Pathological complete response (pCR) after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage: Patient-level meta-analyses of over 27,000 patients.

Laura M. Spring MD[1,3]; Geoffrey Fell MS[2]; Andrea Arfe MS[5]; Rachel Greenup MD, MPH[6]; Kerry L. Reynolds MD[1,3]; Barbara L. Smith MD, PhD[1,3]; Beverly Moy MD, MPH[1,3]; Steven J. Isakoff MD, PhD[1,3]; Lorenzo Trippa PhD[2,4]; Giovanni Parmigiani PhD[2,4]; Aditya Bardia MD, MPH[1,3]

1. Massachusetts General Hospital Cancer Center, Boston, MA
2. Dana-Farber Cancer Institute, Boston, MA
3. Harvard Medical School, Boston, MA
4. Harvard TH Chan School of Public Health, Boston, MA
5. Bocconi University, Milan, Italy
6. Duke University, Durham, NC

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Background (1)

- Traditionally breast cancer trials have focused on adding additional systemic therapies to reduce recurrence risk.
- However, adding therapies can result in additional toxicity and over-treatment for many patients.
- Neoadjuvant (pre-surgical) chemotherapy model offers several additional advantages over adjuvant (post-surgical) chemotherapy, including rapid assessment of treatment response utilizing surrogate biomarkers (eg: pathological complete response, pCR).
- FDA recognizes pCR as a potential surrogate endpoint to support accelerated approval of anti-cancer therapies (eg: neoadjuvant pertuzumab for HER2+ breast cancer).

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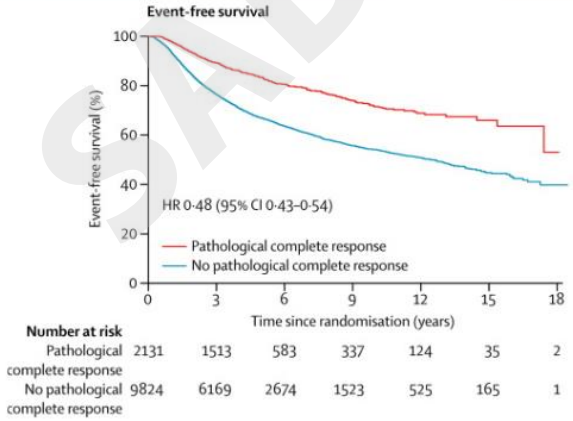
Background (2)



In a landmark study (Cortazar et al.) based on a pooled analysis of 12 clinical trials in localized breast cancer, pCR after neoadjuvant chemotherapy was significantly associated with improved event-free survival (EFS) and overall survival (OS).

Cortazar P, et al. *Lancet* 2014; 384:164–172

Background (3)

- The prognostic significance of pCR after neoadjuvant chemotherapy is relatively well established.
- However, impact of subsequent adjuvant therapy in modulating association between pCR and long-term outcomes is less clear.
- Furthermore, relationship between magnitude of pCR change (Δ pCR) and corresponding change in long-term clinical outcomes (Δ EFS) has not been well established.

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Study Objectives

To conduct a comprehensive meta-analysis of studies on neoadjuvant chemotherapy for localized breast cancer using recapitulated patient level data to evaluate:

- association between pCR and clinical outcomes (EFS and OS) by breast cancer subtype,
- impact of adjuvant chemotherapy on association between pCR and clinical outcomes,
- magnitude of change in pCR (Δ pCR) and corresponding change in clinical outcomes (Δ EFS)

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Methods (1)

- Librarian-led systematic search in PubMed from inception until September 2016 (PRISMA guidelines)
- Inclusion criteria included:
  - published studies of localized breast cancer with 25 patients or more featuring neoadjuvant chemotherapy that reported pCR (*ypT0 ypN0* or *ypT0/is ypN0*) results as well as recurrence and/or survival based on pathologic outcome
- Exclusion criteria included:
  - studies reporting local recurrence only
  - studies featuring neoadjuvant endocrine therapy or neoadjuvant radiation
- Relevant data extracted by two independent reviewers

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Methods (2)

- Individual patient-level data was extracted from each study using plot digitizer software (DigitizeIt) via the method of Guyot et al.
- EFS was used as a representative term for recurrence
- Hazard ratios (HRs), with 95% probability intervals (PIs), measuring the association between pCR and OS or EFS, were estimated using Bayesian piecewise-exponential proportional hazards hierarchical models with pCR as a predictor (random effects model)
- From the model a posterior distribution was estimated from which Kaplan-Meier curves for EFS and OS were derived
- Evaluated association between magnitude of treatment effects on EFS associated with pCR change based on methods described by Berry & Hudis

Guyot et al. B*MC Med Res Methodol* 2012;12(1):9
Berry D & Hudis C. *JAMA Oncol* 2015;1(7):875-876

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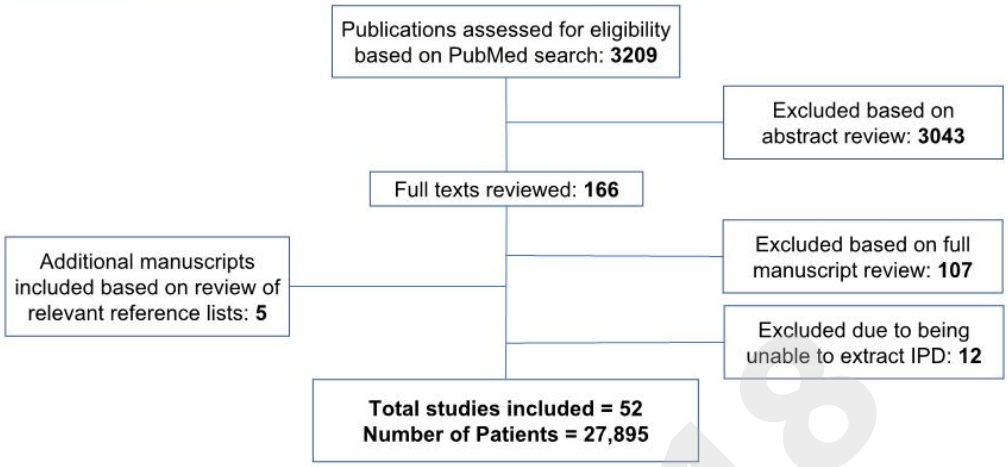
Results: Study Selection



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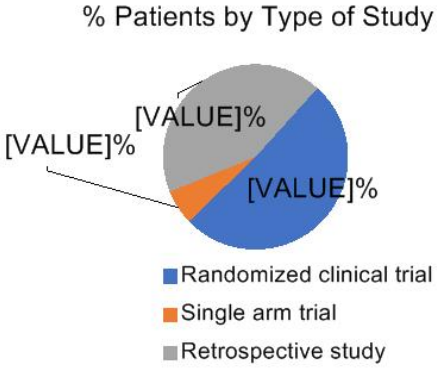
Results: Select Study Characteristics

- Publication dates (range): 1999-2016
- Broad global patient population, including United States, Mexico, Europe, Kuwait, Saudi Arabia, China, Japan, and Korea
- Median follow-up for recurrence (range): 48 months (21.3-107)
- Median follow-up for survival (range): 49.9 months (31.2-118)



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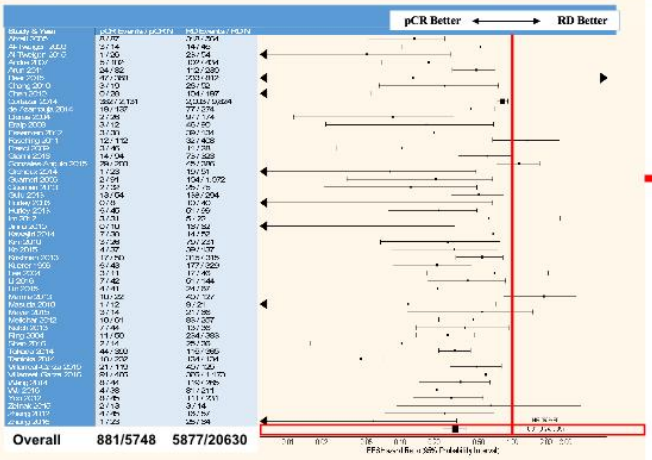
Results: pCR and EFS



Patients who had pCR, compared to those with residual disease (RD), had significantly better EFS (HR 0.31, 95% PI: 0.24-0.39, N = 26,378).

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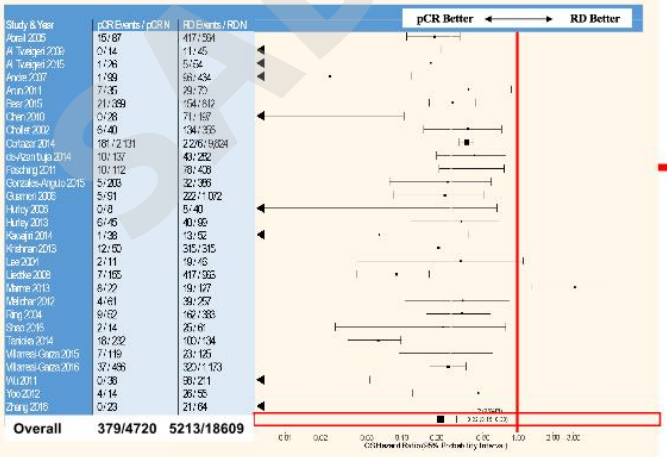
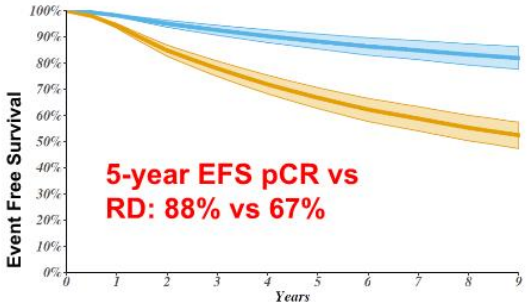
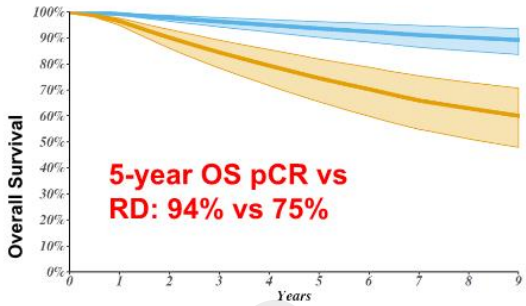
Results: pCR and OS



Patients who had pCR, compared to those with residual disease (RD), had significantly better OS (HR 0.22, 95% PI: 0.15-0.30, N = 23,329).

Results: EFS and OS in Overall Population





Blue: pCR group
Orange: Residual disease (RD) group

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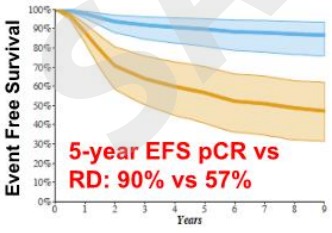
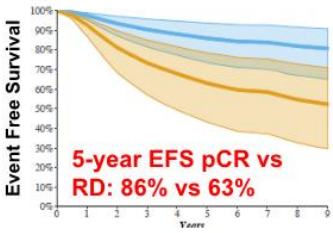
Results: EFS and OS by Subtype

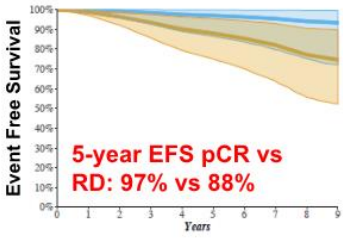
TNBC



HER2+



HR+/HER2-



Blue: pCR group
Orange: Residual disease (RD) group

Similar results seen with OS

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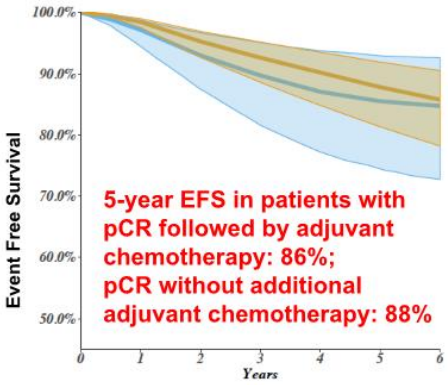
Results: Adjuvant Chemotherapy



Blue: pCR without adjuvant chemotherapy
Orange: pCR with adjuvant chemotherapy

Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes[1]	0.36	0.19-0.67
No[2]	0.36	0.27-0.54

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups[3].

[1] >90% of patients received adjuvant chemotherapy
[2] No more than 10% of patients received adjuvant chemotherapy
[3] Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)

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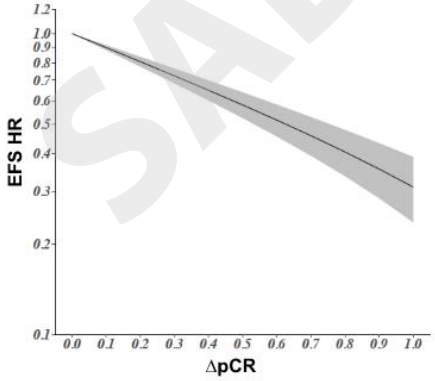
Results: ΔEFS vs. ΔpCR



Change in (Δ) pCR*	Corresponding HR (EFS)	95% PI
0	1	N/A
0.1	0.90	0.88-0.92
0.2	0.81	0.78-0.84
0.3	0.72	0.68-0.77
0.4	0.65	0.60-0.70
0.5	0.58	0.52-0.64
0.6	0.52	0.46-0.58
0.7	0.46	0.39-0.53
0.8	0.40	0.34-0.48
0.9	0.36	0.28-0.43
1	0.31	0.24-0.39

Assuming pCR is a valid surrogate endpoint (i.e. it mediates all treatment effects) and average* pCR of 50%, the magnitude of pCR change is predictive of treatment effects on EFS within a certain amount of uncertainty, based on the model.

ΔEFS vs. ΔpCR (Example)

- For example, the CALGB 40603 trial resulted in pCR improvement of 13% (41% → 54%) with the addition of carboplatin to standard chemotherapy, which would correspond to an EFS HR ~ 0.87 (95% PI: 0.84-0.89), based on our prediction model.
- Assuming 80% power and a 1:1 randomization ratio, 1,381 events must be observed to achieve statistical significance at 0.05 level (two-sided).
- In CALGB 40603 the HR for EFS for carboplatin was 0.84 (95% confidence interval: 0.58-1.22), but this was not statistically significant (only 110 events were observed during follow-up).

- Common theme for neoadjuvant studies, which are typically powered for primary endpoint of pCR and not secondary long-term survival outcomes.

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Strengths and Limitations

- Strengths of the study include:
  - large sample size
  - inclusion of both trial and retrospective studies
  - Inclusion of patients across the globe
  - results highly significant despite inclusion of a variety of neoadjuvant regimens, suggesting the path taken to attain a pCR may not be critical
- Limitations of the study include:
  - variability in study population and regimens received
  - variability in study specific outcome definitions
  - variability in the definition of hormone-receptor positivity
  - inability to assess other surrogate endpoints such as the residual cancer burden index

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Conclusions

- **Achieving pCR following neoadjuvant chemotherapy is associated with significantly improved EFS and overall survival, particularly for triple negative and HER2+ breast cancer.**
- **The similar outcomes with or without adjuvant chemotherapy in patients who attain pCR after neoadjuvant chemotherapy likely reflects tumor biology and suggests adjuvant chemotherapy could potentially be omitted in certain circumstances.**
- **Further research is needed to evaluate the clinical utility of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response.**

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Acknowledgements

Kuerer et al. 1999	Hurley et al. 2006	Chen et al. 2010	Esserman et al. 2012	Hurley et al. 2013	Kawajiri et al. 2014	Ko et al. 2015	
Chollet et al. 2002	Andre et al. 2007	Jinno et al. 2010	Im et al. 2012	Krishnan et al. 2013	Takada et al. 2014	Liu et al. 2015	
Dieras et al. 2004	Eralp et al. 2008	Kim et al. 2010	Melichar et al. 2012	Marme et al. 2013	Tanioka et al. 2014	Mayer et al. 2015	Shao et al. 2016
Lee et al. 2004	Liedtke et al. 2008	Masuda et al. 2010	Yoo et al. 2012	Natoli et al. 2013	Wang et al. 2014	Villarreal-Garza et al. 2015	Villarreal-Garza et al. 2016
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Guarneri et al. 2006	Chang et al. 2010	Wu et al. 2011	Guiu et al. 2013	Groheux et al. 2014	Gonzalez-Angulo et al. 2015	Li et al. 2016	

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