Current prostate cancer: 20 years later

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INTRODUCTION

This short review covers some of the trends and changes that have occurred in the field of prostate cancer in the past 20 years, and attempts to summarize where we are now and where we can go from here.

The most cited publication 20 years ago was the initial report on the use of PSA for monitoring patients with prostate cancer [1]. The research underlying this report was stimulated primarily by the organ-specific occurrence of PSA. The authors found that a highly elevated PSA level is a strong predictor of disease recurrence.

At about the same time the first data were collected on the prognostic value of the Gleason score [2]. These data showed for the first time that men with prostate biopsy specimens with Gleason scores of 2–4 were at little risk of death from prostate cancer within 15 years of diagnosis. Conversely, men with Gleason scores of 7–10 were at high risk of death from prostate cancer if treated conservatively, even when cancer was diagnosed as late as 74 years old. Men with Gleason scores of 5–6 were at a modest risk of death from prostate cancer, and that risk increased slowly for at least 15 years. These were two major scientific advances. The most cited article in 2005 [3] dealt with radical prostatectomy (RP) vs watchful waiting. There has evidently been a shift of interest. What underlies this shift?

EPIDEMIOLOGY OF PROSTATE CANCER

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a national disease registry of >10 000 patients with prostate cancer treated at 31 primarily community-based sites across the USA. The database tracks oncological and health-related quality-of-life outcomes. Because the urologists participating in the project treat according to their usual practice, CaPSURE facilitates the study of trends in the strategies of disease management [4]. Changes over the years in the percentage of patients with low-, intermediate- and high-risk disease (based on the d’Amico classification) are shown in Fig. 1 [5]. In general, it appears that the percentage of high-risk patients diagnosed has been gradually decreasing since the introduction of PSA screening in the late 1980s, from 1989–1992 to 2000–2002. By contrast, the percentage of low-risk patients significantly increased within this period (P < 0.001). The widespread use of serum PSA testing apparently has led to a profound shift from detecting high-risk disease to detecting low-risk disease. Of serious concern with this shift is ‘over-diagnosis’, which might lead to overtreatment of cancers that would not have become symptomatic.

One might think that this trend would be manifest as a better long-term mortality rate; unfortunately, this does not seem to be the case. The mortality rates for Austrian men with cancer of the prostate, rectum, stomach or lung in the period 1970–2001 are shown in Fig. 2 [6]. Although there was a dramatic decrease in stomach cancer mortality and minor decreases for lung and rectal cancer, there was essentially no change for prostate cancer.

The pessimistic view that PSA screening has not improved survival is reinforced by a comparison among countries in the European Union. The incidence of prostate carcinoma varies by a factor of up to four, presumably because of differing use of PSA screening (Fig. 3). An optimist would expect PSA screening to lead to appreciably better mortality values in those countries with high incidences [7]; unfortunately, the differences are only minor (Fig. 3).

DIAGNOSIS OF PROSTATE CANCER

One important issue is whether the tumours in men with low PSA levels are of clinical significance. If they are not, detection is unnecessary and potentially harmful. The use of PSA was reviewed by Hernández and Thompson [8]. The introduction of PSA screening preceded the development of current biopsy techniques (6–12 cores obtained at needle biopsy). The upper limit of normality is generally taken as 4.0 ng/mL, although this threshold has not been validated. One study in the USA found prostate carcinoma in 22% of men with a normal DRE and a PSA level of 2.6–4.0 ng/mL [8]. A Japanese study found a similar prevalence (24%) but no difference in the incidence of prostate cancer between men with a PSA level of 2.0–4.0 ng/mL and those with 4.1–10.0 ng/mL [9]. The available evidence suggests that these tumours are indeed potentially dangerous. For example, studies in Chicago and Austria found similar rates of clinically significant tumours in men with low PSA levels [10,11]. In one series of 82 patients who were treated for metastatic disease, four had PSA levels of ≤2.0 ng/mL [12]. This finding was supported in the Prostate Cancer Prevention Trial [13], in which the prevalence of prostate cancer was investigated in a group of 2950 men (aged 62–91 years) with PSA levels of ≤4.0 ng/mL who were enrolled in the placebo arm. Prostate cancer was diagnosed in 449 men (15.2%), and 67 of the 449 cancers (14.9%) had a Gleason score of ≥7. The prevalence of prostate cancer tended to increase with increasing PSA level, being 6.6% at 0–0.5 ng/mL, 10.1% at 0.6–1.0 ng/mL, 17.0% at 1.1–2.0 ng/mL, 23.9% at 2.1–3.0 ng/mL, and 26.9% at 3.1–4.0 ng/mL.

It might be concluded that there are many men with potentially dangerous prostate cancer that is not diagnosed by current PSA thresholds. Are there perhaps better approaches? Studies have been conducted on finding more specific markers, improving MRI techniques, and developing multivariate nomograms.

NEW MOLECULAR MARKERS

Research to identify new molecular markers is aimed not only at detecting cancer, but also at providing a prognostic estimate of its severity. Potentially predictive biomarkers include thymosin β-15, antizyme, antizyme inhibitor, and collagen XXIII [14]. Thymosin β-15 is elevated in metastatic prostate cancer, and its levels in combination with PSA can predict
recurrence of prostate cancer with more sensitivity and specificity than can PSA level alone. Other promising prognostic biomarkers of prostate cancer include the p53 tumour-suppressor gene, the bcl-2 proto-oncogene, and the Ki-67 proliferative labelling index. A poor prognosis is associated with the presence of mutated p53 in prostate cancer tissue and with overexpression of bcl-2 and Ki-67. Another recent study identified propyl isomerase Pin1 as a potential prognostic marker of prostate cancer; Pin1 expression is directly related to disease recurrence. Patients with higher Pin1 expression have about eight times the risk of recurrence as do those with low Pin1 expression [14].

PCA3DD3 is overexpressed in most prostate carcinomas and their metastases. It cannot be detected in normal tissues or in tissues from other cancers. Research has therefore concentrated on developing the uPM3 amplification assay for detecting PCA3DD3 RNA in urine and histological samples [15,16]. Initially, all 24 prostate cancer samples assessed reacted positively for this marker [15]. Urine samples from 201 patients were then tested prospectively for the marker, with PSA mRNA as a control for prostate cells in the urine. Of the 201 urine samples, 158 contained enough prostate cells for the analysis (79% adequacy). Prostate cancer was found in 62 (39%) of the evaluable patients. The overall sensitivity was 82% (PSA 98%), the overall specificity was 97% (PSA 5%), and the overall accuracy was 87% (PSA 83%). The authors concluded that the clinical performance of the new marker is excellent and that its specificity is far better than that of PSA.

TRANSRECTAL MRI

There have been dramatic recent improvements in the use of transrectal MRI. Detailed images of very small areas can be obtained, and they can be supplemented by dynamic MRI scintigraphy. However, the results depend on the reader’s experience. For example, Füttner et al. [17] determined the accuracy of experienced and less experienced readers in interpreting results of combined T2-weighted fast spin-echo MRI and dynamic contrast-enhanced MRI, compared with results of T2-weighted fast spin-echo alone. Readers were required to differentiate stage T2 from stage T3 prostate carcinoma. Histological analysis was used as a control. In all, 99 patients were included in the study. The performance of the less experienced readers, but not the more experienced readers, was significantly improved with the use of multisection dynamic contrast-enhanced MRI. With contrast-enhanced MRI, the overall sensitivity was 69% (24/35 patients), the overall specificity was 97% (62/64 patients), and the overall accuracy was 87% (86/99 patients).

NOMOGRAMS

Another approximate predictive approach uses nomograms [18–21], instruments that predict outcomes for individual patients. Using algorithms that incorporate many variables, nomograms calculate the predicted probability that a patient will reach a clinical endpoint of interest. Nomograms have been developed to identify high-risk prostate cancer [20] and to determine the risk of seminal vesicle invasion [21]. Their use leads to a statistical statement that is applicable to the individual patient.

TREATMENT OF PROSTATE CANCER

Current unreliability in the diagnosis of prostate cancer is linked to significant
morbidity in the treatment of what might be, in some cases, an essentially harmless condition. This morbidity mainly concerns incontinence and sexual function, and is strongly dependent on the age of the patient.

Litwin et al. [22] compared the effects of RP and irradiation on the sexual function of patients with prostate cancer, on the basis of a multivariate quality-of-life analysis of the CaPSURE patients. They studied 438 men who had a recent diagnosis of early-stage prostate cancer treated with RP or irradiation (96 had irradiation, 124 had RP with no nerve sparing, and 218 had RP with nerve sparing). Beginning immediately after treatment and continuing for 18 months, sexual function was significantly better in the irradiation group than in the two RP groups. A slow but significant improvement in sexual function score was recorded over 2 years in both groups of RP patients. By contrast, the score for the irradiated patients increased during the first 12 months, then significantly declined during the second.

Kundu et al. [23] examined the recovery of erectile function, urinary continence and postoperative complications in 3477 patients who had nerve-sparing RP; the follow-up was 18 months. An erection sufficient for intercourse was reported in 76% of men (1770) who were potent before RP and had bilateral nerve-sparing surgery, and in 53% of men (64) who had unilateral or partial nerve-sparing RP. Potency after bilateral nerve-sparing RP decreased from 93% in patients aged <50 years to only 52% in those aged >70 years. Urinary continence resumed in 93% of all men and was associated with younger age (P = 0.001) but not with nerve-sparing RP, tumour stage, or PSA level. Continence 18 months after RP was 95% in patients aged <50 years and 86% in those aged >70 years.

Klingler and Marberger [24] emphasized that urinary stress incontinence is the most important morbidity after RP, with reported incidences of 8–77%. These authors reviewed possible continence-restoring procedures persisting for 6–12 months after the operation. Techniques included use of an hydraulic artificial urinary sphincter and various types of sling. Although procedures are improving, their success greatly depends on the experience of the surgeon.

The issue of quality of life is particularly important for patients with metastatic prostate cancer who have been physically or chemically castrated. Clark et al. [25] surveyed 201 such patients (median age 71 years, range 45–93) who had received this treatment a median of 2 years previously. Most of the patients were satisfied with the treatment decision, but 23% expressed regret. An important factor might be inadequate communication between physician and patient.

Because of the difficulties in diagnosing and treating prostate cancer, active surveillance has been suggested as an alternative approach [26]. This surveillance would involve frequent PSA testing and repeat biopsies followed by radical treatment, if necessary. It was suggested that active surveillance might spare two-thirds of men with prostate cancer from the side-effects of treatment, without compromising their survival.

CONCLUSION

Prostate cancer remains a fatal cancer; current early-detection approaches increase the risk of over-treatment and unnecessary morbidity, yet miss dangerous tumours. Present screening methods have not been shown to reduce mortality. Nevertheless, current studies aimed at improving the detection and management of prostate cancer might lead to real advances within the next 20 years. The way forward is likely to include active surveillance of patients with low-volume, low-risk disease, and the development of novel biomarkers [27].

CONFLICTS OF INTERESTS

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REFERENCES


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Abbreviations: CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; RP, radical prostatectomy.