Cause of Death in Older Men After the Diagnosis of Prostate Cancer

Melanie Ketchandji, BSc,* Yong-Fang Kuo, PhD,*† Vahakn B. Shahinian, MD, MS,‡ and James S. Goodwin, MD*†

OBJECTIVES: To compare survival and cause of death in men aged 65 and older diagnosed with prostate cancer and with survival and cause of death in a noncancer control population.

DESIGN: Retrospective cohort from a population-based tumor registry linked to Medicare claims data.

SETTING: Eleven regions of the Surveillance, Epidemiology and End Results (SEER) Tumor Registry.

PARTICIPANTS: Men aged 65 to 84 (N = 208,601) diagnosed with prostate cancer from 1988 through 2002 formed the basis for different analytical cohorts.

MEASUREMENTS: Survival as a function of stage and tumor grade (low, Gleason grade < 7; moderate, grade = 7; and high, grade = 8–10) was compared with survival in men without any cancer using Cox proportional hazards regression. Cause of death according to stage and tumor grade were compared using chi-square statistics.

RESULTS: Men with early-stage prostate cancer and with low- to moderate-grade tumors (59.1% of the entire sample) experienced a survival not substantially worse than men without prostate cancer. In those men, cardiovascular disease and other cancers were the leading causes of death.

CONCLUSION: The excellent survival of older men with early-stage, low- to moderate-grade prostate cancer, along with the patterns of causes of death, implies that this population would be well served by an ongoing focus on screening and prevention of cardiovascular disease and other cancers. **J Am Geriatr Soc 57:24–30, 2009.**

Key words: prostate cancer; mortality; survival and comorbidities

From the *University of Texas Medical Branch, Galveston, Texas; †Sealy Center on Aging; and ‡Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan.

Address correspondence to James S. Goodwin, Sealy Center on Aging, 301 University Boulevard, Route 0460, Galveston, TX 77555-0460. E-mail: jsgoodwi@utmb.edu

Once a diagnosis of cancer has been made, it can become the sole focus of medical care. This is understandable, because cancer is typically life threatening and often requires dramatic therapy, but earlier cancer diagnoses, due to screening, and improvements in treatment have been associated with lower cancer mortality, such that, in 2003, there were an estimated 10 million cancer survivors in the United States.[1] Thus, patients are living longer after a diagnosis of cancer, to the point where existing comorbidities may substantially affect their overall survival.

This is particularly true for men diagnosed with prostate cancer. Prostate cancer is the most common form of non-skin cancer diagnosed in men; 75% of cases of prostate cancer occur in men aged 65 and older.[2,3] Prostate cancer can cause early mortality, especially in African-American men who get the disease at a younger age and often have more-aggressive tumors,[2,4] but for many men, prostate cancer may have little effect on their overall survival, especially in those with well- to moderately differentiated tumors, given the slow natural progression and competing risk of death from other causes.[5]

This study examined the primary cause of death in men after the diagnosis of prostate cancer, comparing mortality due to prostate cancer with that from causes other than prostate cancer. Survival and factors predicting survival after a prostate cancer diagnosis were also examined.

METHODS

Data Source

Data from the linked Surveillance, Epidemiology and End Results (SEER) Medicare database were used. SEER is a population-based cancer registry that encompasses an estimated 25% of the U.S. population.[6] It includes information on month and year of diagnosis, stage, histology, and cause of death.[6] The Medicare database covers approximately 97% of Americans aged 65 and older, and linkage to the SEER database was approximately 93% complete.[7] The version of the SEER–Medicare database used for this study included incident cases of cancer through 2002, Medicare

claims through 2004, and SEER cause-of-death information through 2003.

Study Subjects

All men aged 65 to 84 listed in Seer–Medicare who received a primary diagnosis of prostate cancer in 1988 through 2002 in 11 SEER regions (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose, and Los Angeles) were selected, for a total of 208,601 subjects. From this population, three overlapping study cohorts were built for the analytical strategies. First, survival analyses with up to 17 years of follow-up included patients aged 65 to 69 (n = 56,991), 70 to 74 (n = 59,108), 75 to 79 (n = 43,342), and 80 to 84 (n = 21,779) with a known stage. Second, for analyses on cause of death, men aged 65 to 84 and clinically diagnosed with prostate cancer (not from autopsy or death certificate) in 1992 to 1998 were included (n = 103,086), to allow for 5 years of follow-up. Last, for analyses focused on the effect of comorbidities and cancer characteristics on survival, the subjects were limited to those aged 66 to 84 diagnosed in 1992 to 2002 (n = 151,415), because complete Medicare data were unavailable before 1992. To ensure complete information for the last cohort, patients who were not enrolled in both Part A and Part B Medicare for the 12 months before and the 6 months after diagnosis (16,526 cases), who were members of a health maintenance organization (34,465 cases), or whose disease had been diagnosed at autopsy or on a death certificate (1,036 cases) were excluded. Tumor characteristics such as grade (low, Gleason <7; moderate, Gleason = 7; un- or poorly differentiated, Gleason 8–10) and clinical stage (T1 through T4) were derived from the SEER Patient Entitlement and Diagnosis Summary file (PEDSF). Comorbidity, including myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, and diabetes mellitus, was based on the relevant *International Classification of Diseases, Ninth Revision,* diagnosis codes from Medicare claims in the 12 months before diagnosis of cancer (1 inpatient claim or at 2 outpatient or physician claims more than 30 days apart).[8,9] Age and ethnicity were derived from Medicare files to have data comparable in patients and in the noncancer controls.

As a comparison group, a noncancer cohort was developed from the 5% sample of Medicare beneficiaries residing in the SEER areas who did not have any cancer diagnosis in SEER. For the analytical strategies, two overlapping noncancer cohorts were built. First, for survival analyses with up to 17 years of follow-up, men who were residents in a SEER area in 1988 to 2002 were selected. The initial study entry year for these men was assigned randomly to match the distribution for age and years of diagnosis of cancer in men in the prostate cancer cohort. Only subjects aged 65 to 69 (n = 15,192), 70 to 74 (n = 16,040), 75 to 79 (n = 12,245), and 80 to 84 (n = 6,550) were included in the analyses. Next, for analyses of the effect of comorbidities on survival, men aged 66 to 84 years who were residents in a SEER area in 1992 to 2002, had continuous part A and part B Medicare coverage, and were not enrolled in an HMO for at least 18 consecutive months were selected. The initial study entry year for these men was assigned randomly to match the distribution for years of diagnosis of cancer in men in the prostate cancer cohort. In this way, a cohort was constructed of 47,435 men without cancer with follow-up through 2004.

Statistical Analysis

Demographic characteristics of the prostate cancer and noncancer cohorts were compared using chi-square statistics. Based on cause of death recode on SEER PEDSF, 5-year mortality from prostate cancer and other major causes of mortality were calculated for patients diagnosed in 1992 to 1998, stratified according to stage. The Kaplan-Meier method was used to generate survival curves. Multivariate survival analyses, including covariates of age, ethnicity, stage, grade, and comorbidity, were performed using Cox proportional hazards regression. The dependent variable was time to death. Patients were censored at death or at the end of the study (December 31, 2004). All analyses were performed with SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 presents the characteristics of the 99,388 men aged 66 to 84 diagnosed with prostate cancer between 1992 and 2002 and age-matched noncancer controls selected from the 5% Medicare noncancer sample. Of the patients with prostate cancer, 81.0% were diagnosed with clinical Stage T1 or T2 tumors and 71.8% with low- to moderate-grade tumors. The randomly matched noncancer controls were slightly younger, with fewer blacks and a higher prevalence of comorbidities.

Figure 1A to D presents Kaplan-Meier survival curves after a prostate cancer diagnosis for men aged 65 to 69, 70 to 74, 75 to 79, and 80 to 84, stratified according to clinical stage. The cohort is split into four age groups in an attempt to take into account the effect of age and compared with age-matched men without cancer. The survival of men aged 65 to 69 and 70 to 74 with Stage T1 or T2 tumors closely resembles the survival of patients without cancer for the first 7 to 8 years and then becomes worse than the survival of men without cancer. For men aged 75 to 79 and 80 to 84, only Stage T4 prostate cancers had a clear effect on survival rate. Men aged 75 to 79 and 80 to 84 with Stage T1 to T3 tumors had survival rates that closely overlapped each other and the noncancer cohort.

Table 2 presents the results of Cox proportional hazards survival analyses for men aged 66 to 84 with prostate cancer and noncancer controls. Three models are presented. All models control for ethnicity, age, and comorbidity. Model 1 shows the effect of tumor stage on survival without considering tumor grade. Men with Stage T1 cancer had a hazard of death similar to that of the noncancer cohort. Those diagnosed with Stage T3 prostate cancer had a 44% greater hazard of death. In comparison, a prior diagnosis of diabetes mellitus was associated with 47% greater hazard of death. Model 2 examines the effect of histological grade on survival, independent of tumor stage. Men with low- to moderate-grade tumors had a 5% greater hazard of death than noncancer controls, whereas high-grade tumors were associated with a 71% greater hazard of death. When stage and grade were included in the same model, there was

Table 1. Characteristics of 99,388 Men Aged 66 to 84 Diagnosed with Prostate Cancer in 1992–2002 and 47,435 Men without a Cancer Diagnosis

Characteristic	Prostate Cancer n = 99,388	Controls n = 47,435	P-Value[†]
	%	%	
Age, mean ± standard deviation	73.6 ± 4.8	73.0 ± 4.9	<.001
Ethnicity*			
White	83.0	82.1	<.001
Black	10.2	6.1	
Hispanic	1.7	2.7	
Other or unknown	5.1	9.1	
Comorbidity			
Myocardial infarction	1.7	1.9	.03
Congestive heart failure	3.7	4.9	<.001
Peripheral vascular disease	2.0	2.5	<.001
Stroke	3.2	4.3	<.001
Chronic obstructive pulmonary disease	7.3	7.7	.004
Diabetes mellitus	9.8	10.9	<.001
Clinical stage			
T1	26.6	—	
T2	54.4	—	
T3	5.4	—	
T4	5.8	—	
Unknown	7.8	—	
Cancer grade			
Well differentiated	10.6	—	
Moderately differentiated	61.2	—	
Poorly differentiated or undifferentiated	21.3	—	
Unknown	6.9	—	

Note: Patients with prostate cancer and controls had 18 months of Medicare Part A and B without health maintenance organization.

* Information on ethnicity is from Medicare data to allow comparison with the noncancer controls sample. Medicare data on ethnicity during the 1990s substantially underreported Hispanic and Asian ethnicity.

[†] P-values were from t-test or chi-square test for the comparisons of characteristics of patients with prostate cancer and controls.

significant interaction, shown in Model 3. In general, histological grade had a greater effect on survival than does stage at diagnosis.

Table 3 shows the underlying cause of death in the 5 years after a diagnosis of prostate cancer, stratified according to stage at diagnosis and histological grade. Of the 103,086 men diagnosed with incident prostate cancer between 1992 and 1998, 26,740 died between 1992 and 2003. For all men diagnosed with prostate cancer, 5-year mortality from prostate cancer (7.7%) was similar to mortality from cardiovascular disease (7.2%). Mortality from prostate cancer increased with tumor stage and grade. For men with Stage T1 or T2, low- or moderate-grade tumors (59.1% of all cases), mortality from prostate cancer was 2.1%, versus 6.4% from heart disease and 3.8% from other cancers. Even with Stage T3 cancer, men with low- or moderate-grade tumors (60.5% of men with Stage 3 cancer)

experienced higher rates of death from cardiovascular disease (5.2%) than from prostate cancer (4.0%).

DISCUSSION

This study found that, for the two-thirds of men who presented with early-stage prostate cancer, death from heart disease and from other cancers was more common than death from prostate cancer. Men with a diagnosis of early-stage (T1 or T2), low- or moderate-grade prostate cancer did remarkably well in comparison with the general population without cancer, with a mortality risk comparable with that of men without cancer. Comorbid illnesses such as diabetes mellitus and congestive heart failure were important predictors of mortality in these men, and the major causes of death were cardiovascular disease and other cancers—also the two leading causes of death in men without prostate cancer.[10,11]

Previous studies have shown that, over time, the proportion of men with prostate cancer who die from their cancer has steadily declined.[12,13] In the current study, which encompassed men within the prostate-specific antigen screening era, nearly three-quarters of prostate cancer patients presented with localized tumors, and overall, fewer than one-third of deaths at 5 years after diagnosis were due to prostate cancer. Prostate cancer was responsible for a majority of deaths only in men with Stage T4 tumors and accounted for 45% of deaths in men diagnosed with Stage T3, high-grade tumors. Cardiovascular disease was an important cause of death for all men. Having a diagnosis of congestive heart failure carried a hazard of death substantially greater than that associated with a diagnosis of Stage T3, high-grade prostate cancer.

The substantial effect of comorbid conditions on survival and the high rate of mortality related to non-prostate cancer have important implications. First, as others have suggested, decisions about management of localized prostate cancer should incorporate not only life expectancy based on age, but also the important contribution of specific comorbid conditions.[14,15] Second, the choice to use androgen deprivation therapy, now a common treatment even for early-stage prostate cancer,[16] should be made carefully in the presence of significant comorbidity. Recent studies suggest that such therapy can increase the risk of cardiovascular events and exacerbate diabetes mellitus.[17–19] Furthermore, a post hoc analysis of a clinical trial demonstrating overall survival benefit for adjuvant androgen deprivation together with radiation showed a trend for higher mortality in the androgen-deprivation arm in men who had moderate to severe preexisting comorbidity.[20] Finally, a shared model of care, in which patients are followed by a cancer specialist and a primary care physician, may be most appropriate for older men diagnosed with prostate cancer.

A cancer diagnosis can dominate the medical dialogue, such that other important health problems are ignored. For example, one study reported that colorectal cancer survivors received poorer care for chronic conditions than a population without cancer,[21] although this same group of investigators found that breast cancer survivors tended to receive more preventive services than did women without cancer.[22] Patients followed by an oncologist and a primary care physician received the highest proportion of
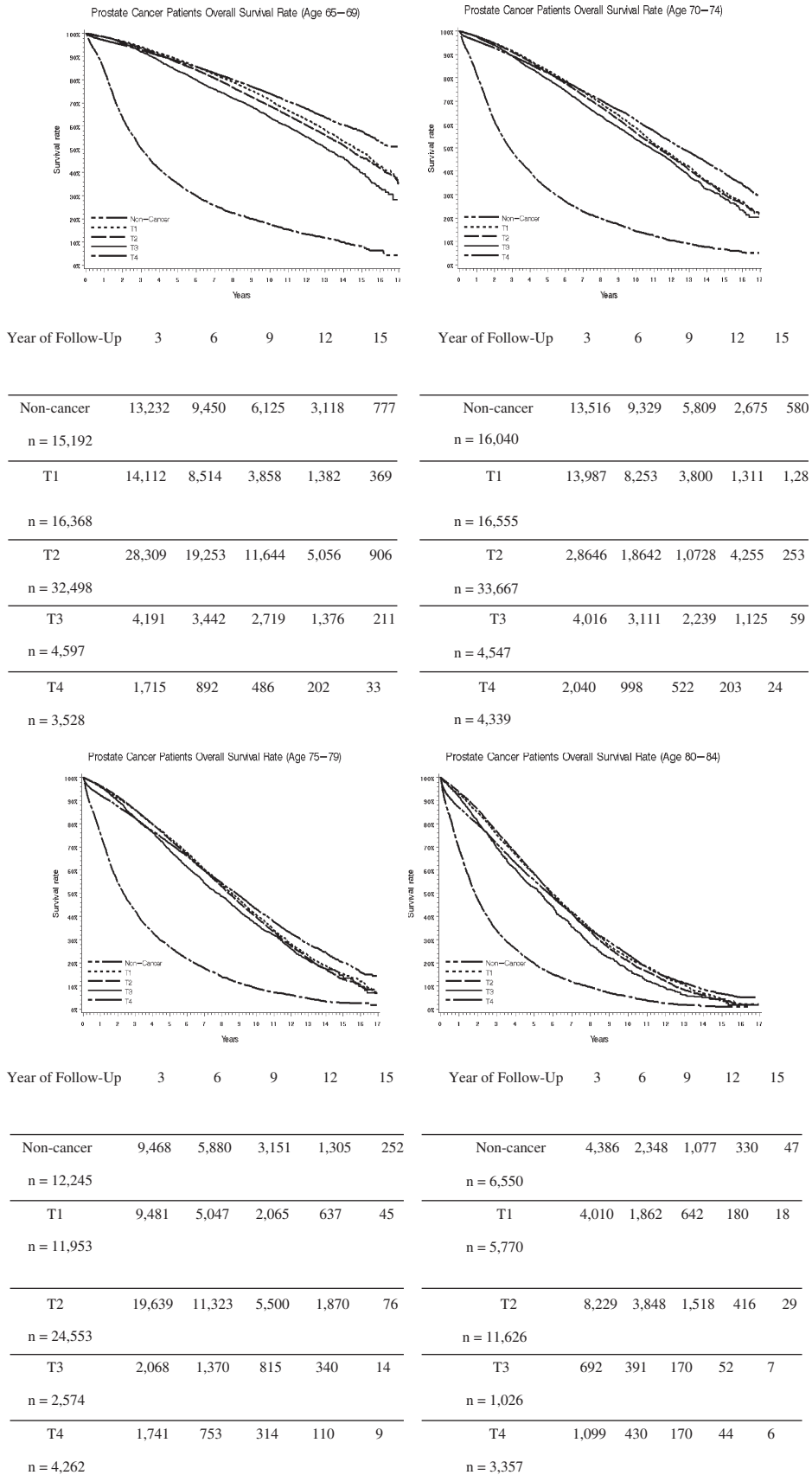
Year of Follow-Up	3	6	9	12	15
Non-cancer	13,232	9,450	6,125	3,118	777
n = 15,192					
T1	14,112	8,514	3,858	1,382	369
n = 16,368					
T2	28,309	19,253	11,644	5,056	906
n = 32,498					
T3	4,191	3,442	2,719	1,376	211
n = 4,597					
T4	1,715	892	486	202	33
n = 3,528					

Year of Follow-Up	3	6	9	12	15
Non-cancer	13,516	9,329	5,809	2,675	580
n = 16,040					
T1	13,987	8,253	3,800	1,311	1,28
n = 16,555					
T2	2,8646	1,8642	1,0728	4,255	253
n = 33,667					
T3	4,016	3,111	2,239	1,125	59
n = 4,547					
T4	2,040	998	522	203	24
n = 4,339					

Year of Follow-Up	3	6	9	12	15
Non-cancer	9,468	5,880	3,151	1,305	252
n = 12,245					
T1	9,481	5,047	2,065	637	45
n = 11,953					
T2	19,639	11,323	5,500	1,870	76
n = 24,553					
T3	2,068	1,370	815	340	14
n = 2,574					
T4	1,741	753	314	110	9
n = 4,262					

Year of Follow-Up	3	6	9	12	15
Non-cancer	4,386	2,348	1,077	330	47
n = 6,550					
T1	4,010	1,862	642	180	18
n = 5,770					
T2	8,229	3,848	1,518	416	29
n = 11,626					
T3	692	391	170	52	7
n = 1,026					
T4	1,099	430	170	44	6
n = 3,357					

Figure 1. Survival curves for men aged 65 to 69 (A), 70 to 74 (B), 75 to 79 (C), and 80 to 84 (D) for 17 years of follow-up.

Table 2. Hazard of Death from Any Cause After a Diagnosis of Prostate Cancer in Men Aged 66 to 84, Compared with Men without Prostate Cancer

Characteristic	Model 1	Model 2	Model 3
	Hazard Ratio (95% Confidence Interval)		
Age (each year increment)	1.10 (1.10–1.10)	1.10 (1.10,1.10)	1.10 (1.09–1.10)
Ethnicity			
White	1.00	1.00	1.00
Black	1.26 (1.23–1.30)	1.28 (1.25,1.32)	1.25 (1.21–1.28)
Hispanic	0.87 (0.82–0.93)	0.87 (0.82–0.93)	0.87 (0.82–0.93)
Other or unknown	0.81 (0.78–0.84)	0.82 (0.79–0.85)	0.80 (0.77–0.83)
Men without cancer	1.00	1.00	1.00
Prostate cancer stage			
1	1.01 (0.98–1.03)		
2	1.09 (1.06–1.11)		
3	1.28 (1.23–1.33)		
4	3.93 (3.80–4.06)		
Unknown	1.50 (1.45–1.55)		
Grade			
Low to moderate		1.05 (1.03–1.07)	
Poor or undefined		1.71 (1.67–1.76)	
Unknown		1.70 (1.65–1.76)	
Grade and stage			
Low to moderate grade			
1			0.96 (0.93–0.99)
2			0.99 (0.97–1.02)
3			1.07 (1.01–1.13)
4			2.71 (2.57–2.87)
Poor or undefined grade			
1			1.32 (1.25–1.40)
2			1.41 (1.36–1.45)
3			1.61 (1.52–1.71)
4			4.73 (4.53–4.95)
Comorbidity			
Heart attack	1.09 (1.03–1.15)	1.09 (1.03–1.15)	1.09 (1.03–1.15)
Congestive heart failure	2.28 (2.21–2.36)	2.28 (2.21–2.36)	2.27 (2.19–2.34)
Peripheral vascular disease	1.47 (1.40–1.54)	1.47 (1.40–1.54)	1.47 (1.40–1.54)
Stroke	1.50 (1.45–1.56)	1.50 (1.45–1.56)	1.51 (1.45–1.56)
Chronic obstructive pulmonary disease	1.67 (1.62–1.71)	1.65 (1.60–1.69)	1.67 (1.63–1.72)
Diabetes mellitus	1.47 (1.43–1.51)	1.46 (1.43–1.50)	1.47 (1.43–1.51)

recommended care. Thus, urologists treating and managing men with prostate cancer should clearly define their role in the patient's management and stress the importance of primary care visits to manage existing chronic conditions.

This study has a number of limitations. First, it was restricted to men aged 65 and older. The effect of a diagnosis of prostate cancer on overall survival may be different in younger men, in whom competing risks for death from other causes would be lower.[23] This would especially be the case for younger African-American men, who are at risk for a more-aggressive form of prostate cancer.[24] Nevertheless, nearly three-quarters of men with prostate cancer are aged 65 and older at the time of diagnosis, so these results are relevant to the majority of patients with the disease. Also, some analyses were specifically stratified into cohorts with men aged 65 to 69, 70 to 74, 75 to 79, and 80 to 84 years,

and it was found that early-stage prostate cancer had a relatively small effect on survival in all groups (Figure 1).

A second limitation of this study is the use of clinical stage instead of American Joint Committee on Cancer staging. Clinical staging does not take into consideration tumor histology, which is why it was included in the models. The accuracy of the underlying cause of death from death certificates is another limitation to the validity of disease-specific mortality rates, although it has been shown that there is good correlation between cause of death obtained from death certificates and medical records in patients with prostate cancer.[25] Finally, type of treatment was not considered in the analyses. This is because studies have shown survival to be good with early-stage prostate cancer regardless of treatment.[26] In addition, strong selection biases linked to treatment decisions would render interpretation of

Table 3. Underlying Cause of Death 5 Years After the Diagnosis of Prostate Cancer

		T1 or T2 Stage		T3 Stage		T4 Stage	
	All Patients	Low or Moderate Grade	Poorly Differentiated or Undifferentiated	Low or Moderate Grade	Poorly Differentiated or Undifferentiated	Low or Moderate Grade	Poorly Differentiated or Undifferentiated
Cause of Death				%			
All patients	100	59.1	13.3	4.2	2.7	2.4	3.3
Overall 5-year mortality	25.94	18.66	28.33	16.85	30.06	56.50	74.48
Cause of death							
Prostate cancer	7.73	2.12	9.78	4.04	13.59	35.19	54.24
Other cancers	3.83	3.70	3.77	3.03	4.01	5.01	3.83
Cardiovascular disease	7.16	6.40	7.26	5.15	6.53	7.75	8.53
Cerebrovascular disease	1.27	1.15	1.36	0.99	0.89	0.91	1.56
Hypertension	0.13	0.11	0.12	0.05	0.14	0.16	0.09
Chronic obstructive pulmonary disease	1.17	1.03	1.30	0.58	0.85	1.39	1.09
Diabetes mellitus	0.45	0.40	0.56	0.30	0.39	0.52	0.44
Renal disease	0.19	0.16	0.21	0.25	0.14	0.20	0.12
Liver disease	0.12	0.11	0.15	0.07	0.04	0.20	0.03
Influenza or pneumonia	0.74	0.60	0.72	0.32	0.67	1.03	1.29
Other infection	0.24	0.21	0.24	0.16	0.18	0.48	0.35
Alzheimer's disease	0.17	0.14	0.17	0.09	0.04	0.08	0.12
Accident	0.36	0.37	0.30	0.16	0.28	0.28	0.24
Suicide	0.16	0.13	0.20	0.16	0.35	0.28	0.24

the relationship between treatments and outcomes highly problematic in observational studies.[27]

In conclusion, the diagnosis of localized, or low- to moderate-grade, prostate cancer has a small effect on life expectancy. Cardiovascular and other diseases are the major threat to life in these cases. For older men with prostate cancer, a focus on prevention and management of comorbid health conditions is an important aspect of their health.

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