Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes


See accompanying editorial on page 1747

ABSTRACT

Purpose
The exact definition of pathologic complete response (pCR) and its prognostic impact on survival in intrinsic breast cancer subtypes is uncertain.

Methods
Tumor response at surgery and its association with long-term outcome of 6,377 patients with primary breast cancer receiving neoadjuvant anthracycline-taxane–based chemotherapy in seven randomized trials were analyzed.

Results
Disease-free survival (DFS) was significantly superior in patients with no invasive and no in situ residuals in breast or nodes ($n = 956$) compared with patients with residual ductal carcinoma in situ only ($n = 309$), no invasive residuals in breast but involved nodes ($n = 186$), only focal-invasive disease in the breast ($n = 478$), and gross invasive residual disease ($n = 4,449$; $P < .001$). Hazard ratios for DFS comparing patients with or without pCR were lowest when defined as no invasive and no in situ residuals (0.446) and increased monotonously when in situ residuals (0.523), no invasive breast residuals but involved nodes (0.623), and focal-invasive disease (0.727) were included in the definition. pCR was associated with improved DFS in luminal B/human epidermal growth factor receptor 2 (HER2)–negative ($P = .005$), HER2-positive/nonluminal ($P < .001$), and triple-negative ($P < .001$) tumors but not in luminal A ($P = .39$) or luminal B/HER2-positive ($P = .45$) breast cancer. pCR in HER2-positive (nonluminal) and triple-negative tumors was associated with excellent prognosis.

Conclusion
pCR defined as no invasive and no in situ residuals in breast and nodes can best discriminate between patients with favorable and unfavorable outcomes. Patients with noninvasive or focal-invasive residuals or involved lymph nodes should not be considered as having achieved pCR. pCR is a suitable surrogate end point 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.

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INTRODUCTION

Neoadjuvant chemotherapy represents an option for patients with early breast cancer when an indication for chemotherapy is given. Pathologic complete response (pCR) has predicted long-term outcome in several neoadjuvant studies and is therefore a potential surrogate marker for survival. However, selected trials comparing different neoadjuvant regimens have failed to demonstrate an association between pCR rate and improved outcome.

Methodologic limitations are likely to be the reason for this unexpected discrepancy. First, no standardized definition for pCR exists. Some trials have applied the pCR definition to the breast tumor only, whereas others have included the axillary nodes. Furthermore, some studies have included the presence of focal invasive cancer or noninvasive cancer residuals in their pCR definition, whereas others have defined pCR as the complete eradication of all invasive and noninvasive cancer. Second, incidence and prognostic impact of pCR vary among
breast cancer—intrinsic subtypes. For example, although patients with luminal A–like breast cancer show a low pCR rate, their overall prognosis is favorable, whereas patients with triple-negative (TN) breast cancer show a high pCR rate but have an unfavorable outcome.9 Including all intrinsic subtypes might therefore attenuate the prognostic information of pCR.

**METHODS**

**Objectives and End Points**

The first aim of this pooled analysis was to compare currently used definitions of pCR and investigate their role in predicting risk of recurrence or death. Individual patient data from case report forms based on local histopathologic assessments allowed evaluation of the following pCR definitions reported in the literature:

- ypT0 ypN0. No invasive or noninvasive residual in breast or nodes.
- ypT0/is ypN0. No residual invasive breast or nodes; noninvasive breast residuals allowed. Used by MD Anderson Cancer Center, Austrian Breast and Colorectal Cancer Study Group, and Neo–Breast International Group.
- ypT0/ii ypN0/+ . No invasive residual in the breast; noninvasive breast residuals and infiltrated lymph nodes allowed. Used by National Surgical Adjuvant Breast and Bowel Project.
- ypT≤1mic ypN0/+ . No gross invasive residuals in the breast; focal invasive and noninvasive residuals in breast and infiltrated lymph nodes allowed. Used by French groups using the Sataloff index.
- ypT1≤1mic ypN0/+ . No gross invasive residual disease scoring systems to determine whether they could differentiate prognostic subgroups of patients with residual invasive breast cancer: ypST staging system according to TNM14; ypPn staging system according to TNM14; and histologic breast regression score (RS) as proposed by Sinn,10 with RS 4 indicating no viable tumor cell residuals of the Sinn score.10

We further investigated three residual disease scoring systems to determine whether they could differentiate prognostic subgroups of patients with residual invasive breast cancer: ypST staging system according to TNM14; ypPn staging system according to TNM14; and histologic breast regression score (RS) as proposed by Sinn,10 with RS 4 indicating no viable tumor cell residuals of the Sinn score.10

The second aim of this analysis was to assess the prognostic relevance of pCR (according to the best definition as identified in the first part of this analysis) in various intrinsic subtypes. Estrogen (ER) and progesterone receptor (PgR) status were considered positive if ≥ 10% of cells stained positive or the Remmele score was ≥ 3,16 taking into account the frequency and intensity of the staining. Human epidermal growth factor receptor 2 (HER2) status was assessed by immunohistochemistry (HER2 positivity if the score was 3) or fluorescent in situ hybridization. Intrinsic breast cancer subtypes were determined according to clinicopathologic criteria recently recommended by the St Gallen panelists.26 Because information on Ki-67 was not available, we used grade to capture cell proliferation. The following definitions were used:

- **Luminal A-like tumors.** ER positive and/or PgR positive, HER2 negative, grade 1 or 2.
- **Luminal B/HER2-negative-like tumors.** ER positive and/or PgR positive, HER2 negative, grade 3.
- **Luminal B/HER2-positive-like tumors.** ER positive and/or PgR positive, HER2 positive, all grades.
- **HER2-positive (nonluminal) –like tumors.** ER negative and PgR negative, HER2 positive, all grades.
- **TN tumors.** ER negative, PgR negative, HER2 negative, all grades.

**RESULTS**

**Patient Baseline Characteristics**

In the current pooled analysis, 6,377 patients with breast cancer received neoadjuvant anthracycline-taxane–based chemotherapy in...
the setting of seven randomized clinical trials (Appendix Table A1, online only). During a median follow-up of 46.3 months (range, 0 to 127 months) and observation of 22,869 patient years, 1,466 relapses (23%) and 775 deaths (12.2%) were observed.

Median age of patients at time of study entry was 50.1 years (range, 21 to 81 years); median tumor size was 4.0 cm (range, 1.2 to 33.0 cm); 5,618 patients had operable and 759 had locally advanced breast cancer. Tumors stained positive for ER in 3,771 (60.4%) and for
PgR in 3,235 patients (51.8%). No data on HER2 status were available in 1,990 patients (31.2%) because measurement of HER2 was only implemented in the study procedures after 2001. All baseline characteristics, except nodal status at baseline, correlated significantly with pCR rates according to the four definitions. In general, patients with the worst prognostic factors seemed to have the best pCR rates (Table 1).

**Correlation Between pCR Rate and Outcome**

Stage ypT0 ypN0 was diagnosed in 955 (15.0%), ypTis ypN0 in 309 (4.8%), ypT0/is ypN+ in 186 (2.9%), ypT1mic ypN0/+ in 478 (7.5%), and ypT > 1mic ypN0/+ in 4,449 patients (69.8%). Prognosis differed between components of pCR definition (DFS: P < .001; OS: P < .001; Figs 1A and 1B). Patients with ypT0 ypN0 tumors experienced better DFS compared with patients with ypTis ypN0 tumors (HR, 1.74; 95% CI, 1.28 to 2.36; P < .001) and showed a trend toward better OS (HR, 1.81; 95% CI, 1.21 to 2.70; P = .005). Their prognosis was also better than that of patients with ypT0/is ypN+ (DFS: HR, 1.51; 95% CI, 1.14 to 2.00; P = .005) or ypT1mic ypN0/+ tumors (DFS: HR, 2.73; 95% CI, 1.19 to 6.24; P < .001) or ypT0/is ypN+ tumors (DFS: HR, 3.18; 95% CI, 2.31 to 4.38; P < .001; OS: HR, 4.05; 95% CI, 2.63 to 6.24; P < .001) or ypT1mic ypN0/+ tumors (DFS: HR, 2.33; 95% CI, 1.81 to 3.01; P < .001; OS: HR, 2.34; 95% CI, 1.61 to 3.41; P < .001; Table 2). Patients with stage ypT0/is ypN+ tumors experienced the worst DFS and OS (Figs 1A and 1B). HR for DFS comparing
Correlation Between Residual Disease Score and Outcome

Overall, histologic breast RS significantly correlated with DFS and OS (P < .001). Patients with noninvasive residuals only did not experience a significantly different outcome compared with those with focal-invasive residuals or minimal or no signs of regression (Table 2; Figs 1C and 1D). Tumor stage after neoadjuvant chemotherapy (ypT) was significantly associated with prognosis (P < .001; Figs 1E and 1F), especially for patients with ypT3, ypT4a-c, and ypT4 disease, who had the worst outcome (Table 2). Comparable results were observed for nodal stage ypN. Patients with ypN2 and ypN3 disease had a median DFS of 70 and 30 months, respectively (Table 2; Figs 1G and 1H). A multivariate Cox regression model showed that all three residual disease scores provided independent prognostic information (Appendix Table A2, online only).

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Prognostic Information of pCR in Various Subpopulations

For the following analysis, pCR was defined as ypT0 ypN0 showing the lowest HR comparing patients with or without pCR. pCR seemed to predict a more favorable outcome independent of age,
Prognosis After pCR by Intrinsic Breast Cancer Subtype

<table>
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<th>Baseline Characteristic</th>
<th>DFS</th>
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<td>98</td>
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<tr>
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**Abbreviations:** DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor.

**Table 3. Prognostic Impact of Pathologic Complete Response on Survival in Various Subgroups**

- Non-significant trends for DFS or OS were found only in small subpopulations (eg, patients age &lt; 35 years [n = 404], patients with cT4a-c [n = 465] or cN3 disease [n = 92]). However, different outcomes in subgroups were observed for histologic type, tumor grade, and ER and PgR status. Importantly, pCR was predictive for neither DFS nor OS in subgroups associated with lower proliferation, namely lobular type, grade 1, and positive ER or PgR status. In contrast, pCR was predictive for DFS and OS in ductal or other histologic types, grade 2 or 3 tumors, and negative ER or PgR status. Low proliferating luminal A–like tumors showed no prognostic impact of pCR, whereas highly aggressive HER2–positive (nonluminal) and TN tumors showed a significant prognostic impact of pCR. A heterogeneous pattern was observed for luminal B–like tumors. Whereas pCR seems to be prognostic in luminal B/HER2-negative tumors, it did not correlate with prognosis in luminal B/HER2-positive tumors (Table 3; Figs 2A to 2E). Comparable results were obtained when only patients receiving trastuzumab were analyzed (data not shown).

- Prognosis according to intrinsic subtype was analyzed separately for patients with or without pCR. Prognosis in patients without pCR was comparable to that in patients receiving systemic treatment after surgery (luminal tumor showing better prognosis than others).
HER2-positive or TN tumors\textsuperscript{27}; Figs 2A to 2E [gold curves]). However, in patients achieving pCR, prognosis was not significantly different for the intrinsic subtypes (DFS: $P = .055$; OS: $P = .70$). In fact, DFS of patients with HER2-positive and TN tumors was better than that of those with luminal B/HER2-positive tumors ($P < .02$; Fig 2F).

**DISCUSSION**

This is, to the best of our knowledge, the first individual patient--based pooled analysis analyzing different pCR definitions for their prognostic impact on survival of patients with breast cancer treated with neoadjuvant anthracycline-taxane--based chemotherapy. The large patient collective included sufficient subpopulations with small residual disease volume (eg, noninvasive residuals only, focal-invasive disease $< 5$ mm, or no invasive tumor in the breast but involved lymph nodes). Over the last decades, these subpopulations have frequently been considered to have achieved pCR. However, we show that these subpopulations have an increased risk of relapse and sometimes of death as well compared with the group of patients with stage ypT0 ypN0 breast cancer. pCR restricted to this stage showed the lowest adjusted HR for DFS and OS compared with the other definitions (Table 2).

We further demonstrate that in subgroups considered to have slowly proliferating tumors, pCR is not associated with prognosis, whereas in subgroups with highly proliferating tumors, pCR can discriminate between patients with good and poor prognosis accurately. The recently proposed clinicopathologic definition of the St Gallen panel nicely recognizes these subgroups. In fact, prognostic impact of pCR is highest in HER2-positive (nonluminal) and TN tumors, where patients achieving pCR show a prognosis comparable to that of patients with luminal A tumors.

Surprisingly, pCR was not prognostic in the luminal B/HER2-positive subgroup irrespective of trastuzumab treatment. In this subgroup, pCR rates were low, despite concomitant anti-HER2 therapies,\textsuperscript{11,28,29} but similar outcomes were observed in the adjuvant trastuzumab studies.\textsuperscript{30}

Inclusion of noninvasive residuals in the pCR definition has been mainly supported by the hitherto largest analysis of the MD Anderson group of 2,302 patients, showing no difference in DFS or OS between patients with ypT0 ypN0 and ypTis ypN0 tumors.\textsuperscript{31} However, the number of patients with ypT0 ypN0 (n = 199) and ypTis ypN0 (n = 78) tumors was much lower than in our analysis, resulting in a much lower statistical power to show prognostic differences. This may be attributed to less intense neoadjuvant treatment, resulting in lower pCR rates. Only 42% of patients received a combination of anthracyclines and taxanes.\textsuperscript{31} Other analyses have failed to show correlation between different pCR definitions and outcome, possibly because of small sample sizes.\textsuperscript{32,33} Another argument for inclusion of low-volume residual disease in the pCR definition has come from biomarker studies. In the case of low pCR rates, these studies become severely underpowered. However,
the more active treatments used today result in pCR rates of 20% to 40%, rendering this argument moot.

We could not assess other pCR scores (eg, residual cancer burden, grading by Miller-Payne). However, we suggest that a more thorough comparison of all these scores is necessary to decide whether more extensive pathologic assessments are necessary.

The prognostic importance of involved lymph nodes after neoadjuvant chemotherapy has already been stressed by others.36,37 However, with the large sample size, we can now demonstrate that the small group of patients with ypT0/is ypN+ tumors has a considerably inferior prognosis, comparable to that of patients with tumor residuals in breast and nodes.

The strengths of this pooled analysis are the large sample size and considerable number of patient years available. All participants participated in prospective trials, receiving comparable anthracycline-taxane-containing neoadjuvant regimens under homogenous national treatment conditions. Although some parameters were incomplete, this data set is currently unique because of the availability of HER2 status. Weaknesses of this analysis are the unavailability of Ki-67 to measure proliferation, the imprecise categorization of breast cancer subtypes because of the lack of gene profiles, and the lack of central assessment of surgical specimens. Because of this, it is possible that the poorer outcome of patients with residual ductal carcinoma in situ could have been the result of invasive parts not being detected because of insufficient histopathologic examination.

We conclude that pCR defined as ypT0 ypN0 is associated with highly favorable outcome. ypTis, ypT1mic, and ypN+ residuals only are associated with increased relapse risk and should therefore no longer be considered as pCR. Extent of residual disease and evidence of regression provide helpful additional prognostic information. pCR is a suitable surrogate end point for patients with HER2-positive (non-luminal), TN, and luminal B/HER2-negative tumors but not for luminal B/HER2-positive and luminal A tumors.

**REFERENCES**


**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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**Data analysis and interpretation:** All authors

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors
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