

# Retrospective Pooled Analysis to Assess Correlation Between Time to Progression and Overall Survival in Patients With Breast Cancer

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## BACKGROUND

- Increased overall survival (OS) is the gold standard for clinical benefit in cancer patients, but survival data from randomized clinical trials (RCTs) are often inconclusive due to subsequent treatments.
- Surrogate measures showing lengthened time to tumor progression (TTP) and/or progression-free survival (PFS) in advanced disease, and disease-free survival (DFS) in the adjuvant setting are clinically valid endpoints and may be acceptable for drug approval.

- In various cancers, researchers have demonstrated the relationship between disease progression and OS by pooling data across studies:
  - Metastatic colorectal cancer<sup>1,2</sup>
  - Colon cancer in the adjuvant setting<sup>3</sup>
  - Non-small cell lung cancer<sup>2</sup>
- We explored the association between disease progression endpoints and survival in metastatic breast cancer using published data.

## METHODS

- A structured literature search was conducted based on prespecified inclusion/exclusion criteria.
- An electronic literature search was conducted using PubMed (July 20, 2006).
  - Individual citations were downloaded into a Reference Manager database.
  - Abstracts and full-text articles were retrieved and examined for relevance.
- Inclusion criteria:
  - RCTs,
  - Confirmed metastatic or advanced breast cancer and receiving treatment,
  - English language,
  - Full-text articles available,
  - Publication date 1994 to present, and
  - Outcomes measured must include survival AND tumor progression OR PFS.
- Summary data were abstracted from studies in first-line or refractory metastatic breast cancer where progression endpoints and OS were reported.
- Data abstraction included:
  - Author(s), journal name, year of publication;
  - Patient characteristics (e.g., mean age, percentage staging, prior therapy);
  - Treatment regimens;
  - Sample size, median follow-up;
  - Number of tumor progressions, median (or mean) TTP; and
  - Number of deaths, median (mean) patient survival.

### Details

- For studies that included three treatment groups, the group with the highest efficacy compared to control, or the high group from dose-ranging studies was included.
- TTP/PFS were combined for analysis:
  - Many studies did not provide the definition used for TTP.
  - Others provided a definition associated with the term PFS (i.e., progressions and deaths counted as events).
  - A small number of studies provided a definition and results for PFS, but these studies did not report results separately for TTP.
  - Where indicated, sensitivity analyses provided further justification for analyzing the two outcomes simultaneously.
- The relationship between progression outcomes and survival was summarized and examined graphically.
  - Unweighted pooled estimates of TTP and OS were computed using median values reported for each treatment group in the included studies.
  - Spearman correlation coefficients were calculated between TTP (and/or PFS) and OS.

Simple linear regression equations were estimated as:

$$Y = a + bX + e$$

Y = Median overall survival per study group

X = Median time to event (TTP or PFS) per study group

b = Increase in survival associated with a 1-month increase in TTP

- Analyses were run with each treatment group weighted by the number of patients randomized to that group.
- Sensitivity analyses were run using unweighted data and using log-transformed data. These results are not shown, since inferences were robust to analytical approach.
- Additional analyses explored possible mediating factors on the relationship between progression and OS. Potential covariates included age, disease stage, hormone status, HER2 status, and first-line versus refractory treatment.

## RESULTS

### Summary of Study Characteristics

Number of Studies	Treatment Types
7	Anthracyclines with taxanes
14	Anthracyclines with chemotherapy
8	Anthracyclines with taxanes and chemotherapy
7	Anthracyclines alone
9	Taxanes with or without chemotherapy
12	Chemotherapy only
11	Hormones only

Initial search yielded 582 studies

68 studies met all eligibility criteria (N = 19,000 patients)

51 studies reported TTP

17 studies reported PFS

- Median age was 55 years (range: 44-75).
- Most patients were in Stage II (55 studies).
- Forty-seven studies were first line for metastatic cancer.
- Eight studies provided HER2 status, 5 of which included only HER2+ patients.
- Forty-eight studies provided hormone status for patients, ranging from 14% to 84% estrogen-receptor positive and/or progesterone-receptor positive.

Table 1. Summary of Endpoints Across All Groups

Number of Studies	Mean Reported TTP (95% CI)	Mean Reported OS (95% CI)	Correlation
51 TTP only	6.9 months (6.4, 7.3)	20.5 months (19.2, 21.7)	r = 0.33*
17 PFS only	7.1 months (6.4, 7.9)	19.7 months (17.7, 21.6)	r = 0.26
68 TTP or PFS	6.9 months (6.6, 7.3)	20.3 months (19.2, 21.3)	r = 0.31*

\* P < 0.05

CI = confidence interval; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

- Regression diagnostics led to exclusion of three studies based on studentized residuals (Figure 1).
- The weighted linear regression coefficient predicts that a 1-month increase in TTP or PFS corresponds to a 1.2-month increase in OS (Figure 2).
- The statistical significance of the overall model F-test indicates a more or less linear association between progression outcomes and survival.
- Age of patients and HER2 status affected the relationship between progression and survival. In HER2+ patients, the effect of delayed progression on survival may be more pronounced (Figure 3).
- The statistical significance of the overall model F-test indicates a more or less linear association between progression outcomes and survival.
- Age of patients and HER2 status affected the relationship between progression and survival. In HER2+ patients, the effect of delayed progression on survival may be more pronounced (Figure 3).

Figure 1. Residual Diagnostics for Regression Using All Studies

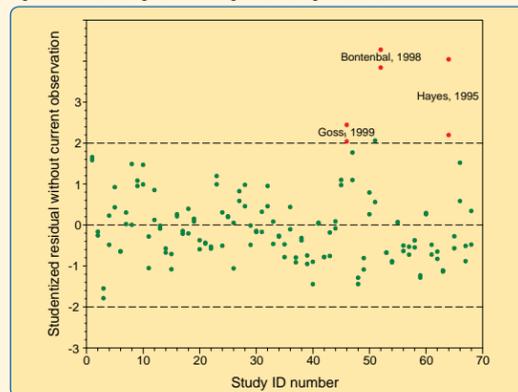
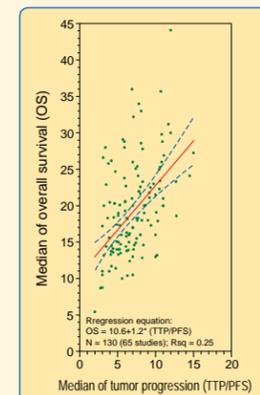


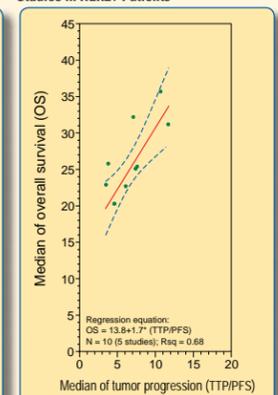
Figure 2. Regression of OS on TTP/PFS Weighted by Sample Size



A 1-month delay in progression in a treatment group was expected to extend OS by 1.22 months (95% CI: 0.85, 1.59).

Note: Slope is shown from weighted regression with three studies excluded. Slope from unweighted regression using all studies = 0.85.

Figure 3. Regression of OS on TTP/PFS Weighted by Sample Size Based On Five Studies in HER2+ Patients



In five studies with only HER2+ patients, delayed progression had a more pronounced impact on OS (slope = 1.7; CI: 0.7, 2.7).

\* N. Engl. J. Med. 2001;344:783-92; Ann. Oncol. 2001;12 Suppl 1:S57-S62; J. Clin. Oncol. 2002;20:719-26; J. Clin. Oncol. 2005;23:4265-74; J. Clin. Oncol. 2006;24:2786-92.

## DISCUSSION

- These findings show that we can expect survival with metastatic breast cancer to be extended by as much as or more than any incremental delay in progression.
- The slope of the simple, weighted regression line was steeper than that reported in either metastatic colorectal cancer<sup>1</sup> or adjuvant colon cancer.<sup>2</sup>
- Slightly different estimates of the magnitude of effect were obtained depending on whether:
  - Analyses were weighted or unweighted,
  - Exclusions were made based on statistical or clinical criteria, and
  - Study characteristics were incorporated.
- The simple plot of progression by survival time displays the wide heterogeneity of results across studies conducted in metastatic breast cancer patients.
- Evaluation of the combined evidence suggests that subgrouping of studies by patient or treatment characteristics may lead to better estimates of the relationship between progression and survival.
- Further work is needed to better understand what determinants are associated with increased survival and whether some subgroups based on tumor types will experience a more substantial survival benefit from delayed progression.
- The simple analysis presented here has limitations. It ignores the original randomization for each study and implies that data from different treatment arms in the same study are not related. Its appeal is simplicity, both for explaining the approach and for presenting results. However, the over-simplification may over- or understate the magnitude of relationship between endpoints.
- A multivariate meta-regression approach is planned to examine relationship between treatment effect on progression and treatment effect on survival.

Table 2. Included Studies

References	
Cancer 1994;73:2337-43.	J Clin Oncol 1994;12:1630-8.
Eur. J Cancer 1995;31A:2169-73.	J Clin Oncol 1995;13:2556-66.
J Clin Oncol 1995;13:2567-74.	Anticancer Res 1995;15:495-501.
J Clin Oncol 1996;14:1146-55.	Semin. Oncol 1996;23:28-33.
Ann. Oncol 1996;7:487-90.	J Clin Oncol 1996;14:1165-72.
J Clin Oncol 1996;14:1858-67.	Ann. Oncol 1997;8:155-62.
J Clin Oncol 1997;15:3141-8.	Ann. Oncol 1997;8:1213-20.
Eur. J Cancer 1997;33:2194-7.	Oncology 1996;55:416-20.
Br J Cancer 1998;77:2257-63.	Ann. Oncol 1998;9:639-45.
J Clin Oncol 1998;16:3720-30.	J Clin Oncol 1999;17:64-73.
J Clin Oncol 1999;17:2355-64.	Am J Clin Oncol 1999;22:593-600.
Breast Cancer Res Treat. 1999;58:141-50.	J Clin Oncol 1999;17:52-63.
Breast Cancer Res Treat. 1999;55:51-9.	J Clin Oncol 1999;17:1413-24.
Breast Cancer Res Treat. 1999;54:117-22.	Clin Breast Cancer 2000;1 Suppl 1:S15-S18.
J Clin Oncol 2000;18:3115-24.	J Clin Oncol 2000;18:2385-94.
J Clin Oncol 2000;18:724-33.	Breast Cancer Res Treat. 2000;61:103-10.
J Clin Oncol 2001;19:943-53.	J Clin Oncol 2001;19:1444-54.
Ann. Oncol 2001;12 Suppl 1:S57-S62.	J Clin Oncol 2001;19:2232-9.
J Clin Oncol 2001;19:1707-15.	Eur. J Cancer 2001;37:1132-40.
N. Engl. J Med 2001;344:783-92.	J Clin Oncol 2002;20:4150-9.
J Clin Oncol 2002;20:3114-21.	Br J Cancer 2002;87:1210-5.
Ann. Oncol 2002;13:1717-29.	Ann. Oncol 2002;13:1225-35.
Br J Cancer 2002;86:1905-8. (242)	J Clin Oncol 2002;20:719-26.
J Chemother. 2003;15:184-91.	Ann. Oncol 2003;14:699-703.
J Clin Oncol 2003;21:968-75.	Eur. J Cancer 2003;39:614-21.
J Clin Oncol 2004;22:2597-93.	Br J Cancer 2004;91:1466-71.
Breast Cancer Res Treat. 2004;86:197-206.	Ann. Oncol 2004;15:1527-34.
Cancer 2004;101:704-12.	J Clin Oncol 2004;22:2313-20.
Ann. Oncol 2004;15:440-9.	J Clin Oncol 2004;22:4683-90.
Ann. Oncol 2004;15:1358-65.	J Clin Oncol 2004;22:2061-8.
J Clin Oncol 2005;23:7081-8.	J Clin Oncol 2005;23:8322-30.
Eur. J Cancer 2005;41:71-80.	J Clin Oncol 2005;23:4265-74.
J Clin Oncol 2005;23:792-9.	J Clin Oncol 2005;23:432-40.
Br J Cancer 2006;94:1233-6.	J Clin Oncol 2006;24:2786-92.

## CONCLUSIONS

- These preliminary results are consistent with findings in other tumor types, indicating that increases in TTP endpoints ultimately correspond to survival benefits for metastatic breast cancer patients.
- Findings suggest that the relationship between disease progression and survival varies by factors such as tumor subtype.

## REFERENCES

- Louvet C, de Gramont A, Tournigand C, Artru P, Maindrault-Goebel F, Krulik M. Correlation between progression free survival and response rate in patients with metastatic colorectal carcinoma. Cancer. 2001 Jun 1;91(11):2033-8.
- Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol. 2006 Sep;7(9):703-4.
- Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2005 Dec 1;23(34):8564-5.

[Complete references for included studies available upon request.]

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