Influence of Lymphadenectomy on Survival for Early-Stage Endometrial Cancer

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Objective

- To use a number of methods to control for confounding and selection bias to examine the association between lymphadenectomy (LAD) and survival in a large cohort of women with endometrial cancer

History

History

- Endometrial Adenocarcinoma
  - 1980s: intracavitary radiation
  - Later: primary surgery with lymph node sampling of high risk patients
  - (+) nodes → pelvic radiation
- Observational studies demonstrated therapeutic benefit for LAD, even if no nodal mets
  - Sampling of nodes → full LAD of pelvic/paraaortic

History

- Two European RCTs (2008, 2009)
  - No association between LAD and survival
  - ? Power
  - ? Quality of dissection
  - ? Ability of nodal status to guide therapy

Materials and Methods

Materials and Methods

- Retrospective Cohort Study using the *National Cancer Data Base*
  - Endometrioid Adenocarcinoma
  - Hysterectomy +/- lymphadenectomy 1998-2011

- Variety of statistical methodologies now available to control for measured and unmeasured confounders

Materials and Methods

- Retrospective cohort study
  - 1500 Commission on Cancer-affiliated hosp
  - Total of 151,089 women
- Data collected on:
  - Pt demographics
  - Clinical data
  - Tumor characteristics
  - Staging
  - Treatment
  - Overall survival

Materials and Methods

- Exclusion criteria
  - Preoperative radiation
  - Primary tumor before diagnosis of uterine cancer
  - Spread of tumor beyond uterus (>T2) or metastasis
- Inclusion criteria
  - Hysterectomy +/- LAD (regardless of nodal status)
  - LN dissection = *any* LN

Grouping

- Staging system
  - Study spanned the American Joint Commission on Cancer staging systems 5-7
    - Converted T stage to uniform nomenclature
    - T1A (limited to endometrium or <50% myometrium)
    - T1B (>50% myometrial invasion)
    - T2 (cervical stromal involvement)
- Other divided groups
  - >/< 10 (+) nodes, age, race, insurance, region of residence, level of education, tumor grade, use of adjuvant radiotherapy, hospital type, mean annual number of cases per hospital

Statistical Factors

- Propensity Score Analysis
- Instrumental Variable Analysis
- Cox Proportional Hazards Analysis & Regression Models
- Greedy 5:1 digit matching algorithm
- Poisson Distribution/Multivariable distribution
- Two-stage residual inclusion methodology
- Logistic Regression Model

Propensity Score Analysis

"…the predicted probability of treatment."

- To calculate:
  - Logistic regression model that included all clinical, oncologic, and hospital characteristics to determine the probability of undergoing LAD
- Marginal Cox proportional hazards regression models were used to estimate the HR of mortality with receipt of LAD accounting for hospital clustering

Instrumental Variable Analysis

"…an analytic methodology that attempts to adjust for measured and unmeasured confounders through application of an exogenous instrument."

- "Instrument" = characteristic assoc with treatment but not outcome
- In this study, the instrument = geographic variation
- Provide pseudorandomization to help control for unmeasured confounding

Models

- Created 2 different methods
  - Propensity score
  - Instrumental variable analysis
- For each methodology, they developed a model to include:
  - Only LAD
  - LAD and all patient & hospital characteristics
  - All the variables in the clinical model as well as adjuvant therapy

Results

Results

151,089 women
(1998-2011)

99,052 (65.6%)
LAD

52,037(34.4%)
No LAD

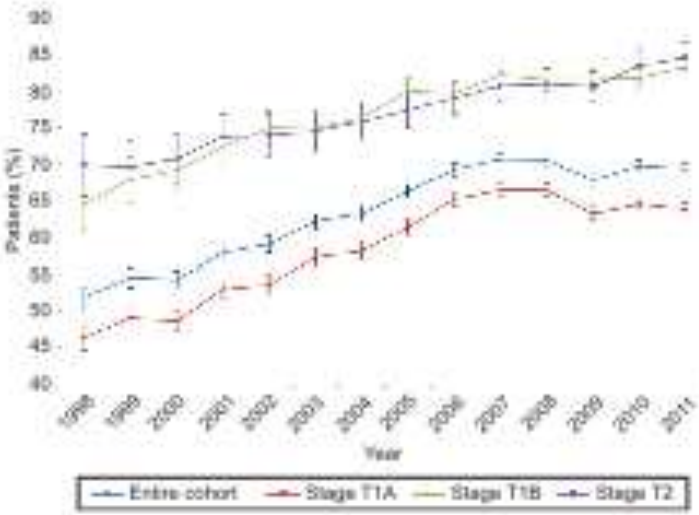

Fig. 1. Trends in performance of lymphadenectomy over time. $P<.05$ for the overall cohort and each subset.

Wright. Lymphadenectomy for Endometrial Cancer. Obstet Gynecol 2016.

Overall rate of LAD:
T1A = 60.7%
T1B = 78.7%
T2 = 77.9%

51.8% - 70.6%

Results

- Regression model adjusted for clinical characteristics (Propensity score, matching, or inverse probability tx):
  - *16% reduction* of mortality (HR 0.84, 95% CI 0.81-0.87)
  - Similar when adjusted for adjuvant therapy (HR 0.85, 95% CI 0.82-0.87)
- Instrumental variable analysis:
  - No statistically significant assoc between LAD and survival (HR 0.75, 95% CI 0.53-1.06
  - Similar after adjustment for adjuvant therapy (HR 0.76, 95% CI 0.54-1.06)

Results

- Stratified by T stage for T1A/T1B:
  - Propensity score models suggested reduced mortality with LAD
  - Instrumental variable analysis found no statistically significant association between LAD and survival

- All the modalities found decreased mortality in women with T2 tumors who underwent LAD

Results

- When limited to only women who underwent LAD, comparing # nodes (<10 nodes, >10 nodes)
  - Instrumental variable analysis demonstrated no association between patients with T1A/T1B tumors

Discussion

Discussion

These findings suggest that LAD is associated with a modest, if any, effect on survival for early-stage endometrial cancer

- Propensity/Regression analysis demonstrated improved survival
- Instrumental Variable analysis did not
  - Unmeasured confounding factors may underlie reported association of survival

Discussion

- Several other trials with similar results
- People continue to question results
  - Quality of LAD
  - Power of study

- If LAD is not directly associated with survival, the procedure provides data regarding adjuvant therapy
  - Potentially avoiding treatment of lower-risk women

"Our data suggest that at the population level, any survival benefit from LAD is likely very small"

Questions?

Thank you!