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Pathologic Complete Response as a Prognostic and Surrogate Endpoint in Neoadjuvant Therapy for Solid Tumors: A Comprehensive Review Beyond Breast Cancer

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Abstract

Background: Neoadjuvant therapy is increasingly used across solid tumors to improve surgical outcome, assess systemic treatment sensitivity, and reduce early metastatic risk. Pathologic complete response (pCR), defined as the absence of residual invasive cancer following neoadjuvant treatment, has been accepted by the U.S. Food and Drug Administration (FDA) as a surrogate endpoint to support accelerated approval in high-risk early-stage breast cancer. However, the strength and generalizability of the association between pCR and long-term clinical outcomes, such as event-free survival (EFS) and overall survival (OS), vary substantially across tumor types and disease subgroups.

Methods: We evaluated recent meta-analyses, randomized trials, and large retrospective studies examining the association between pCR and survival outcomes, including EFS, OS, and recurrence-free survival (RFS), across multiple tumor types (ie. breast cancer, non-small cell lung cancer, melanoma, gastrointestinal malignancies, head and neck cancer, ovarian cancer, bladder cancer, and Merkel cell carcinoma).

Results: In breast cancer, pCR strongly predicts improved EFS and OS, particularly in triple-negative and HER2-positive subtypes, while its predictive value is less pronounced in HR+/HER2- disease. Emerging evidence supports pCR as a prognostic marker in melanoma, NSCLC, gastrointestinal, ovarian, head and neck squamous cell carcinoma, and muscle-invasive bladder cancers, though trial-level correlations vary and data remain limited in several settings. Associations are generally stronger in patient-level analyses than trial-level surrogacy assessments.

Conclusions: These findings highlight both the clinical value and the limitations of pCR as an endpoint. Continued tumor-specific evaluation of pCR using rigorous patient- and trial-level statistical frameworks is warranted to inform regulatory decision-making and optimize neoadjuvant drug development beyond breast cancer.

Keywords: *Pathologic complete response, Breast cancer, Head and neck cancer, Melanoma, NSCLC, Esophageal cancer, Gastrointestinal cancer, Ovarian, Bladder cancer, Merkel cell carcinoma*

Introduction

Neoadjuvant therapies have become a cornerstone in the management of multiple solid tumors, with potential to downstage disease, improve surgical resectability, provide early assessment of treatment sensitivity, and eradicate micrometastatic progression before surgery. With the expansion of neoadjuvant approaches to include targeted therapies and immunotherapies, the identification of robust intermediate endpoints that predict long-term clinical benefit has gained critical importance.

pCR, defined as the absence of residual invasive cancer cells in the resected primary tumor and sampled regional lymph nodes following neoadjuvant treatment (typically ypT0/is ypN0), has been recognized by the FDA as a surrogate endpoint to support accelerated approval specifically in high-risk early-stage breast cancer. Its use in other tumors is exploratory and not validated broadly for regular approval. This position is articulated in the current FDA guidance, *Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval* [1]. The 2020 revision reflects FDA's updated thinking and provides recommendations for trial design, statistical considerations, and acceptable pCR definitions in the neoadjuvant breast cancer setting. This regulatory precedent has motivated growing interest in evaluating pCR as a potential surrogate endpoint in additional tumor types, although its predictive value varies considerably across diseases.

Clinical practice guidelines also reflect the evolving role of treatment response in neoadjuvant care. Recent versions of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology incorporate neoadjuvant systemic therapy pathways and acknowledge that the degree of treatment response—including clinical and pathological response—can inform postoperative management in specific settings. In breast cancer (NCCN Breast Cancer Version 5.2025), neoadjuvant therapy is strongly recommended for HER2-positive and triple-negative subtypes, with the extent of response (including pCR) refining adjuvant treatment decisions, consistent with evidence linking pCR to improved long-term outcomes. In rectal cancer (NCCN Rectal Cancer Version 4.2025), guidelines endorse consideration of nonoperative "watch-and-wait" management for carefully selected patients demonstrating a clinical complete response after neoadjuvant chemoradiation, underscoring the prognostic importance of response assessment even when not strictly defined pathologically [2,3]. For esophageal and gastroesophageal junction cancers (NCCN Esophageal/EGJ Cancers Version 1.2026), pathologic evaluation after neoadjuvant chemoradiotherapy is recommended as part of postoperative planning. NCCN Bladder Cancer (v3.2025) recognizes pCR post-neoadjuvant chemotherapy as prognostic but not a formal decision criterion. NCCN Cutaneous Melanoma (v2.2025) notes pCR/MPR as prognostic, informing de-escalation in responders but not standardized. NCCN NSCLC (v3.2026) emphasizes neoadjuvant chemo-immunotherapy with pCR/MPR as prognostic (e.g., CheckMate-816: pCR patients 95.3% (95% CI 82.7–98.8) 5-year OS) but not mandatory for decisions.

This review synthesizes the available evidence assessing the association between pCR and long-term survival outcomes across multiple solid tumors. We examine both patient-level prognostic associations, where pCR consistently correlates with favorable outcomes, and trial-level surrogacy analyses, where correlations between treatment effects on pCR and survival endpoints are more variable. By integrating data across tumor types, our objective is to provide a balanced and rigorous framework for evaluating the strengths, limitations, and future potential of pCR as an endpoint to guide neoadjuvant drug development, clinical trial design, and regulatory strategies beyond breast cancer.

Material and Methods

A comprehensive systematic literature review was conducted using databases including PubMed, EMBASE, and the Cochrane Library from database inception through December 2025. The literature consists of meta-analyses, randomized clinical trials, and clinical studies evaluating associations between pCR and survival outcomes. Both patient-level and trial-level associations were included if reported.

Results

Breast Cancer

In breast cancer, achieving pCR is strongly associated with improved long-term outcomes, including EFS, disease-free survival (DFS), and OS. A large pooled meta-analysis of 52 studies involving 27,895 patients treated with neoadjuvant therapy demonstrated a robust association between pCR and improved EFS across major subtypes—triple-negative breast cancer (TNBC), HER2-positive disease, and hormone receptor-positive/HER2-negative (HR+/HER2-) disease. Across the entire population, 5-year EFS was 88% in patients achieving pCR compared with 67% in those without pCR, underscoring the prognostic significance of pCR irrespective of subtype (Table 1) [4]. While pCR is a strong patient-level prognostic marker, trial-level surrogacy is weak in some analyses; for example, a meta-regression across 29 randomized trials showed only modest correlation between treatment effects on pCR and DFS ($R^2 = 0.08$) or OS ($R^2 = 0.09$), highlighting variability by subtype and regimen [5].

Subtype-specific analyses further reinforce this relationship. In HER2-positive early breast cancer, a systematic review and meta-analysis of 78 studies (25,150 patients) showed that pCR was associated with significant improvements in survival outcomes, with hazard

Table 1: Breast Cancer

Study	Number of Patients	Number of Trials	Summary of Findings
von Minckwitz et al., 2012 [8]	6,377	7	• ypT0 ypN0 is associated with better DFS compared to ypTis ypN0 (HR = 0.57) and better OS (HR = 0.71) • ypT0 ypN0 is associated with better DFS (HR = 0.31) and OS (HR = 0..25) than ypT0/is ypN+ • Prognostic impact strongest in HER2+ and TNBC; absent in luminal A
Berruti et al., 2014 [5]	14,641	29	• Weak trial-level association between pCR and DFS ($R^2 = 0.08$) or OS ($R^2 = 0.09$)
Broglio et al., 2016 [9]	5,768	36	• HER2+ Breast Cancer: EFS for pCR vs non-pCR was significant (HR = 0.37). Hormone receptor-negative (HR = 0.29); hormone receptor-positive (HR = 0.52).
Cortazar et al., 2014 [7]	11,955	12	• For pCR vs non-PCR: ◦ Overall population: EFS: HR 0.48; OS: HR 0.36 ◦ HR-pos HER2-neg: EFS: HR 0.49; OS: HR 0.43 ◦ HER2-pos: EFS: HR 0.39; OS: HR 0.34 ◦ HR-neg: EFS HR 0.25, OS HR 0.19. ◦ TNBC: EFS HR 0.24; $R^2 = 0.03$ and 0.24 for EFS and OS.
Spring et al., 2020 [4]	27,895	52	• 5-yr EFS: 88% (pCR) vs 67% (no pCR) • Patients with a pCR after NAT had significantly better EFS (HR = 0.31), particularly for TNBC (HR = 0.18) and HER2-pos (HR = 0.32) disease. • pCR after NAT was also associated with improved survival (HR = 0.22).
Huang et al., 2020 [10]	4,330	25	• TNBC: pCR was associated with improved EFS (HR = 0.24) and OS (HR = 0.19). • The 5-year EFS was 86% vs 50% for pCR vs no pCR. • The 5-year OS was 92% vs 58% for pCR vs no pCR.
Davey et al., 2022 [6]	25,150	78	• HER2-pos: pCR predicted better EFS (HR 0.67; 41 studies), RFS (HR 0.69; 18 studies) and OS (HR 0.63; 29 studies).

ratios of 0.67 (95% CI 0.60–0.74) for EFS and 0.63 (95% CI 0.56–0.70) for OS. These benefits were consistent across various HER2-targeted regimens, though the magnitude was greatest in hormone receptor-negative HER2-positive disease [6].

A landmark systematic review and pooled analysis of approximately 12,000 patients from 12 international trials (CTNeoBC) demonstrated that pCR rates vary substantially by subtype: highest in HER2-positive (particularly HR-/HER2+) and TNBC, and lowest in HR+/HER2- disease [7]. Although the association between pCR and long-term outcomes was weaker in HR+/HER2- tumors overall, achievement of pCR in this subgroup still correlated with significantly better EFS and OS, particularly among high-grade tumors. In HER2-positive disease, pCR strongly predicted improved EFS and OS regardless of hormone receptor status, with a more pronounced prognostic effect in HR-/HER2+ tumors than in HR+/HER2+ tumors. Across all subtypes, the collective evidence positions pCR as a strong prognostic marker, with the greatest clinical relevance in TNBC and HER2-positive disease, where both absolute pCR rates and survival correlations are highest.

Non-Small Cell Lung Cancer (NSCLC)

In resectable NSCLC, pCR is a strong patient-level prognostic marker. A meta-analysis of 7,011 patients treated with neoadjuvant chemotherapy (± radiotherapy) showed that pCR was associated with significantly improved outcomes (EFS HR 0.46; OS HR 0.50) [11]. With the introduction of neoadjuvant chemo-immunotherapy, a meta-analysis of eight randomized trials (3,387 patients) demonstrated higher pCR rates (RR 5.58) and improved 2-year EFS (HR 0.57) compared with chemotherapy alone (Table 2) [12].

A recent surrogacy analysis of seven immune checkpoint inhibitor trials (2,385 patients) found a strong patient-level correlation between pCR and 2-year EFS (R^2=0.82), although trial-level surrogacy was only moderate and imprecise (R^2=0.82) [13]. A larger pooled analysis reported weaker trial-level correlations (R^2=0.045 for OS; 0.319 for EFS) [14].

Long-term observational data also support pCR as a prognostic marker. In a 403-patient stage IIIA–IIIC cohort treated with induction chemotherapy, concurrent chemoradiation, and surgery, pCR occurred in 34% and independently predicted improved survival (OS HR 0.27; EFS HR 0.35) [15]. pCR rates were higher in squamous tumors (46%) than non-squamous (27%).

Updated results from major perioperative trials further reinforce this association. In the final 5-year analysis of CheckMate 816, overall 5-year OS was 65.4% in the nivolumab-chemotherapy arm versus 55.0% with chemotherapy alone (HR 0.72, P=0.048). In exploratory subgroup analyses, patients achieving pCR had a 5-year OS of 95.3% (95% CI 82.7–98.8) compared with 55.7% (95% CI 46.9–63.7) in those without pCR [16]. Similar patterns have been observed in AEGEAN and KEYNOTE-671, where higher pCR/MPR rates parallel sustained EFS benefits [17,18].

Ongoing IASLC initiatives continue to standardize pCR/MPR assessment and evaluate their potential as surrogate endpoints for regulatory use in resectable NSCLC.

Melanoma

In resectable stage III melanoma, neoadjuvant immunotherapy—particularly dual checkpoint blockade with PD-1 and CTLA-4 inhibitors—induces high pathologic response rates with strong prognostic value. In the OpACIN-neo trial, interobserver agreement for pathologic response assessment was excellent (κ = 0.879; ICC = 0.965), and patients achieving a pathologic response (<50% viable tumor) had markedly improved outcomes, with 3-year recurrence-free survival (RFS) of 95% versus 37% in non-responders (P < 0.001). An immune-active fibrosis-rich subtype further predicted absence of recurrence and prolonged RFS. Long-term follow-up from the combined OpACIN and OpACIN-neo trials confirmed durable benefit, with pathologic response remaining the strongest predictor of low relapse risk [19,20].

Single-agent PD-1 therapy demonstrates similar prognostic patterns. In a phase Ib trial of neoadjuvant pembrolizumab followed by adjuvant pembrolizumab, no deaths occurred among patients achieving major pathologic response (MPR) or pCR, yielding a 5-year OS of 100% compared with 72.8% in non-MPR patients [21].

Pooled analyses from the International Neoadjuvant Melanoma Consortium (INMC; n = 818) further confirm the prognostic value of pathologic response. In the updated INMC pooled dataset presented at ESMO 2024, patients achieving major or complete pathologic response had 3-year recurrence-free survival of 89%, demonstrating durable disease control across neoadjuvant regimens [22] (Table 3).

Recent phase 3 data further validate neoadjuvant immunotherapy. In the NADINA trial, neoadjuvant nivolumab plus ipilimumab followed by response-adapted adjuvant therapy significantly improved

Table 2: Non-small cell lung cancer.

Study	Number of Patients	Number of Trials	Summary of Findings
Rosner et al., 2022 [11]	7,011	28	• pCR vs non-pCR: OS HR 0.50; EFS HR 0.46
Banna et al., 2024 [12]	3,387	8	• Neoadjuvant chemo-immunotherapy compared to chemo: improved 2-year EFS (HR 0.57) and increased pCR rate (RR 5.58). • No reports were provided about the comparison of EFS for pCR vs non-pCR patients.
Hines et al. 2024 [13]	2,385	7	• At the patient level, the R^2 of pCR with 2-year EFS was 0.82. The odds ratio of 2-year EFS rates by response status was 0.12 (0.07–0.19). • At the trial level, the R^2 for the association of odds ratio of response and HR of EFS was 0.58.
Waser et al., 2024 [14]	6,530	20	• pCR vs no pCR: HR = 0.49 for OS • MPR vs no MPR: HR = 0.36 for OS • pCR vs no pCR: HR = 0.49 for EFS (11 studies, n=2,156) • Trial-level analyses did not show a strong correlation between pCR and OS (R^2 = 0.045) or EFS (R^2 = 0.319).
CheckMate 816 5-yr update [15]	358	1	• pCR vs non-pCR: 5-yr OS 95.3% (95% CI 82.7-98.8) vs 55.7% (95% CI 46.9-63.7) (exploratory) • Pre-surgery ctDNA clearance vs others: 5-yr OS 75.0% vs 52.6%

Table 3: Melanoma and Merkel Cell Carcinoma.

Study	Number of Patients	Number of Trials	Summary of Findings
OpACIN-neo trial [20]	86	1	**Melanoma:** • Pathologic response (<50% viable tumor, including pCR + near-pCR/MPR) achieved in ~74–78% (regimen-dependent; 77% in optimal arm). • pCR (0% viable tumor) in substantial subset (~20–47% across arms). • Estimated 3-year RFS 95% for pathologic responders vs 37% for non-responders (P < 0.001) after median 47-month follow-up.
Study NCT02434354 [21]	30	1	**Melanoma:** • 5-yr OS 100% in MPR/pCR vs 72.8% in non-MPR; no deaths in MPR/pCR
NADINA [23]	423	1	**Melanoma:** • Neoadjuvant nivo+ipi: MPR 59%; 12-mo RFS 95.1% MPR vs 57% non-response; 2-yr EFS 77.3% (HR 0.32–0.40 vs adjuvant nivo) • pCR associated with 5-year EFS of 83% vs. 53% for non-pCR; 5-year OS of 89% vs. 64% for non-pCR • Updated 2-year data (ESMO 2025) show 24-month EFS 77.3% (HR 0.40; 95% CI 0.28-0.57; P<0.001) and DMFS 82.8% (HR 0.43; 95% CI 0.29-0.64; P<0.001) for neoadjuvant vs adjuvant. MPR (59%) strongly predicted 12-month RFS (95.1% vs 57%).
INMC pooled (ESMO 2024) [22]	818	1	**Melanoma:** • 633 (77%) trial pts and 185 (23%) real-world pts • MPR rates 46% (PD-1 mono), 62% (PD-1+CTLA-4), 67% (PD-1+LAG-3); 3-year RFS 89% in MPR achievers (highest prognostic marker). 3-year EFS 64% (PD-1 alone), 76–77% (PD-1+CTLA-4), 82% (PD-1+LAG-3).
PRADO [24]	99	1	**Melanoma:** MPR in 61/99 (61.6%), including pCR in 41/99 (41.4%). MPR patients underwent de-escalated surgery and omitted adjuvant therapy. 2-year RFS was 93% (95% CI 86–100%) in MPR patients.
SWOG S1801 [25]	313	1	**Melanoma:** 2-year EFS 72% with neoadjuvant-adjuvant pembrolizumab vs 49% with adjuvant-only pembrolizumab (HR 0.58; 95% CI 0.39–0.87; P = 0.004).
CheckMate 358 [63]	36	1	**Merkel Cell Carcinoma:** • Neoadjuvant nivolumab: pCR 47.2% (17/36); • no relapses in pCR patients at 19.3-month median post-op follow-up. • RFS at 12 months: 100% vs 59.6% (pCR vs non-pCR); at 24 months: 88.9% vs 52.2%; RFS HR 0.12.

EFS (HR 0.32–0.40 vs adjuvant nivolumab) with an MPR rate of 59%, which strongly predicted outcomes (12-month RFS 95.1% vs 57%) [23]. The PRADO extension showed that MPR enabled de-escalated surgery, with 2-year RFS of 93% in responders [24]. SWOG S1801 similarly demonstrated EFS superiority for neoadjuvant-adjuvant pembrolizumab over adjuvant-only therapy [25].

NCCN Cutaneous Melanoma Guidelines (Version 2.2025) now endorse neoadjuvant immune checkpoint inhibition for resectable stage IIIB–IIID disease and recognize pCR/MPR as important prognostic markers informing postoperative treatment intensity, though not yet validated surrogate endpoints.

Overall, achieving MPR or pCR after neoadjuvant immunotherapy predicts exceptional long-term RFS and OS in melanoma, supporting ongoing shifts toward response-adapted neoadjuvant strategies.

Merkel Cell Carcinoma

In Merkel cell carcinoma (MCC), a rare and aggressive neuroendocrine skin cancer, pCR after neoadjuvant immunotherapy is a strong patient-level prognostic marker, associated with prolonged RFS and excellent long-term outcomes in responders (Table 3).

Although data are limited by disease rarity, emerging evidence from neoadjuvant immune checkpoint inhibitor trials supports high pCR rates and favorable prognosis. In the phase I/II CheckMate 358 trial, neoadjuvant nivolumab (two doses) achieved a pCR rate of 47.2% (17/36 evaluable patients), with additional major pathologic responses observed. No patient achieving pCR experienced relapse at a median postoperative follow-up of 19.3 months, and RFS was markedly improved in responders (12- and 24-month RFS 100% and 88.9%, respectively) [63] (Table 3).

Supporting evidence from case reports and small series demonstrates similar findings with neoadjuvant avelumab, including complete pathologic responses and absence of recurrence at short-term follow-up [64].

Collectively, these findings highlight pCR/MPR as a robust prognostic indicator in resectable MCC treated with neoadjuvant immunotherapy, consistent with the tumor's high immunogenicity. However, trial-level surrogacy remains unestablished due to small cohorts, lack of randomized data, and limited long-term follow-up. Ongoing studies evaluating neoadjuvant combinations and response-adapted strategies may further clarify the clinical utility of pCR, including potential treatment de-escalation in complete responders.

Gastrointestinal Malignancies

In gastric and gastroesophageal junction (GEJ) cancers, pCR after neoadjuvant or perioperative therapy is associated with improved survival at the patient level, but trial-level surrogacy remains limited. Foundational perioperative chemotherapy trials first established modern treatment paradigms. The MAGIC trial (ISRCTN93793971) demonstrated improved 5-year overall survival (OS) with perioperative ECF (epirubicin, cisplatin, and 5-fluorouracil) versus surgery alone (36% vs 23%; HR 0.75; 95% CI 0.60–0.93; P = 0.009), showing pathologic downstaging but without pCR as a primary endpoint [26]. The FLOT4 trial established perioperative FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) as superior to ECF/ECX (epirubicin, cisplatin, and 5-fluorouracil or capecitabine), improving median OS (50 vs 35 months; HR 0.77; 95% CI 0.63–0.94; P = 0.012) and increasing pCR rates (16% vs 6%) (Table 4) [27].

Table 4: Gastrointestinal Cancers.

Study	Number of Patients	Number of Trials	Summary of Findings
MAGIC trial [26]	503	1	Gastroesophageal: • Improved 5-year OS 36% vs 23%; HR 0.75 (95% CI 0.60–0.93), P = 0.009. Significant pathologic T- and N-stage downstaging. pCR not prospectively assessed
FLOT4 Trial [27]	716	1	Gastric: • pCR rate: 16% (Becker Ia) with FLOT vs 6% with ECF/ECX (P<0.001 in phase 2 part; consistent in full trial). Higher major regression with FLOT.
MATTERHORN Trial [28]	948	1	Gastric: • pCR rate: 19.2% (95% CI 15.7-23.0) with durvalumab + FLOT vs 7.2% (95% CI 5.0-9.9) with FLOT alone (P<0.001). • Supports perioperative IO addition; linked to EFS/OS benefits
KEYNOTE-585 (2025 final update) [29]	804	1	Gastric: • pCR rate: 12.9% (95% CI 9.8-16.6) with perioperative pembrolizumab + chemo vs 2.0% (95% CI 0.9-3.9) with chemo alone (P<0.00001). • Final OS showed numerical improvement but non-significant EFS benefit (44.4 vs 25.7 mo; HR 0.81, 95% CI 0.67-0.98; did not meet prespecified threshold) and OS (71.8 vs 55.7 mo; HR 0.86, 95% CI 0.71-1.06; not significant); pCR prognostic but not strong trial-level surrogate.
Sugumar et al., 2025 [31]	11,882	25	Rectal: • No trial-level correlation. On meta-regression analysis, pCR was not correlated with OS (β = 0.37; 95% CI, -0.98 to 1.71; P = .57). • Similarly, pCR was not correlated with DFS (β = -0.84; 95% CI, -2.55 to 0.87; P = .32).
Smyth et al., 2016 [32]	330	1	**Gastroesophageal:** • Mandard TRG 1–2 vs 3–5: 5-year OS 58.8% vs 28.9%; HR 1.94, P = 0.021. Demonstrates prognostic value of histologic regression (retrospective).
Soro et al 2018 [33]	56		**Esophageal:** • pCR vs non-pCR: Median OS 4.1 vs 1.7 yrs; Median DFS 3.1 vs 1.1 yrs (P=0.04)
Murphy et al 2017 [34]	911	1	**Esophageal:** • pCR was associated with better OS (median 71.28 vs 35.87 mo) and higher 5-year OS rate 52% vs 41% compared to non-pCR; was also associated with better RFS (median 70.75 vs 26.07 mo).
Lin et al. 2018 [35]	68	1	**Esophageal:** • pCR is associated with higher 2-year OS rate 81.3% vs 58.3% (P = 0.025).
Wan et al 2019 [36]	6,780	21	Esophageal, esophagogastric junction AC, gastric AC, rectal cancer and pancreatic cancer: • pCR vs non-pCR: OS (HR = 0.50, P < 0.001) and DFS (HR = 0.49, P < 0.001). • In EGJAC/GAC, the correlation of pCR with OS was significant (HR = 0.38, p = 0.02).
Li et al. 2018 [37]	1,143	7	Gastric: • RR of pCR vs non-pCR is 0.5(p<0.0001), 0.34(p<0.0001), and 0.44 (p<0.0001) for 1, 3, 5-year-OS, respectively. • RR for 3-year DFS was 0.43 (p = 0.002)
Petrelli et al. 2017 [38]	10,050	22	Rectal: • Patient level: change of pCR is correlated weakly with change of OS 5-year rate (R^2 = 0.28). 3-year DFS rate and OS was similarly (R^2=0.37). Trial level: R^2 = 0.41 and 0.04 respectively.
Sun et al. 2025 [40]	8,040	38	**Esophageal:** • pCR vs non-pCR (esophageal, post-NCRT): OS HR 0.54 (95% CI 0.52-0.57); DFS HR 0.51 (95% CI 0.46-0.57). Strong patient-level prognostic association
RAPIDO Trial [41]	912	1	Rectal: • pCR rate: 28% with TNT vs 14% with standard CRT (OR 2.37; P < 0.001) • Disease-related treatment failure: 23.7% vs 30.4% (HR 0.75; P = 0.019) • TNT significantly increased pCR, but pCR showed limited trial-level surrogacy for long-term outcomes

Perioperative chemo-immunotherapy further increases pCR but demonstrates variable impact on survival. In MATTERHORN (NCT04592913), durvalumab plus FLOT doubled pCR rates (19.2% vs 7.2%; OR 3.12; 95% CI 2.23–4.37; P < 0.00001) and significantly improved event-free survival (EFS HR 0.71; 95% CI 0.58–0.86; P < 0.001), with final OS HR 0.78 (95% CI 0.63–0.96; P = 0.021) and FDA approval in November 2025 [28].

By contrast, KEYNOTE-585 (NCT03221426) significantly increased pCR with pembrolizumab plus chemotherapy (12.9% vs 2%) but did not achieve statistically significant EFS or OS improvement in final analyses. Final analysis (JCO 2025) showed non-significant EFS benefit (44.4 vs 25.7 mo; HR 0.81, 95% CI 0.67-0.98) and OS (71.8 vs 55.7 mo; HR 0.86, 95% CI 0.71-1.06), neither reaching protocol-defined significance [29]. The DANTE/FLOT8 trial (NCT03421288) reported enhanced histopathologic regression and downstaging with atezolizumab + FLOT versus FLOT alone, though survival follow-up remains ongoing [30].

In rectal cancer, pCR following neoadjuvant chemoradiotherapy (CRT) or total neoadjuvant therapy (TNT) strongly predicts individual patient outcomes—including improved DFS, OS, and reduced recurrence—but does not function as a reliable trial-level surrogate. A comprehensive meta-analysis of 25 randomized trials (11,882 patients) found no significant correlation between treatment-related increases in pCR and improvements in OS or DFS, indicating that pCR does not function as a validated surrogate endpoint in rectal cancer trials [31].

pCR after CRT or total TNT is a strong patient-level prognostic marker in locally advanced rectal cancer, associated with lower rates of local and distant recurrence and superior OS and DFS in responders compared with non-responders.

In high-risk disease, TNT regimens improve both pCR rates and long-term outcomes. The RAPIDO trial (short-course radiotherapy followed by consolidation chemotherapy vs long-course CRT) reported pCR occurred in 28% of patients in the TNT arm versus 14% in the standard CRT arm (OR 2.37; $P < 0.001$), and disease-related treatment failure was reduced to 23.7% versus 30.4% (HR 0.75; $P = 0.019$) [58]. The UNICANCER-PRODIGE 23 trial (neoadjuvant mFOLFIRINOX followed by CRT vs standard CRT) showed improved 3-year DFS (76% vs 69%; HR 0.69; $P = 0.034$) and higher pCR rates in the experimental arm [59]. These data support TNT as a standard of care for high-risk locally advanced rectal cancer.

pCR also has important clinical implications beyond prognosis. Patients achieving complete response may be candidates for organ-preservation strategies, including watch-and-wait approaches, which have been associated with favorable oncologic outcomes and avoidance of permanent stomas in carefully selected patients [2,3].

However, a systematic review and meta-analysis of 25 randomized trials (11,882 patients) found no significant trial-level association between treatment-related differences in pCR and OS or DFS, indicating that pCR does not function as a reliable surrogate endpoint for survival at the trial level [31]. Overall, pCR remains clinically valuable for individual risk stratification and for guiding organ-preservation strategies in selected patients, but current evidence does not support its validation as a surrogate endpoint for survival in rectal cancer trials.

Achievement of pCR after CRT is strongly associated with superior survival in esophageal cancer. In a CRT cohort of 56 patients, Soror et al. reported a median OS of 4.1 years in pCR patients versus 1.7 years in non-pCR patients, and median DFS of 3.1 years versus 1.1 years, respectively ($P = 0.04$) [33]. In a large trimodality series of 911 patients, Blum Murphy et al. observed significantly longer survival, with median OS of 71.3 months vs 35.9 months and median RFS of 70.8 months vs 26.1 months in pCR versus non-pCR patients (both $P < 0.01$) [34]. Similarly reported superior outcomes in patients achieving pCR, with 2-year OS of 81.3% vs 58.3% in non-pCR patients ($P = 0.025$) [35].

Earlier studies by Davies et al. [36], Meredith et al. [37], Donahue et al. [38], and Berger et al. [39] consistently demonstrated markedly improved long-term survival in patients achieving pCR. A 2025 meta-analysis confirmed strong patient-level associations between pCR and survival, with OS HR 0.54 and DFS HR 0.51, consistent across histologic subtypes [40]. A 2024 pooled analysis further showed that overall pCR rates after neoadjuvant therapy were below 30%, with higher pCR rates in squamous cell carcinoma (SCC) than adenocarcinoma [41].

Neoadjuvant immunochemotherapy (PD-1/PD-L1 inhibitors + chemotherapy ± RT) increases pCR and major pathologic response rates, particularly in SCC, although trial-level surrogacy for OS remains weak ($R^2 = 0.07$) [42]. Recent comparative cohorts report pCR rates of 20–30% and improved 3-year OS compared with standard CRT in selected stage III SCC [43].

Overall, pCR remains a meaningful patient-level prognostic marker across gastrointestinal malignancies, but its trial-level surrogacy is weak, supporting its use for risk stratification but not yet as a validated regulatory surrogate.

Head and Neck Cancer

In resectable head and neck squamous cell carcinoma (HNSCC), pCR or MPR after neoadjuvant immunotherapy is associated with substantially improved long-term outcomes at the patient level. Across early-phase trials of neoadjuvant anti-PD-1 agents, reported pCR rates range from10 to15%, and MPR rates range from 20% to 50% with strong prognostic implications [44-46]. In a neoadjuvant pembrolizumab study, pCR occurred in 10% of patients and MPR in 44%, and no recurrences were observed among patients achieving MPR, whereas recurrences occurred predominantly among non-responders [44]. In a phase II trial of nivolumab ± ipilimumab, 2-year DFS was 71% in responders vs 51% in non-responders, with MPR independently predicting better outcomes [45]. A 2021 meta-analysis of neoadjuvant ICI confirmed pCR/MPR linked to superior EFS and OS [46] (Table 5).

Recent phase III data (KEYNOTE-689, 2025) demonstrate improved EFS with perioperative pembrolizumab + standard care (surgery + adjuvant RT ± cisplatin) significantly improves EFS (3-year rates 57.6% vs 46.4%; HR reduction) versus standard care alone, with neoadjuvant pembrolizumab safe and not compromising surgery [47]). Updated meta-analyses (2024–2025) report pooled MPR or pCR rates ranging from 20% to 67% with ICI combinations (higher with chemoimmunotherapy), correlating with improved DFS/OS in responders, though chemoimmunotherapy increases grade 3–4 toxicity [48].

Table 5: Neoadjuvant Immunotherapy in Head and Neck Squamous Cell Carcinoma (HNSCC).

Study	Number of Patients	Number of Trials	Summary of Findings
NCT02296684 [44]	36	1	Pembrolizumab Neoadjuvant–Adjuvant Trial: pCR 10%; MPR 44%. No recurrences among MPR patients; recurrences confined to non-responders.
NCT02919683 [45]	29	1	Nivolumab ± Ipilimumab Neoadjuvant Trial: MPR 45%. 2-year DFS 71% (responders) vs 51% (non-responders). MPR independently predicted DFS and OS.
Shibata et al. 2021 [46]	382	17	Neoadjuvant ICI Systematic Review: Pooled pCR 12%; MPR 37%. pCR/MPR significantly associated with improved EFS and OS.
KEYNOTE-689 (NCT03765918) [47]	714	1	3-year EFS 57.6% vs 46.4% (perioperative pembrolizumab vs SOC); HR 0.73 (95% CI 0.58–0.92; $P = 0.008$). Neoadjuvant pembrolizumab did not compromise surgery.
Zandberg et al. 2025 [48]	624	9	Pooled IO Combination Analysis (2024–2025): MPR/pCR 20%–67% depending on regimen (highest with chemo-IO). Responders showed markedly longer DFS and OS; grade ≥3 toxicity higher with chemo-IO.

These data position pCR/MPR as a meaningful patient-level prognostic marker in HNSCC with neoadjuvant immunotherapy. However, trial-level surrogacy for OS remains unvalidated, and longer follow-up from randomized studies will be required before pathologic response can be accepted as a regulatory surrogate endpoint in this disease.

Ovarian Cancer

In advanced high-grade serous ovarian cancer, pCR after neoadjuvant chemotherapy (NACT) is uncommon (<5–10%) but, when achieved, is strongly associated with improved survival. Because true pCR is rare, most studies use the validated three-tier Chemotherapy Response Score (CRS), with CRS3 indicating complete or near-complete histologic response in the omentum and is considered the pathologic surrogate of chemosensitivity [49] (Table 6).

Across multiple cohorts, CRS3 consistently demonstrates robust prognostic value. In a 133-patient FIGO III/IV cohort, CRS3 was associated with significantly longer progression-free survival (median 24.8 months vs 16.7 months; $P < 0.001$) and improved overall survival ($P = 0.011$) compared with CRS1–2 [50]. Foundational work by Böhm et al first established CRS3 as a marker of favorable prognosis [49], and external validation cohorts-including Lee et al. [51], Singh et al. [52], Rajkumar et al. [53] and Cohen et al. [54] -consistently confirmed that CRS3 is associated with significantly prolonged PFS and OS relative to CRS1-2.

Although rare, pCR is likewise associated with substantially longer recurrence-free and overall survival (often by 12–24 months) compared with patients with residual disease. Recent systematic reviews and meta-analyses [55-57] reaffirm the strong patient-level prognostic value of CRS3 and pCR, but highlight persistent limitations for trial-level surrogacy, including low pCR incidence and variability in histopathologic scoring.

Overall, pCR/CRS3 represents a robust patient-level prognostic marker following NACT in advanced ovarian cancer and may help refine postoperative treatment strategies, while broader validation as a regulatory surrogate endpoint is still evolving.

Bladder Cancer

In muscle-invasive bladder cancer (MIBC), pCR after NAC is a strong patient-level prognostic marker, associated with markedly improved RFS and OS. Patients achieving pCR (ypT0N0) at radical cystectomy experience significantly lower recurrence and mortality risks compared with those with residual disease, reflecting highly chemo-sensitive and immunosensitive tumor biology.

Cisplatin-based neoadjuvant chemotherapy (NAC) established this paradigm. In SWOG 8710, neoadjuvant MVAC increased pCR rates to 38% compared with 15% with surgery alone and improved median overall survival (77 vs 46 months) [60]. Subsequent pooled series and meta-analyses consistently demonstrate 5-year OS exceeding 70–80% in ypT0 patients, compared with ~40–50% in patients with residual disease, confirming pCR as a robust patient-level prognostic marker [61] (Table 6).

Neoadjuvant immune checkpoint blockade has confirmed that immunotherapy-induced pCR also translates into durable survival benefit. In PURE-01, three cycles of pembrolizumab before cystectomy produced a pCR rate of 36.8%. At 3-year median follow-up, event-free survival was 74.4% and overall survival was 83.8%. Importantly, among patients achieving ypT0N0, 36-month recurrence-free survival was 96.3%, and 96.1% (95% CI, 89-100) for ypT1/a/isN0, 74.9% (95% CI, 60.2-93) for ypT2-4N0, and 58.3% (95% CI, 36.2-94.1) for ypTanyN1-3 response, demonstrating near-curative outcomes associated with immunotherapy-mediated tumor eradication [61]

Definitive evidence that increasing pathologic response translates

Table 6: Ovarian Cancer and Bladder Cancer.

Study	Number of Patients	Number of Trials	Summary of Findings
Bohm et al., 2015 [49]	98	1	**Ovarian:** • Development and validation of 3-tier CRS in high-grade serous ovarian carcinoma post-NACT. • CRS3 (complete/near-complete response) vs CRS1-2: prolonged PFS and OS (strong prognostic value, especially in omentum).
Marsh et al., 2025 [50]	133	1	**Ovarian (**FIGO III–IV Multicenter CRS Study**):** • CRS3 vs CRS1-2: median PFS 24.8 months vs shorter ($p < 0.001$); improved OS ($p = 0.011$). • Pathologic response to NACT significantly associated with better PFS/OS.
Choe et al. 2023 [55]	4,287	12	**Ovarian (**CRS Meta-analysis**):** • CRS3 and pCR: OS HR 0.48; PFS HR 0.52
Kim et al. 2024 [56]	5,231	15	**Ovarian (**CRS Meta-analysis**):** • CRS3 vs CRS1–2: OS HR 0.46; PFS HR 0.51
Bhandoria et al. 2024 [57]	3,942	10	**Ovarian:** • pCR vs residual disease: OS HR 0.41; RFS HR 0.44
SWOG 8710 (Grossman et al. 2003) [60]	307	1	**MIBC** (MVAC vs surgery)**:** • Neoadjuvant MVAC vs surgery alone: pCR (ypT0) 38% vs 15%; median OS 77 vs 46 months. Established pCR as a strong prognostic marker after cisplatin-based NAC.
PURE-01 (NCT02736266) [61]	155	1	**MIBC:** • Neoadjuvant pembrolizumab (3 cycles): pCR (ypT0N0) 36.8%. 36-month EFS 74.4%, OS 83.8%. 36-month RFS in ypT0N0: 96.3%, demonstrating near-curative outcomes in pCR patients.
NIAGARA [62]	1063	1	MIBC: • Durvalumab + gemcitabine-cisplatin vs GC alone: 24-mo EFS 67.8% vs 59.8% (HR 0.68; P<0.001); 24-mo OS 82.2% vs 75.2% (HR 0.75; P=0.01). First phase III trial showing that increasing pCR translates into improved survival.

into improved survival now comes from the phase III NIAGARA trial. In this perioperative study of durvalumab plus gemcitabine–cisplatin versus chemotherapy alone, the dual primary endpoints of pCR and EFS were met. At 24 months, EFS was 67.8% with durvalumab versus 59.8% with chemotherapy (HR 0.68; $P < 0.001$), and overall survival was 82.2% versus 75.2% (HR 0.75; $P = 0.01$), establishing perioperative immunochemotherapy as a new standard of care [62].

Taken together, pCR is a validated patient-level prognostic biomarker in MIBC across chemotherapy and immunotherapy platforms. PURE-01 demonstrates the durability of immunotherapy-induced pCR, while NIAGARA provides the first randomized evidence that increasing pCR translates into improved EFS and OS, strengthening the regulatory case for perioperative immunochemotherapy in bladder cancer.

Discussion

This review synthesizes the evidence supporting pCR as an intermediate endpoint in neoadjuvant therapy across solid tumors, with a focus on its prognostic significance and potential role as a surrogate for long-term clinical outcomes. At the patient level, pCR is consistently associated with improved outcomes across tumors. However, trial-level surrogacy is weak or absent in rectal cancer (no correlation per Sugumar 2025), moderate but imprecise in NSCLC (R^2=0.58 per Hines 2024; weaker per Waser 2024), and limited elsewhere due to data immaturity. Regulatory use beyond breast cancer requires tumor-specific validation. The association is most robust and reproducible in breast cancer, particularly in triple-negative and HER2-positive subtypes, and is also well supported in melanoma, NSCLC, muscle-invasive bladder cancer, and head and HNSCC. Emerging evidence suggests comparable prognostic relevance in ovarian cancer using near-complete response metrics such as Chemotherapy Response Score 3 [CRS3]), as well as in Merkel cell carcinoma, and selected gastrointestinal malignancies including gastric, gastroesophageal junction, rectal, esophageal. Notably, the strength of the association between pCR and long-term outcomes varies substantially by tumor biology, molecular subtype, and treatment modality, with the most pronounced effects observed in immunogenic tumors treated with immune checkpoint inhibitors.

From a regulatory standpoint, the FDA's acceptance of pCR as an endpoint reasonably likely to predict clinical benefit—most notably in high-risk, early-stage breast cancer—rests on a combination of strong patient-level prognostic associations and supportive trial-level surrogacy. Outside this validated setting, however, pCR does not yet meet the evidentiary standard required for broad regulatory reliance. Although patient-level correlations between pCR and survival outcomes remain consistent across many tumor types, trial-level surrogacy-defined as the extent to which treatment-induced improvements in pCR reliably translate into proportional gains in long-term survival has been weak, inconsistent, or absent in several malignancies. For example, meta-regression analyses have failed to demonstrate significant trial-level correlations in rectal cancer, have yielded modest and imprecise estimates in NSCLC, and remain severely limited in rare tumor types due to small sample size and a paucity of randomized neoadjuvant trials.

This fundamental distinction between prognostic utility and surrogate validity carries critical implications for both trial design and regulatory decision-making. pCR is clinically valuable for risk stratification, response-adapted management (e.g., watch-and-wait in rectal cancer, de-escalation in melanoma or Merkel cell carcinoma), and organ preservation paradigms. However, in most settings, pCR alone is insufficient to support claims of clinical benefit or to justify accelerated approval outside of contexts in which trial-level surrogacy has been rigorously established. Consistent with guidance from EMA/CHMP, broader regulatory acceptance of pCR will require tumor-specific validation that demonstrates reproducible trial-level surrogacy, standardized pathologic assessment (e.g., immune-modified neoadjuvant criteria in melanoma and Böhm CRS in ovarian cancer), and confirmation of durable clinical benefit in adequately powered prospective studies.

In conclusion, pCR is a clinically meaningful and prognostically powerful endpoint in neoadjuvant therapy across diverse solid tumors. Its role is firmly established in breast cancer and shows strong patient-level promise in multiple other malignancies, particularly in the context of immunotherapy. However, the use of pCR as a regulatory surrogate beyond breast cancer must be determined on a tumor-specific and context-dependent basis. Continued generation of high-quality neoadjuvant trial data, extended follow-up for survival outcomes, harmonization of pathologic response criteria, and robust trial-level validation will be essential to define the appropriate role of pCR in future drug development and regulatory frameworks.

Conflict of Interest

SC is an employee of Nektar Therapeutics and may own its stocks. PH is an employee of Daiichi Sankyo Inc and may own its stocks. JF is an employee of TransThera Sciences Inc and may own its stocks and may own AstraZeneca stocks. NR declares no competing interests related to this work.

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