Patients undergoing radical prostatectomy have a better survival than the background population

Martin Andreas Røder[1], Klaus Brasso[1, 2], Kasper Drimer Berg[1], Frederik Birkebæk Thomsen[1], Lisa Gruschy[1], Ea Rusch[3] & Peter Iversen[1, 2]

ABSTRACT

INTRODUCTION: The objective of this study was to investigate standardised relative survival and mortality ratio for patients undergoing radical prostatectomy for localized prostate cancer at our institution.

MATERIAL AND METHODS: Between 1995 and 2010, a total of 1,350 consecutive patients underwent radical prostatectomy. Patients were followed prospectively per protocol. No patients were lost to follow-up. Overall and cause-specific survival were described using Kaplan-Meier plots. Standardized relative survival and mortality ratio were calculated based on expected survival in the age-matched Danish population using the methods and macros described by Dickmann. The country-specific population mortality rates used for calculation of the expected survival were based on data from The Human Mortality Database. RESULTS: The median follow-up was 3.4 years (range: 0-14.3 years). A total of 59 (4.4%) patients died during follow-up. In all, 17 (1.3%) patients died of prostate cancer. The estimated ten-year overall survival was 89.3%. The cancer-specific survival was estimated to 96.6% after ten years. Relative survival was 1.04 after five years and 1.14 after ten years. The standardized mortality ratio, i.e. observed mortality/expected mortality, was 0.61 and 0.39 at five and ten years, respectively.

CONCLUSION: The overall and cancer-specific ten-year survival in a consecutive series of patients in a non-screened Danish population is ≥ 89%. The survival and mortality ratio is significantly better than expected in the age-matched background population. This finding is likely explained by selection bias. Although the results indicate an excellent outcome in terms of cancer control, the efficacy of prostatectomy for localized prostate cancer remains at debate.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Radical prostatectomy as curatively intended treatment for localized prostate cancer was introduced in Denmark in 1995. Although prostate-specific antigen (PSA)-screening has never been recommended in Denmark, an increased awareness and "grey-scale" screening has resulted in a sharp rise in the prostate cancer incidence during the past 15 years [1]. Consequently, surgical treatment for localized prostate cancer with radical prostatectomy is now being performed in increasing numbers at several institutions. We have previously reported early results, mortality and morbidity. This paper focuses on outcomes in terms of survival – overall, cause-specific, relative – and standardized mortality ratio after ten years in a consecutive series of patients undergoing radical prostatectomy at the Department of Urology, Rigshospitalet.

MATERIAL AND METHODS

Since 1995 patient data were collected prospectively in a database approved by the Danish Data Protection Agency (file#: 2006-41-6256). All data were collected through systematic patient file review after achieving consent from all patients.

Patients with clinically localized prostate cancer (clinical T-category (cT)1-cT2) and a life expectancy of 10-15 years were offered radical prostatectomy. Some patients with clinical suspicion of T3a cancer were offered radical prostatectomy, if biopsy Gleason score and/or preoperative PSA-concentration were low. All patients with a PSA-concentration > 10 ng/ml and/or a Gleason score > 6 had bone scans prior to treatment. Positive scans were supplemented with magnetic resonance imaging to rule out bone metastasis.

Biopsy and specimen Gleason score were assigned according to the International Society of Urological Pathology 2005 guideline for all patients operated after 2006. Pathology evaluation in patients managed before 2006 (498/36.8%) were not re-reviewed. Radical prostatectomy was performed according to P. Walsh. Since 2009, selected patients have been operated with DaVinci robotic-assisted laparoscopic prostatectomy. Limited lymphadenectomy in the obturator fossa were performed in patients with a PSA-concentration > 10 ng/ml and/or a Gleason score ≥ 7 or if suspect lymph nodes were encountered during surgery. The first 131 patients were treated with three months of neoadjuvant gonadotropin-releasing hormone (GnRH) agonist to reduce positive surgical margins and improve survival. This method was abandoned when international trials failed to demonstrate a reduction in risk for biochemical recurrence or survival [2]. GnRH treatment is known to affect pathological evaluation; we therefore do not report the histopathological data for these patients, which constitute 9% of the total cohort.

TABLE 1

Patient characteristics, including patients dying from prostate cancer.

	All patients				Patients dying from PCA	
	median	IQR	n	%	n	%
Preoperative characteristics						
Age, years	63	60-67				
< 56			127	9.4	13	10.2
56-66			852	63.1	2	0.2
> 66			371	27.5	2	0.5
PSA-concentration, ng/ml	8.7	5.9-13.0				
0-4			126	9.3	3	2.4
4.1-10			669	49.6	6	0.9
10.1-20			443	32.9	4	0.9
> 20			11	8.2	4	36.4
cT						
T1			683	50.6	2	0.3
T2			629	46.6	11	1.7
T3a			28	2.8	4	14.3
Biopsy Gleason score						
2-5			154	11.4	2	1.3
6			481	35.6	7	1.5
7			529	39.2	3	0.6
8-10			63	4.7	2	3.2
Not available[a]			123	9.1	3	2.4
Pathological characteristics						
pT						
pT0			6	0.4	0	–
pT2a/b			126	9.3	1	0.8
pT2c			745	55.2	1	0.1
pT3a			223	16.5	4	1.8
pT3b			116	8.6	5	4.3
pT4			3	0.2	0	–
Not available[b]			131	9.7	6	4.6
pN						
Nx			549	40.7	7	1.3
N0			646	47.9	2	0.3
N1			24	1.8	2	8.3
Not available			131	9.7	6	4.6
Margin status						
Margin positive			510	37.8	9	1.8
Margin negative			709	52.5	2	0.3
Not available[a]			131	9.7	6	4.6
Margin positive versus pT			510			
pT2			284	32.6	–	–
pT3a			139	62.3	–	–
pT3b			84	72.4	–	–
pT4			3	100.0	–	–
Specimen Gleason score						
2-5			67	5.0	0	–
6			317	23.5	6	1.9
7			741	54.9	1	0.1
8-10			80	5.9	4	5.0
Not available			145	10.7	6	4.1

cT = clinical T-category; IQR = interquartile range; PCA = prostate cancer; PSA = prostate specific antigen; pN = pathological N-category; pT = pathological T-category.
a) Due to WHO-grading or insufficient material for Gleason scoring.
b) Due to neoadjuvant treatment.

TABLE 2

Survival analysis.

Years following surgery	Relative survival (95% CI)	Standardized mortality ratio (95% CI)
1	1.015 (1.010-1.016)	0.100 (0.025-0.403)
5	1.038 (1.011-1.057)	0.607 (0.419-0.879)
10	1.137 (1.045-1.186)	0.393 (0.197-0.787)

CI = confidence interval.

Data collected for this analysis included age, PSA-concentration, clinical T-category (cT) and biopsy Gleason score, specimen pathology, i.e. pathological T-category (pT)-category, specimen Gleason score and surgical margin status.

Post-operatively, patients were followed with PSA-concentration measurements three and six months after surgery, then twice a year for two years and annually hereafter. No patients received adjuvant hormonal or radiation therapy before biochemical failure, defined as the first confirmed PSA-concentration ≥ 0.2 ng/ml. Patients were followed until death or 31 December 2010.

Causes of death were determined from patient files and/or autopsy reports. Prostate cancer was recorded as the cause of death when prostate cancer was the only cause of death noted and if patients had died following metastatic disease. Survival was calculated from the date of surgery. No patients were lost to follow-up.

Overall and cancer-specific survival was described using the Kaplan-Meier method. Further, survival was analyzed as relative survival and standardized mortality ratio (SMR). Relative survival and SMR were calculated based on expected survival in the age-matched Danish population using the methods and macros described by Dickmann [3]. The country-specific population mortality rates used for calculation of the expected survival were based on data from The Human Mortality Database with rates adjusted using five-year averages over time. The standardized mortality ratio was calculated as observed mortality divided by expected mortality.

Trial registration: not relevant.

RESULTS

A total of 1,350 consecutive patients operated at our institution in the period from 1 August 1995 to 1 August 2010 were included in this analysis. No patients were excluded. Median follow-up was 3.4 years (range: 0-14.3 yrs). A total of 456 and 87 patients were followed for more than five and ten years, respectively.

Patient characteristics are listed in **Table 1**. Median age at surgery was 63 years (interquartile range (IQR): 60-67 years). The median PSA-concentration was 8.7 ng/

ml (IQR: 5.9-13 ng/ml). Preoperative PSA-concentration was not available for one patient.

Surgery was performed by six different surgeons with one surgeon accounting for 52% of the operations. Nerve-sparing procedure was performed in 338 (25%) of the patients. Lymphadenectomy was carried out in 50% of all cases.

A total of 219 patients (16.2%) received additional treatment (first line) after radical prostatectomy. Salvage radiotherapy for patients with confirmed biochemical recurrence was used in 89 (6.6%) patients. A total of 33 patients (31/2.3%) were enrolled in the AdPRO trial (open-label, randomized trial comparing six cycles of docetaxel/chemotherapy versus observation after radical prostatectomy), with 16 patients receiving active treatment. Endocrine treatment for suspected or confirmed distant failure after biochemical recurrence was used for 99 (7.3%) of the patients.

The overall biochemical recurrence-free survival after five and ten years was 72.1% (95% confidence interval (CI): 68.4-75.8) and 64.9% (95% CI: 59.4-70.4), respectively (figure not shown). In all, 59 (4.4%) patients died during follow-up. Seventeen (1.3%) patients died of prostate cancer. The characteristics of patients dying of prostate cancer are listed in **Table 2**. A high preoperative PSA-concentration (> 20 ng/ml), clinically palpable tumour (≥ cT2) and a biopsy Gleason score ≥ 8 were frequent in patients with prostate cancer death. Young age, extra-capsular extension, presence of positive surgical margins, lymph node-positive disease and a specimen Gleason score ≥ 8 were all associated with prostate cancer death in univariate analysis, Table 1. The low mortality did not allow for multivariate analysis.

The estimated ten-year overall survival was 89.3% (95% CI: 85.8-92.8), **Figure 1**. Cancer-specific survival was estimated to 96.6% (95% CI: 94.7-98.5) after ten years of follow-up, **Figure 2**.

Relative survival after five and ten years, respectively, was 1.038 (95% CI: 1.011-1.057) and 1.138 (95% CI: 1.045-1.186). The five- and ten-year SMR was 0.607 (95% CI: 0.419-0.879) and 0.393 (0.197-0.787), respectively, Table 2.

DISCUSSION

Treatment of localized prostate cancer remains controversial. During the past 20-30 years, several treatment options have been suggested.

In patients managed with watchful waiting, i.e. no initial treatment and only hormone manipulation if or when the disease progresses, Johansson et al found a cancer-specific survival for grade 1 tumors (~ biopsy Gleason score ≤ 6-7) of 71.8% in a Swedish cohort of 223 patients [4]. Albertsen et al showed that the natural history of localized prostate cancer was slow, and the cumulative incidence of prostate cancer mortality after 20 years was 0-30% for patients with a biopsy Gleason score ≤ 6 who were in the 55-74-year age range at diagnosis [5]. Likewise, Adolfsson et al found a risk of prostate cancer death at ten years of 16% in an uncontrolled series of 122 patients [6]. Watchful waiting was the preferred treatment for localized prostate cancer in the 1980s, especially in Scandinavia.

The retropubic radical prostatectomy approach was introduced in 1947 by Millin, but never gained popularity as prostate cancer treatment before the late 1970s when it was modified by Walsh. As reported in several

---

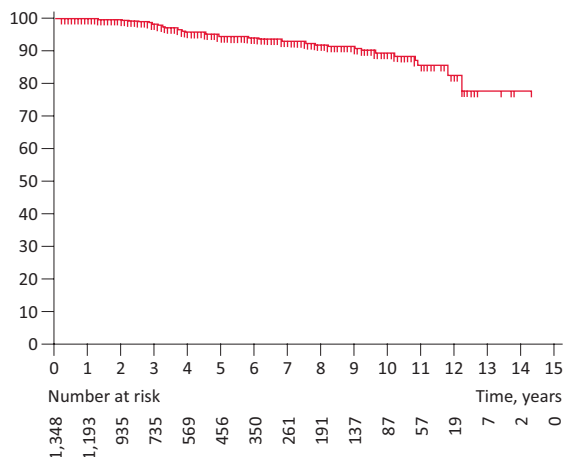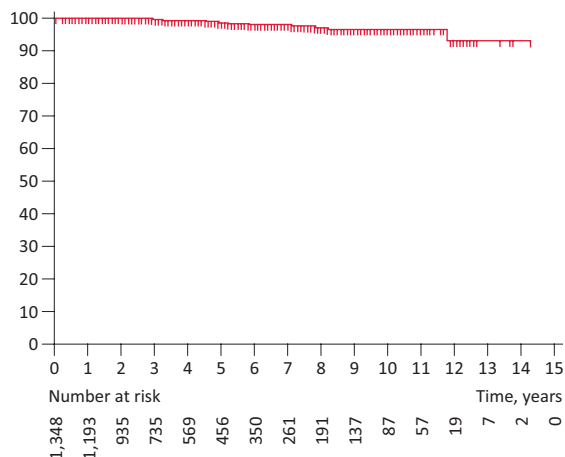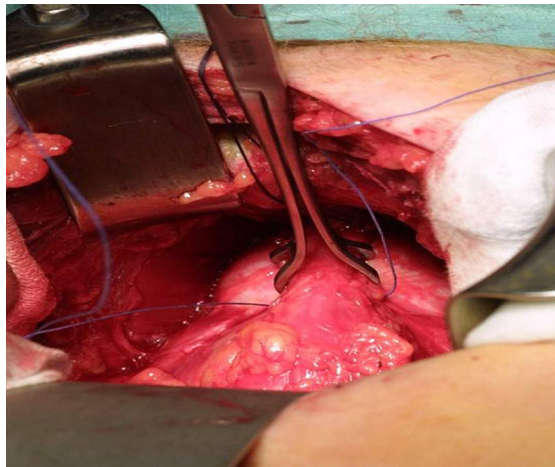**FIGURE 1**

Overall survival.

Number at risk

FIGURE 2

Cancer-specific survival.

Number at risk

Radical prostatectomy.

studies, radical prostatectomy can be performed with low morbidity and perioperative mortality [7, 8]. We have previously published a detailed description of bio-chemical recurrence rates and their association with pre- and post-operative parameters [9].

Survival after cancer therapy remains the best end-point for efficacy of treatment. Several prospective sur-gical series have reported long-term survival after radi-cal prostatectomy [10]. Generally, overall and cause-specific survival are reported in the range from 75-96% after ten years. Comparison across surgical se-ries is complex. Cause-specific survival is influenced by several factors, including cT, PSA-concentration and bi-opsy Gleason score, as well as final specimen Gleason score and pT-category. Selection bias is critical and can explain at least some of the differences in survival. Moreover, PSA-testing and screening has induced a lead-time bias in prostate cancer diagnosis and thus im-proved survival in contemporary radical prostatectomy [11, 12].

So far, radical prostatectomy and watchful waiting or observation are the only two treatment options that have been compared in a randomized setting [13, 14]. The Scandinavian Prostatic Cancer Group-4 (SPCG) rand-omized patients with clinically localised prostate cancer to watchful waiting or radical prostatectomy. The major-ity of patients were diagnosed and included before PSA-testing became commonly used, and 88% had palpable tumour at the time of radical prostatectomy. After a me-dian follow-up of 12 years, the relative risk of prostate cancer mortality was reduced by 38% for patients under-going radical prostatectomy compared with watchful waiting [14]. The absolute risk reduction for prostate cancer death was 6.1% and the number needed to treat was 16. Recent analyses of the SPCG-4 data suggest that the *individual* absolute reduction in the risk of dying of prostate cancer can vary between 0-25% depending on age, cT and biopsy Gleason score. Patients above age 70

have no benefit of radical prostatectomy, regardless of the other variables [15].

The US Prostate Cancer Intervention Versus Observation Trial (PIVOT) randomized PSA-screened pa-tients to radical prostatectomy or observation. The study failed to demonstrate an overall benefit of radical prostatectomy [13]. Cancer-specific survival at ten years in the radical prostatectomy arm was > 90%. Thus, data from the SPCG-4 and PIVOT studies strongly suggest that the benefit of radical prostatectomy compared with deferred endocrine treatment is minimal. Subgroup analysis of PIVOT revealed a possible survival benefit for patients with a higher risk prostate cancer, i.e. a PSA-concentration > 20 ng/ml or a biopsy Gleason score ≥ 8 or ≥ cT2.

We found an estimated prostate cancer-specific survival of 96.6%, and an 89.3% overall survival at ten years. Because of the limited number of deaths, it was not possible to estimate risk factors in a multivariable model. However, as shown in Table 2, there was a trend towards younger age and more aggressive clinical and histopathological features in those patients dying from prostate cancer, but this finding should be interpreted with caution. Longer follow-up is needed to evaluate risk factors associated with prostate cancer mortality. Furthermore, it could be speculated whether the in-creased use of PSA-testing in the Danish population, which has increased the incidence of prostate cancer tremendously, has affected pre- and post-operative par-ameters for patients undergoing radical prostatectomy. At present our data do not have sufficient statistical strength to evaluate this speculation.

Relative survival and standardised mortality ratio in-dicate that survival of patients with prostate cancer man-aged with radical prostatectomy is better than the sur-vival in the background population. This finding is in accordance with results reporting a better than expected survival in patients with prostate cancer in the pre or early PSA-era [16]. Recent results show better survival in men with screening-detected clinically localized prostate cancer compared with the background population re-gardless of treatment [17]. Selection bias is a major and apparent explanation for this. First, patients eligible for radical prostatectomy have low co-morbidity and long life expectancy. Secondly, higher socio-economic status and good general health have been found to correlate with likelihood of PSA-testing and undergoing radical prostatectomy [18, 19]. Also, being diagnosed with a cancer may alter a patient's lifestyle and may lead to an improved survival [20]. Unpublished results from the Danish Diet, Cancer and Health Study indicate that de-spite equal and free access to health care, socio-eco-nomic factors are associated with opportunistic PSA-testing, which consequently may lead to earlier

diagnosis and better survival. We were unable to adjust for differences in survival due to differences in socio-economic status. The data did not allow for stratification on pre- or post-operative parameters on relative survival or standard mortality ratio. Further, data did not allow for evaluation of the impact on year of surgery.

The main limitation of this study is the relatively short follow-up and the low number of events. Thus, ten-year estimates of relative survival and standard mortality ratio are associated with uncertainty. This is reflected in the wide confidence intervals of the estimate. Longer follow-up is needed to confirm our findings 10-20 years after radical prostatectomy.

CONCLUSION

Overall and cancer-specific survival in our consecutive series of patients undergoing radical prostatectomy was ≥ 89% after ten years. Survival was thus significantly better than expected in the age-matched background population. This finding is likely explained by selection bias, i.e. long life-expectancy prior to surgery, impact of socioeconomic factors on opportunistic PSA-testing. However, longer follow-up is needed to confirm this finding at 10, 15 or 20 years after surgery. Although the results confirm an excellent outcome in terms of cancer control, the efficacy of radical prostatectomy as treatment for localized prostate cancer remains controversial, as results from randomized trials demonstrate a modest survival benefit compared with observation, especially among elderly men with low-risk prostate cancer.

CORRESPONDENCE: *Martin Andreas Røder*, Copenhagen Prostate Cancer Center, Section 7521, Rigshospitalet, 2200 Copenhagen N, Denmark. E-mail: andreasroder@gmail.com

REFERENCES

1. Outzen M, Brasso K, Martinussen N et al. Prostate cancer in Denmark 1978-2009 – trends in incidence and mortality. Acta Oncol 2012 Jul 19 (epub ahead of print).
2. Aus G, Abrahamsson PA, Ahlgren G et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int 2002;90:561-6.
3. Dickman PW, Sloggett A, Hills M et al. Regression models for relative survival. Stat Med 2004;23:51-64.
4. Johansson JE, Andren O, Andersson SO et al. Natural history of early, localized prostate cancer. JAMA 2004;291:2713-9.
5. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-101.
6. Adolfsson J, Carstensen J, Lowhagen T. Deferred treatment in clinically localised prostatic carcinoma. Br J Urol 1992;69:183-7.
7. Roder MA, Gruschy L, Brasso K et al. Early complications following open radical prostatectomy. Ugeskr Læger 2009;171:1492-6.
8. Gerber GS, Thisted RA, Scardino PT et al. Results of radical prostatectomy in men with clinically localized prostate cancer. JAMA 1996;276:615-9.
9. Roder MA, Berg KD, Gruschy L et al. First danish single-institution experience with radical prostatectomy: biochemical outcome in 1200 consecutive patients. Prostate Cancer 2011;2011:236357.
10. Boorjian SA, Eastham JA, Graefen M et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes Eur Urol 2012;61:664-75.
11. Albertsen PC, Hanley JA, Barrows GH et al. Prostate cancer and the Will Rogers phenomenon. J Natl Cancer Inst 2005;97:1248-53.
12. Finne P, Fallah M, Hakama M et al. Lead-time in the European Randomised Study of Screening for Prostate Cancer. Eur J Cancer 2010;46:3102-8.
13. Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
14. Bill-Axelson A, Holmberg L, Ruutu M et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011;364:1708-17.
15. Vickers A, Bennette C, Steineck G et al. Individualized estimation of the benefit of radical prostatectomy from the scandinavian prostate cancer group randomized trial. Eur Urol 2012;62:204-9.
16. Zincke H, Oesterling JE, Blute ML et al. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 1994;152:1850-7.
17. Mathers MJ, Roth S, Klinkhammer-Schalke M et al. Patients with localised prostate cancer (t1 - t2) show improved overall long-term survival compared to the normal population. J Cancer 2011;2:76-80.
18. Dalton SO, Schuz J, Engholm G et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: summary of findings. Eur J Cancer 2008;44:2074-85.
19. Zeliadt SB, Etzioni R, Ramsey SD et al. Trends in treatment costs for localized prostate cancer: the healthy screenee effect. Med Care 2007;45:154-9.
20. Humpel N, Magee C, Jones SC. The impact of a cancer diagnosis on the health behaviors of cancer survivors and their family and friends. Support Care Cancer 2007;15:621-30.