Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer
Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer

A report of the Australian Cancer Network Working Party on Management of Localised Prostate Cancer

Endorsed October 2002
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This document is a general guide to appropriate practice, to be followed only subject to the clinician’s judgement in each individual case.

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FOREWORD

This publication provides evidence-based information and recommendations for the management of localised prostate cancer.

Through the generosity of the American Urological Association Inc (AUA), this project has progressed the American Urological report1 The Management of Clinically Localised Prostate Cancer (1995) by a systematic review of the literature until 31 August 1998.

The following report embraces the final recommendations of the multidisciplinary Working Party, which worked within the parameters of Guidelines for the Development and Implementation of Clinical Practice Guidelines (1995)2. No evidence was found from recent literature to warrant substantive changes to the AUA Guidelines. It is the opinion of the Working Party that the AUA Guidelines continue, with some emendations, to provide the best available evidence and that the recommendations be utilised for the management of localised prostate cancer in Australia.

It is important to note, however, that the recommendations in this document do not in any way attempt to address issues associated with screening by digital rectal examination and serum prostatic specific androgen measurement. These have been addressed by the AHTAC document on screening3. The recommendations presented here relate to management following the histological diagnosis of prostate cancer.

The draft recommendations were subjected to robust review and community consultation which has resulted in changes which have undoubtedly improved the document. However, the down-side has been that a considerable period has elapsed since the end of the detailed literature review. An appendix has been included to bring to the attention of the readers of this document some of the areas where potentially important new information has been published during the period of the consultation (Refer Appendix 7); for example, a recently published article by Holmberg et al4. However, none of these articles appear to provide new information of such import that the recommendations should be substantially changed. These will be areas that will require examination in more detail when the recommendations are subjected to their first review.

References


3. AHTAC Prostate Cancer Screening. Australian Health Technology Advisory Committee 1996.


Professor Villis Marshall
Chairman, Working Party
The Management of Localised Prostate Cancer
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The Australian Cancer Network acknowledges:

• The generosity of the American Urological Association, Inc. (AUA) for allowing the Australian Cancer Network (ACN) and its Management of Localised Prostate Cancer Working Party to use the American Urological Association’s ‘Report on the Management of Clinically Localised Prostate Cancer’ as a basis for developing this document. This generosity has been greatly appreciated by all concerned.

• Michael Batterham, who carried out much of the literature searching for this report; his helpfulness and diligence are greatly appreciated. Thanks also to Fiona Thomas for her help in word processing and report preparation, and thanks to Anne Magarey for her help with literature searching and photocopying, and the Australian Cancer Network Working Party on the Management of Localised Prostate Cancer for their helpful input on earlier drafts.

• The patience, skill and cooperation of Dr David Weller and Dr Jennifer Doust of the Cochrane Collaboration, Flinders University of South Australia, who were members of the Working Party and were integral in finalising this evidence-based review.

• Dr Carole Pinnock, for her unfailing support and effort in assisting in the review of the document at every step of its development.

• The NHS R&D National Coordinating Centre for Health Technology Assessment (UK), based at the University of Southampton, which kindly provided us with copies of reports.
EXECUTIVE SUMMARY

The purpose of this document is to update the literature on the management of localised prostate cancer. It will serve as a background document for the Australian Cancer Network’s Working Party on Management of Localised Prostate Cancer, which was formed to agree upon guidelines for management of localised prostate cancer in Australia. The document is prepared for health care providers and also to provide baseline information for a consumer document.

The aim was to agree upon these recommendations by early 1999. The Committee considered two recent documents in some depth: the AHTAC Report on Prostate Cancer Screening (1996), which included material on management of prostate cancer, and the American Urological Association Guidelines on Management of Localised Prostate Cancer (Middleton RG et al, 1995). This latter document was considered by the Committee to be of a very high standing, and the proposal was raised for the Working Party to adopt the guidelines and recommendations in the American Urological Association (AUA) document. Before doing so, however, the Committee required an update of more recent literature (1995 to the present) to review research evidence on the various management approaches to prostate cancer, and to see whether this might impact on the recommendations in the AUA document.

This report focuses, therefore on recent literature on prostate cancer management (while also summarising some earlier literature). This report has examined the AUA guidelines in some detail, and finds no evidence from recent literature that warrants substantive changes to these guidelines.

Key findings:

Prostate cancer—background information

1. The incidence of prostate cancer in Australia has risen since the early 1990s. Disease trends in Australia mirror the US disease trends, possible reasons follow:
   - increased detection of early-stage disease
   - a fall-off in late-stage disease
   - consistent improvements in relative survival for localised and regional stage cancers, and
   - an apparent recent decline in mortality from prostate cancer.
The exact role of prostate cancer detection and treatment strategies in the face of these changing disease trends is yet to be determined.

2. In conjunction with developments in treatment for prostate cancer, there has been considerable research interest in developing a greater understanding of the epidemiology of prostate cancer. Apart from family history, evidence linking prostate cancer with specific risk and protective factors is inconsistent. The role of dietary components such as phyto-oestrogens has attracted particular interest and, while evidence is currently insufficient, may offer the prospect of primary prevention in the future.

3. In order to assist in decisions over treatment, attempts have been made to identify improved markers, which can reliably assess prognosis. Some newer markers show promise; molecular and/or cellular markers for metastatic ability of prostate cancer cells are attracting worldwide research interest. In the meantime, the most accepted approach in assessing prognosis is to review all clinical, imaging and histopathological findings.

Treatments for localised prostate cancer—methodological issues

4. The relative morbidities of various treatment alternatives must always be kept in mind when doctors and patients negotiate treatment decisions for prostate cancer. The next few years should see better information available on the likelihood of individual tumour progression, and it is hoped that randomised control trials will provide definitive evidence on the benefits and harms of the various treatment options for prostate cancer. (Refer chapter 2.)

5. Information on treatments included in this report mostly comes from small cohorts at specialised academic centres. Interpretation of these non-randomised studies requires caution, as outcomes such as survival and complication rates will be influenced by selection procedures of patients into the studies. Also information on grade and stage are often unreliable or unavailable.

6. Patient preference is an important factor in treatment decisions, as the values people place on quality versus quantity of life, their acceptance of risk and fear of complications will influence the acceptability of the various treatment options.
7. Randomised controlled trials are widely advocated to compare various management approaches for prostate cancer. However, recruitment to these trials has been difficult, at best it will be 10 years before results are available. Information from modelling exercises provides some insights into the relative efficacy of treatment options, and although it relies on a number of assumptions and is highly sensitive to patient preferences. (Refer chapter 2)

8. Based on current evidence it is not possible to say with certainty that there is a survival advantage for any of the various management approaches when they are used in similarly-selected patients. To date, the various management approaches have not been adequately compared. (Refer chapter 2)

Radical prostatectomy

9. The two main surgical approaches to radical prostatectomy are retro-pubic and perineal. The advent of laparoscopic pelvic lymph node dissection (PLND) and questioning of the need to always undertake PLND, has led to an increase in use of the perineal approach. Nerve-sparing techniques have seen a reduction in complications in recent years.

10. Published reports of radical prostatectomy have greater patient numbers and years of follow-up than other treatment modalities. When examining survival following radical prostatectomy (and other treatments), it is difficult to separate out the effects of treatment efficacy and selection bias.

External beam radiotherapy

11. Radical radiotherapy is an appropriate treatment for localised prostate cancer. It is generally recommended for patients with no significant risk factors for radiation toxicity and who have a preference for radiotherapy. Men who receive radiotherapy are slightly older than patients undertaking prostatectomy.

Brachytherapy [the insertion of radioactive seeds into the prostate, each of which contains a calculated dose of radioactive isotope, commonly I 125]

12. Brachytherapy is not widely practised in Australia, although its use is growing. Published reports to the time of review of brachytherapy do not, however, provide substantive evidence of any advantage over other
treatments. The studies of this method have the lowest patient numbers and length of follow-up of all of the treatment modalities examined. Potential advantages include its single-session, outpatient nature and high patient acceptance.

No active treatment

13. This approach implies that active therapy is not undertaken at the time of diagnosis of prostate cancer but, rather, symptoms and/or progression of the disease are managed if and when they arise. It is sometimes referred to as 'watchful waiting'. In some cases, patients and doctors opt for a period of no active treatment followed by active intervention. Long-term follow-up of cohorts of patients undergoing no active treatment have been conducted, particularly in Scandinavian countries, with results suggesting comparable outcomes to active treatments. The interpretation of these results is, however, controversial.

Other management approaches

14. Combinations of treatments are also widely used in the treatment of localised prostate cancer. These include other combinations of surgery, hormone treatment, radiotherapy and other treatments, such as hyperthermia and cryotherapy.

This project has progressed the American Urological publication 'The Management of Localised Prostate Cancer', 1995 by critical review of the literature until 31 August 1998.

The multidisciplinary Working Party of the ACN worked within the parameters of 'Guidelines for the Development and Implementation of Clinical Practice Guidelines' 1995. In making final recommendations, the ACN Working Party found no evidence from recent literature to warrant substantive changes to the AUA Guidelines.

Recommendations have been made that reflect the recent literature including pertinent parts of the AHTAC Report on Prostate Cancer Screening (1996).
TREATMENT RECOMMENDATIONS (OPTIONS)—SUMMARY

Options for the management of localised prostate cancer include radical prostatectomy, radiotherapy and no treatment. Radiotherapy includes external beam and interstitial radiotherapy (brachytherapy) treatments.

The panel at this time considers these interventions to be options for the treatment of localised prostate cancer because the data currently available in the literature does not provide sufficient clear cut evidence to indicate the unquestioned superiority of any one form of treatment.

Radical prostatectomy

The patient most likely to benefit from radical prostatectomy is one with a relatively long life expectancy (> 10 years), who has no significant surgical risk factors, low volume low PSA and who, after being informed of the risks and benefits, prefers surgery.

Radiotherapy

The patient most likely to benefit from external beam radiotherapy is one with a relatively long life expectancy (> 10 years), has low volume low PSA, has a moderately differentiated tumour and who, after being informed of the risks and benefits, prefers external beam radiotherapy.

Interstitial radiotherapy (brachytherapy)

The patient most likely to benefit from interstitial radiotherapy is one with low volume low-grade disease with a long life expectancy (>10 years). However, long-term follow up is limited and this needs to be stressed when patients are being informed as to the risks and benefits of this form of treatment.
No initial treatment

The patient most likely to benefit from no initial treatment is one with well to moderately differentiated tumours with low volume disease, low PSA, has a life expectancy less than ten years and who, when fully informed of the risks and benefits of this form of treatment, has a preference for no treatment.

Comment and Key Points

- Crucial to the implementation of any form of treatment is the need to ensure that men are adequately informed regarding the risks and benefits of the possible treatment options. It is recommended that all men considering treatment for localised prostate cancer should at least be provided with written information regarding risks and benefits of the available treatment options.
- Patients need information on treatment to a level of satisfaction that may require a second opinion. This second opinion may be across specialties.
- Australian researchers and cancer organisation should lead the way with a national, coordinated approach to the complex problem of solutions for prostate cancer.
1 METHODS AND BACKGROUND

1.1 Methods for this review

A critical literature review was undertaken for this document. The aim of the review was to determine whether guidelines produced by the American Urological Association required modification. The review provided a resource document for the Working Party. A comprehensive, standardised search protocol was adopted with the aim of identifying as much of the research material relevant to this report as possible. A computerised literature search was undertaken using MEDLINE, EMBASE, and CANCERLIT databases. For the literature search on primary research relating to management of localised prostate cancer, the search terms ‘radical prostatectomy’, ‘radiotherapy’, ‘brachytherapy’, ‘treatment’, ‘watchful waiting’, ‘deferred treatment’, ‘guidelines’, ‘complications’, ‘therapy’, ‘prostate specific antigen’, ‘digital rectal examination’, ‘trans-urethral ultrasound’, and ‘prostate cancer’ were used. Further information was obtained from the Internet and from reference lists of retrieved articles.

Database searches were continued by systematic review until 31 August 1998 for the main body of the report, although some later material was included for sections added in early 1999 on phyto-oestrogens, combined treatments and treatments other than surgery or radiotherapy.

Searching procedures

The medical literature was searched from 1995 to 31 August 1998. The search of the electronic databases resulted in 2488 citations. The abstracts of these citations were scanned and hard copies of 381 papers were made of articles commenting on the issues surrounding the management of prostate cancer. The report includes scientific studies (both randomised and non-randomised trials), editorial reviews, conference proceedings and papers, consensus statements and guidelines developed by medical and other relevant groups, and reports of national health technology assessment and related agencies.

Levels of evidence

As indicated in this report, there were very few level 1, 2 or 3 papers available for the report. This led to a pragmatic decision not to refer to evidence levels continually throughout the report. The majority of the papers included in the report were level 4, that is case series data, and the results of these studies are highly prone to bias. Given the nature of this review (a critical review to support the deliberations of a Working Group), a small number of key papers which were considered by the Group and external reviewers to be highly relevant to the report, and which had been published since the database searches were conducted, were included in the report.
The recent meeting of the International Technology Assessment in Health Care Conference confirmed again that there have been no high quality studies published in this area as yet and that the studies which are presently being conducted are unlikely to report for another 5 to 10 years. The conclusions of the report therefore remain current best evidence.

1.2 Epidemiology of prostate cancer

Summary

- While evidence is accumulating, the epidemiology of prostate cancer is poorly understood, and, with the exception of family history, provides little guidance in identifying those individuals who might best benefit from early detection and treatment of localised prostate cancer.
- There is growing interest in dietary components such as selenium and phyto-oestrogens in the prevention of prostate cancer, although there is insufficient evidence to make firm dietary recommendations.
- Incidence of prostate cancer rose steadily in Australia during the early 1990s but now appears to have peaked.
- In the US a similar peak has been observed (earlier than the Australian peak), accompanied by an apparent recent decline in mortality rates from prostate cancer (see fig 1.2).
- US population data also show increased survival, and reductions in rates of late-stage disease.
- The detection of markers which can identify those localised prostate cancers which are destined to progress and cause morbidity and mortality has been the subject of intense research efforts in recent years; there is, however, no single prognostic parameter that is reliable in assessing prognosis, and the most appropriate approach remains unchanged—to review all clinical, imaging and histopathological findings together.
- The refinement and application of markers (either individual or combined) to predict outcome in prostate cancer remains one of the most important tasks for molecular biologists and epidemiologists.

1.2.1 Risk factors for prostate cancer

While information on risk factors for prostate cancer is accumulating rapidly, there remains a high level of uncertainty over the epidemiology of prostate cancer. Unlike other cancers such as bowel and breast there is a lack of strong epidemiological associations with identifiable risk factors. Hence there is limited capacity to target definite sub-groups in the population for early detection efforts.
Primary risk factors for prostate cancer have been reviewed in the 1996 AHTAC Report on Prostate Cancer Screening (AHTAC, 1996) and the more recent update of this report (Weller et al, 1999). To briefly summarise this material:

**Geographic and racial differences**
- both genetic and exogenous factors are likely to play a role
- incidence varies substantially in countries around the world—although this may be due to differences in case ascertainment in the different countries
- reported age-standardised incidence in Black Americans exceeds that in Japanese men by a factor of around 50 (Garraway & Alexander, 1997)
- the high variability in incidence cannot be explained by genetic factors.

**Diet**
- population studies show high correlations between prostate cancer deaths and total fat consumption (Pienta et al, 1996)
- Giovannucci et al (1993) found, in the Health Professionals Follow-up Study, that intake of animal fat was associated with an increased risk of prostate cancer. Fat from fish, vegetable and dairy sources (except butter) was not found to be related to risk for prostate cancer.

**Genetic and familial factors**
- several studies demonstrate a higher incidence of prostate cancer among the relatives of men with prostate cancer than among the relatives of control groups (Pienta et al, 1996), usually of the order of a two-fold increase in risk for male first-degree relatives (Walsh and Partin, 1997)
- a recent systematic review of the hereditary aspects of prostate cancer concluded that, for first-degree relatives of men with prostate cancer, the relative risk ranges from 1.7 to 8.7; greater numbers of affected family members and early onset among family members are the most significant predictors of risk (McLellan & Norman, 1995).

Carter et al (1993) constructed the following table on family history and risk of prostate cancer:

**Table 1.1 Family history and risk of prostate cancer**

<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>Additional affected relatives</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>60</td>
<td>None</td>
<td>1.5</td>
</tr>
<tr>
<td>50</td>
<td>None</td>
<td>2.0</td>
</tr>
<tr>
<td>70</td>
<td>1 or more</td>
<td>4.0</td>
</tr>
<tr>
<td>60</td>
<td>1 or more</td>
<td>5.0</td>
</tr>
<tr>
<td>50</td>
<td>1 or more</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Other factors

Selenium has been observed to have a protective effect for prostate cancer; like many other dietary components, this requires further verification in large, well-controlled trials (Clark et al, 1998).

The role of phyto-oestrogens in prostate cancer has attracted considerable interest in recent years (Adlercreutz & Mazur, 1997; Hempstock et al, 1998). The western diet is relatively deficient in these substances compared with societies where large amounts of plant foods and legumes are eaten. At present there are no definite recommendations about the dietary amounts needed for prevention of disease.

1.2.2 Trends in incidence and mortality

Prostate cancer incidence and mortality are described in detail in the 1996 AHTAC Report and its recent update (Weller et al, 1999). Briefly;

• in Australia prostate cancer incidence has climbed steadily since the early 1990s, although in the last few years the incidence has peaked (South Australian Health Commission Cancer Registry, 1998)

• on an age-standardised basis the mortality rate from prostate cancer between 1976 and 1993 increased slowly. From 1993 the rate has declined to 1999 (refer Table 1.2 and Fig 1.3)

• data from Surveillance Epidemiology and End Result Program (SEER), a major national Cancer Registry in the US (National Cancer Institute, 1998) show a pattern of prostate cancer incidence which is similar to Australia, although the peak in incidence occurred earlier

• black men have about a 60% higher incidence than white men

Trends in the SEER mortality data have prompted debate over the possible role of early detection and treatment efforts in the declining rates.

Figure 1.1 shows that incidence modestly increased from 1973-1986, rapidly increased from 1987-1992, and declined from 1993-1995. Figure 1.2 shows the recent decline in mortality rates.

Australian data on prostate cancer mortality trends are shown in Table 1.2 and Figure 1.3. They show similar trends to the US data (ABS 1999).
Evidence-based information and recommendations for the management of localised prostate cancer

Figure 1.1 — Incidence of prostate cancer, 1973–1995, SEER data

Figure 1.2 — Mortality rates from prostate cancer, 1973–1995, SEER data

Note: Rates are age-adjusted to the 1970 US standard. Rates from 1973–1987 are based on data from the 9 standard registries. Data from San Jose and Los Angeles are included in the rate calculations for 1988–1995.
Table 1.2  Annual age-standardised* mortality from prostate cancer in Australia, 1976 to 1997 (* Standardised to Australian 1991 population)

<table>
<thead>
<tr>
<th>Year</th>
<th>Age-standardised rate</th>
<th>Year</th>
<th>Age-standardised rate</th>
</tr>
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<tbody>
<tr>
<td>1976</td>
<td>26.75</td>
<td>1987</td>
<td>29.46</td>
</tr>
<tr>
<td>1977</td>
<td>27.56</td>
<td>1988</td>
<td>30.59</td>
</tr>
<tr>
<td>1978</td>
<td>26.82</td>
<td>1989</td>
<td>31.69</td>
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<td>1979</td>
<td>26.87</td>
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<td>1985</td>
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<td>1996</td>
<td>33.14</td>
</tr>
<tr>
<td>1986</td>
<td>28.74</td>
<td>1997</td>
<td>29.27</td>
</tr>
</tbody>
</table>

Source: Australian Institute of Health & Welfare, raw data, Mortality tabulations, Deaths by State of Usual Residence by Cause by Sex by Age Group

Figure 1.3—Annual age-standardised mortality rates of prostate cancer in Australia
1.2.3 Trends in tumour characteristics

There has been a change in the characteristics of tumours identified in US cancer registries, and this may reflect changing treatment patterns (although changes in staging process may also contribute to this trend)—analysis of the SEER database shows an increase in local disease, and a decline in disease with distant metastases at diagnosis (Smart, 1997; Brawley, 1997). An illustration of the influence of trends in treatment on the prevalence of various tumour stages in the population is the decline in the usage of surgical treatments for lower urinary tract symptoms in the US. This has led to a decline in the detection of T1a-b cancer (cancer that is discovered unexpectedly or incidentally in 5% or less of surgically removed prostatic tissue) (Fowler et al, 1997).

1.2.4 Trends in survival

In common with other measures, survival after a diagnosis of prostate cancer has been influenced by changing patterns of detection and treatment of the disease. In general the trend has been toward longer survival. Data from New South Wales indicate that survival increased between 1973–77 and 1988–94, for each degree of spread of the disease (see Table 1.3). Clearly, degree of spread is an important predictor of survival.

Table 1.3 Five year relative survival (%) for prostate cancer by period of diagnosis and spread of disease at diagnosis in NSW, 1973–1994

<table>
<thead>
<tr>
<th>Period</th>
<th>Localised</th>
<th>Regional</th>
<th>Distant</th>
<th>Unknown</th>
<th>Total</th>
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<tbody>
<tr>
<td>1973–77 5 year survival</td>
<td>72.2</td>
<td>39.1</td>
<td>8.0</td>
<td>62.5</td>
<td>52.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>70.2–74.3</td>
<td>34.8–43.3</td>
<td>6.5–9.4</td>
<td>60.0–65.0</td>
<td>50.0–54.3</td>
</tr>
<tr>
<td>1978–82 5 year survival</td>
<td>78.3</td>
<td>49.4</td>
<td>15.0</td>
<td>70.3</td>
<td>59.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>76.7–80.0</td>
<td>45.4–53.5</td>
<td>13.1–16.9</td>
<td>68.1–72.5</td>
<td>57.7–61.6</td>
</tr>
<tr>
<td>1983–87 5 year survival</td>
<td>78.7</td>
<td>50.1</td>
<td>15.6</td>
<td>70.8</td>
<td>63.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>77.2–80.2</td>
<td>46.2–54.0</td>
<td>13.8–17.4</td>
<td>68.8–72.8</td>
<td>61.6–64.9</td>
</tr>
<tr>
<td>1988–94 5 year survival</td>
<td>84.8</td>
<td>62.1</td>
<td>27.7</td>
<td>78.8</td>
<td>78.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>83.8–85.7</td>
<td>59.0–65.2</td>
<td>25.5–29.9</td>
<td>77.5–80.1</td>
<td>77.6–79.7</td>
</tr>
<tr>
<td>Total 5 year survival</td>
<td>81.9</td>
<td>55.9</td>
<td>17.2</td>
<td>74.9</td>
<td>69.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>80.8–82.9</td>
<td>52.5–59.2</td>
<td>15.9–18.5</td>
<td>73.5–76.3</td>
<td>68.4–70.1</td>
</tr>
</tbody>
</table>

Tables 1.2 and 1.3 are included as they provide useful survival data. Table 1.3 presents five (5) year survival after diagnosis and this has improved over the period of the review. In Table 1.2 mortality for a given year is recorded. The two sets of data are not mutually incompatible, as they relate to the number of men diagnosed with prostate cancer and it should be acknowledged that there will be a lead time bias between the data sets.
US data on survival by both grade and stage, from the SEER database (National Cancer Institute, 1998) is shown in Figure 1.4. The data show high five year survival rates (93% overall), and the trend towards increased survival over the previous two decades. While relative survival has increased over time for all grades of cancer, five-year relative survival for advanced disease is 34% and has not improved over time. Survival data analysed by stage do, however, need to be interpreted with caution, due to inadequacies and inconsistencies in staging systems.
1.3 Natural history of prostate cancer

Knowledge of the natural history of prostate cancer is limited, due largely to the organ’s inaccessibility for testing, and this has important implications for the treatment of localised prostate cancer. However, improved diagnostic opportunities in recent years offer new knowledge of the occurrence and development of the disease.

1.3.1 Development of prostate cancer

Studies documenting the natural history of early-stage prostate cancer and characterising its biological potential through the use of serum and tissue markers can provide valuable information for patients and clinicians. Consistently these studies show that prostate cancer is very heterogeneous. The risk of morbidity and mortality from early-stage prostate cancer has been difficult to quantify because of the relatively slow growth rate and long doubling times, averaging 2 to 4 years (Schmid et al, 1993). Histologic evidence of prostate cancer can be found in 30–40% of men aged > 50 years, but only one in four of these cancers will become clinically evident and one in 14 will prove lethal (Abbas & Scardino, 1997).

Often the first detectable change is the development of PIN (prostate intraepithelial neoplasia), simultaneously at different sites in the prostate. Most of these growths stop or recede. The next stage is low-grade changes corresponding to adenocarcinoma, either from existing PIN or from direct transformation of normal epithelium. These very early changes have no known cause, and are equally common in all men. Further development is, however, driven by unknown, partially environmental factors which vary between populations. The difficulty in diagnosing prostate cancer at an early stage is being able to identify the majority of the tumours that are not life threatening, where treatment has no potential to provide benefit to the patient. While histological, molecular, morphological and other markers exist, it is still frequently not possible to predict whether a cancer is destined to spread.

1.3.2 Identification of prognostic markers for prostate cancer

One of the main reasons for developing an improved understanding of the natural history of prostate cancer is to examine which features of the cancer may serve as useful prognostic indicators. The development of reliable prognostic markers to separate individuals with potentially fatal disease from those who will not die from prostate cancer is crucial in developing management strategies for prostate cancer. Without such markers, it is not possible to identify an early stage of prostate cancer for which it could be assumed with a reasonable degree of certainty that the tumour will progress. The means of detection of prostate cancer (eg through screening or clinical presentation) appears to profoundly influence prognosis—tumours identified through transurethral prostatectomy have different prognoses than those identified by Digital Rectal Exam (DRE) or Prostate Specific Antigen (PSA) screening (Soh et al 1997), and it is important to explore potential differences in outcome which may be directly attributable to these differences.
The ability to stage prostate cancer accurately is of vital importance in determining prognosis, and forms the basis on which initial management of patients is decided. For example, extracapsular penetration profoundly affects prognosis and choice of treatment. Strategies for determining tumour characteristics are mainly directed towards diagnosis and clinical staging, and tumour differentiation. Pre-treatment strategies include Digital Rectal Exam (DRE), Transrectal Ultrasound (TRUS), Prostate Specific Antigen (PSA) assay, biopsy and, for further assessment of clinical stage, CT scan, Magnetic Resonance Imaging (MRI), and radionuclide bone scans.

**PSA levels**

PSA levels prior to treatment have been shown to be as important, if not more so, than stage and grade of the tumour. Stages T1 to T2 cancer patients with an initial PSA level of greater than 15 ng/ml fare as poorly as men with stages T3 to T4 disease overall and worse than those with stages T3 to T4 cancer and initial PSA values of less than 15 ng/ml (Zietman, 1994). Few studies reporting survival of patients post-radiotherapy or radical prostatectomy provide data on initial PSA values, but there is substantial potential for bias to occur by the inclusion of different proportions of patients with low versus high initial PSA levels.

Carter et al (1997a), in their historical prospective study of serial PSA measurements at 2- and 4-year intervals from frozen serum samples (see Section 4.2) found:

- if the PSA level was less than or equal to 4.0 ng/ml, nonpalpable prostate cancers were highly likely (34/36, 94%) to be ‘curable’ (that is, organ-confined and with no capsular penetration with Gleason score < 7 and negative margins)
- if pre-treatment PSA level was greater than 4.0 ng/ml and less than or equal to 5.0 ng/ml, cancers were highly likely to be ‘curable’ (32/36, 89%), and a minority were small cancers (12/36, 33%)
- if pretreatment PSA level was greater than 5.0 ng/ml, 96 (30%) of 317 cancers were not amenable to complete surgical removal.

There are some important issues in the measurement of PSA levels. Variation in PSA measurements between laboratories is widely recognised, and there are efforts to achieve international standardisation of PSA assays (Stamey et al, 1998). There are other possible influences on PSA levels, including prostatitis, urinary tract infection, history of trans-urethral resection (TURP), presence of benign prostatic hyperplasia (BPH) and recent prostate biopsy, but there is uncertainty over the degree to which they exert an effect. It is, therefore, most important for the clinician and patient to discuss the clinical relevance of PSA levels.

**Histological grade**

At present it remains difficult to predict which subtypes of cancers will progress; the diagnostic methods currently available cannot individually substage patients with subtypes of prostate cancer as to those requiring no therapy, those requiring local therapy and those requiring local plus systemic therapy. Information on
Evidence-based information and recommendations for the management of localised prostate cancer

Albertsen et al (1998) estimated survival based on a competing risk analysis stratified by age at diagnosis and histologic findings for men diagnosed as having clinically localised prostate cancer and who were managed conservatively. The study found that men with tumours that had Gleason scores (see Glossary, p130) of 2 to 4, 5, 6, 7, and 8 to 10 face a 4% to 7%, 6% to 11%, 18% to 30%, 42% to 70%, and 60% to 87% chance, respectively, of dying from prostate cancer within 15 years of diagnosis depending on their age at diagnosis. The authors concluded that men whose prostate biopsy specimens showed Gleason score 2 to 4 disease faced a minimal risk of death from prostate cancer within 15 years of diagnosis. Conversely, men whose biopsy specimens showed Gleason score 7 to 10 disease faced a high risk of death from prostate cancer when treated conservatively, even when cancer was diagnosed as late as age 74 years. Men with Gleason score 5 or 6 tumours faced a modest risk of death from prostate cancer that increased slowly over at least 15 years of follow-up.

Chodak et al’s analysis (1994) has been reported in the 1996 AHTAC Report, and remains a useful pooled summary on the predictive capacity of histological grade.
Figure 1.5—Survival in relation to age and to Gleason score

Survival (white lower band) and cumulative mortality from prostate cancer (dark grey upper band) and other causes (light grey middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale.

This table is from Albertsen (1998). With permission of JAMA.
Key findings:

- In this analysis, patients with poorly differentiated disease had a significantly lower rate of prostate cancer-specific survival than those with either well- or moderately-differentiated disease (p <.001 in both analyses).
- It is not known whether well-differentiated (low Gleason score) disease progresses invariably to advanced, poorly differentiated (high Gleason score).
- There are, furthermore, difficulties in recording of histologic grade—grades using biopsy specimens may differ from those obtained from the entire surgical specimen from the same patient (because prostate cancers demonstrate a wide spectrum of histologic patterns within individual tumours).

While data from studies on the natural history of prostate cancer suggests that histological grade is important, it is not consistent between studies, and hypotheses regarding rates of progression for early, low-grade prostate cancer versus high-grade disease differ widely. The Gleason grading system is predictive for tumours with either very low (eg <5) or very high (eg 8-10) Gleason scores, but it is of limited value for tumours with intermediate scores (eg 5-7). This is important, as most tumours fall in this intermediate range.

Partin et al (1997) used a combination of PSA, clinical stage and Gleason score to predict pathological stage of localised prostate cancer, and developed nomograms (tables 1.6–1.9), which clinicians can use when counselling individual patients about the probability of their tumour being a specific pathological stage.

The validation bootstrap samples indicate the predictive performance of organ confined disease nomograms and positive lymph node samples in prostate cancer. (Tables 1.10 and 1.11)

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Description</th>
<th>Subject, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Nonpalpable, with ≤5% of tissue with cancer, low grade</td>
<td>74 (1)</td>
</tr>
</tbody>
</table>
T1b  Nonpalpable, with >5% fo tissue with cancer and/or high grade  149 (3)
T1c  Nonpalpable, but prostate-specific antigen elevated  1358 (33)
T2a  Palpable, half of 1 lobe or less  1186 (29)
T2b  Palpable, more than half of 1 lobe, not both lobes  852 (21)
T2c  Palpable, involves both lobes  398 (10)
T3a  Palpable, unilateral capsular penetration  116 (3)

**TOTAL**  4133 (100)


**Table 1.7.1** Distribution by pathological stage

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>Subjects, No. (%)</th>
<th>Organ-confined Disease, No. (%)</th>
<th>Capsular Penetration, No. (%)</th>
<th>Positive seminal Vesicle involvement, No. (%)</th>
<th>Positive lymph Node involvement, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>74 (1)</td>
<td>59 (80)</td>
<td>13 (18)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>T1b</td>
<td>149 (3)</td>
<td>86 (58)</td>
<td>51 (34)</td>
<td>5 (3)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>T1c</td>
<td>1358 (33)</td>
<td>825 (61)</td>
<td>436 (32)</td>
<td>61 (4)</td>
<td>36 (3)</td>
</tr>
<tr>
<td>T2a</td>
<td>1186 (29)</td>
<td>565 (48)</td>
<td>517 (43)</td>
<td>68 (6)</td>
<td>36 (3)</td>
</tr>
<tr>
<td>T2b</td>
<td>852 (21)</td>
<td>274 (32)</td>
<td>422 (50)</td>
<td>86 (10)</td>
<td>70 (8)</td>
</tr>
<tr>
<td>T2c</td>
<td>398 (10)</td>
<td>133 (33)</td>
<td>171 (43)</td>
<td>55 (14)</td>
<td>39 (10)</td>
</tr>
<tr>
<td>T3a</td>
<td>116 (3)</td>
<td>15 (13)</td>
<td>51 (44)</td>
<td>27 (23)</td>
<td>23 (20)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4133 (100)</strong></td>
<td><strong>1957 (48)</strong></td>
<td><strong>1661 (40)</strong></td>
<td><strong>303 (7)</strong></td>
<td><strong>212 (5)</strong></td>
</tr>
</tbody>
</table>

**Table 1.7.2** Distribution of Gleason score by pathological stage
### Table 1.8 Distribution of serum prostatic specific antigen and pathological stage

<table>
<thead>
<tr>
<th>PSA levels ng/mL</th>
<th>Subjects, No. (%)</th>
<th>Organ-confined Disease, No. (%)</th>
<th>Capsular Penetration, No. (%)</th>
<th>Positive seminal Vesicle involvement, No. (%)</th>
<th>Positive lymph Node involvement, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40</td>
<td>943 (23)</td>
<td>599 (64)</td>
<td>303 (32)</td>
<td>28 (3)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>4.1-10</td>
<td>2006 (48)</td>
<td>1009 (50)</td>
<td>809 (40)</td>
<td>122 (6)</td>
<td>66 (3)</td>
</tr>
<tr>
<td>10.1-20</td>
<td>856 (21)</td>
<td>296 (35)</td>
<td>397 (46)</td>
<td>86 (10)</td>
<td>77 (9)</td>
</tr>
<tr>
<td>20.1-30</td>
<td>194 (5)</td>
<td>35 (18)</td>
<td>102 (53)</td>
<td>33 (17)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>30.1-40</td>
<td>69 (2)</td>
<td>11 (16)</td>
<td>24 (35)</td>
<td>18 (26)</td>
<td>16 (23)</td>
</tr>
<tr>
<td>40.1-50</td>
<td>31 (&lt;1)</td>
<td>4 (13)</td>
<td>15 (48)</td>
<td>5 (16)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>34 (1)</td>
<td>3 (9)</td>
<td>11 (32)</td>
<td>11 (32)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>4133 (100)</td>
<td>1957 (48)</td>
<td>1661 (40)</td>
<td>303 (7)</td>
<td>212 (5)</td>
</tr>
</tbody>
</table>

Table 1.8 continued on the next page
Figure 1.—The probability of organ-confined disease as a function of serum prostate-specific antigen level, preoperative Gleason score, and clinical stage.

Figure 2.—The probability of pelvic lymph node involvement status as a function of serum prostate-specific antigen level, preoperative Gleason score, and clinical stage.
Table 1.9   Factors predicting outcome in organ confined prostate cancer

<table>
<thead>
<tr>
<th>GPA Score</th>
<th>Clinical Stage</th>
<th>PSA, 0.0-4.0 ng/mL</th>
<th>PSA, 0.1-10.0 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Organ-Confined Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>90 (84-95)</td>
<td>90 (72-86)</td>
<td>90 (85-92)</td>
</tr>
<tr>
<td>5</td>
<td>82 (73-90)</td>
<td>82 (75-84)</td>
<td>82 (63-79)</td>
</tr>
<tr>
<td>6</td>
<td>78 (68-88)</td>
<td>78 (74-81)</td>
<td>78 (59-64)</td>
</tr>
<tr>
<td>7</td>
<td>43 (34-53)</td>
<td>43 (41-52)</td>
<td>43 (32-45)</td>
</tr>
<tr>
<td>8-10</td>
<td>31 (20-43)</td>
<td>31 (27-45)</td>
<td>31 (17-32)</td>
</tr>
<tr>
<td></td>
<td>Established Capsular Penetration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>9 (4-15)</td>
<td>9 (13-23)</td>
<td>9 (17-23)</td>
</tr>
<tr>
<td>5</td>
<td>17 (9-26)</td>
<td>17 (15-22)</td>
<td>17 (23-20)</td>
</tr>
<tr>
<td>6</td>
<td>19 (11-29)</td>
<td>19 (18-25)</td>
<td>19 (23-23)</td>
</tr>
<tr>
<td>7</td>
<td>44 (35-54)</td>
<td>44 (29-39)</td>
<td>44 (25-38)</td>
</tr>
<tr>
<td>8-10</td>
<td>43 (32-56)</td>
<td>43 (27-44)</td>
<td>43 (17-35)</td>
</tr>
<tr>
<td></td>
<td>Seminal Vesicle Involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>0 (0-3)</td>
<td>0 (1-3)</td>
<td>0 (1-3)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0-3)</td>
<td>1 (2-3)</td>
<td>1 (2-3)</td>
</tr>
<tr>
<td>6</td>
<td>2 (0-4)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>7</td>
<td>6 (1-13)</td>
<td>6 (4-9)</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td>8-10</td>
<td>11 (2-23)</td>
<td>9 (5-16)</td>
<td>11 (7-19)</td>
</tr>
<tr>
<td></td>
<td>Lymph Node Involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>5</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>6</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>7</td>
<td>6 (2-13)</td>
<td>6 (2-13)</td>
<td>6 (2-13)</td>
</tr>
<tr>
<td>8-10</td>
<td>14 (5-27)</td>
<td>14 (5-27)</td>
<td>14 (5-27)</td>
</tr>
</tbody>
</table>

* Numbers represent percent predictive probability (95% confidence interval). Ellipses indicate lack of sufficient data to calculate probability.

PSA indicates prostate-specific antigen.
### Table 1.10

Predictive performance (Median [95% confidence interval]) of organ-confined disease nomograms in 1000 validation bootstrap samples

<table>
<thead>
<tr>
<th>Probability</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.10</td>
<td>99 (99-100)</td>
<td>7 (6-8)</td>
<td>49 (48-51)</td>
<td>92 (88-96)</td>
</tr>
<tr>
<td>≥0.15</td>
<td>98 (97-99)</td>
<td>16 (14-17)</td>
<td>51 (50-53)</td>
<td>88 (85-91)</td>
</tr>
<tr>
<td>≥0.20</td>
<td>97 (96-98)</td>
<td>19 (16-21)</td>
<td>52 (50-53)</td>
<td>88 (85-91)</td>
</tr>
<tr>
<td>≥0.25</td>
<td>94 (93-95)</td>
<td>30 (28-32)</td>
<td>55 (53-56)</td>
<td>84 (82-87)</td>
</tr>
<tr>
<td>≥0.30</td>
<td>92 (91-94)</td>
<td>34 (32-36)</td>
<td>56 (54-57)</td>
<td>83 (81-86)</td>
</tr>
<tr>
<td>≥0.35</td>
<td>88 (86-89)</td>
<td>42 (40-44)</td>
<td>58 (56-59)</td>
<td>79 (76-81)</td>
</tr>
<tr>
<td>≥0.40</td>
<td>80 (78-81)</td>
<td>54 (51-56)</td>
<td>61 (59-62)</td>
<td>74 (72-77)</td>
</tr>
<tr>
<td>≥0.45</td>
<td>75 (73-77)</td>
<td>59 (56-61)</td>
<td>62 (60-64)</td>
<td>72 (70-74)</td>
</tr>
<tr>
<td>≥0.50</td>
<td>70 (68-72)</td>
<td>64 (62-66)</td>
<td>63 (61-65)</td>
<td>70 (68-72)</td>
</tr>
<tr>
<td>≥0.55</td>
<td>54 (52-57)</td>
<td>70 (67-72)</td>
<td>69 (66-71)</td>
<td>65 (64-67)</td>
</tr>
<tr>
<td>≥0.60</td>
<td>49 (47-51)</td>
<td>81 (78-83)</td>
<td>70 (68-73)</td>
<td>64 (62-66)</td>
</tr>
<tr>
<td>≥0.65</td>
<td>41 (38-43)</td>
<td>86 (84-87)</td>
<td>72 (69-75)</td>
<td>62 (60-63)</td>
</tr>
<tr>
<td>≥0.70</td>
<td>19 (17-21)</td>
<td>96 (95-97)</td>
<td>80 (76-84)</td>
<td>57 (55-58)</td>
</tr>
<tr>
<td>≥0.75</td>
<td>14 (12-15)</td>
<td>98 (97-98)</td>
<td>84 (80-89)</td>
<td>56 (54-57)</td>
</tr>
<tr>
<td>≥0.80</td>
<td>8 (6-9)</td>
<td>99 (99-100)</td>
<td>88 (81-93)</td>
<td>54 (53-55)</td>
</tr>
<tr>
<td>≥0.85</td>
<td>1 (1-2)</td>
<td>100 (100-100)</td>
<td>94 (83-100)</td>
<td>53 (52-54)</td>
</tr>
<tr>
<td>≥0.90</td>
<td>1 (1-1)</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>53 (51-54)</td>
</tr>
</tbody>
</table>

### Table 1.11

Predictive performance (Median [95% confidence interval]) of positive lymph node involvement nomograms in 1000 validation bootstrap samples

<table>
<thead>
<tr>
<th>Probability</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.01</td>
<td>99 (97-100)</td>
<td>24 (22-25)</td>
<td>7 (6-7)</td>
<td>100 (99-100)</td>
</tr>
<tr>
<td>≥0.02</td>
<td>90 (88-94)</td>
<td>53 (51-54)</td>
<td>9 (8-11)</td>
<td>99 (99-99)</td>
</tr>
<tr>
<td>≥0.03</td>
<td>90 (85-93)</td>
<td>55 (53-56)</td>
<td>10 (8-11)</td>
<td>99 (99-99)</td>
</tr>
<tr>
<td>≥0.04</td>
<td>84 (79-89)</td>
<td>64 (62-65)</td>
<td>11 (10-13)</td>
<td>99 (98-99)</td>
</tr>
<tr>
<td>≥0.05</td>
<td>72 (65-78)</td>
<td>77 (76-79)</td>
<td>15 (13-17)</td>
<td>98 (98-99)</td>
</tr>
<tr>
<td>≥0.07</td>
<td>72 (65-78)</td>
<td>78 (76-79)</td>
<td>15 (13-17)</td>
<td>98 (98-99)</td>
</tr>
<tr>
<td>≥0.09</td>
<td>54 (47-61)</td>
<td>87 (86-88)</td>
<td>18 (15-22)</td>
<td>97 (97-98)</td>
</tr>
<tr>
<td>≥0.11</td>
<td>47 (40-54)</td>
<td>90 (89-91)</td>
<td>20 (17-24)</td>
<td>97 (96-97)</td>
</tr>
<tr>
<td>≥0.13</td>
<td>45 (38-52)</td>
<td>90 (89-91)</td>
<td>20 (17-24)</td>
<td>97 (96-97)</td>
</tr>
<tr>
<td>≥0.15</td>
<td>42 (35-49)</td>
<td>92 (91-93)</td>
<td>22 (18-26)</td>
<td>97 (96-97)</td>
</tr>
<tr>
<td>≥0.17</td>
<td>34 (28-41)</td>
<td>94 (93-95)</td>
<td>24 (19-29)</td>
<td>96 (96-97)</td>
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<td>≥0.19</td>
<td>24 (19-30)</td>
<td>97 (96-97)</td>
<td>29 (23-36)</td>
<td>96 (95-97)</td>
</tr>
</tbody>
</table>
Tumour size and ploidy

It is widely concluded, based on available autopsy and cystoprostatectomy data, that small-volume tumours (less than 0.2 to 0.5cc) that lack a poorly differentiated element pose little threat to a patient (Corless, 1996). Stamey et al (1993) proposed that tumours larger than 0.5cc were clinically significant, based on a series in which 91% of clinically detected tumours were larger than 0.5cc at resection. There is, however, conflicting evidence over the effect of tumour size on prognosis (Zincze, 1994). Ploidy is also being examined as a prognostic factor in prostate cancer. Normal cells have 46 chromosomes (diploid) while tumour cells often have more or less than this number. Evidence suggests that aneuploid or tetraploid tumours have a worse prognosis than diploid tumours (Myers et al, 1992) (Van Den Ouden et al, 1993), although the independent prognostic value of ploidy over stage and grade is not well understood.

Limitations with current staging and grading modalities

As reported in the update of the 1996 AHTAC Report (Weller et al, 1999), two systems of staging are in common use for prostate cancer. The ‘Jewett system’ (stages A through D) was described in 1975 and has since been modified (Jewett, 1975). In 1997, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer adopted a revised TNM system which employs the same broad T categories as the Jewett system but includes subcategories of T, including a category to describe patients diagnosed through PSA testing. This revised TNM system is clinically useful and more precisely stratifies newly diagnosed patients (American Joint Committee on Cancer, 1997). A thorough review of the controversies of staging in prostate cancer has been published (Montie, 1995).

There are a number of problems with staging and grading modalities currently available. Selley et al (1997) highlight the following limitations (which depend on the selection criteria of patients into studies):

• understaging occurs in 40–65% of men with clinically localised disease, with rates of 63% for extracapsular extension, 23% for positive surgical margins and 8% for positive lymph nodes—there are particular difficulties in identifying stage A (T1) disease
• many of the reported staging studies are carried out on series of men with clinically localised disease who have elected to undergo radical prostatectomy, to allow comparison of clinical stage with pathological stage; these study groups may be biased as men undergoing surgery may be younger and healthier
• many studies comparing imaging techniques have had small numbers and hence lacked adequate statistical power
• although tumour grade, volume and ploidy each correlate with the probability of progression of prostate cancer, the correlations do not provide a definitive prediction; for example, current diagnostic techniques are unable to differentiate between T2 and T3 tumours
the value of clinical staging is hampered by the lack of information relating to the natural history of the disease. In particular, further information is required in relation to T1 and T2 tumours

Further definitions of the T categories will be necessary in the future, probably brought about by refinements in imaging techniques such as MRI.

**Combined criteria**

A number of authors have attempted to combine a range of criteria (e.g., tumour stage, histopathological criteria). Dugan et al. (1996) developed a model which combined tumour grade and volume—using this model, they predicted that surgeons at Mayo Clinic only operated on insignificant cases 0.3 to 14.5% of the time. Epstein et al. (1994) used tumour volume and grade to subdivide nonpalpable tumours into categories of insignificant, minimal, moderate, and advanced.

Smith et al. (1997) hypothesised that prognostic information may be obtained by the serum markers alkaline phosphatase, acid phosphatase, and PSA, and that treatment response may be predicted using these markers.

Increasingly, studies of prostate cancer treatments have included detailed examination of pre-treatment factors in determining prognosis. It appears that multivariate prognostic systems of this nature estimate patient prognosis more accurately than a system based on anatomic factors. For example, Pisansky et al. (1997) examined the outcome of 500 patients treated solely with irradiation for clinical TNM classifications T1–4, NO or NX. They used logistic regression models to construct a risk score equation to characterise patient groups with low, intermediate, or high risks for relapse.

**Key findings**

- Clinical tumour stage, Gleason score, and pre-therapy PSA are independently associated with clinical or biochemical relapse.
- For the low, intermediate, and high risk groups, the relapse-free probabilities at 5 years after irradiation are 92%, 67%, and 24% respectively.

**Newer markers**

The detection of molecular and/or cellular markers for metastatic ability of prostate cancer cells could be used to identify which cancers should be treated at the time of initial diagnosis, and this is an area of major research worldwide. A recent review (Rinker-Schaeffer et al., 1994) found that progression to high metastatic ability has been associated with:
• mutations in the p53 tumour-suppressor gene: altered p53 tumour suppressor gene expression: when analysed across all stages and grades of prostate cancer, this is not a definitively independent prognostic factor, even though mutations and deletions of the p53 gene, as well as over-expression of the p53 protein, have all been documented in prostate cancer (Corless, 1996). Nevertheless, it may be of value when applied to specific subgroups of tumours, particularly those that are Gleason score 2 to 7 (Shurbaji, 1995)

• down-regulation of the expression of a series of cell-surface proteins affecting cell-cell interaction (eg decreasing E-cadherin and KAI-1 expression

• increased expression of cell survival factors (eg bcl-2)

• increases in cell mortality

• increases in tumour angiogenesis

A variety of methods (eg immunocytochemistry, RT-PCR, in situ hybridisation) are being developed to detect these molecular and cellular changes within histological sections of biopsy specimens (Denmeade & Isaacs, 1997). Hopefully, this will eventually allow a more accurate grading system of prostate cancer based on a combination of molecular, cellular and histological criteria.

References—Executive Summary and Chapter 1


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Carter HB(a), Epstein JI, Chan DW, Fozard JL, and Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer [see comments]. JAMA. 1997; 277(18):1456–60; ISSN: 0098-7484


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Evidence-based information and recommendations for the management of localised prostate cancer


McLellan D L and Norman R W. Hereditary aspects of prostate cancer [see comments]. CMAJ. 1995 Oct 1; 153(7):895-900; ISSN: 0820-3946


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2 TREATMENT OF LOCALISED PROSTATE CANCER—BACKGROUND

Summary

• Treatment choices in local prostate cancer are controversial.
• There are methodological limitations in treatment comparisons based on non-randomised studies.
• Comparisons of similar treatments at different centres is also difficult.
• Definitions and monitoring of disease progression have advanced considerably in recent years.
• Pre-treatment investigations such as biopsy have low rates of complications.

2.1 Introduction

The optimal treatment of prostate cancer continues to be a topic of heated debate and persisting uncertainty. Resolution of this debate has been difficult due to qualities inherent in both the disease and the affected individuals, as well as a lack of data from randomised clinical trials evaluating treatment modalities (National Cancer Institute, 1998). As indicated in Chapter 1, the natural history of prostate cancer is prolonged relative to many other or most cancers, and few untreated men with localised prostate cancer succumb to the disease within five years of diagnosis, and only a minority succumb within 10 years. Nevertheless, prostate cancer is the second leading cause of cancer death in Australian men. Prostate cancer however, is more prevalent in elderly men where competing causes of death have significant impact.

2.2 Studies reporting and comparing treatments for localised prostate cancer: overview of methodological issues

Reviewing treatments for prostate cancer presents a number of difficulties; most existing data have come from small cohorts at specialised academic centres. Most of the studies we have identified from the last two years fell into this category. These data had a number of limitations—for example, precise overall and cancer-grade-specific data were usually not available, and data were subject to differential staging bias. In these retrospective studies, interpretation of results may be difficult (Zietman 1994). Sources of difficulty included:
1) **Selection bias**

Overall, men referred for radiotherapy are older, have poorer performance status and thus worse life expectancies than those undergoing radical prostatectomy. In addition, as a group they tend to have poorer prostate cancer-specific prognosis factors including higher presenting PSAs and higher grade and stage cancers. Inclusion in reported series of certain patients selected for radical radiotherapy (for example, those over 70 with other morbidities) who experience morbidity without benefit in survival (Fleming 1993), may also introduce bias when comparing the outcomes of different treatment modalities.

If patient co-morbidity and tumour-related variables are not controlled for (as is frequently the case), comparisons between different treatment options are usually inappropriate.

2) **Measurement bias**

The availability of information on tumour characteristics or outcome may be influenced by the treatment a patient receives. For example, patients given radiotherapy or conservative management tend to be understaged relative to those who undergo prostatectomy; this factor results in an exaggeration of the benefits of prostatectomy (Selley 1997).

3) **High rates of intercurrent illness**

Survival data in patients treated for prostate cancer is greatly complicated by a high rate of morbidity and mortality from other causes. It is also highly influenced by the inclusion in survival analyses of different categories of patients who appear to have very different underlying survival patterns (independent of treatment effects). For example, patients with stages T1 to T2a disease, who have well or moderately differentiated disease, low initial PSA levels and known negative nodes have much greater survival rates than other patients with ‘clinically localised’ prostate cancer.

When historical groups of tumours are compared, it is important to closely examine how patients are selected and how the data are obtained. Unfortunately, information on patient selection is often limited, making comparisons between different studies difficult. It is widely recommended in the literature that new studies examining survival of prostate cancer patients need to be stratified to take into account these differences. Also, since prostate cancer usually grows slowly, long-term results are necessary (in the region of 15 years) to fully assess outcomes, and in 1998 there were only a very small number of trials with such long-term follow-up data.

Lu-Yao & Yao (1997) described a further methodological issue, comparing intention to treat analyses with treatment received analyses. Studies using a treatment-received approach versus ‘intention to treat’ overestimated the benefits of radical prostatectomy (eg outcomes were better in the subset of patients scheduled to have radical prostatectomy who actually had the treatment, than in the whole group). Only a small number of the studies included in this report made
the distinction between results based on intention to treat versus those which were not.

2.3 Measures of tumour progression and treatment outcome

There has until recently been little consistency in the published reporting of tumour progression or treatment outcomes, and, again, this makes comparisons between different studies difficult. Increasingly studies are using biochemical measures such as PSA to monitor tumour progress, due to the unreliability of clinical information. But there are no widely-accepted biochemical ranges applicable to individual treatments. The traditional clinical definition of ‘failure’ of treatment is development of palpable local recurrence, or radiologically or symptomatically evident distant metastases. But this may require long-term follow-up to obtain adequate data.

From the perspective of patients, it is difficult therefore to define ‘cure’ from prostate cancer. Definitions might include:

- lack of clinical progression
- lack of evidence from radiological or other investigations that disease has progressed
- lack of biochemical failure (as determined by PSA levels)
- no reduction in ‘expected’ longevity

Similarly, there is no widespread agreement over the point in time at which ‘cure’ should be assessed. Options might include 5, 10 or 15+ years post-treatment.

Histological monitoring

Histological monitoring has become less commonly used as an intermediate end point for survival data. Both the findings of positive surgical margins and positive repeat biopsy post radiotherapy have been shown to have interobserver variation and poorer predictive value as an indicator for clinical failure than PSA levels. There are widely differing figures; for example, two or more years following irradiation, positive re-biopsy in a palpably normal gland has been reported in 12% to 91% of patients (Hartford & Zietman, 1996), depending on pre-treatment T category and the PSA level at the time of biopsy. It appears likely that the high variability in the reported rates is largely a consequence of these repeat biopsy selection factors (Crook et al, 1993).

PSA levels: ‘biochemical failure’

The PSA test has dramatically refined definitions of failure. An increasing PSA level after treatment indicates persistent local disease, development of subclinical metastases or both. Biochemical relapse may precede clinical failure by months to years. Rising PSA levels have come to be used as intermediate end points, which
allow a comparison of treatment much sooner than evidence of clinical failure or mortality data. The interval from biochemical failure to clinical failure has also been shown to be predictable on the basis of the rate of increase of PSA. However, differences remain between studies in the definition of biochemical failure. For example, some studies use evidence of biochemical failure as a rise above 1.0 ng/ml, while others require a rise above 4.0 ng/ml or a relative rise in the PSA level as their index.

Detectable levels of PSA after surgery are usually a reliable indicator of residual disease, and a proposed threshold nadir of ≤0.3–≤0.6 ng/ml (‘undetectable PSA levels’) to distinguish between freedom from relapse and biochemical failure (Ragde 1997) is increasingly used in the literature. Following radical prostatectomy PSA levels should be undetectable, unless there is residual disease, either local or metastatic. If the PSA post surgery is elevated, the disease invariably progresses and will likely result in clinical relapse, should the patient live long enough.

Ragde et al (1997), and many other authors, emphasise that the interpretation of PSA values after radiation therapy is more complex. Sequential determinations of PSA show decreasing values over time, but there are no standard criteria for how rapid this decrease should be and to what level the PSA should decline before a patient can be assured of long-term freedom from relapse. This is particularly true as irradiation of the prostate will also lead to considerable damage of non-malignant structures (e.g., stromal fibrosis, atrophy and squamous metaplasia of the glands) all of which may contribute to decreasing serum PSA levels independently of cancer cell death. Hence, the exact biological and therapeutic relevance of rises in PSA after radiation therapy is yet to be elucidated.

Following irradiation, serum PSA decreases slowly, reaching nadir values within 1 to 2 years (Ritter et al, 1992). Because irradiated normal prostate tissue can produce some PSA, defining a disease-free state for prostate cancer patients following irradiation is problematic. Requiring that PSA level be undetectable is accepted as being too strict, and most centres have typically used a range between 0.5 and 4 ng/ml. A range of studies has shown that biochemical failure after irradiation can be well predicted by pretreatment factors, in particular the initial PSA level (Hartford, 1996). The probability of failure increases substantially when the initial PSA level is greater than 10 to 15 ng/ml.
References—Chapter 2


3 RADICAL PROSTATECTOMY

Summary

- Information on the effectiveness of radical prostatectomy comes largely from uncontrolled case series and cohort studies. These studies are the most rigorous in terms of patient numbers and years of follow-up. Randomised controlled trials comparing radical prostatectomy to other treatment modalities are not currently available and will not be for some years.

- The consensus in the literature suggests that radical prostatectomy is best performed on patients with localised prostate cancer (low volume/low PSA), in patients with a greater than 10 year life expectancy who are fit for surgery and have not had previous radiotherapy. Patient quality of life issues increasingly are major factors in deciding individual treatments.

- High grade tumours of low volume may be cured by surgery in a moderate percentage of patients.

- Survival following radical prostatectomy is high. Better information on prognostic factors unrelated to treatment allows greater confidence in predicting ‘PSA free survival’ in more recent studies.

- Complications following surgery suggest urinary and sexual function are mainly affected. There is a recent trend towards better outcome of urinary function in the recent literature. The incidence of side effects appears worse from patient reported questionnaire compared to physician reported results.

- Radiotherapy may be used after surgery with low levels of side effects. Survival advantage for this treatment has not yet been proven although prolonged PSA responses do occur.

- Neo adjuvant hormones before radical prostatectomy (RP) appear not to affect the likelihood of recurrence.

3.1 Background

It is widely argued that the aim of any treatment for cancer should be to eradicate the tumour in patients who are treated with curative intent with as little morbidity as possible, and to decrease disease-specific morbidity in those who cannot be cured. For those in the former category, radical prostatectomy offers the best prospect of complete removal of the tumour.

3.1.1 Radical prostatectomy techniques

There is no widespread consensus over the optimum technique for undertaking radical prostatectomy.
Nerve sparing and anatomy-preserving techniques

In 1994, Walsh and his associates published results of their nerve sparing techniques for radical prostatectomy. This technique aims to spare one or both of the neurovascular bundles which carry the nerves required to preserve potency, and appears to have resulted in fewer complications of surgery for patients with clinically localised prostate cancer. Advocating this approach has resulted in a rapid rise in the age-adjusted proportion of men undergoing this treatment. Preliminary data indicate that preservation of as much as possible of the normal anatomy of the sphincter mechanisms and their nerve supplies leads to reduced rates of urinary incontinence (Kaye et al, 1997).

Retropubic versus perineal approach

In recent years the retropubic approach has been more commonly used. It is usually preceded by a pelvic lymph node dissection, and both procedures can be performed through a single incision. While a perineal approach requires a separate incision for pelvic lymph node dissection, its use has been revived with the advent of laparoscopic lymphadenectomy, and the questioning of the need to carry out lymphadenectomy on all patients diagnosed with localised prostate cancer (Selley et al, 1997).

Two studies have directly compared these two main approaches to radical prostatectomy (Haab et al, 1994; Frazier et al, 1992). Both studies reported a greater number of blood transfusions and longer operative times in the retropubic group, with conflicting results on the number of days spent in hospital. There were greater reported levels of impotence and incontinence among the perineal group at 3 months, but no difference in incontinence rates at 6 months.

Prostatectomy is a major operation, with an average operating time of 2–4 hours and an average length of stay in hospital of 3 to 6 days (American Urological Association, 1995), although researchers in the USA (Harris & Thompson 1996) have reported lengths of stay of less than two days. The patient will generally require an indwelling catheter for 10 to 21 days. Long experience with radical prostatectomy in the United States contrasts to many centres in Europe, where radical prostatectomy has been introduced relatively recently (Fenely et al, 1997).

Patient preferences are widely considered to be important in treatment decisions; a study which aimed to determine whether patients with early localised prostate cancer prefer surgical intervention over watchful waiting (Mazur et al, 1996) used structured interviews with 140 male patients seen consecutively at a university-based clinic. The mean age was 66.3; 53% preferred surgical treatment, 42% observation, 4% preferred that their physician make the decision and 1% preferred radiotherapy. The possibility of complete tumour removal was the strongest motivator for surgical excision, while fear of complications was the main determinant of a preference for watchful waiting. Older patients were more likely to prefer expectant management.

3.2 Studies examining survival and
progression rates

Studies which provide data on survival after radical prostatectomy are shown in Table 3.1, and further details on these studies are included in Appendix 1 (a). The majority of studies are case-series, many of which included very large samples and substantial periods of follow-up. There are also retrospective and survival analyses of population-based tumour registry data (Krongrad, 1997; Lu-Yao, 1997), a randomised controlled trial which compared pre-operative hormonal therapy with surgery alone (Witjes, 1997) and one pooled analysis from a number of trials (Gerber, et al., 1996).

Results of these studies on survival rates post-radical prostatectomy are shown in Tables 3.2 to 3.5. On the whole, long-term survival rates in the studies examined were high.

Five year survival rates ranged from 74% to 97% (compared to 57% to 98% in the AUA report—1995). Overall actuarial survival at 15 years of follow-up ranged from 56% to 87% in the studies reviewed, and cause-specific survival at 15 years ranged from 81% to 98%. Two studies examined disease-free actuarial survival at 15 years (61% and 71%), and four studies reported likelihood of undetectable PSA at 10 years, which ranged from 53% to 85%.

Differences in the reported survival rates may reflect lack of standardisation between the trials, including differences in patient and tumour characteristics, data collection and treatment practices. Interpretation of these data is limited by the nature of the studies; they have no control groups, and it is difficult to separate out the independent contribution to the survival data of treatment efficacy and selection bias.

Table 3.2: Actuarial survival post-radical prostatectomy
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amling et al (1998)</td>
<td>Mayo Clinic Rochester, Minn USA</td>
<td>Case series</td>
<td>1987-1995</td>
<td>5568</td>
<td>4774 had clinically localised disease of stage T2c or less</td>
<td>Radical retropubic prostatectomy and pelvic lymphadenectomy</td>
<td>44-83 yrs mean 64.4 yrs</td>
<td>5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85% progression 75%T1c 70%T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catalona (1994)</td>
<td>Washington University</td>
<td>Case series</td>
<td>1983-1993</td>
<td>925</td>
<td>Stage: T1a—2% T1b—6% T1c—13% T2a—29% T2b—40%</td>
<td>Nerve sparing retropubic</td>
<td>63.9 +/- 7.0</td>
<td>Up to 120, 28 +/- 25.4 for non-recurrent cases.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dillioglugi (1997)</td>
<td>Methodist Hospital, Texas</td>
<td>Case series</td>
<td>1983-1995</td>
<td>611</td>
<td>Stage: T1—25% T2—75%</td>
<td>Retropubic</td>
<td>62.8 (40-79)</td>
<td>Mean 30.3 (1-125.5)</td>
</tr>
<tr>
<td>Frohmuler (1995)</td>
<td>Wurzburg Germany</td>
<td>Case series</td>
<td>1969 on</td>
<td>100</td>
<td>Stage: T2—68% T3—23%</td>
<td>Not stated</td>
<td>N ot stated</td>
<td>At least 180 (180-276)</td>
</tr>
<tr>
<td>Gerber (1996)</td>
<td>USA (6), Europe (2)</td>
<td>Pooled analysis</td>
<td>1970-1993</td>
<td>2758</td>
<td>Stage: T1—25.3% T2—72.7%</td>
<td>Retropubic (61%) Perineal (36%)</td>
<td>65 (48-79)</td>
<td>Mean 46 +/- 44</td>
</tr>
<tr>
<td>Krongrad (1997)</td>
<td>National Cancer Institute's Surveillance, Epidemiology and End Results program</td>
<td>Population based retrospective cohort study</td>
<td>1983-1987</td>
<td>3626</td>
<td>Pathologically localised—60.4%</td>
<td>Various</td>
<td>65 (SD +/- 6.4)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lu-Yao (1997)</td>
<td>Cancer-registry patients aged 50-79</td>
<td>Survival analysis</td>
<td></td>
<td>59876</td>
<td>grade 1, 2 6.3</td>
<td>various</td>
<td>(50-79)</td>
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### Table 3.1 cont.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oefelein (1997)</td>
<td>Northwestern University</td>
<td>Case series</td>
<td>1980-1991</td>
<td>116</td>
<td>Stage: T1—8% T2—88%</td>
<td>Retropubic</td>
<td>63.4 (41-76)</td>
<td>Median 84 (28.4-175.2)</td>
</tr>
<tr>
<td>Ohori (1994)</td>
<td>Methodist University</td>
<td>Case series</td>
<td>1983-1993</td>
<td>500</td>
<td>T1a—6% T1b—7% T1c—8% T2a—10% T2b—30% T2c—26% T3—4%</td>
<td>Retropubic</td>
<td>63 (43-79)</td>
<td>Mean = 36 (1-114)</td>
</tr>
<tr>
<td>Trapasso (1994)</td>
<td>UCLA</td>
<td>Case series</td>
<td>1972-1992</td>
<td>601</td>
<td>Stage: T1a—2% T1b—6% T1c—19% T2a—28% T2b—49%</td>
<td>Retropubic</td>
<td>63.5 (44-80)</td>
<td>Median 34 (12-237)</td>
</tr>
<tr>
<td>Walsh (1994)</td>
<td>John Hopkins</td>
<td>Case series</td>
<td>1982-1991</td>
<td>923</td>
<td>Stage: T1a—5% T1b—10% T1c—2% T2a—49% T2b—27% T2c—7%</td>
<td>Anatomical retropubic</td>
<td>59.4 +/- 6.4</td>
<td>53 (12-120)</td>
</tr>
<tr>
<td>Witjes (1997)</td>
<td>Multi-centre prospective</td>
<td>Study started</td>
<td>1991</td>
<td>354</td>
<td>Stage: T2—56% T3—44%</td>
<td>Retropubic vs neoadjuvant hormonal treatment prior to surgery</td>
<td>Not stated</td>
<td>Mean 15</td>
</tr>
<tr>
<td>Zincke (1994a)</td>
<td>Mayo Clinic</td>
<td>Case series</td>
<td>1966-1987</td>
<td>1143</td>
<td>Stage: T1—7% T2a—36% T2b—or—c—57%</td>
<td>RP alone 83% Adjunctive treatment post RP 17%</td>
<td>64 (38-79) +/- 6</td>
<td>Mean 116</td>
</tr>
<tr>
<td>Zincke (1994b)</td>
<td>Mayo Clinic</td>
<td>Case series</td>
<td>1966-1991</td>
<td>3170</td>
<td>Stage: T1—7% T2a—28% T2b—or—c—65%</td>
<td>Retropubic</td>
<td>65.3 (31-81) +/- 6.4</td>
<td>Mean 60.5</td>
</tr>
</tbody>
</table>
Table 3.3  Cause specific actuarial survival rates post-radical prostatectomy

<table>
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</thead>
<tbody>
<tr>
<td>5 year</td>
<td>T2</td>
<td>T1–T2</td>
<td>Grade 1–94%</td>
<td>Grade 2–87%</td>
<td>Grade 3–67%</td>
</tr>
<tr>
<td>10 year</td>
<td>98%</td>
<td>94%</td>
<td>90%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>15 year</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
<td>82%</td>
</tr>
</tbody>
</table>

Table 3.4  Disease free actuarial survival rates post-radical prostatectomy

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</thead>
<tbody>
<tr>
<td>5 year</td>
<td>T1c–85% T2–76%</td>
<td>86%</td>
<td>78%</td>
<td>72%</td>
<td>76%</td>
</tr>
<tr>
<td>10 year</td>
<td>78%</td>
<td></td>
<td>72%</td>
<td>76%</td>
<td>61%</td>
</tr>
<tr>
<td>15 year</td>
<td></td>
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</tr>
</tbody>
</table>

Table 3.5:  Likelihood of undetectable PSA after radical prostatectomy (T1 or T2)

36  Evidence-based information and recommendations for the management of localised prostate cancer
3.3 Recent studies examining complication rates

Trials which have examined complication rates for prostatectomy are summarised in Table 3.6. Further details of the studies are provided in Appendix 1 (b). The complication rates reported in these studies are shown in Table 3.7. Death in the peri-operative period has been reported in 0.2 to 1.2% of men undergoing radical prostatectomy (Andriole 1994, Murphy 1994, Hautmann 1994) (Table 3.7).

The two main approaches to establishing complication rates are 1) to document the rates prospectively, or 2) retrospectively seek information from sources such as patient questionnaires or hospital audits on complications. In general, prospective recording of complication rates provide less biased results.

The two most important complications of radical prostatectomy are incontinence and impotence, and Table 3.7 demonstrates a highly variable range of rates, with death rates of up to 1% being reported in men undergoing radical prostatectomy. Again, this variation likely reflects differences in patient and tumour characteristics, treatment practices, definitions and terminology and methods of data collection. Impotence varied from partial to complete, and definitions of these terms varied between centres. Similarly, definitions of impotence vary, and the results presented in the table reflected neither standardised definitions or survey techniques.

There has been recent interest in the incidence of post-surgical fecal incontinence, a potentially under-reported problem. Bishoff et al (1998) conducted a mail survey of 1,200 radical prostatectomy patients randomly selected from a nationwide database of Department of Defense health care system beneficiaries. Frequency of fecal incontinence among radical perineal patients was significantly higher compared to retropubic prostatectomy patients (p=0.002) (see Table 3.8).

Of patients undergoing radical perineal prostatectomy only 14% and of retropubic only 7% with fecal incontinence had ever told a health care provider about it, even when the incontinence was severe. The authors conclude that fecal incontinence following radical prostatectomy occurs more frequently than previously recognised, particularly in radical perineal prostatectomy patients.

Table 3.8 Incidence of fecal incontinence post-surgery
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geary (1995)</td>
<td>Stanford</td>
<td>Case series</td>
<td>1983-1991</td>
<td>481</td>
<td>Stage T1a-1.5% Stage T1b-6.9% Stage T1c-19.1% Stage T2a-28.9% Stage T2b-33.7% Stage T2c-9.1% Stage T3c-0.4%</td>
<td>Retropubic radical prostatectomy</td>
<td>64.1 +/- 0.3</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Harris (1996)</td>
<td>Houston &amp; Traverse City, Michigan</td>
<td>Case series</td>
<td>Not stated</td>
<td>96</td>
<td>Stage T1-54% Stage T2-44%</td>
<td>Anatomic perineal</td>
<td>Not stated</td>
<td>Average 12 (3-30)</td>
</tr>
<tr>
<td>Herr (1994)</td>
<td>Prostate cancer support group</td>
<td>Patient survey</td>
<td>Not stated</td>
<td>50</td>
<td>Not stated</td>
<td>Not stated</td>
<td>67.8</td>
<td>12-60+</td>
</tr>
<tr>
<td>Jonler (1994)</td>
<td>University of Wisconsin</td>
<td>Patient survey</td>
<td>1990-1992</td>
<td>86</td>
<td>Stage T1 or T2-51% Retropubic, potency sparing (77%) and nerve sparing (23%)</td>
<td>64 (49-75)</td>
<td>22.5 (12-48)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6 Recent trials reporting complications post radical prostatectomy
### Table 3.6 cont.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>1 Sphincter-damaging: 48%</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>2 Sphincter-repairing: 27%</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 Sphincter-preserving: 25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy (1994)</td>
<td>USA</td>
<td>Survey of institutions</td>
<td>1990</td>
<td>2122</td>
<td>AJCC Stage</td>
<td>Various</td>
<td>Not stated (data given by age group)</td>
<td>24–36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage 2–72%</td>
<td>Non-nerve-sparing 70%</td>
<td>Non-nerve sparing 64.5</td>
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<td></td>
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<td></td>
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<td></td>
<td>T1b–10%</td>
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<td>T1c–2%</td>
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<td></td>
<td></td>
<td></td>
<td>T2a–49%</td>
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<td></td>
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<td>T2b–27%</td>
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<td></td>
<td></td>
<td>T2c–7%</td>
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<tr>
<td>Zincke (1994)</td>
<td>Mayo Clinic</td>
<td>Case series</td>
<td>1966–1991</td>
<td>3170</td>
<td>Stage T1–7%</td>
<td>Not stated</td>
<td>65.3 +/- 6.4</td>
<td>Mean 60.5</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>T2a–28%</td>
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<td></td>
<td>T2b, 2c–65%</td>
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</table>
### Table 3.7 Recent complication rates of radical prostatectomy

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</thead>
<tbody>
<tr>
<td>Death (post operative)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>0.2%</td>
<td>1.2%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>32%</td>
<td>34%</td>
<td>7%</td>
<td>19%</td>
<td>19%</td>
<td>8%</td>
<td>5%</td>
<td>34% (a)</td>
<td></td>
<td></td>
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<tr>
<td>Major bleeding</td>
<td></td>
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<tr>
<td>Pulmonary embolism</td>
<td>2.6%</td>
<td>5.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1%</td>
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<tr>
<td>Bladder neck contraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
<td></td>
<td></td>
<td>1%</td>
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<tr>
<td>Obstruction/ irritative sx</td>
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<tr>
<td>Proctitis</td>
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<td></td>
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<tr>
<td>Cystitis</td>
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<tr>
<td>Urethral stricture</td>
<td>20%</td>
<td>0%</td>
<td></td>
<td>60%</td>
<td></td>
<td>1%</td>
<td>12%</td>
<td>32% (b)</td>
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<tr>
<td>Impotence</td>
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<tr>
<td>Rectal complications</td>
<td>2.7%</td>
<td></td>
<td></td>
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Table 3.7 cont.

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</thead>
<tbody>
<tr>
<td>Urethral necrosis</td>
<td>Perineal discomfort/pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>a. 7% of patients suffered complete incontinency and 27% partial</td>
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<td>b. after the introduction of anatomical techniques</td>
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<tr>
<td>c. bowel injury requiring colostomy or long term treatment</td>
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<tr>
<td>d. 32% if those impotent pre-treatment are excluded</td>
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</tbody>
</table>

Note—the percentage of patients suffering from impotence and incontinence in this table is the number of men who are impotent post-operatively divided by the number of men who have been treated. This has been done to remain consistent across the results of all the trials, including those where pre-operative potency and continence status is not known. The percentage includes, however, the percentage of men who were impotent or incontinent prior to treatment, and not just those who suffered these as complications of treatment.
Evidence-based information and recommendations for the management of localised prostate cancer

Radical perineal prostatectomy Retropubic prostatectomy

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Radical perineal prostatectomy</th>
<th>Retropubic prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Weekly</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Monthly</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>16%</td>
<td>8%</td>
</tr>
</tbody>
</table>


3.4 Randomised controlled trials of treatment versus no initial treatment

The data in the preceding tables highlight the difficulties in comparing treatment approaches based on case-series and other non-randomised approaches. While population-based randomised controlled trials of prostate cancer treatments have long been advocated, there are difficulties in establishing such trials, particularly in areas where treatment practices have become established. The randomised clinical trials (RCTs) established to examine this issue have also been described in the 1996 AHTAC Report and its recent update (Weller et al, 1999).

1. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) (Wilt and Brawer, 1997)

This randomised trial was designed to determine whether radical prostatectomy or ‘expectant management’ provides greater length and quality of life for men with clinically localised prostate cancer.

Setting:

Department of Veterans Affairs and National Cancer Institute medical centres, PIVOT aimed to enrol over 1,000 individuals < 75 years of age, although there have been recruitment problems.

Details:

The primary study end point is all-cause mortality. Secondary outcomes include prostate cancer- and treatment-specific morbidity and mortality, health status, predictors of disease-specific outcomes, and cost-effectiveness.

Preliminary results:

Within the first 3 years of enrolment, over 400 men were randomised, and analysis of participants’ baseline characteristics indicated that enrollees were representative of men diagnosed with clinically localised prostate cancer throughout the United States (it is hoped, therefore, that results of PIVOT will be generalisable).

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2. **UK Medical Research Council (AUA, 1995)**

A prospective randomised trial by the UK Medical Research Council was established in the early 1990s. It was discontinued due to recruitment difficulties—the study relied on an unpredictable supply of incidentally-diagnosed cancers (not screen-detected), and there was patient and clinician reluctance to randomise between the defined groups.

It was comparing total prostatectomy, radiotherapy and conservative management, for patient with newly diagnosed T1 and T2 prostate cancer.

3. **Graversen (1990)**

Graversen has now published 15 year follow-up data which, in common with earlier reports on this trial, showed no difference in survival (although the trial has limited numbers and flawed design).

**References—Chapter 3**


Geary ES, Dendinger TE, Freiha FS and Stamey TA. Nerve sparing radical prostatectomy: a different view [see comments]. J Urol. 1995 Jul; 154(1):145–9; ISSN: 0022-5347


Hautmann RE, Sauter TW, Wenderoth UK. Radical retropubic prostatectomy: morbidity and urinary continence in 418 consecutive cases. Urology 1994 Feb; 432 (2 Suppl); 47–51


Walsh PC, Partin AW and Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy: Results at 10 years. J Urol. 1994; 152:1831–1836


Wilt TJ and Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). Oncology (Huntingt). 1997 Aug; 11(8):1133-9; discussion 1139–40, 1143; ISSN: 0890-9091
Witjes WP, Schulman CC and Debruyne F M. Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-3 N0 M0 prostatic carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer. Urology. 1997 Mar; 49(3A Suppl):65-9; ISSN: 0090-4295

Evidence-based information and recommendations for the management of localised prostate cancer

4 EXTERNAL BEAM RADIOOTHERAPY (EBRT)

Summary

- Information on the effectiveness of radiotherapy (RT) comes largely from uncontrolled case series and cohort studies. There are no useful data from randomised controlled studies comparing radiotherapy to other treatment modalities. There is one randomised study external beam radiotherapy (EBRT) vs prostatectomy.

- There is general agreement that EBRT is best indicated for patients with localised prostate cancer (low volume and PSA less than 15 ng/ml) and a life expectancy of greater than 10 years. As with surgery, patient preferences, including consideration of potential side effects, are identified as important when deciding about EBRT.

- The value of EBRT for patients with high grade tumours remains controversial. Selection bias makes comparison to surgery very difficult.

- Survival is high after EBRT in patients with favourable pre-treatment prognostic factors. Biases against external beam radiotherapy have occurred in previously reported series (due to selection of patients with more advanced stages and histological grades). There is less consensus on the definition of PSA recurrence compared with surgery. There is increasingly better information on prognostic factors allowing greater confidence in survival estimation although this is less developed when compared with surgery.

- Bowel side effects, and to a lesser extent sexual side effects, are the main complications of external beam radiotherapy. Patient questionnaires report a higher incidence of these complications compared to physician reported data.

- Surgery following radiation failure has a very high complication rate.

- Combinations of neo-adjuvant and/or adjuvant hormone therapy with EBRT have been shown to delay recurrence and, or possibly lead to improved survival.

4.1 Background

The relatively non-invasive nature of radiotherapy has ensured its continued use as a primary treatment modality for localised prostate cancer. As has been noted in previous reviews, it is difficult to make any direct comparison of outcomes from existing trials of the expected survival of patients who have been treated with radiotherapy versus those who have had other forms of treatment. From trials where data are available, it appears that patients who receive EBRT are more likely to be older and have a higher frequency of high grade tumours and a higher...
Evidence-based information and recommendations about the management of localised prostate cancer

It is also difficult to make comparisons as most patients who are treated with radiotherapy do not undergo pelvic node dissection. The removal of patients with known pelvic node disease from surgical series biases comparisons of survival between the two treatments in favour of the surgical patients.

Conformal radiotherapy

Conformal RT refers to ‘shaping’ the high dose treatment volume to ‘conform’ to the prostate gland, whilst excluding adjacent normal dose-limiting structures such as the rectum. This uses three dimensional CT planning and is becoming a standard method for delivering EBRT. This was first used at the Fox Chase Cancer Centre in 1989 (Corn, 1995). Patient immobilisation may be important in improving success rates and reducing morbidity. In most of the studies which are included in this report, radiotherapy has not been applied to the pelvic lymph nodes. There is variation in whether the seminal vesicles are exposed to radiation treatment.

PSA values are increasingly being used as an outcome measure following radiotherapy, although there is still debate on whether absolute levels, relative levels, the rate of increase or PSA density should be used as an outcome measure. Poor outcome has been suggested in men with a PSA level greater than 4 ng/ml more than 6 months after radiotherapy (Selley et al, 1997), and there is growing evidence for the need for a low nadir if long-term disease-free survival is to be achieved.

Neo-adjuvant or adjuvant androgen deprivation in combination with radiation treatment (EBRT) has been evaluated in patients with early prostate cancer who have a generally poor prognosis or to reduce the prostatic volume prior to radiotherapy. A number of large scale, well controlled trials, have provided evidence that in some groups of men with prostate cancer treatment with temporary androgen deprivation before and during EBRT leads to better rates of local disease control and biochemical progression-free survival (Pilepich et al, 1995 and Laverdierre et al, 1997). Other studies have provided evidence that the use of temporary androgen ablation after EBRT improves progression-free survival (Pilepich 1997, and Laverdierre et al, 1997), local disease control (Laverdierre et al, 1997), cause-specific overall survival (Bolla et al, 1997). These are areas of current active clinical research. Androgen deprivation is also being used in patients post radiotherapy who show signs of biochemical failure, in an attempt to prolong the interval to clinical failure (Zietman et al, 1994b).

4.2 Studies examining survival post-EBRT

Studies examining survival post-EBRT are shown in Table 4.1, and further details on these studies can be found in Appendix 2 (a).
### Table 4.1: Studies which have examined survival post-EBRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagshaw et al (1994)</td>
<td>Radiation Oncology, Stanford</td>
<td>Case series</td>
<td>15 yrs</td>
<td>1245</td>
<td>T1, T2a N0.</td>
<td></td>
<td>120 months</td>
<td></td>
</tr>
<tr>
<td>Hanks (1994)</td>
<td>Fox Chase Cancer Center, Philadelphia USA</td>
<td>randomised trial</td>
<td>1977</td>
<td>444</td>
<td>T1—84</td>
<td>Conventional EBRT</td>
<td>Not given</td>
<td>Up to 10 years</td>
</tr>
<tr>
<td>Hanks (1994)</td>
<td>Fox Chase Cancer Center, Philadelphia USA</td>
<td>randomised trial</td>
<td>1986</td>
<td>455</td>
<td>B2 and C</td>
<td>Cytoreduction and EBRT</td>
<td>Not given</td>
<td>3 years</td>
</tr>
<tr>
<td>Hanks et al (1997)</td>
<td>Fox Chase Cancer Center, Philadelphia USA</td>
<td>Prospective trial to Dec 1993</td>
<td>5 yrs prior to Dec 1993</td>
<td>456</td>
<td>T1, 2AB, Gleason 6 or less</td>
<td>Not given</td>
<td>60 months</td>
<td></td>
</tr>
</tbody>
</table>

continued over the page
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketting Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td>T2a–12%</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>T2b–19%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2c–22%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T3–32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ketting Cancer Center</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ketting Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td>70.4 (SE 0.05)</td>
<td>Mean 44.5 for wider sample of 59,876</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketting Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td>70.4 (SE 0.05)</td>
<td>Mean 44.5 for wider sample of 59,876</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ketting Cancer Center</td>
<td></td>
<td></td>
<td></td>
<td>70.4 (SE 0.05)</td>
<td>Mean 44.5 for wider sample of 59,876</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>cancer registry patients aged 50–79</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2 = 55%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1 = 6.2%</td>
<td>Conventional EBRT</td>
<td>Median = 69 (47–84)</td>
<td>Median = 30 (9–73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2 = 46.6%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T3 = 43.5%</td>
<td>Conventional EBRT</td>
<td>Median = 71 (24–56)</td>
<td>Median = 32 (24–56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T4 = 3.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2 = 38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3 = 45%</td>
<td>Conventional EBRT</td>
<td>Median = 69 (47–84)</td>
<td>Median = 30 (9–73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T4 = 6%</td>
<td></td>
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</tr>
</tbody>
</table>
Overall, the survival data for patients treated with EBRT shows lower rates of survival compared to data for patients treated with brachytherapy. Whether this effect is real, or due to selection bias of patients included in the EBRT trials is unknown. Further information on survival and progression in trials of EBRT is shown in Tables 4.2 to 4.5.

### Table 4.2: Actuarial survival for EBRT—Stage T2N\(x\)Mo

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>5 year</td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td>10 year</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>15 year</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4.3: Actuarial survival for EBRT—stage T1N\(x\)Mo

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year</td>
<td></td>
<td>84%</td>
<td>85%</td>
<td>86%</td>
</tr>
<tr>
<td>10 year</td>
<td>grade 1–90%</td>
<td>54%</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>grade 2–76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>grade 3–53%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 year</td>
<td></td>
<td>40%</td>
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<td></td>
</tr>
</tbody>
</table>

### Table 4.4: Chemical failure post EBRT

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1.5 year</td>
<td>PSA &gt; 4 ng/ml</td>
<td>PSA &gt; 4 ng/ml for 2 successive measurements increase &gt; 10% on prior value &lt; 2 yrs</td>
<td>T1c-2b-1%</td>
<td>T1-2-11%</td>
<td>T1-2-40%</td>
<td>T1-2-40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2c-10%</td>
<td>T3-4-20%</td>
<td>T3-4-58%</td>
<td>T3-4-58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3-19%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 year</td>
<td>54%</td>
<td>74%</td>
<td>T1c-2a-3%</td>
<td>T1-2-30%</td>
<td>T1-2-32%</td>
<td>T1-2-32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2b-14%</td>
<td>T3-4-58%</td>
<td>T3-4-58%</td>
<td>T3-4-58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2c-40%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>T3-57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 year</td>
<td></td>
<td></td>
<td>T1-2-40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3-4-58%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 year</td>
<td></td>
<td></td>
<td>T1-2-60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3-4-82%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.5: Clinical failure post EBRT

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 year</td>
<td>T1–2- 0%</td>
<td>T1–2- 0%</td>
</tr>
<tr>
<td></td>
<td>T3–4- 11%</td>
<td>T3–4- 11%</td>
</tr>
<tr>
<td>3 year</td>
<td>T1–2- 5%</td>
<td>T1–2- 5%</td>
</tr>
<tr>
<td></td>
<td>T3–4- 32%</td>
<td>T3–4- 32%</td>
</tr>
<tr>
<td>10 year</td>
<td>T1–2- 13%</td>
<td>T1–2- 13%</td>
</tr>
<tr>
<td></td>
<td>T3–4- 28%</td>
<td>T3–4- 28%</td>
</tr>
</tbody>
</table>

4.3 Studies examining complication rates

Trials reporting complications post external beam radiotherapy are summarised in Table 4.6, and further study details are shown in Appendix 2 (b). Similar problems of selection bias and reporting bias affected trials which examined complication rates as affected trials that reported on survival. Although there is a grading system which has been developed for sequelae of treatment, this system was infrequently used in the reported studies and there was considerable variation in the complications reported. Acute complications included rectal bleeding, cystitis, diarrhoea, proctitis, hematuria, and skin reactions. In the longer term, the most common complications were urethral stricture, impotence (which is variously defined), rectal and bladder ulceration, chronic cystitis and urinary incontinence (Wasson 1993, Selley et al, 1997).

There was, in common with trials on radical prostatectomy, a mixture of prospective and retrospective approaches in establishing complication rates.
Table 4.6  Studies which have examined complication rates post-EBRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70–7 = 37%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥75 = 34%</td>
<td></td>
</tr>
<tr>
<td>Helgason (1995)</td>
<td>Karolinska Institute</td>
<td>Case series</td>
<td>1990</td>
<td>53</td>
<td>T1 = 4%</td>
<td>Conventional EBRT</td>
<td>Median =70 (53-80)</td>
<td>18–24</td>
</tr>
<tr>
<td>Liebel (1994)</td>
<td>MSKCC</td>
<td>Case series</td>
<td>1988–1993</td>
<td>324</td>
<td>T1c =15%</td>
<td>Conformal EBRT</td>
<td>Median =69 (52-82)</td>
<td>18.5</td>
</tr>
<tr>
<td>Shrader-Bogen</td>
<td>Minnesota</td>
<td>Patient survey</td>
<td>1989–1994</td>
<td>142</td>
<td>A or B</td>
<td>Not stated</td>
<td>75.3 (SD 5.68)</td>
<td>Mean =32</td>
</tr>
</tbody>
</table>

The complication rates reported in these studies are summarised in Table 4.7.
Table 4.7 Complications of external beam radiotherapy

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6%</td>
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<tr>
<td>Pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bladder neck contraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction/ irritative sx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cystitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral stricture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Impotence</td>
<td>80%</td>
<td>57%</td>
<td>52%</td>
<td>25%(a)</td>
<td>77%</td>
<td>42%</td>
</tr>
<tr>
<td>Rectal complications</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Urethral necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Perineal discomfort/pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hematuria</td>
<td></td>
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</tbody>
</table>

a. Actuarial impotence probability 2 years after EBRT

Note— the percentage of patients suffering from impotence and incontinence in this table is the number of men who are impotent post-operatively divided by the number of men who have been treated. This has been done to remain consistent across the results of all the trials, including those where pre-operative potency and continence status is not known. The percentage includes, however, the percentage of men who were impotent or incontinent prior to treatment, and not just those who suffered these as complications of treatment.
References—Chapter 4


Zagars GK. Prostate specific antigen as an outcome variable for T1 and T2 prostate cancer treated by radiation therapy. J Urol. 1994; 152:1786-1791


5  INTERSTITIAL BRACHYTHERAPY

Summary

- Modern, ‘pre-planned’ prostate brachytherapy techniques have led to a worldwide resurgence of this treatment approach.
- Information on the effectiveness of brachytherapy is limited with a maximum of 10-year follow up in few studies.
- The ideal patient for ‘seed’ brachytherapy has localised prostate cancer of low-volume with Gleason score <7 and greater than a 10 year life expectancy.
- Late side effects including sexual and rectal morbidities are significantly less with brachytherapy than after external beam radiotherapy and radical prostatectomy. Acute urinary toxicity varies from minimal to considerable.
- PSA-progression free survival compares favourably with other modalities though data are limited.

5.1  Background

Brachytherapy involves implantation or insertion of small ‘sealed sources’ containing a radioactive isotope into the prostate gland either temporarily or permanently. This allows high doses of radiation to be delivered precisely to the prostate gland, potentially increasing tumour cell kill, without increasing side effects related to irradiation of adjacent tissues such as the rectum. The studies of brachytherapy have primarily conducted in the USA and have been observational case series. Their small patient numbers limits these studies.

Modern brachytherapy techniques include pre-planning of source or seed position with CT or ultrasound. Seeds or catheters are placed directly through the perineum under ultrasound guidance. Iodine-125 is the only isotope available in Australia for low dose rate brachytherapy. Iridium-192 is usually used for HDR (high dose rate) implants. Prior transurethral resection of the prostate (TURP) may be a relative contraindication for the therapy especially if a large portion of the gland is removed. High dose rate temporary brachytherapy is usually performed in combination with external beam radiotherapy for patients with ‘intermediate’ and high risk tumours.
5.2 Studies examining survival and progression rates

Studies examining progression-free survival after modern ‘seed’ brachytherapy are summarised in Table 5.1 and PSA relapse-free survival shown in Table 5.2. Further details on these studies are given in Appendix 3. There are relatively few studies examining brachytherapy and numbers of patients included in these case series tend to be small.

The most mature large cohort series (Ragde et al, 1997) found that:

- 7 year survival was 77%
- 7 year actuarial PSA progression free outcome was 89%
- PSA < 1.0 ng/ml outcome was 87%.

It is difficult to make comparisons between brachytherapy and other treatments based on the limited data available, because of the multiple selection and outcome measurement biases that confound non-randomised case series.

5.3 Studies examining complication rates

The potential advantages for brachytherapy are improved potency rates, particularly when compared with surgery, and small late rectal complication rates compared to EBRT. ‘Seed’ implantation usually involves one night of hospitalisation after the implant and thus requires fewer hospital visits than EBRT. Careful selection of patients and attention to radiation planning technique reduces the problem of post-implant retention. (D’Amico, 1996). Complication rates of ‘seed’ brachytherapy are shown in Table 5.3. These studies represent the current status of knowledge and it will be necessary to monitor the pattern of late complications as they relate to the rectum and bladder as the studies mature. There is high patient acceptance because of short treatment, hospital stay and rapid recovery (Ragde 1997, Kaye 1995).
## Table 5.1  Studies examining survival post-brachytherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
</table>
| Dattoli (33)  | Dept of Radiol, Univrsit Community Hosp, Tampa, FL, USA | Case series | 1991–1994         | 73             | T1c = 0%  
T2a = 3%  
T2b = 22%  
T2c = 26%  
T3 = 49%  | Pd-103 all with combined EBRT | 71 (58–80)  | 24 (12–36)        |
T2a = 32%  
T2b = 50%  
T2c = 0%  
T3 = 13%  | Pd-103 78%  
I-125 22%  
some with EBRT  | 70 (no AD)  | 26.8          |
T2a = 47%  
T2b = 6%  
T2c = 0%  
T3 = 10%  | Pd-103, no EBRT  | Not stated   | 41 (3–72)        |
| Stock (1996)  | Mt Sinai Hospital, New York, USA | Case series | 1990–1996         | 134            | T1b = 1%  
T1c = 28%  
T2a = 27%  
T2b = 37%  
T2c = 9%  
T3 = 0%  | I-125, no EBRT  | Not stated   | 44 (6–74)  dose <140  
25 (6–62)  dose ≥ 140 |
T2a = 5.3%  
T2b = 24%  
T2c = 26%  
T3 = 10%  | I-125, no EBRT  | 74 (51–95)  | 35 (3–70)        |

continued over the page
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>Date of treatment</th>
<th>No of patients</th>
<th>Grade/stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
</table>
T1c = 51%  
T2a = 16%  
T2b = 14%  
T2c = 2%  
T3 = 15% | Pd-103 & I-125, all with EBRT   | 67 (49–83)  | Mean = 33 (24–60) |
| Ragde (1997)    | North West Hospital, Seattle, USA    | Case series | 1/1998–12/1990   | 126            | T1a = 4.1%  
T1b = 3.3%  
T1c = 15.6%  
T2a = 62.3%  
T2b = 13.9%  
T2c = 0.8%  
T3 = 0%  | I-125, no EBRT                  | 70         | 69.3              |
| Critz (1997) (a)| Radiotherapy Clinics of Georgia, Atlanta, USA | Case series | 1984–95          | 363            | T1a = 3%  
T1b = 12%  
T1c = 16%  
T2a = 31%  
T2b = 28%  
T2c = 10%  | Combined retropubic I-125 brachytherapy and EBRT | Median = 60 (12–50) |
| Kaye (1995)     | Dept of Urology, Abbott Northwestern Hospital, Minneapolis, Minnesota, USA | Case series | 1988–1993        | 76             | T1b = 7%  
T2 = 93%  
Psa > 4 =60/76 | Percutaneous I-125 implantation (+/- EBRT) | Mean = 71 (50–83) | Mean = 26.3 (11–60) |
### Table 5.2: Freedom from PSA-failure

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Stage or grade</td>
<td>T1b–T2</td>
<td>Definition of failure</td>
<td>2 consecutive increases in PSA amounting to 2 ng/ml, PSA&gt;4 ng/ml, or post-treatment PSA&gt;half pretreatment PSA</td>
<td>ASTRO PSA&gt;1 and not decreasing</td>
<td>T1–T2 PSA&gt;0.5 ng/ml 2 increases above nadir</td>
</tr>
<tr>
<td>2 year</td>
<td>94.7%</td>
<td>10% 2Y if high risk (PSA&gt;20, or GS≥8, or T≥T2c)</td>
<td>70% at 2 years if iPSA&gt;15 from graph</td>
<td>Overall 73%; 88% at 3 years if iPSA≤15 (from graph)</td>
<td></td>
</tr>
<tr>
<td>3 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 year</td>
<td>Not stated overall 87% 5Y if low risk (PSA≤10, and T≤T2a and GS&lt;6); 30% if intermediate risk (not low or high)</td>
<td>overall: 78% by pretreatment PSA: £ 4.0 ng/ml: 93% 4.1 to 10.0 ng/ml: 87% 0.1 to 20.0 ng/ml: 72% &gt; 20 ng/ml: 45%</td>
<td>Overall 79%; 88% (iPSA&lt;10); 72% (iPSA10–20); 57% (iPSA&gt;20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65%</td>
</tr>
</tbody>
</table>
### Table 5.3: Complications of brachytherapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Incontinence*</td>
<td>18%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Obstruction/irritative sx</td>
<td>28%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Proctitis</td>
<td>9%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>1%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence*</td>
<td>55% (a)</td>
<td>50% (b)</td>
<td>50% (c)</td>
</tr>
<tr>
<td>Rectal complications</td>
<td></td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>Urethral necrosis</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineal discomfort/pain</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(short term)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These patients had these problems before seed implant and therefore not necessarily complications of brachytherapy.

Note—the percentage of patients suffering from impotence and incontinence in this table is the number of men who are impotent post-operatively divided by the number of men who have been treated. This has been done to remain consistent across the results of all the trials, including those where pre-operative potency and continence status is not known. The percentage includes, however, the percentage of men who were impotent or incontinent prior to treatment, and not just those who suffered these as complications of treatment.
References—Chapter 5


Critz FA(b), Levinson K, Williams WH, Holladay D, Holladay C and Griffin V. Prostate-specific antigen nadir of 0.5 ng/mL or less defines disease freedom for surgically staged men irradiated for prostate cancer. Urology. 1997 May; 49(5):668–72; ISSN: 0090-4295.


6 OTHER TREATMENT APPROACHES FOR PROSTATE CANCER

6.1 No initial treatment, or deferred treatment

Summary

- Information on the effectiveness of no active treatment comes from uncontrolled case series. Patients have generally been in older age groups with well differentiated tumours therefore representing a biased sample. There are no randomised trials comparing the relative effectiveness and morbidity of conservative management in comparison with other treatments.

- No active treatment for men with well- and perhaps moderately-differentiated tumours of low volume who have a life expectancy of less than 10 years is widely advocated in the literature. Patient preferences are a major factor in the decision process.

- High grade tumours are generally not recommended for deferred treatment.

- Cancer specific survival is reasonably high in well to moderately differentiated tumours with 10–15 years of follow up. It is hoped that further collection of PSA data will assist in establishing more confident information.

- It is still unclear how patients who choose no active treatment should be observed. Patient reported quality of life for no initial treatment is not known. Morbidity of advanced disease is a significant side effect of this treatment, although quantification of this side effect is difficult.

- Suitable end points for intervention after failed watchful waiting have not been established.

6.1.1 Background

No initial treatment

This strategy is sometimes given the term ‘watchful waiting’. We have avoided this term, as it implies that this approach inevitably leads to some form of progression of the disease. Under this strategy, treatment is reserved for symptoms or complications of prostate cancer, while not necessarily attempting to bring about a ‘cure’ (this approach is more common in Western Europe than in the US or Australia). The average time from diagnosis to the need for palliative treatment is approximately 10 years, depending on characteristics of the tumour—in many men treatment will not be necessary at all, and others may require only minor treatment for the relief of symptoms. It may, however, result in greater quality of
Evidence-based information and recommendations for the management of localised prostate cancer

Life than would active treatment. However, it may miss an important opportunity to bring about a complete cure, and prevent metastatic dissemination.

This form of treatment implies that there will be no active treatment of the patient until lower urinary tract symptoms develop (in which case surgical intervention such as TURP may be required) or metastatic disease becomes evident or symptomatic. Conservative management is still widely advocated in the late 1990s: controversy arises from the uncertainty over the natural history of prostate cancer, the incomplete knowledge over which tumours will progress, and the lack of data concerning the effectiveness of radical treatments.

No active treatment tends to be used particularly for older men and those with more advanced disease (although there is debate over who mostly benefits from this approach). Ideally, it would be used in those patients whose prostate cancer is not destined to progress or lead to morbidity or mortality, but it remains difficult to predict the behaviour of cancers in such a way. There have been substantial difficulties in evaluating the effectiveness of conservative management, largely due to patient and clinician reluctance to randomise patients to no initial treatment.

No initial treatment, followed by either surgery or radiotherapy

This category has been included in the report as there is a substantial group of patients who, after receiving a diagnosis of localised prostate cancer, elect to defer a decision over active treatment, and undertake treatment at a later date.

While it seems logical to undertake potentially curative treatment as early as possible if this is the chosen course, some patients will initially opt for no treatment and subsequently decide upon attempted curative treatment such as surgery and radiotherapy. Currently it is impossible to give advice to this group of patients based on the literature. It is also impossible to advise patients when an initial period of no treatment will compromise their ultimate outcome as there are no data on which to base these decisions.

6.1.2 Studies examining survival and progression rates

Studies examining survival and progression rates in studies of no initial treatment are summarised below:


In this series, all men identified by the Connecticut Tumour Registry with clinically localised prostate cancer diagnosed in 1971 to 1976 who were aged 65 to 75 years at the time of diagnosis were subjects in a life expectancy and mortality study. The authors used a parametric proportional hazards model incorporating tumour histological findings, comorbidity and age at the time of diagnosis to compare cohort survival with that in the general population.

mean follow-up: 15.5 years
Gleason score 2–4: age-adjusted survival not significantly different from the wider population

Gleason score 5–7: maximum estimated lost life expectancy was 4 to 5 years

Gleason score 8–10: maximum estimated lost life expectancy was 6 to 8 years

The authors conclude that tumour histological findings and patient comorbidities were powerful independent predictors of survival. Men with higher-grade tumours (Gleason 5–10) experienced a progressively increasing loss of life expectancy.


Albertsen and colleagues assembled a further cohort of 771 men from the Connecticut Tumour Registry, who were managed conservatively (although offered hormone treatment), and examined survival 15 years post-diagnosis. Again in this analysis, prostate cancer mortality was highly correlated with Gleason score:

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Death from prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4</td>
<td>6%</td>
</tr>
<tr>
<td>5–6</td>
<td>20%</td>
</tr>
<tr>
<td>7</td>
<td>45%</td>
</tr>
<tr>
<td>8–10</td>
<td>63%</td>
</tr>
</tbody>
</table>

- Men with high Gleason score had a significant risk of death from prostate cancer even when diagnosed up to the age of 75 years
- Men with lower Gleason scores had a more modest risk of death even when the diagnosis was made at an earlier age


This study was based on patients diagnosed at the Karolinska Hospital in Sweden who were prospectively followed in a surveillance protocol followed by treatment when the tumour progressed with symptoms. Using a survival plot, the projected disease-specific survival rate at 15 years was 62%. These authors concluded that deferred treatment is a valid option for patients with clinically localised low-grade prostate cancer and a life expectancy of 10 years or less, but that ‘there is probably room for efficacious local treatment in patients with localised prostate cancer and a life expectancy longer than 10 years’.


There are now 15 year follow-up data in the Johanssen et al study (1997). This study followed a group of 642 patients with prostate cancer of any stage, consecutively diagnosed between 1977 and 1984 at a mean age of 72 years, with
complete follow-up to 1994. Prostate cancer accounted for 37% of all deaths. Among 300 patients with localised disease (T0–2), 11% died of prostate cancer.

In the group with localised disease, the 15 year survival rate was similar in 223 patients with deferred treatment (81%, 95% CI, 72%–89%) and in 77 who received initial treatment (81%, 95% CI, 67%–95%).

The authors found an overall, long-term corrected survival rate which was slightly higher than the whole of Sweden.

5) **Borre et al (1997)**

This study from the Danish Cancer Society analysed the impact on mortality of prostate cancer managed only with palliative treatment in 719 patients from a single Danish county. At a follow-up point at which 98% of patients had died, prostate cancer was responsible for 62% of the deaths; the authors conclude that prostate cancer which presents clinically is a biologically aggressive disease and, in the absence of effective therapy, results in a high disease-related morbidity and mortality.

This study included patients with all stages of cancer, but in the subset of 208 patients with clinically localised prostate cancer, the survival rate was only 71% at 5 years and 42% at 10 years (worse rates than the previously-reported studies of deferred treatment). A number of study characteristics may have contributed to these findings:

- data were collected retrospectively
- patients were relatively elderly
- most were symptomatic
- most had locally advanced carcinoma or disseminated disease
- the population may have differed from the other studies

6) **Chodak et al's study (1994)**

This study, which was included in the AUA Report (Middleton RG et al, 1995) and has been widely discussed in the literature, found that a similar outcome can be achieved for at least 10 years with initially conservative management of low or intermediate grade prostate cancer, in comparison to active treatment. This pooled analysis of non-randomised studies of observation plus delayed hormone therapy (which included a fairly extensive examination for bias) demonstrated an 87% 10 year disease-specific survival with low or intermediate grade tumours. There were insufficient numbers to draw reasonable conclusions about individuals with high grade disease in this study.

7) **Brasso et al (1998)**

Given that expectant management is widespread in Denmark, examination of Danish survival data warrants examination. Brasso et al (1998) analysed data from patients with clinically localised prostate cancer age 55–74, recorded on the Danish Cancer Registry in the period 1943 to 1986 and surviving 10 or more
years. Of these patients 978 (74%) had died, and an excess mortality rate of 1.72 was observed in the 55–64 age group, and 1.5 in the 65–74 age group. In patients where the cause of death was evaluable, prostate cancer was the direct cause of death in 42.9% of cases, and a contributing cause in 21.5% of cases.

8) Lu-Yao & Yao (1997)
The ‘no-intervention’ arm of this population-based analysis of cancer registry data, examining overall- and prostate-cancer-specific survival in men undergoing active or conservative management is one of the largest cohorts available. Ten-year prostate-cancer-specific survival for those in the conservative management group, by grade of cancer, was:

- low grade: 93% (95% CI 91–94)
- intermediate grade: 77% (95% CI 74–80)
- high grade: 45% (95% CI 40–51)

As described in Table 3.3, this compares with cause-specific actuarial survival rates post-radical prostatectomy of: low grade—94%, intermediate grade—87% high grade—67%.

**Table 6.2: Survival rates in patients undergoing watchful waiting**
### Table 6.1: Trials reporting survival in patients undergoing no active treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Study type</th>
<th>No of patients</th>
<th>Grade/Stage</th>
<th>Method</th>
<th>Average age at diagnosis</th>
<th>Months followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolfsson et al (1998)</td>
<td>Patients diagnosed at the Karolinska Hospital, Stockholm</td>
<td>Case series</td>
<td>122</td>
<td>T2</td>
<td>surveillance</td>
<td>120 or more</td>
<td></td>
</tr>
<tr>
<td>Albertsen et al (1995)</td>
<td>All men identified by the Connecticut Tumour Registry with clinically localised prostate cancer diagnosed in 1971–1976 aged 65–75 years at the time of diagnosis</td>
<td>Case series</td>
<td>451</td>
<td>TA1—14%, TA2—24%, TBx—49%</td>
<td>Surveillance only or surveillance and hormonal therapy</td>
<td>65–75 years (mean 70.9 years)</td>
<td>Mean = 15.5 years</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting</td>
<td>Study type</td>
<td>No of patients</td>
<td>Grade/stage</td>
<td>Method</td>
<td>Average age at diagnosis</td>
<td>Months followed</td>
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<td>-----------</td>
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</tr>
<tr>
<td>Johansson et al (1997)</td>
<td>Patients with prostate cancer of any stage, consecutively diagnosed between 1977 and 1984</td>
<td>Case series, made comparisons with general population data</td>
<td>642, of whom 223 received no initial treatment</td>
<td>T0—18% T1a—2—33% T3—4—49%</td>
<td>Watchful waiting</td>
<td>Mean = 72 years</td>
<td>Mean = 168 (126–210)</td>
</tr>
</tbody>
</table>
6.2 Cryotherapy

Transrectal ultrasound-guided percutaneous transperineal prostate cryoablation is attracting interest particularly in the US, and is used in some centres as a primary treatment alternative to surgery or irradiation, as a salvage treatment for recurrent cancer after irradiation, and for debulking of large symptomatic primary tumours (Schmidt et al, 1998). Cryotherapy induces cell lysis in the prostate by direct application of low temperatures.

Very little data are available for cryoablation in localised prostate cancer. Series based on small numbers, such as a study in Germany by Derakhshani et al (1998) involving 48 patients, offer little to evaluate this form of treatment. Long-term follow-up and prospective studies are necessary to define the clinical significance of this procedure.

Long et al (1998) have been conducting an ongoing prospective pilot study of the use of cryosurgical prostate ablation in treating patients with non-metastatic prostate cancer. Results in 145 patients with mean follow-up of 36 months show overall actuarial rates at 42 months for maintaining PSA to be less than 0.3 and less than 1.0 were 59% and 66% respectively; the overall actuarial progression-free rate at 60 months was 56%.

In certain circumstances large gland volumes prevent adequate freezing of the prostate. Cryotherapy has been used as a salvage treatment following radical prostatectomy, with substantial morbidity, although results are based on very small numbers.
While cryotherapy involves the freezing of prostate tissue, there is also interest in the use of local tumour heat treatments, based on laboratory studies (Peschke et al, 1998), although adequate trial data are currently unavailable.

6.3 Combined treatments

There has been a significant shift in the US towards multi-modality therapy (Pisters et al, 1999). Radical prostatectomy plus hormonal treatment is a treatment approach which is becoming more widespread. Androgen ablation prior to radical prostatectomy has attracted interest: results of a number of randomised studies have shown a significant pathologic downstaging and a decrease in the rate of positive surgical margins using neoadjuvant therapy in stage B cancers (Fradet, 1996).

In a randomised controlled trial of 213 patients, Goldenberg et al (1996) demonstrated a reduced rate of positive margins following radical prostatectomy without adversely affecting postoperative recovery with the use of neoadjuvant androgen ablation. There are no data available of the impact on patient survival for using combined treatments such as these.

6.4 Salvage treatments

While few data are available in Australia, data from a US longitudinal disease registry of patients with prostate cancer suggest approximately 1 in 5 patients receive second cancer treatments within a mean of 3 years following initial local treatment for prostate cancer. The likelihood of receiving second treatment was lowest in patients initially treated with radical prostatectomy in patients from this registry (Grossfeld et al, 1998).

Salvage radical prostatectomy is a treatment option for patients with recurrent cancer following radiation therapy. Based on a series of 86 patients who underwent salvage radical prostatectomy, post-irradiation Gleason score and DNA ploidy were independent predictors of distant metastasis-free survival and cancer-specific survival (Cheng et al, 1998).

The role of salvage radiotherapy is at present unclear. In a Californian study 69 patients were diagnosed with presumed local tumour recurrence after radical prostatectomy, 60 of whom were referred to radiotherapy for salvage treatments (Do et al, 1998). Tumour recurrence was detected biochemically, with or without a palpable nodule on DRE. Univariate and multivariate analyses revealed that both PSA > 1.0ng/ml at the time of salvage radiotherapy, and perineural invasion were significant predictors of prognosis for biochemical relapse after salvage radiotherapy.

Apart from the studies relating to ‘no active treatment’, few data are available to assess the likely impact on survival and other patient outcomes of alternative treatment approaches.
References—Chapter 6


Borre M, Nerstrom B and Overgaard J. The natural history of prostate carcinoma based on a Danish population treated with no intent to cure [see comments]. Cancer. 1997 Sep 1; 80(5):917–28; ISSN: 0008-543X


7 EVIDENCE OF TREATMENT EFFECTIVENESS FROM POPULATION-LEVEL DISEASE TRENDS AND MODELLING ANALYSES

Summary

- Rates of active treatment for localised prostate cancer have increased substantially in the past decade, and this may have impacted on prostate cancer disease trends.

- The decline in rates of late-stage disease, and the apparent fall in mortality from prostate cancer observed in the US population have been proposed as evidence that early detection and treatment efforts are effective.

- These descriptive data are, however, insufficient to draw conclusions about treatment effectiveness at this time.

- Similarly, modelling techniques have failed to produce definitive results, and are extremely sensitive to patient preferences.

7.1 Trends in treatment patterns

Analysis of patterns of treatment enables comparisons to be made with trends in prostate cancer incidence, mortality and survival at a population level. Recent SEER data (National Cancer Institute, 1998) provided population based information regarding treatment patterns and the impact increased early detection efforts on treatment practices.

Figure 7.1 shows the trends in incidence in patients with localised or regional stage disease analysed by type of treatment for 1983–1995. The data show that in the US, the increased incidence of prostate cancer between 1986 and 1992 was accompanied by increases in more active therapy (radical prostatectomy or radiation therapy) for localised and regional cancers.

Further analysis of these data reveals that recent treatment patterns in the US for local/regional cancers vary by age. Radical prostatectomy is more frequent among men under age 70, radiation therapy in those aged 70–79, and conservative therapy (no treatment or hormonal therapy) in those aged over 79 years. Treatment for advanced cancers has not changed over time with about 65% of patients receiving hormonal therapy.
There is interest in whether small, indolent cancers have been more actively treated in recent years. Soh et al (1997) have examined trends in pathological features and prognosis of patients treated with radical prostatectomy between 1983 and 1985 in 754 consecutive patients (treated by a single surgeon), and found no change in pathological stage or progression rate. Given the trends in incidence, mortality, stage and grade and survival described in Chapter 1, there is interest in examining the ways in which early detection and treatment of prostate cancer may have influenced these population measures. This issue requires wider analysis in multi-centre studies.

7.2 Population impact of increased detection and treatment of prostate cancer

7.2.1 Survival

As described in Chapter 1, survival rates from prostate cancer have improved steadily in recent years, and it is likely that this is due in part to changing treatment patterns. Increased detection of early prostate cancer through PSA testing has influenced the pattern of prostate cancer in the population. The potential impact on survival, incidence and mortality is dealt with in some detail in the recent update of the 1996 AHTAC Report (Weller et al, 1999). In particular,
increased screening and treatment is likely to lead to increased detection of less aggressive prostate tumours (with longer survival times), and this appears evident in population studies (Helgesen et al, 1996; Gilliland et al, 1996). Improved survival data may, however, be artefactual. The increased use of screening tests such as PSA may simply bring forward the time of diagnosis without altering the course of the disease (lead-time bias), or lead to the discovery of a greater proportion of slower-growing tumours (length bias).

7.2.2 Incidence and mortality

The impact of increased screening activities on incidence of prostate cancer has important implications for the management of localised prostate cancer. It is still not possible to say whether increased detection and treatment of prostate cancer is having an effect on mortality in the population. The drop in prostate cancer mortality observed in the SEER data poses important questions: will the decline be sustained? If so at what level? It is important to monitor these data over the coming years, and make comparisons with high-quality Australian registry-based data. On the basis of these population data, we are some way off concluding, that screening and treatment activities are having an impact on mortality.

7.2.3 Stage distribution in the population

The reduction in stage at diagnosis, observable at population level in the US SEER data, may be due to either the removal of advanced cases from the prevalent population, or to early detection and treatment of cases before they have reached the advanced disease state (or to both). While falling rates of advanced disease in the population would be a necessary prelude to reductions in mortality, they are insufficient in themselves to imply mortality reductions (Stephenson & Stanford, 1997), and there remains controversy over the interpretation of reductions in advanced disease rates (Gann, 1997).

7.3 Models examining outcomes of treatments for prostate cancer

In the absence of definitive evidence on the effectiveness of various treatments for prostate cancer, decision analysis and modelling approaches have attracted widespread interest.

Decision analyses of prostate cancer treatment have been widely reported, particularly an analysis by Fleming (1993) which was included in the 1996 AHTAC Report, and concluded that radical prostatectomy and radiation therapy may benefit selected groups of patients with localised prostate cancer—particularly younger patients with higher-grade tumours. A more recent decision analysis concluded that there is likely to be a quality-adjusted treatment benefit for radical prostatectomy for younger men and treatment harm for older men (Kattan et al, 1997). Tailored patient and clinician decisions remain necessary, especially for men older than 70 in good health but with aggressive cancers.
These models rely on a range of assumptions about progression rates and treatment benefits and have frequently been challenged on the basis of inaccuracies in these underlying assumptions (Beck et al, 1994). Because of the uncertainty regarding the data used in the construction of the models, the models have not been able to provide more definitive answers to the question of which treatment has the greatest likelihood of benefit in which clinical situation. The models have also been shown to be highly sensitive to patient preferences Kattan et al (1997). This implies that even when better quality data does become available, it will be critical to elucidate patient preferences and include these in the decision making process.

References—Chapter 7


Soh S, Kattan MW, Berkman S, Wheeler TM and Scardino PT. Has there been a recent shift in the pathological features and prognosis of patients treated with radical prostatectomy? [see comments]. J Urol. 1997 Jun; 157(6):2212-8; ISSN: 0022-5347


The American Urological Association (AUA) documents, on which these recommendations have been extensively based, contains a number of recommendations on the management of prostate cancer. These were generated by The American Urological Association Prostate Cancer Clinical Guidelines Panel, and were based on the outcome estimates available in their literature review, and on panel opinion.

The Panel produced three different kinds of recommendation, based on the strength of evidence and the panel’s assessment of patient needs and preferences:

• Standard: a policy was considered a standard if the health and economic outcomes of the alternative interventions are sufficiently well-known to permit meaningful decisions and there is virtual unanimity about which intervention is preferred,

• Guideline: a policy was considered a guideline if the health and economic outcomes of the alternative interventions are sufficiently well-known to permit meaningful decisions and an appreciable but not unanimous majority agree on which intervention is preferred, and

• Option: a policy was considered an option if

  1) the health and economic outcomes of the interventions were not sufficiently well-known to permit meaningful decisions

  2) preferences among the outcomes were not known

  3) patients’ preferences were divided among alternative interventions, and/or

  4) patients were indifferent about the alternative interventions

The Panel defined a standard as having the least flexibility, a guideline significantly more flexibility, and an option as the most flexible. The Panel considered that options could exist because of insufficient evidence or because patient preferences were divided or unknown.

In the Panel’s recommendations, those regarding treatment choices were labelled options mostly because of insufficient evidence. None of the Panel recommendations fitted the above definition of a guideline.

The Panel's recommendations apply to the ‘standard patient’, which they defined as a man who has clinically localised prostate cancer (adenocarcinoma of the prostate). The panel focused on clinical stage T2 disease, but considered that recommendations could also be applied to patients diagnosed with stage cT1c disease (detected by elevated PSA). The recommendations were not developed for patients with stage T1a/b (A1/A2) or clinical T3–T4 (C) disease.
In this chapter, the AUA recommendations are presented largely as the appear in the 1995 document, with some minor changes in wording from the Australian Cancer Network Working Party. The Recommendations considered to be standard are those that all patients could reasonably expect to be applied in the management of localised prostate cancer. After each of the recommendations is a ‘comment’ which draws from literature reviewed in earlier chapters of this document, and input from the Working Group.

8.1 **Assessment of patient’s life expectancy, overall health status and tumour characteristics prior to treatment decisions (Standard)**

**Summary of recommendation**

As a standard, the Panel considered an assessment of the patient’s life expectancy, overall health status and tumour characteristics to be necessary before any treatment decisions could be made.

**Level IV**

**Life expectancy**

Life expectancy, rather than patient age, should be the factor considered in treatment selection. Therefore, the panel did not set a specific chronological cutoff point. When a man’s life expectancy is relatively long, prostate cancer can be a cause of morbidity and mortality. On the other hand, at an advanced patient age, or when life expectancy is relatively short, competing hazards for mortality reduce the chance that a man will suffer from disease progression or die from prostate cancer.

**Health status**

The patient’s overall health status is the sum of all conditions and includes both patient and family history as well as the present state of the patient’s well-being and the degree of any coexistent disease. There are two reasons to evaluate the overall health status prior to deciding on an intervention: (1) Overall health status influences life expectancy; (2) overall health status may affect patient response to adverse events resulting from particular interventions.

**Tumour-related prognostic factors**

The histological grade, volume, PSA and stage of the tumour should be considered when assessing the potential natural history and treatment options for prostate cancer. Small, well-differentiated cancers progress more slowly and are less likely to be life threatening than large, poorly differentiated tumours which have a greater potential to be biologically aggressive and clinically significant.
Level IV (predominantly) and Level III-2

Comment

Recent literature reinforces the need for assessment of patient’s life expectancy, overall health status and tumour characteristics prior to treatment decisions. Growing expertise in identifying prognostic factors that are unrelated to treatments received gives added weight to this recommendation.

8.2 Provision of information on benefits and harms of available treatments to patients (STANDARD)

Summary of recommendation

As a standard, a patient with clinically localised prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, radical prostatectomy, radiotherapy and no initial treatment. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient. There should also be a discussion about less commonly-used treatments such as cryotherapy, and the degree to which use of these treatments is supported by evidence Porterfield (1977), Pinnock et al (1998).

Level IV

The panel defined radical prostatectomy to include complete removal of the prostate, vassal ampullae and seminal vesicles. The panel defined radiotherapy to include external beam and/or interstitial (brachytherapy) treatments. Surveillance was defined as periodic monitoring of the patient’s prostate cancer and its effects.

The patient should be informed that depending on his condition and initial choice, subsequent interventions may be appropriate.

Level IV

Comment

Recent literature, Pinnock, et al (1998) and AUA (1995), reinforces this information and suggests that patients are increasingly expecting the provision of comprehensive information on harms and benefits. There is growing interest in the training of health professionals to develop skills in presentation of such ‘harm versus benefit’ information, to enable fully informed, negotiated treatment decisions between patients and doctors.
8.3 Incorporation of patient preferences into treatment decisions (STANDARD)

Summary of recommendation

As a standard, the patient’s preference, based on his attitude toward the course of the disease and the benefits and harms of the different interventions, should be considered in determining his treatment.

Level IV

Keypoint:

- Psychosocial factors need to be given significant recognition, particularly the need for education with regard to therapeutic choices and which would be optimal for the individual.

Comment


8.4 Treatment recommendations (OPTIONS)

Summary of recommendations

Options for the management of localised prostate cancer include radical prostatectomy, radiotherapy and no treatment. Radiotherapy includes external beam and interstitial radiotherapy (brachytherapy) treatments.

The panel at this time considers these interventions to be options for the treatment of localised prostate cancer because the data currently available in the literature do not provide sufficient clear cut evidence to indicate the unquestioned superiority of any one form of treatment.

Radical prostatectomy

The patient most likely to benefit from radical prostatectomy is one with a relatively long life expectancy (>10 years), with no significant surgical risk factors, low volume low PSA and who, after being informed of the risks and benefits, prefers surgery.
Level IV (predominantly) and Level III-2

Radiotherapy

The patient most likely to benefit from external beam radiotherapy is one with a relatively long life expectancy (> 10 years), who has low volume low PSA and a moderately differentiated tumour and who, after being informed of the risks and benefits, prefers external beam radiotherapy.

Level IV (predominantly) and Level III-2

Interstitial radiotherapy (brachytherapy)

The patient most likely to benefit from interstitial radiotherapy is one with low volume low grade disease with a long life expectancy (> 10 years). However, long-term follow up is limited and this needs to be stressed when patients are being informed as to the risks and benefits of this form of treatment.

Level IV

No initial treatment

The patient most likely to benefit from no initial treatment is one with well to moderately differentiated tumours with low volume disease, low PSA, has a life expectancy less than 10 years and who, when fully informed of the risks and benefits of this form of treatment, has a preference for no treatment.

Level IV (predominantly) and Level III-2

Comment

Crucial to the implementation of any form of treatment is the need to ensure that men are adequately informed regarding the risks and benefits of the possible treatment options. It is recommended that all men considering treatment for localised prostate cancer should be at least provided with written information regarding risks and benefits of the current treatment options.

References—Chapter 8


9 FUTURE RESEARCH INTO PROSTATE CANCER

9.1 Recommendations for future research

Summary of recommendations

- New and better methods to diagnose and manage localised prostate cancer;
- Prospective, randomised, controlled studies of the issues concerning prostate cancer, especially controlled studies of competing treatments for the management of localised prostate cancer;
- Studies of how prostate cancer and its treatments affect (patient) quality of life,
- Methods of effectively delivering information to patients to allow them to effectively evaluate their options and incorporate their preferences, and
- Research into psychosocial aspects.

Recommendations for randomised controlled trials

There is a pressing need for properly designed and controlled, prospective, randomised clinical trials to study effectiveness of competing treatment modalities for localised disease. In particular, randomised, controlled trials are needed to compare surveillance with the accepted active treatments.

Properly designed efficacy studies of treatment modalities will provide reliable descriptive data for the patients studied. The descriptive factors should include age, tumour stage, tumour grade, ploidy, PSA, performance status and comorbidity, as well as cost factors and validated measures of quality of life over the course of a trial. End points measured in a trial should include risk of local recurrence, risk of metastatic disease and risk of prostate cancer death.

Following are additional suggested study topics for each of the three major treatment modalities:

- Radical prostatectomy: Methods of improving preoperative staging, better selection to reduce the number of patients with extraprostatic disease and reduce treatment complications; strategies to reduce the cost of the procedure; better ways to disseminate advances in surgical techniques to the urological community; treatments for patients with pathologically proven (pT3) extraprostatic disease; and treatments for patients with evidence of serologic (PSA) failure.
Evidence-based information and recommendations for the management of localised prostate cancer

- **Radiotherapy**: Ways to reduce treatment morbidity; ways to standardise treatment; the role of conformal therapy and of radiosensitizers; strategies to reduce the cost of treatment; optimal treatment at progression; mature data on long term follow-up of existing radiotherapy patients; stage-specific complications data on existing series and PSA and biopsy data; research approaches investigating escalating radiation dose eg temporary brachytherapy implants.

- **No active treatment**: Optimal schedule of follow-up and optimal interventions at evidence of progression.

Among the other topics and issues that need to be addressed in rigorously designed clinical trials are:

- New technologies for the treatment of clinically localised prostate cancer
- Research into the decision-making process by men, their GPs, urologists, radiation oncologists, medical oncologists and other health professionals
- Trade-offs between survival and quality of life—including analysis of methods by which patients make treatment choices and the role played by quality-of-life factors in those choices
- Opportunities for chemoprevention of prostate cancer and dietary interventions, hormonal therapy and retinoid therapy
- New strategies for the use of hormonal treatments
- Combined therapies for prostate cancer
- Development and validation of surrogate measures of long-term prostate cancer outcomes (eg validation of PSA failure as a surrogate for cancer survival)

**Patient quality of life (QoL)**

Research is needed for determining how prostate cancer and its treatments affect quality of life (QoL). Such research would include the second topic in the foregoing list: analysis of trade-offs between survival and quality of life and how QoL factors affect patients’ treatment choices. Needed also are improved methods for enhancing patient involvement in a meaningful and efficient decision-making process and improved methods for providing unbiased information to patients and physicians about emerging processes and outcomes of care. Psychosocial aspects, including the impact of QoL on incontinence, sexuality and other cancer related issues (eg survival, confrontation with mortality). The best models for developing supportive care to improve QoL through support groups, nurse counsellors and other activities need to be explored and further developed. Evaluation of all these initiatives needs to be an integral part of the process. A satisfactory model which has had wide cross disciplinary impact is the Psychosocial Breast Guidelines. These provide a template for research in individual cancers.
Further research needs

With the increasing emphasis on efficient allocation of health care resources, it will be necessary to develop methods to assess the costs related to treatment of prostate cancer. These include the costs of early detection, of treatment and of complications from treatment. It would be useful as well to be able to assess the financial impact of intervention on productive longevity and the costs related to disability, long-term care and management of metastatic disease, and to compare these data with similar data regarding the financial impact of the disease itself.

It would also be helpful for future research to have a prostate cancer registry established for all prostate cancer cases in Australia.

Comments

The need for well-designed prospective randomised controlled trials clearly remains, although with the recent failure of the UK trial, and difficulties with other RCTs, there would appear to be the need for major international efforts to address the problems (including recruitment, contamination of controls) experienced in these trials.

The recommendation for further research on tumour and other characteristics as predictors of prognosis is reinforced by recent literature. In particular, it appears that multivariate prognostic systems can estimate patient prognosis more accurately than systems based on anatomical factors; cooperative, multi-institutional research collaborations may be necessary to validate findings such as these. Knowledge and expertise is growing rapidly in this area (particularly with the advent of newer prognostic markers at the molecular and genetic level), and the potential exists to greatly improve the predictability of which cancers are destined to progress.

The recommendations for further research to refine the various treatment options are unchallenged.

There has been an increasing number of prostate cancer-specific quality of life measures in recent years, and this has added considerably to outcome assessment in prostate cancer treatments.

The recommendation for further research on cost-effectiveness of prostate cancer treatments, and for adequate registries for prostate cancer, is reinforced by recent literature.

In common with studies reporting active treatments, interpretation of these long-term trials of deferred treatment requires methodological qualification:

- the mean age in these series is generally older than for the active treatment series, and few of these patients would normally be considered for radical prostatectomy;
- it seems logical that there would be a higher number of non-disease-related deaths in older men as opposed to younger ones— that is, the increased
intercurrent death rate in an older population will lower the cancer-specific death rate;
• over-representation of patients with low volume and low grade disease who are at low risk of tumour progression and at particularly low risk of increased mortality; and
• in the Johansson (1997) study, detection of events was by clinical signs or symptoms—not by serial PSA measurements—and had all data dealt with symptomatic progression.

Steinberg et al (1998) recently reviewed the literature on studies examining no initial active treatment. They conclude that no active treatment is probably the best treatment option for men with well and perhaps moderately differentiated, low volume prostate cancer who have a life expectancy of less than ten years. They argue, however, that the conclusion derived from no active treatment studies of older men cannot and should not be applied to younger, healthier men or to those with more advanced or aggressive disease—if treated ineffectively many of these men will die of prostate cancer.

Clearly, then, interpretation of studies on no active treatment remains controversial. In the absence of results from randomised trials, there is no widespread agreement over the degree to which results of the trials of no active treatment are widely applicable, in terms of their patient and tumour characteristics, treatment regimes, and follow-up practices.

In summary, this document has progressed the American Urological publication The Management of Localised Prostate Cancer (1995) by systematic review of the literature until August 1998.

The final recommendations of the multidisciplinary Working Party of the ACN, which worked within the parameters of Guidelines for the Development and Implementation of Clinical Practice Guidelines (1995). In making final recommendations the ACN Working Party found no evidence from recent literature to warrant substantive changes to the recommendations included in the American Urological Association publication.

References—Chapter 9


APPENDIX 1

Radical prostatectomy study details

a. Studies on progression and survival
1) Catalona (1994)—12% of the 925 patients who had been treated by radical prostatectomy had cancer recurrence by 5 years. Of these, 68% had a detectable level of PSA as the only indication of relapse. The average interval to cancer recurrence was 24 +/-21.5 months (range 1 to 101). Higher preoperative PSA levels were significantly associated with cancer recurrence. There was a lower rate of recurrence in patients with stage T1c than for patients with T1a or b, but this may have been due to a shorter average length of follow-up.
2) Dillioglugil (1997)—showed that PSA progression after radical prostatectomy usually occurred during the first 2 years.
3) Frohmuller (1995)—published the results of a consecutive series of 100 patients treated by radical prostatectomy at University of Wurzburg since 1969 and followed for at least 15 years. Even though more than 30 of these patients had locally advanced tumours, the overall survival rate closely matched the life expectancy of an age matched control population (51% survival at 15 years for patients versus 44% for controls). The 10 year non-progression survival rate for patients with poorly differentiated tumours (including locally advanced) was 58%, which compares favourably with the computed 10-year survival rate of untreated patients with poorly differentiated tumours in the study by Chodak et al (1994) of 26%.
4) Gerber (1996)—pooled data from 8 institutions of 20 who had been invited to participate. These were Duke University, University of Utah, Baylor College of Medicine, University of Wurzburg, Erasmus University, University of Chicago, Vanderbilt University and Eastern Virginia Medical School. The actuarial cancer-specific mortality rate at 10 years in patients with well-differentiated, moderately differentiated and poorly differentiated adenocarcinoma was 6%, 20% and 23% respectively.
5) Krongrad (1997)—analysed data from the SEER database for patients diagnosed and treated with radical prostatectomy between 1983 and 1987. The first date was chosen because it marked the introduction of the anatomical retropubic approach to prostatectomy, and the later date was chosen because of the observation that the age-specific stage at diagnosis redistributed after 1987 as a result of the more widespread usage of PSA testing. The 10 year disease-specific survival rate ranged from 75% to 97% for patients with well-differentiated and moderately differentiated cancers and from 60% to 86% for patients with poorly differentiated cancer. The overall survival rate ranged from 57% to 86% for patients with well-differentiated and moderately differentiated cancers and from 50% to 66% for patients with poorly differentiated cancers.
6) Oefelein (1997)—followed 116 men with clinically localised but high grade prostate cancer. 20 of the men were excluded from the analysis because of positive evidence of lymph node dissemination.

7) Ohori (1994)—analysed a consecutive series of patients for survival following prostatectomy. Survival was strongly associated with the grade of the tumour and whether the tumour was confined to the prostate gland. Overall the 5 year non-progression rate was 76%. For patients with poorly differentiated tumours the non-progression rate at 5 years was 85%, compared to 46% for patients with cancer extending outside the gland. Impalpable tumours detected by an elevated PSA level were as likely to be poorly differentiated as palpable disease but were significantly more likely to be confined to the prostate.

8) Trapasso (1994)—A retrospective review was performed on 725 patients with clinically localised prostate cancer. Of these 54 had neoadjuvant hormonal or radiation therapy and 70 had microscopic nodal involvement. Patients were followed for both clinical signs of recurrence and with PSA. PSA doubling time was a predictor of distant metastases. There had been a statistically significant improvement in disease free survival rates for patients treated in 1987 and subsequent years compared to those patients treated prior to 1987 (86% compared to 78%).

9) Walsh (1994)—reviewed the experience at John Hopkins Hospital after 10 years of anatomical radical retropubic prostatectomy. There was no evidence that survival rates had been affected by attempts at preservation of the neurovascular bundles.

10) Witjes (1997)—was a prospective randomised study of radical prostatectomy versus neoadjuvant hormonal therapy prior to surgery. The early data confirmed high understaging percentages in clinical staging. In the short period of follow-up of patients to date, there appeared to be a statistically significant smaller number of patients with positive margins in the neoadjuvantly treated group with a clinical T2 tumour but not in the T3 group.

11) Zincke (1994a)—was a retrospective analysis of 1143 consecutive patients.

12) Zincke (1994b)—analysed survival and complications following prostatectomy for a large series of patients treated over 25 years at the Mayo Clinic. Adjuvant therapy had been used in 26% of patients. This study gave quite extensive breakdown of survival rates by stage and grade. The crude survival rates for the entire group of patients at 10 and 15 years were 75% and 60%, respectively, which were comparable to expected survival rates of 67% and 46%, respectively, derived from 1980 Minnesota life tables for male patients of similar age.

13) Amling et al (1998)—sought to analyse trends in the clinical stage and pathologic outcome of patients with prostate cancer who underwent radical prostatectomy. They studied 5,568 patients with prostate cancer (4,774 with clinically localised disease of stage T2c or less) who underwent pelvic lymphadenectomy and radical retropubic prostatectomy. Patient age, preoperative serum PSA level, clinical stage, pathologic stage, Gleason
score, and tumour ploidy were assessed. Outcome was based on clinical and PSA (increases in PSA level of 0.2 ng/ml or more) progression-free survival. Decreases in patient age (from 65 to 63 years old; P<0.001) and serum PSA level (median, from 8.4 to 6.8 ng/ml; P<0.001) were observed over the study period. The percentage of patients with clinical stage T1c prostate cancer increased from 2.1% in 1987 to 36.4% in 1995 (P<0.001), and clinical stage T3 cancer decreased from 25.3% to 6.5% (P<0.001). Nondiploid tumours decreased from 38.3% to 24.6% (P<0.001), and the proportion of patients with pathologically organ-confined disease increased from 54.9% to 74.3% (P<0.001). More cT1c than cT2 tumours were diploid (80% versus 72%; P<0.001), had a Gleason score of 7 or less (75% versus 65%; P<0.001), and were confined to the prostate (75% versus 57%; P<0.001). Five-year progression-free survival was 85% and 76% for patients with clinical stage T1c and T2, respectively (P<0.001). The authors suggested that since the advent of PSA testing, patients referred to the institution in question for radical prostatectomy had shown a significant migration to lower-stage, less-nondiploid, more often organ-confined prostate cancer at the time of initial assessment.

b. Studies on complication rates

1) Fowler (1995)—Performed a postal survey of men who were Medicare beneficiaries who underwent radical prostatectomy between 1988 and 1990. 420 patients were sampled, equally across the years. 367 men responded (response rate 91%). 12% of men who had had EBRT had a medium or large problem with dripping of urine, compared to 23% of men who had had a prostatectomy.

Although a much higher proportion of men who had radiotherapy were able to achieve erections firm enough for intercourse, there was not a significant difference between the proportion of men who had concerns about sexual functioning between the surgical and radiotherapy groups. There was higher proportion of patients who reported problems with pain or discomfort of bowel action or frequent bowel movements following radiotherapy compared with surgical patients. A greater proportion of patients who had been treated with radiotherapy remained concerned about their prostate cancer.

2) Geary (1995)—Erectile dysfunction was evaluated in 459 men with prostate cancer before and after radical prostatectomy. Of these, 33% had erectile dysfunction pre-operatively. Of the 308 patients who had no erectile dysfunction prior to surgery, 51 (17%) remained potent after surgery. Post-operative potency was statistically related to the number of neurovascular bundles spared, frequency of intercourse preoperatively, absence of seminal vesicle or lymph node involvement with cancer, absence of postoperative incontinence or strictures, patient age and cancer volume.
3) Harris (1996)—give the results of a case series of patients using an anatomical radical perineal prostatectomy. This series resulted in 97.5% of patients achieving full urinary control and approximately 37% of patients retaining sexual function.

4) Helgasson (1997)—identified all 450 men who were alive and had been diagnosed with prostate cancer in 1992 in the area of Stockholm and who were 50 to 80 years old at the time. This included men who were all stages of disease and included 22 men who had radical prostatectomy and 37 men who had had external radiation. A questionnaire was sent to 431 men and 435 randomly selected men with a similar age distribution who did not have prostate cancer. The response rate was 79% of prostate cancer patients and 73% of the reference group. In this study, more men who had had external radiation reported a decrease in sexual function compared with their youth than did men who had had radical prostatectomy, although the numbers in each group were small (35 of 37 in the radiotherapy group and 19 of 22 in the prostatectomy group). 77% of men in the reference group reported a similar decrease in sexual function.

5) Herr (1994)—surveyed 50 patients with moderate to severe urinary incontinence following radical prostatectomy. 26% reported being limited in their usual activities as a result of incontinence and more than half reported moderate to severe emotional distress. Patient satisfaction with the decision to undergo surgery appeared to be a function of time. Of the 18 patients who were evaluated at 1–3 years postoperatively 17% said they would not undergo the operation again, compared with 27% at 3 to 5 years and 53% evaluated after 5 years.

5) Jonler (1994)—administered the same questionnaire as Fowler et al to a consecutive series of patients at their own institution who had been treated at least 12 months previously. The response rate was 92%. 47% of patients used a pad and 59% leaked daily. Prior to surgery 16% reported problems with impotence, but post surgery 51% reported a substantial problem. The rates of complications were higher than in most of the reported literature (which is mostly based on case notes or physician evaluations) but is consistent with the results found by Fowler, et al. Overall, 24% had some persisting degree of physical unpleasantness as a result of the surgery, but 74% were satisfied with the results of the surgery and 88% said that they would undergo surgery again.

6) Kaye (1997)—assessed the effects of three types of apical dissection on urinary continence after radical retropubic prostatectomy and evaluated possible contributing factors. 280 patients were evaluated: in Group 1 (sphincter-damaging) 134 patients underwent the original technique of ligating and transecting the venous complex; in Group 2 (sphincter-repairing), 76 patients had the venous complex with part of striated sphincter incorporated within anastomotic suture(s); and in Group 3 (sphincter-preserving), 70 patients had the venous complex alone ligated using the ‘bunching’ technique of Myers. Continence was achieved in 93% overall, with 90%, 93% and 99% achieving continence in Groups 1, 2 and 3, respectively. The mean time to continence was 68 days overall, taking 100,
52 and 30 days for the respective groups. Twenty patients (7%) did not achieve full continence; 15 had minor incontinence and five severe, with none of the latter being in Group 3. The group (preservation of external sphincter), age and freedom from development of anastomotic strictures were the most important factors both in regaining continence and decreasing the time to continence.

7) Murphy (1994)—conducted a survey for the American College of Surgeons Commission on Cancer in association with the American Cancer Society and American Urological Association. Responses were received from 484 hospitals on 2,122 patients. Potency status was noted for 1,266 patients of whom 207 were reported to be impotent pre-operatively (16%) compared to 64% post-operatively.

8) Shrader-Bogen (1997)—mailed a self administered questionnaire to patients who had clinically localised prostate cancer. The questionnaire consisted of 3 parts: a functional assessment, a treatment outcome questionnaire and a demographic survey. The response rate was 86%. After age adjustment, the radiotherapy group had more bowel dysfunction and the surgical group had more urinary problems and sexual dysfunction. The complications persisted long after treatment. The effect of treatment on overall quality of life was assessed by FACT-G questionnaire. This showed no significant difference between the two treatment groups.

9) Talcott (1997)—this study used self completed questionnaires sent to men who had a radical prostatectomy for clinically localised prostate cancer. Questionnaires were sent prior to surgery and 3 and 12 months post surgery. In this series, nerve sparing prostatectomy improved post-operative sexual function less than previously reported. Men who underwent the nerve sparing procedure were also younger and had less advanced cancers than men who were not treated with the nerve sparing procedure. This may introduce a selection bias into the results of the nerve sparing operation.

10) Walsh (1994)—reported on the experience at Johns Hopkins Hospital after 10 years of anatomical radical retropubic prostatectomy. Anatomical factors rather than the preservation of autonomic innervation were the major factors responsible for improved urinary control associated with an anatomical approach to radical prostatectomy. This series shows a generally improved rate of urinary continence following anatomical radical prostatectomy, and in the 8% of patients for whom there were problems these were mostly mild. Of the 503 patients who were potent preoperatively and followed for a minimum of 18 months, 68% were potent postoperatively. The three factors that were correlated with the return of sexual function were age, clinical and pathological stage, and preservation of the neurovascular bundle. There was also a significant improvement in the preservation of sexual function after the introduction of the anatomical surgical technique. Case records were also checked against a self completed questionnaire completed at 18 months post-surgery. Overall, the results were similar, but in 5% of patients the case records stated that the patient
was potent and the questionnaire stated that the patient was impotent and in 5% the reverse was the case.

11) Zincke (1994)—reviewed 3170 consecutive patients who had been treated for clinically localised prostate cancer at the Mayo clinic over a 25 year period. In that time there had been 10 operative deaths (0.3%), all before 1988.

References—Appendix 1


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Witjes WP, Schulman CC and Debruyne FM. Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-3 N0 M0 prostatic carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer. Urology. 1997 Mar; 49(3A Suppl) 65–9; ISSN: 0909-4295


APPENDIX 2

External beam radiotherapy study details

a. Studies examining progression and survival

1) Corn (1995)—is a comparative study of PSA normalisation between conformal and conventional EBRT, with the conformal group showing significantly greater rates of PSA normalisation.

2) Hanks (1994)—reports on three sources of survival data for patients treated with EBRT. The Patterns of Care Study reports on data collected by a visiting radiation oncologist and physicist for randomly selected patients at a number of facilities throughout the USA. The Radiation Therapy Oncology Group has carried out a number of randomised controlled trials of patients treated with radiotherapy in the USA. The RTOG study from 1977 shows that after 10 years, 9 of the 104 men with T1 and T2 cancers had died of causes related to their prostate cancer and 80 had died of other causes. This study selected patients who would otherwise have been suitable for surgery, so the results of this trial may be more comparable to those of radical prostatectomy studies.

3) Leibel (1994)—17% of the patients in this study had androgen deprivation therapy prior to radiotherapy as they had larger than average volume prostate glands.

4) Zagars (1994)—looked at pre-treatment PSA and nadir PSA values as predictors of recurrent disease in men treated with EBRT. Both were highly significant as predictors. The nadir PSA value was achieved typically at 6 to 12 months. PSA values begin to increase approximately 4 to 5 years before the appearance of clinically overt disease.

5) Zietman (1994a)—measured survival data post EBRT in those patients for whom a pre-treatment PSA level was available. The initial PSA was a powerful predictor of probable failure after conventional radiation therapy and was independent of stage, grade, patient age and prior TURP. Cure (defined as at least 8 years post-treatment with no sign of chemical or clinical failure) was unlikely unless the serum PSA level decreased to less than 1.0ng/ml. As a comparison, any level of PSA post prostatectomy represents the presence of residual tumour.

6) Zietman (1995)—1044 men with T1–4NxM0 prostate cancer treated by conventional external beam radiation therapy at the Massachusetts General Hospital between 1977 and 1991 were analysed. At 10 years only 40% of the T1–2 group remained disease free. When subdivided by grade, the well-differentiated tumours (Gleason 1–2) exhibited a 53% actuarial 10-year disease-free survival, moderately differentiated (Gleason 3) 42%, and poorly differentiated (Gleason 4–5) 20%. The corresponding values for the T3–4
men were 33% for Gleason 1-2, 20% for Gleason 3, and 10% for Gleason 4-5. Overall the value for T3-4 tumours was 18% at 10 years. When compared with recently reported data on selected T1-2 patients who were managed by expectant observation there was no advantage over the first decade (and certainly no disadvantage) in terms of metastasis-free survival or disease-specific survival for the irradiated Gleason 1-3 patients. However, a gain was seen for those with Gleason 4-5 tumours.

7) Hanks et al (1997)—this study examined 5 year outcomes of treatment for patients with prostate cancer treated largely with conformal three-dimensional radiation therapy. (There were 456 consecutive patients, treated prior to 31st December 1993.) Biochemical failure was defined as 2 consecutive rises in the PSA equalling or exceeding 1.5 ng/ml

For patients with localised disease (defined as T1, 2AB disease, Gleason sum 6 or less):
- 5 year biochemically free of failure (by pre-treatment PSA)
- PSA <10ng/ml: 85%
- PSA 10 to 19.9ng/ml: 66%
- PSA > 20ng/ml: 31%

8) Bagshaw et al (1994)—Bagshaw and colleagues examined 1245 patients treated with EBRT. The mean survival for all patients without evidence of distant metastases but irrespective of T stage, histopathological grade or lymph node status, was 10 years (compared to 15 years for an age-matched cohort), prostate cancer specific survival at 15 years: 52% analysis of subgroups: best outcome: in cases of stage T1, T2a with histopathologically confirmed negative lymph nodes, survival at 15 years was 53% (identical to that of age-matched cohort)

9) El-Galley et al (1995)—this study examined 191 patients who received radical radiotherapy between 1982 and 1992. A multivariate analysis was undertaken to identify significant prognostic factors impacting on survival and relapse.
- median follow-up: 40 months
- actuarial cause-specific 5 year survival rate: 63%
- actuarial cause-specific 10 year survival rate: 35%

The multivariate analysis showed that T category and Gleason score were significant predictors for survival.

b. Studies examining complications

1) Fowler (1996)—used a postal survey of 5% of all Medicare beneficiaries treated by EBRT in 1989-1991 in Georgia, Connecticut and Michigan. The survey excluded all those with confirmed distant metastases at the time of diagnosis. Data was collected in 1994 and was compared with a national survey of Medicare patients who had had a radical prostatectomy. Of the
799 eligible subjects sampled, 662 responded (response rate = 83%). 41 were then excluded because they had also had a radical prostatectomy, brachytherapy or treatment before 1987. There was a significant difference in the age of the patients between the surgical and the radiotherapy group (see above). 153 of the patients had undergone a TURP before radiation, but there was no statistically significant difference in measures of incontinence, sexual function and general quality of life between those radiotherapy patients who had had a previous TURP and those who had not. Of the patients who had radiotherapy, 74% were mostly satisfied, pleased or delighted with the results of the treatment, 11% had mixed feelings and 5% were mostly dissatisfied.

2) Helgason (1995)—assessed sexual capacity and its impact on the patient’s quality of life after external radiation therapy. 50% reported that decreased erectile capacity affected their quality of life ‘much’ or ‘very much’. Of the 53 patients who were surveyed, 19 had also had anti-androgen therapy and 13 had other confounding factors such as heart attack, diabetes, high blood pressure or prostatectomy.

3) Helgason (1997)—sent a questionnaire to 431 patients in Stockholm aged 50–80 years diagnosed with prostate cancer. Waning sexual function related strongly to side-effects of treatment. This could not be related to confounding effects. ‘In particular, confounding could not explain the greater risk of impotence after radical prostatectomy compared to external beam radiation therapy.’

4) Leibel (1994)—17% of patients in this study had androgen deprivation therapy to decrease prostatic volume. Complications were not given by type but only classified as gastrointestinal or genitourinary. 43% of patients had RTOG grade 2 or greater acute toxicity symptoms. In terms of late complications 6 of the 324 had Grade 2 or greater rectal complications and 9 had grade 2 or greater urinary complications.

5) Mantz (1997)—examined the proportion of patients with potency problems following EBRT for localised prostate cancer. This showed extremely high potency rates. For those patients who became impotent, the median time to impotence was 14 months. There was no significant difference in the decrease in potency between patients who had been treated with EBRT and normal males (Massachusetts Male Aging Study) in the age group 50 to 65, but an increase in potency problems amongst those older than 65 with potency problems treated with EBRT.

6) Shrader-Bogen (1997)—used a self administered questionnaire mailed to patients who had clinically localised prostate cancer treated with either radical prostatectomy or EBRT.

References—Appendix 2


Zagars GK. Prostate specific antigen as an outcome variable for T1 and T2 prostate cancer treated by radiation therapy. J Urol. 1994; 152:1786-1791


APPENDIX 3

Brachytherapy study details

a. Studies examining progression and survival
1. Adolfsson (1994)—examined the treatment of 37 patients who had been treated with iodine-125 implantation. At the time of follow-up, 9 had died of prostate cancer. In addition, the rate of complications was high and in 2 cases led to the death of the patients. Due to the poor outcome and the high rate of complications the institution had abandoned digitally directed retropubic I-125 implantation. The reason for the high complication rate is obscure as most received a dose < 160 Gy.

2. Blasko (1995)—this is probably the largest series of patients treated with brachytherapy. It only includes patients with moderately or well differentiated tumours and therefore a minimal likelihood of extracapsular extension. The PSA level had decreased to less than 1.0 ng/ml in 97% at 48 months after implantation.

3. Kaye (1995)—used ultrasound or ultrasound plus fluoroscopic guidance for placement of iodine-125. Survival data include some patients who were treated with external beam radiation as well as radiotherapy. Patients with large prostates (greater than 60 to 70 gm) were excluded from the analysis.

4. Stock (1996)—patients who had prostate volumes greater than 55cc were treated with 3 months of leuprolide and flutamide prior to radiation therapy to hormonally downsize the tumour before brachytherapy. These patients were implanted with Pd-103. Pd-103 was also used for patients with Gleason scores of 7 or greater. Biochemical failure was defined as 2 consecutive increases in PSA levels above the nadir level, or in those patients who were treated hormonally a rise in PSA > 1ng/ml. Decreases in PSA often reach a nadir level by 18 to 24 months post implant.

5. Wallner (1994)—this trial reports survival results for brachytherapy which are comparable to that of prostatectomy, with high preservation of sexual potency and moderate morbidity.

6. Zelefsky & Whitmore (1997)—this study examined 1078 patients with biopsy-proven adenocarcinoma of the prostate who were treated at the Memorial Sloan-Kettering Cancer Centre between 1970 and 1987. All patients underwent bilateral pelvic lymphadenectomy before implantation. Median follow-up was 11 years. They used permanent implantation of 125iodine via a retropubic approach. The authors conducted multivariate analyses which identified nodal involvement, high grade disease, clinical stage B3/C and implant doses of less than 140 Gy as independent predictors of local relapse.
Local recurrence-free survival rates for patients with negative nodes were:

- 5 years—69%
- 10 years—44%
- 15 years—24%

Distant metastases-free survival rates:

- 5 years—59%
- 10 years—36%
- 15 years—21%

7. Ragde et al (1997)—in this trial there were 126 consecutive patients (T1: 23%, T2: 77%) treated with iodine-125 radionuclides, in the period 1988–90. Mean follow-up was 69.3 months, prebiopsy PSA values were available for all patients. PSA failure was defined by either 2 consecutive increases from nadir value or failure to attain an arbitrary serum PSA value of 1.0 or 0.5 ng/ml at last follow-up 7 year survival was 77%, 7 year actuarial PSA progression free outcome was 89%, PSA £ 1.0ng/ml outcome was 87%. The authors noted that these biochemical outcomes were comparable to endpoints resulting from radical prostatectomy and EBRT.

8. Critz et al (1997)—this study examined the combination of brachytherapy and EBRT. Treatment results of men with prostate cancer staged with pelvic lymph node dissection were examined. Disease freedom was defined by PSA nadir of 0.5ng/ml or less.

There were 363 men with clinical stage T1 or T2, surgical stage node-negative prostate cancer, and they were simultaneously irradiated with retropubic iodine 125 prostate implant followed by EBRT. Average pre-treatment PSA was 13.6 (range 0.3 to 188), and median follow-up 5 years.

5 year disease-free survival:

- overall: 78%
- by pre-treatment PSA:
  - ≤ 4.0 ng/ml: 93%
  - 4.1 to 10.0 ng/ml: 87%
  - 10.1 to 20.0 ng/ml: 72%
  - > 20 ng/ml: 45%

10 year disease-free survival: 65%

The study raises the possibility that combined EBRT and brachytherapy may have better results than either treatment alone.
b. Studies examining complication rates

1. Kaye (1995)—potency was assessed in 72% of the patients. Of the 44 who were potent before the implant, 75% of them were still maintaining erections adequate for intercourse at 1 year.

2. Stock (1996)—this study showed a high preservation of erectile function and very low rates of morbidity.

3. Wallner (1994)—of the 38 patients who were sexually potent prior to implantation, 81% remained potent at 3 years.

References—Appendix 3


APPENDIX 4

Staging systems for prostate cancer

This appendix on staging is extracted from the Update of the AHTAC Report (Weller et al, 1999), and covers TNM definitions, AJCC stage groupings, and the Jewett system. The material originates from the National Cancer Institute’s Cancer Web netsite (1998). The section on Gleason histological grading has been extracted from Selley (1997).

TNM definitions

Primary tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically inapparent tumour not palpable nor visible by imaging
T1a Tumour incidental histologic finding in 5% or less of tissue resected
T1b Tumour incidental histologic finding in more than 5% of tissue resected
T1c Tumour identified by needle biopsy (eg because of elevated PSA)
T2 Tumour confined within prostate*
T2a Tumour involves one lobe
T2b Tumour involves both lobes
T3 Tumour extends through the prostatic capsule**
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

*Note: Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.
Regional lymph nodes (N)
Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the N classification): pelvic (NOS), hypogastric, obturator, iliac (internal, external, NOS), periprostatic, and sacral (lateral, presacral, promontory [Gerota’s], or NOS). Distant lymph nodes are outside the confines of the true pelvis and their involvement constitutes distant metastasis. They can be imaged using ultrasound, computed tomography, magnetic resonance imaging, or lymphangiography, and include: aortic (para-aortic, periaortic, lumbar), common iliac, inguinal, superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal (NOS) nodes.

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in regional lymph node or nodes

Abbreviation: NOS, not otherwise specified

Distant metastasis*** (M)
MX  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
M1a Nonregional lymph node(s)
M1b  Bone(s)
M1c Other site(s)

*** Note: When more than one site of metastasis is present, the most advanced category (pM1c) is used.

Histopathologic grade (G)
GX  Grade cannot be assessed
G1  Well differentiated (slight anaplasia)
G2  Moderately differentiated (moderate anaplasia)
G3–4 Poorly differentiated or undifferentiated (marked anaplasia)

AJCC stage groupings
Stage I
T1a, N0, M0, G1
Stage II
T1a, N0, Mo, G2, 3-4
T1b, N0, M0, Any G
T1c, N0, M0, Any G
T1, N0, M0, Any G
T2, N0, M0, Any G

Stage III
T3, N0, M0, Any G

Stage IV
T4, N0, M0, Any G
Any T, N1, M0, Any G
Any T, any N, M1, Any G

The Jewett staging system is as described below.

Stage A
Stage A is clinically undetectable tumour confined to the prostate gland and is an incidental finding at prostatic surgery.

Substage A1 well-differentiated with focal involvement, usually left untreated
Substage A2 moderately or poorly differentiated or involves multiple foci in the gland

Stage B
Stage B tumour confined to the prostate gland
Substage B0 nonpalpable, PSA-detected (Bostwick, 1994)
Substage B1 single nodule in one lobe of the prostate
Substage B2 more extensive involvement of one lobe or involvement of both lobes

Stage C
Stage C is a tumour clinically localised to the periprostatic area but extending through the prostatic capsule; seminal vesicles may be involved
Substage C1 clinical extracapsular extension
Substage C2 extracapsular tumour producing bladder outlet or ureteral obstruction

**Stage D**

Stage D is metastatic disease

- **Substage D0** clinically localised disease (prostate only), but persistently elevated enzymatic serum acid phosphatase titers
- **Substage D1** regional lymph nodes only
- **Substage D2** distant lymph nodes, metastases to bone or visceral organs
- **Substage D3** D2 prostate cancer patients who relapsed after adequate endocrine therapy

**Gleason histological grading**

Biopsy specimens are graded histologically based on the architectural differentiation of the tumour cells, (Gleason, 1966) and this has been reported to be a good, although imperfect, method of predicting lymph node metastases.

The predominant histological system is the Gleason grading system in which sections of tumour are graded from 1 (least aggressive) to 5 (most aggressive). The two predominant patterns from each tumour are added to give a score ranging from 2 to 10. Tumours with a score of less than 7 tend to have a good prognosis, while those with a score of 7 and above tend to have a poorer prognosis (Ellis & Lange, 1994).

Higher Gleason score is associated with more aggressive tumours and several studies have shown Gleason score to be the best predictor of progression. (Epstein, Carmichael et al, 1993) Preoperative Gleason score correlates with tumour volume and extracapsular extension, (Stamey, McNeal et al, 1988), but not with positive margins. (Fendler & Perrin, 1994) The relationship between Gleason score and tumour grade has been found to be highly significant ($p<0.0001$), but the correlation between the two is relatively poor ($r=0.25$). (Epstein, Carmichael, 1994) Disease progression is more likely to occur in men with tumours of higher grade than those with a lower grade. In a series of 504 patients undergoing radical prostatectomy in the USA, 13% of those with Gleason scores of less than 7 had progressed at 5 years, compared with 59% of those with a Gleason score of 7 or more ($p<0.0001$) (Epstein, Carmichael, 1993).

**References—Appendix 4**


Stamey TA, McNeal JE, Freiha FS and Redwine E. Morphometric and clinical studies on 68 consecutive radical prostatectomies. J Urol 1988 Jan; 139(6); 1235–41

APPENDIX 5

ACN Management of Localised Prostate Cancer Working Party Members

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APPENDIX 6

Guideline Development Process

A Working Party was established by The Australian Cancer Network (ACN) to review the American Urological Association Inc (AUA) report The Management of Clinically Localized Prostate Cancer. Given the existence of these American guidelines, which were based on an extensive systematic review, the most appropriate process in developing Australian guidelines was considered to be the establishment of an expert panel to review the guidelines. This was coupled with a new, critical review of literature from 1995 to August 1998 aimed at summarising recent publications and assessing whether substantive changes to the AUA recommendations were required. The two bodies of data have been welded into the current document.

The NHMRC Guidelines for the Development and Implementation of Clinical Practice Guidelines (1995) were used to facilitate the process.

The Working Party was multidisciplinary, and its membership consisted of members from urology, epidemiology, medical oncology, radiation oncology and consumers. As the task was oriented towards the AUA document, there was a predominance of urologists.

Members of the Working Party reviewed the AUA document, 2,488 papers were critically reviewed and 381 papers were identified as containing material apposite to the document under preparation. Appropriate amendments were made and observations included in the process. There were three face–to–face meetings of the Working Party, numerous reviews and revisions were conducted by mail, email and telephone and meetings with the Chair and Secretariat. This approach was appropriate to the methodology of the day.

The draft copy was submitted to the Health Advisory Committee (HAC) of NHMRC and then to public review. Fourteen submissions were made and these were circulated to all members of the Working Party and their replies and public submissions were reviewed by an executive group. The resultant document was resubmitted to HAC and was approved for a second public review. The response to this review attracted twenty submissions and was substantially more detailed than the first. This related substantially to brachytherapy and comment on the absence of a significant component of the psychosocial aspects of prostate cancer; the latter topic was not considered in any detail by the Working Party as it was not addressed in the AUA document.

Subsequent review by a special committee and an expert reviewer led to editorial and format changes.
The overall process has been demanding and has taken two years to meet all required criteria. A difficulty has been occasioned by the time taken, a number of clinicians noting and wishing to include new material after the cut-off date in the document. As a further systematic review additional to the completed critical review would be very time consuming, it is not considered practical to accede further information at this time.

With the reduction to one public consultation for guideline documents, this difficulty should be in large part overcome.

A consumer document paralleling the Information and Recommendation document was published and launched in February 2002.

In view of the time lapse in development of the Recommendations, a revision should be planned within three years, together with revision of the consumer document. Significant attempt to promote clinical trials involving single or multi-modal therapies should be canvassed.
APPENDIX 7

Additional References

This appendix has been included as a result of suggestions raised during the review process. It contains information that was thought may be of assistance to readers of this document, as it highlights areas where changes have occurred in the literature after the time of its comprehensive review.

The contents of this appendix are in no way exhaustive of the literature, which formed the basis of this report.

However, these areas amongst others, will require systematic review and critical appraisal to achieve an exhaustive update of available information. This may then result in changes to the emphasis of the current recommendations.

Written:


Online:

Written:


Vicini FA, Kestin LL, Martinez AA. Prostatectomy, external beam radiation therapy, or brachytherapy for localized prostate cancer. JAMA, 1999 May 5; 281(17):1583–4


Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer. (DRAFT). National Breast Cancer Centre and National Cancer Control Initiative, July 2002.


This last paper provides important new information on the basis of a randomised controlled trial and reports an improved cancer specific survival for men undergoing radical prostatectomy compared with watchful waiting. However, no difference was observed in the overall survival. An article in the same issue of the New England Journal of Medicine by Walsh (2002) provides a comprehensive critique of the paper and places these observations in perspective. It also examines the potential impact these findings may have on the future treatment options for localised prostate cancer.

A companion article by Steineck et al. (2002) examined the quality of life in these men and found a higher incidence of erectile dysfunction (80% vs 45%) and incontinence (49% vs 21%) in men undergoing radical prostatectomy versus watchful waiting. On the other hand, men undergoing watchful waiting had a higher incidence of urinary outflow obstruction (44% vs 28%). Bowel function, prevalence of depression, well-being and the subjective quality of life were similar in the two groups.

Figure 1: Trends in age-standardised incidence and mortality rates for prostate cancer—Australia 1983–1999.

Cancers of the prostate and breast, and colorectal cancer

![Graph showing trends in age-standardised incidence and mortality rates for prostate cancer—Australia 1983–1999.](image)
References


APPENDIX 8

Submissions From Public Consultations

Submissions from 1st stage public consultation
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GLOSSARY

This glossary is included in this document with the cooperation of the Australian Prostate Cancer Collaboration and Dr Carole Pinnock.

**Actuarial survival**
A method of calculating survival over time.

**Adrenal glands**
Small glands lying on top of the kidneys which produce a small amount of male hormone.

**Anaemia**
A lack of red cells in the blood. It can cause tiredness, paleness, weakness and sometimes heart problems.

**Androgens**
Male hormones. The most active male hormone, testosterone, is produced by the testicles. Other male hormones are produced by the adrenal glands.

**Anti-androgens**
Drugs which block the effects of male hormones.

**Asymptomatic**
Not having symptoms, symptom-free.

**Benign**
Not cancerous.

**Benign prostate enlargement**
Non-cancerous enlargement of the prostate. Overgrowth of normal prostate tissue.

**Bone scan**
A test in which a radioactive chemical is injected, then x-rays trace its path throughout the body. The chemical goes to parts of the bone which are abnormal, such as areas of cancer, infection or arthritis. Bone scans can be unreliable, and so are often used to give guidance, rather than answers, to a problem.

**BPH (benign prostatic hyperplasia)**
A condition causing non-cancerous enlargement of the prostate.
Evidence-based information and recommendations for the management of localised prostate cancer

Biopsy of the prostate

Removal of small pieces of tissue, in this case, from the prostate. Tissue samples are taken from different areas of the prostate, and then examined under the microscope to see if they are cancerous.

Brachytherapy

A type of radiotherapy of the prostate— involves the insertion of radioactive seeds directly into the prostate which are retained (low dose brachytherapy). An alternative form (high dose brachytherapy) involves treatment by temporary insertion of radio-active catheters into the prostate.

CAT (CT) scan

A series of x-ray pictures are taken in a circle around the body which are processed by a computer.

Complete remission (also, complete response)

This is the term used when, after treatment, there is no sign of any cancer. It is not necessarily the same as ‘cure’, as some cancer cells may be hidden.

Coping strategies

Mental strategies or behaviours used to help a person deal with stressful situations. Coping strategies may be influenced by personality style and the specific situation, and may change over time.

Cystitis

Inflammation of the bladder, often caused by infection.

Cystoscope

A tiny tube with a lighted end which slides along the urethra and is used to examine the bladder.

Depression

A general and long-lasting feeling of being down, often associated with tearfulness, guilt or irritability. Other features include loss of interest or pleasure in activities, lowered energy levels, poor concentration and troubles with sleep and appetite.

Digital rectal examination (DRE)

An examination of the prostate through the wall of the rectum. The doctor inserts a finger in the rectum and feels the shape of the prostate. Irregularities may be caused by cancer.

Dry ejaculation

After a radical prostatectomy, a man may achieve orgasm, but produce no ejaculate. This is because the glands which produce much of the fluid in the ejaculate are removed. See also reverse ejaculation.
Ejaculate

Fluid produced at ejaculation, which contains sperm and secretions from glands such as the prostate, seminal vesicles and testicles.

Five-year survival rate

A scientific measure used to determine the success of a treatment. It measures the number of people who are alive five years after a particular treatment. It does not mean the patient will only live for five years after having treatment.

General anaesthetic

A drug given to stop a person feeling pain. A general anaesthetic causes temporary loss of consciousness.

Gleason score

A way of grading cancer cells. Low grade cancers (Gleason score 2, 3, 4) are slower growing than high grade (Gleason scores 8, 9, 10) cancers. The pathologist identifies the two most common tissue patterns and grades them from 1 (least aggressive) to 5 (most aggressive). The Gleason score is given as two numbers added together to give a score out of ten (for example, 3 + 4 = 7). The first number is the most common pattern seen under the microscope and the second number is the next most common.

Grade

A way of describing how abnormal the cancer cells look, and consequently how aggressive or fast-growing the cancer is likely to be. The most commonly used grading system is the Gleason score, which ranges from 2-10 (see above).

Hormone resistance

Prostate cancer cells are dependent on testosterone or male hormone for growth. Withdrawal of male hormone by surgery or by means of drugs is therefore a means of controlling its growth. However cancer cells may develop which do not need testosterone for growth. The cancer is then said to be ‘hormone resistant’.

Hormones

Natural chemical substances that are produced by one body organ, and travel through the bloodstream to other organs where they exert their effects. A well-known example is insulin, which regulates the blood sugar level.

Hot flush

A sudden rush of heat to the face, neck, sometimes chest and back. It can be associated with hormone therapy for prostate cancer.
**Hyperthermia**
Higher than normal temperature. In the case of prostate cancer, a way of destroying tissue by heating.

**Impotence**
Inability to achieve an erection firm enough for penetration.

**Incontinence**
Inability to hold or control the loss of urine or faeces.

**Indolent**
Refers to the type of cancer cells which grow only slowly.

**LHRH (luteinising hormone releasing hormone)**
This is produced by the hypothalamus in the brain and stimulates the pituitary (another part of the brain) to produce LH (luteinising hormone). This, in turn causes cells in the testicles to produce testosterone, the male hormone.

**LHRH agonists**
Drugs that interfere with the production of LH (see above) by the pituitary.

**Libido**
Sex drive.

**Local anaesthetic**
The technique of making a small part of the body numb, so that minor operations can be performed without pain, while allowing the patient to remain awake.

**Locally recurrent**
Cancer that has recurred (come back) after treatment, but which is confined to the prostate or nearby tissues only.

**Lymph**
A clear, sometimes faintly yellow fluid containing white cells, that is collected from the tissues throughout the body, flows in the lymphatic vessels (through the lymph nodes), and is eventually added to the venous blood circulation.

**Lymph glands**
Lymph nodes.

**Lymph nodes**
Small, generally pea-sized pieces of tissue found all over the body but easier to feel in the neck, armpits, and groins. They act as filters for foreign substances and commonly become inflamed if there is an infection nearby. They can also harbour cancer cells that have spread from elsewhere.
Malignant
Cancerous.

Margin-positive
See Surgical margins.

Medical oncologist
A specialist in the treatment of cancer using chemotherapy.

Metastasis
The secondary or distant spread of cancer, away from its primary (initial) site in the body.

Metastatic
Relating to secondary cancer.

Monitoring
The process in which patients are followed up after initial diagnosis and treatment. It may include clinical examination and/or the regular performance of tests.

MRI (magnetic resonance imaging)
A way of imaging the inside of the body using magnetic forces and without using x-rays.

Nodules
Small lumps.

Oncologist
A specialist in the treatment of cancer.

Orchidectomy (also orchectomy)
A type of operation which removes the testicles, but usually leaves the scrotal sac or scrotum.

Partial remission (or response)
The situation when, following treatment, signs of the disease process have partially resolved but have not disappeared completely.

Pelvis/pelvic
The area of the body below the waist and surrounded by the hip and pubic bones.

Pituitary
Part of the brain which produces hormones which stimulate the testicles to produce testosterone (male hormone) and other hormones.

Primary
The site where the cancer began.
**Prognosis**
The course and likely outcome of a disease, as estimated by a person’s doctor or treatment team.

**Prostatectomy**
An operation to remove all or part of the Prostate.

**Prostatitis**
Inflammation of the prostate. It can be caused by bacteria.

**Protocol**
A well defined program for treatment.

**PSA (Prostate specific antigen)**
A protein produced by the cells in the prostate, which is usually found in the blood in larger amounts when prostate cancer is present. It can be used as a test for prostate cancer or to monitor its recurrence.

**Psychosocial**
Referring to the emotional psychological, social and spiritual aspects of human life.

**Quality of life (QoL)**
A person’s overall appraisal of their situation and wellbeing.

**Radiation oncologist**

**Radical prostatectomy**
An operation which removes the prostate and the seminal vesicles. This is usually done through a cut in the lower abdomen.

**Radiotherapy**
The use of radiation as x-rays or electrons to kill tumour cells.

**Rectum**
The last part of the bowel, leading to the anus, and through which stools pass.

**Recurrence**
The re-occurrence of cancer some time after it was first treated.

**Reliability (of a test)**
The ability to measure something in a reproducible and consistent fashion.

**Response**
A change in the size or extent of disease due to treatment.
Retrograde ejaculation
Also called reverse ejaculation. This may occur after surgery for benign conditions of the prostate. The ejaculate travels back into the bladder instead of exiting out through the penis. This means a man is usually infertile (cannot produce offspring in the conventional way), but he can still achieve orgasm.

Scrotum
A pouch of skin which contains the testicles and some other parts of the male reproductive system. It hangs outside the body and below the penis.

Secondary tumour
Spread of cancer from where it began to another part of the body. The secondary cancerous growths are known as metastases or ‘secondaries’. The process of spread is known as metastasis.

Seminal vesicles
Glands that lie very close to the prostate and produce secretions which form part of the ejaculate.

Staging
The process of determining the extent of the disease. A system for describing how far the cancer has spread. The most common is the TNM system described in Appendix 1.

Stricture
Scar tissue which obstructs fluid flow; in the case of a urethral stricture, urine flow is obstructed.

Support
People on whom the patient can rely for emotional caring, and reinforcement of a sense of personal worth and value. Other components of support may include practical help, guidance, feedback and someone to talk to.

Surgical margins
After a radical prostatectomy, the edges of the tissue which has been removed are examined to see if cancer cells are present. If they are not (negative surgical margins) the chance is higher that all of the cancer has been removed.

Survival—disease free
The proportion of people surviving without evidence of disease to a given time, such as five years.
Survival—prostate cancer specific
The proportion of people who do not die of prostate cancer in a given periods, such as five years.

Systemic
Relating to the whole body.

Testicles
Glands which produce sperm and the male hormone, testosterone. They are found in the scrotum.

Testosterone
The major male hormone. It is produced by the testicles.

TRUS (trans-rectal ultrasound)
A means of imaging the prostate in order to locate cancer. The ultrasound probe is placed in the rectum.

Tumour
Any swelling. In the context of cancer, the word usually refers to malignant (cancerous) lumps.

TURP (trans-urethral resection of the prostate)
This is a common operation for benign enlargement of the prostate, but only occasionally used to treat prostate cancer. An instrument is inserted, under anaesthetic, along the urethra (urine tube) and removes prostate tissue which may be blocking the flow of urine.

Urethra
The tube which carries urine and ejaculate along the length of the penis and to the outside.
QUALITY OF EVIDENCE RATINGS

I: Evidence obtained from a systematic review of all relevant randomised controlled trials.

II: Evidence obtained from at least one properly-designed randomised controlled trial.

III–1: Evidence obtained from well-designed controlled trials without randomisation.

III–2: Evidence obtained from well-designed cohort or case-control analytic studies preferably from more than one centre or research group.

III–3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

IV: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is a statutory body within the portfolio of the Commonwealth Minister for Health and Ageing, established by the National Health and Medical Research Council Act 1992. The NHMRC advises the Australian community and Commonwealth; State and Territory Governments on standards of individual and public health, and supports research to improve those standards.

The NHMRC advises the Commonwealth Government on the funding of medical and public health research and training in Australia and supports many of the medical advances made by Australians.

The NHMRC also develops guidelines and standards for the ethical conduct of health and medical research.

The Council comprises nominees of Commonwealth, State and Territory health authorities, professional and scientific colleges and associations, unions, universities, business, consumer groups, welfare organisations, conservation groups and the Aboriginal and Torres Strait Islander Commission.

The Council meets up to four times a year to consider and make decisions on reports prepared by committees and working parties following wide consultation on the issue under consideration.

A regular publishing program ensures that Council’s recommendations are widely available to governments, the community, scientific, industrial and educational groups.

The Council publishes extensively in the following areas:

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