Impact of PSA implementation and combined radiation and hormonal therapy (RT + HT) on outcome of prostate cancer patients

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ABSTRACT

Advances in the diagnosis and management of prostate cancer have been associated with changes in clinico-epidemiological characteristics and cancer-specific mortality. Secular trends of prostate cancer patients and its correlation with PSA implementation and the introduction of combined radiation and hormonal therapy (RT + HT) were assessed in a cohort of 910 cancer patients with histologically confirmed prostate cancer diagnosed between 1992 and 2005, and included in a hospital-based database. Relative survival before and after 1999 (when RT + HT for locally advanced disease was introduced) was compared.

The mean age at diagnosis decreased from 72.9 years in 1992–1996 to 68.7 in 2003–2005 and the median PSA from 34 to 8 ng/ml. In patients with stages II and III, there was an increase in the indication of RT with or without HT and a decrease in the indication of surgery (from 87.5% to 44.2%). The overall relative 5-year survival increased from 67.3% (95% CI 60.2–75.2) to 92.9% (95% CI 87.3–98.9). The same trend in stage II and stage III cancer patients was found.

There was an increase in survival coincidentally with a shift towards lower stages and PSA levels at presentation. Besides other factors, changes in death rates since 1999 could be explained by secular variations in the treatment of the disease, particularly the implementation of RT + HT in intermediate and high-risk locally advanced prostate cancer.

1. Introduction

Prostate cancer is one of the most common cancers in developed countries and the most common among men in industrialised countries. Prostate cancer incidence is characterised by a very large geographic variability, with high rates in the USA, Canada and Nordic European countries and low rates in Asia. However, there has been a gradual increase in

the incidence of prostate cancer since the 1960s in many countries and in most continents.[1–5] The increased availability of prostate-specific antigen (PSA) testing around 1990 has probably exerted the greatest effect on the registration of new cases of prostate cancer. In addition, the earlier diagnosis of prostate cancers has contributed to the reduction of prostate cancer-specific mortality,[5–9] although other practices known to alter disease prognosis have changed concurrently with the spread of PSA screening. Treatment options for prostate cancer have expanded greatly, including the advent of nerve-sparing surgical techniques, innovations in radiotherapy which enabled more men to be treated with higher doses of radiotherapy and hormonal treatment, – a treatment previously reserved for advanced cancers, – added to radiotherapy for men with high-risk, early-stage disease.[10,11]

The present study aimed to investigate the extent to which this pattern of an increasing trend in the incidence of prostate cancer and a decline in mortality seen in other industrialised countries were present in the area of Barcelona, Spain. We analysed the evolution of prostate cancer in a series of hospital cases over a 14-year period (1992–2005) in terms of incidence, clinical-epidemiological characteristics and cancer-specific mortality based on a retrospective review of a hospital-based cancer registry.

2. Patients and methods

We collected data on prostate cancer from the Hospital del Mar tumour registry (RTHMar). Hospital del Mar is a 450-bed acute-care university-affiliated hospital in the city of Barcelona (Catalonia, Spain). The RTHMar exhaustively records all neoplasms from patients diagnosed and treated at Hospital del Mar. RTHMar follows the standard criteria of the International Agency for Research on Cancer (AIARC).[12] Through a series of indicators obtained periodically, the RTHMar allows monitoring of the quality of the health care provided to patients and evaluating the clinical repercussions derived from diagnostic and therapeutic changes.

For the purpose of the present study, at the end of 2006 we retrieved all cases of prostate cancer with histological confirmation diagnosed from 1992 to 2005. The main variables available for each patient were clinical stage, PSA at diagnosis, Gleason score, risk of extraprostatic extension, initial treatment modality (treatment of recurrences or disease progression is not included in the registry) and vital status. The TNM classification system of the American Joint Committee on Cancer (AJCC, 1997) was used for clinical staging.[13] In patients with localised disease, risk stratification was based on the classification system of D'Amico and colleagues[14] and was defined as low (PSA < 10 ng/ml, Gleason score of 6 or lower, and a T-stage of T2a or lower), intermediate (PSA of 10–20 ng/ml, T2b, or a Gleason of 7) and high (PSA > 20 ng/ml, a Gleason score of 8 or higher, or T2c).

Patients were grouped into four calendar periods, 1992–1996, 1997–1999, 2000–2002 and 2003–2005. The first 5-year period was selected to obtain a similar number of patients in each interval. All cases were followed until 31st December 2006. A linkage with the Catalonia Mortality Registry was carried out manually in order to obtain the date and the specific

cause of death of patients who died outside the hospital. The survival time was defined as the interval between the date of diagnosis and the date of death or the date of the last follow-up. Five-year relative survival (ratio between the observed survival and survival of the reference population of the same age and sex) was computed using as reference the mortality of the city of Barcelona; it was estimated by the web-assisted estimation of the relative survival (WAERS) programme.[15]

Relative survival was compared for two periods, before and after 1999 when combined radiation therapy (RT) and hormonal treatment (HT) were introduced. The primary objective end-point of the study was to investigate secular trends in prostate cancer-specific mortality and their relationship with the implementation of PSA testing and the use of RT + HT in the treatment of stage II and stage III prostate cancers.

2.1. Statistical analysis

The chi-square (χ^2) test and the Student's t-test were used for the comparison of categorical variables and continuous variables, respectively. The Mantel-Haenszel χ^2 test for trend was applied to identify differences in the rates of the different variables along the 14 years studied. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using a statistical package for the social sciences (SPSS) v 15 software package (Chicago, Illinois, USA). As this was an exploratory analysis of several temporal trends in disease management, we did not specifically control for multiple comparisons.

3. Results

The study cohort consisted of 910 patients with histologically confirmed prostate cancer diagnosed and treated at Hospital Universitari del Mar who were diagnosed for the first time between 1992 and 2005. Clinical characteristics of the patients at the time of diagnosis grouped into the four calendar periods are shown in Table 1. The median age at diagnosis decreased significantly ($p < 0.001$) from 72.9 years in 1992–1996 to 68.7 years in 2003–2005, as well as the median PSA value (from 34 to 8 ng/ml, $p < 0.01$) and the percentage of patients with stage IV (from 33.3% to 9.6%). In addition, the percentage of patients with stage II local disease increased from 10.1% to 55.8% and the percentage of patients with stage III locally advanced lesions from 4.2% to 11%.

There was no significant trend in pathological grade distribution over the study period. After the year 2000 when sextant biopsy was implemented, there was an increase from 4.8% to 15.5% of patients with prostatic intraepithelial neoplasia (PIN). There was a trend towards lower pathological stage in recent years. The percentage of patients in the high-risk group also decreased from 52.2% in 1992–1996 to 35.2% but the differences were not statistically significant (χ^2 for trend 0.318).

With regard to management of prostate cancer, the percentage of patients undergoing radical oncological treatment increased from 42.7% in 1992–1996 to 79.1% in 2003–2005 (85–90% of local tumours and 15–20% of metastatic tumours). As

Table 1 – Clinical characteristics at diagnosis according to study periods.

Feature	Calendar period			
	1992–1996	1997–1999	2000–2002	2003–2005
Number of patients	168	190	241	311
Age, years, mean*	72.9	70.9	70.8	68.7
PSA, ng/ml				
Median level	34	14	10	8
⩽9 ng/ml (%)	25.2	34.9	48.5	54.7
10–19 ng/ml (%)	15.7	29.2	19.0	22.9
⩾20 ng/ml (%)	59.1	35.8	32.5	22.4
Patients with PSA >20 ng/ml, number (%)*	100 (59.2)	68 (35.8)	84 (34.9)	70 (22.2)
Gleason score of the prostatectomy specimen, number (%)				
2–6	85 (50.6)	89 (46.8)	66 (27.4)	128 (41.1)
7	35 (20.8)	52 (27.4)	81 (37.7)	111 (35.7)
8–10	48 (28.6)	49 (25.9)	84 (34.9)	72 (23.1)
AJCC stage, number (%)				
0	0	4 (2.1)	11 (4.6)	44 (14.1)
I	3 (1.8)	2 (1.1)	1 (0.4)	2 (0.6)
II	17 (10.1)	45 (23.7)	107 (44.3)	182 (58.5)
III	7 (4.2)	8 (4.2)	17 (7.0)	40 (12.8)
IV	56 (33.3)	25 (13.2)	32 (13.3)	30 (9.6)
Unknown	85 (50.6)	106 (55.8)	73 (30.3)	13 (4.2)
Extracapsular extension risk, number (%)				
Low	22 (13.1)	29 (15.3)	29 (12.0)	47 (15.1)
Intermediate	58 (34.5)	90 (47.4)	114 (47.3)	155 (49.8)
High	88 (52.4)	71 (37.4)	98 (40.7)	109 (35.1)

* $p < 0.001$.

shown in Table 2, surgery alone or combined with other modalities decreased slightly from 47.3% to 39.4% during the study period. In contrast, radiotherapy alone or combined with androgen deprivation therapy increased from 0.7% to 45.1%. Androgen deprivation therapy alone decreased from 50% to 13%. On the other hand, regarding initial treatment modalities in patients with stage II and stage III prostate cancers, the percentage of patients in which surgical treatment was indicated decreased from 87.5% in 1992–1996 to 44.2% in 2003–2005. As shown in Fig. 1, there was a progressive increase in the indications of HT + RT in the later period.

The overall survival at 1 year increased from 85.9% in the 1992–1998 period to 94.2% in the 1999–2005 period, and the overall survival at 5 years from 52.8% to 75.4%. There was an improvement in the overall relative survival at 5 years before and after 1999, from 67.3% (95% confidence interval [CI] 60.2–75.2%) to 92.9% (95% CI 87.3–98.9%) (Fig. 2). On the other hand, in patients with localised prostate cancer (stages II and III), the overall relative survival at 5 years was 85.3% (95% CI

71.4–102.0%) for the 1992–1998 period and 101.8% (95% CI 95.1–109.0%) for the 1999–2005 period (Fig. 3). The same tendency was observed in patients with localised tumours with intermediate and high risk for extracapsular extension. In this subset of prostate cancer patients the overall relative survival at 5 years was 88.3% (95% CI 74.7–104.2%) for the 1992–1998 period and 103% (95% CI 96.6–111.0%) for the 1999–2005 period.

4. Discussion

The present review of secular trends of prostate cancer over a 14-year period based on 910 patients attended in a reference hospital in the Barcelona area confirms an increase in survival during the last years, coincidentally with a shift towards lower stages and PSA levels at presentation suggesting an influence of early detection by PSA testing (lead-time bias). In addition, to other factors, changes in death rates since 1999 could be explained by secular variations in the treatment

Table 2 – Treatment modalities according to study periods.

Treatment	Calendar period			
	1992–1996	1997–1999	2000–2002	2003–2005
Surgery alone or combined with other modalities	69 (47.3)	91 (60.3)	85 (42.1)	97 (39.4)
Radiotherapy alone or combined with hormonal therapy	1 (0.7)	24 (15.9)	46 (22.8)	111 (45.1)
Androgen deprivation therapy alone	73 (50.0)	32 (21.1)	55 (27.2)	32 (13.0)
Chemotherapy alone or combined with other modalities	3 (2.1)	4 (2.6)	16 (7.9)	6 (2.4)

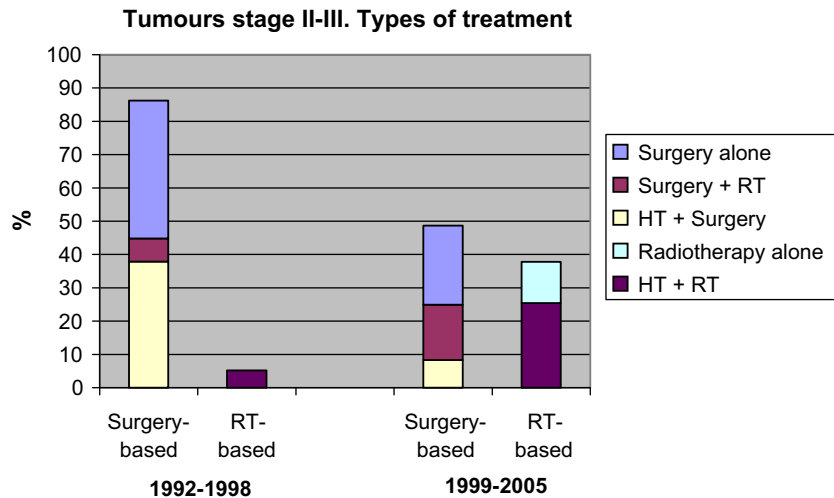**Tumours stage II-III. Types of treatment**

Fig. 1 – Types of treatment in stage II and stage III prostate cancers.
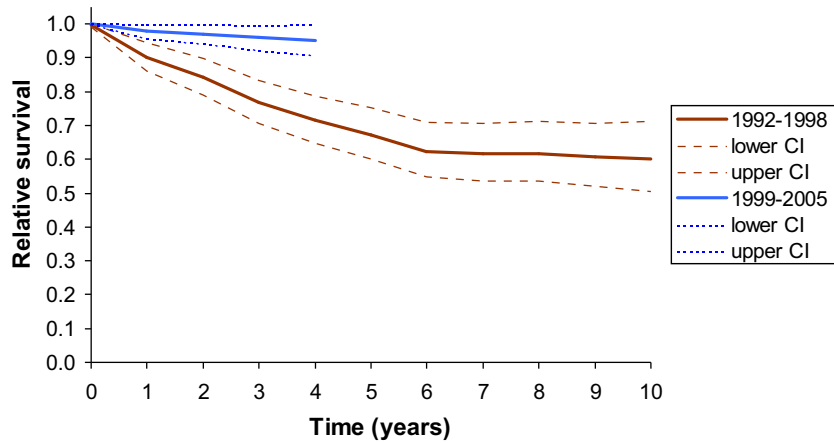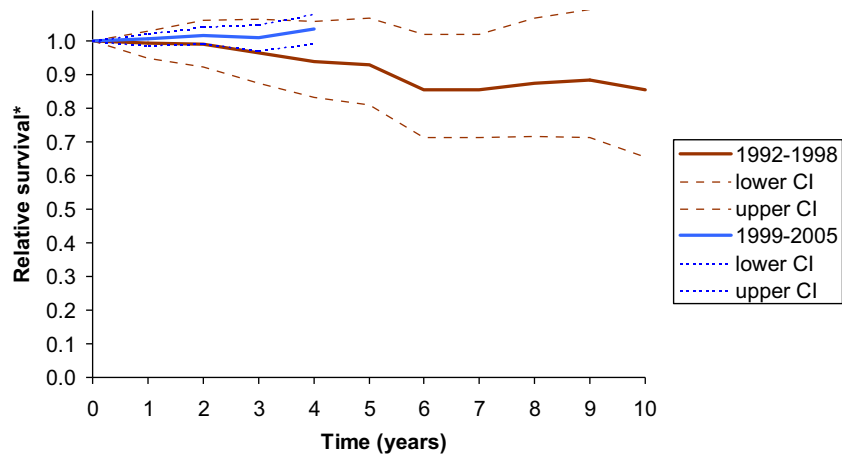

Fig. 2 – Relative survival of patients with prostate cancer for the 1992–1998 and 1999–2005 calendar periods.

* Compared with the survival of the general population of same age and sex

Fig. 3 – Relative survival of patients with stage II and stage III prostate cancers for the 1992–1998 and 1999–2005 calendar periods.

of prostate cancer, particularly the implementation of HT + RT in patients with intermediate and high-risk prostate cancers. These findings are consistent with epidemiological trends in prostate cancer over the last years reported by others.[16–18]

A diagnosis of prostate cancer was established with a PSA level progressively lower. Between 1992 and 1996, 60% of cases presented a PSA level ⩾ 20 ng/ml, whereas between 2003 and 2005, PSA values < 10 ng/ml accounted for more than 50% of the cases. In addition, the median age at the time of diagnosis decreased steadily over the years suggesting an earlier diagnosis of the disease probably due to an increased 'diagnostic intensity'.[19,20] However, PSA testing is a matter of controversy because scientific evidence that early detection decreases morbidity and mortality is lacking. In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trials on prostate-cancer mortality,[21] after 7–10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the screening group (annual PSA testing for 6 years and digital rectal examination for 4 years; subjects and health care providers received the results and decided on the type of follow-up evaluation) and the usual care (control) group (usual care sometimes included screening, as some organisations have recommended). In fact, overdiagnosis of asymptomatic cancers that will have no impact on length of life is considered a potential drawback of systematic PSA testing.[22–24]

We also found a decrease in the percentage of patients with stage IV prostate cancer from 33.3% in 1992–1996 to 9.6% in 2003–2005, in relation to the increasing number of patients referred with earlier stages of disease. The increase in clinically localised prostate cancer may be explained by an increment of diagnostic testing together with an increase of the referral of urologic patients to the hospital. However, most of the increase in clinically localised prostate cancer probably reflects diagnosis of latent disease which would go unnoticed without screening, rather than a true increase in incidence of new cases. In the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) longitudinal, observational database of men recruited from more than 30 urologic practices across US,[25] the proportion of patients with low-risk tumours rose significantly from 29.8% in 1989–1992 to 45.3% in 1999–2001. In relation to the degree of differentiation, an important shift in the distribution of cases was not observed, although there was a tendency towards an increase of Gleason 7 prostate cancer at the expense of well-differentiated tumours. On the other hand, despite an increase in patients with stage II and stage III prostate cancers, the distribution of the risk categories did not show significant changes over the study period.

In relation to treatment of prostate cancer, the number of patients undergoing radical oncological treatment increased in parallel to the increase in the local forms of the disease. Radiation therapy, which was almost inexistent in 1992–1996, was the most frequent modality (combined with hormonal therapy or alone) in 2003–2005. The overall decrease of androgen deprivation therapy alone is explained by the decrease of metastatic prostate cancers. The percentage of patients undergoing surgical treatment also showed an important decrease along the years. In the CaPSURE study,

there has been a sharp increase in the use of brachytherapy (from 3.1% to 12%) and androgen deprivation therapy (from 3.1% to 21.7%), and a decrease for prostatectomy and external-beam radiotherapy.[23]

The landmark clinical trial of Bolla and colleagues[26] comparing external irradiation with external irradiation plus goserelin (an agonist analogue of gonadotropin-releasing hormone that reduces testosterone secretion) in patients with locally advanced prostate cancer provided evidence of improvement in local control and survival with the introduction of combined RT + HT. However, in a recent Scandinavian Prostate Cancer Group Study, radical prostatectomy reduced prostate cancer mortality and risk of metastases with little or no further increase in benefit 10 or more years after surgery.[27] In addition to improvement of treatment, the improvement in survival in the present study is more likely a result of a diagnostic lead time introduced by an increased use of PSA. This is also corroborated by the large drop in PSA at diagnosis during the time periods and the change in mean age at diagnosis.

In summary, there was an increase in survival of patients with prostate cancer during the last 14 years in this Barcelona area coincidentally with a shift towards lower stages and PSA levels at presentation, suggesting an influence of early detection by PSA. In addition to other factors, changes in death rates since 1999 could be explained by secular variations in the treatment of the disease, particularly the implementation of RT + HT in patients with intermediate and high-risk locally advanced prostate cancer.

Conflict of interest statement

None declared.

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REFERENCES

1. McDavid K, Lee J, Fulton JP, Tonita J, Thompson TD. Prostate cancer incidence and mortality rates and trends in the United States and Canada. *Public Health Rep* 2004;**119**:174–86.

2. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. *BJU Int* 2002;**90**:162–73.

3. Quaglia A, Parodi S, Grosclaude P, Martinez-Garcia C, Coebergh JW, Vercelli M. Differences in the epidemic rise and decrease of prostate cancer among geographical areas in Southern Europe. An analysis of differential trends in

incidence and mortality in France, Italy and Spain. *Eur J Cancer* 2003;**39**:654–65.

4. Kvåle R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst* 2007;**19**:1881–7.

5. Vercelli M, Quaglia A, Marani E, Parodi S. Prostate cancer incidence and mortality trends among elderly and adult Europeans. *Crit Rev Oncol Hematol* 2000;**35**:133–44.

6. Bouchardy C, Fioretta G, Rapiti E, et al. Recent trends in prostate cancer mortality show a continuous decrease in several countries. *Int J Cancer* 2008;**123**:421–9.

7. Baade PD, Coory MD, Aitken JF. International trends in prostate-cancer mortality: the decrease is continuing and spreading. *Cancer Causes Control* 2004;**15**:237–41.

8. Cayuela A, Rodríguez-Domínguez S, Martín VE, Candau BR. Recent changes in prostate cancer mortality in Spain. Trends analysis from 1991 to 2005. [Article in Spanish]. *Actas Urol Esp* 2008;**32**:184–9.

9. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007;**8**:773–83.

10. Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in 1975–2004: an ecological study. *Lancet Oncol* 2008;**9**:445–52.

11. Etzioni R, Feuer E. Studies of prostate-cancer mortality: caution advised. *Lancet Oncol* 2008;**9**:407–9.

12. Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG. Cancer registration: principles and methods. Lyon, France: International Agency for Research on Cancer, 1991. IARC Scientific Publications No. 95.

13. Prostate. In: *American joint committee on cancer: AJCC cancer staging manual.* 6th ed. New York, NY: Springer; 2002. p. 309–16.

14. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;**280**:969–74.

15. Clèries R, Valls J, Esteban L, et al. WAERS: an application for web-assisted estimation of relative survival. *Med Inform Internet Med* 2007;**32**:169–75.

16. Luján Galán M, Páez Borda A, Chiva Robles V, Santonja Garriga C, Romero Cajigal I, Berenguer Sánchez A. Epidemiological trends in prostate cancer over the last years. [Article in Spanish]. *Arch Esp Urol* 2004;**57**:817–25.

17. Inghelmann R, Grande E, Francisci S, et al. Regional estimates of prostate cancer burden in Italy. *Tumori* 2007;**93**:380–6.

18. Varenhorst E, Garmo H, Holmberg L, et al. The national prostate cancer register in Sweden 1998–2002: trends in incidence, treatment and survival. *Scand J Urol Nephrol* 2005;**39**:117–23.

19. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. *JAMA* 1995;**273**:548–52.

20. Hemminki K, Rawal R, Bermejo JL. Prostate cancer screening, changing age-specific incidence trends and implications on familial risk. *Int J Cancer* 2005;**113**:312–5.

21. Andriole GL, Grubb 3rd RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;**360**:1310–9.

22. Naitoh J, Zeiner RL, Dekernion JB. Diagnosis and treatment of prostate cancer. *Am Fam Physician* 1998;**57**:1531–9.

23. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from US prostate cancer incidence trends. *J Natl Cancer Inst* 2002;**94**:981–90.

24. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;**360**:1320–8.

25. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004;**22**:2141–9.

26. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;**337**:295–300.

27. Bill-Axelson A, Holmberg L, Filén F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst* 2008;**100**:1144–54.