCA Mutation Carriers and Noncarriers: A Single-Institution Experience. J Clin Oncol 2011; 29: 3739–46. [PubMed: 21900106]

32. Wu J, Li S, Jia W, Su F. Response and prognosis of taxanes and anthracyclines neoadjuvant chemotherapy in patients with triple-negative breast cancer. J Cancer Res Clin Oncol 2011; 137: 1505–10. [PubMed: 21830158]

33. Fasching PA, Heusinger K, Haeberle L, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011; 11: 486. [PubMed: 22081974]

34. Masuda H, Masuda N, Kodama Y, et al. Predictive factors for the effectiveness of neoadjuvant chemotherapy and prognosis in triple-negative breast cancer patients. Cancer Chemother Pharmacol 2010; 67: 911–7. [PubMed: 20593180]

35. Esserman LJ, Berry DA, DeMichele A, et al. Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results From the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012; 30: 3242–9. [PubMed: 22649152]

36. Im S-A, Lee KS, Ro J, et al. Phase II trial of preoperative paclitaxel, gemcitabine, and trastuzumab combination therapy in HER2 positive stage II/III breast cancer: the Korean Cancer Study Group BR 07–01. Breast Cancer Res Treat 2012; 132: 589–600. [PubMed: 22094934]

37. Yoo C, Ahn J-H, Jung KH, et al. Impact of immunohistochemistry-based molecular subtype on chemosensitivity and survival in patients with breast cancer following neoadjuvant chemotherapy. J Breast Cancer 2012; 15: 203–10. [PubMed: 22807938]

38. Melichar B, Hornychová H, Kalábová H, et al. Increased efficacy of a dose-dense regimen of neoadjuvant chemotherapy in breast carcinoma: a retrospective analysis. Med Oncol 2012; 29: 2577–85. [PubMed: 22392196]

39. Zhang G-C, Qian X-K, Guo Z-B, et al. Pre-treatment hormonal receptor status and Ki67 index predict pathologic complete response to neoadjuvant trastuzumab/taxanes but not disease-free survival in HER2-positive breast cancer patients. Med Oncol 2012; 29: 3222–31. [PubMed: 22547076]

40. Marmé F, Aigner J, Lorenzo Bermejo J, et al. Neoadjuvant epirubicin, gemcitabine and docetaxel for primary breast cancer: Long-term survival data and major prognostic factors based on two consecutive neoadjuvant phase I/II trials. Int J Cancer 2013; 133: 1006–15. [PubMed: 23400797]

41. Krishnan Y, Alawadhi SA, P S S, Gopal M, Thuruthel S. Pathological responses and long-term outcome analysis after neoadjuvant chemotheraphy in breast cancer patients from Kuwait over a period of 15 years. Ann Saudi Med 2013; 33: 443–50. [PubMed: 24188937]

42. Guarneri V, Dieci MV, Barbieri E, et al. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol 2013; 24: 2990–4. [PubMed: 24013581]

43. Natoli C, Vici P, Sperduti I, et al. Effectiveness of neoadjuvant trastuzumab and chemotherapy in HER2-overexpressing breast cancer. J Cancer Res Clin Oncol 2013; 139: 1229–40. [PubMed: 23604446]

44. Hurley J, Reis IM, Rodgers SE, et al. The use of neoadjuvant platinum-based chemotherapy in locally advanced breast cancer that is triple negative: retrospective analysis of 144 patients. Breast Cancer Res Treat 2013; 138: 783–94. [PubMed: 23542956]
45. Guiu S, Arnould L, Bonnetain F, et al. Pathological response and survival after neoadjuvant therapy for breast cancer: A 30-year study. The Breast 2013; 22: 301–8. [PubMed: 22863283]
46. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014; 15: 1137–46. [PubMed: 25130998]
47. Tanioka M, Sasaki M, Shimomura A, et al. Pathologic complete response after neoadjuvant chemotherapy in HER2-overexpressing breast cancer according to hormonal receptor status. The Breast 2014; 23: 466–72. [PubMed: 24742606]
48. Takada M, Ishiguro H, Nagai S, et al. Survival of HER2-positive primary breast cancer patients treated by neoadjuvant chemotherapy plus trastuzumab: a multicenter retrospective observational study (JBCRG-C03 study). Breast Cancer Res Treat 2014; 145: 143–53. [PubMed: 24682674]
49. Kawajiri H, Takashima T, Aomatsu N, et al. Prognostic significance of pathological complete response following neoadjuvant chemotherapy for operable breast cancer. Oncol Lett 2014; 7: 663–8. [PubMed: 24527070]
50. Wang J, Xu B, Yuan P, et al. HER2 as a predictive factor for successful neoadjuvant anthracycline chemotherapy of locally advanced and early breast cancer. Int J Biol Markers 2014; 29: e187–192. [PubMed: 25041784]
51. Bear HD, Tang G, Rastogi P, et al. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial. Lancet Oncol 2015; 16: 1037–48. [PubMed: 26272770]
52. Gonzalez-Angulo AM, Parinyanitikul N, Lei X, et al. Effect of adjuvant trastuzumab among patients treated with anti-HER2-based neoadjuvant therapy. Br J Cancer 2015; 112: 630–5. [PubMed: 25584488]
53. Zelnak AB, Nikolinakos P, Srinivasiah J, et al. High pathologic complete response in Her2-positive, early-stage breast cancer to a novel nonanthracycline neoadjuvant chemotherapy. Clin Breast Cancer 2015; 15: 31–6. [PubMed: 25065563]
54. Ko ES, Han H, Han B-K, et al. Prognostic Significance of a Complete Response on Breast MRI in Patients Who Received Neoadjuvant Chemotherapy According to the Molecular Subtype. Korean J Radiol 2015; 16: 986. [PubMed: 26357493]
55. Villarreal-Garza C, Soto-Perez-de-Celis E, Sifuentes E, et al. Outcomes of Hispanic women with lymph-node positive, HER2 positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab in Mexico. The Breast 2015; 24: 218–23. [PubMed: 25698148]
56. Groheux D, Giacchetti S, Delord M, et al. Prognostic impact of 18F-FDG PET/CT staging and of pathological response to neoadjuvant chemotherapy in triple-negative breast cancer. Eur J Nucl Med Mol Imaging 2014; 42: 377–85. [PubMed: 25432784]
57. Mayer EL, Gropper AB, Harris L, et al. Long-term follow-up after preoperative trastuzumab and chemotherapy for HER2-overexpressing breast cancer. Clin Breast Cancer 2015; 15: 24–30. [PubMed: 25205424]
58. Zhang P, Yin Y, Mo H, et al. Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: a randomized phase 2 trial. Oncotarget 2016.
59. Li J, Chen S, Chen C, et al. Pathological complete response as a surrogate for relapse-free survival in patients with triple negative breast cancer after neoadjuvant chemotherapy. Oncotarget 2016.
60. Shao Z, Chaudhri S, Guo M, Zhang L, Rea D. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: An Observational Study. Oncol Res 2016; 23: 291–302.
61. Al-Tweigeri T, AlSayed A, Alawadi S, et al. A multicenter prospective phase II trial of neoadjuvant epirubicin, cyclophosphamide, and 5-fluorouracil (FEC100) followed by cisplatin–docetaxel with or without trastuzumab in locally advanced breast cancer. Cancer Chemother Pharmacol 2015; 77: 147–53. [PubMed: 26563257]

62. Liu S, Duan X, Xu L, et al. Nuclear Gli1 expression is associated with pathological complete response and event-free survival in HER2-positive breast cancer treated with trastuzumab-based neoadjuvant therapy. Tumor Biol 2015; 37: 4873–81.
63. Villarreal-Garza C, Bargallo-Rocha JE, Soto-Perez-de-Celis E, et al. Real-world outcomes in young women with breast cancer treated with neoadjuvant chemotherapy. Breast Cancer Res Treat 2016; 157: 385–94. [PubMed: 27189008]
64. Bonnefoi H, Piccart M, Bogaerts J, et al. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1–00): a randomised phase 3 trial. Lancet Oncol 2011; 12: 527–39. [PubMed: 21570352]
65. Mieog JSD, van der Hage JA, van de Velde CJH. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev 2007.
66. Kong X, Moran MS, Zhang N, Haffty B, Yang Q. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. Eur J Cancer 2011; 47: 2084–90. [PubMed: 21737257]
67. Prowell TM, Pazdur R. Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer. N Engl J Med 2012; 366: 2438–41. [PubMed: 22646508]
68. Barker A, Sigman C, Kelloff G, Hylton N, Berry D, Esserman L. I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy. Clin Pharmacol Ther 2009; 86: 97–100. [PubMed: 19440188]
69. Carey LA, Winer EP. I-SPY 2 — Toward More Rapid Progress in Breast Cancer Treatment. N Engl J Med 2016; 375: 83–4. [PubMed: 27406352]
70. Earl H, Provenzano E, Abraham J, et al. Neoadjuvant trials in early breast cancer: pathological response at surgery and correlation to longer term outcomes – what does it all mean? BMC Med 2015; 13: 234. [PubMed: 26391216]
71. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 2017; 376: 2147–59. [PubMed: 28564564]
72. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018; 19: 115–26. [PubMed: 29175149]
73. Sikov WM, Berry DA, Perou CM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015; 33: 13–21. [PubMed: 25092775]
74. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014; 15: 747–56. [PubMed: 24794243]
75. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018; 19: 497–509. [PubMed: 29501363]
76. Sikov WM, Berry DA, Perou CM, et al. Abstract S2–05: Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/− carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance). Cancer Res 2016; 76: S2–05–S2–05.
77. von Minckwitz G, Loibl S, Schneeweiss A, et al. Abstract S2–04: Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). Cancer Res 2016; 76: S2–04–S2–04.
78. von Minckwitz G, Untch M, Blohmer J-U, et al. Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes. J Clin Oncol 2012; 30: 1796–804. [PubMed: 22508812]

79. Symmans WF, Wei C, Gould R, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 2017; 35: 1049–60. [PubMed: 28135148]

Translational Relevance

Prior studies have highlighted the prognostic significance of pathological complete response (pCR) after neoadjuvant chemotherapy in breast cancer. However, the clinical impact of adjuvant chemotherapy following pCR is not known. In the largest individual patient-level meta-analysis to date on the topic (N= 27,895), we demonstrated pCR was strongly associated with improved event free and overall survival, and the receipt of additional cytotoxic chemotherapy following surgery did not further improve outcomes. The study results support the use of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response and has broad implications for the drug approval process.

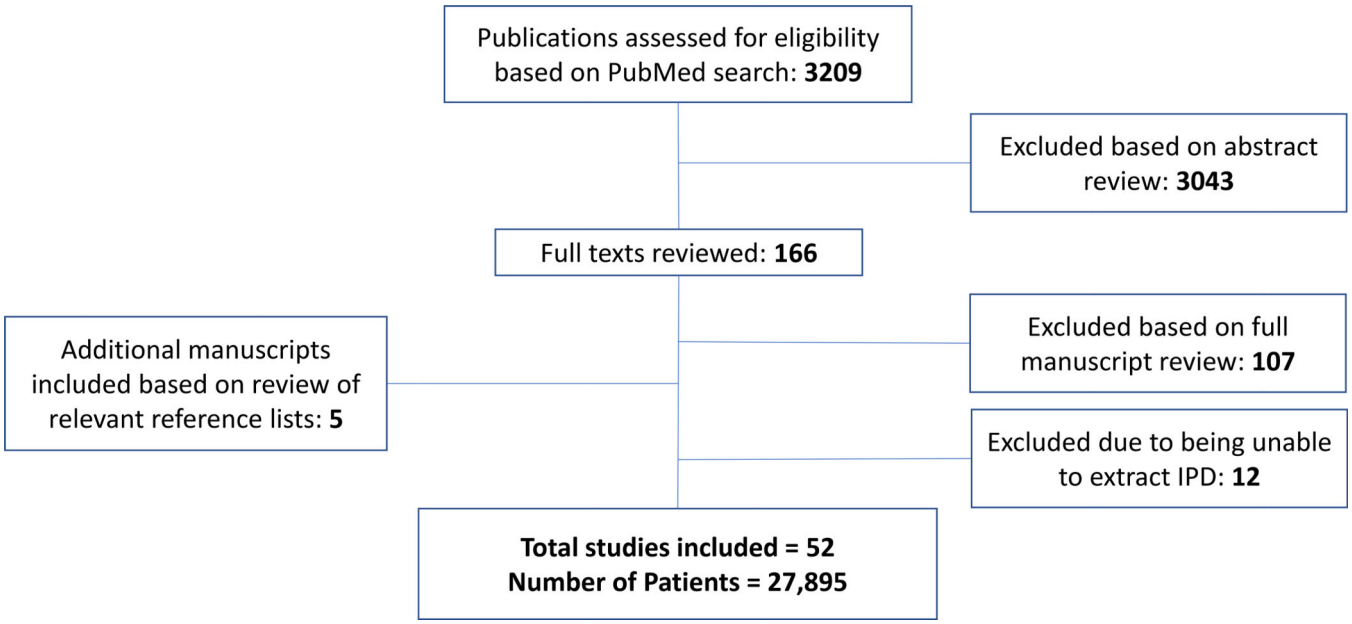
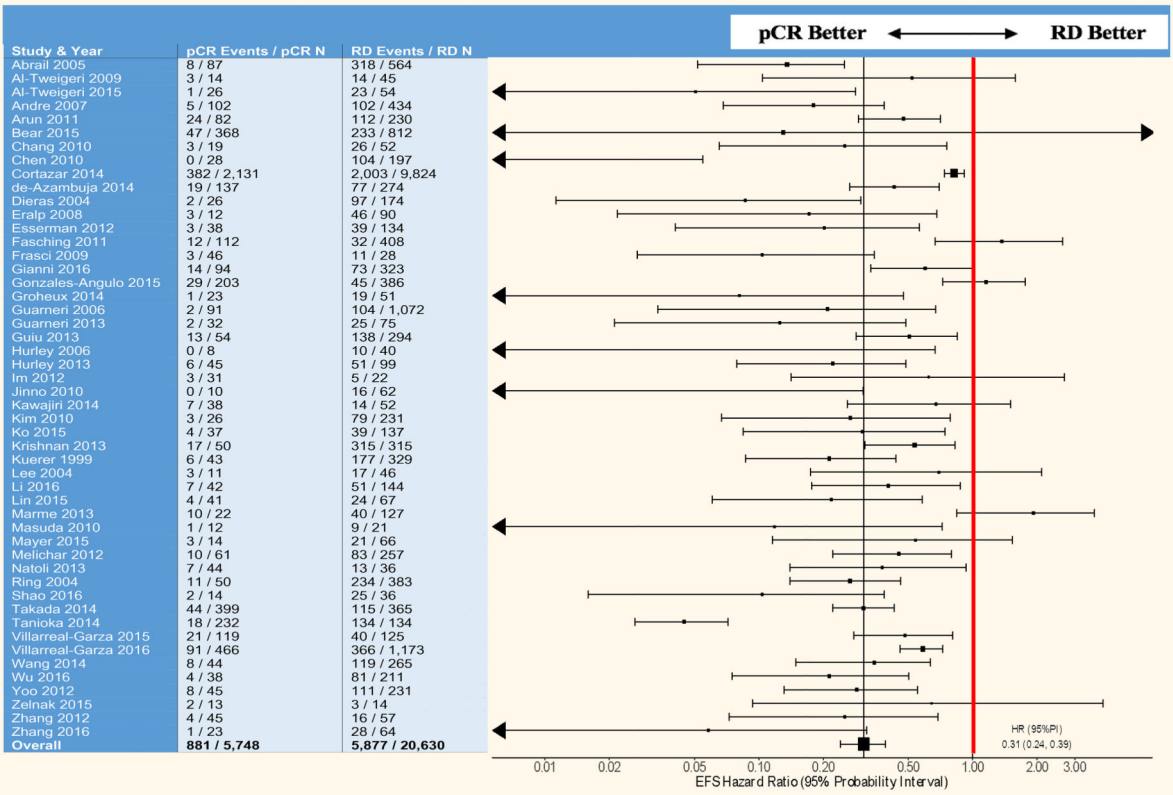


Figure 1. Selection of studies for meta-analysis

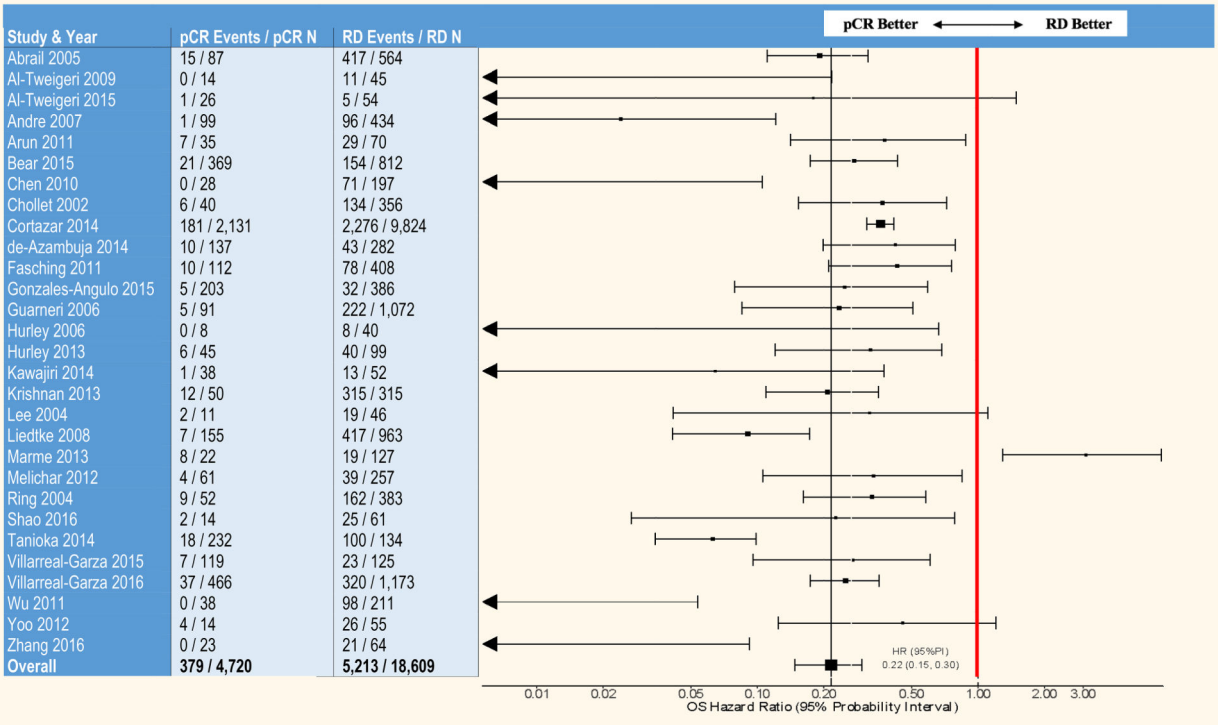
Based on the search criteria, 3,209 citations with associated abstracts were reviewed. Of these, a total of 166 were selected for full review and ultimately 52 studies met the criteria for inclusion.

A



Study & Year	pCR Events / pCR N	RD Events / RD N
Abrail 2005	8 / 87	318 / 564
Al-Tweigeri 2009	3 / 14	14 / 45
Al-Tweigeri 2015	1 / 26	23 / 54
Andre 2007	5 / 102	102 / 434
Arun 2011	24 / 82	112 / 230
Bear 2015	47 / 368	233 / 812
Chang 2010	3 / 19	26 / 52
Chen 2010	0 / 28	104 / 197
Cortazar 2014	382 / 2,131	2,003 / 9,824
de-Azambuja 2014	19 / 137	77 / 274
Dieras 2004	2 / 26	97 / 174
Eralp 2008	3 / 12	46 / 90
Esserman 2012	3 / 38	39 / 134
Fasching 2011	12 / 112	32 / 408
Frasci 2009	3 / 46	11 / 28
Gianni 2016	14 / 94	73 / 323
Gonzales-Angulo 2015	29 / 203	45 / 386
Groheux 2014	1 / 23	19 / 51
Guarneri 2006	2 / 91	104 / 1,072
Guarneri 2013	2 / 32	25 / 75
Guiu 2013	13 / 54	138 / 294
Hurley 2006	0 / 8	10 / 40
Hurley 2013	6 / 45	51 / 99
Im 2012	3 / 31	5 / 22
Jinno 2010	0 / 10	16 / 62
Kawajiri 2014	7 / 38	14 / 52
Kim 2010	3 / 26	79 / 231
Ko 2015	4 / 37	39 / 137
Krishnan 2013	17 / 50	315 / 315
Kuerer 1999	6 / 43	177 / 329
Lee 2004	3 / 11	17 / 46
Li 2016	7 / 42	51 / 144
Lin 2015	4 / 41	24 / 67
Marme 2013	10 / 22	40 / 127
Masuda 2010	1 / 12	9 / 21
Mayer 2015	3 / 14	21 / 66
Melichar 2012	10 / 61	83 / 257
Natoli 2013	7 / 44	13 / 36
Ring 2004	11 / 50	234 / 383
Shao 2016	2 / 14	25 / 36
Takada 2014	44 / 399	115 / 365
Tanioka 2014	18 / 232	134 / 134
Villarreal-Garza 2015	21 / 119	40 / 125
Villarreal-Garza 2016	91 / 466	366 / 1,173
Wang 2014	8 / 44	119 / 265
Wu 2016	4 / 38	81 / 211
Yoo 2012	8 / 45	111 / 231
Zelnak 2015	2 / 13	3 / 14
Zhang 2012	4 / 45	16 / 57
Zhang 2016	1 / 23	28 / 64
Overall	**881 / 5,748**	**5,877 / 20,630**

B



Study & Year	pCR Events / pCR N	RD Events / RD N
Abrail 2005	15 / 87	417 / 564
Al-Tweigeri 2009	0 / 14	11 / 45
Al-Tweigeri 2015	1 / 26	5 / 54
Andre 2007	1 / 99	96 / 434
Arun 2011	7 / 35	29 / 70
Bear 2015	21 / 369	154 / 812
Chen 2010	0 / 28	71 / 197
Chollet 2002	6 / 40	134 / 356
Cortazar 2014	181 / 2,131	2,276 / 9,824
de-Azambuja 2014	10 / 137	43 / 282
Fasching 2011	10 / 112	78 / 408
Gonzales-Angulo 2015	5 / 203	32 / 386
Guarneri 2006	5 / 91	222 / 1,072
Hurley 2006	0 / 8	8 / 40
Hurley 2013	6 / 45	40 / 99
Kawajiri 2014	1 / 38	13 / 52
Krishnan 2013	12 / 50	315 / 315
Lee 2004	2 / 11	19 / 46
Liedtke 2008	7 / 155	417 / 963
Marme 2013	8 / 22	19 / 127
Melichar 2012	4 / 61	39 / 257
Ring 2004	9 / 52	162 / 383
Shao 2016	2 / 14	25 / 61
Tanioka 2014	18 / 232	100 / 134
Villarreal-Garza 2015	7 / 119	23 / 125
Villarreal-Garza 2016	37 / 466	320 / 1,173
Wu 2011	0 / 38	98 / 211
Yoo 2012	4 / 14	26 / 55
Zhang 2016	0 / 23	21 / 64
Overall	**379 / 4,720**	**5,213 / 18,609**

Figure 2. A-B. Association of pCR with (A) event free survival and (B) overall survival

Forest plot of the overall hazard ratio (HR) estimate with the 95% probability interval (PI) for the association of pathologic complete response (pCR) with the long term outcomes (A) event free survival (EFS) and (B) overall survival (OS), as compared to residual disease (RD). For comparison, the raw study specific HR estimates are reported. The location of the box indicates the estimated HR for that study; the size of the box represents the relative number of events per study. HR & 95% PI for overall effects are also reported. The dashed line oriented at 1 represents the Null of no difference.

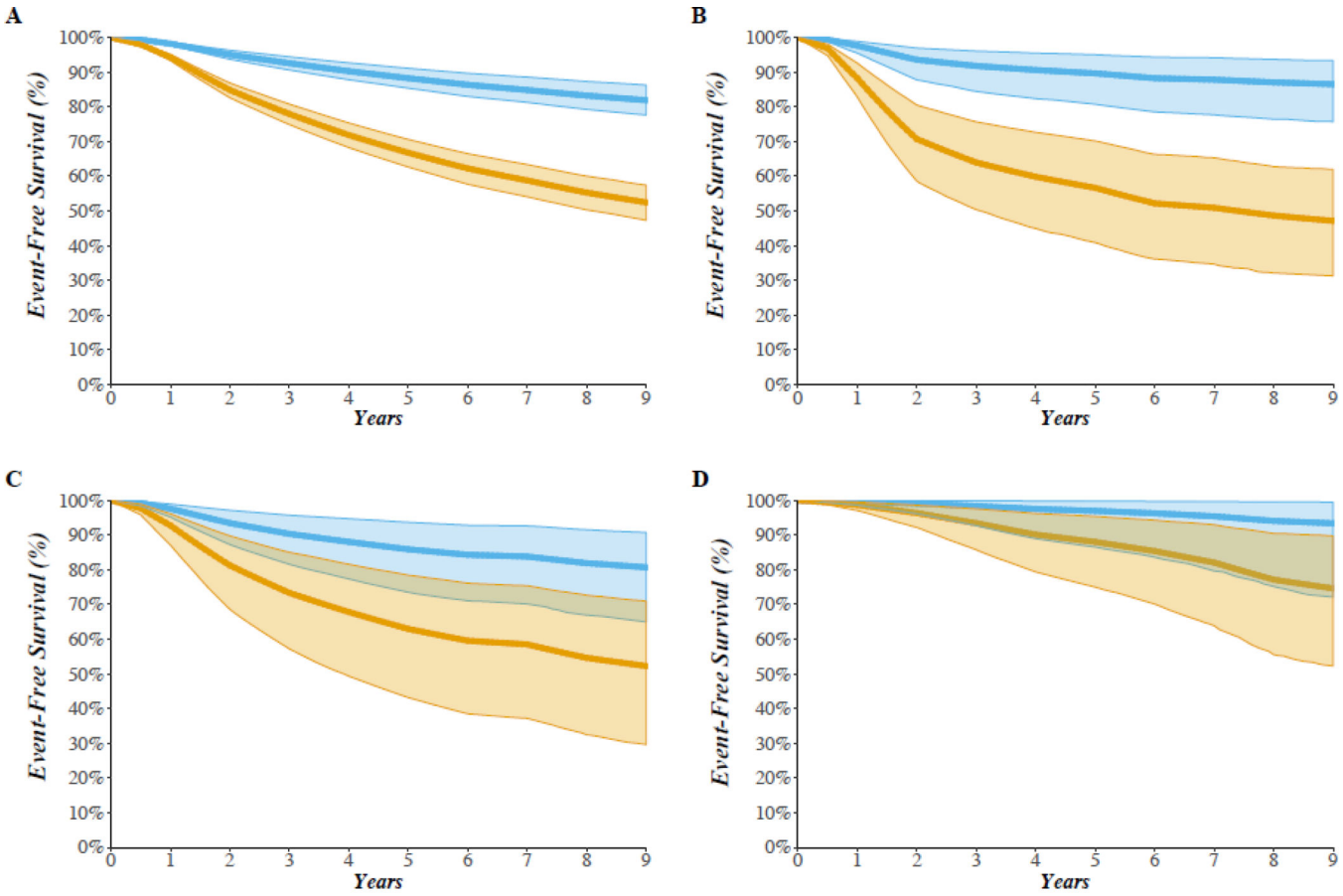


Figure 3. A-D. Relationship between pCR and EFS overall and among the major breast cancer subtypes

Kaplan-Meier curves depicting the relationship between pathologic complete response (pCR) and event free survival (EFS) overall (A), in triple negative breast cancer (B), HER2-positive breast cancer (C), and hormone receptor-positive breast cancer (D), based on hazard ratio data from the studies. The blue line represents the pCR group and the orange line represents the residual disease group. The shaded regions represent the 95% pointwise probability interval for their respective color.

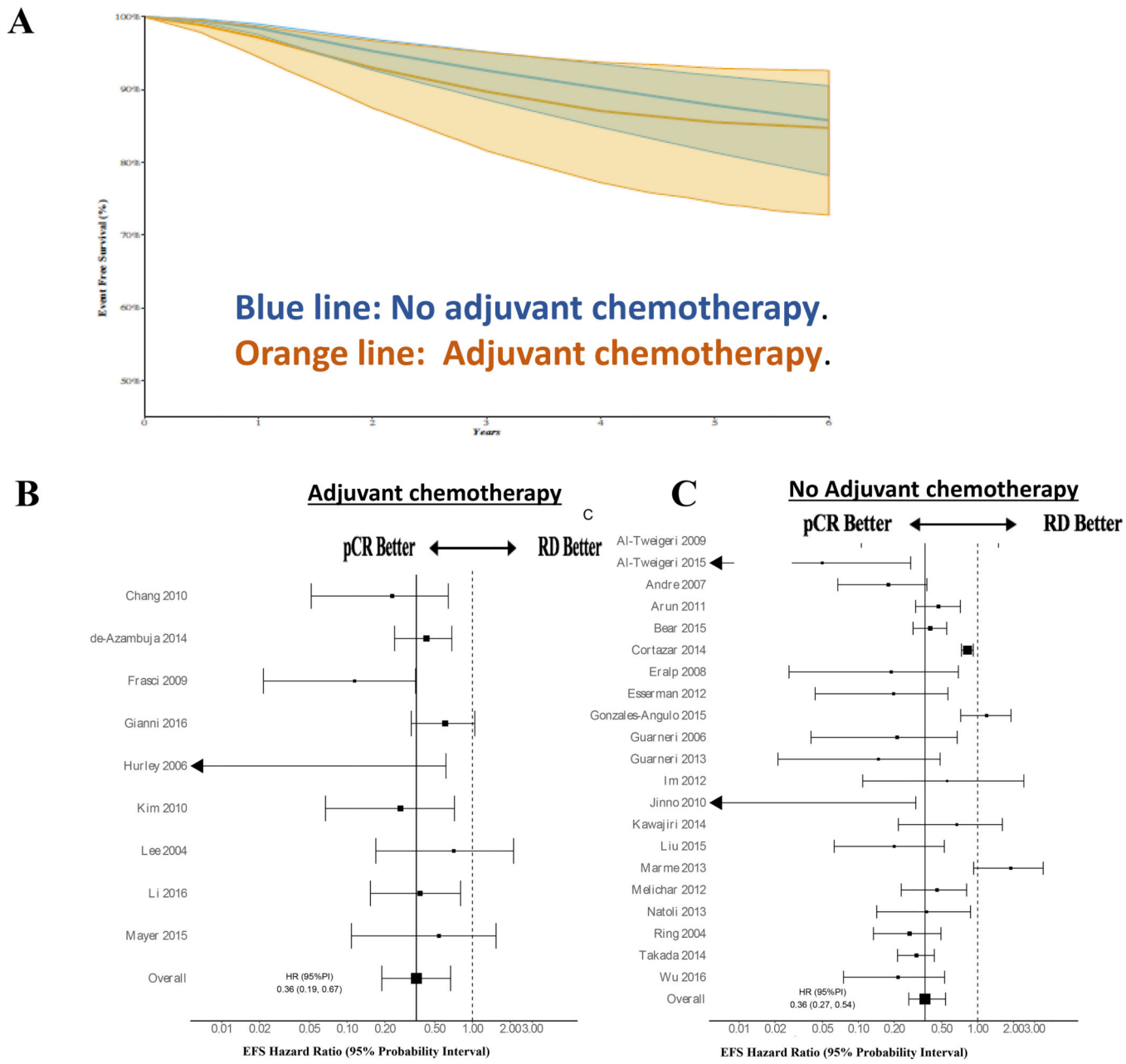


Figure 4. A-B. Impact of adjuvant chemotherapy on the relationship between pCR and EFS

(A) Kaplan-Meier curves depicting the relationship between pathologic complete response (pCR) and event free survival (EFS) based on receipt of chemotherapy. The color blue represents the patient subpopulation where 10% or less of the patients received adjuvant chemotherapy. The color orange represents the patient subpopulation where 90% or more of the patients received adjuvant chemotherapy. The shaded regions represent the 95% pointwise probability interval for their respective color. (B) The left forest plot is representative of the populations with at least 90% of patients receiving adjuvant chemotherapy while the forest plot on the right is representative of the populations with at most 10% of patients receiving adjuvant chemotherapy, with both comparing pCR to

residual disease (RD). The hazard ratio (HR) estimate with the 95% probability interval (PI) are shown overall. For comparison, the raw study specific HR estimates are reported. The location of the box indicates the estimated HR for that study; the size of the box represents the relative number of events per study. The dashed line oriented at 1 represents the Null of no difference.

Table 1:

Patient and study characteristics of included manuscripts

First Author	Year	Study type	Evaluable sample size	Subtypes included	Definition pCR	Measure of recurrence	Recurrence median follow-up (mo)	Survival median follow-up (mo)	Survival median follow-up (mo)
Kuerer	1999	Pooled (NRCT)	372	All	ypT0/is ypN0	DFS	58.00	58.00	58.00
Chollet	2002	Pooled (NRCT)	396	All	ypT0 ypN0	DFS	96.00	96.00	96.00
Dieras	2004	RCT	200	All	ypT0/is ypN0	DFS	31.00	NA	NA
Lee	2004	NRCT	57	All	ypT0/is ypN0	DFS	48.00	48.00	48.00
Ring	2004	Retrospective	435	All	ypT0/is ypN0	DFS	53.00	53.00	53.00
Abrial	2005	Retrospective	651	All	ypT0/is ypN0	DFS	91.20	91.20	91.20
Guarneri	2006	Retrospective	1163	All	ypT0/is ypN0	PFS	107.00	118.00	118.00
Hurley	2006	NRCT	48	HER2+	ypT0/is ypN0	PFS	43.00	43.00	43.00
Andre	2007	Retrospective	534	All	ypT0/is ypN0	RFS	31.20	31.20	31.20
Eralp	2008	Retrospective	102	All	ypT0/is ypN0	DFS	43.00	NA	NA
Liedtke	2008	Retrospective	1118	All	ypT0/is ypN0	NA	NA	36.00	36.00
Al-Tweigeri	2009	NRCT	59	All	ypT0/is ypN0	DFS	60.00	60.00	60.00
Frasci	2009	NRCT	74	TNBC	ypT0/is ypN0	DFS	41.00	NA	NA
Chang	2010	NRCT	71	All	ypT0/is ypN0	RFS	22.80	NA	NA
Chen	2010	Retrospective	225	All	ypT0/is ypN0	DFS	32.50	32.50	32.50
Jinno	2010	NRCT	71	All	ypT0 ypN0	DFS	29.00	NA	NA
Kim	2010	Retrospective	257	All	ypT0/is ypN0	DFS	21.30	NA	NA
Masuda	2010	Retrospective	33	All	ypT0/is ypN0	DFS	24.00	NA	NA
Arun	2011	Retrospective	317	All (BRCA+ enriched)	ypT0/is ypN0	RFS	38.40	38.40	38.40
Fasching	2011	Retrospective	520	All	ypT0 ypN0	DDFS	33.60	33.60	33.60
Wu	2011	Retrospective	249	All	ypT0/is ypN0	DFS	48.20	48.20	48.20
Esserman	2012	NRCT	172	All	ypT0/is ypN0	RFS	46.80	NA	NA
Im	2012	NRCT	53	HER2	ypT0/is ypN0	RFS	40.00	NA	NA
Melichar	2012	Retrospective	318	All	ypT0/is ypN0	RFS	68.00	68.00	68.00
Yoo	2012	Retrospective	276	All	ypT0/is ypN0	PFS	32.30	32.30	32.30

First Author	Year	Study type	Evaluable sample size	Subtypes included	Definition pCR	Measure of recurrence	Recurrence median follow-up (mo)	Survival median follow-up (mo)	Survival median follow-up (mo)
Zhang	2012	Retrospective	102	HER2	ypT0 ypN0	DFS	25.90	NA	NA
Guarneri	2013	Retrospective	107	All	ypT0/is ypN0	DFS	ND	NA	NA
Guiu	2013	Retrospective	348	All	ypT0/is ypN0	DFS	84.00	NA	NA
Hurley	2013	Retrospective	144	TNBC	ypT0/is ypN0	PFS	48.00	45.60	45.60
Krishnan	2013	Retrospective	365	All	ypT0/is ypN0	DFS	49.00	49.00	49.00
Marme	2013	Pooled (NRCT)	149	All	ypT0 ypN0	DFS	82.80	82.80	82.80
Natoli	2013	Retrospective	80	HER2	ypT0/is ypN0	DFS	32.00	NA	NA
Cortazar	2014	Pooled (RCT/NRCT)	11955	All	ypT0/is ypN0	EFS	64.80	64.44	64.44
de Azambuja	2014	RCT	419	HER2	ypT0/is ypN0	EFS	45.30	45.30	45.30
Groheux	2014	Retrospective	74	TNBC	ypT0/is ypN0	EFS	31.00	NA	NA
Kawajiri	2014	Retrospective	90	All	ypT0/is ypN0	DFS	53.00	53.00	53.00
Takada	2014	Retrospective	764	HER2	ypT0/is ypN0	DFS	42.00	NA	NA
Tanioka	2014	Retrospective	366	HER2	ypT0/is ypN0	RFS	55.00	55.00	55.00
Wang	2014	Retrospective	309	All	ypT0/is ypN0	DFS	60.00	NA	NA
Al-Tweigeri	2015	NRCT	80	All	ypT0/is ypN0	DFS	43.00	43.00	43.00
Bear	2015	RCT	1186	HR+/HER2−, TNBC	ypT0/is ypN0	DFS	56.40	56.40	56.40
Gonzalez-Angulo	2015	Retrospective	589	HER2	ypT0/is ypN0	RFS	45.00	45.00	45.00
Ko	2015	Retrospective	174	All	ypT0/is ypN0	RFS	54.80	NA	NA
Liu	2015	Retrospective	108	HER2	ypT0/is ypN0	EFS	32.00	NA	NA
Mayer	2015	Pooled (NRCT)	80	HER2	ypT0/is ypN0	RFS	105.60	NA	NA
Villarreal-Garza	2015	Retrospective	244	HER2	ypT0/is ypN0	DFS	47.00	47.00	47.00
Zelnak	2015	NRCT	27	HER2	ypT0/is ypN0	DFS	52.20	NA	NA
Gianni	2016	RCT	417	HER2	ypT0/is ypN0	PFS	60.00	NA	NA
Li	2016	Retrospective	186	TNBC	ypT0/is ypN0	RFS	48.10	NA	NA
Shao	2016	Retrospective	50	TNBC	ypT0/is ypN0	PFS	54.50	54.50	54.50
Villarreal-Garza	2016	Retrospective	1639	All	ypT0/is ypN0	DFS	50.80	50.80	50.80
Zhang	2016	RCT	87	TNBC	ypT0/is ypN0	RFS	55.00	55.00	55.00

Abbreviations: pCR, pathologic complete response; mo, month; RCT, randomized clinical trial; NRCT, non-randomized clinical trial; ER+, estrogen receptor-positive; HR+, hormone receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; TNBC, triple negative breast cancer; DFS, disease free survival; PFS, progression free survival; RFS, relapse free survival; DDFS, distant disease free survival; EFS, event free survival; NA, not applicable