Prostate cancer: natural history and surgical treatment of localised disease

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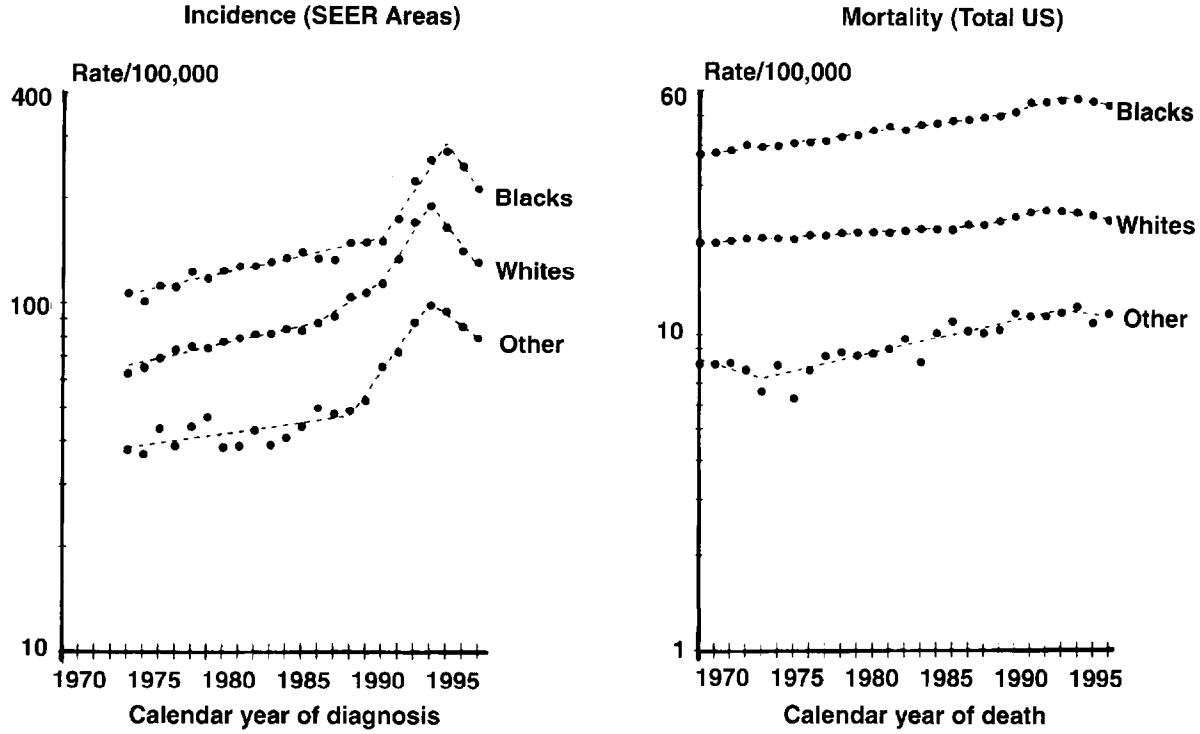
Epidemiological background

Prostate cancer is the most frequent malignancy in males and presents clinically as a tumour with a number of puzzling features: the incidence of prostate cancer is strongly age-dependent, prostate cancer is rare below the age of 50 years. There are large differences in the incidence of clinical prostate cancer and mortality, but not with respect to focal disease [1]. There is uncertainty about precursor lesions. While high grade prostatic intraepithelial neoplasia (HG-PIN) is well established as a precursor of moderately and poorly differentiated cancer, a precursor lesion which reflects the genetic make-up of the frequent well-differentiated disease is not available [2]. There is a remarkable discrepancy between mortality and incidence, which has been increasing recently and will be discussed later on in this paper. In spite of the very strong epidemiological evidence for the environmental impact on the progression of focal disease to clinically relevant disease, only very few risk factors, such as selenium [3] and vitamin E [4] have been confirmed to be involved in a prospective, comparative setting.

Incidence and mortality

Incidence and mortality rates in Europe amount to approximately 100 000 and 40 000. Prior to the recent increase in incidence of prostate cancer the incidence mortality ratio in Europe amounted to approximately 2.5/1 [5]. From the United States, estimates for the year of 2001 are available. It is expected that 198 100 cases will be diagnosed and that 31 500 of these will die of the disease, an incidence mortality ratio of 6.3. As of 1996, there has been a steep rise in the incidence of prostate cancer in the United States [6]. Since 1993 a decrease was seen and then incidences seem to level off from 1995 at an age-adjusted rate of approximately 140 per 100 000 [6]. In the United States, prostate cancer is the most frequently diagnosed cancer and the second most frequent cause of cancer death in males. Prostate cancer mortality has been decreasing in the United States by about 4.4% annually from 1994–1997 [6]. Fig. 1 shows the relationship of incidence and mortality in the United States for the years of 1970 to 1995 [7]. Further details can be found in a study by Stanford et al. [8].

The increase of incidence in the United States is accompanied by a dramatic shift to locally confined and non-metastatic disease [8] (Fig. 2). The increase of incidence, the stage shift and the decrease in mortality are all, at least in part, attributed to increased use of prostate specific antigen (PSA)-driven early diagnosis and screening [7]. Similar changes are also seen in Europe when comparing incidence and stage distribution in areas with well-functioning cancer registries where screening has become prevalent like in the area of Rotterdam where a randomised screening trial is being conducted [9]. The most dramatic observation in the report by Rietbergen et al. relates to 24% of metastatic disease reported in a contemporary regional cancer registry compared with less than 1% of bone metastases in the prevalence screen of the Rotterdam section of the 'European Randomised Study of Screening for Prostate Cancer' (ERSPC) [9]. In some part, the increase in incidence is related to an increase in longevity of the male population in many countries. It has been predicted that due to increasing longevity alone by the year 2020 there would be an increase of 67% in prostate cancer incidence [10]. While the decrease in prostate cancer mortality is most pronounced in the United States, where screening is very prevalent, a decrease in mortality is also reported from areas of the world where screening is not prevalent, especially from the United Kingdom [11]. In addition, in the Netherlands, in 1997, a 5% decrease in prostate cancer mortality has been observed. There is documentation in this country that screening is not prevalent and amounts to $<10\%$ of the male population at risk per year [12].



Calendar Period: 1969–1995							
Race	APC	Join Point	APC	Join Point	APC	Join Point	APC
Whites	2.4 (1.8, 3.1)	1985	6.9 (2.5, 11.6)	1989	18.4 (10.7, 26.6)	1992	-12.8 (-15.7, -9.8)
Blacks	2.3 (1.8, 2.8)			1989	17.0 (12.4, 21.8)	1993	-14.0 (-20.2, -7.4)
Other	1.5 (0.3, 2.7)			1987	16.2 (10.8, 21.9)	1992	-7.5 (-12.9, -1.7)

Calendar Period: 1973–1995							
Race	APC	Join Point	APC	Join Point	APC	Join Point	APC
Whites	0.7 (0.6, 0.8)			1987	3.1 (1.8, 4.4)	1991	-1.9 (-2.6, -1.1)
Blacks	1.6 (1.4, 1.7)			1988	3.2 (1.3, 5.2)	1992	-1.7 (-3.5, 0.1)
Other	-3.3 (-12.4, 6.8)			1973	2.6 (2.0, 3.3)	1992	-1.8 (-8.0, 4.9)

Fig. 1. Age-adjusted (1970 U.S. standard) prostate cancer incidence and mortality rates for Surveillance, Epidemiology, and End Results (SEER) areas and prostate cancer mortality for the total United States [7].

The very pronounced increase in the incidence of prostate cancer, especially in the locally confined and potentially curable stages has also led, in most European countries, to an increase of cases treated by radical prostatectomy and the different modalities of radiotherapy. Since this increase in the rate of locally confined disease is due to the use of a new diagnostic modality (PSA-based early diagnosis), the time of diagnosing prostate cancer has advanced with respect to the time of the clinical diagnosis compared with the time the diagnosis was made in the past. Lead time is produced. Studies utilising serum repositories that were established many years ago, have allowed estimations of lead times to be in the range of 5–10 years [13–15]. The production of lead time together with the phenomenon of an increase of the incidence mortality ratio suggests a considerable degree of overdiagnosis. A likely explanation would be the diagnosis of a large proportion of cases with the type of focal disease described by pathologists as latent carcinoma and as incidental carcinoma found in prostatic specimens removed for benign disease (BPH). This, however, does not seem to be the case because most tumours diagnosed by PSA-driven biopsy by far exceed the average volume of 0.02 ml that has been attributed to focal disease [16,17]. It is therefore very likely that lead time (and overdiagnosis) are produced not only by the diagnosis of what might be called 'minimal' or 'clinically insignificant' disease [18,19], but also by diagnosing slowly progressing larger tumors and possibly even due to locally advanced or lymph node metastatic tumours, which may show a very slow progression rate [20].

Natural history of locally confined disease

A number of prospective and retrospective studies address the issue of the natural course of localised

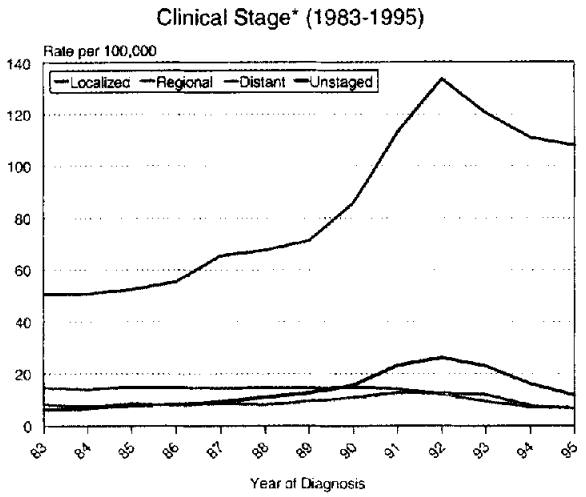


Fig. 2. Prostate cancer SEER incidence rates by stage [8].

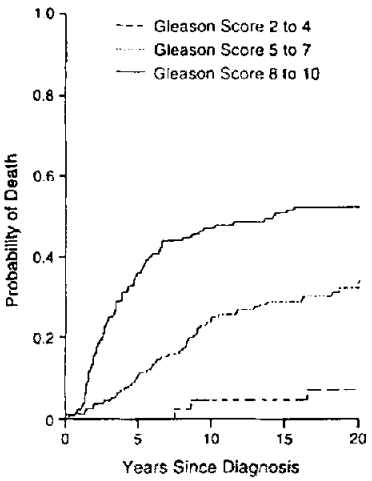


Fig. 3. Cumulative disease-specific mortality in 451 localised prostate cancer (PC) patients, 154 (34.1%) died of PC within 15.5 years [22].

prostate cancer. However, all these studies include cancers that were diagnosed prior to the era of PSA screening, which started around 1989. Still, by correcting for stage and grade of differentiation at the time of diagnosis, relevant endpoints such as disease-free survival, cancer-specific survival and overall survival can be evaluated. A complete review of the natural history data is not warranted in the present context. Chodak et al. [21] provided a literature-based summary of 5 of the available large natural history studies. In spite of the fact that the overrepresentation of well-differentiated disease (grade 1) of 60.1% of cases suggests a strong bias in that direction, the study provides valid data with respect to the impact of grade on cancer-specific 10 year survival, which amounts to 81%, 58% and 26% for grade 1, grade 2 and grade 3, respectively, in the 819 cases included in this study. Albertsen et al. [22] presented a retrospective population-based cohort study of 451 men aged 65 to 75 years, who were treated only with immediate or delayed hormonal therapy from 1971 to 1976. The mean follow-up was 15.5 years. Age-adjusted survival for men with well-differentiated tumours (Gleason score 2–4), moderately differentiated tumours (Gleason score 5–7) and poorly differentiated tumours (Gleason score 8–10) was reported. Co-morbidities were analysed, prostate cancer unrelated mortality did not differ between the groups of men within the compressed Gleason scores. An independent pathological review was carried out in this study. Forty four (9.8%), 160 (35.5%) and 130 (28.8%) of the 451 cancer cases fell within the compressed Gleason groups 2–4, 5–7 and 8–10, respectively. In 170 men, histological details were not retrievable. Fig. 3 shows the cumulative mortality after diagnosis by compressed Gleason scores. The 3 curves differ significantly. At the time of evaluation 154 men (34.1%) had died of prostate cancer, 221 (49.0%) had died of other causes. The 15 year disease-specific mortality for Gleason 2–4, 5–7 and 8–10 cases was 9%, 28% and 51%. This study was updated in 1998 [23]. At that time, a total of 767 similar patients in the age group 55–74 years were included. Pathological revision was in expert hands and carried out by Donald F. Gleason. At that time, men with Gleason scores 2–4, 5, 6, 7 and 8–10 were separated and showed 15-year disease-specific mortality rates of 4–7%, 6–11%, 18–30%, 42–70% and 60–87%, respectively, within 15 years depending on their age at diagnosis (55–59 versus 70–74 years). Grading is considered to be one of the most important independent prognostic factors in locally confined disease. On this basis, the data in this study must be considered of great relevance, despite being a retrospective analysis. The value of the data is further enhanced by the fact that grading was carried out on biopsy and/or transurethral resection (TUR) specimens (and not on radical prostatectomy specimens), information that is available at the time of diagnosis when therapeutic decisions are taken. The value of grading biopsy specimens is limited by the observation of frequent biopsy undergrading [24]. However, the large differences in determining moderately and poorly differentiated disease by biopsy are only to a much lesser degree reflected in differences of disease-specific survival calculated for biopsy and radical prostatectomy grading [25].

The information presented up to this point provides an important baseline for decision-making in the management of localised prostate cancer. Other important parameters such as the PSA level, the clin-

ical T category, the age of the patient, co-morbidity and the effect of the different treatment modalities on quality of life must be taken into consideration. Unfortunately, large gaps in our present knowledge make it impossible to establish a conclusive algorithm for the use of surveillance (watchful waiting), radiotherapy either by seed implantation or external beam irradiation, or radical prostatectomy. Nevertheless, based on the data shown, it is very unlikely that a 70 year old man with a Gleason score 2–5 tumour on biopsy will benefit from any form of potentially curative management. On the other hand, the same man with a Gleason 8–10 tumour will have a risk of dying of prostate cancer of 60% at 10 years. If this tumour can be diagnosed in a confined state, aggressive treatment is warranted.

Case selection and staging

It is unclear at this time, especially on an individual basis, which patient can be expected to derive benefit from early aggressive management. It is, however, undisputed that only early radical prostatectomy or early radiotherapy offer a chance of cure from this disease. Once prostate cancer has progressed beyond the confines of the prostate, cure is not possible but it is by no means certain that a given patient will die of his disease. Considering the large number of uncertainties about individual outcome such as co-morbidity, tumour aggressiveness, aspects of quality of life, etc., the decision to proceed to treatment depends on a balanced view of these parameters to the best of the knowledge of the treating physician and, subsequently on the rather personal preference of a given patient who should take into account as many as possible of the available uncertainties. An almost impossible task. Clearly, as testified by the rapidly increasing numbers of radical prostatectomies not only in the United States (>100 000/year), but also in most European countries, the decision to proceed to either radical prostatectomy or radiotherapy is taken with increasing frequency. Still, even in the United States, the proportion of men who elect to be managed by surveillance measures (watchful waiting), at least initially, has remained stable at a level of about 30% [8].

Staging

Staging is best carried out according to the internationally agreed TNM system of 1992 or 1997. T categories and biopsy grading remain important in spite of their inaccuracy. Catalona et al. [26] have shown that with stage T1a (found on TUR prostate), T1c (normal rectal examination, elevated PSA), T2a (less than one half lobe involved) and T2b (more than one half lobe involved), 0%, 40%, 20% and 60–76% of men after radical prostatectomy were shown to have locally extensive tumours classified as pT3 or higher. Many authors have studied the distribution of grading within various systems in comparing biopsy with radical prostatectomy specimens. There is consensus that if a well-differentiated tumour is diagnosed on biopsy, the chance of finding moderately or poorly differentiated disease in a radical prostatectomy specimen is in the range of 40–60% [24]. The clinical relevance of this discrepancy, however, is to a large degree uncertain. It has recently been shown that systematic education of pathologists can decrease the discrepancy in grading between biopsy and radical prostatectomy specimens in a clinically relevant manner [27]. Several algorithms have been designed to predict the local extension of the tumour. Clearly, prostate specific antigen (PSA) alone is not sufficiently predictive. Even algorithms utilising PSA, clinical T stage and biopsy grading suffer from large confidence intervals [28,29].

The determination of the M and N categories is also burdened with uncertainties. Regional lymph node metastases (N1–3) can only be visualised if they are larger than 1–1.5 cm in diameter, which is rarely the case. Fortunately, with PSA-driven diagnostic procedures, the prevalence of lymph node metastases for localised disease has decreased from approximately 25% to approximately 3% or less [9]. Algorithms already mentioned above [28,29] allow the identification of patients at a very low and a high risk of lymph node metastases. If a low risk is predicted, it has become common practice not to carry out a lymph node dissection prior to radical prostatectomy or radiotherapy. If, on the other hand, a chance of lymph node metastases of at least 25%, such as in moderately or poorly differentiated T3 tumour is predicted, a less invasive laparoscopic lymph node dissection may be the most appropriate way of excluding nodal metastases. There is controversy as to whether patients with lymph node metastases can derive any benefit from radical prostatectomy or radiotherapy. There is, however, agreement that regional lymphatic spread indicates that a given tumour can not be cured. Favourable survival data in non-randomised settings may often reflect the effect of adjuvant endocrine treatment, which is known to delay progression. Computed tomography (CT) scan or magnetic resonance imaging (MRI) scan is expensive and superfluous studies in most men with locally confined disease, especially if prediction of positive

lymph nodes by available algorithms amounts to less than 10%. This applies to most patients who present with locally confined prostate cancer.

Metastatic disease (M1a = subregional lymph node metastases, M1b = bone metastases, M1c = soft tissue metastases) is also best classified within the TNM system. Para-aortic lymph node metastases are rarely seen and can occasionally be identified on CT or MRI scans carried out in men with a high algorithm-based risk. If such studies are positive, an attempt of transabdominal cytological puncture of suspicious nodes is warranted. There is consensus now that in men with PSA values of 10 ng/ml or less, bone scans should not be carried out because they will turn out to be positive in only approximately 3% of cases [30]. At the author's institution, bone scans are also not carried out in men with PSA values up to 20 ng/ml for similar reasons. With PSA values around 50 ng/ml the prevalence of positive bone scans rises to approximately 20% which suggests a rational indication for carrying out bone scans during follow-up, as long as patients remain asymptomatic [31]. Radio-immunological imaging based on prostate-specific membrane antigen (PSMA) is available. However, its usefulness is hampered by the fact that the isotope targeted by the respective antibody has an intracellular location. This, in fact, means that only dead prostate cancer cells can be visualized. The technique (ProstaScint, Cytogen Corporation, Princeton, NJ, USA) has recently been utilized in a multicentre study of 2154 patients with prostate cancer [32]. A significant correlation between PSA levels and ProstaScint predictions was found for recurrences of cancer in the prostate bed and for pelvic metastases. However, histological confirmation was not routinely obtained in this retrospective study. Probably the best available data [33] relate to biopsy-proven local recurrences. In this setting, ProstaScint had a positive predictive value of 50% and a negative predictive value of 70%. The development of clinically applicable tests based on extracellular epitopes of PSMA is in progress. At this moment, carefully designed clinical studies with histological confirmation are necessary, routine clinical use is debatable because of the high false-positive and false-negative rates. Positive bone scans require X-ray confirmation to exclude other reasons, especially degenerative changes or old traumatic changes as possible reasons for bone scan positivity. Lung and liver metastases in locally confined disease are so rare that chest X-rays and ultrasound studies of the liver are not considered necessary in locally confined disease.

Surgical treatment

The techniques of surgical management of prostate cancer have been carefully described in various textbooks and separate publications. At this time, radical retropubic prostatectomy is the most commonly utilised procedure. An excellent recent description of this technique with all details, potential pitfalls, indication and complications has been given by Walsh [34]. His development of an approach that is strictly oriented toward dealing with the anatomy of the vascular supply and of the neurovascular bundles responsible for erectile function has contributed in a major way to the large increase in the use of radical retropubic prostatectomy since the mid-1990's. The older and more traditional operation, however, is total perineal prostatectomy which was originally described by Young [35] with significant technical alterations proposed by Belt [36] and Weldon [37]. Most recently, laparoscopic radical prostatectomy has been developed and popularised by Guillonneau and Vallancien [38] who reported their initial results in 260 consecutive cases. Claimed advantages and disadvantages of these techniques, as well as the specific complications are described in the respective references.

In summary, the following advantages/disadvantages of the different techniques can be described as follows:

Radical retropubic prostatectomy

The technique is very well described and can be reproduced by experienced surgeons. Functional results depend on the experience and skill of the surgeon. The lower abdominal access and retroperitoneal approach are commonly utilised in urology which makes it easy to include a radical retropubic prostatectomy in teaching programs. While control of haemorrhage at the level of the plexus of Santorini can be achieved with relative ease in proper recognition of the anatomy, the dissection and preservation of the neurovascular bundles may go hand in hand with some blood loss, the results depend on the surgeon's skills, but also on the previous state of sexual function, age and the clinical/pathological stage. Intra- en postoperative complications include blood loss, rectal injury and postoperative stricture of the area of the anastomosis between the bladder neck and urethra. Obviously, a pelvic lymph node dissection can be easily added to this approach. Radical retropubic prostatectomy in the hands of a skilled surgeon is an elegant operation with a high likelihood of complete removal of locally confined cancer

(undetectable PSA in 68 of 955 cases) [39], as well as a high rate of preservation of continence (39% dry, 98% dry or minimal loss of urine) and of sexual function (86% at 18 months) described recently by Walsh [40]. Unfortunately, there is evidence that the results achieved in centres of excellence cannot be reached in the urological community as a whole. A recent survey of medicare patients treated by radical prostatectomy between 1988 and 1990 revealed considerably higher percentages of incontinence, erectile failure and anastomotic strictures in 20% of cases [41]. A recent retrospective evaluation of large institutional series [42] and a prospective quality of life evaluation after radical prostatectomy and radiotherapy of screen-detected and clinical routine cases, clearly do not match the results obtained by the centres of excellence.

Total perineal prostatectomy

The perineal approach also requires expertise and surgical skill. The approach is not commonly used in urological practice. If a lymph node dissection is desired, this will either have to be done in a separate procedure or the patients will have to be repositioned for a total perineal prostatectomy. Total perineal prostatectomy requires a extreme lithotomy position with the perineum parallel to the floor of the operating room. Cooperation between anaesthetists is difficult to achieve in settings where a large number of anaesthetists work with the urological surgeons. Total perineal prostatectomy utilises a different plane of dissection staying within a sheet of the pelvic fascia, which is removed at the time of radical retropubic prostatectomy. This, on the one hand, may lead to less blood loss because the plexus of Santorini does not have to be transected, on the other hand, it has been stated that positive margins of resection are more frequently encountered with this procedure than with radical retropubic prostatectomy [43]. This finding is disputed by others [44]. While rates of continence may be similar to radical prostatectomy, preservation of potency after total perineal prostatectomy is less well documented, but considered to be feasible. Probably the rate of rectal injury is slightly higher with the perineal approach. Anastomotic strictures may be less frequent and postoperative recovery is fast and usually uneventful.

Laparascopic radical prostatectomy

The international experience is limited. Results obtained in individual centres, however, are promising. Preservation of continence seems to be superb. Postoperative recovery is fast and blood loss is reported to be minimal. Long-term results with respect to cancer control are not yet available, the same is true for results relating to maintenance of sexual function [38].

Cancer control

It is very unfortunate that valid randomised trials comparing radical prostatectomy to watchful waiting or even comparing radical prostatectomy to radiotherapy are not available. Historical comparisons of institutional series must be considered of very little value in a disease in which very important prognostic factors have been identified. Of the 3 most important prognostic factors, T category, grade of differentiation and PSA only the latter can be identified with acceptable accuracy. Unrecognised prognostic factors may be present, co-morbidity and intercurrent deaths have a strong impact on commonly used cancer-related endpoints such as survival free of disease and disease-specific survival. Many attempts of historical comparisons of outcome with watchful waiting, radical prostatectomy and radiotherapy have been undertaken. A more recent attempt shows an advantage of radical prostatectomy and external beam radiotherapy above the use of high-dose brachytherapy by the use of palladium-103 seeds. In spite of the use of previously validated risk groups utilising the best possible pretreatment information, the data have to be looked at with great caution and do not match the level of certainty that can be achieved by properly conducted randomised clinical trials [45].

Survival and disease-specific survival oriented outcome data after radical prostatectomy and other potentially curative forms of treatment of locally confined prostate cancer have to take into consideration the natural history of cases that can be matched on the basis of pretreatment evaluation and the resulting prognostic factors. It is for this reason that much attention is given in this chapter to recent developments in epidemiology and to the natural history of locally confined disease. The problem around potentially curative management of prostate cancer, as it presents itself today, has been elegantly phrased by Whitmore in 1988 [46] in 4 questions.

- Is cure necessary?
- Is cure possible?
- Is cure necessary in those in whom it is possible?
- Is cure possible in those in whom it is necessary?

Hopefully these questions will be answered, at least in part, by the two ongoing randomised trials in Scandinavia and in the United States or by the European and American randomised studies of

screening for prostate cancer. In the meantime, the natural history of the host (age and co-morbidity) as well as favourable prognostic factors at the time of diagnosis (low PSA, no palpable tumour, a single positive biopsy with a Gleason grade of <6) may be reason enough with considerations of quality of life put into the equation to consider watchful waiting, at least for some time. Considering natural history data for this or similar groups of men [21–23] it is evident that little can be gained by aggressive management of tumours with favourable prognostic factors in elderly men. Even in those who escape radical prostatectomy, recent evidence shows a median time to metastatic progression of 8 years in approximately one-third of these cases over a period of 7 years [47]. Unfortunately, uncertainties about the identification of prognostic factors prior to treatment and uncertainty about the surrogate value of these prognostic factors in the individual patient add doubt to decision making. Catalona et al. and several other authors have shown poor correlation between cT categories and pT categories. Stage pT3 or higher in their series was found in 40%, 20% and 60–76% in clinical T1c, T2a and T2b tumours, respectively [26]. Several other authors have confirmed similar degrees of underestimation of the grade of malignancy between biopsy and radical prostatectomy specimens [48,25]. Narain et al. [25] have compared disease-free survival by biopsy and radical prostatectomy grading. They found that a biopsy grade of less than 7 was associated with a poorer disease-free survival if compared with a similar specimen score, a specimen Gleason score of >7 was related to a poorer disease-free survival at 5 years as compared with the biopsy score of >7 ($P < 0.001$). No difference was seen if biopsy and specimen scores were both found to be Gleason 7. It is impossible at this time, also with the use of Partin's tables to establish conclusively candidates for watchful waiting. Confidence intervals are wide and the resulting uncertainties are difficult to accept for patients and treating physicians.

In the absence of valid randomised trials comparing either radical prostatectomy or radiotherapy to surveillance, the strongest argument for the effectiveness of radical prostatectomy would be a demonstration of 'cure' in cases with moderately differentiated or, preferably, in cases with poorly differentiated disease. In other words, a demonstration that 'cure is possible in those for whom it is necessary'. There is evidence that prostate cancer that is clinically judged as having extended beyond the confines of the prostate (T3 disease) is eligible for cure. In one series, most of the cases that were disease-free at 44 months were in a group of men who were overstaged by rectal examination [48]. In the large series reported from the Mayo Clinic, the results are more favourable, but are influenced by the fact that 54% of the eligible 232 patients with stage C disease received adjuvant endocrine treatment [49]. In considering grade, the data presented by Jewett et al. [50] have governed the views of clinicians for many years. In this series of 103 patients all followed for 15 years or longer, no single patient with poorly differentiated disease survived 15 years without recurrence. More recently, information has become available that necessitates a revision of this view.

Several institutional series have shown by using disease-free survival as an endpoint that poorly differentiated cancers can be eradicated in a significant proportion of cases. Fig. 4 gives an example [16]. Similar data have been reported from Hopkins [51].

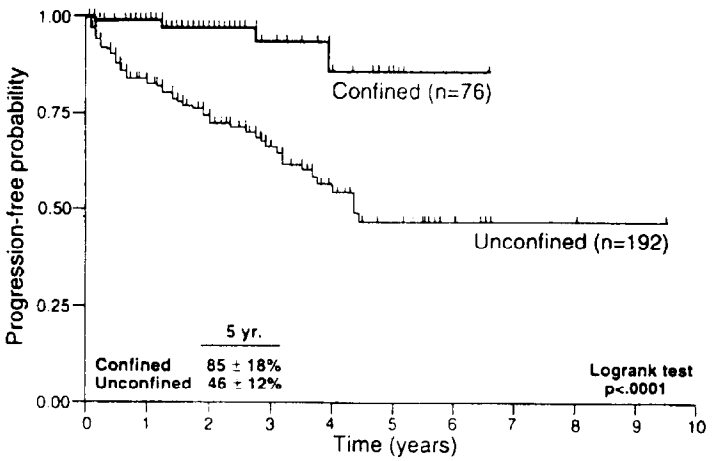


Fig. 4. Actuarial probability of freedom from progression for patients with poorly differentiated cancer (Gleason score 7 or more) in a radical prostatectomy specimen [56].

Table 1
Localized PC: population-based study of 10 year survival

- 59 876 men aged 50–79 years diagnosed in 1983–1993 in 9 SEER regions
- Average f.u. 44.5 months

Treatment

radical prostatectomy (RP)	$n = 24\,257$
radiotherapy (RT)	$n = 15\,721$
watchful waiting (WW)	$n = 19\,898$

- Evaluation of disease-specific, overall and relative survival by grade 1-3

Lu Yao et al., 1997 [52].
f.u., follow-up.

Table 2
10 year survival in locally confined G3 PC ($n = 9965$, 16.6%)

	RP (%)	RT (%)	WW (%)
Life expectancy (age-matched)	62	52	47
PC-specific [a]	67	53	45
PC-specific [b]	76	52	43
Overall	54	33	17
Relative	87	63	36

[a] intention to treat.
[b] treatment received.
Lu Yao et al., 1997 [52].
RP, radical prostatectomy; RT, radiotherapy; WN, watchful waiting; G3PC, grade 3 prostate cancer.

Maybe the strongest evidence is derived from the SEER database. Almost 60 000 patients (Table 1), either treated by surveillance, radical prostatectomy or external beam radiotherapy are compared with respect to disease-specific, overall and relative survival. Table 2 depicts the data reported in [52] with respect to 9965 cases with grade 3 disease. In this study, because of the non-randomised character of the comparison, quantitative statistics are not applied. It is, however, remarkable and in line with natural history-based expectations that the results obtained for grade 1 disease are virtually identical for all 17 723 patients included. Ten year disease-specific survival amounts to 94%, 90% and 93% in the intention to treat analysis for radical prostatectomy, radiotherapy and surveillance, respectively. Small differences are seen for grade 2 disease, large differences in disease-specific and overall survival, however, occur with respect to poorly differentiated cancers. Similar comparisons can be made and similar results can be obtained in comparing the data of the pooled analysis of natural history reports with a pooled analysis of results of radical prostatectomy from several institutions [53]. A review of the issue has recently been given by Scardino et al. [54].

Summary

In summary, there is increasing and convincing evidence that radical prostatectomy is effective in locally confined, poorly differentiated prostate cancer. Diagnostic efforts, therefore, should be targeted toward this disease and probably also, based on the natural history evidence, toward moderately differentiated disease, mainly Gleason score 7. It is unclear, at present, how this can be achieved. Further improvement of our diagnostic capabilities is urgently needed. Hopefully ongoing randomised studies comparing radical prostatectomy to surveillance and studies comparing radical prostatectomy to radiotherapy are urgently desired. The randomised screening studies, which are ongoing, will provide important information with respect to the effect of treatment. If prostate cancer mortality in those men who are randomised to screening turns out to be better than in those randomised to control, this will also be an indication of the effectiveness of treatment. Also, the screening studies and associated natural history studies based on serum repositories and follow-up in non-screened patients will provide important information with respect to the natural history of prostate cancer in relation to PSA and changes of PSA over time.

Finally, quality of life with and without treatment will have to be evaluated, in a prospective manner, in multicentre settings according to validated criteria such as those presented by Litwin [55,42]. The outcomes of such studies will have to be added as utilities to data relating to traditional endpoints such as cancer-specific and overall survival.

In the meantime, clinical practice will be determined by the fact that the only way to cure prostate cancer is early diagnosis and aggressive management. Encouragement comes from the increasing volume of evidence showing that poorly differentiated disease can be eradicated as long as it is locally confined.

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