Second Cancers as Competing Causes of Death After Radical Prostatectomy

Michael Froehner,*,† Rainer Koch, Oliver W. Hakenberg and Manfred P. Wirth‡

From the Departments of Urology (MF, MPW), and Medical Statistics and Biometry (RK), University Hospital "Carl Gustav Carus", Technical University of Dresden, Dresden, and Department of Urology, University of Rostock, Rostock (OWH), Germany

Purpose: We analyzed the risk of dying of a second cancer after radical prostatectomy for clinically localized prostate cancer.

Materials and Methods: We studied 1,910 patients who consecutively underwent radical prostatectomy between 1992 and 2004. These patients had a median age of 65 years, a median prostate specific antigen of 7.6 ng/ml and a median followup of 5.9 years. Overall disease specific, comorbid, second cancer specific and other mortality data were used as study end points in competing risk analyses. Fatal second cancers were subdivided into 10 categories. The numbers of observed deaths from second cancers were compared with expected rates using cancer registry data.

Results: The risk of dying of a second cancer within 10 years after radical prostatectomy was 4.1%. This death rate was lower than that of comorbidity (5.8%) and prostate cancer (5.4%). Among second cancers colorectal cancer (0.74%), lung cancer (0.69%) and lymphoma, myeloma or leukemia (0.66%) were the most common causes of death after 10 years. Whereas the mortality rates from the other second cancers were within the expected range, fatal lung cancer occurred significantly less frequently than expected.

Conclusions: The low probability of dying of a second malignancy within 10 years after surgery (about 4%) and the nevertheless relatively large contribution of second cancers to competing mortality (about 40%) reflect the good general health status of men selected for radical prostatectomy.

Key Words: prostatic neoplasms; survival; mortality; neoplasms, second primary; selection bias

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* Correspondence: Department of Urology, University Hospital "Carl Gustav Carus", Technical University of Dresden, Fetscherstrasse 74, D-01307 Dresden, Germany (telephone: +49-351-4582447; FAX: +49-351-4584333; e-mail: Michael.Froehner@uniklinikum-dresden.de).

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To benefit from the curative treatment of early prostate cancer an adequate life expectancy is required. In a recently updated randomized trial there was no detectable difference between radical prostatectomy and watchful waiting for clinically diagnosed localized prostate cancer in men 65 years or older.[1] This remarkable observation emphasizes the need for a better understanding of long-term survival characteristics in elderly candidates for curative treatment of early prostate cancer.

Several studies have investigated the relationship between comorbidity and competing mortality in patients with early prostate cancer.[2–5] However, little attention has been paid to the significance of second cancers in this setting. In addition to their role as a cause of competing mortality, second cancers are of clinical interest as a possible late complication of radiotherapy for prostate cancer. Related studies have revealed conflicting results to date.[6–8] In this study we determined the risk of dying of second cancers in men who

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Table 1. *Demographic characteristics of study population*

Mean (median) pt age	64.2 (65.0)
Mean (median) yrs followup (censored pts only)	6.4 (5.9)
Total man-yrs followup (all pts)	12,071
Mean (median) ng/ml prostate specific antigen*	11.6 (7.6)
% Organ confined disease (pT2pN0)	62
% Locally advanced disease, node neg (pT3-4pN0)	25
% Pos lymph nodes	9
% No tumor stage available	4
% Gleason score 2–6	48
% Gleason score 7	31
% Gleason score 8–10	19
% No Gleason score available	3
% History of neoadjuvant hormonal treatment	18

* Only patients without a history of neoadjuvant hormonal treatment.

underwent radical prostatectomy for clinically localized prostate cancer and compared the figures with the expected rates in this population.

MATERIALS AND METHODS

Patient Sample

A total of 1,910 consecutive patients who underwent radical prostatectomy for clinically localized prostate cancer at a university hospital between December 1, 1992 and December 31, 2004 were studied. Institutional review board exemption was obtained. The demographic data were collected from medical records and the demographic characteristics of the patient population are provided in table 1.

Study End Points

Overall disease specific (deaths from uncontrolled prostate cancer recurrence were considered events), comorbid (all noncancer deaths other than accident or suicide were considered events), second cancer specific (deaths from uncontrolled malignancy other than prostate cancer were considered events) and other mortality (suicide or accident) were used as study end points. Fatal second cancers were subdivided into 10 categories (table 2). Information on the cause of death was collected from physicians, relatives, cancer registries and local authorities by written, facsimile or telephone inquiries. Only 1 patient was lost to followup.

Calculation of Expected Number of Cancer Deaths

The expected numbers of deaths from different cancers were determined by obtaining the incidence of cancer deaths using a web based service of the Robert Koch Institute in Berlin.[9] At this web site raw and age adjusted mortality rates for different types of cancer may be obtained for Germany, stratified by age and gender. Several parameters were entered into the program including gender (male), region (Germany), cancer localization (possible categories in table 2), indicator (age adjusted rate), standard population (European), year (last year available, 2003), age group (45 to 84 years this range fitted best to that of this sample which was 45 to 79 years with a median of 65.0) and data aggregated during 10 years (1994 to 2003). The expected numbers of cancer deaths were calculated by multiplying the obtained incidences per 100,000 per year by the man-years of followup of all 1,910 patients.

Statistical Analysis

The individual contributions of different causes of death were analyzed by competing risk analysis resulting in an estimation of cumulative incidence rates for the different correlated risks.[10] The calculation of confidence intervals

Table 2. *Probability of death within 10 years after radical prostatectomy (competing risk analysis) and comparison of death from second cancers with expected figures based on estimated incidence of death in comparable population[9]*

Cause of Death	10-Yr Mortality (%)	95% CI	No. Observed Deaths*	Expected Incidence/ 100,000/yr[9]	Expected Deaths[9]	p Value
Overall	15.7	13.2–18.5	176	Not available	Not available	Not available
Prostate Ca	5.4	3.8–7.1	59	Not available	Not available	Not available
Competing causes overall	10.3	8.1–12.4	117	Not available	Not available	Not available
Non Ca causes†	5.8	4.1–7.4	63	Not available	Not available	Not available
Other causes‡	0.37	0.00–0.80	5	Not available	Not available	Not available
Second Ca overall	4.1	2.7–5.6	49	534.6§	64§	0.07
Colorectal Ca	0.74	0.18–1.30	8	73.3	9	0.99
Lung Ca	0.69	0.07–1.32	7	166.8	20	0.0022
Lymphoma, myeloma or leukemia	0.66	0.11–1.21	8	46.6	6	0.49
Gastric or duodenal Ca	0.58	0.00–1.25	5	37.8‖	5‖	0.55
Pancreatic Ca	0.47	0.02–0.91	7	31.5	4	0.50
Hepatocellular or cholangiocellular Ca	0.45	0.10–0.89	5	18.5	2	0.24
Brain tumor	0.23	0.00–0.49	4	14.0	2	0.53
Bladder Ca	0.12	0.00–0.29	2	19.4	2	0.39
Renal cell Ca¶	0.08	0.00–0.24	1	Not available	Not available	Not available
Ca of unknown primary	0.06	0.00–0.19	2	Not available	Not available	Not available

* Including deaths occurring more than 10 years after surgery.
† Other than suicide or accident.
‡ Suicide or accident.
§ Other than prostate cancer (53.2/100.000 per year).
‖ Only gastric cancer.
¶ Patient died of recurrent renal cell carcinoma diagnosed and initially treated before radical prostatectomy.