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ORIGINAL REPORT

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

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A B S T R A C T

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 = 955) 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 residues 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.[1] Pathologic complete response (pCR) has predicted long-term outcome in several neoadjuvant studies and is therefore a potential surrogate marker for survival.[2,3] However, selected trials comparing different neoadjuvant regimens have failed to demonstrate an association between pCR rate and improved outcome.[4]

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.[5,6] Furthermore, some studies have included the presence of focal invasive cancer[7] or noninvasive cancer residuals in their pCR definition,[6] whereas others have defined pCR as the complete eradication of all invasive and noninvasive cancer.[8] 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. Used by the German study groups (German Breast Group [GBG] and Arbeitsgemeinschaft Gynäkologische Onkologie—Breast Group [AGO-B]) as part of the Sinn score.[10]

ypT0/is ypN0. No invasive residual in 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.[6,11,12]

ypT0/is ypN0/+. No invasive residual in the breast; noninvasive breast residuals and infiltrated lymph nodes allowed. Used by National Surgical Adjuvant Breast and Bowel Project.[5,13]

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.[7]

Therefore, to compare the impact of the components of the definition on prognosis, the following distinct subgroups according to their residual tumor extent after neoadjuvant chemotherapy were used: ypT0 ypN0, ypTis ypN0, ypT0/is ypN+, ypT1mic ypN0/+, and ypT>1mic ypN0/+ (no pCR according to any definition).

We further investigated three residual disease scoring systems to determine whether they could differentiate prognostic subgroups of patients with residual invasive breast cancer: ypT staging system according to TNM[14]; ypN staging system according to TNM[14]; and histologic breast regression score (RS) as proposed by Sinn,[10] with RS 4 indicating no viable tumor cell residuals in the breast, RS 3 indicating only noninvasive residuals in the breast, RS 2 indicating only focal (< 5 mm) invasive residuals in the breast, RS 1 indicating minimal signs of tumor regression, and RS 0 indicating no signs of regression.

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,[15] 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.[16] 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.

Histologic type, tumor grade, and ER, PgR, and HER2 status were assessed in the primary tumor core biopsy sample by the local pathologist. In 510 patients, missing data for ER and PgR status from pretreatment biopsies were substituted with information available at surgery.

Patients

Between 1998 and 2006, the GBG and AGO-B study groups conducted seven prospective clinical trials that explored neoadjuvant systemic chemotherapy in patients with operable or nonoperable primary breast cancer. The study designs of GeparDuo (NCT00793377),[17] GeparTrio pilot[18] and main study (NCT00544765),[19,20] GeparQuattro (NCT00288002),[8,21] AGO 1,[22] PREPARE (Preoperative Epirubicin Paclitaxel Aranesp Study; NCT00544232),[23,24] and TECHNO (Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant; NCT00795899)[25] have been reported in detail in a review.[26] All trials were approved by the relevant ethics committees. All patients provided written informed consent for study participation and data collection.

All seven trials had comparable main eligibility criteria. Diagnosis of invasive breast cancer was histologically confirmed in all patients by core biopsy. Female patients needed to have measurable disease of the breast tumor either by palpation, ultrasound, or mammography. Tumor size had to be at least 2 cm in the majority of trials, except for the AGO1 trial, which only accepted patients with a tumor size of ≥ 3 cm, and the most recent GeparQuattro trial, which accepted patients with a tumor size ≥ 1 cm according to ultrasound measurements. Locally advanced (cT4a-d) and inflammatory breast cancers were eligible for all trials except GeparDuo. In patients with bilateral disease, the largest tumor was evaluated for response. For the Techno study, only patients with HER2-positive disease were eligible. Patients with primary metastatic disease, other prior malignancies, or prior treatment for invasive breast cancer were excluded in all trials.

All seven trials used chemotherapy with anthracyclines and taxanes. Only patients who received at least one cycle of systemic treatment were included in the analysis. In the GeparQuattro and Techno studies, patients with HER2-positive tumors (n = 622) received trastuzumab simultaneously with neoadjuvant chemotherapy as well as postoperatively to complete 1 full year of treatment. Patients with ER- and/or PgR-positive tumors should receive adjuvant endocrine treatment for at least 5 years. Adjuvant radiotherapy was recommended for patients who underwent breast-conserving surgery as well for patients underwent mastectomy but had initial stage cT3, cT4, cN2, or cN3 disease according to national guidelines.

Statistics

Individual patient data regarding baseline characteristics, histopathologic results at surgery, and follow-up were extracted for this pooled analysis from the original databases from all 6,377 patients participating in these trials. As defined in the protocols, patients with missing data for histologic response were counted as having no response.

Baseline parameters were correlated with pCR using two-sided χ^2 or Fisher's exact test. Disease-free (DFS) and overall survival (OS) were calculated from date of registration to local or distant invasive relapse, death, or last follow-up and plotted as Kaplan-Meier curves. Log-rank *P* values were calculated for different pCR definitions and residual disease scores. Hazard ratios (HRs), 95% CIs, and corresponding *P* values between categorized score values were calculated using Cox regression analysis. Prognostic information of the residual disease scores was compared in a Cox regression model. This test was also used with pCR as categorized covariate to determine the prognostic impact of pCR in various subgroups. Cox regression models were conducted as full models including all factors in the final model regardless of their statistical significance; dummy variables were used for categorized covariates, and patients with missing values for any factor were excluded from these analyses. SPSS 14.0 (SPSS, Chicago, IL) was used to perform all analyses.

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

Table 1. Baseline Patient Characteristics (N = 6,377) and Corresponding pCR Rates

Characteristic	All Patients		Patients by Subtype											
			ypT0 ypN0			ypT0/is ypN0			ypT0/is ypN0/+			ypT0/is/mic ypN0/+		
	No.	%	No.	%	*P*	No.	%	*P*	No.	%	*P*	No.	%	*P*
All patients	6,377	100.0	955	15.0		1,261	19.8		1,456	22.8		1,928	30.2	
Age, years					< .001			< .001			< .001			< .001
< 35	404	6.3	99	24.5		125	30.9		147	36.4		179	44.3	
35-39	640	10.0	111	17.3		152	23.8		171	26.7		224	35.0	
40-49	2,109	33.1	340	16.1		442	21.0		511	24.2		676	32.1	
50-59	1,901	29.8	244	12.8		326	17.1		390	20.5		526	27.7	
≥ 60	1,323	20.7	161	12.2		216	16.3		237	17.9		323	24.4	
Tumor stage					< .001			< .001			< .001			< .001
cT1	216	3.4	39	18.1		54	25.0		60	27.8		76	35.2	
cT2	4,277	67.8	719	16.8		937	21.9		1,060	24.8		1,377	32.2	
cT3	1,060	16.8	107	10.1		151	14.2		185	17.5		254	24.0	
cT4a-c	465	7.4	49	10.5		63	13.5		73	15.7		108	23.2	
cT4d	294	4.7	32	10.9		46	15.6		63	21.4		93	31.6	
Missing	65	1.0												
Nodal status					.001			< .001			.258			.128
cN0	2,681	48.0	513	19.1		673	25.1		725	27.0		936	34.9	
cN1	2,636	47.2	391	14.8		525	19.9		644	24.4		878	33.3	
cN2	225	4.0	35	15.6		42	18.7		59	26.2		80	35.6	
cN3	47	0.8	7	14.9		9	19.1		15	31.9		19	40.4	
Missing	788	12.4												
Histologic type					< .001			< .001			< .001			< .001
Ductal invasive	4,972	80.1	800	16.1		1,060	21.3		1,233	24.8		1,623	32.6	
Other type	389	6.3	79	20.3		94	24.2		106	27.2		125	32.1	
Lobular invasive	844	13.6	51	6.0		75	8.9		91	10.8		141	16.7	
Missing	172	2.7												
Tumor grade					< .001			< .001			< .001			< .001
1	231	3.9	10	4.3		17	7.4		19	8.2		28	12.1	
2	3,318	56.0	319	9.6		434	13.1		522	15.7		790	23.8	
3	2,380	40.1	530	22.3		685	28.8		771	32.4		939	39.5	
Missing	448	7.0												
ER status					< .001			< .001			< .001			< .001
Negative	2,268	37.6	590	26.0		754	33.2		843	37.2		1,022	45.1	
Positive	3,771	62.4	287	7.6		413	11.0		501	13.3		785	20.8	
Missing	338	5.3												
PgR status					< .001			< .001			< .001			< .001
Negative	2,794	46.3	640	22.9		834	29.8		952	34.1		1,179	42.2	
Positive	3,235	53.7	238	7.4		334	10.3		392	12.1		626	19.4	
Missing	348	5.5												
HER2 status					< .001			< .001			< .001			< .001
Negative	3,060	69.8	454	14.8		557	18.2		644	21.0		889	29.1	
Positive without trastuzumab	665	15.2	119	17.9		155	23.3		185	27.8		255	38.3	
Positive with trastuzumab	662	15.1	181	27.3		271	40.9		295	44.6		370	55.9	
Missing	1,990	31.2												
Subtype					< .001			< .001			< .001			< .001
Luminal A	1,637	39.0	105	6.4		146	8.9		184	11.2		312	19.1	
Luminal B/HER2 negative	357	8.5	40	11.2		55	15.4		63	17.6		96	26.9	
Luminal B/HER2 positive without trastuzumab	395	9.4	47	11.9		68	17.2		83	21.0		122	30.9	
Luminal B/HER2 positive with trastuzumab	356	8.5	79	22.2		115	32.3		123	34.6		173	48.6	
HER2 positive (nonluminal) without trastuzumab	239	5.7	66	27.6		79	33.1		93	38.9		122	51.0	
HER2 positive (nonluminal) with trastuzumab	298	7.1	98	32.9		152	51.0		168	56.4		191	64.1	
Triple negative	911	21.7	282	31.0		326	35.8		362	39.7		440	48.3	
Missing	2,184	34.2												

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR pathologic complete response; PgR, progesterone receptor.

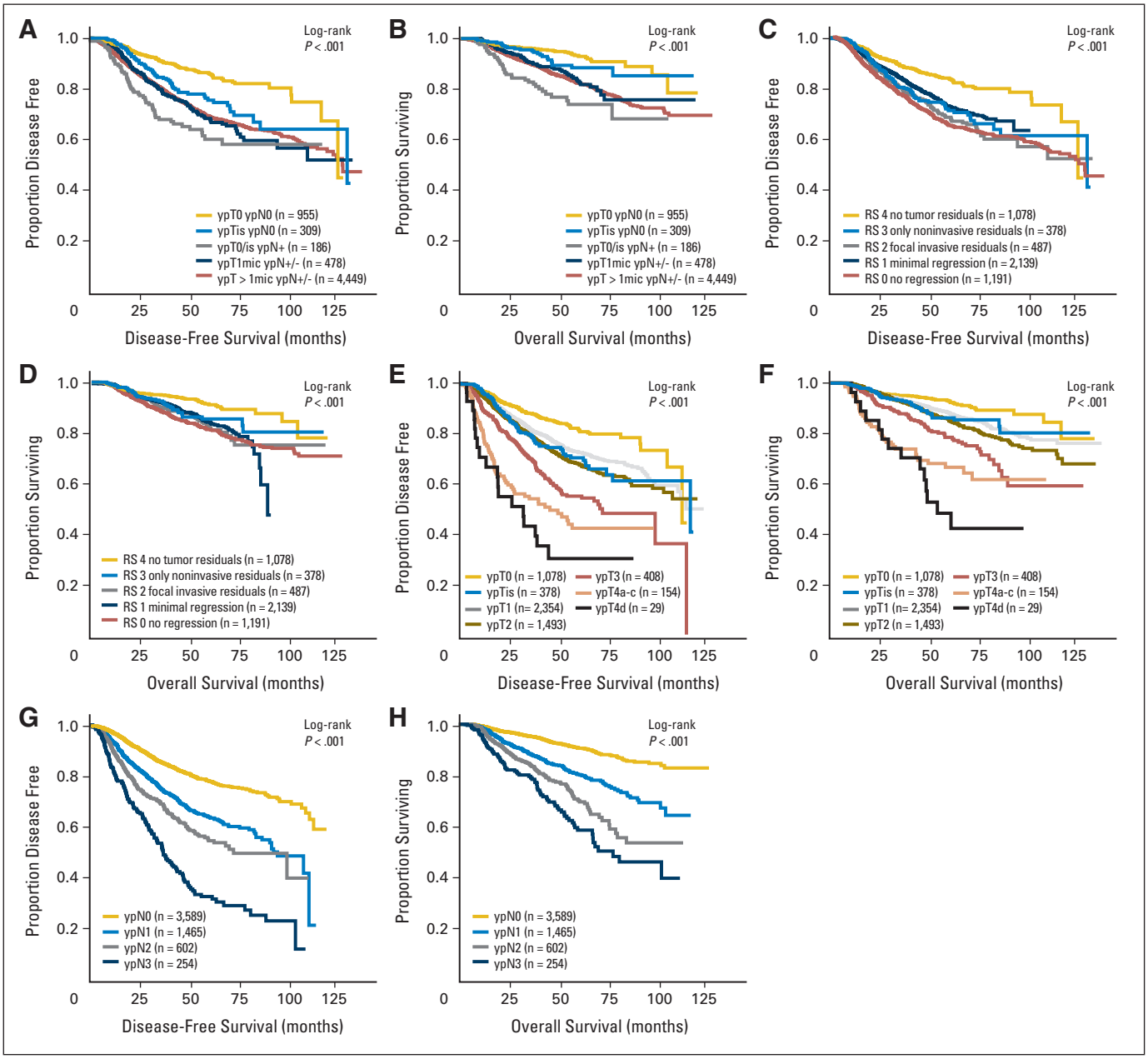

Fig 1. Prognostic impact of various definitions of pathologic complete response on survival. (A) Disease-free (DFS) and (B) overall survival (OS) in 6,377 patients according to no residual tumor (ypT0 ypN0), noninvasive residuals only (ypTis ypN0), and invasive residual in breast or nodes (ypT≥1 or ypN+); (C) DFS and (D) OS in 5,273 patients according to histologic breast regression score; (E) DFS and (F) OS in 5,894 patients according to postoperative tumor size (ypT stage); (G) DFS and (H) OS in 5,910 patients according to postoperative nodal (ypN) stage. RS, regression score.

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, 1.41; 95% CI, 0.87 to 2.29; $P = .166$). Their prognosis was also better than that of patients with ypT0/is ypN+ (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

Table 2. Prognostic Impact of Residual Disease Scoring Systems on DFS and OS

Score	All Patients No.	All Patients %	No. of Patients With Event	DFS HR	DFS 95% CI	DFS *P**	No. of Patients Who Died	OS HR	OS 95% CI	OS *P**
pCR definition	6,377									
ypT0 ypN0	955	15.0	112	1.0			50	1.0		
ypTis ypN0	309	4.8	65	1.74	1.28 to 2.36	< .001	24	1.41	0.87 to 2.29	.166
ypT0/is ypN+	186	2.9	57	3.18	2.31 to 4.38	< .001	35	4.05	2.63 to 6.24	< .001
ypT1mic ypN0/+	478	7.5	125	2.33	1.81 to 3.01	< .001	59	2.34	1.61 to 3.41	< .001
ypT>1mic ypN0/+	4,449	69.8	1,108	2.24	1.84 to 2.72	< .001	607	2.54	1.90 to 3.39	< .001
ypT staging system	5,894									
ypT0	1,078	18.3	145	1.0			69	1.0		
ypTis	378	6.4	90	1.78	1.37 to 2.31	< .001	40	1.61	1.09 to 2.37	.017
ypT1	2,354	39.9	514	1.56	1.29 to 1.87	< .001	255	1.53	1.17 to 1.99	.002
ypT2	1,493	25.3	377	1.86	1.54 to 2.26	< .001	197	1.89	1.44 to 2.48	< .001
ypT3	408	6.9	144	2.96	2.35 to 3.72	< .001	76	2.97	2.14 to 4.11	< .001
ypT4a-c	154	2.6	66	4.62	3.45 to 6.18	< .001	40	5.01	3.39 to 7.4	< .001
ypT4d	29	0.5	18	6.74	4.13 to 11.08	< .001	14	7.97	4.49 to 14.16	< .001
ypN staging system	5,910									
ypN0	3,589	60.7	599	1.0			254	1.0		
ypN1	1,465	24.8	418	1.88	1.66 to 2.13	< .001	227	2.29	1.92 to 2.74	< .001
ypN2	602	10.2	199	2.50	2.13 to 2.94	< .001	130	3.64	2.4 to 4.50	< .001
ypN3	254	4.3	140	4.54	3.77 to 5.46	< .001	81	5.23	4.07 to 6.72	< .001
Histologic breast RS	5,273									
RS 4 (no viable tumor residuals)	1,078	20.4	145	1.0			69	1.0		
RS 3 (only noninvasive residuals)	378	7.2	90	2.21	1.82 to 2.68	< .001	40	2.13	1.62 to 2.81	< .001
RS 2 (only focal invasive residuals)	487	9.2	126	1.61	1.34 to 1.95	< .001	60	1.70	1.30 to 2.23	< .001
RS 1 (minimal signs of regression)	2,139	40.6	437	1.98	1.56 to 2.51	< .001	221	1.89	1.34 to 2.67	< .001
RS 0 (no signs of regression)	1,191	22.6	372	1.79	1.37 to 2.33	< .001	197	1.61	1.09 to 2.38	.017

Adjusted analyses of pCR definitions†	All Patients No.	All Patients %	No. of Patients With Event	DFS HR	DFS 95% CI	DFS *P**	No. of Patients Who Died	OS HR	OS 95% CI	OS *P**
GBG	3,938									
ypT0 ypN0	645	16.4	58	1.0			16	1.0		
No pCR	3,293	83.6	735	4.04	3.07 to 5.31	< .001	371	7.39	4.45 to 12.3	< .001
MD Anderson	3,938									
ypT0/is ypN0	854	21.7	92	1.0			26	1.0		
No pCR	3,084	78.3	701	3.51	2.79 to 4.40	< .001	361	5.99	3.99 to 9.00	< .001
NSABP	3,938									
ypT0/is ypN0/+	979	24.9	131	1.0			48	1.0		
No pCR	2,959	75.1	662	2.77	2.27 to 3.38	< .001	339	3.66	2.67 to 5.01	< .001
French	3,938									
ypT0/is/mic ypN0/+	1,340	34.0	221	1.0			303	1.0		
No pCR	2,598	66.0	572	2.11	1.78 to 2.49	< .001	84	2.80	2.17 to 3.60	< .001

Abbreviations: DFS, disease-free survival; GBG, German Breast Group; HR, hazard ratio; NSABP, National Surgical Breast and Bowel Project; OS, overall survival; pCR, pathologic complete response; RS, regression score.
**P* values refer to pairwise comparison of each group with reference group.
†Adjusted by multivariate Cox regression analyses including all factors, as categorized in Table 1.

patients with or without pCR according to the various pCR definitions was highest for ypT0 ypN0 (4.04) and decreased monotonously for ypT0/is ypN0 (3.51), ypT0/is ypN0/+ (2.77), and ypT0/is/mic ypN0/+ (2.11).

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).

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,

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

Baseline Characteristic	No. of Patients	No. of Patients With Event	DFS HR†	DFS 95% CI	DFS *P*†	No. of Patients Who Died	OS HR†	OS 95% CI	OS *P*†
Age, years									
< 35	404	98	2.91	1.56 to 5.46	.001	49	1.88	0.84 to 4.18	.124
35-39	640	168	1.59	1.00 to 2.51	.048	83	2.76	1.20 to 6.35	.016
40-49	2,109	460	2.15	1.54 to 3.00	< .001	228	2.38	1.43 to 3.95	.001
50-59	1,901	424	2.52	1.68 to 3.78	< .001	217	2.11	1.23 to 3.63	.007
≥ 60	1,323	317	2.60	1.60 to 4.25	< .001	198	3.84	1.80 to 8.16	< .001
Tumor stage									
cT1	216	51	1.49	0.67 to 3.32	.32	25	2.54	0.60 to 10.79	.207
cT2	4,277	840	2.17	1.70 to 2.76	< .001	412	2.69	1.82 to 3.98	< .001
cT3	1,060	296	2.31	1.37 to 3.88	.002	160	2.99	1.32 to 6.76	.009
cT4a-c	465	143	2.05	1.04 to 4.02	.037	88	1.24	0.60 to 2.57	.559
cT4d	294	123	2.24	1.05 to 4.81	.038	80	1.72	0.69 to 4.24	.242
Nodal status									
cN0	3,056	527	1.98	1.42 to 2.76	< .001	246	1.85	1.14 to 2.99	.01
cN1	2,810	760	2.19	1.67 to 2.88	< .001	412	2.30	1.56 to 3.41	< .001
cN2	285	103	4.59	1.68 to 12.54	.001	62	21.17	1 to 748	.002
cN3	92	52	29.0	0.12 to > 1,000	.051	38	39.97	0.12 to > 1,000	.04
Histologic type									
Ductal invasive	4,972	1,145	2.36	1.90 to 2.92	< .001	589	2.65	1.90 to 3.66	< .001
Other type	389	97	3.04	1.47 to 6.27	.003	55	4.41	1.40 to 14.14	.012
Lobular invasive	844	188	1.13	0.60 to 2.15	.70	102	1.22	0.50 to 2.99	.666
Tumor grade									
1	231	34	0.80	0.19 to 3.35	.76	14	21.46	0 to > 1,000	.6
2	3,318	693	1.47	1.08 to 1.99	.014	345	1.68	1.05 to 2.70	.03
3	2,380	652	3.61	2.74 to 4.75	< .001	364	3.93	2.64 to 5.86	< .001
ER status									
Negative	2,268	653	4.20	3.22 to 5.48	< .001	398	5.52	3.71 to 8.22	< .001
Positive	3,771	734	1.26	0.92 to 1.71	.14	326	1.25	0.78 to 2.01	.36
PgR status									
Negative	2,794	779	3.38	2.65 to 4.31	< .001	441	4.04	2.82 to 5.79	< .001
Positive	3,235	607	1.37	0.96 to 1.97	.08	282	1.53	0.86 to 2.73	.15
HER2 status									
Negative	3,060	605	2.98	2.13 to 4.15	< .001	324	4.15	2.43 to 7.09	< .001
Positive without trastuzumab	665	153	2.10	1.27 to 3.48	.004	84	2.05	1.03 to 4.10	.04
Positive with trastuzumab	662	124	2.85	1.69 to 4.83	< .001	36	14.11	1.93 to 103.03	.009
Subtype									
Luminal A	1,637	240	1.305	0.71 to 2.39	.39	100	1.16	0.47 to 2.85	.75
Luminal B/HER2 negative	357	79	5.950	1.46 to 24.25	.013	38	5.13	0.70 to 37.43	.11
Luminal B/HER2 positive without trastuzumab	395	80	1.180	0.59 to 2.36	.64	38	0.94	0.37 to 2.41	.90
Luminal B/HER2 positive with trastuzumab	356	62	1.227	0.63 to 2.37	.54	11	29.72	0.63 to > 1,000	.28
HER2 positive (nonluminal) without trastuzumab	239	68	3.953	1.89 to 8.28	< .001	43	4.91	1.75 to 13.77	.002
HER2 positive (nonluminal) with trastuzumab	298	60	8.738	3.17 to 24.12	< .001	25	13.80	1.87 to 102	.01
Triple negative	911	253	6.020	3.92 to 9.25	< .001	161	12.41	5.82 to 26.49	< .001

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor.

*Group size listed in Table 2.

†HRs and *P* values refer to comparison of survival in patients with or without pathologic complete response.

tumor size, nodal status, or HER2 status (Table 3). Nonsignificant trends for DFS or OS were found only in small subpopulations (eg, patients age < 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

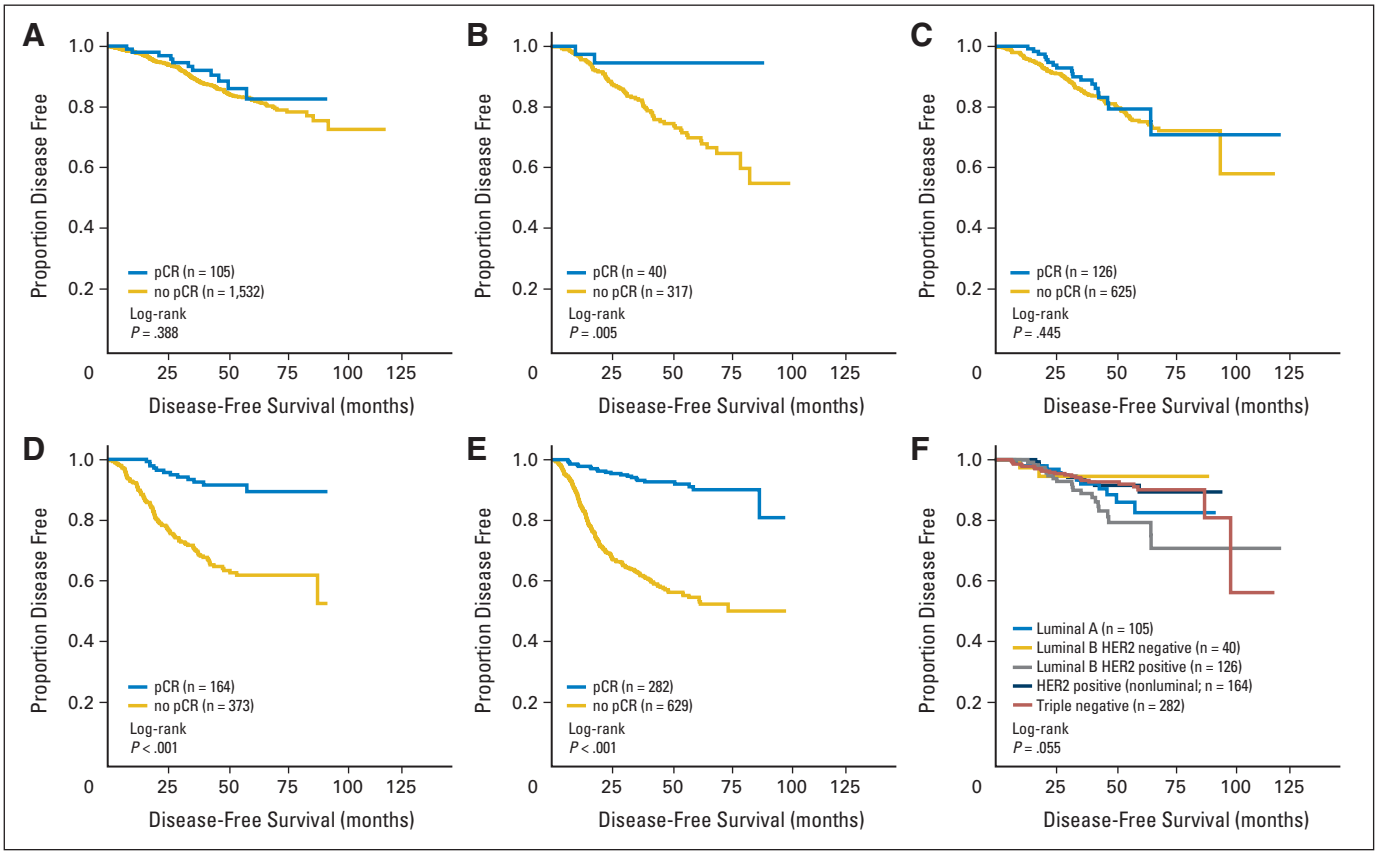

Fig 2. Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. (A) Patients with luminal A–like tumors, (B) luminal B/human epidermal growth factor receptor 2 (HER2) –negative–like tumors, (C) luminal B/HER2-positive–like tumors, (D) HER2-positive (nonluminal) –like tumors, and (E) triple-negative tumors; (F) comparison of DFS in 717 patients achieving pCR according to breast cancer intrinsic subtype.

HER2-positive or TN tumors[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,[11,28,29] but similar outcomes were observed in the adjuvant trastuzumab studies.[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.[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.[31] Other analyses have failed to show correlation between different pCR definitions and outcome, possibly because of small sample sizes.[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,[34] grading by Miller-Payne[35]). 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 patients 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 (nonluminal), TN, and luminal B/HER2-negative tumors but not for luminal B/HER2-positive and luminal A tumors.

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