13-Year Outcomes Following Treatment for Clinically Localized Prostate Cancer in a Population Based Cohort

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Purpose: Because data from randomized trials initiated after the introduction of prostate specific antigen testing are unavailable, we performed a retrospective, population based study to estimate prostate cancer specific survival and overall survival after surgery, radiation or observation to manage clinically localized prostate cancer.

Materials and Methods: From the Connecticut Tumor Registry we identified Connecticut residents 75 years or younger diagnosed with clinically localized prostate cancer between January 1, 1990 and December 31, 1992. We obtained information from physician offices concerning treatments received by 1,618 patients who underwent surgery (802), external beam radiation therapy (702) or no initial therapy (114) and subsequent medical outcomes. Treatment comparisons were adjusted for pretreatment Gleason score, prostate specific antigen and clinical stage along with age at diagnosis and comorbidities using 3 methods, including categorization by risk, a proportional hazards model and a propensity score.

Results: At an average followup of 13.3 years 13% of patients had died of prostate cancer, 5% had died of other cancers and 24% had died other noncancer causes. Patients undergoing surgery were younger, and had more favorable histology and lower pretreatment prostate specific antigen compared to patients undergoing radiation. Patients who elected observation had significantly worse cause specific survival than those who elected surgery. They also fared worse than men who received radiation therapy but the difference was not statistically significant, possibly because of the small number of prostate cancer deaths to date.

Conclusions: Our findings suggest that patients undergoing surgery for clinically localized prostate cancer may have a cancer specific survival advantage compared to those electing radiation or observation. However, only a randomized trial can control for the many known and unknown confounding factors that can affect long-term outcomes.

Key Words: prostate, prostatic neoplasms, outcome assessment (health care), prostatectomy, radiotherapy

In the absence of data from randomized trials men with clinically localized prostate cancer identified by PSA testing (T1c disease) face a dilemma when selecting treatment. Should they undergo surgery, request radiation or consider a program of active surveillance? All 3 strategies have strong support from data derived from large case series. Data from a recently reported randomized trial in Sweden suggest that men presenting with stage T1a, T1b and T2 prostate cancer have a survival advantage after 10 years when electing surgery vs observation. The survival advantage is modest and may not be realized in contemporary American men because of the significant lead time introduced by PSA testing and the length of time effects associated with repeat PSA testing.[1]

While contemporary surgical and radiation case series provide some information concerning outcomes, they often fail to control for multiple factors that can confound comparisons, including tumor factors, such as stage and grade, as well as host and environmental factors, such as age, comorbidities, geographic location and year of diagnosis. Most studies do not show outcomes achieved in community practice.

We provide data concerning long-term prostate cancer specific and overall survival outcomes in men diagnosed in community settings with clinically localized prostate cancer who were treated with surgery, radiation or observation during the same period and in the same geographic area. Because men who elect different treatment strategies often differ by several factors known to impact survival, data were collected concerning pretreatment PSA, tumor histology, clinical stage, patient age and comorbidities at diagnosis.

Patient Population

In 1998 the CTR identified a population based cohort of 3,739 Connecticut residents 75 years or younger when they were diagnosed with clinically localized prostate cancer between January 1, 1990 and December 31, 1992. After obtaining appropriate approvals from state and local institutional review boards we assembled data retrospectively on 2,060 of these men from ambulatory medical records located between 1998 and 2004. Information was available from CTR files on an additional 443 men. Of these 2,503 men we excluded 502 who had advanced disease or initial PSA 50 ng/ml or higher. Of the remaining 2,001 men 1,862 were initially treated

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with surgery, external beam radiation or observation. The remainder were treated using multiple strategies. Complete information, including pretreatment biopsy Gleason score, PSA, clinical stage, age and comorbidity score, was available on 1,618 men.

Clinical Information

Clinical information, including patient pretreatment PSA value, biopsy Gleason score, DRE findings, staging studies, comorbidities and age, was gathered from ambulatory records located in physician offices situated throughout the state of Connecticut and in Westerly, Rhode Island. In many instances physician offices were visited on more than 1 occasion to obtain followup information concerning PSA and subsequent interventions. Histology slides of initial biopsies were re-read in 2003 by a single pathologist and the resulting contemporary Gleason scores were used for analysis. Patient tumor burden was classified using the American Joint Committee on Cancer staging system and medical comorbidities were assessed using the Charlson classification system.[2] Information concerning the date and cause of death was obtained from the CTR, which is located at the Connecticut Department of Public Health.

Statistical Analyses

Three statistical methods were used to adjust for differences among patients receiving surgery, radiation therapy and observation. They were 1) stratification into low, intermediate and high risk categories according to the system developed by D'Amico et al,[3] 2) a proportional hazards model and 3) a propensity score.

After separating patients into the 3 D'Amico risk categories Kaplan-Meier curves were used to compare cause specific and overall survival for each of the 3 treatment groups. To minimize any residual confounding arising from this risk stratification adjusted comparisons were also made using a proportional hazards model including pretreatment Gleason score, PSA, clinical stage, age at diagnosis and Charlson comorbidity score (0–1 vs greater than 1). Results of the proportional hazards model are expressed as HRs for patients undergoing radiation therapy or observation relative to those undergoing surgery, which was the reference group. From this model we also calculated cause specific and overall survival curves for the 3 treatment groups. Each survival curve was standardized to the average covariate profile for each D'Amico risk category.

In addition to the proportional hazards model, adjusted comparisons were also made using a propensity score, which was calculated for each patient receiving surgery or radiation. Since these 2 groups were comparable in size, the 13 terms used in the proportional hazards model could be included more easily and reliably. Probabilities of surgery were grouped by deciles and these deciles were used as strata in a proportional hazards model.

As patient followup moves beyond age 70 years, competing risks become much more important. In a cause specific Kaplan-Meier or Cox model survival analysis treating deaths from other causes as censored observations can overestimate cumulative prostate cancer mortality.[4] If competing risks differ among compared groups, as in this study, comparisons of cause specific survival are distorted. To avoid this problem we performed competing risk analysis using methods previously reported.[5]

RESULTS

Table 1 lists the number of patients in each of the 3 comparison groups. Each group was defined in 2 ways, that is men who actually received the treatment and those who were intended to receive the treatment. Also shown for each of these groups are median patient age, the percent who had significant comorbidities, the distribution of biopsy Gleason scores, patient pretreatment PSA and DRE findings, and D'Amico risk categories. Since the distributions under the 2 definitions of treatment were similar, only results derived from intent to treat analysis are presented.

Patients who underwent or were scheduled to undergo surgery tended to be younger and have a more favorable histology distribution and lower pretreatment PSA compared with those who received radiation or were scheduled to receive radiation. Patients treated with observation tended to be older but they had a more favorable distribution of histology and lower pretreatment PSA compared with treated patients. The D'Amico risk categories highlight the differences in risk profile among the 3 groups.

On June 1, 2005, 75% of the patients had more than 12.8 years of followup, 50% had more than 13.3 and 25% had more than 13.9. Median followup across the 3 treatment groups and 3 risk groups varied minimally (13.1 to 13.6 years) and they showed no obvious trends. During followup 208 patients (13%) died of prostate cancer, 77 (5%) died of other cancers and 384 (24%) died of other noncancer causes.

Prostate Cancer Specific Survival

Figure 1 shows cause specific survival curves for each of the 3 treatment groups stratified by D'Amico risk categories. In each

TABLE 1. *Pretreatment characteristics in men and tumors, and vital status at time of analysis*

	No Initial Therapy	Received/Intended	
		Surgery	Radiation
No. men	114	596/802	642/702
Median age	70	65/65	71/71
% Charlson comorbidity score greater than 1	11	4/4	10/10
% DRE findings:			
1 Nodule	8	34/34	32/31
Multiple nodules 1 side	4	3/3	6/6
Nodule 2 sides	—	2/—	4/4
% Gleason score:			
2–4	17	3/3	3/3
5	15	5/5	6/6
6	46	53/49	46/46
7	11	27/29	25/25
8–10	11	12/14	20/20
% Initial PSA (ng/ml):			
0–3.9	27	11/11	9/9
4–9.9	44	46/43	40/39
10–19	17	28/29	29/29
20–49	12	15/17	22/23
Median	6.6	9.1	10.3
% D'Amico risk category:			
Low	58	35/32	26/26
Intermediate	20	39/38	36/36
High	22	26/30	38/38
% Vital status:			
Alive	43	75/73	44/45
Dead of prostate Ca	16	6/8	17/18
Dead of another Ca	4	4/5	5/5
Dead of other causes	37	15/14	33/33

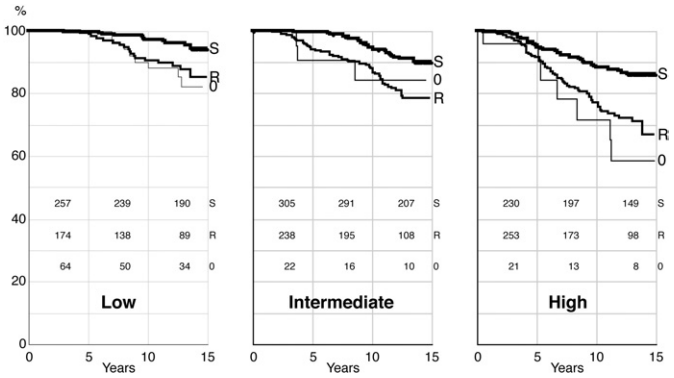

FIG. 1. Cause specific survival in 3 treatment groups stratified by D'Amico risk category. *S*, surgery. *R*, radiation therapy. *O*, observation.

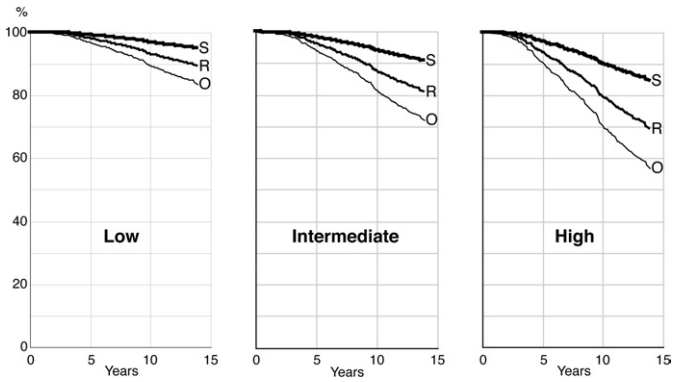

FIG. 2. Cause specific survival in 3 treatment groups with standardization via proportional hazards model to average covariate profile in each D'Amico risk category. *S*, surgery. *R*, radiation therapy. *O*, observation.

of the risk categories those who elected surgical treatment had better cause specific survival than those who elected radiation therapy or observation. Relative to men in the surgery group prostate cancer mortality rates in the radiation therapy and observation groups were 3.0 and 3.8 times higher in the lower D'Amico risk category, 2.5 and 2.2 times higher in the intermediate category, and 2.3 and 3.4 times higher in the highest risk category, respectively. Average mortality rates were 2.5 and 3.2 times higher for radiation therapy and observation compared with surgery across all categories, as estimated from a stratified Cox model. The ratios for radiation and observation were significantly greater than 1 but they were not significantly different from each other.

Table 2 shows that in each D'Amico risk category there was a slightly less favorable distribution of pretreatment Gleason scores and PSA in patients receiving radiation therapy compared with the other 2 treatment groups. Adjustments for these differences were made using a proportional hazards model. Figure 2 shows the resulting cause specific survival comparisons. Even after this more refined adjustment for pretreatment differences cause specific survival in the surgery group was statistically significantly higher than in the other 2 groups. Across all categories average prostate cancer mortality rates in patients receiving radiation therapy or observation were 2.2 (95% CI 1.6–3.1) and 3.4 (95% CI 1.9–5.9) times higher, respectively, compared to that in patients undergoing surgery. The 2 values were significantly greater than 1. Prostate cancer mortality rates in patients initially being observed were 1.5 (95% CI 0.9–2.6) times higher relative to those receiving radiation therapy. The nonsignificant difference may reflect the smaller sample size of the observation group.

In a comparison restricted to patients who underwent surgery or radiation therapy the prostate cancer mortality rate ratio was 2.5 (95% CI 1.7–3.5) times higher in those receiving radiation therapy when the adjustment was performed using covariates directly in the Cox model and 2.3 (95% CI 1.6–3.3) when using propensity scores as strata in a stratified Cox model. Estimated 10-year cause specific survival in patients with surgery, radiation therapy or observation was 97%, 93% and 90% in the lowest risk category, 94%, 88% and 81% in the middle risk category, and 90%, 80% and 70%, respectively, in the highest risk category.

TABLE 2. *Pretreatment characteristics of men and tumors in each treatment group in each D'Amico risk category*

D'Amico Risk Category	No. Initial Therapy		
	None	Surgery or Intent	Radiation or Intent
Low:	66	258	185
Median age	70	64	71
% Charlson score greater than 1	12	3	8
% DRE 1 nodule	5	35	32
Median Gleason score	6	6	6
Median initial PSA (ng/ml)	4.7	6.0	6.2
% Prostate Ca deaths	12	4	10
Medium:	23	308	250
Median age	72	65	72
% Charlson score greater than 1	4	3	10
% DRE 1 nodule	4	37	31
% Multiple/bilat nodules	9	4	12
Median Gleason score	6	7	7
Median initial PSA (ng/ml)	11.0	11.2	12.1
% Prostate Ca deaths	13	8	17
High:	25	236	267
Median age	71	66	71
% Charlson score greater than 1	12	5	11
% DRE 1 nodule	20	29	28
% Multiple/bilat nodules	8	11	14
Median Gleason score	8	7	8
Median initial PSA (ng/ml)	20.8	21.0	21.7
% Prostate Ca deaths	28	13	24

Competing Risk and Overall Survival

Figure 3 shows the results of the competing risk analysis. Because of the large number of terms in the regression models and the small number of prostate cancer deaths in some risk categories, separate analysis for each category was not possible. Figure 3 is based on fitted percents for a standardized comparison of the 3 treatment groups with the standard profile set to an age at diagnosis of 65 years and the values of the other pretreatment variables (comorbidity, Gleason score, PSA and DRE finding) set to the average of their distributions in the entire data set. As expected, the estimates of the percents of men dying from prostate cancer were lower than those derived from the complement of the corresponding cause specific survival and closer to the actual percents listed on the bottom of table 1.

The overall pattern of outcomes was similar to that seen in figures 1 and 2. Radiation therapy outcomes were intermediate between surgery and observation. At 10 years estimated case fatality rates for surgery, radiation therapy and observation were 4.4%, 9.3 % and 13.5%, respectively. When calculations

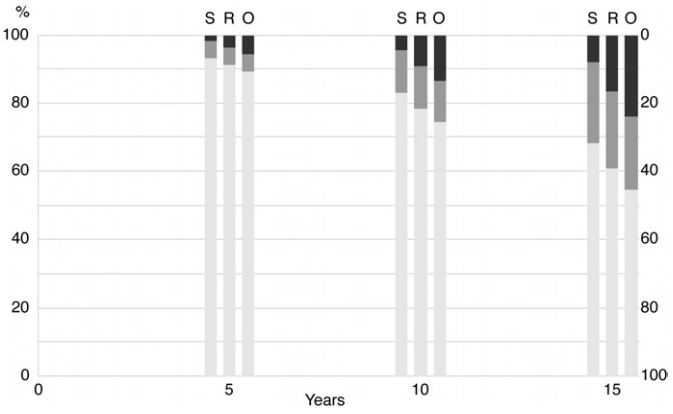

FIG. 3. Estimated percent of patients dead of prostate cancer (black bars), dead of other causes (dark gray bars) and alive (light gray bars) in each treatment group 5, 10 and 15 years after diagnosis. Percents were estimated from competing risk analysis. Treatment groups were standardized to age 65 years at diagnosis, and to average pretreatment comorbidity, Gleason score, PSA and tumor stage distributions in entire data set. *S*, surgery. *R*, radiation therapy. *O*, observation.

were repeated for an age at diagnosis of 70 years, projected competing cause mortality increased by approximately 10% but the estimated cumulative percent of deaths from prostate cancer in each treatment group did not change appreciably.

Figure 4 shows adjusted overall survival curves for the 3 treatment groups. Patients who underwent surgery were an average of 5 years younger than men in the other 2 groups and they had less comorbidity. However, even after adjustment for differences in patient factors and tumor characteristics overall survival of those who elected surgery was still considerably better than that of either of the other 2 groups. Survival differences between those men electing radiation therapy and observation were much smaller. The mortality rate ratio was 1.2 (95% CI 0.9–1.5) times higher in patients undergoing observation compared to those undergoing radiation therapy.

DISCUSSION

Our findings suggest that within 10 years of diagnosis radical prostatectomy may provide a significant survival advantage over radiation therapy or observation when offered to men with clinically localized prostate cancer. Our findings also suggest that radiation therapy may offer a small advantage over observation within the same period. Furthermore, our findings suggest that a survival advantage for surgery appears to occur in men in all risk categories, including those who present with high grade disease.

Direct comparisons of our findings with data from other case series are difficult because most groups report outcomes stratified by only a single variable, such as baseline PSA, tumor grade or clinical stage. Using the classification scheme popularized by D'Amico et al[3] we compared our results with theirs. Men undergoing radical prostatectomy and classified as being at low, intermediate or high risk for progression in our series had a 3%, 6% and 10% 10-year prostate specific mortality rate, respectively. D'Amico et al reported prostate cancer specific mortality rates of 2%, 4% and 10%, respectively, after 10 years in their series. Men undergoing radiation therapy in our series had a 7%, 12% and 20% 10-year prostate cancer specific mortality rate for low, intermediate and high risk disease, respectively. D'Amico et al reported rates of 3%, 8% and 25%, respectively.

When we compared our findings to those reported by Bill-Axelson et al,[1] we also saw similar trends. We noted a prostate cancer specific mortality rate of 16% at 10 years in men electing observation, while Bill-Axelson et al reported a 15% rate. In men undergoing radical prostatectomy we reported a 6.5% prostate cancer specific mortality rate at 10 years, while they reported a rate of 10%.

A major limitation of our study is the lack of randomization. Despite every effort to control for known confounders it is entirely plausible that some unmeasured factor(s) affected the survival rates observed in our study. Our analysis did not adjust for percent positive biopsies, pretreatment PSA velocity, percent Gleason grade 4 or 5 in a biopsy specimen, perineural invasion, prostate gland volume, hypogonadism or 5α-reductase inhibitor use. Any or all of these factors may have confounded our results.

We were surprised to see that men undergoing observation in our series had a higher prostate cancer specific mortality rate compared to the Swedish study.[1] Presumably men diagnosed in Connecticut were diagnosed earlier rather than later in the course of disease as a consequence of PSA testing. The superior survival of men undergoing surgery may reflect a selection bias favoring younger, health conscious males presenting for PSA testing, while men with comorbidities chose not to undergo PSA testing.

Another limitation of our study concerns the changing prevalence of prostate cancer as a consequence of repeat PSA testing. Contemporary patients are much more likely to harbor smaller volume, low grade disease compared to men in this study. While our results support the conclusions of the Swedish randomized trial,[1] our results may not generalize to contemporary patients. Furthermore, we did not explore the morbidity associated with surgery, radiation or observation. Quality of life considerations would have added another layer of complexity when interpreting treatment outcomes.

We were surprised to find no significant survival advantage in men electing radiation therapy compared to observation. Our study may have been under powered because of the relatively small sample size of men electing observation. Alternatively men treated during 1990 to 1992 may have had poorer results because of the relatively low radiation

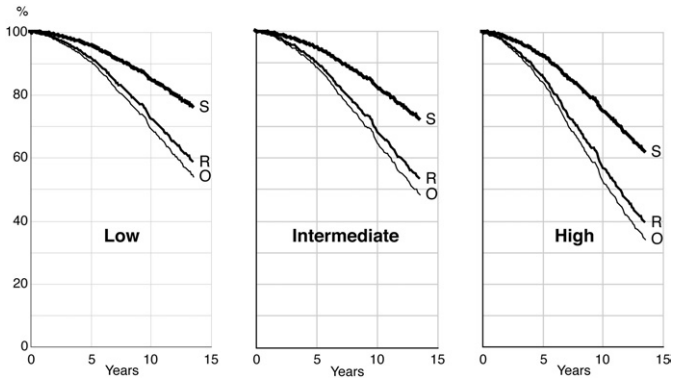

FIG. 4. Overall survival in 3 treatment groups with standardization via proportional hazards model to average covariate profile in each D'Amico risk category. *S*, surgery. *R*, radiation therapy. *O*, observation.

doses used compared to contemporary standards. At this point we can only surmise whether newer radiation techniques translate into a survival benefit.

CONCLUSIONS

Until results become available from 2 large, contemporary, randomized trials that are currently under way[6,7] our results challenge the concept that men with high grade prostate cancer are less likely to benefit from radical surgery. Our results suggest that radical prostatectomy may provide a survival advantage over radiation therapy or observation.

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APPENDIX

Participants: practicing urologists in Connecticut and Westerly, Rhode Island, and medical institution staff at Hartford Hospital, Hartford; Yale New Haven Hospital, New Haven; St. Francis Hospital and Medical Center, Hartford; Bridgeport Hospital, Bridgeport; Waterbury Hospital, Waterbury; Hospital of St. Raphael, New Haven; Danbury Hospital, Danbury; New Britain General Hospital, New Britain; Norwalk Hospital, Norwalk; St. Vincent's Medical Center, Bridgeport; Stamford Hospital, Stamford; Middlesex Hospital, Middletown; St. Mary's Hospital, Waterbury; Lawrence and Memorial Hospital, New London; Manchester Memorial Hospital, Manchester; Greenwich Hospital Association, Greenwich; Mid-State Medical Center, Meriden; Griffin Hospital, Derby; Bristol Hospital, Bristol; John Dempsey Hospital, Farmington; William W. Backus Hospital, Norwich; Charlotte Hungerford Hospital, Torrington; Windham Community Memorial Hospital, Willimantic; Milford Hospital, Milford; Day Kimball Hospital, Putnam; Rockville General Hospital, Rockville; Bradley Memorial Hospital, Southington; Sharon Hospital, Sharon; New Milford Hospital, New Milford; Johnson Memorial Hospital, Stafford Springs, Connecticut; and Westerly Hospital, Westerly, Rhode Island.

Abbreviations and Acronyms

CTR	=	Connecticut Tumor Registry
DRE	=	digital rectal examination
PSA	=	prostate specific antigen

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