

Using Cure Models to Estimate Biological Cure

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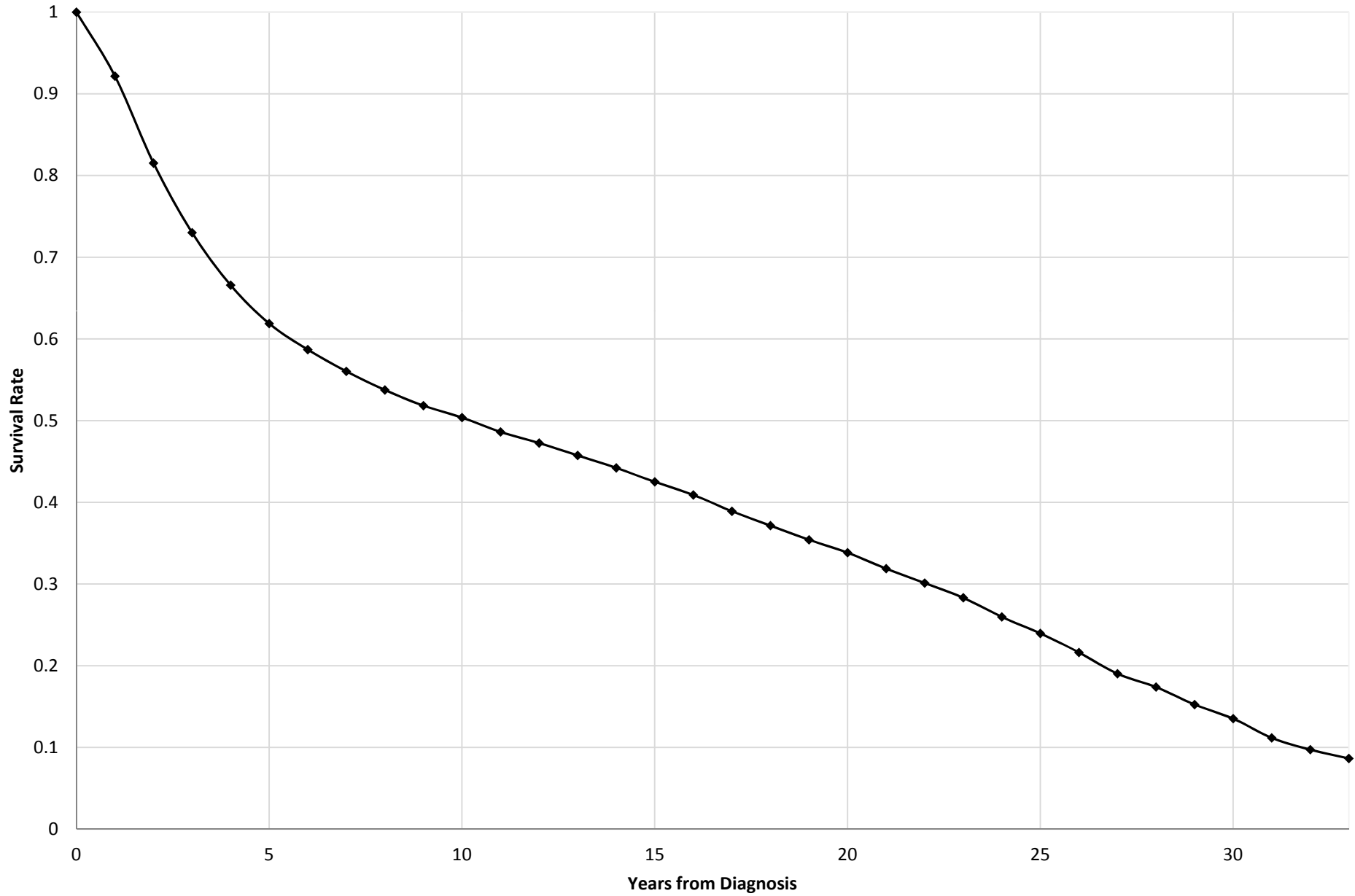
NAACCR Presentation June 5, 2012

“Statistical Cure”

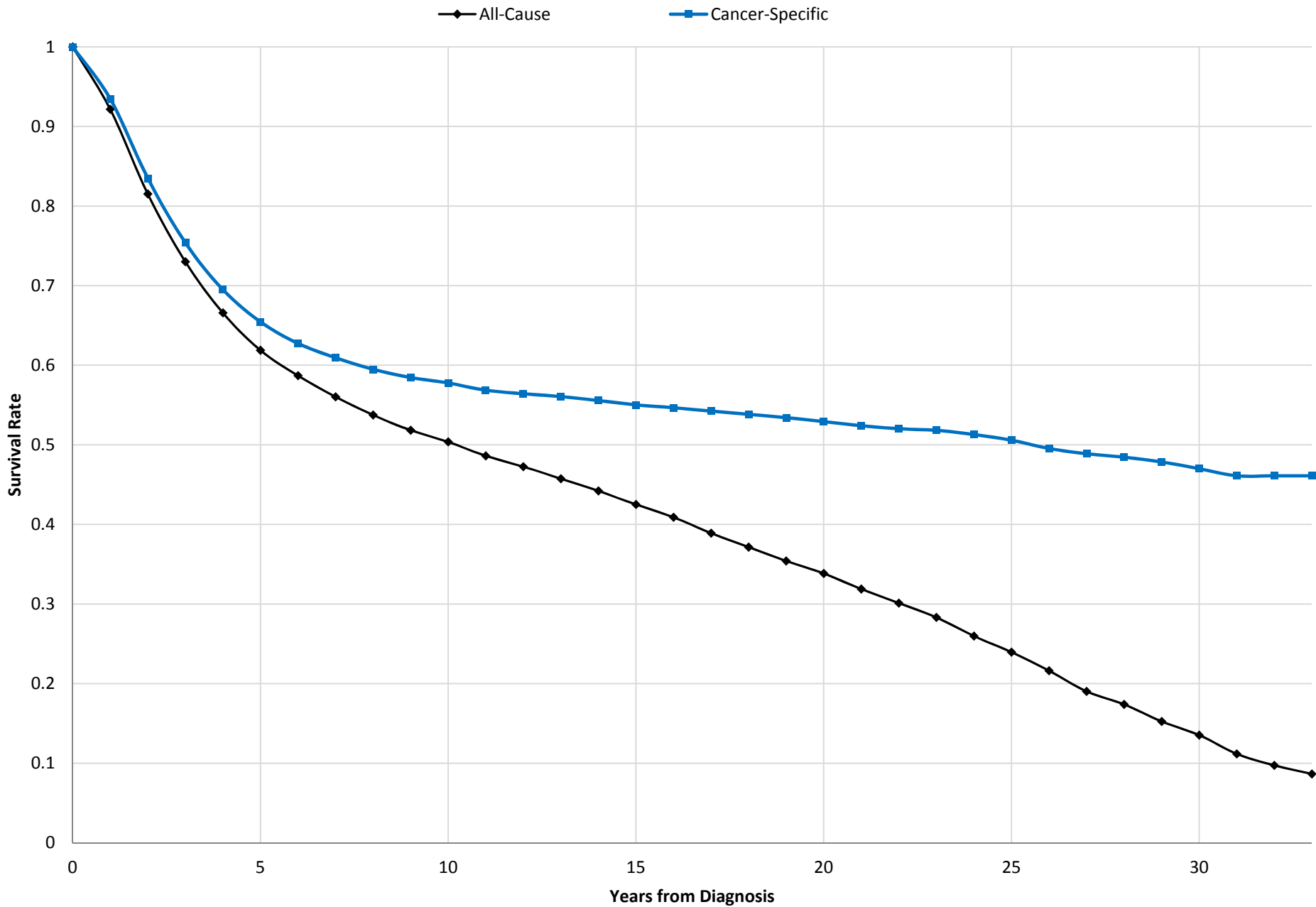
- Fraction of cancer patients whose mortality rate equals the mortality rate of the cancer free population.
 - Excess mortality is zero.
 - The cured fraction is assumed to never experience a cancer death.
 - Estimate of biological cure (population based measure)
- **NOT** personal cure- probability of an individual dying of non-cancer related causes.

Survival Estimates
Colorectal Cancer, Regional Stage, 55-64 year olds

—◆— All-Cause

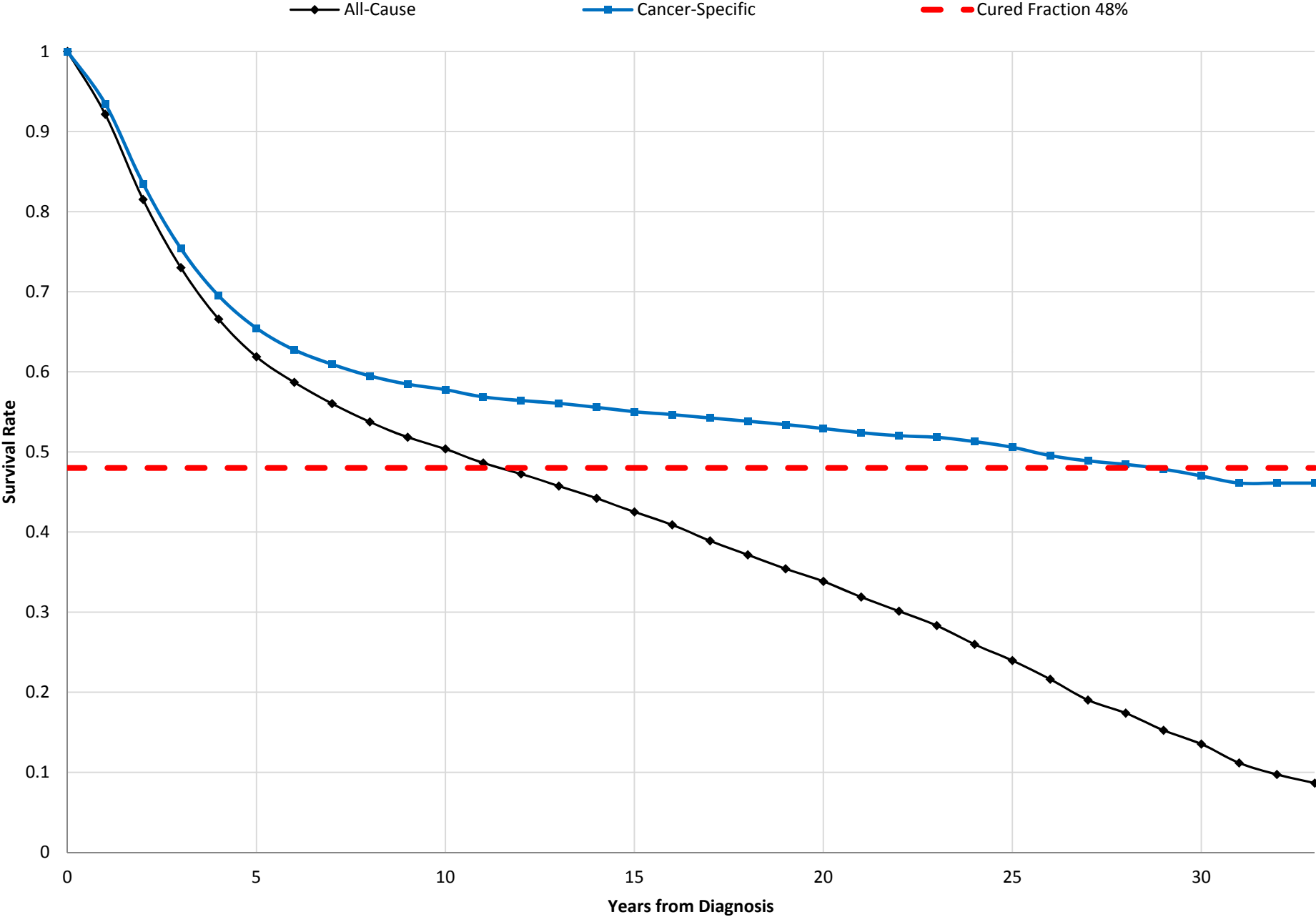


Survival Estimates Colorectal Cancer, Regional Stage, 55-64 year olds



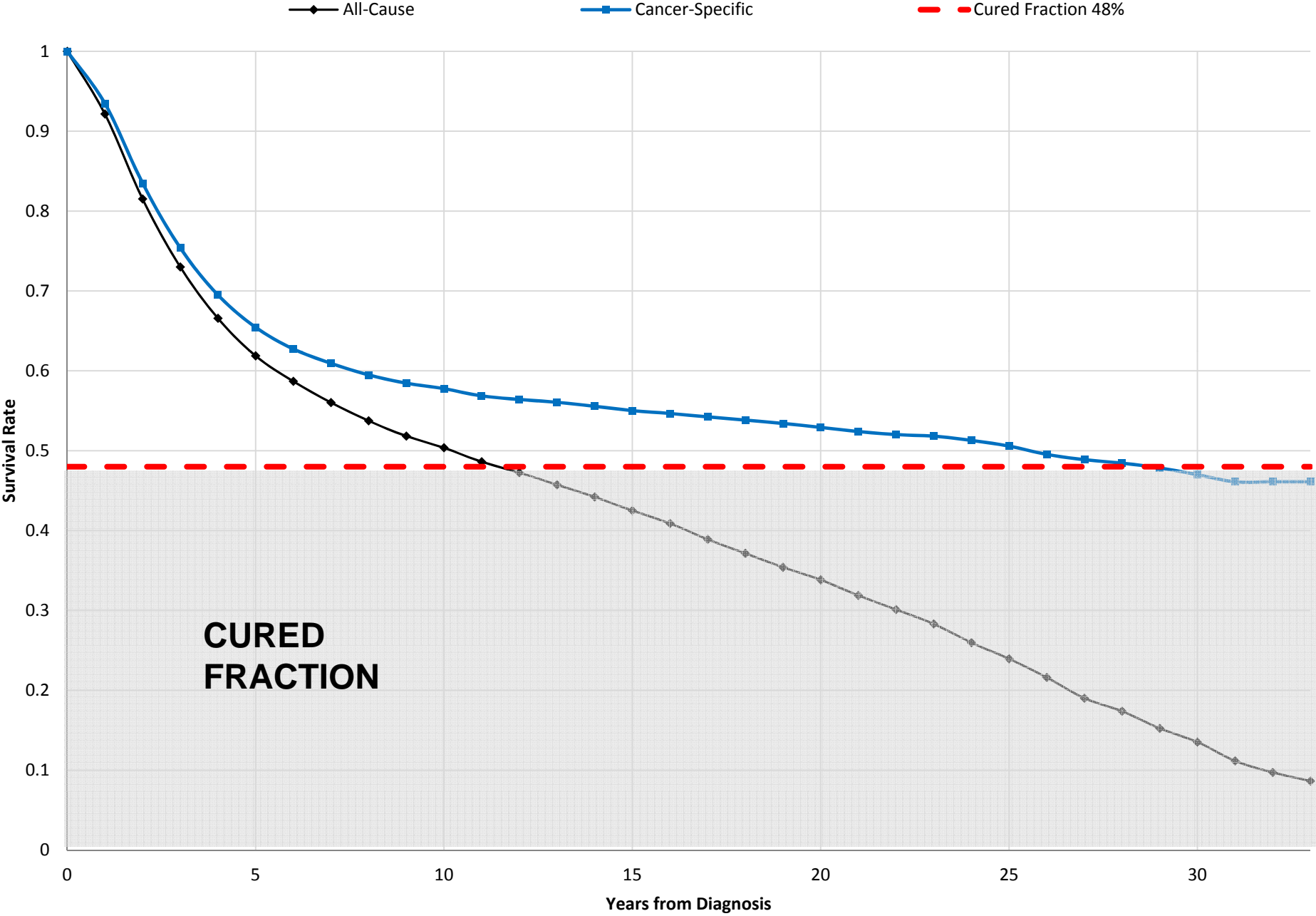
Survival Estimates

Colorectal Cancer, Regional Stage, 55-64 year olds



Survival Estimates

Colorectal Cancer, Regional Stage, 55-64 year olds



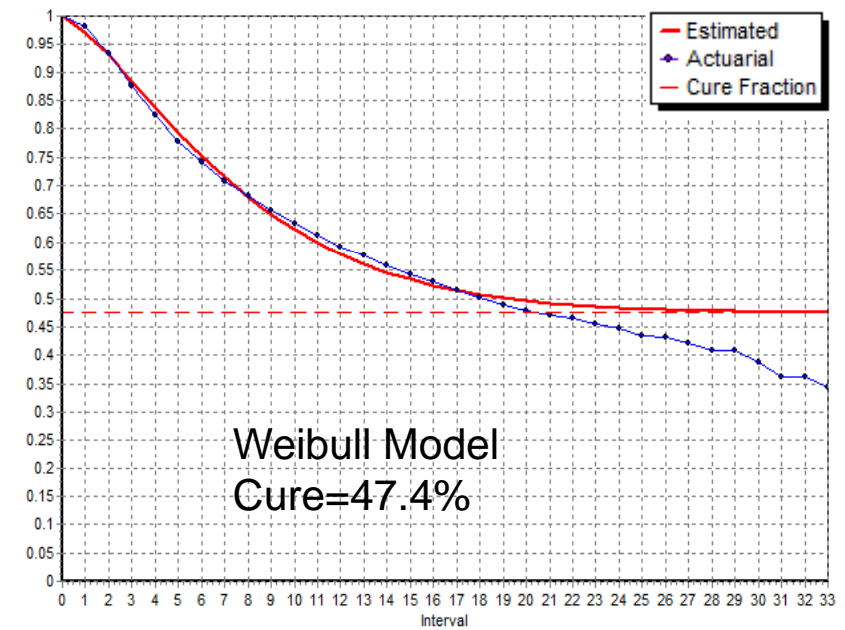
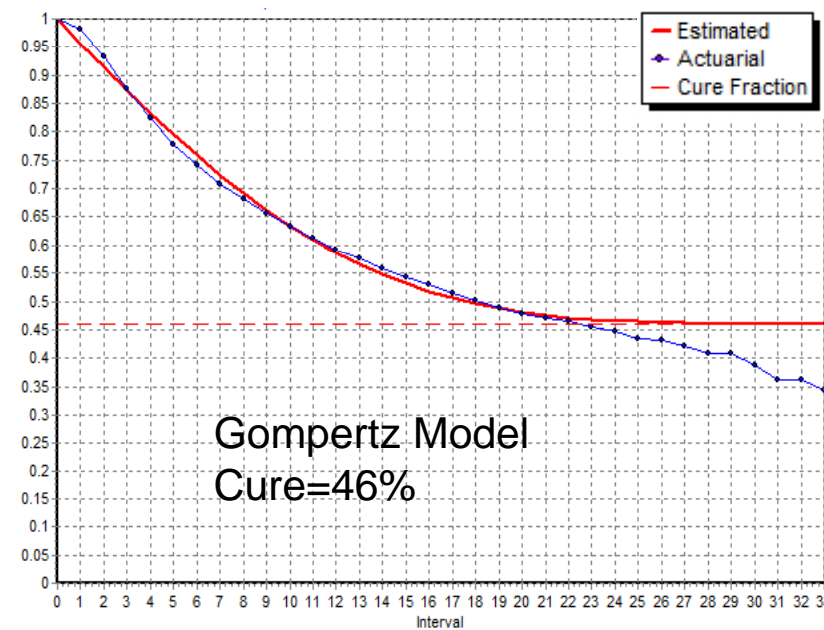
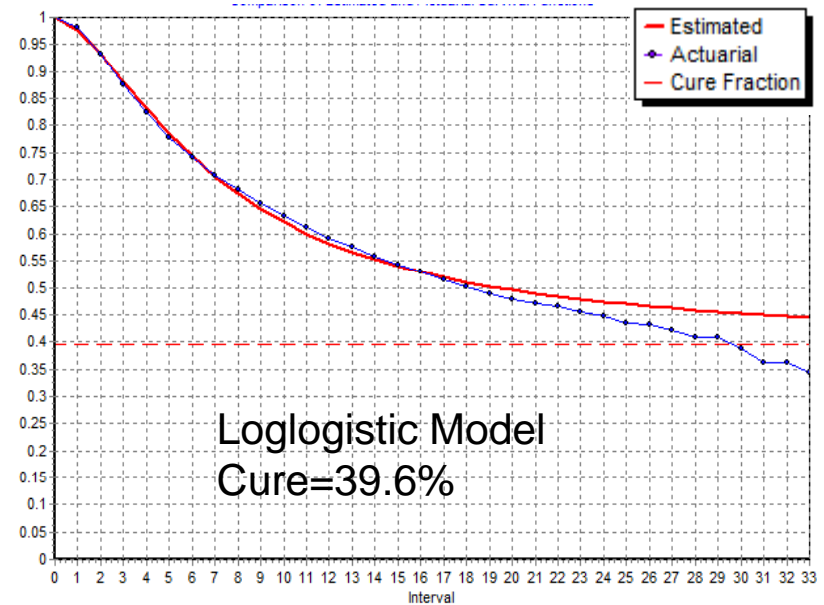
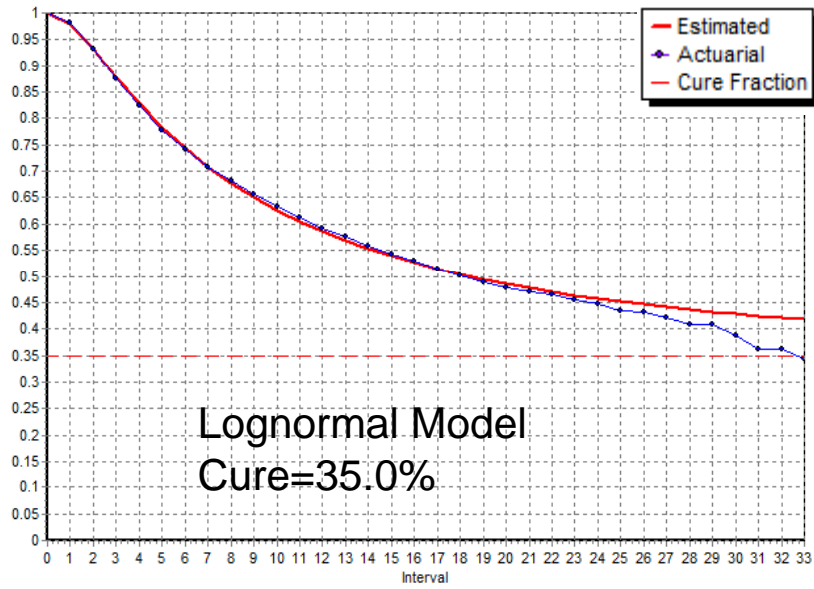
Importance of measuring **Statistical Cure**

- Patient survival is one of the most important questions in cancer research.
- Cure models give us more information about patient survival
 - Predict proportion of patients cured from cancer.
 - Predict time until cured
 - Estimates survival time of patients not cured.
- “Net survival” estimate-- not influenced by other cause mortality

Cure is difficult to estimate

- Results can be unreliable
- Sometimes cure cannot be estimated from the data

Regional Stage Breast Cancer, 45-54 year olds.



Criteria

- Follow up time $> 2/3$ median survival*
- % Coefficient of Variation (CV) $< 10\%$ †
- Cure \leq last survival estimate

*Yu et al., *Statistics in Medicine*, 2004

†Rosner, *Fundamentals of Biostatistics*, 1995

Purpose

- To investigate criteria to assess the reliability of estimates from mixture cure models.
- To develop a method to easily summarize and evaluate if cure can be estimated.
- To identify cancer subgroups where a cure fraction can be estimated.

Example Study of Breast and Colorectal Cancer

Study population

- SEER 9: San Francisco-Oakland SMSA, 1973+', 'Connecticut - 1973+', 'Detroit (Metropolitan) - 1973+', 'Hawaii - 1973+', 'Iowa - 1973+', 'New Mexico - 1973+', 'Seattle (Puget Sound) - 1974+', 'Utah - 1973+', 'Atlanta (Metropolitan) - 1975+'
- Selection criteria:
 - Years of Diagnosis: 1975-2007
 - Known Age: 45-74 Years
 - Cases actively followed with malignant behavior
 - Female
- Exclusions
 - Death certificate and autopsy only diagnosis
 - Secondary and later primaries
 - Those alive without survival time
 - Those with missing death certificate information

Example Study of Breast and Colorectal Cancer (CRC)

Study population

Site	Age	N	Localized	Regional	Distant	Unknown
Breast	45-54	89365	56%	36%	5%	2%
	55-64	95681	58%	33%	7%	2%
	65-74	90039	62%	29%	7%	2%
CRC	45-54	14832	37%	39%	21%	3%
	55-64	28515	36%	39%	21%	3%
	65-74	44243	38%	38%	20%	4%

Example Study of Breast and Colorectal Cancer Methods

- SEER*Stat software to obtain standard life tables of net survival (survival in the absence of other causes of death)
- Stratified by SEER historic stage, age group
- Maximum follow-up time 33 years.
 - Begin at date of diagnosis (1975-2007)
 - End at death or study cutoff (December 2008)



Example Study of Breast and Colorectal Cancer Methods

2 Estimates of Net Survival:

- Relative Survival (Ederer II method)
 - Ratio of observed survival to survival of US general population
- Cause-Specific Survival
 - Uses death certificate information to determine if death is cancer related
 - Censors other cause death.

Example Study of Breast and Colorectal Cancer Methods

Parametric Mixture Cure Model:

$$S(t) = C + (1-C)G(t; \mu, \sigma)$$

Net Survival Cured Fraction Uncured Fraction *
Survival Function

Tested 3 distributions for $G(t)$:

	Distribution	Survival Function $G(t)$	Parameterization
1	Lognormal	$G(t; \mu, \sigma) = 1 - \Phi[(\ln\{t\} - \mu) / \sigma]$	$\mu = \mu$ $\sigma = \sigma$
2	Loglogistic	$G(t; \lambda, \rho) = [1 - (\lambda t)^\rho]^{-1}$	$\mu = -\ln \lambda$ $\sigma = 1/\rho$
3	Weibull	$G(t; \lambda, \rho) = \exp[1 - (\lambda t)^\rho]$	$\mu = -\ln \lambda$ $\sigma = 1/\rho$

Example Study of Breast and Colorectal Cancer Methods

Used Cansurv software to fit Mixture Cure Model

The screenshot shows the 'relative_LL.srs' window with three tabs: 'Input File', 'Model Specifications', and 'Output Specifications'. The 'Model Specifications' tab is active.

Model:

- Standard Survival Model (No Cure)
- Cure Model (Estimate Cure C)
Caution: Cure fraction represents extrapolation beyond the end of observed data and may be sensitive to model assumptions. Sufficient follow-up is required. [More information](#)
- Mixture Cure Model
- Mixture Cure Model with Power Function (delta)

Distribution G(t):

- Lognormal
- Loglogistic
- Weibull
- Gompertz
- SemiParametric

Computation Specifications:

- Maximum Number of Iterations: 50
- Convergence of Derivatives: 0.000001
- Convergence of Parameters: 0.000001
- Try different starting values beta(1:end)
- Number of deviations per parameter n: 3
- Distance of deviations d: 0.5

Model: $S(t) = C + (1-C)G(t; \mu, \sigma)$; $G(t; \mu, \sigma) = \left[1 + \exp\left(\frac{\log t - \mu}{\sigma}\right) \right]^{-1}, \sigma > 0$

[More information](#)

Include in Analysis:

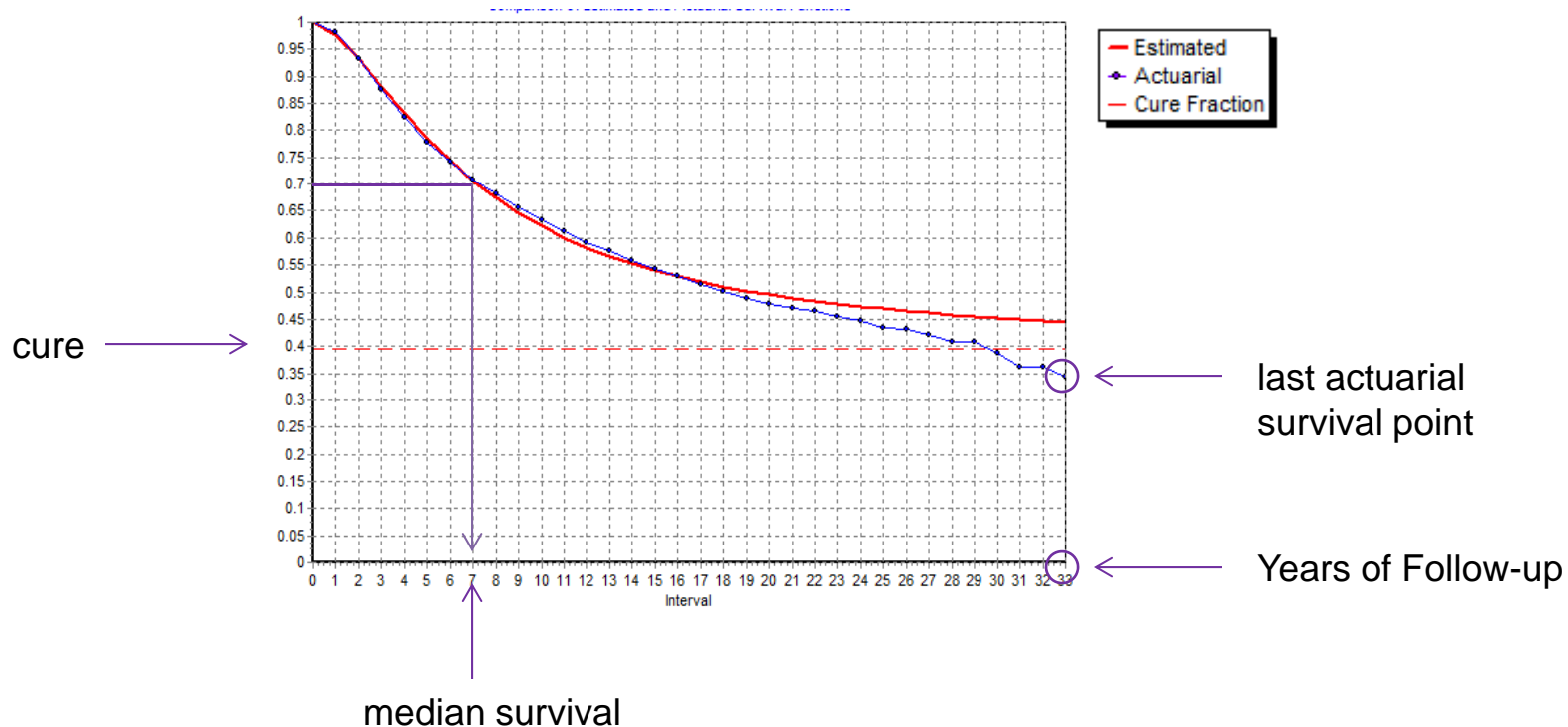
Variable Name	Categorical	Stratum	Mu	Sigma	Cure (C)	Power (Delta)
Cure_groups	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SEER historic stage A_cure_breast	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Age 45-54,55-64,65-74 cure	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Buttons: Add Transformed Parameter, Delete Transformed Parameter

Free software available at: <http://surveillance.cancer.gov/cansurv/index.html>

Results - Statistics

- Cure estimate and confidence interval
- Median survival time for the uncured
- Last actuarial survival estimate and confidence interval



Female_Breast:Localized

Net Survival - Distribution

Cure Estimate and 95% CL

55-64 years-cs-LL

55-64 years-cs-LN

55-64 years-cs-W

55-64 years-rel-LL

55-64 years-rel-LN

55-64 years-rel-W

0.0

0.2

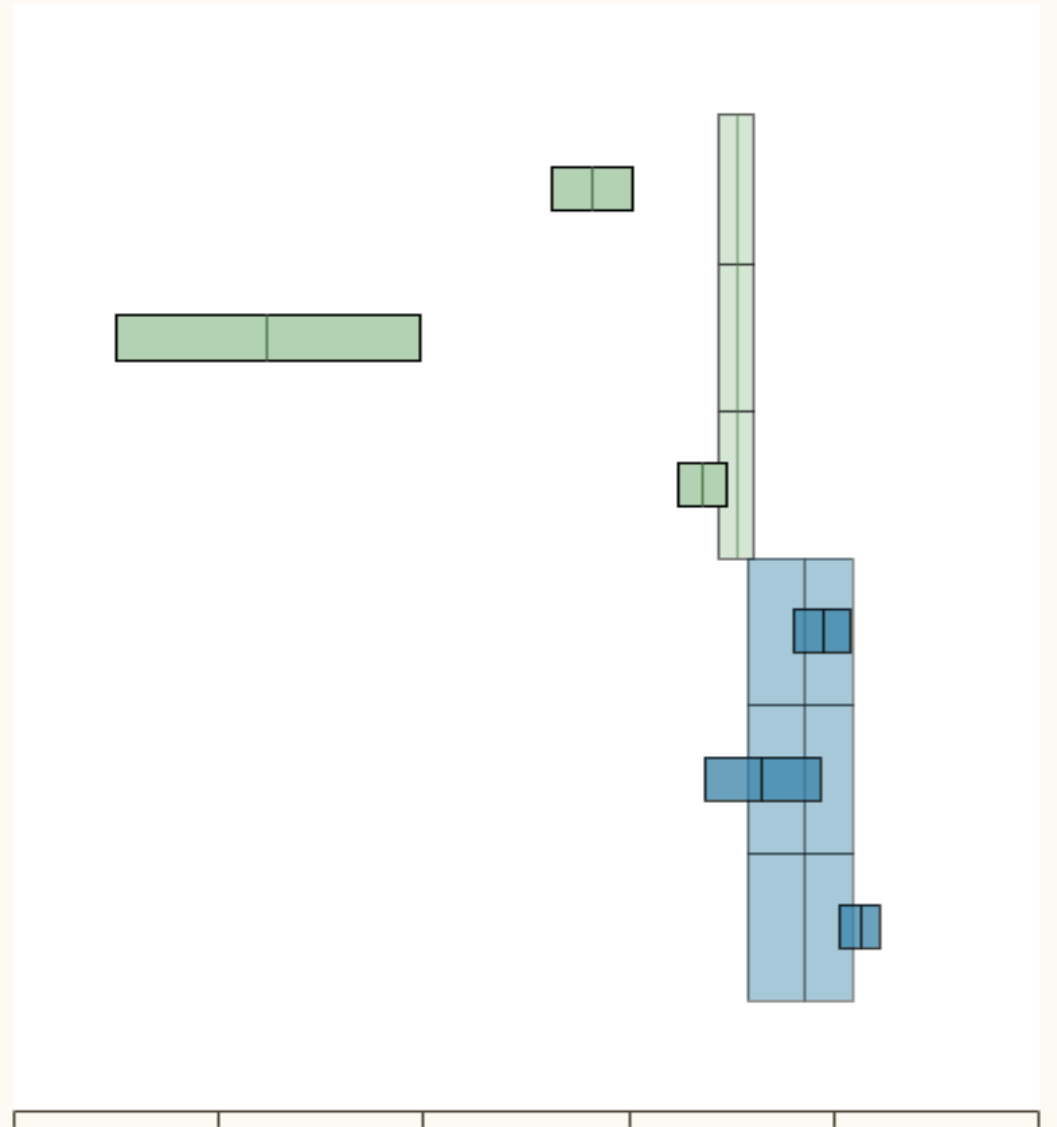
0.4

0.6

0.8

1.0

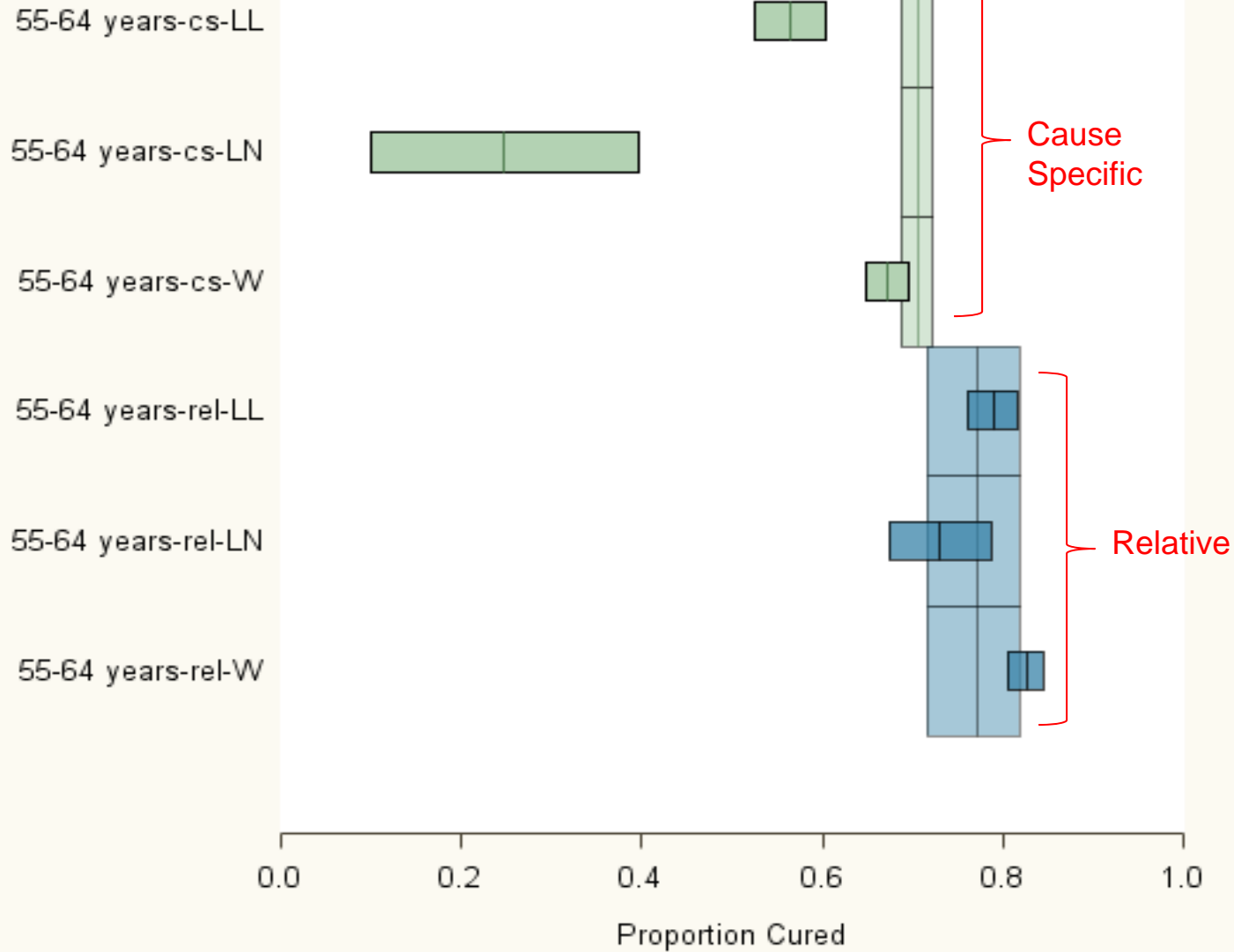
Proportion Cured



Female_Breast:Localized

Net Survival - Distribution

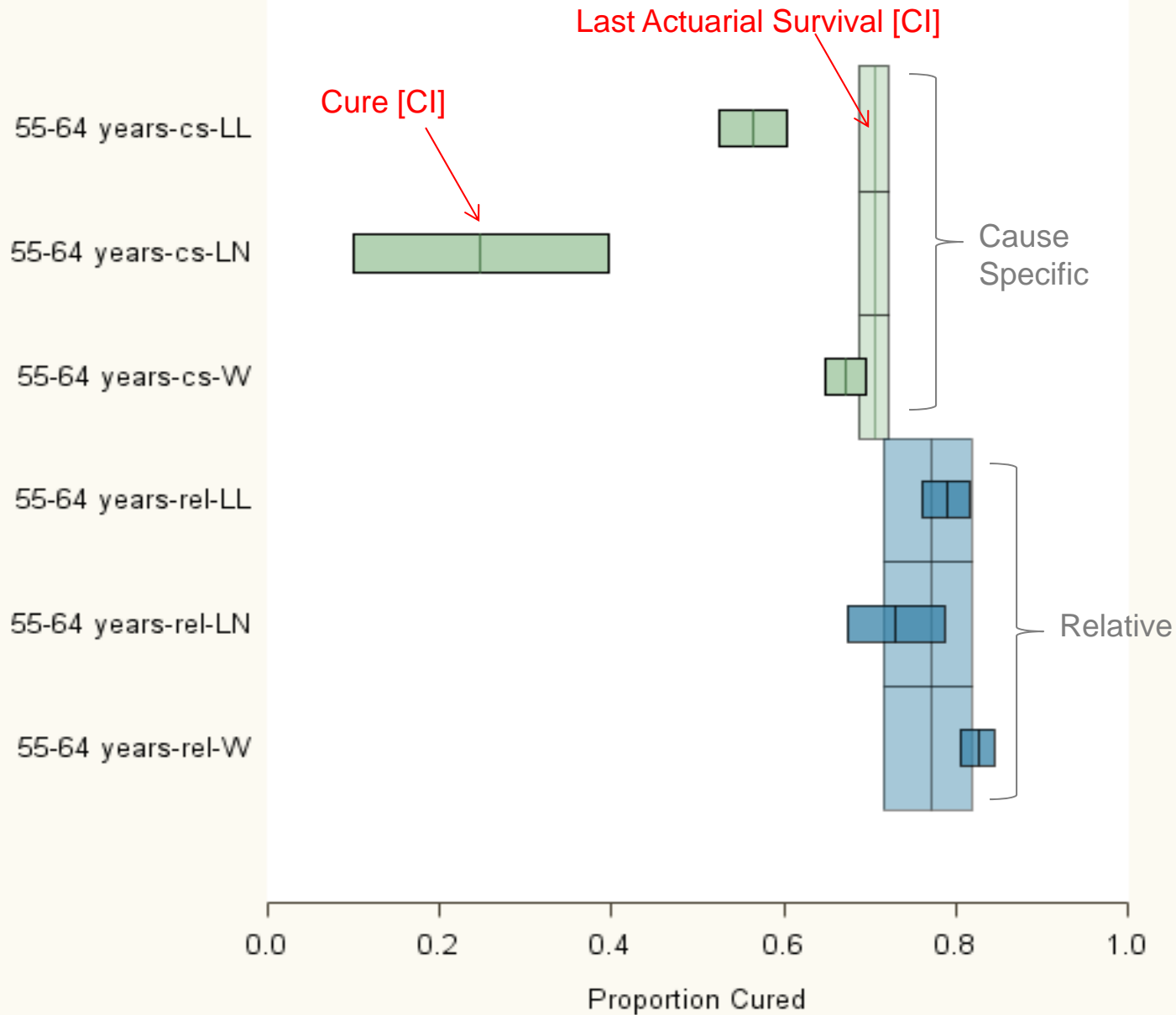
Cure Estimate and 95% CL



Female_Breast:Localized

Net Survival - Distribution

Cure Estimate and 95% CL



Female_Breast:Localized

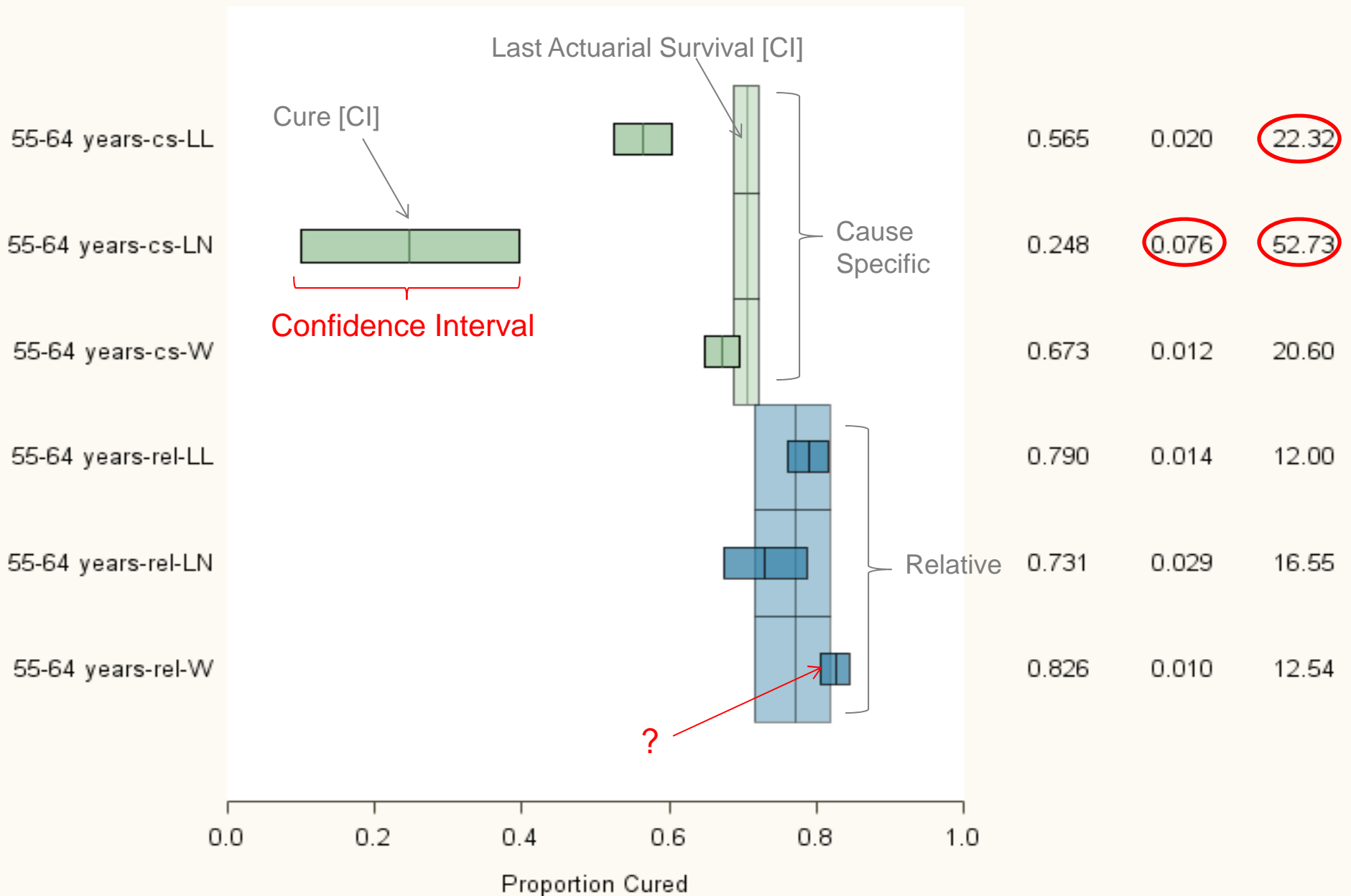
Net Survival - Distribution

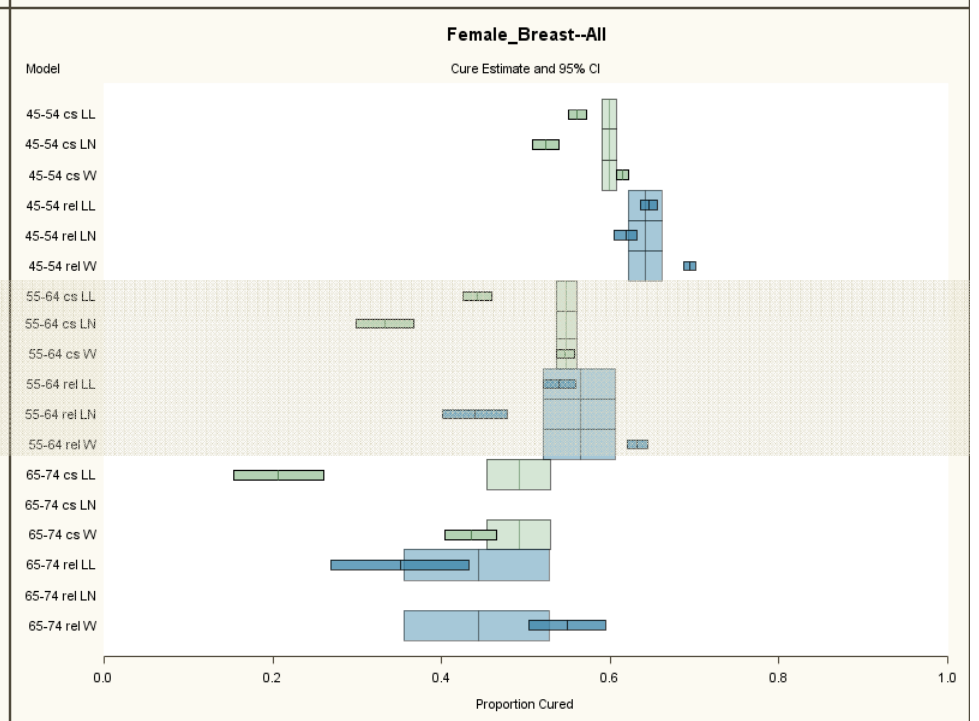
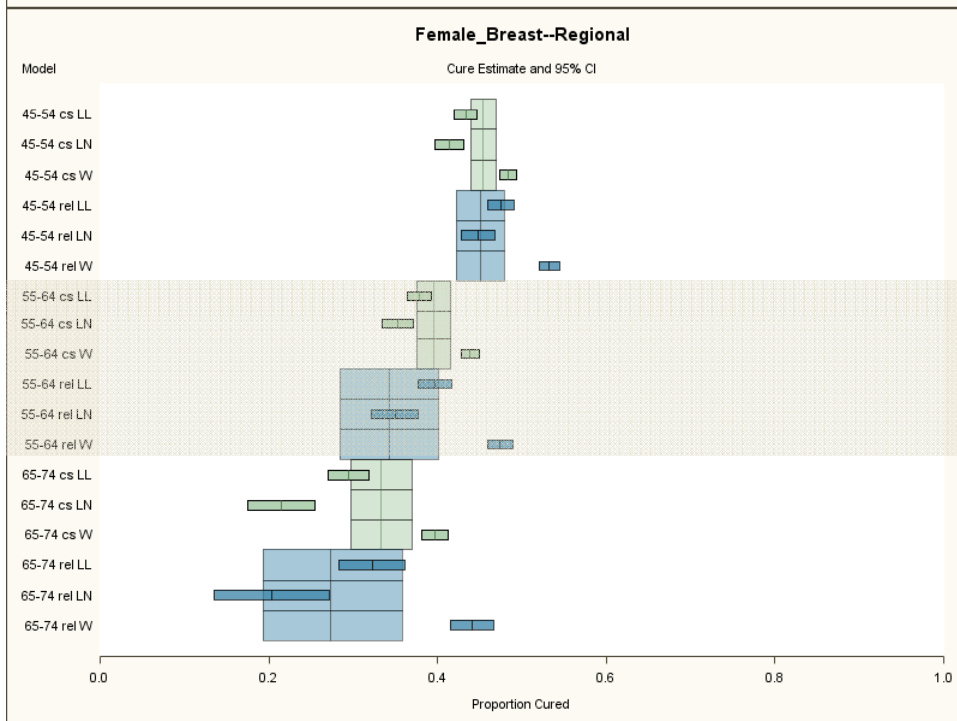
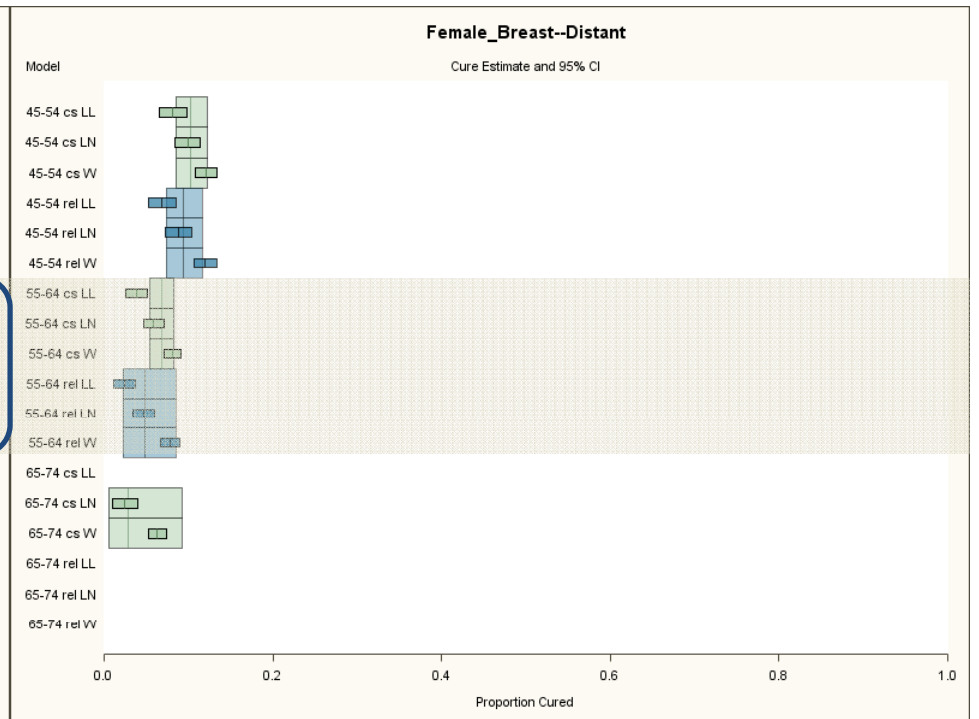
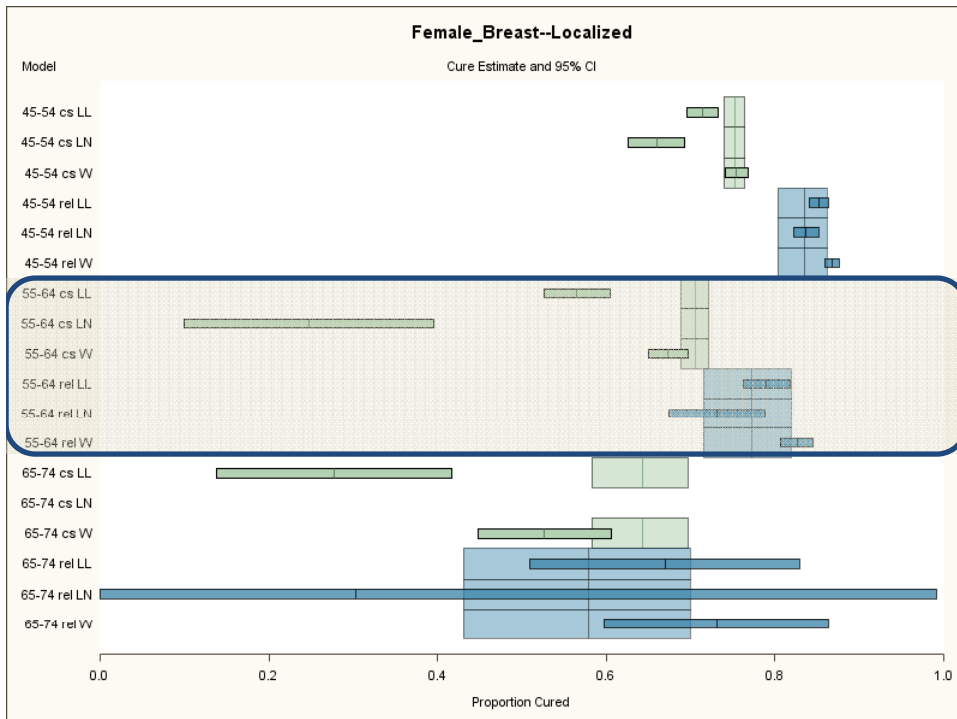
Cure Estimate and 95% CL

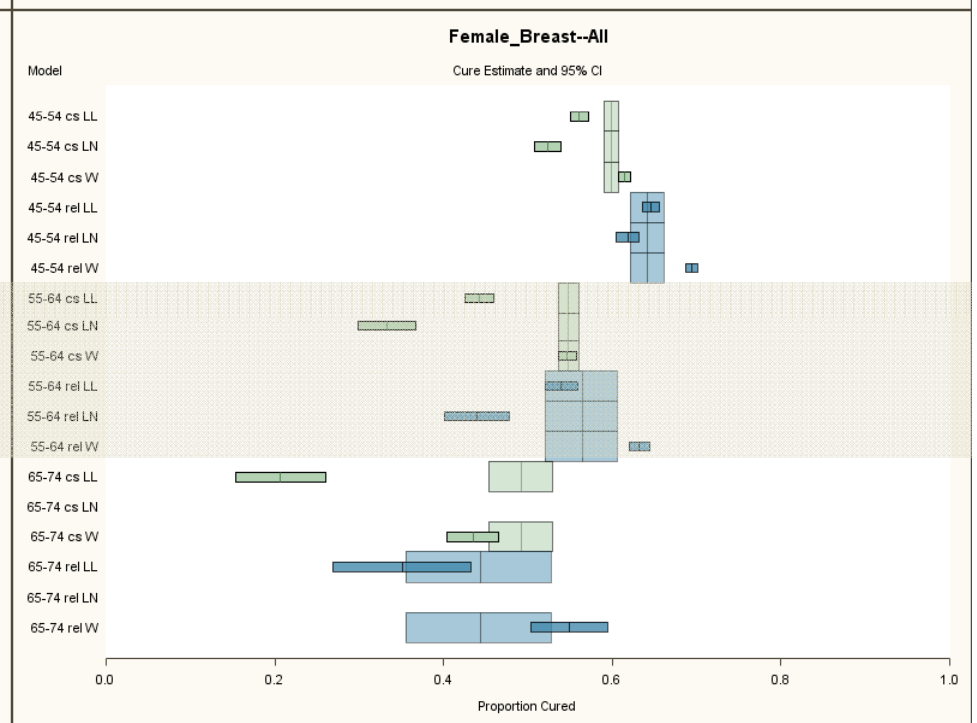
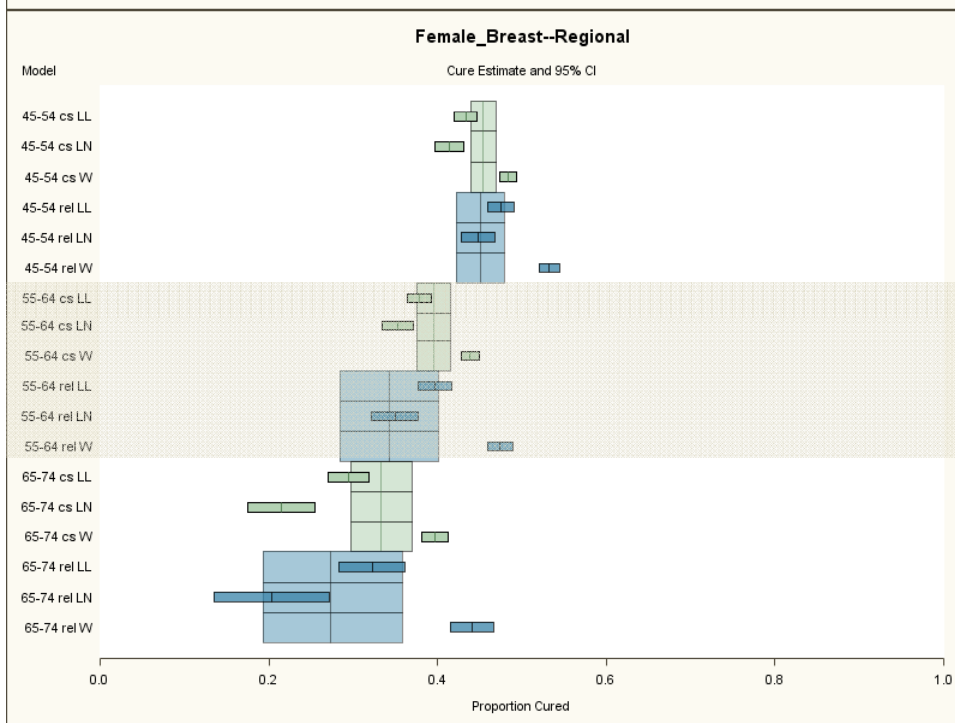
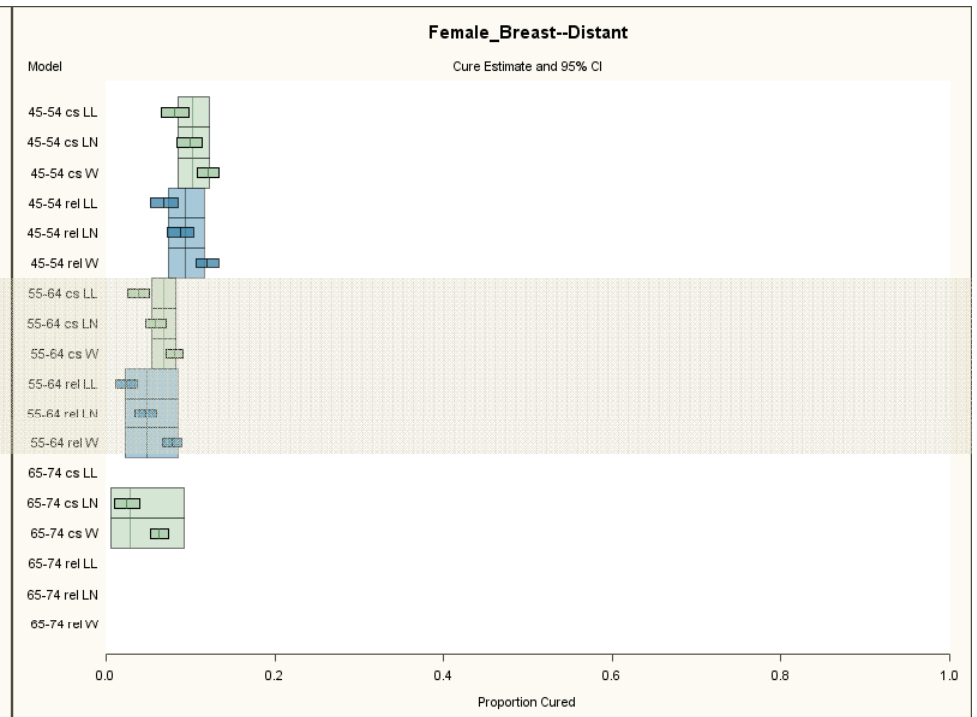
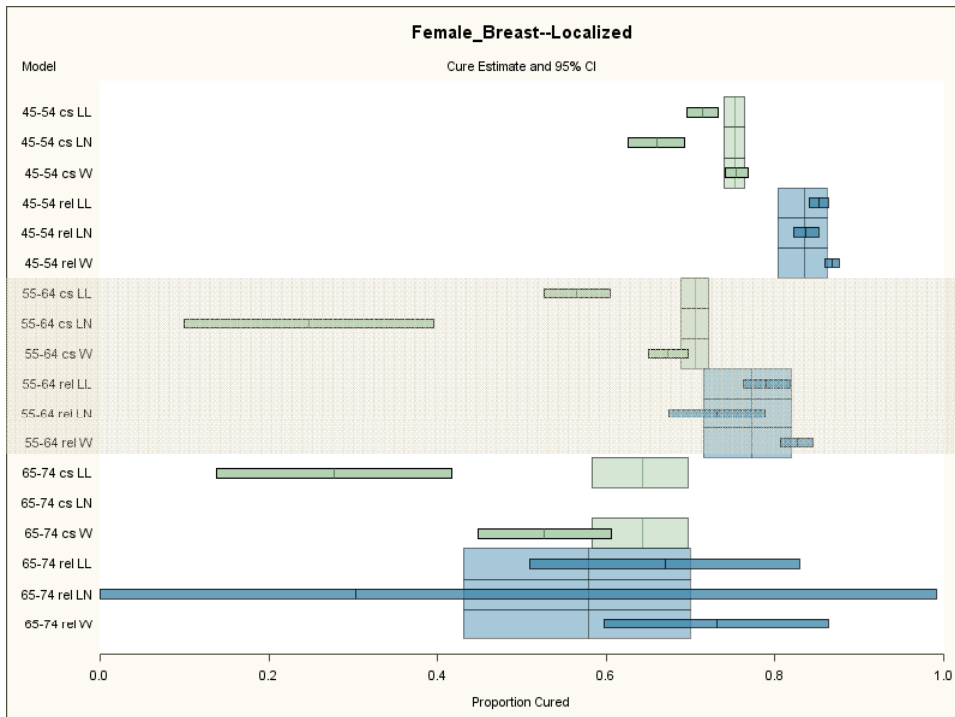
Cure

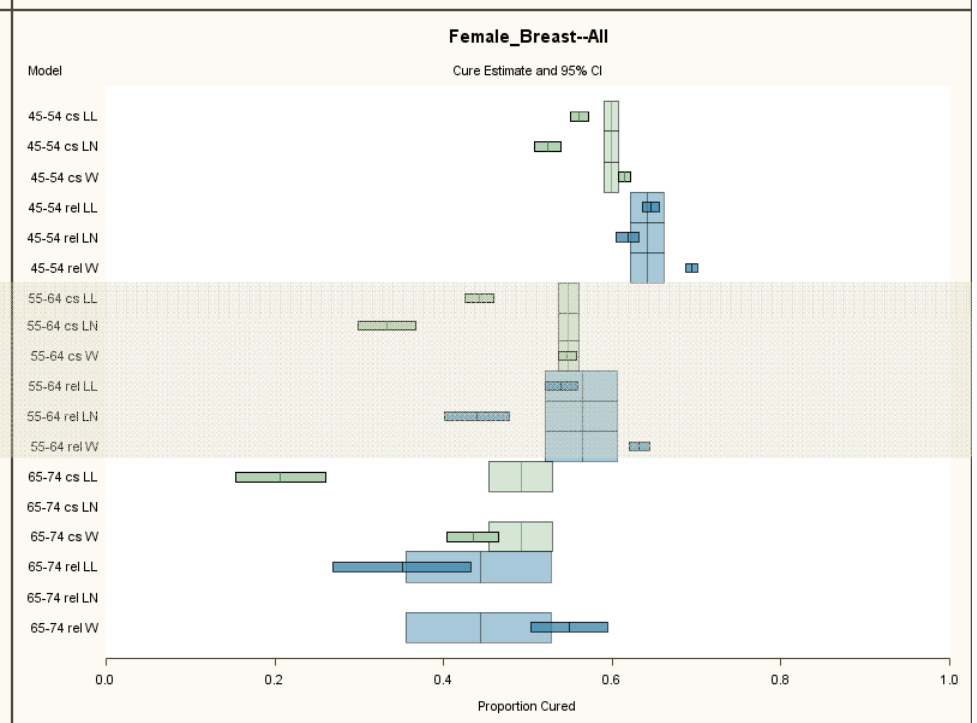
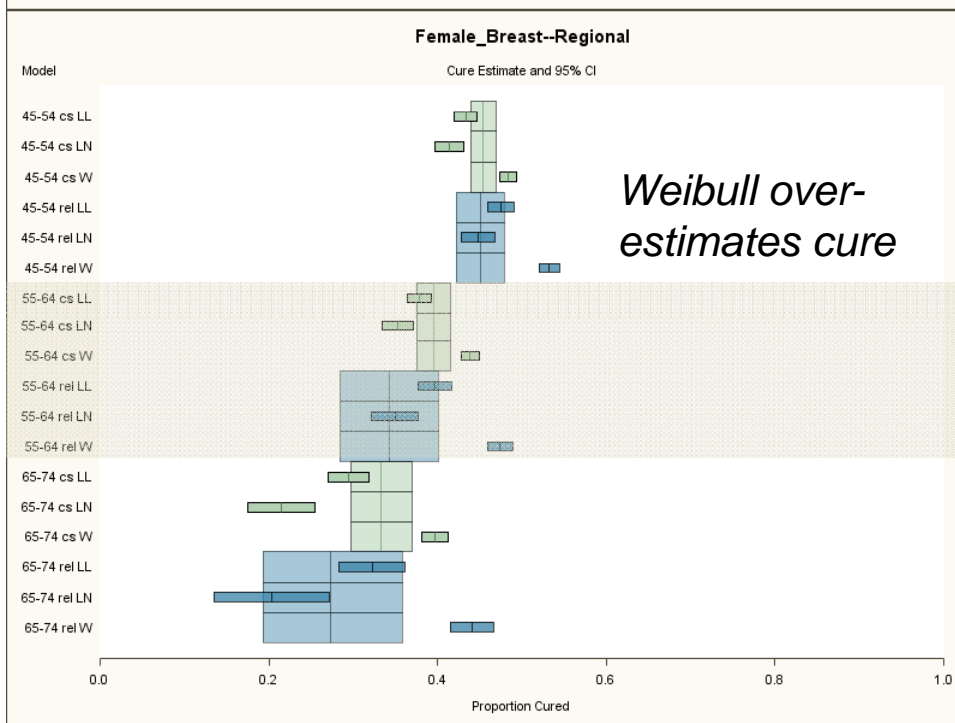
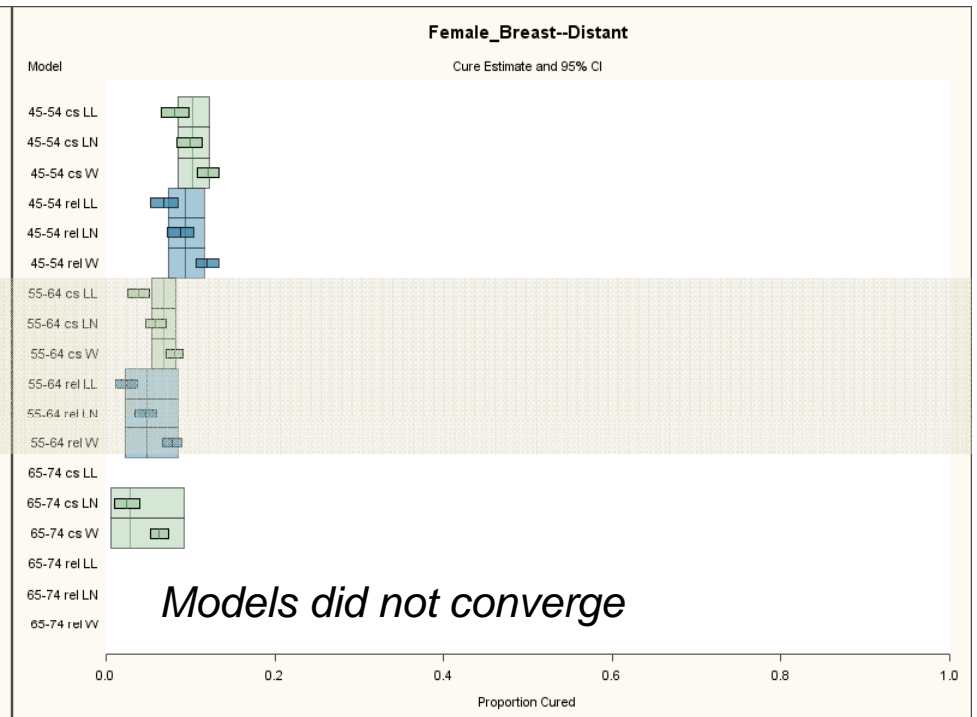
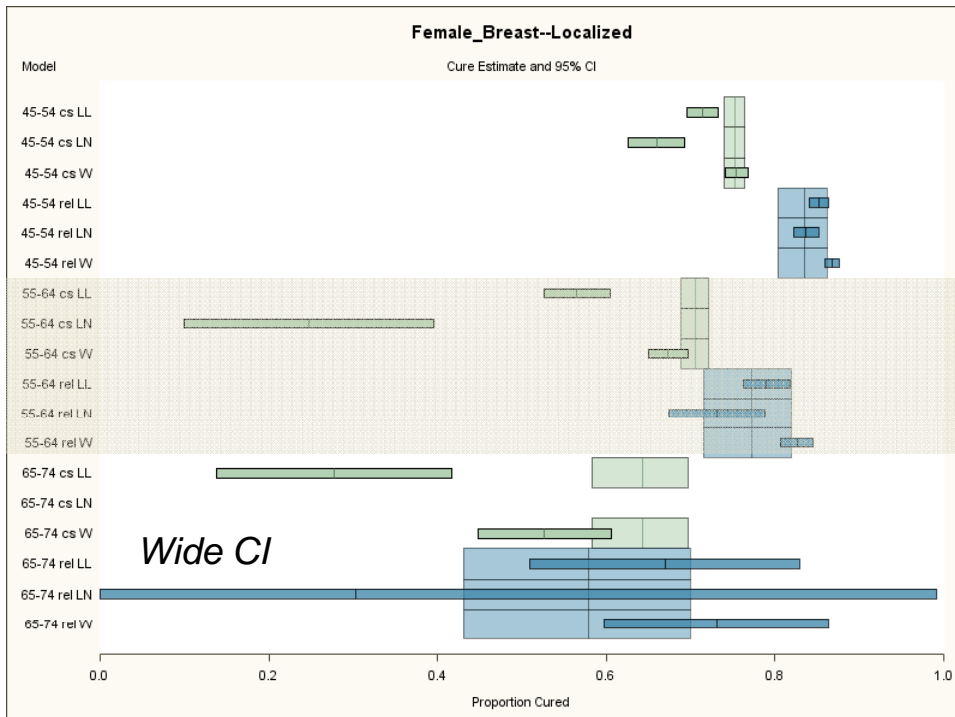
Cure SE

Median

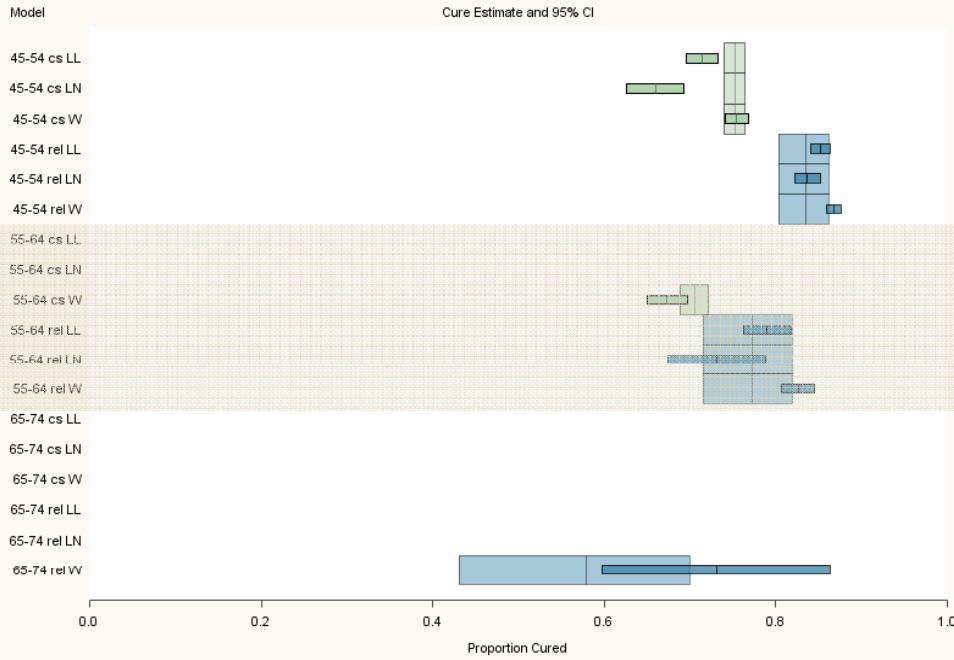




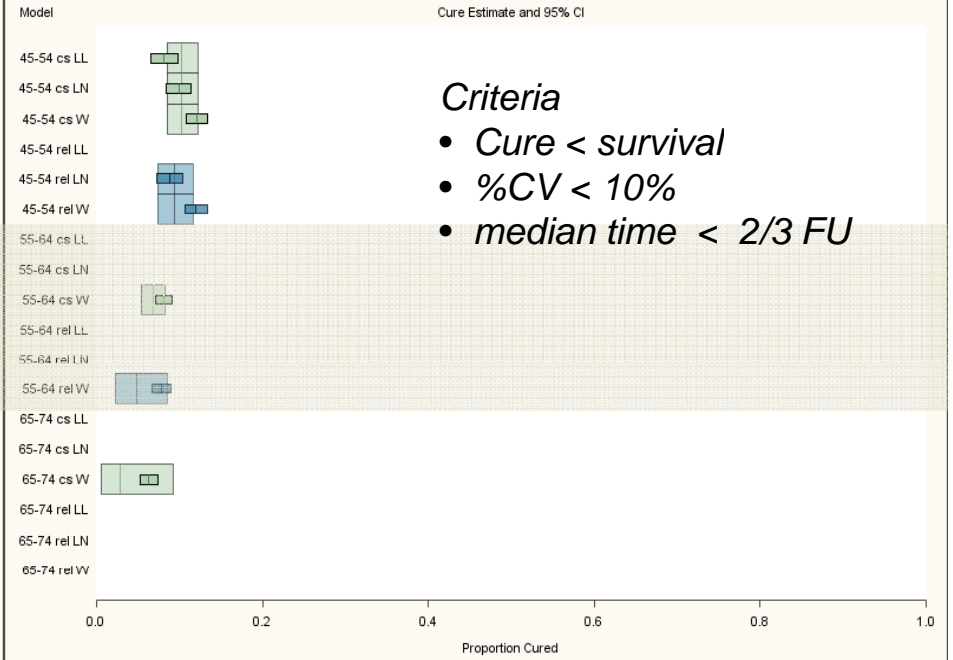




Female_Breast--Localized



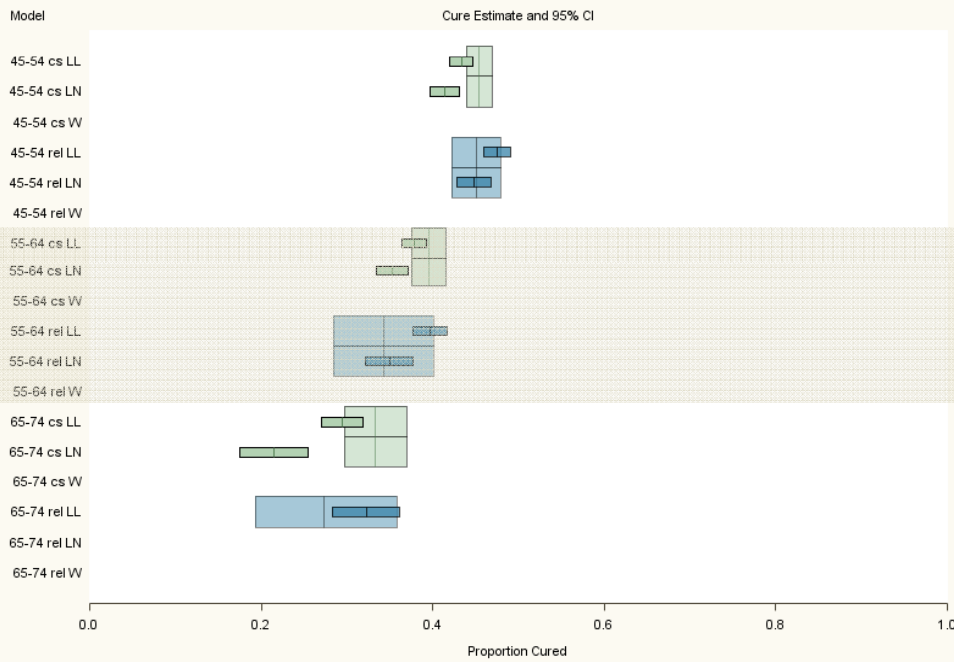
Female_Breast--Distant



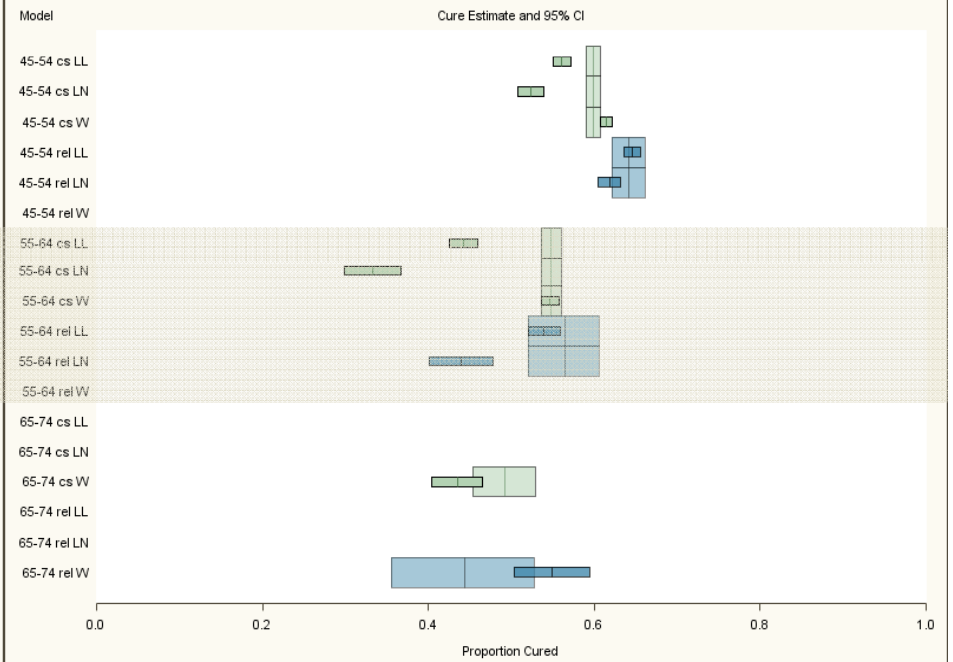
Criteria

- *Cure < survival*
- *%CV < 10%*
- *median time < 2/3 FU*

Female_Breast--Regional



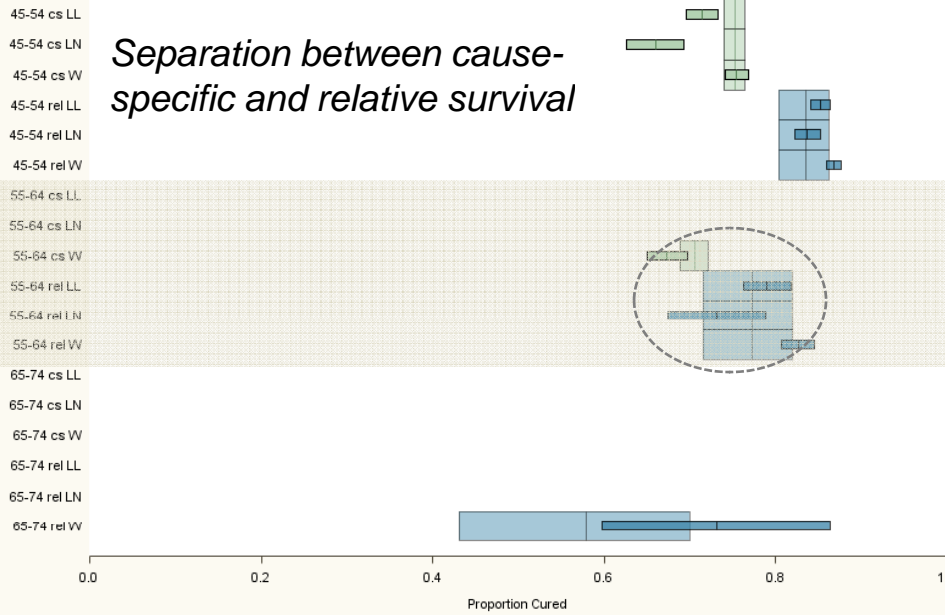
Female_Breast--All



Female_Breast--Localized

Cure Estimate and 95% CI

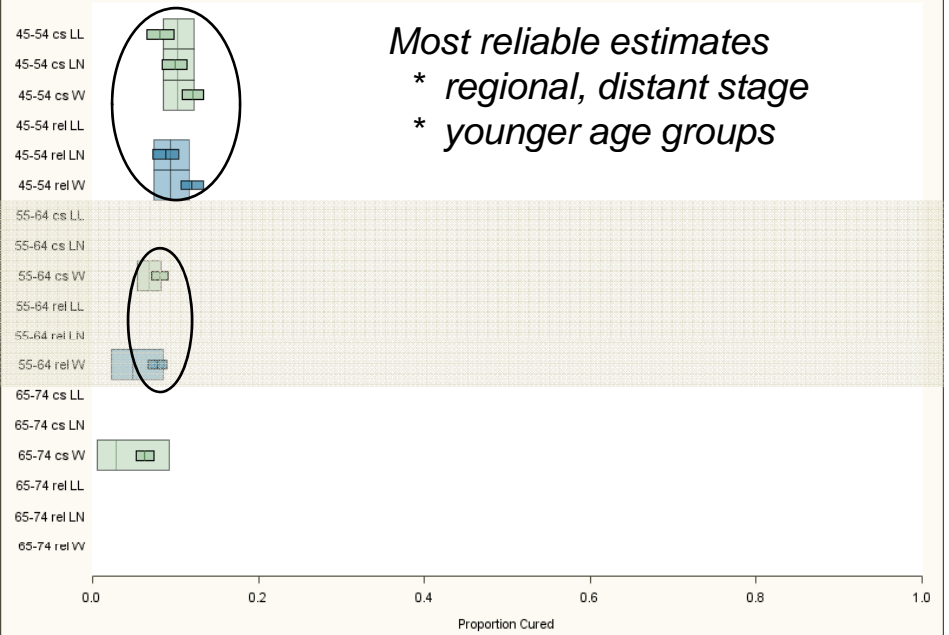
Model



Female_Breast--Distant

Cure Estimate and 95% CI

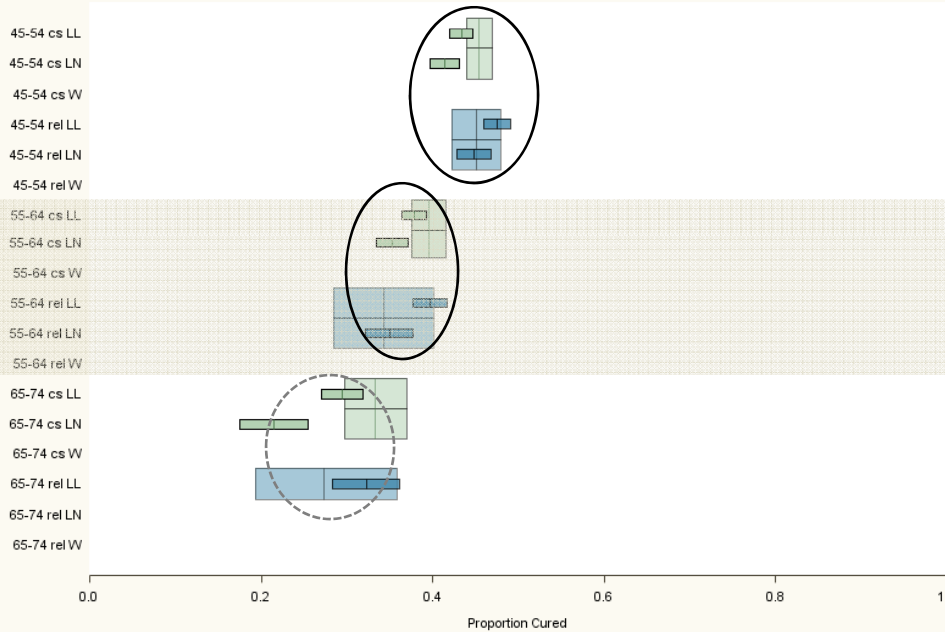
Model



Female_Breast--Regional

Cure Estimate and 95% CI

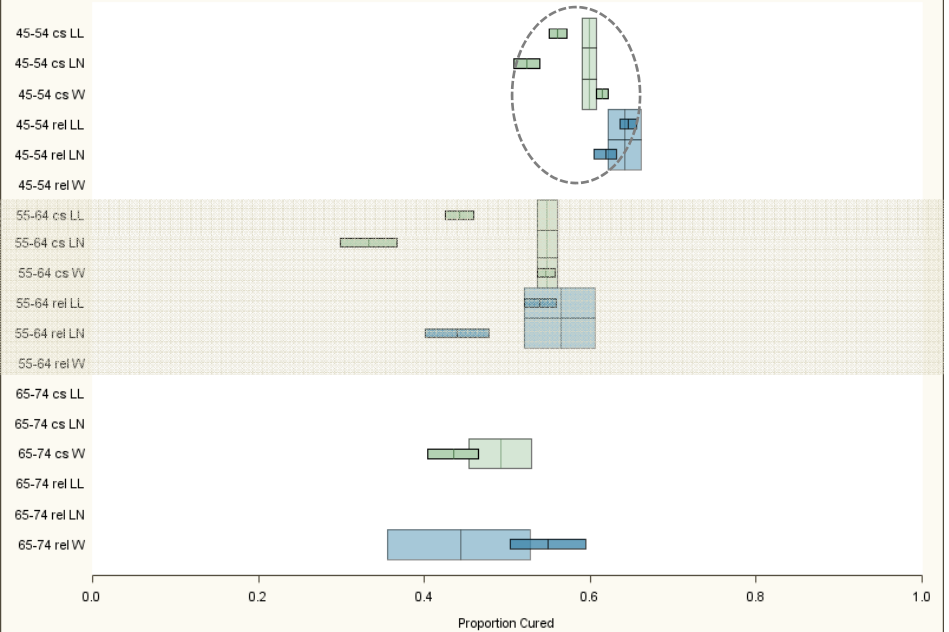
Model



Female_Breast--All

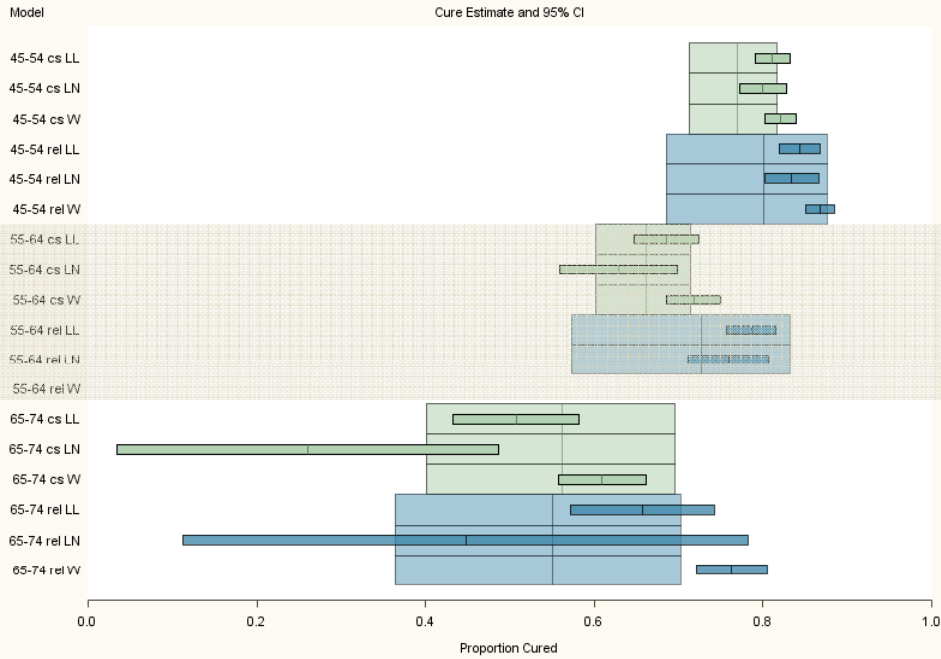
Cure Estimate and 95% CI

Model



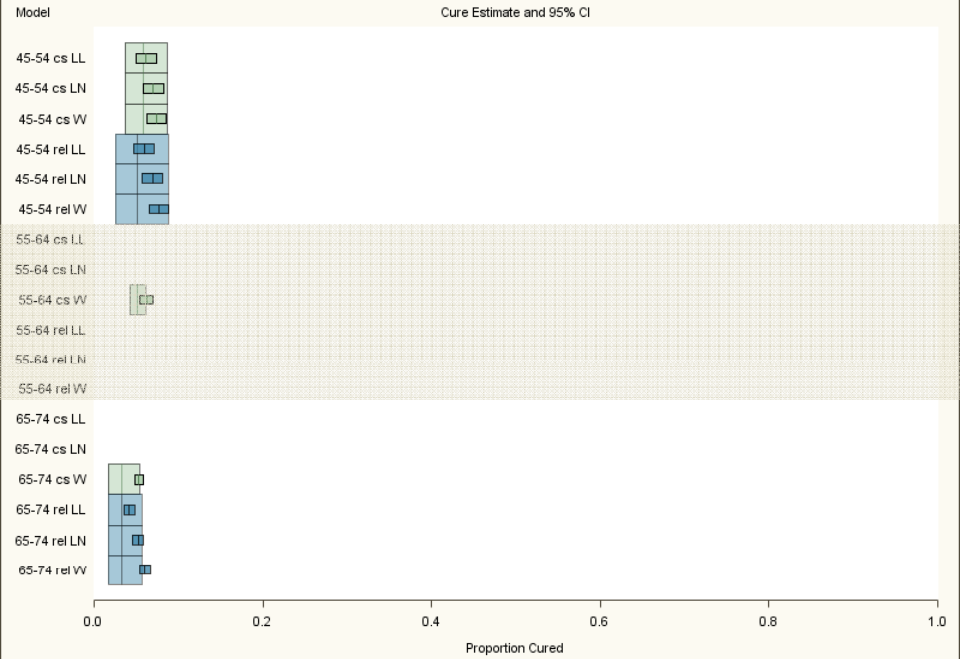
Female_CRC--Localized

Cure Estimate and 95% CI



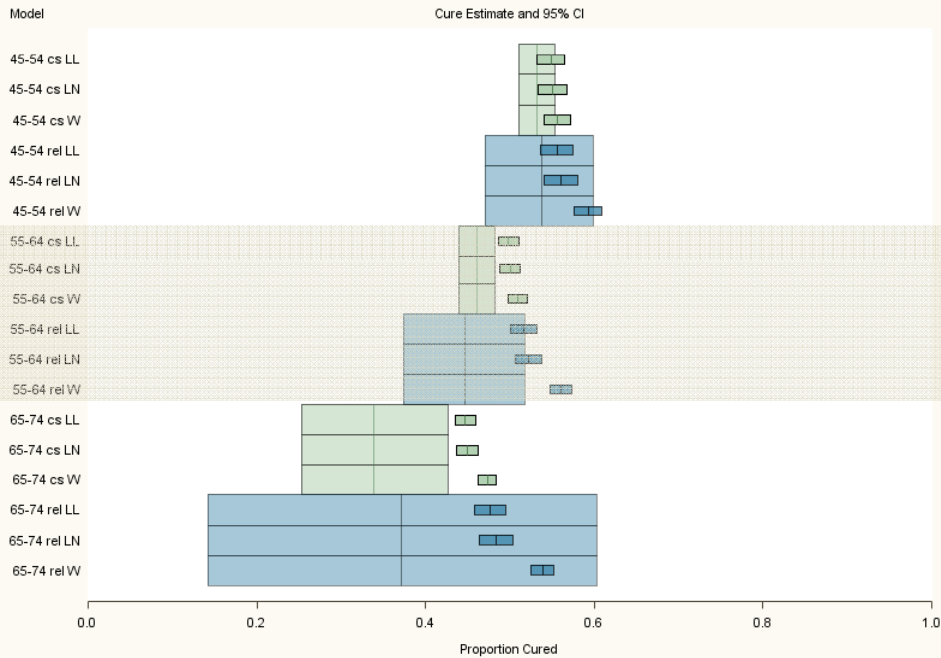
Female_CRC--Distant

Cure Estimate and 95% CI



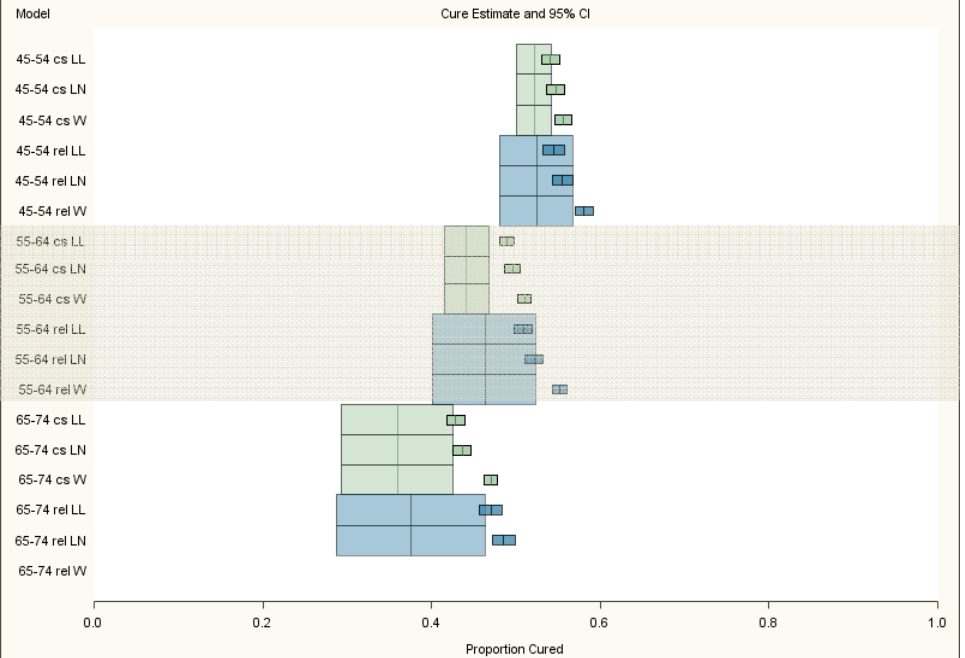
Female_CRC--Regional

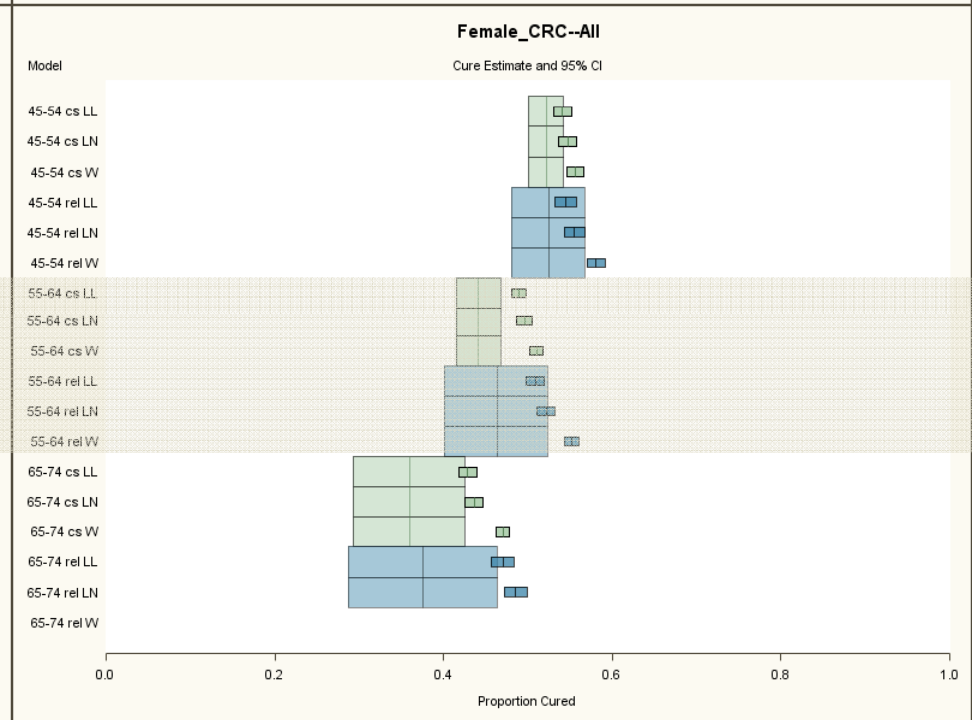
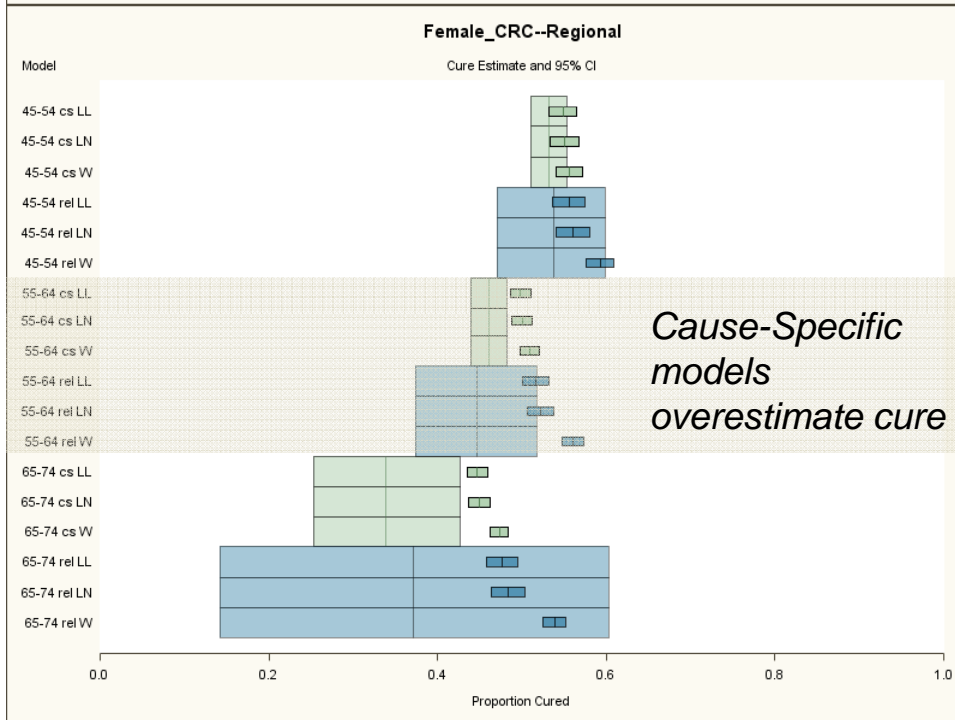
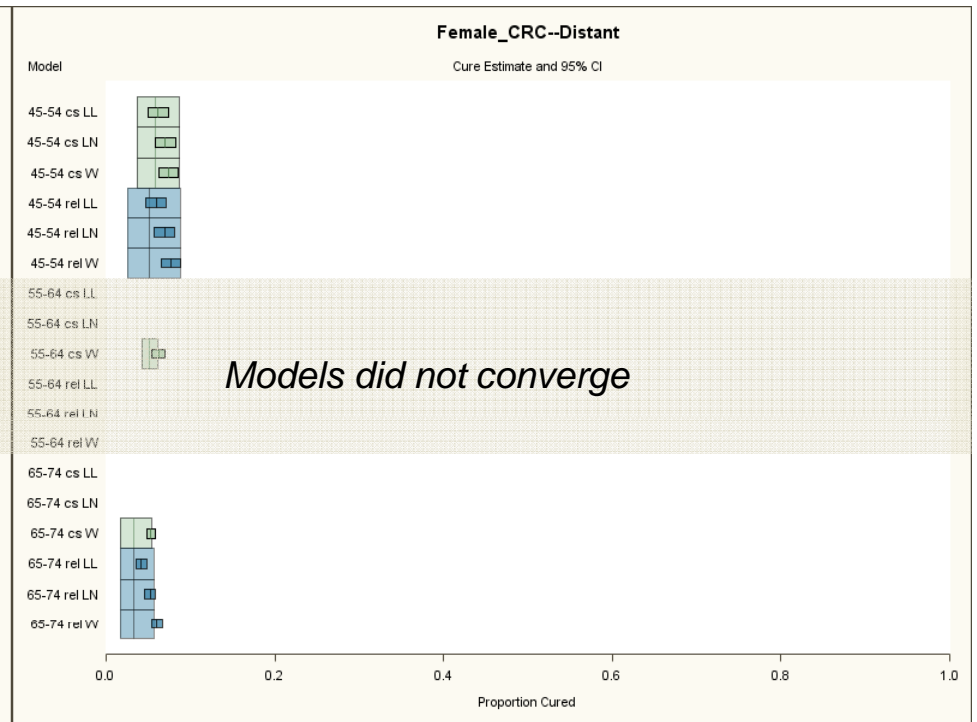
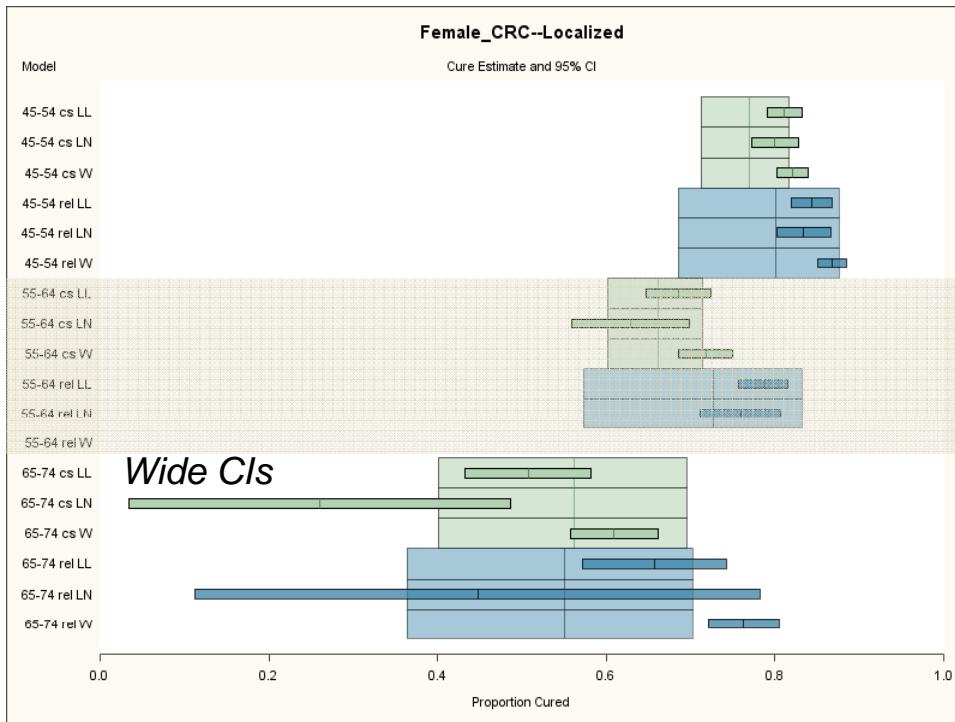
Cure Estimate and 95% CI



Female_CRC--All

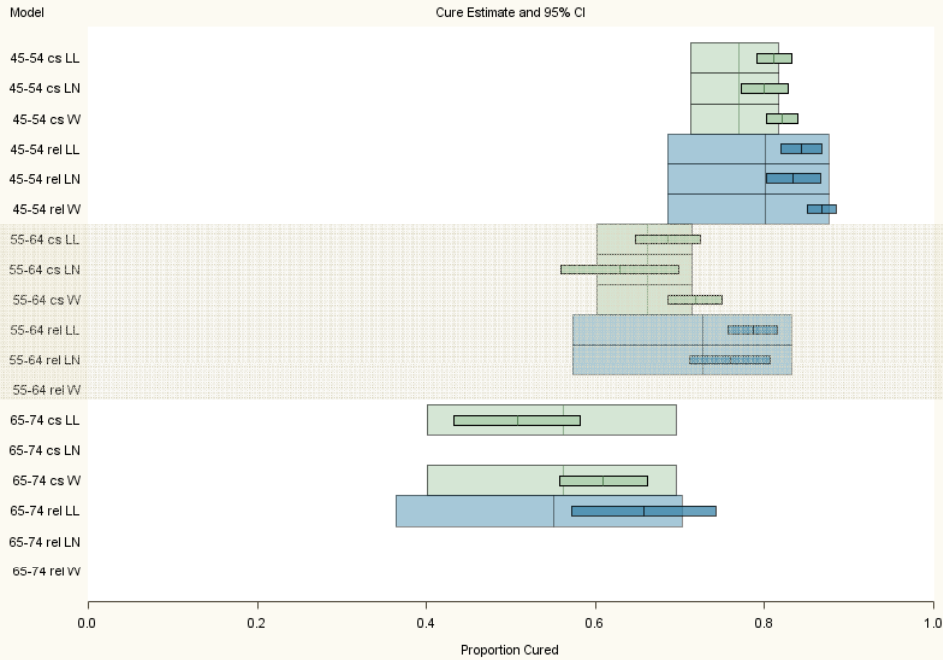
Cure Estimate and 95% CI





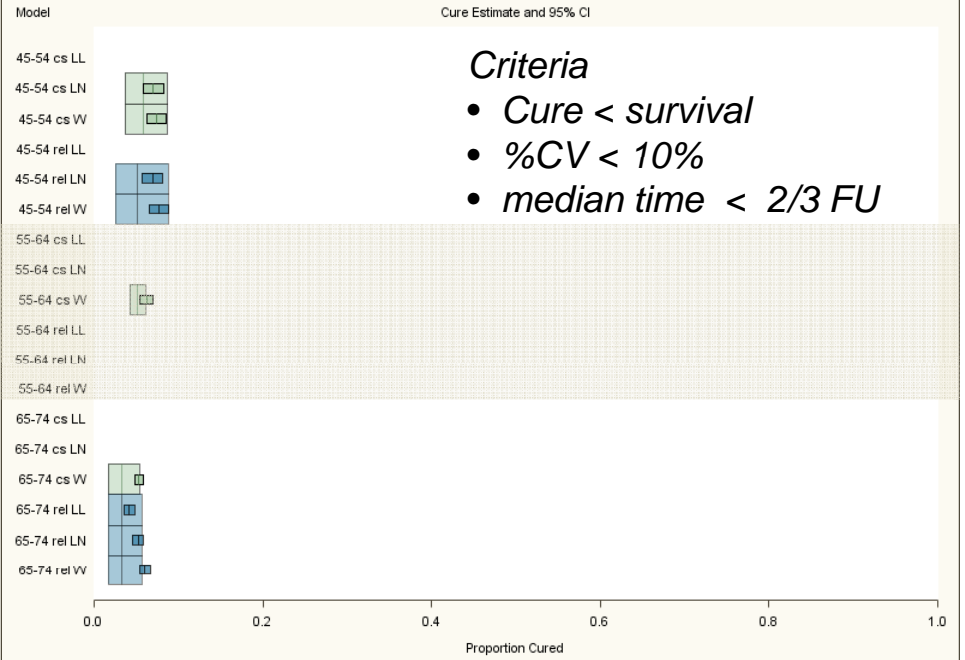
Female_CRC--Localized

Cure Estimate and 95% CI



Female_CRC--Distant

Cure Estimate and 95% CI

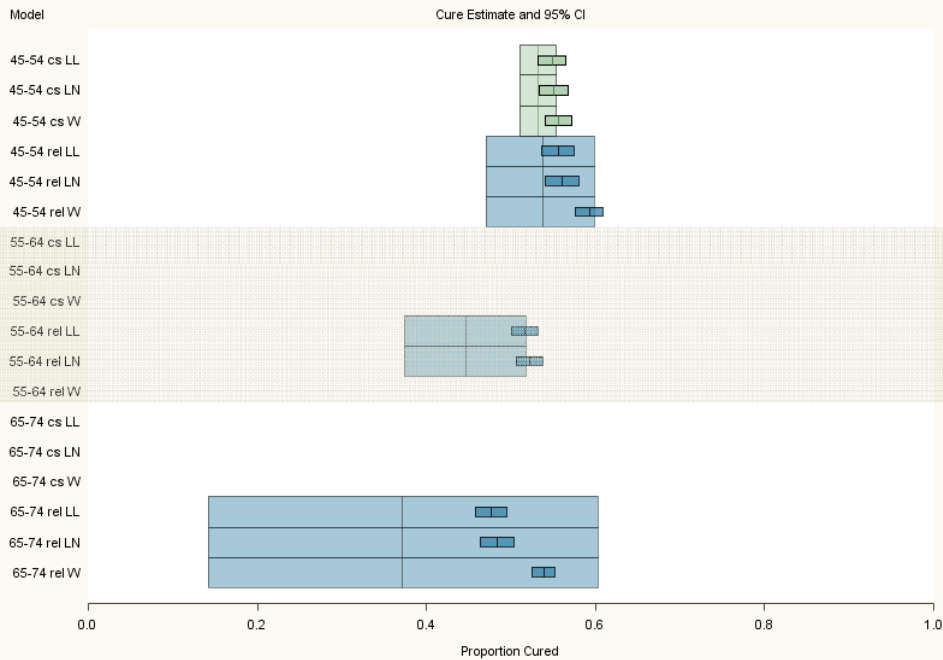


Criteria

- *Cure < survival*
- *%CV < 10%*
- *median time < 2/3 FU*

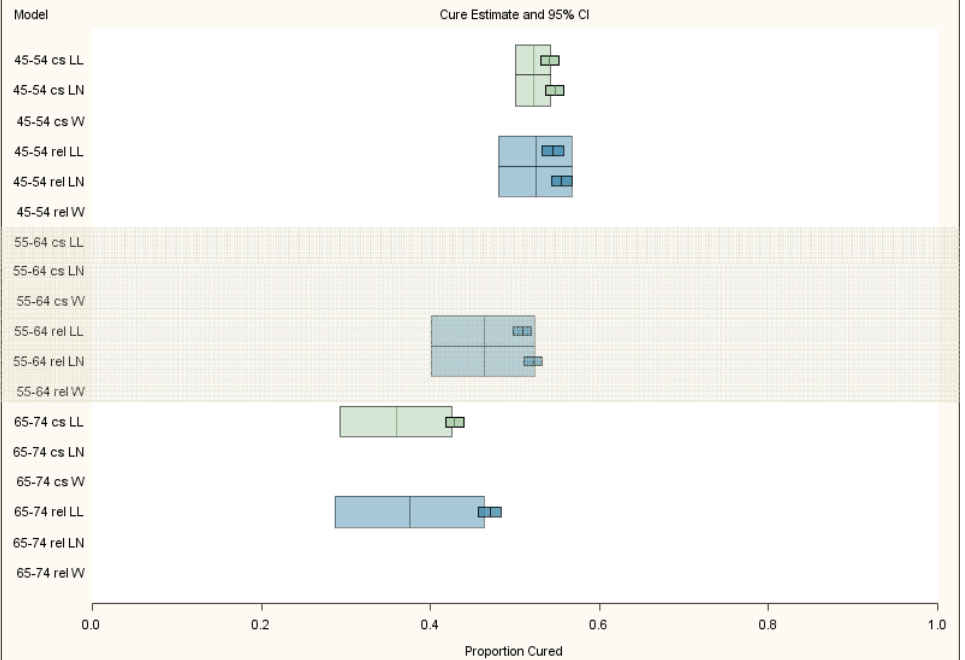
Female_CRC--Regional

Cure Estimate and 95% CI



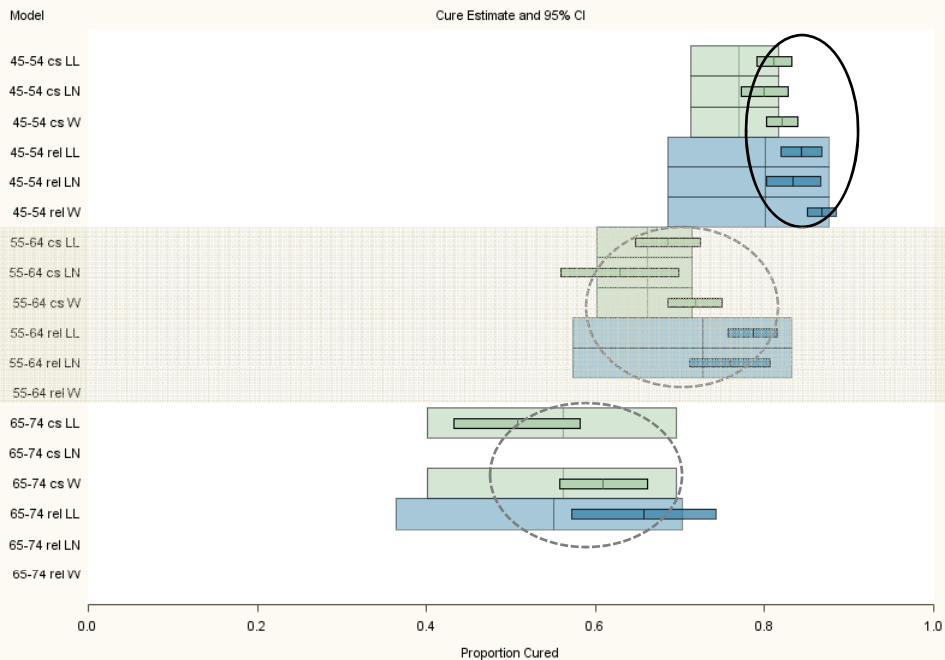
Female_CRC--All

Cure Estimate and 95% CI



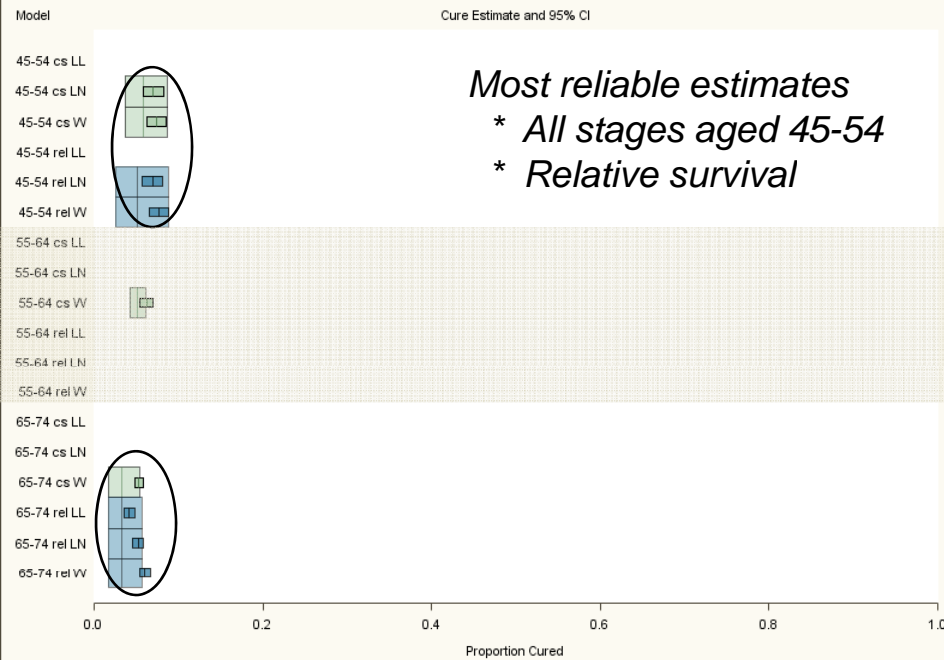
Female_CRC--Localized

Cure Estimate and 95% CI



Female_CRC--Distant

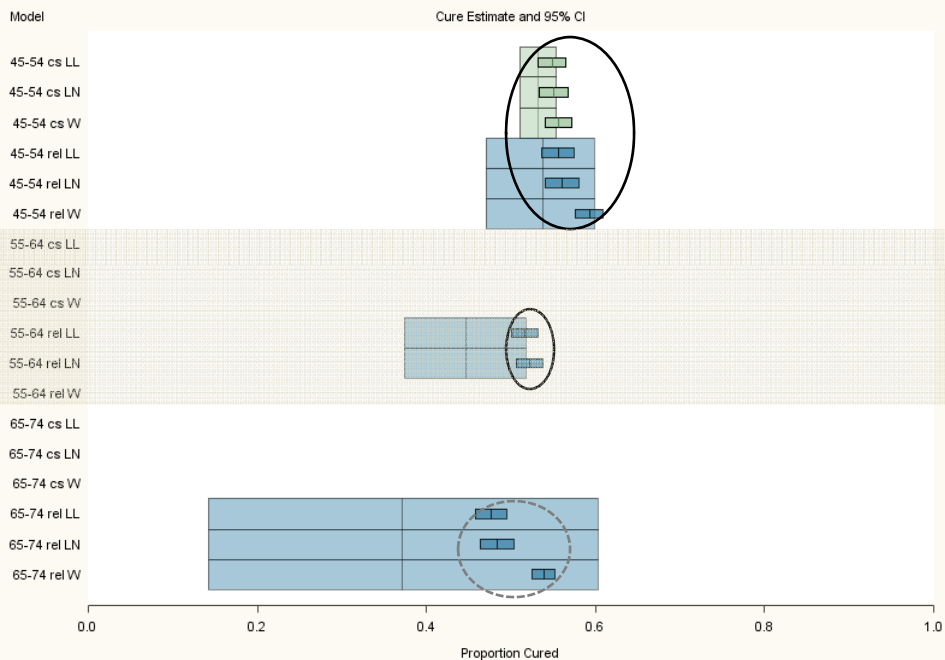
Cure Estimate and 95% CI



Most reliable estimates
 * *All stages aged 45-54*
 * *Relative survival*

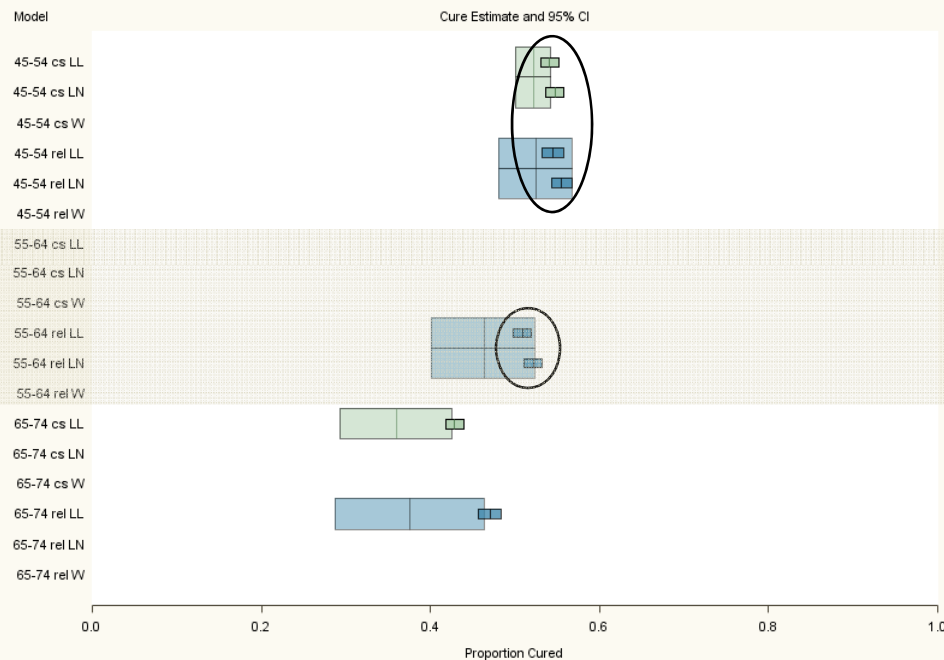
Female_CRC--Regional

Cure Estimate and 95% CI



Female_CRC--All

Cure Estimate and 95% CI



Cure Estimates -- Summary

Stage	Age	Breast Cancer	Colorectal Cancer
L	45-54	66% - 87%	80% - 87%
L	55-64	67% - 83%	63% - 79%
L	65-74	73%	51% - 66%
R	45-54	41% - 47%	55% - 59%
R	55-64	35% - 40%	52%
R	65-74	21% - 32%	48% - 54%
D	45-54	8% - 12%	7% - 8%
D	55-64	8%	6%
D	65-74	6%	4% - 6%
All	45-54	52% - 65%	54% - 56%
All	55-64	33% - 55%	51% - 52%
All	65-74	43% - 55%	43% - 47%

Conclusions -- subgroups

- **Site**
 - Breast cancer
 - Regional, distant stage
 - Cause-specific survival
 - Colorectal cancer
 - Relative survival
- **Stage : Regional**
 - Localized stage and inconsistent estimates
 - Increase in median survival relative to follow-up time
 - Differences in survival tail for Cause-Specific and Relative.
 - Distant stage and convergence problems.
 - cure estimates are close to zero.
- **Age: 45-54, 55-64**
 - 65-74 convergence problems, wide CIs
 - Cure decreases slightly with age, but less effect with advanced stage disease.

Conclusions-- criteria

- **Median time for uncured < 2/3 follow up**
 - localized disease with older age groups
- **% CV < 10%**
 - Distant stage disease where estimates are close to zero
 - Localized disease with older age groups.
- **Cure < last survival estimate**
 - Weibull distribution
 - All stages combined
 - Regional colorectal cancer, cause-specific estimates

Future Steps

- Additional cancer sites
- Adjust for diagnosis year in model
- Flexible models