Screening for Prostate Cancer—More Questions than Answers

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Whether prostate cancer screening should be applied to the male population or not, remains an extensively debated issue (1, 2). Reference can be made to the favorable results of breast cancer screening and the surprisingly unfavorable results of lung-cancer screening (3). Since 1993 the American Urological Association (AUA) and the American Cancer Society (ACS) have recommended annual prostate-specific antigen (PSA) testing and rectal examinations beginning at age 50 for early prostate cancer detection and at age 40 in men belonging to identifiable risk groups (4, 5). In most European countries, particularly in Northern Europe, routine application of screening procedures for prostate cancer is not accepted for a number of reasons: There is limited knowledge about the natural history of prostate cancer diagnosed at screening and the increasing gap between lifetime incidence and mortality suggests that there is a substantial risk of over-diagnosis and subsequent over-treatment. There is no reliable information on the effectiveness of treatment from randomized trials. The benefit of prostate cancer screening, in terms of reducing prostate-cancer-specific mortality, has not yet been shown. Adami and co-workers question whether even a randomized trial of screening for prostate cancer meets the ethical requirements (6). In this article the issues that fuel the prostate cancer screening debate are reviewed.

IS PROSTATE CANCER AN IMPORTANT HEALTH PROBLEM?

Incidence and mortality

The age and common co-morbidity of prostate cancer patients, coupled with an often slow rate of growth, have in the past resulted in widespread adoption of conservative policies of surveillance and palliative treatment rather than active treatment in many countries. However, incidence and mortality rates show the importance of the disease.

The 1992 report of The Netherlands Cancer Registry shows an incidence of 4915 cases in a male population of approximately 7.5 million. The crude rate is 65.5 cases per 100000 person-years, the European standardized rate is 70.2 cases per 100000 person-years. The mortality amounts to 2222 men, the crude rate is 29.6 cases per 100000 person-years, the European standardized rate is 32.8 per 100000 person-years. Prostate cancer occurs mainly in men over 60 years of age; incidence and mortality rates are only 5.5% and 2.2%, respectively, between the ages of 40 and 60 years, both rates rising steeply thereafter. Prostate cancer is the second most common cancer in males after lung cancer (7). The prostate cancer incidence-rates are still rising, whereas the rates for lung cancer incidence are decreasing. The rise in incidence by far exceeds the modest rise in mortality.

Geographical patterns

The incidence of prostate cancer has risen dramatically over the past two decades, the United States ranking as having the highest incidence in the world. The effect of increasing male longevity and, above all, the increasing awareness and screening activities are responsible for this phenomenon. The increase in incidence is almost entirely due to the detection of localized disease, with no appreciable increase in metastatic disease. The mortality rates remained relatively constant (8, 9), Potosky et al. also state that the 'epidemic of prostate cancer' is probably the result of the increasing detection of tumors as a result of increased prostate-specific antigen (PSA) screening.

Within Europe the highest incidence is recorded in Sweden and most Northern European countries, while the lowest incidence is found in the Mediterranean countries (10). The increased incidence in Europe is not as marked as that in the USA; however, as a result of increasing male longevity alone, Boyle et al. expect an increase of 67% in

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Table 1

Percentage of men with latent prostate cancer at autopsy by age groups

Age Years	Franks (14) (n = 210)	Gaynor (15) (n = 1050)	Hølund (16) (n = 173)	Sakr (17) (n = 152)	Overall
30–39	0	4	0	27	16/91 = 18%
40–49	0	5	12.5	34	24/198 = 12%
50–59	29	10	8.7	–	38/302 = 13%
60–69	30	18	12.5	–	41/163 = 25%
70–79	40	28	25.8	–	119/400 = 30%
80–89	67	39	37.1	–	61/145 = 42%
90^{+}	100	40	60	–	7/12 = 58%

prostate cancer in the European community by the year 2020 (11). Since public awareness and screening activities are likely to increase, this may be an optimistic view.

Lifetime risk

An alternative way to look at prostate cancer as a public health problem is to assess the cumulative risk or lifetime risk. In The Netherlands the cumulative risk of being diagnosed with prostate cancer between the age of 0 and 74 years is 4.8%. The cumulative risk of prostate-cancer-specific death between the age of 0 and 74 is 1.4% (7). However, prostate cancer develops mainly in elderly men, thus it is useful to calculate the accumulation of risks over time for the subset at risk, i.e. men of 50 years of age and older, in order to observe the impact of the disease within this age group. Seidman and associates estimated the probability in 50-year-old white males of eventually developing prostate cancer at 9.5% using the SEER data relating to the period 1975 to 1980. The estimated risk of dying from prostate cancer was 2.9% (12).

Comment

These figures indicate that prostate cancer is a serious public health problem. The fact that the population in most western countries is ageing and the life expectancy is increasing emphasizes the importance of this disease. The epidemiological importance of a disease, however, does not in itself provide justification for screening, pending definitive evidence of effectiveness.

NATURAL HISTORY

The natural course of prostate cancer is in some aspects poorly understood. Knowledge of the natural course of a given disease is a prerequisite for the application of screening as a public health policy (13). Screening for any disease is unlikely to reduce disease-specific mortality if most early, localized cancers that are detectable never progress within the lifespan of the host, and most aggressive cancers are already too advanced for curative treatment when detection is possible. On the other hand, screening may reduce mortality if most early, localized cancers that are detectable eventually progress and biologically aggressive cancers offer a window of opportunity during which detection and cure are possible.

Latent cancer

One of the unique properties of prostate cancer is the high prevalence of histological changes recognizable as cancer in surgical or in autopsy specimens and the much lower incidence of clinical disease. Prostate cancer is very often found at autopsy, the prevalence increases with age (14–17). Such tumors are called 'latent' carcinomas. In Table 1 the results of four autopsy series are described. The differences in prevalence are probably the result of differences in preparative techniques, interval of sections, fixation and staining methods. The cumulative risk that a 50-year-old man will possibly have such a histological malignancy is approximately 30%.

Unfortunately, the characteristics in terms of grade of differentiation, tumor volume and stage were not described in these series.

More recently, information about unsuspected prostate carcinoma has become available from prostate specimens removed at the time of cystoprostatectomy, performed for cancer or other pathologic conditions of the bladder (18–20). These prostate cancers, not identifiable with digital rectal examination (DRE), are stated to be compatible with the autopsy cancers. The results of three such cystoprostatectomy series are described in Table 2.

These cystoprostatectomy series show a prevalence of approximately 40%, which indicates again that the prostate cancers that are clinically diagnosed are only the proverbial 'tip of the iceberg'. Stamey and co-workers (21) observed a similar prevalence in a series of 139 consecutively performed cystoprostatectomies. Fifty-three of the 55 men with prostate cancer had normal DRE findings. In this paper it is assumed that cancer progression is proportional to the tumor volume. The 1973–1977 SEER data (22) were used to calculate the lifetime probability at birth of a man having a diagnosis of prostate cancer. This was estimated on 8% (Stage A disease was

excluded from this evaluation). This figure was compatible with the observation that 8% of the 55 cases of prostate cancer were 0.5 ml or larger. This led to the conclusion that tumors smaller than 0.5 ml are probably clinically insignificant. Ohori and associates (20) compared their series of cystoprostatectomy cancers (in which the Stamey et al. series were included) with a series of radical prostatectomy specimens performed for clinically detected prostate cancer. They concluded that unsuspected carcinoma found at autopsy or cystoprostatectomy is usually small, well or moderately differentiated and confined to the prostate.

The natural course of clinically diagnosed prostate cancer

At the time of diagnosis, prostate cancer has often spread beyond the prostate. In the USA and in most European countries more than 40% was not organ confined or metastatic in the prescreening era (23). In The Netherlands the stage distribution of 4708 cases of prostate cancer diagnosed between the years 1989 and 1994 in the Amsterdam cancer registry region has recently been described. In Table 3 the stage distribution is shown in total numbers and percentages. Of these cancers, 24% had already metastasized at the time of diagnosis, with 60% clinically confined to the prostate (24).

Once prostate cancer has metastasized the prognosis is poor. Cure is impossible and median survival is in the range of 30 months despite endocrine treatment (25). Series of untreated metastatic prostate cancer are out-of date and probably unreliable but they showed that two-thirds of patients died within 9 months after diagnosis. In 485 cases of untreated metastatic prostate cancer, the average duration of the disease from the first symptoms to death was 31 months (26). In the series of 701 cases described by Nesbit et al. the mean survival was 21 months after diagnosis (range <1–180 months). The prostate-cancer-specific mortality rate was 82% (27).

Table 2

Characteristics of prostate cancer found incidentally at cystoprostatectomy. All with normal findings on digital rectal examination (DRE)

	Montie (18)	Kabalin (19)	Ohori (20)
Mean age (range)	62 (34–80)	64 (31–83)	–
Number (normal DRE)	72	66	90
Number of cancers (%)	33 (46%)	25 (38%)	90 (–)
Gleason Score ≥ 6 (%)	12 (36%)	–	–
Gleason pattern ≥ 4	–	0 (0%)	10 (11%)
Capsular penetration (%)	7 (21%)	0 (0%)	3 (3%)
Positive margins	2 (6%)	0 (0%)	0 (0%)
Seminal vesicle invasion (%)	1 (3%)	0 (0%)	0 (0%)
Positive lymph nodes	0	0	0

Table 3

Stage distribution of 4 708 cases of prostate cancer diagnosed between 1989 and 1995 in the Amsterdam region (Visser & Horenblas, NTvG 52, 1996 (24))

Stage	TX	T1	T2	T3	T4	Total
M0/MX	230	744	1 846	566	183	3 569
M0/MX (%)	4.9	15.8	39.2	12.0	3.9	75.8
M+	173	30	539	208	189	
M+(%)	3.7	0.6	11.4	4.4	4.0	24.2

Abbreviations: M0 = no metastases, MX = metastases unknown, M+ = metastases, TX = tumor stage unknown, T1 = diagnosis through transuretral resection of the prostate, T2 = tumor within the prostatic capsule, T3 = tumor with evidence of extracapsular growth, T4 = tumor with evidence of invasion of the bladderneck or pelvic diaphragm or pelvis.

Deferred treatment series

Information concerning the natural course of clinically diagnosed prostate cancer is available from several series of patients who were treated conservatively with observation and delayed hormonal therapy.

Handley et al. reported a series of 278 patients diagnosed with prostate cancer in the period between January 1978 and December 1985. They received no further treatment after the diagnosis until symptomatic progression occurred. Ninety-five percent of patients were diagnosed by trans-urethral resection of the prostate. Metastases were present in 19.4% of patients. The disease was considered clinically localized in 75% of cases. Nevertheless, only 30% survived 5 years compared with the expected survival rate of 65% for an age-matched population. Prostate cancer was the cause of death cited in 42% of all patients at 5 years. The survival rate for well-differentiated prostate cancer was no different from that of an age-matched population (28).

Johansson and co-workers are the authors of a paper with the title: 'High 10-year survival rate in patients with early, untreated prostatic cancer'. A subset of 223 patients with localized prostate cancer was selected from a cohort of 654 men with prostate cancer. The grade distribution showed 66% well-differentiated tumors, 30% grade 2 and 4% grade 3 tumors. The mean age was 72 years. During the mean observation period of 123 months (range 81–165 months) 34% showed progression, 56% died, but prostate cancer was considered the cause of death in 8.5% of these 223 men (29). In a later report with a mean observation of

12.5 years, prostate cancer was considered the cause of death in 10% of the original 223 patients (30).

In their most recent report the observations concerning the total cohort of 648 consecutive cases of prostate cancer with an average observation time of 168 months (range 126–210 months) are described. By the end of the observation period 84% of patients in the original cohort had died. Thirty-seven percent of the deceased were considered to have died of prostate cancer. In a further 7%, prostate cancer was considered a contributory cause. Of the initial 159 (25%) patients with metastasized disease, 78% died from their disease, while in 6% their disease was considered a contributory factor. The corrected 15-year survival rate was 71.8% among patients without distant metastases detected at diagnosis and 5.7% among those with metastases. In the initially untreated group of 223 men the prostate-cancer-specific mortality was 11% (31).

The series conducted by Johansson, together with five other series were included in a pooled analysis by Chodak et al. (32). Actuarial survival statistics showed that grade is the most important parameter in predicting survival. The mortality rate attributable to prostate cancer among men with grades 1 and 2 disease was 13% at 10 years versus 66% in men with grade 3 disease. Ten years after diagnosis metastases had occurred in 19% (grade 1), 41% (grade 2) and 74% (grade 3) of cases.

The overall favorable result of conservative management within these series, however, gives too optimistic a view of the reality. These series have been criticized severely for selection bias. This can be illustrated through comparison of the grade distribution within this pooled analysis and the grade distribution in the general population. The grade distribution shows 59% grade 1 tumors, 32% grade 2 tumors and 8% grade 3 tumors. The grade distribution in the general population of the previously described Amsterdam region shows 25% grade 1 tumors, 36% grade 2 tumors and 32% grade 3 tumors (24). Further criticism came from Aus and co-workers. These authors indicated that age was not evaluated as a risk factor with respect to the endpoints. The average age of 70 in the Chodak series is high. This group concluded that low cause-specific mortality rates at 10 years of follow-up in series on deferred treatment comprising older patients with high competing mortality could not be extrapolated to younger patients with a low competing mortality (33).

In order to estimate the long-term survival of 65–75 year-old men (mean 70.9) with conservatively treated newly diagnosed localized prostate cancer (between 1971 and 1976), Albertsen et al. recently conducted a study in such a way that biases observed in the series by Chodak and Johansson were minimized. The collected data were population based and the original pathologic specimens were reviewed. The original hospital charts were reviewed in order to obtain a consistent score for patient co-morbidities. Two important findings were demonstrated for this cohort: (a) Tumor histologic features are highly predictive of survival and (b) patient co-morbidities are nearly as potent a predictor of survival as tumor histologic findings.

Men having low grade (Gleason score 2–4) prostate cancer face no apparent loss in life expectancy compared with a relevant general population (34). This favorable outcome may be due to the natural history of the tumor or of the host. Moreover, since the health condition of the host has a significant impact on survival, a selection of healthier men with longer life expectancy than average may benefit from early detection and treatment.

Comment

One of the most important issues in the prostate cancer screening dilemma is the fact that many cancers for various reasons will never be a threat to the hosts well being within his lifespan. If prostate cancer screening detects unimportant cancers, this will lead to treatment of men for whom it is not necessary.

The series described above, however, indicate that prostate cancer is a progressive and potentially lethal disease when managed conservatively. Two factors appear to be decisive in the question of whether prostate cancer is able to kill the host. (a) The biologic activity which is represented by the grade of the tumor. Poorly differentiated tumors metastasize within a short period of time and are generally lethal. (b) The time during which the tumor can progress is determined by the co-morbidity and the age of diagnosis. It is still under discussion which factors are responsible for the intrinsic biologic activity, i.e., why some tumors become aggressive and others remain latent. This can also be observed from the doubling time of prostate cancer, which shows that 79% of all patients have a doubling time of more than 24 months. Doubling times were faster in patients with higher stages and grades. This also implies that high volume tumors are generally more dangerous than small tumors (35, 36).

Are latent cancers and clinical cancers indistinguishable? According to some authors this is not the case. Ohori & Scardino showed that clinically detected adenocarcinoma of the prostate differs from that found incidentally at autopsy in important pathological features, such as volume, grade and extent. (20, 37, 38)

A series of papers from Stanford University show that the biological aggressiveness of the cancer is directly related to tumor volume and histologic grade (39, 40). Small, well-differentiated prostate cancers will not pose a threat to the host. However, using the current diagnostic tests, determining which lesions are still confined to the prostate, which will progress and therefore require active treatment, and which will remain slow growing or inert is a debated issue and will be addressed within this paper.

PRIMARY PREVENTION

Miniscule focuses of prostate cancer are already present in young adult men (17). The prevalence of focal cancers found at autopsy varies little among different countries and races (41), whereas the incidence of clinical disease shows a considerable variation. These findings suggest that environmental and genetic factors may promote the occurrence of life-threatening prostate cancer. This hypothesis is reinforced by the observation that the mortality of prostate cancer in Japanese migrants increases to half that of the indigenous population within two generations (42).

In a cohort of approximately 14000 men, dietary and lifestyle characteristics were evaluated in relation to subsequent prostatic cancer risk. An increase in the consumption of beans, lentils and peas, tomatoes, raisin, dates, and other dried fruit was associated with significantly decreased prostate cancer risk (43–45). A high-fat diet is associated with a high risk because of increased androgen activity (46–48). Genetic factors are related to the rare but clinically significant occurrence of prostate cancer in familial cases (49, 50).

Comment

Further identification of environmental and genetic factors that have an influence on prostate cancer incidence will take some time. A variety of agents are being evaluated in vitro and in vivo but it is not expected that results will be available at short notice (51–54). The question of whether dietary measures or the use of chemopreventive agents can prevent prostate cancer will have to be tested in large randomized trials. Treatment of prostate cancer has adverse effects. The primary prevention of prostate cancer appeals to many who are struggling with the treatment of the disease. However, effectiveness costs, side effects, duration of the preventive treatment and difficulties in implementation will have to be studied first. Primary prevention trials and randomized screening trials for prostate cancer have been initiated. It is not yet known whether any of these approaches will reduce prostate cancer morbidity and mortality.

SECONDARY PREVENTION: RATIONALE FOR SCREENING

The series described by Nesbit and Bumpus (26, 27) show that if prostate cancer is diagnosed when symptoms are present and left untreated, almost all patients die from the disease. Curative treatment of prostate cancer is impossible once the disease has spread beyond the prostate (55). At this time 40% of newly diagnosed cases are not localized when diagnosed. In a large series of men treated with radical prostatectomy for clinically localized prostate cancer, over 50% had pathological evidence of extracapsular disease and 23% had positive margins (56). These patients are at risk for progression. Patients treated with radiotherapy have also shown significant rates of both biochemical and clinical progression (57). Through the application of early detection regimes, if they are effective, cancer will be diagnosed at an earlier stage in its biological development.

Feasibility of early detection

It has been shown that early detection of prostate cancer is possible. The identification of PSA as a diagnostic tool has been a major contribution to the diagnostic arsenal (58). Catalona et al. reported on 10251 men aged 50 years and older without a history of prostate cancer who were initially screened with a serum PSA level. Men with a PSA level of 4 ng/ml or higher underwent both digital rectal examination (DRE) and transrectal ultrasonography (TRUS). A biopsy was performed if either of these procedures revealed abnormal or suspicious findings. This group was compared with a group of 266 concurrently studied patients who were referred for TRUS and biopsy because of an abnormal DRE. Sixty-three percent of 244 patients whose cancers were detected on initial PSA-based screening had localized disease versus 43% of the 47 patients in the comparison group. Four men (1.6%) had positive bone scan and bone biopsy. Fifteen men (6.1%) had lymphnode metastases. (59). In a more recent report 6630 men were screened through determination of serum PSA and a DRE. In 1167 men who had a biopsy, 264 cases of prostate cancer were detected. Only three of these patients were found to have advanced disease. Of the remaining 261 patients, 162 were treated with radical prostatectomy. Seventy-one percent of these men had organ-confined cancer (60). Mettlin and associates reported on the 164 cases of prostate cancer detected in a cohort of 2999 participants of the American Cancer Society—National Prostate Cancer Detection Project. These men were screened through PSA, DRE and TRUS. One hundred and three men were treated by radical prostatectomy. Sixty-two percent of cancers were pathologically confined to the prostate (61).

Comment

The results of these case-finding studies show that early detection is possible. There is a shift towards earlier-stage prostate cancer with any form of PSA-based screening. The percentage of metastasized cancer is significantly lower when compared to series of prostate cancers not detected through screening. This stage reduction, however, does not provide evidence to show that prostate cancer screening will decrease prostate cancer mortality. Two biases are associated with screening: bias as a result of increased survival in the screened group due to detection of the tumor earlier without genuinely prolonging life (lead time bias) and bias due to detecting slower-

growing tumors, which would never have led to mortality due to prostate cancer, in the screened men (length time bias). A randomized controlled trial with prostate cancer mortality as endpoint is needed to avoid these biases. Not only would this avoid selection bias, but also by using reduction of prostate-cancer-specific mortality as the measure of outcome rather than survival after diagnosis, lead and length time bias can be avoided. In one study it was estimated that the lead-time will average 5.5 years. In a nested case control study of men without co-morbidity providing plasma samples before a ten-year follow-up, the baseline PSA level could have moved the diagnosis of prostate cancer forward by an average of 5.5 years. Lead-time distributions for aggressive and non-aggressive tumors were the same, indicating that there is a window of opportunity for detecting aggressive cancers before they have reached a stage beyond cure (62).

DIAGNOSIS OF PROSTATE CANCER: SCREENING TESTS AND THEIR PERFORMANCE

Three methods in various combinations are commonly used in the early detection of prostate cancer. Palpation of the prostate through DRE is the traditional method. In 1967 an additional diagnostic tool became available: Transrectal ultrasonography of the prostate (TRUS) (63). This was the first method actually to visualize the prostate itself. Criteria for recognition of prostate cancer were defined in the subsequent years (64). The identification of PSA has added to the methods available for early detection of prostate cancer (65).

Prostate specific antigen

PSA is a 34 K Dalton serine protease, which can be detected in semen and male serum (66). It is part of the human kallikrein family. The production takes place in the epithelial cells of the prostate, especially in adenomatous and prostate cancer tissue (67). Recently, other PSA-producing sources such as the pancreas and salivary glands in both men and women have been identified (68, 69). It is unclear whether this will have clinical consequences in the near future. In daily practice, however, PSA is still regarded as prostate specific. PSA is most probably metabolized in the liver (70).

PSA is not tumor specific; several benign conditions may increase the serum PSA concentration. Benign prostate hyperplasia is the most common cause of elevated PSA levels. Aus and co-workers showed that after transurethral resection of the prostate with a benign histopathologic specimen, PSA should be expected to be within the normal range (71). Prostatic needle biopsy, prostatic massage, transrectal ultrasonography (72) and DRE (73) may all lead to an increase in serum PSA. It is likely that ejaculation leads to a transient increase in serum PSA (74, 75), although unchanged levels (76, 77) and decrease (78) have been described. The consequence is that blood samples should be taken before further examination of the prostate.

PSA in nested case control studies

Serum PSA rises slowly with age and increasing prostatic volume. The average increase is small (0.3 ng/ml per gram of tissue) (79) in comparison with the 3.5 ng/ml per gram of malignant tissue (80). The concept of the more pronounced PSA increase in prostate cancer was evaluated retrospectively in four nested case control studies (62, 81–83). In large groups of men, blood samples were drawn and stored for many years. This allowed comparison of PSA values in those who developed clinically evident prostate cancer and in those that did not. The advantage of this method is that no assumptions will have to be made for clinical relevance of the detected cancers. The results, however, are entirely dependent on the reliability of the data provided by the cancer registry. In the study by Gann et al. (62), a single PSA level would have detected nearly 80% of all aggressive cancers within 5 years and about 50% appearing 9 or 10 years later. Only 96 out of 1098 men who were not diagnosed with prostate cancer had a false-positive test result. Optimal validity was achieved at a PSA cutoff of 3.3 ng/ml. Whittemore et al. calculated the sensitivity and specificity for a PSA cutoff level of 4 ng/ml and for clinical cancer being diagnosed within 7 years. In men younger than 65 years the sensitivity was 65%, the specificity was 94%. In men of 65 years and older the sensitivity was 100% and the specificity was 70%.

All studies agree that PSA determination is a suitable test for early detection.

PSA threshold value

In the early studies of prostate cancer detection a cutoff value of 4.0 ng/ml was arbitrarily chosen as the upper limit of normal (58). This PSA cutoff is used mainly to limit the number of men who have to undergo the more laborious screening tests such as DRE and TRUS. In a later study, biopsies were performed if the PSA level was above 4 ng/ml or DRE indicated a suspicion of cancer (84). Receiver operating characteristic (ROC) curve analysis showed the 4 ng/ml cutoff value to be optimal. A similar analysis performed earlier by Labrie and associates showed optimal sensitivity and specificity (respectively 81% and 85%) at a PSA threshold of 3 ng/ml, and using the same PSA assay (85). It should be noted that a description of the performance of tests in prostate cancer screening through sensitivity, specificity and positive predictive value is hampered by the fact that the denominator is not known. Instead of the true prevalence of prostate cancer within the study population, the number of positive biopsy results is used.

PSA in screening

The possibility of detecting prostate cancer with increasing PSA levels has been demonstrated repeatedly in case finding studies and population-based screening projects. Generally 70% to 80% of all cancers are detected in the PSA range above 4 ng/ml, in approximately 10–17% of the population (60, 86–89). At normal PSA values DRE and in some cases TRUS are responsible for the detected cancers. Crawford et al. (90) described the detection of prostate cancer in 31953 eligible subjects screened in centers throughout the USA. Among 1307 subjects who underwent biopsy, 322 cases of prostate cancer were detected. The cancer detection rate for PSA was 3.6% and for DRE 3.0%. This percentage was 4.7% when both tests were positive. The positive predictive value for elevated PSA levels was 31.6%. For DRE this was significantly lower at 25.5%. Thirty-one percent of cancers were missed by DRE and diagnosed through PSA only. DRE detected 27.6% of cancers that would have been missed by PSA. Again the description of the properties of PSA as a screening test is difficult since not all men in the population under study undergo biopsy. The true number of prostate cancer cases remains unknown. It must be assumed that impalpable and invisible cancers are also present at PSA levels below a cutoff of 4 ng/ml. This implies that the positive predictive values, sensitivity and specificity values reported in the literature are incomparable and incorrect. These values are dependent on the screening tests used and the biopsy indications. If TRUS had been used in the latter study, it is likely that more cases of cancer would have been detected at PSA levels below 4 ng/ml. This would have altered the described values.

The most important observation, however, is the fact that PSA is the strongest predictor for prostate cancer and that DRE is of limited additional value.

The use of PSA and DRE in a screening setting will detect prostate cancer in approximately 4% of subjects (60, 86, 89). This is only true for population-based screening programs. In a clinic population of symptomatic urological patients, detection rates up to 14.6% have been described (91). This shows that the detection is strongly population dependent.

DRE

DRE has been used for the detection of prostate cancer in several large series. Chodak et al. used DRE as the sole test in the screening of 1672 men aged 51–70 years. A detection rate of 1.4% was found (92). Although 68% of these cancers were clinically localized, 50% of these patients showed capsular penetration after examination of the radical prostatectomy specimen. It was concluded that DRE detects prostate cancer relatively late.

Pedersen et al. (93) diagnosed 13 cases of prostate cancer in 1163 screened men (1.1%). Both a urologist and a general practitioner did the examinations. The positive predictive value within this population was 29%, 35% for the urologists and 27% for the general practitioner. This illustrates the dependence of DRE on experience and quality of performance. Smith & Catalona also showed a considerable interexaminer variability. The agreement among urologists was only fair. The interexaminer variability was greater between faculty and resident examiners showing that experience plays an important role in DRE (94).

However, despite its shortcomings, DRE significantly increases the detection rate that can be achieved with PSA alone.

TRUS

Prostate cancer can be visualized by TRUS as a hypo-echoic structure within the peripheral zone of the prostate (95). However, not all hypo-echoic lesions prove to be prostate cancer and not all cases of prostate cancer appear to be hypo-echoic. Terris et al. examined 51 patients with normal DRE findings by TRUS before they underwent radical cystoprostatectomy for transitional carcinoma of the bladder. The ultrasound findings were compared with the pathological slides. In eight patients a hypo-echoic lesion proved to be cancer. Nine patients had abnormal TRUS findings but no cancer. Seven patients with normal TRUS findings had prostate cancer. Based on these results the positive predictive value is 47%, the sensitivity 53% and the specificity 75% (96). Lee et al. performed biopsies on 256 patients with a hypo-echoic lesions and detected 104 cancers. The positive predictive value of 41% decreased to 24% when DRE was normal, and to 12% when PSA was below 4 ng/ml. TRUS alone had a positive predictive value of 5% (97). This is in line with the observations within the American Cancer Society National Prostate Cancer Detection Project. In this study the positive predictive value of TRUS at PSA levels above 4 ng/ml is significantly higher (33%) than that of DRE (27%). Under a PSA level of 4 ng/ml the positive predictive values for DRE and TRUS are similarly low (respectively 6.4% versus 5.4%) (86). This shows that if DRE and TRUS are used for the detection of prostate cancer at PSA levels below 4 ng/ml, the additional value is limited. This is also confirmed by the receiver operator characteristic curve analysis by Ellis et al. PSA, DRE and TRUS were evaluated in 1001 six-sector prostate needle biopsies. This analysis showed that PSA is the best predictor of prostate cancer with an area under the curve of 0.64. The areas for DRE and TRUS were 0.58 and 0.50 respectively (98). Again, the additional values for DRE and TRUS under a PSA level of 4 ng/ml were limited. DRE or TRUS alone each detected 5 cancers out of the total 253 cases at a cost of 133 additional biopsies (13.3% of all biopsies performed).

The role of TRUS in screening for prostate cancer is more controversial than the use of DRE. In accordance with DRE it is a strongly investigator-dependent technique but, above all, it is relatively expensive and time consuming. Undisputed however, is the value of TRUS for the visualization of the prostate and in guiding the biopsy needle in the case of systematic sextant biopsies.

Stage T1C prostate cancer

Through the combined use of PSA, DRE and TRUS in the diagnostic procedure for detection of prostate cancer, it became clear that some cases of prostate cancer are neither visible, nor palpable and were identified by needle biopsy. This has led to a new category in the TNM classification of prostate cancer: Stage T1C i.e. tumor identified by needle biopsy (99). From the previously described autopsy series it becomes clear that 40% of men over 50 years of age harbor malignant cells within their prostates. Only a small subset of these cancers form a threat to their host. One of the first questions that rose was whether T1C tumors are different from incidental tumors found at autopsy? Several authors have reported on the characteristics of T1C prostate cancer. Epstein et al. described a case series of 157 consecutive men who underwent radical prostatectomy for clinical stage T1C disease. Sixteen percent of tumors were considered as insignificant and 10% as minimal lesions, based on tumor volume and grade (100). Stage T1C tumors resemble stage T2 cancers more closely than incidental prostate cancers detected at cystoprostatectomy. Their volume is about 50 times greater (20, 101, 102). One difference between T2 and T1C cancers was the gland size. The prostates harboring T1C cancers were significantly larger, which might explain the impalpability (103).

Improvement of the specificity of PSA-based screening: reducing the number of biopsied men

A high PSA level, abnormal findings on DRE and/or TRUS increase the chance of diagnosing prostate cancer in a screened man. At low or intermediate PSA levels the false-positive rate is high, which results in a high number of unnecessary biopsies. The use of DRE and TRUS will reduce the number of unnecessary biopsies; however, stage T1C prostate cancers that are not rendered visible by TRUS or are impalpable will be missed. T1C cancers form a potentially curable subset that amounts to 25 to 40% of all cancers diagnosed within most screening programs.

Prostate-specific antigen density (PSA-D)

PSA as a screening test identifies more cases of prostate cancer than DRE and/ or TRUS. A complicating factor in PSA-based screening is the fact that elevated PSA levels are caused by both benign prostate hyperplasia and prostate cancer. PSA alone is unable to discriminate between these conditions. The finding that PSA levels are proportional to the volume of benign prostate tissue and the volume of the cancer present (79) has led to the assessment of PSA corrected for total prostate volume in an attempt to avoid unnecessary biopsies. Babaian et al. suspected the presence of cancer to be greater if the volume of the prostate measured through TRUS is smaller than 25cc at elevated PSA levels (104, 105). The results of Benson et al. suggest that the quotient of PSA and the prostate volume may be useful in distinguishing prostate cancer and BPH (106, 107). An ROC curve analysis for PSA-D in a prospective evaluation suggested that the best cutoff point for biopsies was a PSA-D value of 0.15. Thus suggesting that the normal prostate volume at a PSA level of 4 ng/ml is 26 cc (108), which is in line with the findings of Babaian et al. Littrup et al. concluded that PSA-D was superior to other tests and test combinations, a 16–55% reduction in biopsies could be achieved with a respective loss of otherwise diagnosed cancers of 4–25% (109). Although there is some reason for optimism, several authors have reported that the use of PSA-D at a cutoff level of 0.15 results in half of the tumors being missed and that biopsies should be indicated by PSA rather than by PSA-D (110–112). Loss of cancers detected not only depends on PSA-D threshold value but also on the characteristics of the population. A ROC curve analysis by Ohori and associates showed a higher specificity for PSA-D but only in a small subset of patients, those with a PSA value >10 ng/ml and PSA-D below 0.15 (113). Similar findings were obtained by Brawer et al. (114).

The use of PSA-D will improve the specificity at the cost of loss in cancer detection. It may prove useful in well-defined subsets of screened men. One of the major disadvantages of the use of PSA-D is that the prostate volume has to be measured by transrectal ultrasound, which is time consuming, and expensive.

Age-specific reference ranges

PSA not only rises slowly with prostate volume, but also with age (115, 116). In order to make PSA a more discriminating tumor marker for detecting significant cancers in older men and to find more potentially curable cancers in younger men, Oesterling et al. suggest the use of four different PSA threshold values, 2.5 ng/ml; 3.5 ng/ml; 4.5 ng/ml and 6.5 ng/ml in men in the fourth, fifth, sixth and seventh decades respectively. The use of these ranges in men aged 60 years and older saved 5.5% of biopsies at the cost of 0.6% of cancers detected (117). The hospital records of 4579 patients with stage T1C, T2 or T3A prostate cancer who underwent radical prostatectomy were reviewed. Subsequent simulation of age-specific reference ranges showed an increase in detection of 18% in younger men and a decrease in detection of 22% in the older men. Ninety-five percent of missed cancers would have favorable pathological findings (118). El-Galley et al. concluded that the use of age-adjusted PSA is the most valuable for

patients over the age of 70, of whom 22% would be spared TRUS with biopsy (119). Catalona et al., however, found that the number of biopsies performed for the detection of one case of prostate cancer remains constant over the age groups suggesting that the use of age-specific reference ranges does not enhance the specificity (84). Furthermore, application of age-specific reference ranges in men 50 to 59 years old would have resulted in a 45% increase of biopsy indications and a projected increase of 15% in cancer detection. In the sixth and seventh decades the increased PSA threshold level would save respectively 15% and 44% of biopsies at the cost of 8% and 44% respectively of organ-confined tumors. This study concludes that the use of PSA at a cutoff level of 4 ng/ml is preferable.

Ratio of free and total prostate-specific antigen (free/total ratio)

A major part of PSA in serum of prostate cancer patients occurs as a complex between PSA and α_1-antichymotrypsin (ACT). Patients with prostate cancer have a significantly higher proportion of complexed PSA (PSA–ACT) than those with benign prostate hyperplasia (120). Thus, men with a relatively high free PSA are more likely to have benign disease. The ability of the free/total ratio to discriminate prostate cancer and benign prostate hyperplasia was demonstrated in a retrospective non-randomized analysis (121). This concerned well-defined cases of BPH: men with a prostate volume of at least 40 cc and negative biopsies and men with biopsy-proven prostate cancer and normal gland volumes. The conclusion was that measurement of the percentage of free PSA improves the specificity of prostate cancer screening in selected men. This has repeatedly been confirmed in similarly designed studies. The results described in the article by van Cangh and associates (122) are in line with these observations, but they also point out that the use of the free/total ratio in screening appears problematic because of the low prevalence of prostate cancer. In fact, within the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC), the discriminating ability of the free/total PSA ratio, at a cut off value of 0.20, led only to a small improvement in area under the receiver operating characteristics curve which, due to large numbers, was statistically significant (123). The use of a free/total ratio of 0.18 in addition to the PSA cutoff in the Göteborg (Sweden) site of the ERSPC would save 42% of biopsies at a cost of 12% of cancers detected (all men underwent biopsy if PSA was greater than 3 ng/ml). When compared to a PSA cutoff level of 4 ng/ml, both sensitivity and specificity improved by using a free/total ratio of 0.18 (124). In a subsequent study by Bangma et al. similar results were obtained in the PSA range between 4 and 10 ng/ml. The use of a free/total ratio of 0.20 or less in combination with DRE would reduce the number of biopsies by 38% with 12% of carcinomas remaining undetected. However, the combination of DRE and PSA-density value of 0.12 or more shows an identical performance (125). A major advantage of the use of the free/total ratio above PSA-D lies in avoiding the use of transrectal ultrasonography.

Various cutoff levels for the free/total ratio have been suggested, varying between 0.15 and 0.21 (126), but cutoff values for clinical practice have not yet been established.

Comment

The reduction in negative effects of false-positive indications for prostate biopsies leads inevitably to a decrease in prostate cancer detection. Knowledge of the undetected cancers is limited, i.e. although these cancers are often locally confined, it is not known whether they would be potentially lethal and inability to detect these cancers would narrow the window of opportunity within a screening program. The use of age-specific reference ranges seems to have little impact on the number of false-negative biopsy indications and cancer detection but merely shifts the detection towards a younger age group. Since the value of mass screening for prostate cancer is unknown, it is questionable whether this shift will improve the overall outcome of screening.

PSA-D and the use of the free/total ratio of serum PSA will reduce the number of false-positive biopsy indications. Cutoff values will have to be further evaluated. The major advantage of using the free/total ratio lies in the reduction of the workload by omitting TRUS.

TRUS guided systematic sextant biopsy

The use of TRUS with the possibility of taking multiple transrectal core biopsies of the prostate using fast spring-loaded biopsy devices has become the standard procedure in the diagnosis of prostate cancer. The procedure is relatively safe and can be performed in an outpatient setting without the use of anesthesia. Minor adverse effects that are often reported are transient hematospermia and hematuria. Infection is a less innocuous complication and may lead to septicemia and even death (127, 128). Fortunately these complications are rare. Septicemia occurs in 0.3 to 3.5% of cases (129, 130). Mortality has only been described in case reports.

The data derived from the autopsy series and cystoprostatectomy series show that the pool of prostate cancers is very large. A small number of these cancers are thought to be a potential threat to the host.

One of the concerns in early detection of prostate cancer is the sensitivity of the biopsy procedure. Terris et al. introduced the concept of systematic sextant biopsy (131). Of the 442 cancers detected in 816 patients only 10% had a tumor volume of less than 0.5 cc and thus considered insignificant. In a series of T1C cancers the percentage of insignificant cases was 16% (100), indicating that although insignificant cases are detected, the majority is considered large enough to be potentially dangerous.

Failure to detect potentially dangerous cancers is also undesirable. Daneshgari et al. calculated the probability of detecting low volume cancer (0.034–5.1 cc). They found that the size of the prostate as well as the size and distribution of the lesions within the gland determine the chance of diagnosis by sextant biopsy. The chance of missing a tumor was 27%. Furthermore, a needle angle of 30° gave significantly better results than 45° or 60°. Sextant biopsies were superior to random biopsies (132).

In a retrospective series of 123 men a second sextant biopsy procedure within 6 months revealed 28 additional (23%) cases of prostate cancer. Ten of these cases were found in 66 rebiopsied men in the PSA range between 4 and 10 ng/ml (133). The accuracy of diagnosis may not only be related to the tumor volume but also to the gland volume in which the tumor resides. The positive predictive values for a positive biopsy of PSA greater than 4 ng/ml were reduced from 54% to 14% when gland volume increased from less than 20 cc to greater than 100 cc (134). Uzzo et al. showed similar findings in a multivariate analysis that patients diagnosed with cancer had significantly smaller prostates (135).

To improve the detection rate by biopsy and to reduce the sampling error Eskew et al. (136) increased the number of biopsies according to the prostate volume measured by TRUS; 13–18 biopsies in a 5-region pattern are taken. The detection increased by 35% using this concept. No significant difference was found in tumor volume or Gleason score between the tumors found with the systematic sextant biopsy pattern and those detected in the additional series of biopsies. However, it should be noted that these figures come from a small series that needs further confirmation.

Prediction of stage, grade and insignificant disease

Several parameters are considered important in the prognosis of prostate cancer. Large tumor volume, high grade of differentiation and extracapsular extension are associated with a poor prognosis. Since prostate cancer screening detects prostate cancer in more men than are likely to experience disease progression, it would decrease the uncertainty if the stage, grade and extent of the tumor were known before the choice of treatment. Cases have been reported in which radical prostatectomy had been performed for biopsy-proven cancer and after examining the specimen, no cancer was found (137).

Prediction of insignificant disease

Terris et al. (131) treated 17 patients with less than 3 mm of well-differentiated cancer in one of six biopsies by radical prostatectomy. The tumor volumes of these patients ranged from 0.04 to 10.1 cc. Eleven of these 17 patients (65%) had volumes of less than 0.5 cc. This ratio, however, was reduced to 10% by taking a second set of sextant biopsies. Ravery et al. stressed the fact that a single positive biopsy in six does not predict a low-volume prostate cancer on an individual basis (138). Twenty-four radical prostatectomies were performed for prostate cancer detected with one positive biopsy out of six. Capsular penetration was present in 29% and seminal vesicle invasion in 8%. If less than 10% of the biopsy core length was invaded by tumor, all were free of extracapsular involvement. If the whole biopsy length was involved, all patients had extracapsular cancer. The volume of cancer in the biopsy specimen, as a predictor for the volume of cancer in the radical prostatectomy specimen, was evaluated by Cupp et al. (139). Regression analysis revealed a direct correlation. However, of 13 patients with 5% cancer or less, only 1 had a tumor volume of less than 0.5 cc. They concluded that the biopsy specimen does not provide enough information for decisions on an individual basis. According to Epstein et al., insignificant tumor is predicted with 73% accuracy by a PSA-D of less than 0.1 and no adverse pathological finding on needle biopsy or a PSA-D of 0.1 to 0.15 with less than 3 mm low to intermediate grade cancer in only one needle biopsy core (140).

Prediction of grade

When the grade of the biopsy specimen is compared with the radical prostatectomy specimen, undergrading is common (141, 142). Possible explanations are:

- The tendency to undergrade limited amounts of Gleason pattern 3 on needle biopsy.
- The sampled nodule is correctly staged but multifocal higher-grade tumor is present elsewhere.
- Heterogeneity of the grade within the tumor nodule induces sampling error (143). The ability to predict tumor grade can be enhanced by considering the PSA value and PSA density (144).

Prediction of stage

The clinical stage is a poor predictor for the stage at radical prostatectomy (56). Capsular penetration and seminal vesicle invasion can to some extent be predicted by the preoperative serum PSA concentration, Gleason patterns and the percentage of cancer in the biopsy specimen (145). D'Amico et al. used the calculated prostate cancer volume to predict capsular penetration in clinically localized disease (146). PSA, prostate volume and Gleason score are the parameters used. The formula was the result of a logistic regression multivariate analysis on 104 radical prostatectomy specimens.

Partin et al. showed that the combination of Gleason score in the biopsy specimen, clinical stage and PSA provide the best separation to predict the final pathological stage. The analysis of 703 men undergoing radical prostatectomy resulted in probability curves and nomograms that can be helpful in making clinical recommendations for men with clinically localized prostate can-

cer (147). In the most recent report the clinical and pathological data of 4133 men treated with radical prostatectomy in four different centers were combined and the nomograms were updated. In the validation analysis, 72.4% of the time the nomograms correctly predicted the probability of a pathological stage to within 10% (148). This will enable patients and physicians to make more informed treatment decisions. Nevertheless, the uncertainties around the pretreatment evaluation are not excluded by using these nomograms. The development of improved sampling methods and better prognostic parameters is imperative.

Re-screening interval

The frequency of screening for any cancer is a compromise between unnecessary testing and the subsequent effects of false-positive test results and the risk of missing curable cancer with less frequent testing. Prostate cancer screening has not been shown to be useful but is subject to study. Still, screening upon request takes place and optimization of all aspects of the detection procedure is desirable. Several studies have used a yearly re-screening interval. Mettlin et al. (88) reported on the annual detection rates in the first five years of the National Prostatic Cancer Detection Project of the American Cancer Society. These were respectively 2.8%; 2.0%; 1.1%; 2.1% and 1.9% in the first to fifth screening rounds. Initially in this study biopsies were not routinely taken at PSA levels above 4 ng/ml, but later, biopsies were taken if the elevated PSA could not be explained by benign gland enlargement. Cancers within the screening interval were not reported. Labrie et al. (149) described an initial detection rate of 3.4% With the use of a PSA cutoff of 3 ng/ml, DRE and TRUS. In the subsequent yearly visits the detection rates were 0.6%; 0.7% and 0.3% (TRUS was not used as a screening tool in the yearly re-screening visits). Smith and associates (150) observed a decrease in detection frequency from 3% below 1% after 48 months using PSA-based screening with a cutoff of 4 ng/ml and a six-monthly re-screening program. The proportion of clinically advanced cancer also decreased from 6% to 2%. The proportion of high-grade disease after surgery decreased from 11 to 6%. No interval cancers were detected.

To our knowledge no reports on interval cancers in prostate cancer screening are available, which indicates that a one-year screening interval is too short. In a recent paper by Carter et al. a 2-year screening interval is suggested for men with PSA levels of less than 2 ng/ml. This was based on the observations that (i) PSA conversions in prostate cancer cases to greater than 5 ng/ml when the initial level was less than or equal to 2 ng/ml are rare (4%) within 2 years and (ii) when the pretreatment PSA level is below 5 ng/ml, prostate cancer is highly likely to be curable (151). Determination of the proper re-screening interval is mandatory. Answers may come from the European Randomized Study of Screening for Prostate Cancer where a 4-year re-screening interval is used and from further knowledge concerning PSA doubling time and tumor characteristics.

TREATMENT OF PROSTATE CANCER

Early detection of prostate cancer can only be useful if treatment for localized prostate cancer is effective. Furthermore, the previously described reports on the natural course of clinically localized prostate cancer and deferred treatment series may give the impression that treatment is not necessary. Three options for therapy are commonly used: radical prostatectomy, radiotherapy and deferred treatment or watchful waiting. There is still discussion concerning the optimal management of localized prostate cancer. In fact only two randomized treatment studies have been reported. The first study compares radical prostatectomy and watchful waiting (152). No difference in overall survival after 15 years of follow-up was found. However, the study was never completed and lacks the necessary power, as was recognized by the authors. One-third of the included 142 patients were lost to follow-up and there was an imbalance in age between the two groups. Furthermore, staging of the lymph node status and bone scans were not performed. The second study compares radical prostatectomy and radiotherapy (153) and found a significantly lower progression rate after surgery. This study has also been criticized on methodological grounds. The randomization procedure was not entirely blinded, and the difference in the number of patients included in the treatment groups (56 received radiation and 41 underwent radical prostatectomy) is unexplained. Recently, large randomized trials have been initiated to compare radical prostatectomy and watchful waiting (154, 155) but the results will not be available for at least another decade.

The current opinions regarding treatment are based on a combination of personal observations and data from reports of uncontrolled studies. In absence of evidence, attempts have been made to develop practical guidelines for the treatment of patients with prostate cancer (156, 157). The outcome concerning survival and treatment complications allowed no conclusion to be drawn. It was advised that the information about the treatment options should be passed on to newly diagnosed patients.

Comparison between radical prostatectomy and radiotherapy is hampered by differences in staging. Surgical staging includes a lymph-node dissection. In patients found to have positive lymph nodes, a radical prostatectomy is not performed. Only a small percentage of men treated with radiotherapy undergo a lymph-node dissection. If the lymphnode status is known to be negative the results of radiotherapy appear to be similar to surgical series (158): 85% of patients were free of local disease at 10

Table 4

10-year disease specific survival-percentage with 95% confidence interval, in patients with clinically localized prostate cancer by intention to treat and treatment received. (Lu-Yao, Lancet 349, 1997 (160))

	Intention to treat			Treatment received		
	Rp	Rt	Wawa	Rp	Rt	Wawa
G1	94 (91–95)	90 (87–92)	93 (91–94)	98 (97–99)	89 (87–92)	92 (90–93)
G2	87 (85–89)	76 (72–79)	77 (74–80)	91 (89–93)	74 (71–77)	76 (73–78)
G3	67 (62–71)	53 (47–58)	45 (40–51)	76 (71–80)	52 (46–57)	43 (38–48)

Abbreviations: Rp = radical prostatectomy, Rt = radiotherapy, WaWa = watchful waiting, G1 = well differentiated, G2 = moderately differentiated, G3 = poorly differentiated.

years and 15% had died of PC. In a recent series the 10 and 15 year actuarial survival rates were 63.7% and 49.6% respectively. The cause-specific survival rates were 84.2% and 80% respectively (159).

A further obstacle lies in the fact that prostate cancer is generally understaged at clinical examination. The clinical stage and biopsy grade are poor predictors of the pathological stage and grade. This might overestimate the benefit of radical prostatectomy. On the other hand, the results of radical prostatectomy may be underestimated because surgically treated patients are usually younger and in better health. Albertsen et al. (34) have demonstrated that existing co-morbid disease is highly predictive of overall survival above and beyond patient age. Because of their lower mortality from other causes, men treated with radical prostatectomy would have a greater chance of having a cancer-related death. This may lead to increased rates of metastases and death in surgically treated men, which may decrease apparent cancer-specific survival rates in comparison with other forms of therapy.

The results of radical prostatectomy in 2758 men with clinically localized prostate cancer were assessed in a multi-institutional pooled analysis by Gerber et al. (160). Tumor grade appeared to be the most important preoperative factor in determining outcome. The disease-specific survival rates 10 years after surgery were: 94% for grade 1, 80% for grade 2 and 77% for grade 3 disease. Metastases-free survival rates at 10 years were 87%; 68% and 53% for the respective grades. Lu-Yao and Yao have carried out a survey of 59876 prostate cancer patients treated with radical prostatectomy, radiotherapy or watchful waiting (161). Again, the cancer grade significantly affects overall survival. Patients with grade 3 disease had a much lower overall survival than their age-matched cohort in all treatment groups. The 10-year disease-specific survival was poor in all three treatment groups as can be observed in Table 4. Values for relative and disease-specific survival, however, were higher in the radical prostatectomy and radiotherapy group than in the deferred treatment group. The therapy options were assessed by intention to treat and treatment received to reduce bias because of exclusion from therapy of patients with positive lymph nodes. Staging, age and general health biases were not avoided. Comparison with the age-matched cohorts shows that patients undergoing surgery have a higher overall survival than their age-matched counterparts. This may be due to selection of healthier patients for radical prostatectomy but it cannot be excluded that the higher disease-specific survival within this group also plays a role. Adequate adjustment for co-morbidity is essential when comparing overall mortality across treatment groups but its impact on prostate cancer-specific survival is modest (34). Thus the observed differences between the treatment options should be interpreted with caution.

Since grade 3 disease is associated with low disease specific survival whatever the treatment chosen, the question rises whether grade 3 disease is curable? Partin et al. (162) studied the outcome of 72 men with Gleason score 8–10 on needle biopsy. Twenty-nine of these men had positive lymphnodes. In the remaining men the actuarial likelihood of having undetectable serum PSA at 5 years was 43%. It was concluded that if the lymphnodes are negative, men with high-grade disease are suitable candidates for radical prostatectomy. With the proper evaluation some of the most aggressive tumors can be cured (163, 164).

Adverse effects from treatment

Quality of life after cancer treatment has become a major issue in the choice of treatment. However, quality of life is not easy to assess. Litwin et al. used validated Health Related Quality Of Life (HRQOL) measures and new prostate-targeted items in three treatment groups (radical prostatectomy (98 men); radiotherapy (56 men) and observation alone (60 men)) and compared the findings with an age-matched cohort (273 men). They concluded that there were no differences in general HRQOL. The sexual, urinary and bowel function score in the disease-targeted HRQOL in both treatment groups differed significantly from the control group. The difference in scores between surgery and radiotherapy was not significant. The patients in the observation group experienced significantly more role limitations due to emotional problems than both treatment groups (165).

Table 5

Summary of four reports on adverse effects after treatment for prostate cancer

	Wasson (165)	Fowler (166)	Davidson (167)	Walsh (168)	
Therapy	Radiation	Surgery	Surgery	Surgery	Surgery
Mortality	0.2%	1.1%	0.6%	1.5%	–
Any incontinence	6.1%	26.6%	30%	5.9%	8%
Complete incontinence or artificial sphincter implant	1.2%	6.8%	6%	6%	0.3%
Any bowel injury	11.4%	2.7%	–	–	–
Bowel injury requiring long-term treatment	2.3%	1.3%	–	–	–
Stricture	4.5%	12.4%	20%	32%	
Impotence	41.4%	84.6%	61%	57%	32%

Incontinence, erectional dysfunction and bowel problems are often reported as adverse effects after treatment for prostate cancer. Table 5 presents a summary of four reports on adverse effects (166–169). Variations seen depend strongly on criteria and methods of evaluation. Potency seems to be better preserved in patients receiving radiotherapy. In a report by Bagshaw et al. (170) on 900 patients receiving radiotherapy treatment, potency was preserved in 86% of patients post-treatment and 50% of patients maintained erectile function 7 years post-therapy. Incontinence is more frequent in surgically treated patients, whereas bowel problems are more pronounced in patients treated with radiotherapy.

RISKS OF SCREENING

Serious complications of venous puncture, rectal examination and transrectal ultrasound have not been described. The screening tests are generally well accepted. The patients acceptance of the ultrasound-guided transrectal biopsy procedure is very high, 70 to 92% of patients report no significant pain or discomfort during the biopsy procedure (171–173). A process evaluation was carried out within the European Randomized Study of Screening for Prostate Cancer (174). This showed that 95% of all participants are willing to be re-screened. This indicates that patients do not experience too much discomfort from the screening procedure. The complications of the biopsy procedure have been described previously, as are the complications of treatment for prostate cancer. A second survey carried out by Fowler et al. (175) showed that 89% of patients would choose surgery again despite significant adverse effects. Eighty-one percent appreciated the treatment as positive. Expectant management is shown to increase anxiety among patients.

COMMENT

Considering the incidence and mortality of prostate cancer, this disease constitutes a significant health problem. Furthermore, the impact of the disease is expected to increase in the near future because of the ageing population and increasing awareness of the disease. Once the cancer has spread beyond the prostate, cure is generally impossible. The best treatment option is still under discussion, and randomized studies are on their way. However, the results are not expected within a decade.

It has been shown that early detection is technically possible but the optimal screening strategy has not been determined yet.

Stage reduction of screen-detected prostate cancer has been described. This, however, does not prove that early detection provides evidence for a decrease in cancer mortality. Prostate cancer treatment is not successful in all cases. Lead- and length-time bias are closely related to the phenomenon of stage reduction.

The prevalence of prostate cancer in autopsy studies is high. It is estimated that 10–25% of these insignificant cancers are detected by the current diagnostic tests (37). However, the detection of prostate cancer in the population is 4 to 5 times higher than the incidence of clinically diagnosed prostate cancer. More men are treated for the disease than are at risk of dying from it. Part of the subsequent treatment may be considered overtreatment. Men who would not have died from the disease have a high chance of having to live with the adverse effects of treatment. However, it has been shown that men are willing to trade the reduction of risk of prostate cancer-related death and mortality for adverse effects (175).

The incidence of prostate cancer in the USA has risen dramatically, which is mainly explained by the increased awareness and early detection activities (8, 9). Recently, a decline in incidence has been reported in the Utah and Connecticut center of the Surveillance Epidemiology and End Result study areas of the National Cancer Institute of the United States (SEER) (176, 177). Furthermore, a 6.3% decrease in prostate cancer mortality was observed (178). This was most evident in men under age 75. In this group the decline was 7.4%, whereas the decline in men over 75 amounted to 3.1%. No explanation has been offered for this phenomenon, but the possibility that this trend is the result of early detection and treatment cannot be ruled out at this time.

CONCLUSION

At this moment it is not known whether prostate cancer screening will reduce the mortality from this disease. This will have to be demonstrated in large prospective randomized studies such as the ones initiated in Europe and the United States of America (179).

Results, however, are not expected to be available within the next ten years. Men who wish to be screened should be fully informed about the risks, adverse effects and potential benefits.

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