Breast Cancer Patients Receiving Guideline-Concordant Adjuvant Therapy Regimens Have Better All-Cause and Disease-Specific Survival: New Findings from Rural Georgia

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Strong evidence that adjuvant therapies (chemo, radiation, hormonal therapies) can improve survival for women with invasive, non-metastatic breast cancer.

- **From randomized controlled trials (e.g.):**

- **From observational studies (e.g.):**
Background & Motivation

• But still significant limitations in the knowledge base:
  - Preponderance of evidence for guideline development so far derived from experimental studies – with strong internal validity, but limited generalizability to full range of invasive breast cancer cases.

  - Observational studies are of increasingly high quality, capitalizing on large, efficient secondary data bases linking central cancer registry data to insurance claims files (e.g., SEER-Medicare, SEER-Medicaid).

However......
  - Such data sources typically have limited geographic or population coverage. For example: large urban communities, one or more states or regions (but not a nation), elderly only, patients with certain types of insurance.

  - Multiple statistical challenges, especially selection bias threat.

  - Most studies focus on individual interventions, either alone or sometimes in combination. Little evaluation to date of the survival impact of guideline-concordant therapeutic regimens.
Study Objectives

• Investigate whether chemo-, radiation, and hormonal therapy regimens that are jointly guideline concordant (GC) improve survival outcomes among women diagnosed with invasive breast cancer in a rural region of the United States.

This will lead us to:

- Define GC “packages” of adjuvant therapies, conditional on patient characteristics, including type of surgery received.
- Develop population-based patient sample for valid inferences about quality of care and outcomes in “rural America.”
- Try to detect and statistically correct for selection bias at the patient level (via propensity score weighting & instrumental variables approaches)
- Identify data gaps and how to fill them for stronger analyses going forward.
SWGA comprises 33 largely rural counties: 82% of the population (724,000 during the 2001-2003 study period) resides in non-metro areas.

- Median household income is 72% of U.S. Average. About 21% of population lives below the Federal poverty line, compared with 12.4% nationally.
- About 38% of population is African-American.
- About 85% of cancer patients receive care at some Commission on Cancer-approved cancer center.
Data Sources and the Study Sample

• Patient demographic and treatment information drawn from CDC-supported study, “Determinants of Early Termination of Cancer Therapy” (SIP 05-07, awarded to Emory University in 2005)*

• Study population consisted of all women residing in SWGA diagnosed with breast cancer in 2001-2003 (N=1,289)
  - Received at least first 12 months of treatment post-dx in SWGA (N=1,096)
  - Diagnosed with 1st primary early-stage (AJCC I, II, or IIIA) breast cancer (N=908)
  - Did not receive neo-adjuvant (pre-surgical) therapy and met other study exclusion criteria (N=845)

• Cases initially identified by Georgia Comprehensive Cancer Registry (GCCR)

• Detailed treatment data collected via chart abstraction, using customized electronic data collection tool. Trained abstractors pulled charts at the 4 CoC-approved cancer centers and 23 smaller (“Other”) hospitals in SWGA.

• All-cause mortality and breast-cancer specific mortality through 2009 based on cause-of-death codes in GCCR & using NCI rules for cause-specific death.

### Chemotherapy Recs
(42 observations missing data needed for determination)

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor Characteristics</th>
<th>Chemotherapy Recommendation</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 years</td>
<td>Lymph node positive or tumor size ≥ 1 cm</td>
<td>Yes</td>
<td>n=526</td>
</tr>
<tr>
<td>≤ 70 years</td>
<td>Lymph node negative and tumor size &lt; 1cm</td>
<td>Discretionary</td>
<td>n=78</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td></td>
<td>Discretionary</td>
<td>n=261</td>
</tr>
</tbody>
</table>

### Radiation Therapy Recs
(69 observations missing data needed for determination)

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Tumor Characteristics</th>
<th>Radiation Therapy Recommendation</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS</td>
<td></td>
<td>Yes</td>
<td>n=436</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>≥ 4 positive lymph nodes or tumor size ≥ 5 cm</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1-3 positive lymph nodes and tumor size &lt; 5cm</td>
<td>Discretionary</td>
<td>n=103</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>Lymph node negative and tumor size &lt; 5 cm</td>
<td>No</td>
<td>n=299</td>
</tr>
</tbody>
</table>

### Hormonal Therapy Recs
(135 observations missing data needed for determination)

<table>
<thead>
<tr>
<th>ER/PR Status</th>
<th>Hormonal Therapy Recommendation</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR Positive</td>
<td>Yes</td>
<td>n=591</td>
</tr>
<tr>
<td>ER/PR Negative</td>
<td>No</td>
<td>n=181</td>
</tr>
</tbody>
</table>
Defining Guideline Concordance – and the Associated Key Independent Variable for Survival Analyses

**GC-Y:** Yes, patient is guideline concordant (GC) because she received recommended care or did not receive care that was not recommended

**GC-N:** Patient Not guideline concordant

**GC-D:** Guideline leaves it as a *discretionary* matter of judgment whether patient should receive the indicated care

- Patient is **GC-Y overall for breast cancer adjuvant therapy** if she is GC-Y jointly for chemo-, radiation, and hormonal therapy.
- Similarly, patient is **GC-N overall** if she is GC-N for any of the 3 adjuvant therapies.
- Patient is **GC-D overall** if she GC-D for one or more adjuvant therapies and not GC-N for any therapy.
## Receipt of Guideline-Concordant Adjuvant Therapy in SWGA Breast Cancer Sample

<table>
<thead>
<tr>
<th>Guideline Type</th>
<th>No. of patients</th>
<th>% of Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jointly Guideline Concordant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>163</td>
<td>33.4</td>
</tr>
<tr>
<td>No</td>
<td>282</td>
<td>19.3</td>
</tr>
<tr>
<td>Discretionary</td>
<td>400</td>
<td>47.3</td>
</tr>
<tr>
<td><strong>Chemotherapy Guideline Concordant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>308</td>
<td>38.0</td>
</tr>
<tr>
<td>No</td>
<td>178</td>
<td>22.0</td>
</tr>
<tr>
<td>Discretionary</td>
<td>325</td>
<td>40.1</td>
</tr>
<tr>
<td><strong>Radiation Therapy Guideline Concordant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>558</td>
<td>70.9</td>
</tr>
<tr>
<td>No</td>
<td>132</td>
<td>16.8</td>
</tr>
<tr>
<td>Discretionary</td>
<td>97</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Hormonal Therapy Guideline Concordant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>560</td>
<td>78.1</td>
</tr>
<tr>
<td>No</td>
<td>157</td>
<td>21.9</td>
</tr>
</tbody>
</table>
Analyzing Determinants of Breast Cancer Survival

No Bias Correction (but do adjust for covariates)

Factors Associated with Receipt of Care, Health Behaviors, and Competing Risks
- Insurance Status
- Race/ethnic Status
- Marital Status
- Comorbidity Status
- Area-level SES
- Urban -Rural Status
- Area Educ Status

Factors Associated with Tumor Development
- Stage at Diagnosis
- Hormonal Status
- Tumor Grade
- Age

Unobserved Factors Influencing Tx and Outcome and/or Poor Balance of Covariate Values across GC “arms”

Receipt of Guideline Tx: Yes, No, or Discretionary

Survival (all-cause and disease-specific)
Analyzing Determinants of Breast Cancer Survival: Bias Correction via Inverse Probability Propensity Score Weighting

**Factors Associated with Receipt of Care, Health Behaviors, and Competing Risks**
- Insurance Status
- Race/ethnic Status
- Marital Status
- Comorbidity Status
- Area-level SES
- Urban-Rural Status
- Area Educ Status

**Factors Associated with Tumor Development**
- Stage at Diagnosis
- Hormonal Status
- Tumor Grade
- Age

**Receipt of Guideline Tx: Yes, No, or Discretionary**

**Bias Correction (Weights)**

**Survival (all-cause and disease-specific)**

**Poor Balance of covariate values across GC “arms”**

**Facility-level Variable(s)**
- Cancer Center where Patient was Treated
Analyzing Determinants of Breast Cancer Survival: Bias Correction via 2-Stage Residual Inclusion (2SRI) Model

Factors Associated with Receipt of Care, Health Behaviors, and Competing Risks
- Insurance Status
- Race/ethnic Status
- Marital Status
- Comorbidity Status
- Area-level SES
- Urban-Rural Status
- Area Educ Status

Survival (all-cause and disease-specific)

Unobserved Factors Influencing Tx and Outcome

Receipt of Guideline Tx: Yes, No, or Discretionary

Instrumental Variable(s)
- Style of Practice at Cancer Center where Patient was Treated (as indexed here by the facility itself)

Bias Correction (Residuals)

Factors Associated with Tumor Development
- Stage at Diagnosis
- Hormonal Status
- Tumor Grade
- Age
Regression Model General Specifications

(1) “Adjusted” model:

Survival = S( GC-Y, GC-D, \( X_{\text{pat}} \)),

where functional form is the Cox proportional hazards (PH) model; the included GC variables levels are GC-Y and GC-D (with GC-N the reference category); and \( X_{\text{pat}} \) is a vector of patient-level covariates.

(2) Propensity Score-Weighted (“IPWT”) model*:

(a) Propensity(GC-Y, GC-N, GC-D) = M( \( X_{\text{pat}} \), \( X_{\text{pro}} \))

where M represents a multinomial logistic regression model (with GC-N here as the reference category); and \( X_{\text{pat}} \) and \( X_{\text{pro}} \) are patient and provider variables for predicting GC status.

(b) Create the (inverse probability) weight for each patient:

\[ w = \left( \frac{1}{\text{predicted probability of her actual GC status}} \right) \]

(c) Survival = S( [GC-Y]*w, [GC-D]*w, \( X_{\text{pat}} * w \) )


Regression Model General Specifications (cont)

(3) Two-stage residual inclusion (2SRI) instrumental variables model*

(a) First-stage regression: Probability(GC-Y, GC-N, GC-D) = M(all covariates from second-stage regression, IV’s) = M( X_{pat}, X_{pro} ) in the specification used here
(b) For each patient, compute the 3 residuals......
   r(GC-Y) = (actual value of GC-Y minus predicted GC-Y)
   r(GC-N) = (actual value of GC-N minus predicted GC-N)
   r(GC-D) = (actual value of GC-D minus predicted GC-D)
(c) Second-stage regression:
   \[
   \text{Survival} = S( \text{GC-Y}, \text{GC-D}, r(\text{GC-Y}), r(\text{GC-D}), X_{\text{pat}} )
   \]

### All-Cause Survival Analyses: Key Findings from Alternative Cox PH Models (N=623; Deaths=153)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>IPWT HR (95% CI)</th>
<th>2SRI HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC-N</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>GC-Y</td>
<td>0.56 (0.39-0.93)</td>
<td>0.42 (0.23-0.78)</td>
<td>0.54 (0.28-1.03)</td>
</tr>
<tr>
<td>GC-D</td>
<td>0.84 (0.56-1.27)</td>
<td>0.75 (0.47-1.18)</td>
<td>0.77 (0.47-1.26)</td>
</tr>
<tr>
<td>Stage I</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Stage II</td>
<td>1.93 (1.29-2.90)</td>
<td>2.33 (1.34-4.05)</td>
<td>1.92 (1.21-3.02)</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>6.64 (4.12-10.70)</td>
<td>7.24 (3.73-14.06)</td>
<td>5.85 (3.38-10.11)</td>
</tr>
<tr>
<td>Age &lt; 50</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Age 50-64</td>
<td>1.26 (0.74-2.17)</td>
<td>1.17 (0.58-2.36)</td>
<td>1.27 (0.68-2.36)</td>
</tr>
<tr>
<td>Age 65+</td>
<td>2.61 (1.46-4.66)</td>
<td>2.41 (1.07-5.46)</td>
<td>2.77 (1.32-5.79)</td>
</tr>
<tr>
<td>Married</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Not Married</td>
<td>1.79 (1.24-2.57)</td>
<td>1.73 (1.13-2.64)</td>
<td>1.72 (1.16-2.56)</td>
</tr>
<tr>
<td>r(GC-Y)</td>
<td>NA</td>
<td>NA</td>
<td>0.97 (0.27-3.45)</td>
</tr>
<tr>
<td>r(GC-D)</td>
<td>NA</td>
<td>NA</td>
<td>0.55 (0.23-1.33)</td>
</tr>
</tbody>
</table>

*Not significant at p=0.05:* Race/ethnic Status (Black-White), Insurance Status, Area-level SES, Urban-Rural Status, Area Educ Status, Comorbidity Status, Treatment Delay Status, Hormonal Status, Tumor Grade
Breast Cancer-specific Survival Analyses: Key Findings from Alternative Cox PH Models (N=623; Deaths= 98)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>IPWT HR (95% CI)</th>
<th>2SRI HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC-N</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>GC-Y</td>
<td>0.54 (0.31-0.93)</td>
<td>0.45 (0.23-0.78)</td>
<td>0.48 (0.18-1.31)</td>
</tr>
<tr>
<td>GC-D</td>
<td>0.59 (0.35-1.00)</td>
<td>0.55 (0.29-1.01)</td>
<td>0.51 (0.20-1.34)</td>
</tr>
<tr>
<td>Stage I</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Stage II</td>
<td>2.36 (1.38-4.04)</td>
<td>2.62 (1.27-5.41)</td>
<td>2.36 (1.31-4.26)</td>
</tr>
<tr>
<td>Age &lt; 50</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Age 50-64</td>
<td>1.23 (0.67-2.24)</td>
<td>1.07 (0.49-2.33)</td>
<td>1.22 (0.61-2.47)</td>
</tr>
<tr>
<td>Age 65+</td>
<td>2.31 (1.18-4.52)</td>
<td>1.97 (0.73-5.32)</td>
<td>2.26 (0.98-5.23)</td>
</tr>
<tr>
<td>Married</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Not Married</td>
<td>1.21 (0.78-1.88)</td>
<td>1.29 (0.80-2.09)</td>
<td>1.20 (0.72-1.99)</td>
</tr>
<tr>
<td>r(GC-Y)</td>
<td>NA</td>
<td>NA</td>
<td>0.73 (0.12-4.39)</td>
</tr>
<tr>
<td>r(GC-D)</td>
<td>NA</td>
<td>NA</td>
<td>0.90 (0.20-4.01)</td>
</tr>
</tbody>
</table>

Not significant at p=0.05: Race/ethnic Status (Black-White), Insurance Status, Area-level SES, Urban-Rural Status, Area Educ Status, Comorbidity Status, Treatment Delay Status, Hormonal Status, Tumor Grade
Snap-shot of Model Performance Statistics

**Adjusted Cox PH approach:**
- **All-Cause:** Schoenfeld Residuals test of PH assumption: Of the 20 included variable levels associated with $X_{pat}$ in survival model, only 2 (being uninsured and having some comorbidity) were significantly different from 0 at p=0.05.
  
  Harrell’s Concordance (C) goodness-of-fit statistic = 0.7401.
- **Breast Cancer-specific:** Schoenfeld Residuals test for PH assumption: Only 1 of the 20 $X_{pat}$ variable levels was significantly different from 0.
  
  Harrell’s C statistic = 0.7599

**IPWT (Propensity Score Weighted) approach:**
- In the *unweighted* sample of covariates used for survival analyses, 11 of 13 variables exhibited significant imbalance of values across the key independent variable (GC-Y, GC-N, GC-D). After PS weighting, no significant imbalances.
- Coefficient of concordance (c) for multinomial model generating PS scores = 0.7875
2SRI Approach:

• Strength of instrumental variable (facility where treated) in the first-stage regression: F statistic for null that IV = 0 was 29.7 (p<0.05).
• Similar good performance for alternative constructions of IV, including “percent of women GC-Y at each facility.”
• For Cox PH survival analysis, Harrell’s C statistic = 0.7446 for All-Cause model and 0.7602 for Breast Cancer-specific model.

Missing Values Analysis:

• Given high-quality registry and detailed records abstraction, no variable missing more than 5% of values, except Hormonal Status – that is, ERPR (Estrogen Receptor- Progesterone Receptor) Status.
• Imputed ERPR through multiple-imputation approach (in Stata), thus raising available sample for multivariable analyses from 623 to 721.
• But virtually no impact on patterns of significant predictors in models
Conclusions, in Brief......

• Breast cancer patients in rural Georgia receiving guideline concordant adjuvant therapy had significantly better All-Cause and Breast Cancer-specific survival – based on Cox PH model analyses controlling for multiple clinical and demographic factors, as well as potential patient-level selection bias.

• It is feasible to operationally define GC “packages” of care to investigate impact of bundles/episodes of care on outcomes → how to define “performance” in P4P schemes
Conclusions, in Brief......

• Most significant limitation: **data gaps** → no info on treatment patterns and patient characteristics (e.g., insurance status) for period between completion of initial cancer treatment and death.

• Correspondingly, single most important advance to improve such **secondary data analyses** would be creation of longitudinal patient profiles: clinical, demographic, SES, treatment patterns, and outcome.

• Important archetype already exists: NCI’s SEER-Medicare data base. Next key step: extend the concept by augmenting population-based cancer registry data with multiple public & private administrative files to cover all ages & geographic areas.

• And then amplify further by adding the **patient’s perspective**: not only PRO’s, but reports on barriers and facilitators to care.
That way, we’ll be on a better road for evaluating the quality of cancer care.
Study Sponsored by:

Community Partners:

Phoebe Putney Cancer Center, Albany, GA
Tift Medical Center, Tifton, GA
Archbold Medical Center, Thomasville, GA
South Georgia Medical Medical Center, Valdosta