# Risk of Recurrence and Chemotherapy Benefit for Patients with Node-Negative, Estrogen Receptor-Positive Breast Cancer: Recurrence Score Alone and Integrated with Pathologic and Clinical Factors

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## SUPPLEMENTARY MATERIAL

*Additional Methodology Description. RS* was included in the multivariate analysis using a 2-degree-of-freedom natural spline as described by Royston and Parmar.[15] This results in two factors in the model:

$f_1(RS) = RS$ (linear component)

$f_2(RS) = \max\{0,(RS-k_2)^3\} - c\max\{0,(RS-k_1)^3\} - (1-c)\max\{0,(RS-k_3)^3\}$ (nonlinear component)

where $k_1$, $k_2$, and $k_3$ are the knots and $c = (k_3-k_2)/(k_3-k_1)$. The knots were placed at *RS* values of $k_1$=5, $k_2$=18, and $k_3$=90, reflecting the 10th, 50th, and 90th percentiles of *RS* observed in NSABP B-14. Natural splines constructed in this manner are smooth curves that are linear beyond the boundary knots (in this case, for *RS* below 5 and *RS* above 90).

The variance of the extrapolated estimate of the cumulative hazard at 10 years for TransATAC was computed using martingale methods.[17] Since the extrapolated estimate can be expressed as the sum of the usual Breslow estimate at 8 years plus 2 times the difference between the 9-year and 8-year estimates, and since martingale increments are uncorrelated, the variance of the extrapolated 10-year estimate is equal to the variance of the 8-year estimate plus 4 times the variance estimate of the 8-to-9-year increment.

For NSABP B-14, the Kaplan-Meier estimate of the 10-year incidence of distant recurrence was calculated for each risk group. For the TransATAC study, the Nelson-Aalen cumulative hazard estimate was extrapolated from 9 years to 10 years, as was done for the baseline cumulative hazard estimate, and transformed to obtain the incidence. The variance of each estimate was calculated using the delta method, and a meta-analysis estimate of the 10-

year incidence was computed as the weighted average of the two study estimates, weighting by the inverse variance.

*Additional Results*. The Breslow estimate of the baseline cumulative hazard function for distant recurrence in the NSABP B-14 study is shown in Fig S-1. The estimate at 10 years is found at the intersection of this curve with the vertical line at this time. The estimated baseline cumulative hazard function for distant recurrence in the TransATAC study is shown in Fig S-2, along with the calculation for estimating the cumulative hazard at 10 years for TransATAC, under the assumption that the hazard between 9 and 10 years is the same as the hazard between 8 and 9 years. This assumption appears reasonable, since the shape of the estimated cumulative hazard curve suggests that the hazard is approximately constant from year 6 onwards.

Predictiveness curves for *RSPC* and *RS* for this patient population are shown in Fig S-3. These are plots of the risk estimate for each patient in the population against the population quantile of the risk estimate. There are 1444 points in this plot, one for each patient in the risk assessment evaluation set. The jumps and plateaus in the predictiveness curve for *RS* occur because the meta-analysis used *RS* rounded to the nearest whole number as the covariate. The horizontal reference line at 14.0% is the weighted average Kaplan-Meier estimate of the overall risk of distant recurrence at 10 years.

The predictiveness curve for *RSPC* is usually farther from the population average risk than is the *RS* curve, indicating better risk separation of the population using *RSPC*. The separation is observed in both the region of high risk and the region of low risk.

Figure S-4 shows *RS* and *RSPC* risk assessments and 95% confidence intervals (CI) are shown for 10 patients randomly selected from the NSABP B-14 population and 10 patients randomly selected from the TransATAC population.

Figure S-5 illustrates the patient-specific meta-analysis calculation combining the 10-year log cumulative hazard estimates for a variety of specified covariate values. The meta-analysis CIs are narrower than the CIs for the log cumulative hazard from either of the individual studies. In Figure S-6, the same log cumulative hazard estimates and CIs are transformed to estimates of the 10-year risk of distant recurrence. Again the meta-analysis CIs are narrower than the individual study intervals.

Figures S-7 and S-8 show the distribution of the covariates *RS*, tumor grade, tumor size, and patient age in the risk assessment evaluation set (node-negative patients) for the individual NSABP B-14 and TransATAC studies.

## SUPPLEMENTARY FIGURE LEGENDS

**Fig S-1.** Breslow baseline cumulative hazard estimate for NSABP B-14. The arrow shows the estimated cumulative hazard at 10 years.

**Fig S-2.** Baseline cumulative hazard estimate for TransATAC. The black line is the Breslow estimate. The two rectangles in the upper right corner are of identical dimension. The arrow shows the extrapolation estimate of the cumulative hazard at 10 years.

**Fig S-3.** Predictiveness curves for *RSPC* and *RS* based on the meta-analysis in the patients with N0, ER+ breast cancer (N= 1444).

**Fig S-4.** Estimated 10-year risk of distant recurrence and 95% confidence interval using *RSPC* and *RS* for 10 randomly-selected patients from NSABP B-14 and 10 from the TransATAC. TG = tumor grade, TS = tumor size.

**Fig S-5.** NSABP B-14, TransATAC, and meta-analysis estimates of log cumulative hazard for distant recurrence at 10-years, with 95% confidence intervals.

**Fig S-6.** NSABP B-14, TransATAC, and meta-analysis estimates of 10-year risk of distant recurrence, with 95% confidence intervals.

**Fig S-7.** Distribution of covariates *RS*, tumor grade, tumor size, and patient age in the 647 Meta-analysis-evaluable NSABP patients. All patients are node-negative.

**Fig S-8.** Distribution of covariates *RS*, tumor grade, tumor size, and patient age in the 797 node-negative TransATAC patients.

Fig S-1

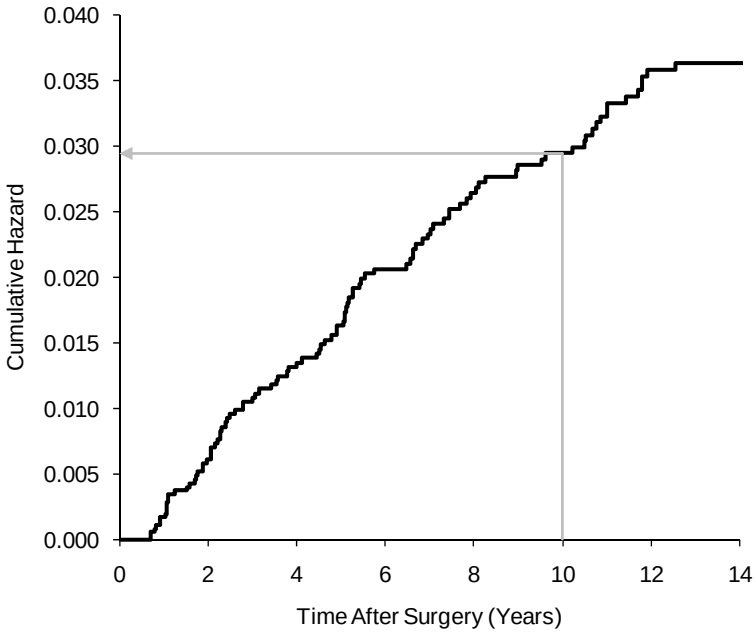

0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Cumulative Hazard
0
2
4
6
8
10
12
14
Time After Surgery (Years)

Fig S-2.

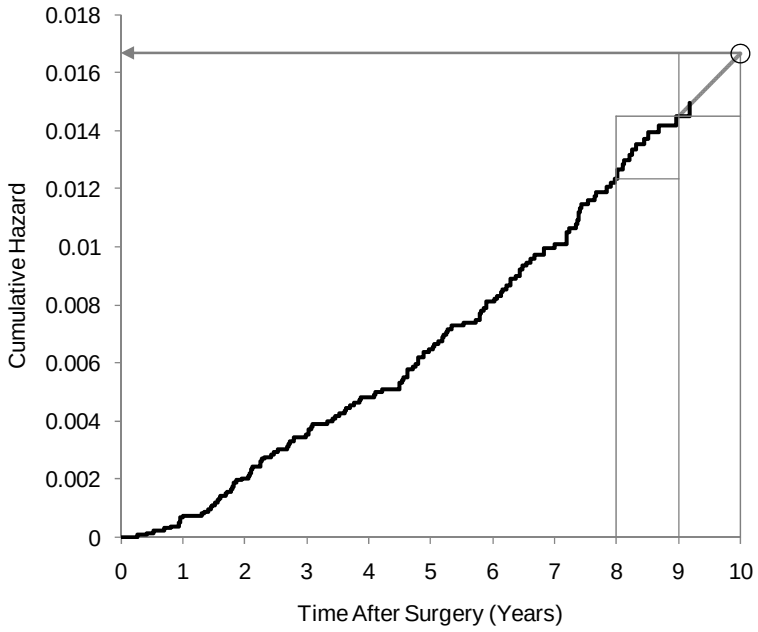

0.018
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
Cumulative Hazard
0
1
2
3
4
5
6
7
8
9
10
Time After Surgery (Years)

Fig S-3

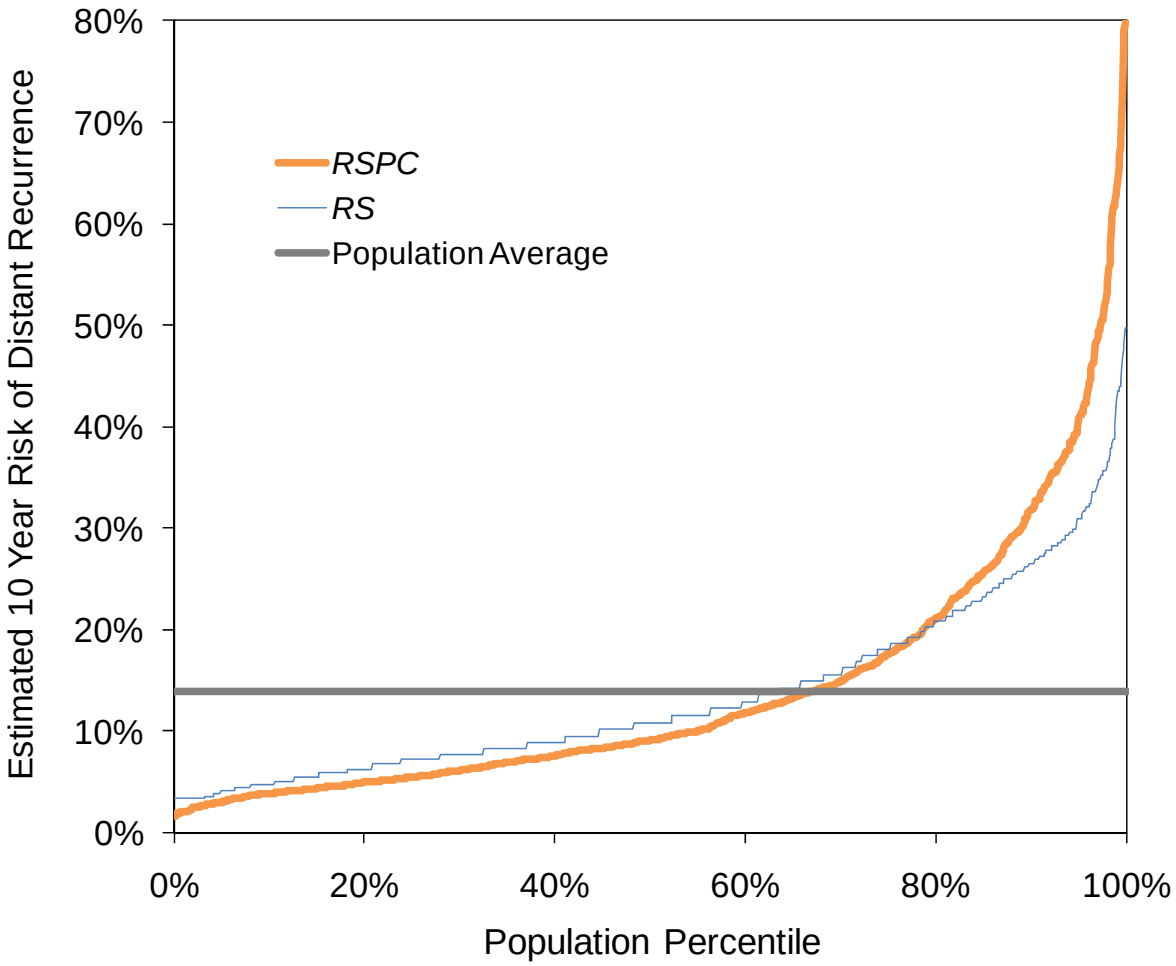

80%
70%
60%
50%
40%
30%
20%
10%
0%
Estimated 10 Year Risk of Distant Recurrence
RSPC
RS
Population Average
0%
20%
40%
60%
80%
100%
Population Percentile

Fig S-4

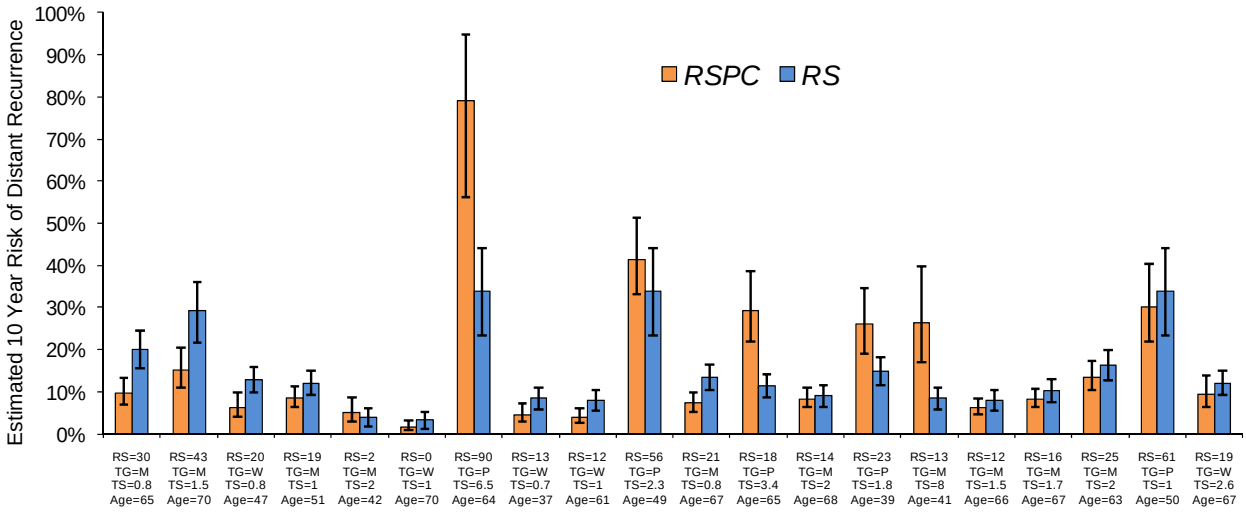

Estimated 10 Year Risk of Distant Recurrence
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
RSPC
RS
RS=30 TG=M TS=0.8 Age=65
RS=43 TG=M TS=1.5 Age=70
RS=20 TG=W TS=0.8 Age=47
RS=19 TG=M TS=1 Age=51
RS=2 TG=M TS=2 Age=42
RS=0 TG=W TS=1 Age=70
RS=90 TG=P TS=6.5 Age=64
RS=13 TG=W TS=0.7 Age=37
RS=12 TG=W TS=1 Age=61
RS=56 TG=P TS=2.3 Age=49
RS=21 TG=M TS=0.8 Age=67
RS=18 TG=P TS=3.4 Age=65
RS=14 TG=M TS=2 Age=68
RS=23 TG=P TS=1.8 Age=39
RS=13 TG=M TS=8 Age=41
RS=12 TG=M TS=1.5 Age=66
RS=16 TG=M TS=1.7 Age=67
RS=25 TG=M TS=2 Age=63
RS=61 TG=P TS=1 Age=50
RS=19 TG=W TS=2.6 Age=67

Fig. S-5

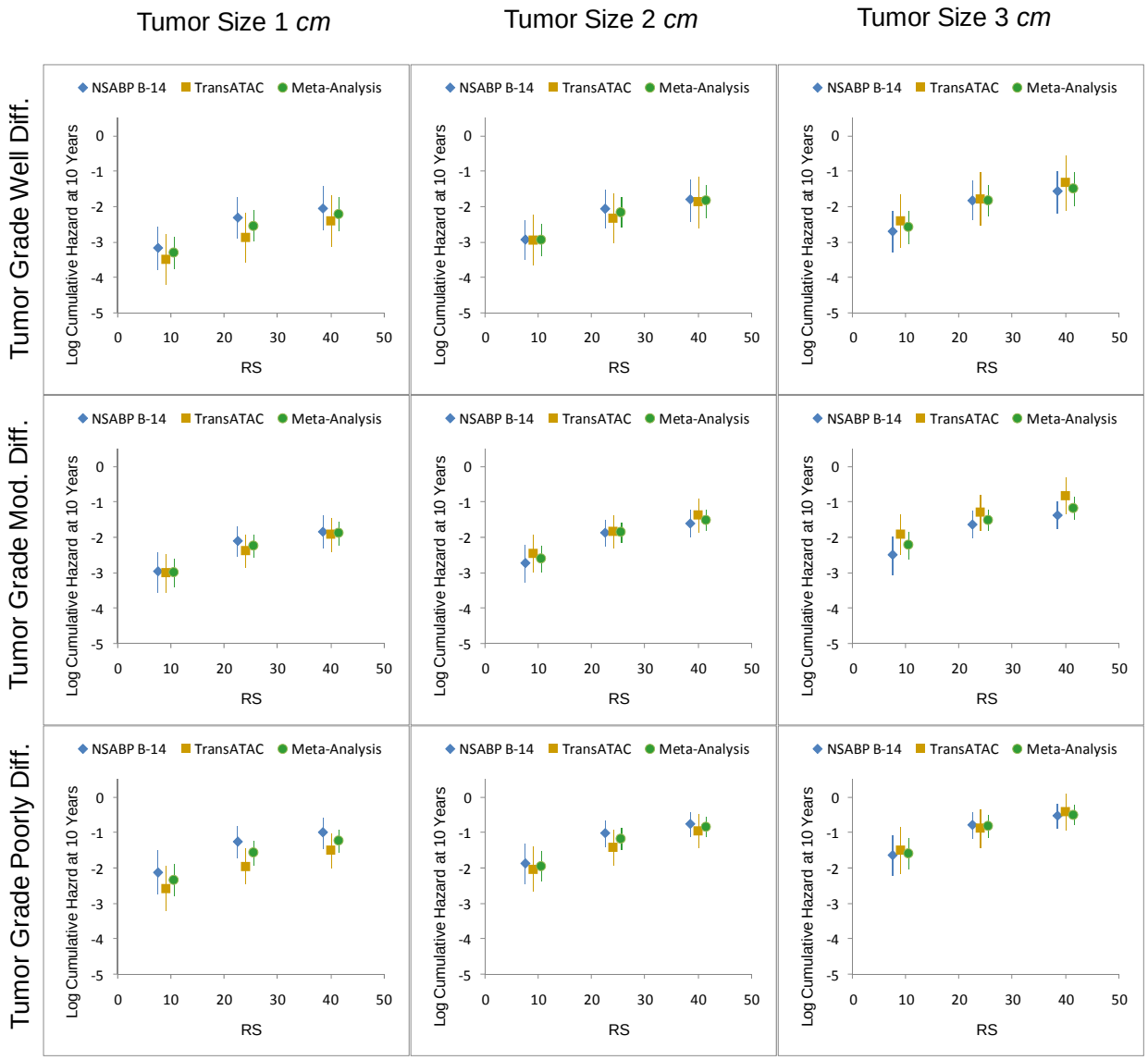

Tumor Size 1 *cm*
Tumor Size 2 *cm*
Tumor Size 3 *cm*
Tumor Grade Well Diff.
Tumor Grade Mod. Diff.
Tumor Grade Poorly Diff.
NSABP B-14
TransATAC
Meta-Analysis
Log Cumulative Hazard at 10 Years
RS

Fig. S-6

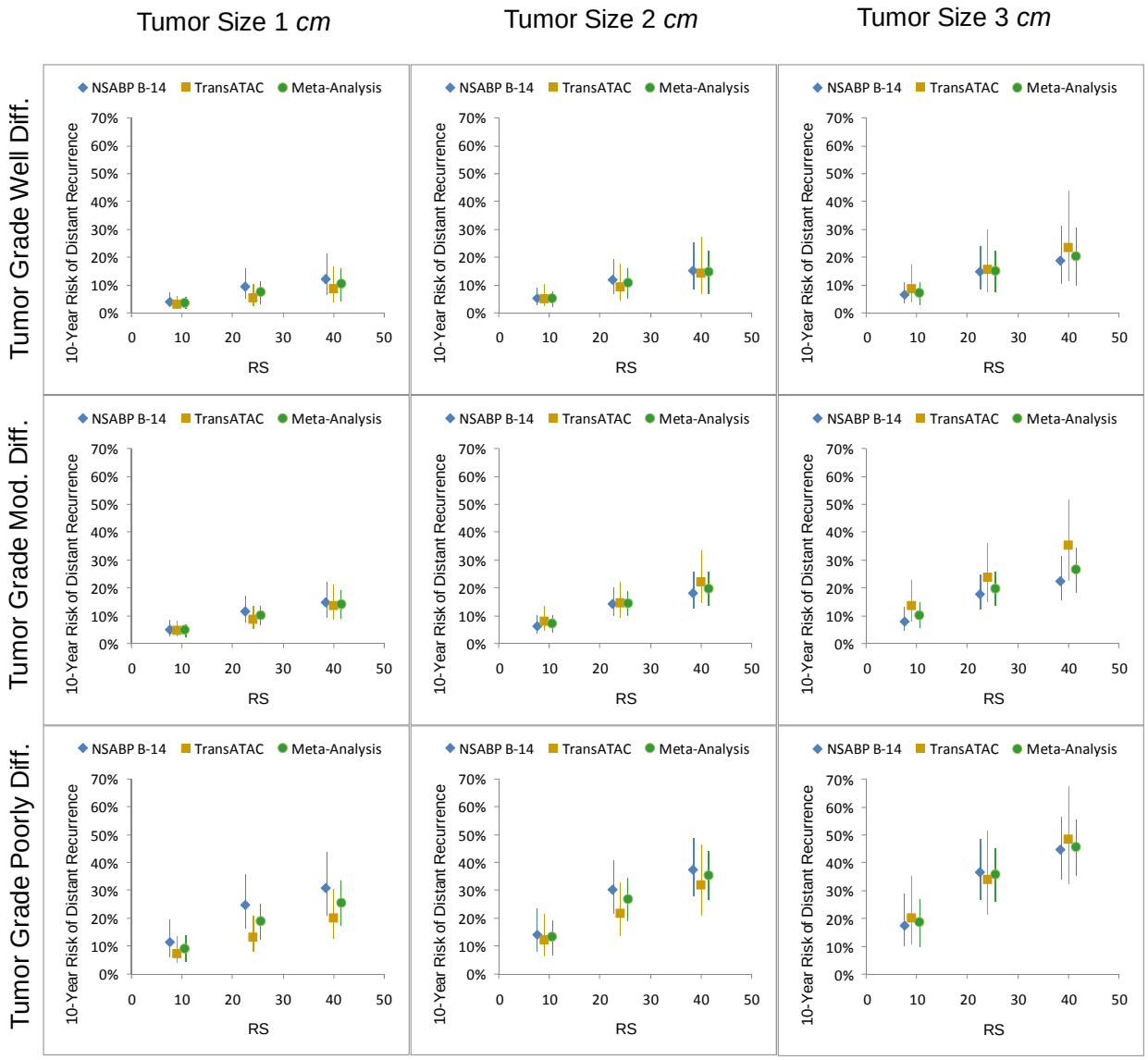

Tumor Size 1 *cm*
Tumor Size 2 *cm*
Tumor Size 3 *cm*
Tumor Grade Well Diff.
Tumor Grade Mod. Diff.
Tumor Grade Poorly Diff.
NSABP B-14
TransATAC
Meta-Analysis
10-Year Risk of Distant Recurrence
RS

Fig S-7

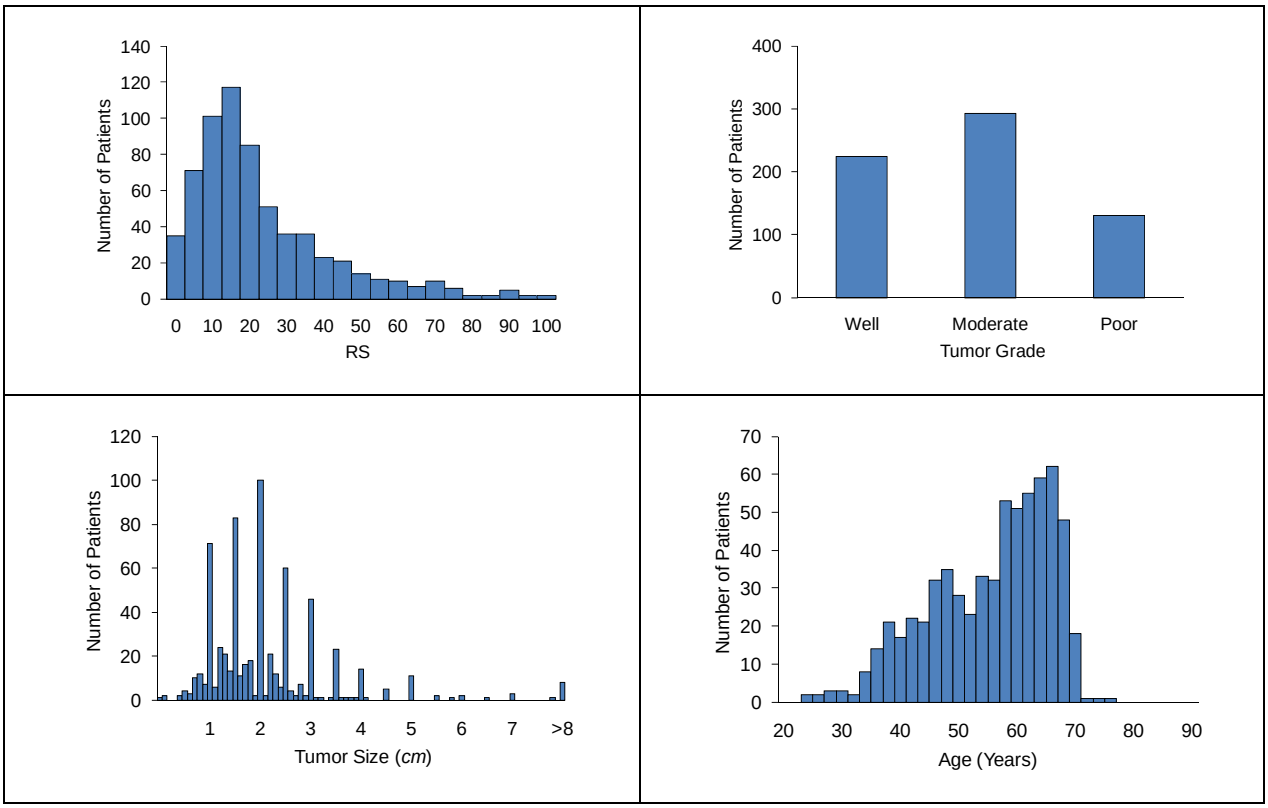
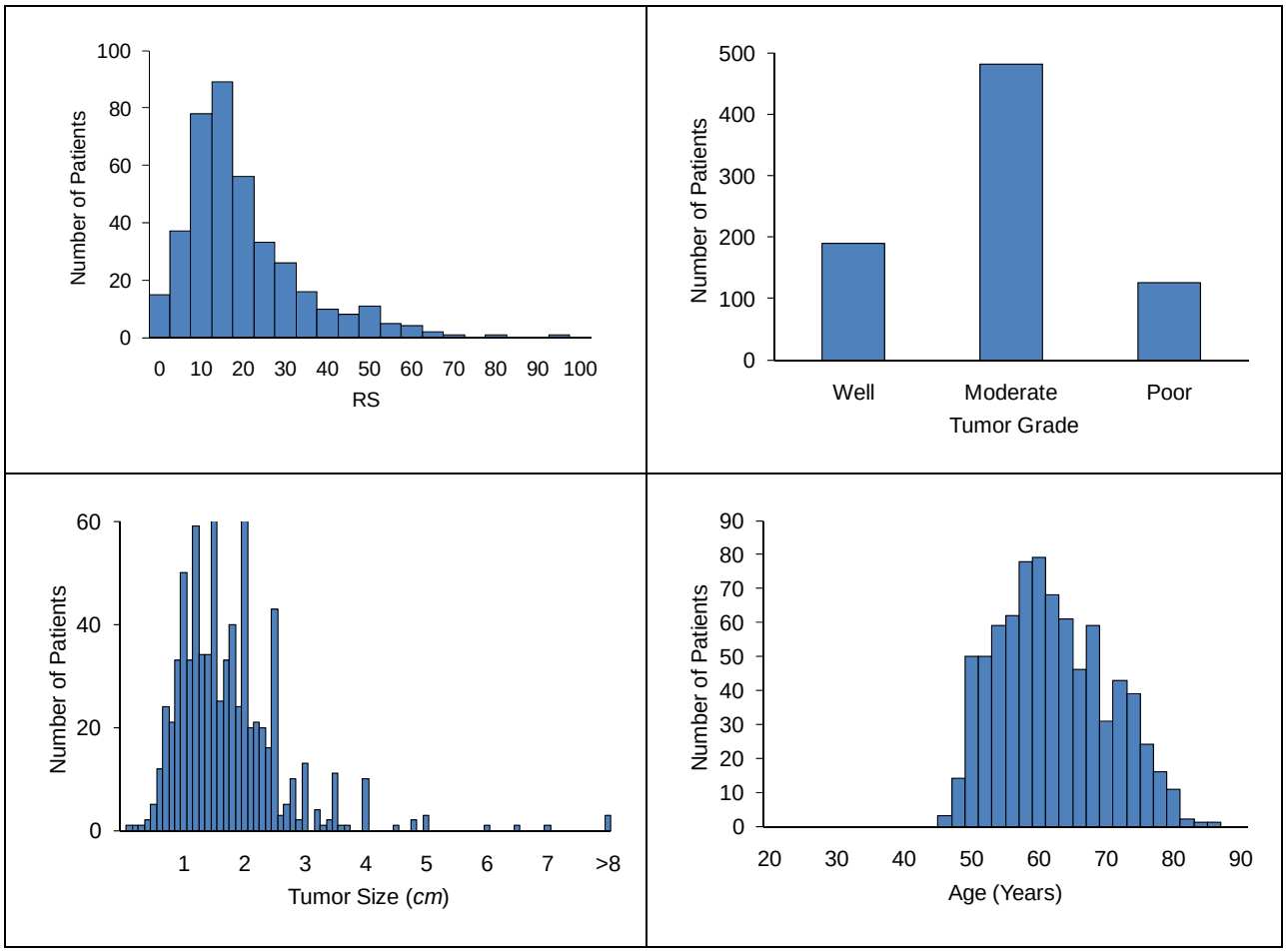

Number of Patients
RS
0 10 20 30 40 50 60 70 80 90 100
0 20 40 60 80 100 120 140
Number of Patients
Well
Moderate
Poor
Tumor Grade
0 100 200 300 400
Number of Patients
Tumor Size (cm)
1 2 3 4 5 6 7 >8
0 20 40 60 80 100 120
Number of Patients
Age (Years)
20 30 40 50 60 70 80 90
0 10 20 30 40 50 60 70

Fig S-8.


Number of Patients
RS
0 10 20 30 40 50 60 70 80 90 100
0 20 40 60 80 100
Number of Patients
Well
Moderate
Poor
Tumor Grade
0 100 200 300 400 500
Number of Patients
Tumor Size (*cm*)
1 2 3 4 5 6 7 >8
0 20 40 60
Number of Patients
Age (Years)
20 30 40 50 60 70 80 90
0 10 20 30 40 50 60 70 80 90