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Aggressive Treatment of Early Stage Prostate Cancer from Retrospective  
Data: An Instrumental Variables Approach

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# SF298 REPORT DOCUMENTATION PAGE

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<b>13. ABSTRACT (Maximum 200 Words)</b> Instrumental variables (IV) techniques were used to estimate the outcome differences between aggressive treatment and conservative management among marginal patients with early stage prostate cancer and determine what type of patients may be safely shifted from aggressive to conservative treatment. We demonstrated IV that group patients in groups that have different rates of aggressive treatment but do not differ in demographic, tumor, or comorbidity characteristics, satisfying criteria for valid IV analyses. We demonstrated that, for a population of 100 patients, aggressive treatment of an additional 3 or 4 marginal patients would result in one more patient surviving three years. Patient characteristics and treatment patterns were contrasted across patients grouped by IV to describe the set of clinically localized prostate cancer patients at the practice margins for receiving aggressive treatment and who would benefit from increased utilization of aggressive treatments. We concluded that these are men aged 65-69 with co-morbidity and grade I tumors, aged 70-74 with no co-morbidity and grade I tumors, aged 65 to 74 with co-morbidity and with Phase II/III tumors and age 75-84 with grade II/III tumors regardless of comorbidity. These patient groups coincide with theoretical predictions. Cost-effectiveness analyses and radiation vs. prostatectomy analyses will ensue.				
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## INTRODUCTION

Prostate cancer is the most frequent cancer among American men and is the second leading cause of cancer-related deaths in all males.<sup>1</sup> With the advent of widespread screening with prostate-specific antigen (PSA), increasing numbers of men have been diagnosed with asymptomatic, localized, prostate cancer.<sup>2</sup> Among patients with clinically localized disease it is not known whether conservative management, i.e., "watchful waiting" or aggressive treatment, i.e., radiation therapy or radical prostatectomy, has better effectiveness. This is because men who are diagnosed with early stage prostate cancer may die of other causes before prostate cancer progresses enough to affect health. Both radical prostatectomy and radiation treatment have high rates of complications such as sexual impotence, urinary incontinence, and infection which adversely affect health. There is also a risk of surgical mortality with prostatectomy. Ideally, clinicians would identify men whose life expectancy was short enough that their prostate cancer would not be expected to progress substantially in their remaining lifetime. These men would receive conservative treatment (and no complications from aggressive treatment). For the rest, the benefit of aggressive treatment would be worth the risk of complications and they would receive aggressive treatment. However, although current prognostic factors for prostate carcinoma provide important information for patient care, the ideal method with which to incorporate the information attained from tumor-related factors (clinical stage, histologic grade, and PSA level), patient age, and comorbidity into a manageable prognostic score has not been found. The purpose of this study is to use instrumental variables techniques to estimate the outcome differences between aggressive treatment and conservative management among marginal patients with clinically localized disease; combine the health outcome and cost estimates to estimate true cost-effectiveness ratios; and using measured characteristics such as patient age, tumor grade, and the extent of co-morbid conditions, determine whether and what type of patients may be safely shifted from aggressive to conservative treatment.

## BODY

The approved revised Statement of Work follows below. It was revised to reflect tasks that will be completed during the recently approved one-year no-cost extension for this project. This report presents results from Tasks 1-3. Task 4 and 5 are the topic of the extension period.

- Task 1.* Describe the factors that are related to the sorting of patients into conservative or aggressive treatments, Months 1-15.
- Obtain data from SEER-HCFA linked databases and AMA Master File (Months 1-2).
  - Create analytic files (Months 3-4).
  - Construct and validate instrumental variables (Months 5-6).
  - Construct and validate treatment variables (Months 5-6).
  - Conduct analysis (Months 7-18) Examine patient-specific factors (demographic, co-morbidity, and tumor-related) and a series of factors related to treatment variation and theoretically unrelated to unmeasured confounders (candidate instrumental variables).
  - Prepare and submit manuscript (Months 19-21).
- Task 2.* Estimate unbiased treatment effects for marginal patients using instrumental variables techniques. Estimate for: (1) conservative vs. aggressive treatment and (2) given aggressive treatment, radiation vs. prostatectomy, Months 19-36,
- Analyses of treatment effects on crude survival (Months 19-21).
  - Analyses of treatment effects on re-treatment-free survival (Months 20-36).
  - Analyses of treatment effects on Medicare costs (Months 23-36).
  - Prepare and submit manuscript (Months 26-36).
- Task 3.* Contrast the patient characteristics and treatment patterns across patients grouped by instrumental variables to describe the set of clinically localized prostate cancer patients who are at the practice margins for receiving aggressive treatment, Months 25-27.
- Prepare tables for conservative vs. aggressive treatment (Month 25).
  - Prepare tables for radiation vs. prostatectomy, given aggressive treatment (Month 26).
- Task 4.* Combine the medical outcome and cost estimates to estimate true cost-effectiveness ratios to demonstrate whether aggressive treatments have been over- or under-utilized, Months 37-38.
- Estimate cost-effectiveness ratios for conservative vs. aggressive treatment (Month 37-38).
  - Estimate cost-effectiveness ratios for radiation vs. prostatectomy, given aggressive treatment (Month 37-38).
- Task 5.* Policy paper and report writing, Months 38-42.
- Prepare and submit a policy-oriented paper that presents cost-effectiveness and a detailed description of the marginal patients likely to be affected by shifts in treatment allocation algorithms (Month 38-41).
  - Prepare and submit the final project report (Month 42).

## **Task 1: Describe Factors Related to Choice of Aggressive vs. Conservative Treatment.**

### **Databases Acquired**

The primary databases acquired for this study were:

1. Medicare data files merged with SEER Program data (the SEER-Medicare linked data) for *all* SEER Program sites;
2. A list of all radiation treatment centers providing service in the region containing each registry, including zip code of location and years in operation; and
3. Area Resource File (ARF) of area provider counts.

Data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) program and from Medicare claims that have been linked with SEER data for approximately 93 percent of persons with cancer aged 65 and older at the time of cancer diagnosis.<sup>3</sup> SEER and Medicare records have been linked for cancers diagnosed from 1986 through 1995. SEER is funded by the National Cancer Institute. Participating registries collect data for all cancer patients diagnosed within their defined geographic area. Data include month and year of diagnosis, age at diagnosis, race, tumor stage and grade, and initial (first four months post-diagnosis) cancer treatments. The Patient Entitlement and Diagnosis Summary File (PEDSF) is the file in the SEER-Medicare linked database that includes all of the SEER-derived data. Medicare files from the Health Care Financing Administration included demographic and enrollment information and all bills submitted for inpatient hospital care, outpatient hospital care, and physician services. The diagnoses on inpatient bills (coded using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM)) were the source of co-morbidity information for this report. County-level area characteristic variables were constructed from the 1990 Bureau of Health Professions' Area Resource File (<http://www.arfsys.com/>).

### **Analytic File Construction**

#### **Sample Selection**

Prostate cancer cases were included from population-based SEER cancer registries in four states (Connecticut, Iowa, New Mexico, and Utah) and four metropolitan areas (Atlanta, Georgia; Detroit, Michigan; San Francisco-Oakland, California; and San Jose, California). Men with prostate cancer were identified who met the following inclusion criteria: diagnosed between 1986 and 1995, age 65 or older at the time of diagnosis, first primary prostate cancer, zip code of residence in the geographic area of the included registries, and either received radical prostatectomy or the tumor stage was coded as local. Men who received radical prostatectomy were included even if the tumor stage was not coded as local. They were considered to have been initially presumed to have localized disease. This assumption was required because SEER records only the most definitive stage, hence cases who may have been initially presumed to have localized disease but who underwent radical prostatectomy may have been "up-staged" at the time of surgery. In addition, men were excluded if they did not have full Medicare coverage throughout the time period or if there was missing data for one of the study variables. There were 38,967 cases remaining after application of these criteria. Table 1 displays the characteristics of the study population.

Table 1. Description of Study Subjects

Characteristic	Level	N	Conservative%	Aggressive %
			(n=17,446)	(n=21,521)
<b>Age Group</b>	<b>65-59</b>	10394	15.2	36.0
	<b>70~74</b>	12059	22.5	37.8
	<b>75~79</b>	9107	27.0	20.4
	<b>80~84</b>	4771	21.2	5.0
	<b>85~89</b>	2020	10.7	0.7
	<b>90~94</b>	516	2.8	0.1
	<b>&gt;95</b>	100	0.6	0.0
<b>Race</b>	<b>White</b>	34352	86.3	89.7
	<b>Black</b>	3735	11.6	8.0
	<b>Native</b>	59	0.2	0.1
	<b>Asian</b>	286	0.8	0.7
	<b>Other</b>	535	1.2	1.5
<b>Grade</b>	<b>I:Well differentiated</b>	11023	40.2	18.6
	<b>II: Moderately differentiated</b>	18853	37.2	57.4
	<b>III: Poorly differentiated</b>	6457	14.2	18.5
	<b>IV: Undifferentiated</b>	320	0.8	0.8
	<b>Grade Unknown</b>	2314	7.5	4.7
<b>Number of Co-morbid Conditions</b>	<b>0</b>	14112	25.4	45.0
	<b>1 ~ 2</b>	9669	22.9	26.3
	<b>3 ~ 4</b>	9862	30.6	21.0
	<b>5 ~ 6</b>	2835	10.3	4.8
	<b>7+</b>	2489	10.7	2.9

## Variable Definition

Cases were considered to have had aggressive treatment (n=21,521) if they had either radiation treatment (SEER radiation treatment codes 1=beam radiation, 2=radioactive implants, or 4=beam and radioactive implants/isotopes) or radical prostatectomy (SEER site-specific surgery codes 50, 58, 60, 68, standing for radical/total prostatectomy with or without lymph node dissection and with or without reconstructive surgery as well as codes 70 and 78 standing for cystoprostatectomy or radical prostatectomy, pelvic extension with/without lymph node dissection. Because SEER collects treatment data through 4 months diagnosis, Medicare bills were also examined to identify whether patients had received radical prostatectomy. Conservative treatment (n=17,446) included those for whom it was known that neither radical prostatectomy nor radiation treatment were received (cases whose radiation or surgery treatment status were unknown had been excluded from eligibility).

Sociodemographic variables included age at diagnosis, race, and socioeconomic status. Age and race were obtained from the PEDSF file and were individual-level variables. Socioeconomic variables were

measured at the county level from the Area Resource File and included mean income and percent rural residents.

Measures reflecting the type of provider to whom men had access included the number of urologists per capita in the county, distance to the nearest radiation treatment facility, distance to the nearest hospital that performed radical prostatectomies, differential distance to the nearest prostatectomy hospital (distance to the nearest hospital that performed prostatectomies minus the distance to the nearest non-prostatectomy hospital) and per capita measures of prostatectomy hospital, radiation center, and urologist availability. Distances were calculated using the longitude and latitude for the centroid of the subject's residence zip code and the longitude and latitude of for the centroid of the zip code of the relevant provider. The number of radical prostatectomies performed by each hospital in the geographic regions was determined from the Medicare files. From this each hospital was classified as a radical prostatectomy hospital if it provided any radical prostatectomy in the year of diagnosis. We obtained from each SEER registry a list of all radiation treatment centers providing service in the area covered by the registry. The lists contained the zip code of each center and the years between 1984 and 1995 that each center provided services. Measures reflecting the area healthcare market characteristics included percent of residents enrolled in HMOs from the Area Resource File, the number of radical prostatectomy hospitals per capita within a 40 mile radius of the subject, and the number of radiation treatment centers per capita within a 40 mile radius of the subject.

Clinical characteristics include the tumor grade and co-morbidity. Tumor grade was as recorded by SEER as well-differentiated (corresponding to Gleason score 2-4), moderately differentiated (Gleason score 5-7), poorly differentiated (Gleason score 8-10), undifferentiated, or grade unknown. Comorbid conditions were any condition except prostate cancer present on inpatient bills during the one year before diagnosis and through 122 days after diagnosis. The ICD-9-CM codes for these conditions were linked to Clinical Classifications for Health Policy Research (CCHPR) codes ([www.ahrq.gov/data/hcup/his95/index.html](http://www.ahrq.gov/data/hcup/his95/index.html)) and the number of unique CCHPR codes was counted as one measure of co-morbidity (total comorbid conditions). Co-morbidity was also represented as a modified Charlson score where a higher score indicates a greater burden of co-morbid illness.<sup>4</sup> The Charlson score was calibrated to predict mortality in breast cancer<sup>5</sup> and assigns weights to selected conditions depending on their empirical relationship to mortality risk. Both the Charlson score and the total count of chronic conditions have been used to predict mortality in prostate cancer.<sup>6</sup>

## **Validation of Instrumental Variables**

### **Overview of Instrumental Variable Estimation Techniques**

In medical outcomes research, instrumental variable (IV) estimation<sup>7,8</sup> initially involves specifying a set of instrumental variables or "instruments" that satisfy the following two criteria: (1) the variable must be related to the possibility of patients receiving a particular treatment; and (2) the variable must have no effect on outcomes either directly or indirectly (e.g., through relationships with unmeasured confounding factors such as patient severity and unrecorded treatments). The first criterion is necessary to observe treatment variation across patients grouped by the instrument and can be established by analysis of the available data. The second criterion is necessary to insure that treatment variation observed from grouping patients using the instrument is not related to confounding factors such as patient severity. Because many confounders are unmeasured, the second criterion must remain an assumption. Consequently, researchers must build a strong theoretical case for acceptance of the validity of the second criterion. Estimated correlations between instruments and measured confounders may be used to bolster the case.

If a single instrument is used that divides patients into two groups, treatment effects can be estimated through a simple comparison of treatment and outcome rates across the two groups. IV analysis is more powerful, though, if several instruments are used and comparisons are made simultaneously across many patient groups defined by the instruments. Two-stage least squares (2SLS) has been shown to be the optimal method to combine the effects of several instruments in a single analysis. Each treatment decision in this study was specified using the following two equation format and estimated using 2SLS:

• **Treatment Choice Equation:**  $T_i = \alpha + \gamma_1 * A_i + \gamma_2 * G_i + \gamma_3 * C_i + \gamma_4 * I_i + \varepsilon_i + \theta_i$

**Outcome Equation:**  $O_i = \delta + \beta_1 * A_i + \beta_2 * G_i + \beta_3 * C_i + \beta_4 * T_i + \nu_i + \theta_i$

where:

- $O_i$  = 1 if health outcome occurs (e.g. mortality within a time interval, re-treatment within a time interval), 0 otherwise. Cost equations will use total patient health care costs within the given time interval;
- $A_i$  = measured patient demographic characteristics;
- $G_i$  = measured tumor characteristics;
- $C_i$  = a set of binary variables based representing patient co-morbidities;
- $T_i$  = a binary variable equal to 1 if a patient received a specified treatment, 0 otherwise;
- $\theta_i$  = unmeasured “confounding variables” that are related to both choice of treatment and outcomes;
- $\varepsilon_i, \nu_i$  = the net impact of unmeasured variables that distinctly affect treatment choices and health outcome, respectively;
- $I_i$  = a set of binary variables that group patients according to values of instrumental variables that affect outcomes only through their impact on treatment choice.

Our treatment variable  $T_i$  is a binary variable indicating whether the patient was treated. The objective is to obtain unbiased estimates of  $\beta_4$ . Because “ $\theta$ ” is in both the treatment and outcome equations, the estimate of the treatment choice parameter in equation (2) will be biased if ordinary least squares (OLS) is applied to equation 2.<sup>9,10</sup> In the first stage of the estimation procedure, the treatment choice equation (i.e., equation (1)) is estimated using ordinary least squares. Equation 1 includes a set of binary variables,  $I_i$ , that group patients based on the value of each patient’s instruments. The predicted values of treatment probabilities from the first stage regressions for each patient, “ $T$ -hat” are then substituted for  $T_i$  in equation (2). In the second stage, equation (2) is estimated using OLS. Because  $A_i$  and  $G_i$  and  $C_i$  are specified in both equations, the only source of variation in  $T$ -hat used to estimate  $\beta_4$  is the variation in treatment rates across patient groups defined by the instruments. In addition, because we assumed that the instruments are unrelated to the unmeasured confounding factors “ $\theta$ ”, the estimate of  $\beta_4$  that results from this process will be unbiased and attributable only to treatment rate differences across patients grouped by the set of instruments.

## Evaluating the Validity of the Candidate Instrumental Variables

To be suitable instruments, variables must satisfy the following two criteria: (1) be related to the possibility of patients receiving a particular treatment and (2) have no effect on outcomes either directly or indirectly (e.g. through relationships with unmeasured confounding factors such as patient severity and unrecorded treatments). Because many confounders are unmeasured, the second criterion must remain an assumption. However, by comparing rates of *measured* confounders between groups of patients defined by the candidate instruments, we can provide evidence in support of the assumption. Table 1 compares patients grouped according to treatment received (aggressive vs. conservative) and Tables 2 through 8 group patients according to the each of the candidate instrumental variables.

Table 1 shows that patients who are aggressively treated are younger, have a higher tumor grade, earlier disease stage, and a lower prevalence of most co-morbidities than patients who are treated conservatively. In contrast, Tables 2 through 7 show that although patients who have greater access to aggressive treatments have a higher rate of aggressive treatment than patients with lower access, there is little systematic difference between these groups with respect to measured confounders, relative to the differences seen between the treated and untreated groups.

**Table 2: Cancer Comparison of Patients According to #Radiation Centers Per Capita in 40 miles**

Grouped According to Quartiles of #Radiation Centers Per Capita Within 40 Miles From The Zip Code of Patient's Residence (n=38,967)					
VAR_NAME	Level	0.005	(0.005,0.009]	(0.009, 0.014]	>0.014
% Treated Aggressively		59.5	54.2	57.4	49.2
AGE	65-59	27.1	27.2	27.3	25.2
	70~74	31.6	30.9	31.8	29.4
	75~79	23.0	23.6	23.1	23.9
	80~84	12.1	11.5	11.7	13.5
	85~89	4.7	5.2	4.8	6.0
	90~94	1.2	1.4	1.1	1.6
	>95	0.2	0.2	0.2	0.4
RACE	White	86.6	87.0	88.7	90.2
	Black	10.2	11.9	9.2	7.6
	Native	0.3	0.1	0.1	0.2
	Asian	0.1	0.1	1.0	1.6
	Other	2.8	1.0	1.0	0.5
GRADE	I: Well differentiated	25.3	31.0	26.0	31.8
	II: Moderately differentiated	50.9	45.2	51.4	45.0
	III: Poorly differentiated	16.8	16.3	16.6	16.5
	IV: Undifferentiated	1.0	0.6	0.7	0.9
	Grade Unknown	5.9	7.0	5.3	5.8
Number of Comorbid Illnesses	No ILL	39.8	34.0	39.1	31.2
	1 ~ 2	21.6	26.1	24.3	27.9
	3 ~ 4	24.6	25.7	23.6	27.4
	5 ~ 6	7.4	7.3	7.2	7.1
	ILL>=7	6.5	6.9	5.9	6.4
%HMO in county	<=17.290	41.9	33.2	52.0	70.0
	(17.290,21.223]	15.4	45.9	20.2	7.3
	21.223]	42.7	20.9	27.8	22.7
Average Income (\$1000)	<=15.949	30.1	27.7	21.0	21.3

	<b>(15.949, 18.787]</b>	37.2	35.1	10.7	20.6
	<b>(18.787, 23.937]</b>	20.3	20.7	24.8	33.7
	<b>&gt;23.937</b>	12.3	16.5	43.5	24.4
%Rural in zip code	<b>=0</b>	51.4	60.8	54.0	47.5
	<b>&gt;0</b>	48.6	39.2	46.0	52.5

**Table 3: Comparison of Patients According to # Prostatectomy Hospitals Per Capita in 40 miles**

<b>Grouped According to Quartiles of #Prostatectomy Hospitals Per Capita Within 40 Miles From The Zip Code of Patient's Residence (n=38,967)</b>					
<b>VAR_NAME</b>	<b>Level</b>	<b>&lt;=0.014</b>	<b>(0.014,0.020]</b>	<b>(0.020,0.026]</b>	<b>&gt;0.026</b>
<b>% Treated Aggressively</b>		<b>60.6</b>	<b>55.1</b>	<b>55.7</b>	<b>49.3</b>
<b>AGE</b>	<b>65-59</b>	26.4	26.1	27.5	26.6
	<b>70~74</b>	31.3	31.4	31.6	29.6
	<b>75~79</b>	24.3	23.3	22.6	23.3
	<b>80~84</b>	12.0	12.3	11.7	13.0
	<b>85~89</b>	4.7	5.4	5.0	5.6
	<b>90~94</b>	1.1	1.3	1.4	1.6
	<b>&gt;95</b>	0.2	0.2	0.2	0.3
<b>RACE</b>	<b>White</b>	84.8	89.5	87.4	90.8
	<b>Black</b>	11.7	9.1	10.1	7.3
	<b>Native</b>	0.2	0.1	0.1	0.3
	<b>Asian</b>	0.1	0.3	1.4	1.2
	<b>Other</b>	3.1	1.0	1.0	0.4
<b>GRADE</b>	<b>I: Well differentiated</b>	23.8	27.3	27.5	34.6
	<b>II: Moderately differentiated</b>	52.2	49.5	49.4	42.4
	<b>III: Poorly differentiated</b>	17.0	16.6	16.4	16.2
	<b>IV: Undifferentiated</b>	1.1	0.6	0.6	1.0
	<b>Grade Unknown</b>	5.9	6.0	6.1	5.8
<b>Number of Comorbid Illnesses</b>	<b>No ILL</b>	43.0	38.7	33.2	29.9
	<b>1 ~ 2</b>	19.8	23.2	27.9	28.6
	<b>3 ~ 4</b>	23.3	24.4	26.2	27.4
	<b>5 ~ 6</b>	7.4	7.3	7.0	7.5
	<b>ILL&gt;=7</b>	6.6	6.5	5.7	6.7
<b>%HMO in county</b>	<b>&lt;=17.290</b>	35.5	38.0	60.3	67.7
	<b>(17.290,21.223]</b>	21.1	41.2	14.5	4.6
	<b>21.223]</b>	43.4	20.8	25.2	27.6
<b>Average Income (\$1000)</b>	<b>&lt;=15.949</b>	22.3	18.3	16.9	42.2

(\$1000)					
	(15.949, 18.787]	35.0	32.6	17.7	17.0
	(18.787, 23.937]	25.3	18.2	29.4	27.6
	>23.937	17.4	30.8	36.0	13.3
%Rural in zip code	=0	54.6	52.7	59.0	45.3
	>0	45.4	47.3	41.0	54.7

**Table 4: Comparison of Patients According to #Urologists Per Capita in County of Patient's Residence**

Grouped According to Quartiles of #Urologists Per Capita in County of Patient's Residence (n=38,967)					
VAR_NAME	Level	<=0.0065	(0.0065, 0.107]	(0.107,0.147]	>0.147
% Treated Aggressively		53.0	58.0	51.1	60.1
AGE	<b>65-59</b>	25.5	27.0	25.4	29.1
	<b>70~74</b>	30.4	30.7	30.3	32.3
	<b>75~79</b>	23.8	23.0	24.2	22.3
	<b>80~84</b>	13.0	12.8	12.8	10.5
	<b>85~89</b>	5.6	4.9	5.7	4.5
	<b>90~94</b>	1.5	1.4	1.3	1.1
	<b>&gt;95</b>	0.3	0.2	0.4	0.2
RACE	<b>White</b>	83.2	94.4	95.3	85.1
	<b>Black</b>	15.0	4.6	3.7	10.3
	<b>Native</b>	0.2	0.1	0.1	0.1
	<b>Asian</b>	0.1	0.4	0.1	2.3
	<b>Other</b>	1.6	0.5	0.8	2.1
GRADE	<b>I : Well differentiated</b>	29.2	30.5	27.9	26.2
	<b>II: Moderately differentiated</b>	46.0	47.9	48.5	51.7
	<b>III: Poorly differentiated</b>	16.7	15.6	17.4	16.3
	<b>IV: Undifferentiated</b>	1.1	0.7	0.5	0.8
	<b>Grade Unknown</b>	7.0	5.3	5.8	5.1
Number of Comorbid Illnesses	<b>No ILL</b>	33.6	34.2	39.3	38.3
	<b>1 ~ 2</b>	23.0	28.5	24.7	25.3
	<b>3 ~ 4</b>	27.9	24.8	23.9	23.4
	<b>5 ~ 6</b>	8.0	7.0	6.7	7.0
	<b>ILL&gt;=7</b>	7.5	5.6	5.5	6.1
%HMO in county	<b>&lt;=17.290</b>	48.6	65.0	35.8	56.2
	<b>(17.290,21.223]</b>	28.7	4.9	30.1	10.0
	<b>21.223]</b>	22.7	30.1	34.2	33.8
Average Income (	<b>&lt;=15.949</b>	36.1	42.9	15.9	7.8

\$1000)					
	(15.949, 18.787]	42.3	12.8	20.3	15.6
	(18.787, 23.937]	21.6	26.0	24.0	30.2
	>23.937	0.0	18.2	39.9	46.4
%Rural in zip code	=0	50.7	30.3	50.1	70.9
	>0	49.3	69.7	49.9	29.1

**Table 5: Comparison of Patients According to Differential Distance to Prostatectomy Hospital (Distance to Prostatectomy Hospital minus Distance to Non-Prostatectomy Hospital)**

Grouped According to Quartiles of Differential Distance to Prostatectomy hospital (n=38,967)					
VAR_NAME	Level	<-2.162	(-2.162,0]	(0,3.215]	>3.215
% Treated Aggressively		58.5	57.6	55.7	48.7
AGE	<b>65-59</b>	28.0	27.6	26.8	24.2
	<b>70~74</b>	32.0	31.2	31.3	29.3
	<b>75~79</b>	22.3	23.2	23.5	24.6
	<b>80~84</b>	11.7	11.8	11.7	13.8
	<b>85~89</b>	4.6	4.9	5.2	6.1
	<b>90~94</b>	1.2	1.2	1.2	1.7
	<b>&gt;95</b>	0.2	0.2	0.3	0.3
RACE	<b>White</b>	93.8	86.2	79.6	91.4
	<b>Black</b>	4.0	10.8	17.5	7.6
	<b>Native</b>	0.1	0.1	0.1	0.3
	<b>Asian</b>	0.6	1.1	0.9	0.3
	<b>Other</b>	1.5	1.8	1.9	0.4
GRADE	<b>I: Well differentiated</b>	27.8	27.7	27.3	30.3
	<b>II: Moderately differentiated</b>	49.2	48.7	48.9	46.8
	<b>III: Poorly differentiated</b>	16.2	17.3	16.0	16.5
	<b>IV: Undifferentiated</b>	0.8	0.6	0.7	1.2
	<b>Grade Unknown</b>	6.0	5.8	7.1	5.2
Number of Comorbid Illnesses	<b>No ILL</b>	37.3	39.1	37.2	30.9
	<b>1 ~ 2</b>	25.2	24.8	23.4	25.6
	<b>3 ~ 4</b>	24.2	23.5	25.7	28.4
	<b>5 ~ 6</b>	7.1	7.0	7.4	7.7
	<b>ILL&gt;=7</b>	6.3	5.6	6.3	7.5
%HMO in county	<b>&lt;=17.290</b>	51.8	39.4	34.9	73.7
	<b>(17.290,21.223]</b>	19.2	21.9	30.6	12.0
	<b>21.223]</b>	29.1	38.7	34.5	14.3
Average Income /	<b>&lt;=15.949</b>	20.8	15.8	16.1	47.4

Income ( \$1000)					
	<b>(15.949, 18.787]</b>	21.9	24.1	30.5	27.8
	<b>(18.787, 23.937]</b>	28.3	29.2	27.6	15.0
	<b>&gt;23.937</b>	29.0	31.0	25.8	9.8
%Rural in zip code	<b>=0</b>	49.1	69.9	72.3	20.5
	<b>&gt;0</b>	50.9	30.1	27.7	79.5

**Table 6: Comparison of Patients According to Distance to the Nearest Radiation Center**

Grouped According to Quartiles of Distance to The Nearest Radiation Center (n=38,967)					
VAR_NAME	Level	<2.858	(2.858, 5.296]	(5.296,12.733]	>12.733
% Treated Aggressively		55.5	57.5	57.7	50.1
AGE	<b>65-59</b>	25.6	27.6	28.3	25.1
	<b>70~74</b>	30.1	32.3	32.3	29.1
	<b>75~79</b>	24.4	22.8	22.2	24.1
	<b>80~84</b>	12.9	11.1	11.2	13.9
	<b>85~89</b>	5.3	4.8	4.6	6.0
	<b>90~94</b>	1.3	1.2	1.2	1.6
	<b>&gt;95</b>	0.3	0.2	0.2	0.3
RACE	<b>White</b>	84.8	84.2	85.7	98.0
	<b>Black</b>	12.1	12.7	12.3	1.2
	<b>Native</b>	0.1	0.1	0.0	0.4
	<b>Asian</b>	1.9	0.5	0.4	0.2
	<b>Other</b>	1.2	2.5	1.5	0.2
GRADE	<b>I: Well differentiated</b>	27.9	28.1	27.8	29.4
	<b>II: Moderately differentiated</b>	48.5	47.9	48.7	48.4
	<b>III: Poorly differentiated</b>	16.7	16.5	16.6	16.4
	<b>IV: Undifferentiated</b>	0.8	0.6	0.7	1.2
	<b>Grade Unknown</b>	6.1	6.9	6.2	4.6
Number of Comorbid Illnesses	<b>No ILL</b>	37.4	38.1	37.5	31.8
	<b>1 ~ 2</b>	24.5	23.5	25.1	26.1
	<b>3 ~ 4</b>	24.6	25.1	24.1	27.5
	<b>5 ~ 6</b>	7.4	6.9	7.3	7.5
	<b>ILL&gt;=7</b>	6.2	6.3	6.0	7.1
%HMO in county	<b>&lt;=17.290</b>	47.9	29.7	35.5	88.0
	<b>(17.290,21.223]</b>	20.6	30.9	25.0	4.9
	<b>21.223]</b>	31.5	39.4	39.5	7.1
Average Income (\$1000)	<b>&lt;=15.949</b>	15.0	11.3	15.2	58.7

	<b>(15.949, 18.787]</b>	23.4	28.1	27.9	23.3
	<b>(18.787, 23.937]</b>	26.6	28.8	31.7	13.3
	<b>&gt;23.937</b>	35.0	31.8	25.3	4.7
%Rural in zip code	<b>=0</b>	74.7	81.6	49.7	5.0
	<b>&gt;0</b>	25.3	18.4	50.3	95.0

**Table 7: Comparison of Patients According to Distance to the Nearest Prostatectomy Hospital**

Grouped According to Quartiles of Distance to The nearest RP Hospital (n=38,967)					
VAR_NAME	Level	<1.054	(1.054,3.385]	(3.385, 7.542]	>7.542
% Treated Aggressively		57.0	56.1	57.9	49.8
AGE	<b>65-59</b>	27.1	26.7	28.4	24.6
	<b>70~74</b>	31.3	31.3	32.0	29.1
	<b>75~79</b>	22.8	23.4	22.6	24.7
	<b>80~84</b>	12.4	11.7	10.9	13.9
	<b>85~89</b>	4.9	5.2	4.6	6.1
	<b>90~94</b>	1.4	1.4	1.2	1.4
	<b>&gt;95</b>	0.2	0.3	0.3	0.3
RACE	<b>White</b>	88.2	77.8	88.6	98.0
	<b>Black</b>	9.2	18.7	9.4	1.0
	<b>Native</b>	0.1	0.1	0.0	0.4
	<b>Asian</b>	1.2	1.1	0.4	0.2
	<b>Other</b>	1.3	2.3	1.5	0.3
GRADE	<b>I: Well differentiated</b>	29.1	26.8	27.3	29.9
	<b>II: Moderately differentiated</b>	47.9	48.5	49.6	47.5
	<b>III: Poorly differentiated</b>	16.5	16.8	16.2	16.8
	<b>IV: Undifferentiated</b>	0.7	0.7	0.6	1.3
	<b>Grade Unknown</b>	5.9	7.1	6.3	4.5
Number of Comorbid Illnesses	<b>No ILL</b>	36.9	38.5	37.9	31.5
	<b>1 ~ 2</b>	25.9	22.8	24.8	25.8
	<b>3 ~ 4</b>	24.1	24.9	24.4	27.7
	<b>5 ~ 6</b>	7.0	7.4	7.0	7.6
	<b>ILL&gt;=7</b>	6.1	6.4	5.8	7.2
%HMO in county	<b>&lt;=17.290</b>	50.3	34.3	37.1	79.4
	<b>(17.290,21.223]</b>	19.2	27.7	25.5	9.2
	<b>&gt;21.223</b>	30.5	38.0	37.4	11.5
Average Income (	<b>&lt;=15.949</b>	23.9	9.3	15.8	51.2

\$1000)					
	(15.949, 18.787]	25.2	27.7	24.2	25.6
	(18.787, 23.937]	24.9	30.6	31.4	13.4
	>23.937	26.0	32.4	28.6	9.8
%Rural in zip code	=0	60.7	93.7	53.1	3.5
	>0	39.3	6.3	46.9	96.5

## Treatment Choice Analysis

Analysis of factors associated with treatment choice is the first stage of the two-stage least squared IV analysis. However, evaluating factors associated with treatment choice is important in its own right as it is important to understand to what extent non-prognostic variables are nevertheless associated with treatment choice in early stage prostate cancer.

Continuous independent variables were grouped by quartile and the first quartile was used as the reference category in all analyses. Single variable logistic regression tested the univariate associations of each independent variable with whether aggressive or conservative treatment was received. Multivariable logistic regression analysis of the odds of aggressive vs. conservative treatment was used to estimate the effect of the socioeconomic, access to care, and healthcare market area characteristics after controlling for patient age, race, and clinical characteristics. To describe the patient characteristics associated with the most treatment variation between areas with high vs. low access to healthcare providers, Fisher's exact test compared the proportion aggressively treated among patients with high vs. low access. Table 8 presents the univariate and multivariate logistic regression results.

Men older than 69 were significantly less likely to received aggressive treatment than men aged 65-69, with men age 80 or older particularly unlikely to receive aggressive treatment. Men whose race was other than white were less likely to receive aggressive treatment even after adjusting for tumor grade, comorbidity and area socio-economic and access to care measures. Men with less well differentiated or unknown tumor grade were more likely to receive aggressive treatment. Men with comorbidities were less likely to receive aggressive treatment than were those with no comorbidities. A county mean yearly income of more than \$15,949 (the lowest quartile of county mean income) was associated with a greater odds of aggressive treatment. Although residents of rural areas had a lower odds of aggressive treatment in univariate analyses, they had a slightly increased odds of treatment when adjusted for other covariates. Similarly, although living in an area with a higher HMO penetration was associated with an increased odds of aggressive treatment in univariate analyses, the association did not persist after adjustment for covariates. These covariates included the access to care as well as clinical characteristics described above.

All measures of the types of providers to which men had access (these were also to be the instrumental variables in the full IV two-stage analysis) were significantly associated with aggressive treatment. Men who had more radiation centers and prostatectomy hospitals per capita had significantly lower odds of aggressive treatment, indicating that after controlling for the population size, as well as distance-based measures of access to care, as the number of providers increases, aggressive treatment decreases. This is compatible with other research that providers in more highly competitive environments are more likely to adhere to recognized practice guidelines. During this era, there was increasing recognition that aggressive treatment should not be automatically selected for all men due to the reasonably good ten-year survival rates from prostate cancer. In contrast to these findings, residents of counties in the second and fourth quartiles of per capita urologist availability were more likely to receive aggressive treatment than were residents of counties in the first or third quartile of urologist availability (OR 1.31; 95% confidence interval 1.20, 1.42 and OR 1.11; 95% confidence interval 1.02, 1.21, respectively). This finding is difficult to interpret. The distance-based measures all uniformly found that residents of areas with longer absolute or relative distances to aggressive treatment providers were less likely to receive aggressive treatments. However, distance to prostatectomy hospitals and

differential distance to prostatectomy hospitals were highly correlated (Pearson Correlation coefficient=0.90) and may account for the reduction of effect for these two variables in the multivariate model.

While it makes sense for clinicians to sort patients for observation vs. aggressive treatment based on tumor-related prognostic factors, age, and comorbidity, optimal sorting rules are not known. Several researchers have devised multivariate nomograms or prognostic models for predicting which patients have surgically amenable disease. The nomograms combine PSA and grade or PSA and clinical stage to predict pathological stage, i.e., seminal vesicle involvement, a positive margin or lymph node metastases.<sup>11-13</sup> The nomograms have been faulted because they provide relatively crude probabilities that cluster around 50%. Hence, although current prognostic factors provide important information for patient care, the ideal method to incorporate the information attained from tumor-related factors (clinical stage, histologic grade, and PSA level), age, and comorbidity into a manageable prognostic score has not been found.<sup>14</sup>

There is limited research documenting how clinicians are actually sorting patients for treatments. With so little guidance, it is not surprise that treatment variation exists<sup>15,16</sup> Desch et al.<sup>17</sup> showed using Virginia Cancer Registry data that aggressive treatment was negatively related to patient age and their number of comorbidities and was positively related to the average income of the zip code containing the patient residence and year of diagnosis. Provider counts (radiation oncologists and urologists) in the county of patient residence did not affect treatment choices. Distance to the nearest radiation oncologist did not affect the choice of aggressive treatment but lowered the probability that hormonal therapy (orchiectomy) was used instead of aggressive treatment. Klabunde et al.<sup>18</sup> demonstrated relationships between aggressive treatment and the patient's race and the average educational attainment in the area surrounding the patient's residence. Potosky et al.<sup>19</sup> used data from Seattle and San Francisco and showed that HMO Medicare patients were more likely to receive aggressive treatment than Medicare fee-for-service patients.

**Table 8. Univariate and Multivariate Logistic Regression Results of Factors Associated with Receiving Aggressive Treatment for Early Stage Prostate Cancer.**

		Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Age	95+	0.01	0.01, 0.03	0.01	0.01, 0.03
	90-94	0.01	0.01, 0.02	0.01	0.01, 0.02
	85-89	0.03	0.02, 0.03	0.03	0.02, 0.03
	80-84	0.10	0.09, 0.11	0.09	0.08, 0.10
	75-79	0.32	0.30, 0.34	0.30	0.28, 0.32
	70-74	0.71	0.67, 0.75	0.70	0.66, 0.75
	65-69	1.00	-	1.00	-
Grade	Grade Unknown	1.34	1.23, 1.47	1.45	1.31, 1.62
	IV: Undifferentiated	2.04	1.63, 2.55	2.88	2.20, 3.77
	III: Poorly differentiated	2.82	2.65, 3.01	3.67	3.41, 3.96
	II: Moderately differentiated	3.33	3.18, 3.50	3.55	3.35, 3.75
	I: Well differentiated	1.00	-	1.00	-
Race	White	1.00	-	1.00	-
	Other	1.29	1.08, 1.53	0.69	0.56, 0.85
	Asian	0.86	0.68, 1.09	0.82	0.61, 1.08
	Native	0.34	0.20, 0.60	0.42	0.22, 0.83

	Black		0.66	0.62, 0.71	0.48	0.44, 0.52
Comorbidities, n	7+		0.15	0.14, 0.17	0.19	0.17, 0.22
	5-6		0.26	0.24, 0.28	0.31	0.28, 0.34
	3-4		0.39	0.37, 0.41	0.43	0.41, 0.46
	1-2		0.65	0.61, 0.68	0.61	0.57, 0.65
	0		1.00	-	1.00	-
County per capita HMO enrollment, %	>21.223		1.47	1.40, 1.54	1.04	0.97, 1.11
	(17.290,21.223]		1.05	1.00, 1.11	0.93	0.86, 1.01
	<17.290		1.00	-	1.00	-
County mean yearly income, \$1,000	>23.937		1.69	1.59, 1.79	1.13	1.03, 1.24
	(18.787, 23.937]		1.45	1.37, 1.53	1.14	1.05, 1.23
	(15.949, 18.787]		1.44	1.36, 1.52	1.26	1.17, 1.36
	<15.949		1.00	-	1.00	-
Percent rural residents in zip code	%RURL>0		0.90	0.87, 0.94	1.08	1.01, 1.16
	0		1.00	-	1.00	-
Radiation centers per capita in 40 miles	>0.014		0.66	0.62, 0.70	0.78	0.71, 0.86
	(0.009,0.014]		0.91	0.87, 0.97	0.96	0.88, 1.05
	(0.005,0.009]		0.81	0.76, 0.85	0.96	0.88, 1.04
	<0.005		1.00	-	1.00	-
Prostatectomy hospitals per capita in 40 miles	>0.026		0.63	0.60, 0.67	0.74	0.67, 0.82
	(0.020,0.026]		0.82	0.77, 0.87	0.82	0.75, 0.90
	(0.014,0.020]		0.80	0.75, 0.85	0.81	0.75, 0.89
	<0.014		1.00	-	1.00	-
County Urologists per capita	>0.147		1.34	1.27, 1.40	1.11	1.02, 1.21
	(0.107,0.147]		0.93	0.88, 0.98	0.73	0.67, 0.79
	(0.065,0.107]		1.23	1.15, 1.30	1.31	1.20, 1.42
	<0.065		1.00	-	1.00	-
Differential distance to prostatectomy hospital, miles	>3.215		0.67	0.64, 0.71	0.90	0.82, 0.99
	(0,3.215]		0.89	0.84, 0.95	1.06	0.97, 1.15
	(-2.162,0]		0.96	0.91, 1.01	1.04	0.97, 1.12

	<-2.162		1.00	-	1.00	-
Distance to radiation center, miles	>12.733		0.80	0.76, 0.85	0.75	0.67, 0.83
	(5.296,12.733]		1.10	1.03, 1.16	1.03	0.96, 1.12
	(2.858, 5.296]		1.09	1.03, 1.15	0.98	0.91, 1.05
	<2.858		1.00	-	1.00	-
Distance to prostatectomy hospital, miles	>7.542		0.75	0.71, 0.79	0.91	0.81, 1.02
	(3.385, 7.542]		1.04	0.98, 1.10	0.99	0.91, 1.07
	(1.054,3.385]		0.97	0.91, 1.02	0.98	0.91, 1.06
	<1.054		1.00	-	1.00	-

## **Task 2: Unbiased Treatment Outcome Estimates for Marginal Patients**

The following tables present the results of the two-stage least squares IV analyses for three-year survival. Analyses of other treatment outcomes (re-treatment-free survival and Medicare costs) will be conducted during the extension year as part of the cost-effectiveness analyses in Task 4 as these outcomes involve different Medicare claims files than have been used for the rest of the analyses.

Table 9 presents a detailed description of percent treated and percent surviving three years according to percentile of each IV. From this table in univariate fashion it can be observed that areas with the lowest aggressive treatment rate tend also to have lower survival rates. Table 10 presents the two-stage IV analysis results. To examine the sensitivity of results to the fineness/coarseness of IV specification, in Table 10 five scenarios are displayed in which each IV is specified in 20 categories (5% groupings), 10 categories (10% grouping), etc. Also presented are the F-tests for over-identification.

The estimate in Table 10 is for the coefficient,  $\beta_4$ , of "T-hat" (predicted treatment probability from the first stage) where "T-hat" represents the variation in treatment rates across patient groups defined by the instruments. Because we assumed (and supported this assumption) that the instruments are unrelated to the unmeasured confounding factors, the estimate of  $\beta_4$  is unbiased and attributable only to treatment rate differences across patients grouped by the set of instruments. This unbiased treatment effect can be interpreted as follows. For a treatment estimate of 0.25 (Table 10) this means that a four percentage point increase in aggressive treatment rate will result in a one percentage point increase in three-year survival for patients at the practice margins. For a treatment estimate of 0.33, this means that a three percentage point increase in aggressive treatment rate will result in a one percentage point increase in three year survival. As a reference point, the increase in treatment rate going from the highest quartile of differential distance (closer to prostatectomy than non-prostatectomy hospital) to the lowest quartile of differential distance (farther from prostatectomy than non-prostatectomy hospital) was ten percent. Increasing the aggressive treatment rate in the farthest quartile to that observed in the closest quartile could be expected to result in a 2.5 to 3.3 percentage point increase in three-year survival. As another way of looking at these results, since the estimates in Table 10 range from 0.24 to 0.35, for a population of 100 patients, aggressive treatment of an additional 3 to 4 patients would result in one more patient surviving three years.

**Table 9: Distributions of Instrumental Variables, and %Treatment and %Survival by levels of each IV**

VAR_NM	PCTL5	PCTL0	PCTL15	PCTL20	PCTL25	PCTL30	PCTL35	PCTL40	PCTL45	PCTL50	PCTL55	PCTL60	PCTL65	PCTL70	PCTL75	PCTL80	PCTL85	PCTL90	PCTL95	PCTL100
RAD_RT40	0.000	0.000	0.004	0.004	0.005	0.005	0.007	0.008	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.017	0.019	0.021	0.025	2.000
%Aggress	47.07		67.34	64.03	69.40	66.60	55.08	54.68	53.01	48.17	56.37	59.27	58.70	55.64	62.43	52.87	48.28	48.13	45.73	46.41
%Survival	80.05		86.09	83.98	86.14	84.22	81.21	81.60	79.72	77.92	82.71	83.89	83.93	83.05	85.07	81.66	79.07	78.63	76.18	79.00
RP_RT40	0.000	0.010	0.010	0.011	0.014	0.016	0.017	0.017	0.019	0.020	0.021	0.022	0.023	0.024	0.026	0.028	0.030	0.033	0.038	3.000
%Aggress	48.52	61.06	65.72	68.43	61.07	57.62	53.12	55.00	58.46	51.61	58.52	60.31	60.29	51.54	47.54	52.42	51.49	47.99	49.24	45.43
%Survival	79.25	84.26	84.59	84.34	83.75	83.99	81.53	79.91	83.03	81.14	82.03	84.25	84.36	80.91	80.20	80.03	80.37	78.34	80.86	76.80
URO_RATE	0.000	0.000	0.038	0.058	0.065	0.065	0.065	0.081	0.095	0.107	0.126	0.126	0.136	0.146	0.147	0.156	0.174	0.182	0.281	22.542
%Aggress	48.70		54.99	59.93	55.12	55.12	57.31	58.42	58.30	58.42	52.26	54.05	50.37	47.17	60.27	57.80	65.63	60.92	55.44	59.31
%Survival	79.88		81.31	86.10	78.74	78.74	82.43	83.25	83.34	80.94	81.67	82.34	82.34	80.29	84.15	82.24	84.00	84.45	82.63	84.31
AGG_RAT	0.759	0.825	0.861	0.911	0.927	0.939	0.980	1.009	1.014	1.016	1.042	1.043	1.043	1.043	1.044	1.044	1.045	1.121	1.183	2.170
%Aggress	39.31	46.47	46.05	44.33	47.12	54.46	53.98	58.38	59.67	57.74	60.48	57.49	57.67	57.38	60.52	55.65	56.74	64.49	61.40	65.45
%Survival	80.16	79.96	81.95	78.50	79.78	80.72	81.30	83.08	82.50	82.74	81.95	80.91	81.39	79.29	80.10	82.21	81.09	86.52	84.25	85.13
DIF_DIST	12.394	-6.521	-4.248	2.979	2.162	1.368	0.525	0.000	0.000	0.000	0.000	0.672	1.521	2.290	3.215	4.612	8.925	21.835	35.903	299.226
%Aggress	55.22	56.39	56.11	62.41	62.25	60.22	57.94	56.84	56.84	55.39	56.59	56.59	56.59	54.05	56.87	51.15	52.29	46.27	45.17	48.66
%Survival	83.05	84.02	83.67	84.79	84.15	82.44	82.70	82.06	82.06	82.12	81.76	80.34	80.69	80.34	80.69	77.28	79.60	80.06	79.05	79.63
RADDIST	0.000	0.000	1.635	2.392	2.858	3.395	3.879	4.318	4.714	5.296	5.851	6.582	7.758	9.811	12.733	19.706	29.957	40.954	67.630	363.370
%Aggress	56.40	56.40	53.85	55.27	54.74	58.88	56.71	56.50	56.20	59.21	56.63	56.00	57.00	58.27	60.80	51.87	52.11	52.82	48.90	44.79
%Survival	81.85	81.85	82.75	78.30	79.63	81.94	82.25	82.24	82.48	82.88	81.78	82.71	82.56	83.05	83.39	80.21	81.75	82.38	81.45	78.45
MRPDIST	0.000	0.000	0.000	0.000	1.054	1.876	2.274	2.645	3.063	3.385	3.748	4.342	5.023	6.029	7.542	10.877	17.907	27.449	41.977	299.226
%Aggress	57.18	57.18	49.37	53.04	57.71	55.47	58.32	55.41	58.00	60.53	61.36	56.02	50.21	48.02	46.49	48.48	48.48	80.35	80.35	79.35
%Survival	82.70	82.70	81.13	80.29	81.73	80.08	83.31	79.91	81.42	84.11	82.65	84.48	79.15	80.04	80.35	79.15	82.76	80.04	80.35	79.35

The p-value for over-identification was significant in the first four models in Table 10 and non-significant for the model in which all IV were dichotomized at their median value. A significant over-identification F test means that the IV have direct effects on outcome either through their own effects or through correlation with an unmeasured confounder. This is not desirable, since to be a valid IV, a variable should not be associated with treatment outcome. When examined further (data not shown), the two radiation treatment center IV (per capita radiation centers and distance to radiation a center) are the source of the significant over-identification. The other IV are able to be specified in quartiles or even more finely without resulting in over-identification. This suggests that the additional treatment choice between radiation and surgery when aggressive treatment is desirable may be the source of this. Other models that dichotomize the radiation center IV and specify the other IV in quartiles or finer result in a treatment estimate that is within the range identified but without over-identification (the IV are not related to the outcome variable). It is therefore appropriate to conclude that the treatment effect estimate is within the range from 0.24 and 0.35.

**Table 10: T Test for Treatment Effect and Over Identification F Test From Two-Stage Least Squares Analysis, Controlling for All Clinical, Demographic and Socioeconomic Variables; Five Scenarios About Instrumental Variable Groupings (5 percentile, decile, quintile, quartile, and median groupings).**

	TREATMENT EFFECT		OVER-IDENTIFICATION TEST	
	Estimate	T TEST P VALUE	F VALUE	P VALUE
5%	0.241657	<.0001	1.44	0.0029
10%	0.245716	<.0001	1.78	0.0005
20%	0.250235	<.0001	2.42	0.0002
25%	0.258032	<.0001	2.08	0.0055
50%	0.346191	<.0001	1.36	0.2349

### • **Task 3. Describing the Marginal Patients**

We had a priori hypotheses about the subgroups of subjects who would have high treatment variation between high and low access areas. Theory predicts that treatment variation will be greatest for men with characteristics associated with the most uncertainty about the benefits of aggressive treatment.<sup>20</sup> Because older men with comorbidity and low tumor grade would have little expected benefit from treatment (overall life expectancy less than prostate cancer-specific life expectancy),<sup>21</sup> we expected that most providers would agree that these patients should not have aggressive treatments and there should be little treatment variation (low aggressive treatment rate regardless of access). Similarly, most providers will agree that young men with higher tumor grade and no co-morbidity may benefit from aggressive treatment and there should be little treatment variation (high aggressive treatment rate regardless of access).<sup>21</sup> Between these extremes there is uncertainty about the benefits of aggressive treatment and this should be reflected in greater treatment variation. We expected the most uncertainty and hence the most treatment variation for men under age 75. Among this age group, for men with grade I tumors we expected the most uncertainty for men age 65-69 with co-morbidity and for men aged 70-74 without co-morbidity. For men with grade II/III tumors under age 75 we expected the most uncertainty and hence the most treatment variation for those with co-morbidity. Some treatment uncertainty was also expected for men aged 75 to 84 with higher grade tumors. Table 11 displays the anticipated relative magnitude of treatment variation we expected for various combinations of age, grade, and co-morbidity. For each row in Table 11, we compared the percent aggressively treated in high access vs. low access areas using Fisher's exact test. High access areas were defined as areas below the median differential distance to a prostatectomy hospital and low access areas had differential distances above the median. The results of these comparisons are displayed in Table 12. As predicted, the most treatment variation (as measured by the percentage point difference in treatment rate between close and far groups and by the Fisher's exact test results) was seen for men aged 65-69 with co-morbidity and grade I tumors, aged 70-74 with no co-morbidity and grade I tumors, and aged 65 to 74 with co-morbidity with grade II/III tumors. In addition, there was some treatment variation for men aged 75-84 with grade II/III tumors regardless of comorbidity.

Table 11. Expected Amount of Agreement Among Providers About Whether To Treat Aggressively.

GROUP				Expected Amount of Agreement Among Providers <sup>A</sup>
AGE	GRADE	COMORBIDITY <sup>c</sup>	GROUP N	
65-70	I	NO COMORBID	1914	+
		WITH COMORBID	860	?
	II/III	NO COMORBID	5241	+++
		WITH COMORBID	1809	?
70-74	I	NO COMORBID	2259	??
		WITH COMORBID	1111	--
	II/III	NO COMORBID	5703	++
		WITH COMORBID	2203	??
75-84	I	NO COMORBID	2517	?
		WITH COMORBID	1581	---
	II/III	NO COMORBID	5878	?
		WITH COMORBID	2890	?
85&UP	I	NO COMORBID	428	-
		WITH COMORBID	353	---
	II/III	NO COMORBID	906	--
		WITH COMORBID	680	--
<b>TOTAL</b>				
Extent of expected agreement characterized as +++ = strong agreement to treat aggressively; --- = strong agreement to not treat aggressively; ?? = high degree of uncertainty about whether to treat and all others represent levels of uncertainty between these designations.				

**Table 12. Comparison of the Proportion Aggressively Treated Among High Vs. Low Access To Aggressive Treatment, as Measured by Differential Distance<sup>a</sup> to a Prostatectomy Hospital.**

GROUP				NEAR		FAR		Fisher Exact Test <sup>b</sup>
AGE	GRADE	COMOBIDITY <sup>c</sup>	GROUP N	%AGG TRT	CELL N	%AGG TRT	CELL N	
65-70	I	NO COMOBID	1914	56.0181	1105	53.5229	809	
		WITH COMOBID	860	46.5553	479	38.3202	381	A
	II/III	NO COMOBID	5241	87.9588	3106	84.8244	2135	B
		WITH COMOBID	1809	82.4092	1046	76.1468	763	B
70-74	I	NO COMOBID	2259	52.7090	1292	45.2947	967	C
		WITH COMOBID	1111	35.2554	607	32.7381	504	
	II/III	NO COMOBID	5703	82.3583	3299	79.0349	2404	B
		WITH COMOBID	2203	74.7565	1232	63.9547	971	C
75-84	I	NO COMOBID	2517	33.5531	1365	30.0347	1152	
		WITH COMOBID	1581	16.9306	821	15.0000	760	
	II/III	NO COMOBID	5878	54.0879	3278	51.1923	2600	A
		WITH COMOBID	2890	34.8642	1546	30.8036	1344	A
85&UP	I	NO COMOBID	428	4.9261	203	4.0000	225	
		WITH COMOBID	353	3.4884	172	1.6575	181	
	II/III	NO COMOBID	906	12.8480	467	10.4784	439	
		WITH COMOBID	680	5.6657	353	3.9755	327	
<b>TOTAL</b>				<b>58.78</b>	<b>20,371</b>	<b>52.44</b>	<b>15,963</b>	

<sup>a</sup>Differential distance was calculated as the distance to the nearest prostatectomy hospital minus the distance to the nearest non-prostatectomy hospital and categorized as "near" if less than the median differential distance or "far" if greater than the median.

<sup>b</sup> A=p<0.05; B=p<0.01; C=p<0.001

<sup>c</sup> Comorbidity grouped according to Charlson score 0 vs. 1+.

## KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments included

- Acquiring, downloading, reading, and documenting the numerous files from the SEER-Medicare linked data for all prostate cancers from eleven SEER registries;
- Obtaining the zip code and years of operation for all radiation treatment centers in the eleven SEER areas;
- Locating and obtaining a detailed data dictionary that was not provided with the data. Researching the voluminous data dictionary to understand the Medicare files;
- Constructing and validating a case selection algorithm to apply the study inclusion and exclusion criteria;
- Evaluating data quality of key variables;

- Constructing candidate instrumental variables from the Medicare data, Area Resource File, and Radiation Treatment Center zip code locations;
- Demonstrating that selected attributes of patients' residence area (the candidate instrumental variables) group patients such that the groups have different rates of aggressive treatment but do not differ meaningfully in demographic, tumor, or comorbidity characteristics supporting the conclusion that the IV analyses yield unbiased estimates of treatment effect for patients at the practice margins;
- Demonstrating that when patients are grouped according to these IV, higher survival rates are observed for those IV groupings that have a higher prevalence of aggressive treatment;
- Determined that increased survival can be expected if aggressive treatment rates are increased for patients at the practice margins;
- Documented that the estimated treatment benefits apply to categories of men who a priori theory predicted to be at the practice margins because of a higher degree of uncertainty about treatment benefit: men aged 65-69 with co-morbidity and grade I tumors, aged 70-74 with no co-morbidity and grade I tumors, aged 65 to 74 with co-morbidity and with Phase II/III tumors and age 75-84 with grade II/III tumors regardless of comorbidity.

## **REPORTABLE OUTCOMES**

The SEER-Medicare linked database is very large and complex. We have developed experience working with the data and have developed a library of programs and files. This will increase the efficiency of analyses for future projects. A series of technical reports have been produced and are periodically shared with other researchers interested in these data. A manuscript has been drafted on factors related to treatment choice for prostate cancer and one is in development regarding the three-year survival IV analysis results.

Previous researchers have documented that factors other than prognostic patient characteristics (age, grade, and comorbidity) influence treatment choices. The unique contribution of our work is that it not only documents that area characteristics representing access to providers of aggressive treatments predict treatment choice, but also it documents that these practice variations are associated with different three-year survival rates and describes the clinical and demographic characteristics of patients for whom there is the most variation in aggressive treatment rates when patients are grouped by access to aggressive treatments. The significance of the latter is that the unbiased IV treatment effect estimates pertain directly to these patients.<sup>20</sup> Thus we are able to make more specific policy recommendations about the types of patient (age, tumor grade, and comorbidity) for whom aggressive treatments should be increased in low access areas. In addition to the remaining work (IV analyses of re-treatment-free survival and cost-effectiveness analyses), discussions have been held with other researchers about extending the analyses to consider cost-effectiveness of alternative androgen suppression strategies in advanced prostate cancer.

## **CONCLUSION**

Aggressive treatment appears to be underutilized for early stage prostate cancer. For geographic areas with low aggressive treatment rates, clinicians should consider increasing aggressive treatment among men aged 65-69 with co-morbidity and grade I tumors, aged 70-74 with no co-morbidity and grade I tumors, aged 65 to 74 with co-morbidity and with Phase II/III tumors and age 75-84 with grade II/III tumors regardless of comorbidity. If, after all relevant clinical factors (e.g. PSA level) are considered, the clinician who practices in an area with low aggressive treatment rate is still undecided about whether to recommend aggressive treatment for a man with these characteristics, these data suggest that aggressive treatment should be selected.

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- ALL DATA PRESENTED IN THIS REPORT ARE UNPUBLISHED AND SHOULD BE PROTECTED

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