# Disease Risk Scores: Use in a Retrospective Analysis Regarding Correlation between Time to Adjuvant Chemotherapy Treatment (TTAC) and Disease Outcomes in Early Breast Cancer

**May 19th, 2015**

*Ravi Ramjeesingh, Bingshu E. Chen, Joseph Pater, Wendy R. Parulekar*

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

# Optimal Time to Adjuvant Chemotherapy Administration

- *Earlier is better!*
  - Minimal tumour burden after primary surgical resection
  - Biological stimulus for growth after tumour removal

# Optimal Time to Adjuvant Chemotherapy Administration

- Literature shows mixed results
  - Differences in burden of disease
  - Chemotherapy regimens
  - Time intervals evaluated
  - Retrospective analyses using registry data, single institutional data

# Rationale for Project

- Data inconsistent
- Variable quality
- More accurate assessment of association might be provided by prospectively compiled, phase III datasets

# Dataset

- A retrospective analysis of 4 phase III NCIC Clinical Trials Group (NCIC CTG) led studies involving women diagnosed with stage 1 to 3 breast cancer between 1984 to 2005

# Phase III Trial Dataset for Analyses

- NCIC CTC MA.4-Tamoxifen +/- CMF
- NCIC CTG MA.5- CMF vs CEF
- NCIC CTG MA.12- Tamoxifen vs placebo after chemotherapy
- NCIC CTG MA21- DD ECT vs ACT vs CEF

# Phase III Trial Dataset for Analyses

- Eligible for analyses
  - Enrolled on studies
  - No evidence of advanced disease
  - Received chemotherapy
- Final sample size: 3837

# Study Population

- 22% Stage 3
- 94% < 60 years
- 99% PS 0,1
- 60% BMI > 25
- Timing of adjuvant therapy

  < 4 weeks:  789 (21%)

  4 to <8 weeks: 2664 (59%)

  8 to 12 weeks: 749 (19.5%)

NCIC CTG
NCIC GEC

# Results: Univariate Analysis: OS

| | OS | | | | |
|---|---|---|---|---|---|
| **Interval Between Last Sx to Chemo Start (sTTC)** | **# of Deaths** | **5 yr OS** | **p-value** | **10 yr OS** | **p-value** |
| **<4 weeks** | 228/774 | 81.4 | ref | 69.6 | ref |
| **4-<8 weeks** | 603/2263 | 83.7 | 0.1446 | 71.5 | 0.2028 |
| **8-12 weeks** | 157/742 | 86.3 | **0.0138** | 77.3 | **0.0004** |
| **>12 weeks** | 8/35 | 82.9 | 1.000 | 77.0 | 0.5675 |

# Results: Multivariate Analysis: OS

| | OS |
|---|---|
| Variable | P-value |
| Surgery to Chemotherapy Start | |
| <4 weeks | Ref |
| 4-<8 weeks | 0.7762 |
| 8-12 weeks | 0.4251 |
| >12 weeks | 0.6861 |

Significant Variables From the Analysis included: Age, BMI, PS (2), Menopause status (Pre/Post), Pathological Stage (3), ER Receptor status, Nodal Status (N1/N2/N2), Chemotherapy (EC+T/AC+T//CEF)

# Results

- We postulated that the differences between univariate and the multivariate results might be better understood by the use of disease risk score which is a more clinically intuitive way of representing the covariate data
  - i.e. higher risk patients are offered chemotherapy earlier

# Disease Risk Score Calculation

Risk Score= -0.0235*age + 0.129*bmi-0.0206*(PS=1) + 0.758*(PS=2) + 0.273*(post menopausal) - 0.328*(Partial mastectomy)- 0.479*(unknown surgery)+0.124*(pStage2)+0.687*(pStage=3) + 0.125*(chemo='AC‘)-0.436*(chemo='AC+T') - 0.493*(chemo='CEF')-0.782*(chemo='EC+T') + 0.545*(er_sta='Negative')+0.535*(N1 stage) + 0.619*(N2 Stage) + 1.443*(N3 Stage) + 0.00179*(No Hormone Given)

# Disease Risk Score Method

- Post-hoc disease risk score analysis was performed
- Calculated using the linear predictors of the Cox proportional hazards model
- Tertile of the disease score was used to divide the population into low, median and high risk groups
- Linear trend test was used to investigate the association between risk groups and TTAC

# Frequency (%) of Cases by Disease Risk Score

| | Definitive Surgery to Chemotherapy Start (p trend = 0.69) | | | | |
|---|---|---|---|---|---|
| **Predicted Risk** | <4 weeks | 4-8 week | 8-12 weeks | >12 weeks | Total |
| **Low** | 241 (20.5) | 659 (56.2) | 263 (22.4) | 10 (0.9) | 1173 (100) |
| **Medium** | 238 (19.8) | 729 (60.5) | 226 (18.8) | 12 (0.9) | 1205 (100) |
| **High** | 231 (19.1) | 731 (60.5) | 233 (19.3) | 13 (1.1) | 1208 (100) |

# Conclusion

- Within the 12 week context – time to adjuvant therapy did not impact outcome
- Similar results for disease free survival (DFS)
- Multivariable analyses confirmed recognized predictors of disease outcome: age, menopausal status, PS, stage of disease, nodal status, type of chemotherapy received

# Conclusion

- Analysis of the disease risk scores did not identify differences in time to adjuvant therapy for low, medium and high risk groups
- This suggests there were no trend in higher risk disease patients being treated earlier compared to later