



The American Urological Association
Prostate Cancer Clinical Guidelines Panel

Report on

The Management of Clinically Localized Prostate Cancer

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CLINICAL PRACTICE GUIDELINES

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The Prostate Cancer Clinical Guidelines Panel consists of board-certified urologists and other experts in prostate cancer management. This *Report on the Management of Clinically Localized Prostate Cancer* was extensively reviewed by nearly 40 urologists throughout the country in early 1995. The panel finalized its recommendations for the AUA's Practice Parameters, Guidelines and Standards Committee, chaired by Winston K. Mebust, MD, in June 1995. The AUA Board of Directors approved these practice guidelines in July 1995.

The Summary Report also underwent independent scrutiny by the Editorial Board of the *Journal of Urology*, was accepted for publication in August 1995 and appeared in its December issue. A *Patient's Guide* and a *Technical Supplement* have also been developed; both are available from the AUA.

The American Urological Association expresses its gratitude for the dedication and leadership demonstrated by the members of the Prostate Cancer Clinical Guidelines Panel in producing this guideline.

Dedication

This report is dedicated to the memory of William H. Cooner, MD, who lent invaluable support, time and encouragement to the efforts of the panel.

Introduction

Prostate cancer is the most common nondermatologic malignancy and the second most common cause of cancer death among men in the United States. In 1995, an estimated 244,000 new cases were anticipated, and prostate cancer deaths were estimated at 40,400 (Wingo, Tong and Bolden, 1995). For a white male born in 1988-1990, the lifetime risk of developing clinically apparent prostate cancer is 13.34 percent. For an African-American male, the risk is 11.27 percent (Miller, Hayes, Potosky, et al., 1993). Lifetime risks of death from prostate cancer in these two groups are 3.18 percent and 3.96 percent, respectively. Because of an aging U.S. population, the number of men recognized to have prostate cancer will rise dramatically over the next 20 years. During the next 10 years, it is estimated that there will be a 90-percent increase in prostate cancer detection and a 37-percent increase in prostate cancer deaths (Carter and Coffey, 1990).

Enhanced early detection techniques using digital rectal examination (DRE) and prostate specific antigen (PSA), as well as more public awareness of prostate cancer, have greatly increased rates of diagnosis. One result has been a shift toward more tumors detected at lower stages. In 1982, an American College of Surgeons survey found the following percentages, by clinical stage, of newly diagnosed prostate tumors: stage T1 (A), 25.9 percent; stage T2 (B), 28.9 percent; stages T3-T4 (C), 14.9 percent; stage M1 (D2), 24.9 percent (Murphy, Natarajan, Pontes, et al., 1982). A 1990 survey found that more newly diagnosed tumors were organ confined: stage T1 (A), 29.3 percent; stage T2 (B), 37.7 percent; stages T3-T4 (C), 12.5 percent; and stage M1 (D2), 20.6 percent (Mettlin, Jones and Murphy, 1993). At a number of institutions where PSA is an integral part of early diagnosis, as many as 99 percent of prostate cancers diagnosed during serial PSA-based screening have been clinically organ confined, and 75 percent pathologically organ confined (Catalona, Smith, Ratliff, et al., 1993).

With this growth in numbers of locally confined tumors found through early detection efforts has come greater scrutiny of the methods of treatment. A 1988 National Institutes of Health (NIH) consensus conference, employing an implicit approach to the development of conclusions, compared the efficacy of surgical therapy and radiotherapy. It was not possible, based upon available data, to determine the optimal treatment for localized disease (NIH Consensus Development Panel, National Cancer Institute's Monograph No. 7, 1988).

Since that time, the publication of a number of series on the management of clinically localized prostate cancer by surveillance (no treatment) has increased the uncertainty as to the optimal treatment for this stage of disease. For low-grade tumors, these series have generally reported cancer-specific survivals with management by surveillance that do not differ significantly from cancer-

specific survivals following treatment by surgery or radiotherapy for periods up to 10 years (Johansson, Adami, Andersson, et al., 1992; Whitmore, Warner and Thompson, 1991). Pooled analyses and decision analyses employing data from surveillance series have further clouded the question of optimal treatment for localized disease (Chodak, Thisted, Gerber, et al., 1994; Fleming, Wasson, Albertsen, et al., 1993).

Recognizing the need for a systematic analysis of the literature regarding the available methods of treatment for localized prostate cancer, and in the absence of a randomized, prospective comparison of these methods, the American Urological Association (AUA) in 1989 convened the Prostate Cancer Clinical Guidelines Panel to conduct a comprehensive survey and analysis of published data. This document, *Report on the Management of Clinically Localized Prostate Cancer*, is the product of that effort.

This report, as its title indicates, focuses on the treatment of tumors confined within the prostate, specifically clinical stage T2 (B) tumors. ("Stage" in this document means "clinical stage" unless "pathological stage" is specified.) Inevitably discussed in this report are stages other than T2, questions regarding staging methods and various issues related to the diagnosis as well as treatment of prostate cancer in general. However, the panel's analysis and recommendations are intended to apply only to treatment of clinically localized prostate cancer.

The report summarizes the methodology employed by the panel, displays the outcomes evidence extracted from the prostate cancer treatment literature and recommends practice policies for the management of clinical stage T2 (B) prostate cancer insofar as the evidence permits. The report also includes analysis of the limitations in the treatment literature regarding outcomes evidence and makes recommendations for further research.

A summary of this report has been published in the *Journal of Urology* December 1995: Vol. 154, pgs. 2144 – 2148. A 12-page *Patient's Guide* including illustrations of the progressions of prostate cancer is available to assist the physician in discussing treatment options with the patient. Also available is a *Technical Supplement* providing more detailed displays of the data analysis.

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Executive summary:

Report on the management of clinically localized prostate cancer

Methodology

In developing recommendations for the management of clinically localized prostate cancer, the AUA Prostate Cancer Clinical Guidelines Panel extensively reviewed the prostate cancer treatment literature from 1966 to December 1993 and extracted all relevant data to estimate as accurately as possible desirable and undesirable outcomes of the alternative treatment modalities. The panel followed an explicit approach to guideline development (Eddy, 1992). This approach emphasizes use of scientific evidence in estimating outcomes of interventions. When panel opinion is necessary, the explicit approach calls for explaining why and discussing the factors considered. For a full description of the methodology, see Chapter 1.

Background

Of the malignant conditions that arise primarily within the prostate gland, by far the most frequently occurring type is adenocarcinoma. Because of the rarity of other primary neoplasms within the gland, the terms “prostate cancer” and “carcinoma of the prostate” are generally understood to be synonymous with “adenocarcinoma.”

Adenocarcinoma of the prostate is the most commonly diagnosed visceral neoplasm in men. The estimated 244,000 new cases diagnosed in 1995 represent 36 percent of cancers in men, compared with 14 percent for lung cancer and 10.4 percent for colorectal cancer, the next two most frequently diagnosed cancers (Wingo, Tong and Bolden, 1995). The 40,400 deaths from prostate cancer anticipated in 1995 represent 14 percent of all cancer deaths in men, placing prostate cancer second only to lung cancer mortality (33 percent) and ahead of colorectal cancer mortality (9.4 percent).

Natural history

Prostate cancer has a wide spectrum of growth rates. Many tumors pursue a relatively indolent

course over many years. Others advance rapidly by local extension and/or metastasis. Evaluation of the effect of active intervention must take into account the course the disease would follow if allowed to proceed without interference. Active treatment of a prostatic cancer destined never to present a clinical problem would not be expected to improve patient outcomes over treatment by surveillance alone. Prostate cancer aggressiveness, however, does tend to increase with time (Adolfsson and Tribukait, 1990). Given sufficient time, small localized tumors can be expected to become large, multifocal, non-localized tumors (Whitmore, Warner and Thompson, 1991), with decreasing likelihood of cure. “Cure” is defined in this report as lifetime freedom from disease.

Thus, patient longevity becomes a major consideration, especially since techniques to distinguish rapidly growing from slow-growing tumors are still evolving. Treatment of prostate cancer depends to a significant degree upon the patient’s age, functional level and medical status. Factors such as tumor volume (stage) and grade, along with evaluation of nuclear chromatin content and nuclear roundness, allow some prediction of a tumor’s biologic potential. However, at present, such factors are not all fully applicable to individual patients because of the many exceptions to these predictive indices.

Staging

Accurate determination of tumor stage is important, in that therapy is highly dependent upon the knowledge of whether the tumor is localized to the gland. Several staging systems for prostate cancer have been described. The two most often used are the Jewett-Whitmore (ABCD) system and the American Joint Committee (TNM) system. They are shown in Table 1 on page 13. A new clinical stage has been designated primarily for PSA-detected prostate cancers. In the TNM staging system, these tumors are categorized as stage T1c and in the Jewett-Whitmore staging system as stage B0.

Clinical staging has improved in recent years, but considerable inaccuracy remains. The result can be understaging or, to a lesser extent, overstaging as compared with surgical or pathologic staging. This

has confounded accurate evaluation of treatment modalities based solely upon clinical staging.

Methods available for the staging of clinically localized prostate cancer include digital rectal examination (DRE), serum prostate specific antigen (PSA), serum acid phosphatase, transrectal ultrasonography (TRUS), computerized tomography (CT) scan and magnetic resonance imaging (MRI). For determination of distant metastases, staging methods include CT scan, MRI and radioisotopic bone scan. In the panel's opinion and based on growing evidence from recent studies, many of the methods available do not necessarily provide useful information and may not be required for patients with clinically localized prostate cancer.

Regarding clinical staging, several conclusions can be drawn from the medical literature that affect clinical practice:

(1) CT scan and MRI may not be required in the staging evaluation of patients with clinically localized prostate cancer. These tests can often detect gross extraprostatic disease, but that degree of spread can usually be predicted by the serum PSA concentration, DRE or TRUS at time of biopsy. Capsular perforation, seminal vesicle invasion and pelvic lymph node involvement most often are microscopic phenomena and cannot be diagnosed by either CT scan or MRI.

(2) Evidence is mounting that the majority of patients who are candidates for a radical prostatectomy or radiotherapy have a very low risk of having positive pelvic lymph nodes. When the serum PSA concentration, tumor grade and local clinical stage used together are below certain levels, a pelvic lymph node dissection may not be necessary because, as noted on page 15, the probability of positive lymph nodes is extremely low.

(3) From the results of two large clinical studies (Chybowski, Larson-Keller, Bergstralh, et al., 1991; Oesterling, Martin, Bergstralh, et al., 1993), it appears that a staging radionuclide bone scan may not be necessary for patients with newly diagnosed, untreated prostate cancer who have no skeletal symptoms and a serum PSA of 10 ng/ml or less.

Treatment alternatives and treatment outcomes

The following treatment alternatives in current use for managing localized prostate cancer, either alone or in various combinations, were analyzed by the AUA Prostate Cancer Clinical Guidelines Panel:

radical prostatectomy, external beam radiotherapy, brachytherapy (interstitial radiotherapy) and surveillance (also known as expectant management, watchful waiting or observation). Treatment methods considered investigational are thermotherapy, cryotherapy, androgen deprivation and chemotherapy. The panel categorized a treatment method as investigational if the number of patients treated has been inadequate for evaluation and/or if follow-up has been inadequate to provide sufficiently precise outcome estimates.

Treatment outcomes

For assessing the benefits and harms of treatment interventions for stage T2 (B) prostate malignancy, the panel considered the following outcomes as most important to the patient:

(1) Survival at 5, 10 and 15 years (overall survival, disease-specific survival, progression-free survival and metastasis-free survival);

(2) Progression rates at 5, 10 and 15 years (metastatic, local and biochemical); and

(3) Complications of treatment. Although all complications were evaluated, the most important are: death from treatment, incontinence, impotence (erectile dysfunction), cystitis, proctitis, major bleeding, pulmonary embolism, rectal injury and bladder neck contracture/urethral stricture.

Survival at 5, 10 and 15 years

Clinically localized prostate cancer (stages T1 and T2) is rarely lethal within the first 5 years after diagnosis. The overall death rate during this period is low and usually secondary to comorbid processes. Almost any treatment for localized prostate cancer would appear to have an excellent survival result at 5 years. Survival at 10 years and 15 years allows a more accurate assessment of the influence of prostate cancer treatment on patient survival.

It is not enough to assess survival independently of tumor progression status. Comorbid processes associated with advanced age will often determine survival. However, morbidity from cancer progression may occur for years prior to death. It is therefore reasonable to inform patients not only about the risk of dying from prostate cancer, but also about the risk of developing metastatic disease or any evidence of tumor recurrence during follow-up. Thus, outcomes of cancer-specific metastasis-free and tumor-free survival should be assessed in addition to overall survival rates.

Progression rates at 5, 10 and 15 years

After surgery or radiotherapy, most recurrence or progression of adenocarcinoma of the prostate will become biochemically (PSA) apparent by 5 years, but a few patients may have lengthy delays before the progression becomes clinically apparent. It is therefore important to continue to assess progression rates to 10 years and beyond. Progression rates may or may not influence the patient directly. Many times progression will be defined as the development of any evidence of tumor. This recurrence is often asymptomatic and found only through surveillance examinations.

Obviously, either local recurrence or symptomatic metastatic prostate cancer is of extreme importance to patients diagnosed with localized disease. However, biochemical failures, usually in the form of rising serum PSA, may also negatively impact patients from a psychologic standpoint. Men with prostate cancer understand that a rising serum PSA often precedes eventual symptomatic recurrence.

Complications and harms of treatment

Treatment-related death, the most serious adverse outcome from treatment of prostate cancer, is uncommon. Other adverse outcomes from treatment, such as incontinence, impotence (erectile dysfunction), cystitis, rectal injury and bleeding, are more common and have variable degrees of negative impact on patient well-being. The reported incidences and estimates of these adverse outcomes are important to a patient making decisions regarding treatment. Some of the complications are much less common today than in older reports because of newer technology and advancements in technique. It is important to stratify the complications relative to era of treatment. (See Appendix A, Figures A-7 to A-31.)

Analysis of outcomes data from the literature

The panel was impressed by the massive amount of literature available on prostate cancer, but the vast bulk of the literature is not usable for extracting and combining data to assess treatment outcomes and develop practice recommendations. Of 12,501 papers reviewed, the panel was able to retrieve only 165 with acceptable data on outcomes from treatment of localized prostate cancer. (See page 9 for an explanation of the review process.) Moreover, in these 165 articles, there are significant differences among treatment series regarding such

characteristics as patient age, tumor grade and pelvic lymph node status. For example, patients undergoing radical prostatectomy are on average 3 years younger than those undergoing external beam radiotherapy and 7 years younger than those reported to have been followed with surveillance.

It is striking that only about one in seven patients reported in the literature was followed even for 5 years and that a very small fraction was followed for 10 or 15 years. Estimates of important outcomes—notably survival and progression rates at 5, 10 and 15 years—are likely to be inaccurate if such small numbers of patients are available for analysis.

Tumor grades are relatively comparable in patients treated actively (with surgery or radiation); but for patients followed with surveillance, there are data on very few patients who have high-grade tumors. Also, there is scant information on pelvic lymph node status in patients receiving external beam radiotherapy or followed with surveillance, leaving open the possibility of dramatic differences in the stages of patients' tumors.

Because of the significant differences among treatment series and the consequent inability to make meaningful estimates from data available for the treatment outcomes of patient survival and tumor progression, the panel concluded that it would be methodologically unsound to compare treatment modalities directly with regard to these outcomes. Nevertheless, the panel did decide to present data results in the form of summary outcomes tables 3–4 (pages 25-26), as well as graphically in Figures 1–13 (pages 28-31), to show the range of outcomes data reported for the different modalities. The ranges of frequency reported for the 25 most common treatment complications are shown in Table 5 (page 27). Frequency rates for the most important of these complications are depicted graphically as well in Figures 14–16 (page 31).

Treatment recommendations

The panel generated its practice policy recommendations based on the outcome estimates available and on panel opinion. The recommendations were graded according to levels of flexibility based on the strength of the evidence and the panel's assessment of patient needs and preferences. Three levels—standards, guidelines and options—are defined on page 8. A standard has the least flexibility. A guideline has significantly more flexibility, and

(Continues on page 6)

Recommendations: Standards

- As a standard, an assessment of the patient's life expectancy, overall health status and tumor characteristics is necessary before any treatment decisions can be made.

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. (See U.S. Life Expectancy Table in Appendix C.)

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.

Tumor characteristics: The histologic grade and stage of the tumor 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 tumors which have a greater potential to be biologically aggressive and clinically significant.

- As a standard, a patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, radical prostatectomy, radiotherapy and surveillance. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient.

The panel defines radical prostatectomy to include complete removal of the prostate, vasal ampullae and seminal vesicles. The panel defines radiotherapy to include external beam and/or interstitial (brachytherapy) treatments. Surveillance is 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.

- 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.

Recommendations: Treatment options

Options for management of localized prostate cancer include radical prostatectomy, radiotherapy and surveillance. Radiotherapy includes external beam and interstitial (brachytherapy) treatments. The panel considers these interventions to be options because data from the literature do not provide clear-cut evidence for the superiority of any one treatment. Provided for each option, however, are a description of the patient most likely to benefit from the intervention and a brief summary of the intervention's advantages and disadvantages.

- **Radical prostatectomy:** Based on the panel's interpretation of the literature and panel opinion, the patient most likely to benefit from radical prostatectomy would have a relatively long life expectancy, no significant surgical risk factors and a preference to undergo surgery.

The major advantage of radical prostatectomy is its potential for total removal of the cancer and "cure" in properly selected patients. "Cure" is defined as lifetime freedom from disease. Potential harms include urinary incontinence and erectile dysfunction. Because the cancer may not be completely eradicated, disease progression may occur.

- **Radiotherapy:** Based on the panel's interpretation of the literature and panel opinion, the patient most likely to benefit from radiotherapy would have a relatively long life expectancy, no significant risk factors for radiation toxicity and a preference for radiotherapy.

The advantages of radiotherapy are that it has a potential for cure and that it is well tolerated in the majority of men when modern techniques are used. Its principal potential harms include radiation cystitis and proctitis and erectile dysfunction. Because the prostate remains in place, persistence and progression of the disease may occur.

- **Surveillance:** Based on the panel's interpretation of the literature and panel opinion, patients most likely to benefit from surveillance are those with a shorter life expectancy and/or a low-grade tumor.

Benefits of surveillance for low- or intermediate-grade, localized prostate cancer include a lack of treatment-related morbidity with only marginal compromise of disease-specific survival at 5 to 10 years of follow-up. Because the prostate is neither removed nor irradiated, progression of the disease is more likely to occur.

an option is the most flexible. None of the panel's recommendations, however, fits the guideline category defined on page 8.

The standard patient

The panel's recommendations apply to the standard patient, defined as a man who has clinically localized prostate cancer (adenocarcinoma of the prostate). For this report, the panel focused on clinical stage T2 (B) disease. Based on the opinion of the panel, recommendations may 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. For a detailed discussion of prostate cancer staging, see pages 13-15.

Literature limitations and recommendations for research

Limitations in the literature

The medical literature for stage T2 prostate cancer is, overall, clearly deficient in usable data on which to base comparable estimates for outcomes of treatments and to make practice policy recommendations. The deficiencies are such that the Prostate Cancer Clinical Guidelines Panel was unable to develop, based on evidence from the literature, treatment-comparable outcome estimates for the most important outcomes: patient survival and tumor progression at 5, 10 and 15 years. Major limitations can be summarized as follows:

- **Few randomized controlled trials:** Most of the data come from case series not subjected to the rigors of a carefully performed, prospective, centrally controlled clinical trial. Indeed, most of the studies the panel reviewed in its literature search were clinical series based on "convenience samples," patients available in the clinical setting where the research was done. The majority of the other limitations summarized on this page stem from the paucity of randomized controlled trials.

- **Insufficient data:** Many articles do not report all outcomes (such as cancer-specific, metastasis-free and tumor-free survival). Also, there are few data on high-grade tumors in patients managed by surveillance, or on pelvic lymph node status in patients managed by external beam radiotherapy as well as surveillance. In another very important example, many articles do not specify ages of patients

despite the effect of age on survival and the significant differences in average patient age for different treatment modalities. In still another example, many articles reporting complications from treatment do not report "zero complications." For instance, an article may not refer to incontinence in its list of treatment-related complications. Readers are left to wonder whether the complication did not occur or if it was omitted from the report.

- **Data variability:** Examples of variability abound in the literature. For instance, staging methodology often varies between studies, not only with regard to clinical staging versus surgical staging, but with regard to differences in types of lymph node dissections (not all of which are comparable). Patient populations differ greatly in the literature, as do such important factors as means and length of follow-up.

- **Publication bias:** Because not all physicians publish, case-study results may not be generally representative. Moreover, studies with negative or equivocal results are less likely to be submitted for publication and less likely to be published if submitted.

Recommendations for future research

Most research needs can be grouped in three categories: (1) new and better methods to diagnose and manage localized prostate cancer; (2) prospective, randomized, controlled studies of the issues concerning prostate cancer, especially controlled studies of competing treatments for the management of localized prostate cancer; and (3) studies of how prostate cancer and its treatments affect patient quality of life.

- 1 In the first category, **needs for new methods of cancer diagnosis and monitoring** include the need for a more sensitive, more specific tumor indicator. As clinically useful as serum PSA values have become, they lack important properties such as prostate-cancer specificity.

Needed also are biochemical, radiographic and/or genetic methods to assist in staging and to determine reliably which cancers are biologically aggressive and which are clinically insignificant. For detecting potentially life-threatening cancers while still localized, it would be useful to have a genetic marker that can identify men likely to develop such a tumor in their lifetimes.

- 2 In the second category, **randomized, prospective, controlled studies** of competing treatments for managing localized prostate cancer are clearly a

pressing need, especially comparative studies investigating surveillance vis-à-vis active treatments.

Properly designed efficacy studies of treatment modalities will provide reliable descriptive data for the patients studied. The descriptive factors should include age, tumor stage, tumor 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 disease progression (including objective measures of symptoms associated with progression), risk of metastatic disease and risk of prostate cancer death.

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

- **Radical prostatectomy:** Methods of improving preoperative staging, reducing the number of patients with extraprostatic disease and reducing treatment complications; strategies to reduce the cost of the procedure; better ways to disseminate advances in surgical technique to the urologic community; treatments for patients with pathologically proven (pT3) extraprostatic disease; and treatments for patients with evidence of serologic (PSA) failure.
- **Radiotherapy:** Ways to reduce treatment morbidity; ways to standardize treatment; the role of three-dimensional 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.

- **Surveillance:** 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 localized prostate cancer;
- 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 including 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 (e.g., validation of PSA failure as a surrogate for cancer survival).

③ Finally, the third category of research needs consists of research into **how prostate cancer and its treatments affect patient quality of life**. Such research would include the second topic in the above list: analysis of trade-offs between survival and quality of life and of the role played by quality-of-life factors in patients' treatment choices. Needed as well are improved methods for involving the patient in a meaningful and efficient decision-making process and for providing unbiased information to patients and physicians about emerging processes and outcomes of care.

Chapter 1: Methodology

Methods and definitions

The AUA Prostate Cancer Clinical Guidelines Panel developed the recommendations in this *Report on the Management of Clinically Localized Prostate Cancer* following an explicit approach to development of practice policies (Eddy, 1992). The explicit approach attempts to arrive at recommendations through mechanisms that take into account the relevant factors for making selections from alternative interventions. Such factors include estimation of outcomes from the interventions, consideration of patient preferences regarding those outcomes (including costs engendered by the interventions) and assessing when possible the relative priority of the interventions for a share of limited health care resources. Emphasized is the use of scientific evidence in estimating the outcomes of interventions. When panel opinion is necessary, the explicit approach calls for an explanation of why it is necessary and discussion of the factors considered.

To develop recommendations for this report, the panel made an extensive effort to review the literature on stage T2 (B) prostate cancer from 1966-1993 and to estimate outcomes from the alternative treatment modalities as accurately as possible. Unfortunately, the paucity of randomized, controlled trials and lack of comparability among treatment series regarding the most important outcomes, survival and disease progression, made methodologically sound estimations impossible for comparing alternative treatment modalities.

The review of the evidence began with a literature search and extraction of data as described on page 9. The data available in the literature were displayed in evidence tables. From these tables, the panel attempted to develop estimates of outcomes for major treatment alternatives (radical prostatectomy, radiotherapy and surveillance). In Chapter 3, outcomes are analyzed in detail.

The panel generated its practice policy recommendations based on the outcome estimates available and on expert opinion. The recommendations were graded according to three levels of flexibility based on the strength of the evidence and the panel's assessment of patient needs and preferences.

Levels of flexibility are defined as follows (Eddy, 1992; American Academy of Family Physicians, 1995):

- **Standard:** A policy is 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 is considered a guideline if the health and economic outcomes of the interventions are sufficiently well-known to permit meaningful decisions and an appreciable but not unanimous majority agree on which intervention is preferred.
- **Option:** A policy is considered an option if (1) the health and economic outcomes of the interventions are not sufficiently well-known to permit meaningful decisions, (2) preferences among the outcomes are not known, (3) patients' preferences are divided among alternative interventions and/or (4) patients are indifferent about the alternative interventions.

Standards obviously have the least flexibility. Guidelines have considerably more flexibility, and options are the most flexible. In this report, the terms are used to indicate the strength of the recommendations. A recommendation was labeled a standard if the panel concluded that it should be followed by virtually all health care providers for virtually all patients. A recommendation would be labeled a guideline if the panel thought it appropriate not for all, but for a significant majority of patients. None of the recommendations in this report, however, fits the guideline category.

Recommendations in this report regarding treatment choices were labeled options mostly because of the inability to estimate outcomes meaningfully from the evidence available. Because the evidence does not permit direct comparison of the most important outcomes among alternative treatment modalities, the comparative recommendations for these modalities are presented as treatment options rather than as guidelines or standards (page 38).

Another reason for labeling a recommendation an option is that patient preferences may be

unknown or divided because of complications from the treatment, in which case it is particularly important to consider preferences of individual patients in selecting from among alternative interventions.

Literature search

To extract scientific evidence about the outcomes from alternative interventions for treating stage T2 (B) prostate cancer, the panel performed a literature search utilizing the MEDLINE database. The database was searched several times up to December 1993, using the MESH subject heading “prostatic neoplasms.” All citations recovered were imported into a bibliographic database software system (Papyrus Bibliography System; Research Software Design, Portland, Oregon).

Members of the panel reviewed abstracts for 12,501 articles on prostate cancer published from 1966 to 1993. Each abstract was independently reviewed by two panel members. If either member thought the article appeared relevant, it was retrieved. On the basis of abstract review, 1,453 articles were retrieved. After a summary review of these articles, the panel found 926 of the 1,453 articles (64 percent) acceptable for detailed review. Of the 926 articles, 396 were found relevant to stage T2 (B) prostate cancer and were accepted for extraction of outcomes data.

Figure A-1 in Appendix A of this report shows graphically, by year, the number of articles the panel retrieved on the basis of abstract review. Evident in this graph is the dramatic increase over time in the number of papers published. Figure A-2 shows sources of articles from the English-language literature. Also see Appendix A for the bibliography in Table A-1 of sources of articles from which outcomes data were extracted. (Articles cited in the text of this report, for referencing particular points discussed, were not necessarily among articles the panel reviewed to extract outcomes data.)

Data extraction

A comprehensive data-extraction form was devised by the panel and staff to capture as much pertinent information as possible from each article. A sample of the form is in Appendix B. The selected articles were divided among the panel members, who extracted the data to complete the form.

During the finely detailed data-extraction process, 231 of the 396 stage T2 articles were rejected for the following reasons: 6 percent because information on patients could not be separated according to treatment used; 8 percent because of updated data available in a later paper; 12 percent because information on patients' cancers could not be separated according to stage; 16 percent because of absent data; 27 percent because of irrelevant data; and 31 percent for other, miscellaneous reasons. The net result was 165 articles with stage T2 outcomes data extracted (see Appendix A, Figures A-5 and A-6).

Each of the 165 articles was reviewed and the data extracted separately by two panel members, who then met to resolve any differences. Their result was entered into a database software system (PARADOX) by staff, who also verified all data entries. The data were entered by series. Series in this report are groups of patients stratified by parameters such as primary treatment modality.

Subsequent to data extraction, the panel attempted to follow a process in which the extracted data would be combined by meta-analysis to yield outcome estimates for alternative treatment modalities. The meta-analytically derived estimates would then be arrayed in an outcomes table to compare the modalities.

Meta-analysis is a term that has been used in a variety of contexts in the medical literature. In its most general definition, meta-analysis is any process of utilizing the results of multiple studies to determine a final estimate for a given parameter. For this report, the definition was restricted to include only formal mathematical methods of combining the results of multiple studies. Various methods can be used. The techniques employed depend upon the nature of the studies to be combined, the degree to which the studies are similar and the types of data available. In its most restrictive definition, meta-analysis includes only the classical (non-Bayesian) techniques used to combine randomized controlled trials.

Data inadequacy

As noted previously (page 8), after examining at length the data on management of localized prostate cancer, the panel had to conclude that these data do not provide sufficient evidence to allow valid comparisons of treatments. Therefore, meta-analytic combination by any method is inappropriate.

A major reason is that the data are from clinical series, and data from clinical series are frequently

not comparable. Pooling such data can lead to large, uncharacterizable biases. In the case of prostate cancer, the differences between series are especially significant. For example, it is known that patients who are older are more likely to be found in series on treatment by surveillance or radiation. Many studies, however, do not specify ages of the patients. In another example, patients in nonrandomized studies will likely have different grades of disease. Yet, grade data are frequently not available. In still another example, stage data are sometimes based on clinical staging and sometimes on surgical staging. For patients not undergoing surgery, clinical staging is generally used, whereas authors of surgical series frequently reclassify patients based on surgical stage. This implies that nonsurgical series may include more higher-stage patients.

Particularly problematic are survival and disease-recurrence data (including overall survival, disease-specific survival, recurrence-free survival and time to recurrence). The problems include differences in reporting of follow-up, differences in methods of reporting survival and biases in losses to follow-up.

Data display for survival and disease progression

Having determined that combining the outcomes data from different series is inappropriate, the panel debated several methods for displaying the data. These methods included crude combinations in an outcomes table, graphs with outcomes and sizes of each study shown or simply graphs with the outcomes from each study. All of these methods have the disadvantage that the reader might infer differences for alternative treatments that cannot be justified.

The panel chose the simplest forms of display (pages 25-26, 28-31). In the graphical displays, the circles indicate the rate reported by each series for overall survival, progression-free survival, metastasis-free survival or disease-specific survival. The data are also shown in tabular form with the minimum and maximum percentages reported but no mean or median estimates. The tables indicate whether reported results are based upon actuarial calculations (life tables or Kaplan-Meier) or whether they are “actual” (observed, nonactuarial), that is, representing a ratio of an actual number of survivors over a denominator that may have some reduction for dropouts. As noted on page 23, because many patients are lost to follow-up, die of unknown causes or fail to have consistent testing or to have

the data recorded, “actual” rates might not accurately represent the impact of the disease or its treatment in the general population. For this reason, the word “actual” when used to denote such data appears in quotes.

Treatment complications data

The problems that exist with regard to data for survival and disease progression also exist with regard to data for complications of treatment. The lack of randomized trials and differences in patient populations and treatment techniques frequently result in data not generalizable across studies. Differences in reporting data add to the problems. For example, many investigators do not list all complications in the results sections of their studies. They may list only the complications that occur. Uncommon complications like perioperative death are thus not included in many studies. To use such studies in a meta-analysis combining results of multiple studies, a zero rate must be assumed for complications not reported. Otherwise, if data were combined only from those studies where a complication occurs, the estimate of frequency of occurrence would be artificially high.

Because of the various problems with regard to the complications data, the panel chose not to combine these data from the different studies in order to estimate frequency of occurrence for alternative therapies. The panel elected instead to display the complications data using the same method as for survival and progression data. For each of the most important complications, such as perioperative death, impotence (erectile dysfunction), rectal injury and incontinence, a graph indicates the reported frequency rates for that complication (see Figures 14–16, page 31). The data are shown in tabular form as well (page 27), with reported high and low rates to indicate a range but with no mean or median estimates. In Chapter 3, tables and graphs are explained in detail.

Literature citations and panel opinions in discussion sections

The discussion sections in Chapter 2 provide primarily descriptive and explanatory information about the natural history of prostate cancer, the Gleason grading system and systems and methods

used for clinical staging. Also provided in Chapter 2 are individual overview discussions of the treatment alternatives analyzed by the AUA Prostate Cancer Clinical Guidelines Panel: radical prostatectomy, external beam radiotherapy, brachytherapy (interstitial radiotherapy) and surveillance. Advantages and disadvantages of each of these treatment options are discussed on pages 38-41 of Chapter 4, following the panel's treatment recommendations.

Some of the studies cited in the discussion sections in Chapters 2 and 4 are in addition to articles reviewed by the panel for data extraction and analysis. Among the additional articles are papers published after December 1993. As noted on page 9, December 1993 was the cutoff date in the literature search to obtain articles for the purpose of extracting outcomes data. However, the discussion sec-

tions also include information from more recent studies published in 1994.

Although these discussion sections contain primarily descriptive and explanatory information, some sections also contain panel opinions based on evidence from studies cited in the text of the discussion. In particular, the section in Chapter 2 on staging methods (pages 13-15) contains panel opinions questioning the need to use methods such as computerized tomography (CT) scan and magnetic resonance imaging (MRI) for patients with clinically localized prostate cancer. Reasons for panel opinions are stated explicitly in this and other sections, but it should be recognized that no attempt was made to subject the evidence cited to a rigorous review process like that described on pages 9-10 of this chapter.

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Chapter 2: Prostate cancer and its management

Background

Prostate cancer is the most commonly diagnosed visceral neoplasm in men. The estimated 244,000 new cases diagnosed in the United States in 1995 represent 36 percent of cancers in men, compared to 14 percent for lung cancer and 10.4 percent for colorectal cancer, the next two most frequently diagnosed cancers (Wingo, Tong and Bolden, 1995). The 40,400 deaths from prostate cancer anticipated in 1995 represent 14 percent of all cancer deaths in men, placing prostate cancer second only to lung cancer mortality (33 percent) and ahead of colorectal cancer mortality (9.4 percent).

Of the malignant conditions that arise primarily within the prostate gland, by far the most frequently occurring type is adenocarcinoma. Because of the rarity of other primary neoplasms within the gland, the terms “prostate cancer” and “carcinoma of the prostate” are generally understood to be synonymous with “adenocarcinoma.”

Anatomically, four glandular prostatic regions are recognized: (1) the transition zone, a bilobar area lying on each side of the distal two-thirds of the supramontanal prostatic urethra in the unenlarged state, but which can, following the development of benign prostatic hyperplasia, occupy as much as 95 percent of the entire gland volume; (2) the central zone, which occupies the major portion of the cephalad half of the prostate; (3) the peripheral zone, which occupies most of the distal half of the gland and (4) the periurethral glands lining the urethra.

Approximately 75 percent of prostatic carcinomas arise in the outer gland (a combination of the central and peripheral zones), and many of these cancers are multifocal. The remaining 25 percent arise in the transition zone. The volume of the largest area of involvement, if in the peripheral or central zones, correlates with overall tumor stage. The periurethral glands are rarely involved in malignant change.

A nonglandular area, the fibromuscular stroma, lying on the anterior gland surface as well as comprising the internal and external urethral sphincters,

is devoid of carcinomatous change as its components do not include glandular tissue.

Natural history and grade classification

Prostate cancer has a wide spectrum of growth rates. Many tumors pursue a relatively indolent course over a number of years. Others advance rapidly by local extension and/or metastasis. Evaluation of the effect of active intervention must take into account the course the disease would follow if it were allowed to proceed without interference. Active treatment of a prostatic cancer that is destined never to present a clinical problem to the patient would not be expected to improve patient outcomes over treatment by surveillance alone. Prostate cancer aggressiveness, however, does tend to increase with time (Adolfsson and Tribukait, 1990). Given sufficient time, small localized tumors can be expected to become large, multifocal, nonlocalized tumors (Whitmore, Warner and Thompson, 1991), with decreasing likelihood of cure. “Cure” is defined in this report as lifetime freedom from disease.

Thus, because techniques for distinguishing rapidly growing from slow growing tumors are still evolving, patient longevity becomes a major factor in determining treatment. Treatment of prostate cancer depends to a significant degree upon the patient’s age, functional level and medical status. Because a younger, healthier patient may be exposed to a longer period of risk for disease progression, metastases and death, consideration of intervention rather than management by surveillance may be more compelling in this patient. Risks for death from untreated disease are presented in this report (pages 40-41), but long-term results are poorly understood. Of concern is a recent article suggesting that even low-grade tumors may have as high as a 55 percent likelihood of resulting in cancer death within 15 years of follow-up (Aus, Hugo-sson and Norlén, 1994). The older patient with a shorter period at risk may have a lesser chance of prostate cancer death. The age at which the risk of

cancer death reaches an “acceptable” level, so that treatment is unnecessary, is not known.

Histologic grade is currently one of the most common methods for classifying tumor aggression levels, and the most common system currently in use is the Gleason grading system based on architectural criteria (Gleason, 1977). A primary grade from 1 to 5, with 5 being the most aggressive, is assigned to the pattern occupying the greatest area of the specimen. A secondary grade is assigned to the pattern occupying the second largest area. These two grades are then added to get a Gleason score, which ranges from 2 to 10. It is generally agreed that tumors with a Gleason score ≤ 6 have lower biologic aggressiveness and those with a Gleason score ≥ 7 are biologically aggressive tumors.

Pathologists can have difficulty, however, distinguishing grade 3 histologic patterns from grade 4 histologic patterns for assigning primary or secondary grades. The distinction is important. Studies relating component grades to spread of cancer have shown that metastases almost never occur with grade 3, but occur often with grades 4 and 5 (McNeal, Villers, Redwine, et al., 1990). Consequently, whereas $3 + 3 = 6$ is a favorable Gleason score, $4 + 2 = 6$ or $2 + 4 = 6$ is not. Certainly not favorable are $4 + 3 = 7$, $3 + 4 = 7$, $5 + 2 = 7$ and $2 + 5 = 7$. The value of the Gleason system may thus depend, in some cases, on the pathologist’s proper categorization of grade 3. Still, the system is a vast improvement over earlier, purely descriptive attempts at classification.

Factors such as tumor grade and volume (stage), along with evaluation of nuclear chromatin content and nuclear roundness, allow some prediction of a tumor’s biologic potential. However, at the present time, such factors are not fully applicable to individual patients because of the many exceptions that exist to these predictive indices.

The natural history of untreated prostate cancer is discussed in detail on pages 18-19 of this chapter in the description of surveillance as a treatment alternative.

Staging

Several staging systems for prostate cancer have been described in the literature. The two used most often are the Jewett-Whitmore ABCD system (Prout, 1973) and the TNM system (Beahrs, Henson, Hutter, et al., 1992). Table 1 provides a comparison of the two systems. Both systems have un-

Table 1. TNM and Jewett-Whitmore staging systems

STAGE		
TNM	Jewett-Whitmore	Description
TX		Tumor cannot be assessed
T0		No evidence of tumor
T1a	A1	Tumor an incidental finding at TURP involving 5% or less of tissue resected
T1b	A2	Tumor an incidental finding at TURP involving more than 5% of tissue resected
T1c	B0	Nonpalpable tumor identified because of elevated PSA
T2a	B1	Tumor involves one-half of a lobe or less
T2b	B1	Tumor involves more than one-half of a lobe, but not both lobes
T2c	B2	Tumor involves both lobes
T3a	C1	Unilateral extracapsular extension
T3b	C1	Bilateral extracapsular extension
T3c	C2	Tumor invades one or both seminal vesicles
T4a	C2	Tumor invades bladder neck and/or external sphincter and/or rectum
T4b	C2	Tumor invades levator muscles and/or is fixed to the pelvic sidewall
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	D1	Metastasis in a single lymph node, 2 cm or less at greatest dimension
N2	D1	Metastasis in a single lymph node more than 2 cm, but not more than 5 cm at greatest dimension, or in multiple lymph nodes none more than 5 cm at greatest dimension
N3	D1	Metastasis in a lymph node more than 5 cm at greatest dimension
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1	D2	Distant metastasis

dergone modifications because of the need to accommodate evolving concepts of prostate cancer.

Accurate determination of tumor stage is important, in that therapy is highly dependent upon knowledge of whether or not the tumor is localized to the gland. Clinical staging has improved in recent years, yet considerable inaccuracy remains. This, at times, results in understaging and, to a lesser extent, overstaging as compared with surgical or pathologic staging. This has confounded accurate evaluation of treatment modalities based solely upon clinical staging.

Methods used in clinical staging of prostate cancer

Methods available for staging of clinically localized prostate cancer include digital rectal examination (DRE), serum prostate specific antigen (PSA), serum acid phosphatase, transrectal ultrasonography (TRUS), computerized tomography (CT) scan and both body and endorectal magnetic resonance imaging (MRI). For determination of distant metastases, staging methods include CT scan, MRI and radioisotopic bone scan. In the panel's opinion, based on growing evidence from recent studies, many of the methods available do not necessarily provide useful information and may not be required for patients with clinically localized prostate cancer.

CT scan and MRI

Approximately 50 percent of patients with newly diagnosed prostate cancer undergo a CT scan and/or MRI to assess locoregional spread (Stamey and McNeal, 1992). Yet, for most patients, these staging modalities provide little useful information and may not be necessary. Capsular perforation, seminal vesicle invasion and pelvic lymph node involvement most often are microscopic phenomena and, if so, cannot be diagnosed by either CT or MRI (Rifkin, Zerhouni, Gatsonis, et al., 1990). These tests can often detect gross extraprostatic disease, but that degree of spread can usually be determined from the serum PSA concentration, DRE or TRUS at time of biopsy. For these reasons, CT and MRI may not be required in the staging evaluation of patients with clinically localized prostate cancer.

Prostate cancer detected by PSA

Beginning in 1987, PSA has gradually achieved widespread clinical use, initially as a tumor marker for monitoring response to treatment, and more recently as an indicator of early, potentially curable prostate cancer (Brawer, Chetner, Beatie, et al., 1992; Catalona, Smith, Ratliff, et al., 1991; Cooner, Mosley, Rutherford, et al., 1990; Labrie, Dupont, Suburu, et al., 1992).

It is well established that serum PSA can identify patients with prostate cancers not detectable by DRE, thus increasing the number of nonpalpable prostate cancers being diagnosed. As shown in Table 1 in the TNM staging system, "PSA-detected" cancers are classified as stage T1c; in the Jewett-Whitmore staging system, they are referred to as stage B0 (Stormont, Farrow, Myers, et al., 1993).

Studies indicate that most nonpalpable, PSA-detected prostate cancers are of sufficient volume to classify them as clinically important (Brendler, Carmichael, Walsh, et al., 1993; Epstein, Walsh, Carmichael, et al., 1994; Oesterling, Suman, Zincke, et al., 1993; Scaletscky, Koch, Eckstein, et al., 1993). There is no evidence that PSA-detected prostate cancers are different from small DRE-detected tumors.

Pelvic lymph node dissection

Pelvic lymph node dissection (PLND) has long been considered the gold standard in evaluation of regional metastases from prostate cancer. Although PLND can provide staging information obtainable by no other method, the procedure increases time in surgery and can increase patient morbidity. Potential complications include hemorrhage, lymphocele, infection and vascular and neurologic injuries which occur in as many as 20 percent of those patients undergoing PLND (Donohue, Mani, Whitesel, et al., 1990; Kavoussi, Sosa, Chandhoke, et al., 1993).

Evidence is mounting that most patients who are candidates for a radical prostatectomy or radiotherapy have very low risk for positive pelvic lymph nodes. One study found that patients with a primary tumor volume less than 4 cc (1.5-2.0 cm in diameter) do not have lymph node metastases (Stamey, McNeal, Freiha, et al., 1988). Another study noted that only 6 of 274 patients (2 percent) with palpable disease in one lobe (clinical stage T2a/T2b) had positive pelvic lymph nodes, in contrast to 23 percent of 84 patients with palpable disease in both lobes (clinical stage T2c) (Walsh, 1988). The Stanford group found in patients with clinical stage T2a/T2b disease that no patients having sextant needle biopsy specimens positive in only one lobe had positive lymph nodes, and only 8 percent of patients having biopsy specimens positive in both lobes had lymph node metastases (Daniels, McNeal and Stamey, 1992). In two other large contemporary series of almost 600 patients, in which the cancers were detected using PSA screening, the incidence of positive pelvic lymph nodes was approximately 5 percent (Danella, deKernion, Smith, et al., 1993; Petros and Catalona, 1992).

In a study reviewing 1,632 patients with clinically localized prostate cancer who had undergone bilateral pelvic lymphadenectomy at the Mayo Clinic, the overall incidence of positive pelvic lymph nodes was 12 percent (Bluestein, Bostwick, Bergstralh, et al., 1994). Using logistic regression analysis, serum PSA was found to be the best predictor of pelvic lymph node metastases.

However, the predictive power of serum PSA could be enhanced considerably by taking into account the tumor grade and clinical stage. Using all three clinical parameters together, a statistical model was generated that allows the practicing urologist to accurately estimate the probability of pelvic lymph node involvement. The model indicates that when the serum PSA concentration, tumor grade and local clinical stage are below certain levels, the probability of positive lymph nodes is extremely low. A pelvic lymph node dissection may not be necessary (Bluestein, Bostwick, Bergstralh, et al., 1994).

Radionuclide bone scan

The most sensitive method to detect bony metastases is radionuclide bone scan. Of late, evidence has accumulated suggesting that bone scans may be eliminated for selected patients. Based on two large-scale clinical studies, Oesterling and colleagues have determined that serum PSA concentration can be used to reliably predict bone scan findings in patients with newly diagnosed prostate cancer.

In the first clinical study, the investigators evaluated, retrospectively, 521 randomly selected patients who presented with newly diagnosed, untreated prostate cancer (Chybowski, Larson-Keller, Bergstralh, et al., 1991). All were evaluated with regard to local clinical stage as determined by DRE, biopsy tumor grade, serum acid phosphatase, prostatic acid phosphatase concentration, serum PSA and bone scan findings. Of all the clinical parameters available to predict the presence of skeletal metastases, PSA was the best in predicting the results of a radionuclide bone scan. For a serum PSA concentration of 10 ng/ml or less, the probability of skeletal metastases (positive bone scan) is extremely low—less than 1.5 percent.

In order to confirm these initial findings, a second investigation was conducted to assess the ability of serum PSA to predict bone scan findings (Oesterling, Martin, Bergstralh, et al., 1993). Medical records of 2,064 consecutive patients with prostate cancer were reviewed. Patients with prior treatment (androgen deprivation therapy, radical prostatectomy or radiotherapy) were excluded. As with the previous study, irrespective of the tumor grade and local clinical stage, the serum PSA value was the best predictor of the bone scan results. Combining tumor grade, local clinical stage or both with PSA did not enhance the predictive power of PSA. This second investigation also confirmed the observation that patients with a low serum PSA

concentration (less than 10 ng/ml) rarely have skeletal metastases.

From the results of these two large clinical studies, it appears that a staging radionuclide bone scan may no longer be necessary for the patient with newly diagnosed, untreated prostate cancer who has no skeletal symptoms and a serum PSA concentration of 10 ng/ml or less.

Treatment alternatives

The evolution of therapeutic modalities for treatment of prostate cancer has been continuous over the past several decades, making it difficult to assess the comparative value of each modality. Also, the treatment options for a particular patient are subject to a number of constraints. First is an assessment of the patient's life expectancy based upon actuarial and comorbidity information, his functional status and his own wishes regarding therapy. Another important concern is whether the malignancy is believed to be confined within the gland or whether it has spread either regionally or distantly.

The following treatment alternatives in current use for managing localized prostate cancer, either alone or in various combinations, were analyzed by the AUA Prostate Cancer Clinical Guidelines Panel: radical prostatectomy, external beam radiotherapy, brachytherapy (interstitial radiotherapy) and surveillance (also known as expectant management, watchful waiting or observation).

Treatment methods that the panel considered investigational are thermotherapy, cryotherapy, androgen deprivation and chemotherapy. A treatment method was categorized as investigational if the panel found the number of patients treated inadequate for evaluation and/or if follow-up has been inadequate to provide sufficiently precise outcome estimates.

Treatment alternative: Radical (total) prostatectomy

Patient selection

Surgical removal of the prostate gland is "curative" only if all the tumor is removed. "Cure" is defined as lifetime freedom from disease. Therefore, the appropriate patient for radical prostatectomy has the disease clinically confined to the prostate, with no area of extension beyond the capsule or fixation of the gland and no evidence of regional or

distant disease. This would include selected patients with clinical stage T1 or T2 biopsy-proven tumors. Evidence suggests that not all of these patients need to undergo a pelvic lymph node dissection or a radionuclide bone scan before radical prostatectomy (see pages 14-15).

The appropriate patient also has these characteristics: (1) an expected longevity longer than the expected morbidity of his cancer if left untreated; (2) no significant surgical risk factors; and (3) a willingness to undergo surgery following a discussion of risks, postoperative side effects, natural history and options (Gibbons, 1993).

Life expectancy of the patient

Although relentless, the growth pattern of intermediate- and low-grade prostate cancers (Gleason score ≤ 6) is such that the cancer might not represent a significant threat to the patient in his lifetime. An assessment of the patient's overall health status is therefore mandatory before any treatment recommendations can be made. This should include information regarding age and cause of death of parents, familial longevity and diseases (for example, hypertension, cardiovascular, metabolic), and past and current health problems.

Patients with localized prostate cancer might be candidates for treatment by surveillance or delayed therapy if they have a low-grade tumor and a life expectancy of 10 years or less (Whitmore, 1993), whereas patients with a greater life expectancy might be considered candidates for radical prostatectomy.

Performance of radical prostatectomy

Radical prostatectomy is performed using either the retropubic or perineal approach. Walsh and associates have provided considerable insight into the periprostatic anatomy over the last 10 years, which has reduced the complications associated with the retropubic procedure (Walsh, 1992). Techniques include precise control of bleeding from the dorsal vein complex, to allow a more precise anatomic dissection of the apex, and identifying the branches of the pelvic plexus that innervate the corpora cavernosa so that they can be preserved and sexual function can be maintained. These "nerve-sparing" techniques have subsequently been incorporated into the perineal procedure (Weldon and Tavel, 1988).

The goal of both the retropubic and perineal approaches is to remove the entire prostate gland, both seminal vesicles, both ampullae of the vas and the surrounding tissues including the bladder neck.

The bladder neck opening is then contoured as necessary to the size of the urethral stump where an end-to-end anastomosis is performed. The principles of the operations are well established, with usual operating times of 2 to 4 hours. Hospitalizations of 3 to 6 days are the rule, and the patient has an indwelling catheter for 10 to 21 days.

Treatment alternative: External beam radiotherapy

Technological improvements

Advances in radiation oncology over the last several years have substantially improved external beam radiotherapy for prostate cancer. Technological improvements allow the radiation beam to be more precisely targeted to the prostate and seminal vesicles, sparing normal tissues to a greater degree from harmful effects of radiation. Computer technology now permits accurate three-dimensional delineation not only of the prostate and seminal vesicles, but of the normal rectum, bladder and other structures (conformal therapy). This facilitates individually customized therapeutic blocks, sharply focusing the radiation beam on the target volume.

Moreover, recent advances in clinicopathologic understanding of the likelihood of seminal vesicle extension, the location of the prostatic apex, the importance of day-to-day prostate motion and the therapeutic efficacy of lymph node irradiation have all contributed to improvements in external beam radiotherapy. The full effects of these advances in a therapeutic context will become clearer over the next several years as data from long-term follow-up become available.

Patient selection

Patients selected for external beam radiotherapy should have a relatively long life expectancy and no significant factors for radiation toxicity. For instance, bilateral femoral hip replacements can significantly interfere with the delivery of radiotherapy. In addition, patients with systemic lupus erythematosus, other unusual collagen vascular diseases and inflammatory bowel diseases such as ulcerative colitis are candidates for an alternative therapy.

Known pelvic nodal metastasis is a strong contraindication to external beam radiotherapy. Studies by both Memorial Sloan-Kettering (Fuks, Leibel, Wallner, et al., 1991) and the Radiation Therapy Oncology Group (Hanks, Krall, Pilepich, et al., 1992) reported that only about 10 percent of patients with node-positive disease at presentation

remain free of disease at 10 years, and there is no indication of a plateau in the disease-free survival curve. This indicates that node-positive patients, with perhaps rare exceptions, cannot be cured using current radiotherapy techniques and may require an alternative therapy.

Patients likely to benefit most and have the best results from external beam radiotherapy are generally those who are also ideal candidates for radical prostatectomy. Patients with T2a tumors will have much better long-term disease-free survival than patients with T2b or T2c tumors (Glick, Philput, El-Mahdi, et al., 1990; Kaplan, Prestidge, Bagshaw, et al., 1992; Kuban, El-Mahdi and Schellhammer, 1989b; Schellhammer, Whitmore, Kuban, et al., 1989). Patients with well-differentiated tumors, normal acid phosphatases and PSA values ≤ 10 -15 ng/ml have markedly improved outcomes compared to patients with either higher-grade tumors or higher PSA values at time of presentation. This has been well documented (Asbell, Martz, Pilepich, et al., 1989; Duncan, Warde, Catton, et al., 1993; Forman, Zinreich, Lee, et al., 1985; Landmann and Hunig, 1989; Perez, Garcia, Simpson, et al., 1989; Pisansky, Cha, Earle, et al., 1993; Russell, Dunatov, Hafermann, et al., 1991).

Target volume

Historically, pelvic lymph nodes were included in the radiation treatment volume as they were known to be positive in a significant percentage of patients. Some reports showed improved survival when the lymph nodes were treated, versus historic controls (Bagshaw, 1984; Epstein and Hanks, 1993; McGowan, 1981); and regional nodal radiotherapy was known to be effective in other types of cancers.

However, there are many who now doubt the importance or efficacy of regional pelvic radiotherapy. As noted previously, the most mature reports of patients with involved lymph nodes clearly indicate that, at 10 years, the overwhelming majority will have developed metastatic disease (Fuks, Leibel, Wallner, et al., 1991; Hanks, Krall, Pilepich, et al., 1992). Moreover, there is no evidence of a plateau in the disease-free survival curves, suggesting that radiation to involved pelvic nodes is incapable of curing a meaningful number of patients. Finally, prospective randomized trials have demonstrated no advantage to pelvic nodal radiation when compared with the results of prostate radiotherapy alone (Asbell, Krall, Pilepich, et al., 1988; Asbell, Martz, Pilepich, et al., 1989; Pilepich, Krall, Johnson, et al., 1986).

Whether to include seminal vesicles in target volume is also uncertain. Depending upon the precise characteristics of the stage T2 prostate cancer, the risk of seminal vesicle invasion can vary from 5 to 40 percent (Marks and Anscher, 1992; Mukamel, deKernion, Hannah, et al., 1987; Oesterling, Brendler, Epstein, et al., 1987). Most patients with seminal vesicle invasion will have minimal involvement (less than 16 percent of the gland). Yet, even in the most favorable subsets of T2 disease, it is not rare for seminal vesicles to be significantly infiltrated by tumor.

For the majority of patients with T2 tumors, the seminal vesicles can be included in the target volume with minimal added morbidity. However, the volume of irradiated rectum will definitely increase. Also, in occasional patients, the seminal vesicles extend laterally and posteriorly for a significant distance, with consequently greater risk of morbidity. It is reasonable in such cases to carefully weigh the increased risk of morbidity against the benefits of treating the seminal vesicles, especially if the tumor is classified in the most favorable substages of T2 disease.

Treatment alternative: Brachytherapy (interstitial radiotherapy)

Patient selection

Patient selection criteria for brachytherapy are similar to those for external beam radiotherapy. In general, operative mortality is low, but complications are not infrequent (see Table 5, page 27). For transperineal ultrasound-guided implantation approaches, widely variable complications have been reported (Blasko, Ragde and Grimm, 1991; Iversen, Bak, Juul, et al., 1989; Smalley and Noble, 1992). Although some reports show negligible complications, longer follow-up and other corroborative series are needed (Bertermann, et al., 1991; Blasko, Ragde and Grimm, 1991; Bosch, Forbes, Prassvinichai, et al., 1986; Carey, Lippert, Constable, et al., 1988; Fowler, Barzell, Hilaris, et al., 1979; Iversen, Bak, Juul, et al., 1989).

Prior transurethral resection of the prostate (TURP) is a relative contraindication to prostate brachytherapy. Because patients with prior TURP have a much higher incidence of late urinary complications (Blasko, Ragde and Grimm, 1991), extreme caution in minimizing urethral dose is important. Extensive corpora amylacea also present a theoretical contraindication to implantation with low-energy radionuclides (^{125}I and ^{103}Pd). The high

electron density of the corpora amylacea may absorb the radiation emitted from these low-energy sources.

Finally, patients with high-grade tumors or with large tumor volume (expressed either as a volumetric estimate or as advanced clinical stage) are not well suited for brachytherapy. No widely utilized brachytherapy techniques implant either the seminal vesicles or extracapsular tissue.

Techniques

Brachytherapy techniques involve two separate choices: which type of radionuclide and which method of administration. Isotopes can be chosen from a variety of radionuclides, taking into account such factors as dosimetry scheme, half-life, type of emission and tissue penetration. Brachytherapy may also be augmented by external beam radiotherapy, as well as by high-technology modifications that are still investigational.

There are two methods of administration. In the earlier approach (1965 – 1985), the prostate was exposed retropubically. Then the radionuclide “seeds” were inserted by means of hand-positioning the carrier needles, attempting to encompass the entire prostate mass by gross estimation. Several drawbacks to this method have been reported. One is inferior control of localized disease when compared with external beam radiotherapy (Kuban, El-Mahdi and Schellhammer, 1989a; Morton and Peschel, 1988; Schellhammer, El-Mahdi, Higgins, et al., 1987; Schellhammer, Whitmore, Kuban, et al., 1989; Smalley and Noble, 1992).

Errors have also been documented in evaluating prostate size, and thus in the numbering and spacing of seeds (Stone, Forman, Sogani, et al., 1988). Because distribution of seeds was difficult, the radiation dose was nonhomogeneous (Gore and Moss, 1983; Kandzari, Belis, Kim, et al., 1982; Sogani, DeCosse, Montie, et al., 1979). Seeds migrated and were usually passed out through the urethra (Sommerkamp, Rupprecht and Wannemacher, 1988; Steinfeld, Donahue and Plaine, 1991). Finally, some authors have been concerned about the low doses delivered by ^{125}I and ^{103}Pd (Anderson and Ling, 1991; Dale, 1985; Fowler, 1989, 1991; Smalley and Noble, 1992). Data the panel extracted on complications of brachytherapy were based on this earlier, retropubic approach.

The newer method of administering the radiation (1984-present) places the seeds much more precisely via the perineal percutaneous route. This approach uses a perforated template on the perineum to position the carrying needles and transrectal ul-

trasound to monitor accurate distribution of the seeds. Anesthesia may be used, but no open surgery is necessary. The transperineal method provides more homogeneous delivery of the radiation dose to the prostate, but some concern has been expressed about adequately accessing the prostate base and seminal vesicles. More important, this method has not yet produced outcome results with long enough follow-up to be able to evaluate the potential advantages and risks. In the panel’s opinion, however, there is no evidence that results from the transperineal method are inferior to those from the retropubic method.

Treatment alternative: Surveillance

Basis for management by surveillance

The notion that no active treatment can be used for a disease process is not unusual. A classic example is the common cold. However, for such a policy of “no active treatment” or “surveillance” to be used for a neoplasm in which morbidity or mortality can occur, one or more of the following criteria must be met: (1) The neoplasm must have a low risk of morbidity and mortality; (2) The impact of treatment upon morbidity or mortality must be negligible, minimal or of unknown effect; and (3) The harms of treatment must outweigh the benefits.

With regard to the first criterion, evidence suggests that low-grade, low-stage prostate cancer untreated may not produce any symptoms for prolonged periods. Only in some patients will morbidity or death from the disease ensue. Autopsies of men who died from other causes reveal a substantial number with occult prostate cancer. The rate is as high as 80 percent in older men (Franks, 1954). A study using assiduous sectioning techniques to investigate young men found carcinoma present in 9 percent, 16 percent and 26 percent of men in their third, fourth and fifth decades, respectively (Sakr, Haas, Cassin, et al., 1993).

Of men with untreated prostate cancer followed up to 10 years, most series suggest that the majority do not die of prostate cancer but with it. Most of these series included older men at a higher risk of death from other causes and men with less lethal forms of prostate cancer (well differentiated, low stage). In one series (George, 1988), although 5 patients died of prostate cancer, 48 died of other causes (4 percent versus 40 percent of the study population). In another series (Adolfsson, Carstensen and Lowhagen, 1992), of the 38 percent of patients who died, 7 percent died of prostate cancer and 31 percent of other causes.

In regard to the second criterion—that the impact of treatment on prostate cancer may be minor—three bodies of evidence support this contention. First, using contemporary measures of treatment efficacy, many patients with clinically localized prostate cancer when treated for cure have been shown to be at risk for disease recurrence. In the case of radical prostatectomy, a guiding principle holds that if the tumor is confined to the prostate and the prostate is removed, likelihood of “cure” (lifetime freedom from disease) is high. Unfortunately, the disease may not, in fact, be organ confined. In the United States, as many as 50 percent of patients undergoing radical prostatectomy will be found to have disease outside the prostate capsule or in the seminal vesicles or to have a positive surgical margin (Morton, Steiner and Walsh, 1991; Wahle, Reznicek, Fallon, et al., 1990). These patients have a higher risk of disease recurrence than do patients with organ-confined tumors (Paulson, Moul and Walther, 1990).

Some patients will be found to have a measurable PSA following radical prostatectomy, indicating persistent disease (Stein, deKernion, Smith, et al., 1992). Using PSA as an indicator of failure, patients treated with radiotherapy have also been noted to have a high risk of relapse. One article reported that as many as 80 percent of patients treated with radiotherapy have a rising PSA within a relatively short period of follow-up (Stamey, Ferrari and Schmid, 1993). Another article reported that if PSA and clinical relapse are combined, the risk of disease relapse within 4 years following radiotherapy is 40 percent (Zagars and von Eschenbach, 1993).

The second body of evidence indicates that a policy of surveillance alone is often associated with prolonged, morbidity-free survivals. A number of investigators have presented the results of a surveillance policy for localized prostate cancer (Adolfsson and Carstensen, 1991; George, 1988; Johansson, Adami, Andersson, et al., 1992; Jones, 1992; Madsen, Graverson, Gasser, et al., 1988; Rana, Chisholm, Christodoulou, et al., 1993; Stenzl and Studer, 1993; Waaler and Stenwig, 1993; Whitmore, Warner and Thompson, 1991). It must be noted that many of the patients were older and that, in many series, patients with focal disease detected on transurethral resection of the prostate (TURP) were included (stage T1a). Nevertheless, it is instructive to recognize that 10-year disease-specific survivals of between 40 and 92 percent were realized, with most studies in the 80 to 90 percent range.

Finally, in a recent decision analysis, treatment of localized prostate cancer for “cure” was calculated to result in only minimal improvements in quality-adjusted life expectancy (Fleming, Wasson, Albertsen, et al., 1993). The authors stratified patients by age and tumor grade and made estimates of treatment efficacy and risk of metastatic disease. Using the highest estimate of a positive effect of treatment on life expectancy as well as the highest risk of developing metastatic disease, the resultant increase in quality-adjusted life expectancy was no more than 4 years in the youngest patients studied. Using the median estimate for the risk of metastatic disease and the highest efficacy of treatment, the authors found that improvement of quality-adjusted life expectancy was less than 1 year. With virtually all other estimates, treatment had a negative effect on quality-adjusted life expectancy.

Another study (Beck, Kattan and Miles, 1994), using more recent data from Chodak, Thisted, Gerber, et al. (1994), concluded that improvement in quality-adjusted life expectancy for radical prostatectomy compared with surveillance was 1.01, 2.41 and 2.68 years for well-differentiated, moderately well-differentiated and poorly differentiated tumors, respectively.

The candidate for surveillance

There are two general principles in selecting the ideal patient for surveillance: (1) a tumor of low biologic activity (which poses the lowest threat of metastasis); and (2) a relatively short period of time at risk for disease progression.

With regard to low biologic activity, tumor characteristics thought to be associated with the longest disease-free survival include: low grade, low stage, low volume and (because it is often associated with tumor volume) low PSA.

As to short period at risk, because tumor progression will occur in most patients with untreated prostate cancer, given sufficient time, the ideal patient for surveillance has a relatively short life expectancy. Methods to estimate life expectancy include age (see U.S. Life Expectancy Table in Appendix C), as well as information on other disease processes that the patient may have. These data can be integrated to establish the period of time at risk for disease progression and thereby determine whether surveillance is an appropriate treatment option.

Finally, a patient may choose surveillance for management of prostate cancer because of a desire to avoid or defer the side effects of other forms of therapy.

Surveillance in practice

Following the diagnosis of prostate cancer and appropriate staging to assure that metastatic disease is not present, treatment alternatives are discussed with the patient. Surveillance is presented as one of these treatment options. If the patient elects a program of surveillance, he is informed that the status of his prostate tumor will be monitored periodically. Monitoring may take any number of forms, but will generally include, as a minimum, DRE and PSA. The frequency of monitoring is often based upon a number of factors including measures of the tumor's biologic activity (stage, grade, volume, PSA) and the age and medical status of the patient. Patients may be informed that periodic monitoring should also include a close relationship with their

physician, including an understanding that should symptoms or signs develop which the patient feels may be related to the tumor, he should contact the physician at that time.

One principle of surveillance as a management modality for localized prostate cancer is that other forms of intervention may be employed at any time. For example, if evidence suggests that there is a need for further treatment, then radical prostatectomy, radiotherapy or other forms of therapy may be undertaken. (The patient is then no longer a "surveillance patient.") However, the patient must understand at the outset that the delay inherent in surveillance may compromise the effectiveness of any subsequent treatment, if any should become necessary.

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Chapter 3:

Outcomes of treatments for localized prostate cancer

Types of outcomes

Outcomes of therapeutic medical interventions may be direct or indirect. Direct outcomes affect patients' lives directly and are experienced directly. Some direct outcomes, such as pain from treatment, occur immediately and are short-term. Others, such as impotence (erectile dysfunction), may occur on a continuing basis over a period of time. Still others, such as the effect of treatment on life expectancy, can be considered future outcomes. Patient preferences may differ as to relative benefits/harms between different types of direct outcomes, for example, the risk of erectile dysfunction compared with the future benefit of longer life expectancy as a result of the same treatment.

Indirect outcomes are measures, such as the level of serum PSA, that are affected by treatment but not experienced by patients directly. Such measures may provide data about the probability of future outcomes. For example, rising PSA can be of great importance when assessing the effectiveness of cancer treatment and the probability of future progression of the disease.

In treating prostate cancer, differences between direct and indirect outcomes are less important than in treating many other diseases. The major consideration is where patients place the emphasis with regard to impact on their lives. Some patients are concerned with adverse direct outcomes such as urinary incontinence or erectile dysfunction to the point that they may opt for a less morbid treatment, even if the probability of "cure" (lifetime freedom from disease) is notably less than for the rejected treatment (Singer, Tasch, Stocking, et al., 1991).

However, for many men with adenocarcinoma of the prostate, the most compelling reason for seeking treatment is the hope of "cure." Given the choice, these men may choose the risk of incontinence or erectile dysfunction for an improved chance of "cure." They are usually well informed and recognize the prognostic implications of indirect measures such as rising PSA.

For assessing benefits and harms of intervention for stage T2 (B) prostate malignancy, the AUA Prostate Cancer Clinical Guidelines Panel considered the following outcomes the most important to the patient: (1) **survival at 5, 10 and 15 years** (overall survival, disease-specific survival, progression-free survival and metastasis-free survival); (2) **progression rates at 5, 10 and 15 years** (metastatic, local and biochemical); and (3) **complications of treatment**. Although all treatment complications were evaluated, the most important are: death from treatment, incontinence, impotence (erectile dysfunction), cystitis, proctitis, major bleeding, pulmonary embolism, rectal injury and bladder neck contracture/urethral stricture.

Survival at 5, 10 and 15 years

Clinically localized prostate cancer (stages T1 and T2) is rarely lethal within the first 5 years after diagnosis. The overall death rate during this period is low and usually secondary to comorbid processes. Almost any treatment for localized prostate cancer would appear to have an excellent survival result at 5 years. Survival at 10 years and 15 years allows a more accurate assessment of the influence of prostate cancer and its treatment on patient survival.

It is not sufficient to assess survival independently of tumor progression status. Comorbid processes associated with advanced age will often determine overall survival. However, morbidity from cancer progression may occur for years prior to death. It is therefore reasonable to inform patients not only about the risk of dying from prostate cancer, but also about the risk of developing metastatic disease or evidence of tumor recurrence. Outcomes of disease-specific, progression-free and metastasis-free survival should be assessed in addition to overall survival rates.

Progression rates at 5, 10 and 15 years

After surgery or radiotherapy, most recurrence or progression of adenocarcinoma of the prostate will

become biochemically (PSA) apparent by 5 years, but a few patients may have lengthy delays before the progression becomes clinically apparent. Thus, it is important to continue to assess progression rates to 10 years and beyond. Progression rates may or may not influence the patient directly. Many times progression will be defined as the development of any evidence of tumor. This recurrence is often asymptomatic and found only through surveillance examinations.

Obviously, either local recurrence or symptomatic metastatic prostate cancer is of extreme importance to patients diagnosed with localized disease. However, biochemical failures, usually in the form of rising serum PSA, will also negatively impact patients from a psychologic standpoint. Men with prostate cancer understand that a rising serum PSA often precedes eventual symptomatic recurrence.

Complications and harms of treatment

Death from treatment is the most serious (though uncommon) immediate adverse outcome for a patient diagnosed with prostate cancer. Other adverse outcomes from treatment, such as incontinence, impotence (erectile dysfunction), cystitis, rectal injury and bleeding, are much more common and have variable degrees of negative impact on patient well-being. The reported incidences and estimates of these adverse outcomes are important to a patient making decisions regarding treatment. Some of the complications are much less common today than in older reports because of newer technology and advancements in technique. It is therefore important to stratify the complications relative to era of treatment. (See Appendix A, Figures A-7 to A-31.)

Cost, inconvenience and indirect quality-of-life issues

Although such issues as cost and inconvenience are important, no meaningful data are readily available from the literature. These are areas in need of future research (see Chapter 5, page 45).

Variability of outcomes data

The panel was impressed by the massive amount of literature available on the topic of prostate cancer. However, as discussed in Chapter 1 and in the Limitations section (page 42) of Chapter 5, the vast

bulk of the literature is not usable for extracting and combining data to assess treatment outcomes and develop comparative estimates for these outcomes.

Of 12,501 papers reviewed, the panel was able to retrieve only 165 with acceptable data on outcomes from treatment of localized prostate cancer. (See page 9 for a discussion of the review process.) Moreover, in these 165 articles, there are significant differences among treatment series regarding such characteristics as patient age, tumor grade and pelvic lymph node status. The differences are summarized in Table 2 (page 23).

Table 2 makes clear that patients receiving the various forms of treatment are not similar. For example, patients undergoing radical prostatectomy are on average 3 years younger than those undergoing external beam radiotherapy and approximately 7 years younger than those reported to have been followed with surveillance.

It is also striking that only about one in seven patients reported in the literature was followed even for 5 years and that a very small fraction was followed for 10 or 15 years. Estimates of important outcomes, particularly of survival and progression rates at 5, 10 and 15 years, are likely to be inaccurate if such small numbers of patients are available for analysis.

Tumor grades are relatively comparable in patients treated actively (by surgery or radiotherapy); but for patients followed with surveillance, there are data on very few patients who have high-grade tumors. In addition, there is scant information on pelvic lymph node status in patients receiving external beam radiotherapy or followed with surveillance, which leaves open the possibility of dramatic differences in the stages of patients' tumors.

Summary outcomes tables and graphs

Because of the significant differences in the literature among treatment series and the consequent inability to make meaningful estimates from available data for the most important outcomes, those of patient survival and tumor progression, the panel concluded that it would be methodologically unsound to compare treatment modalities directly with regard to survival and progression.

Nevertheless, in order to show the range of outcomes data reported for the different modalities, the panel decided to display results of the data extracted. Results are displayed in summary outcomes

Table 2. Variability of characteristics in series¹ reporting stage T2 prostate cancer treatment outcomes

Series characteristic	TYPE OF TREATMENT			
	Radical prostatectomy	External beam radiotherapy	Brachytherapy	Surveillance
Mean age of patients	62.7 (range: 34-84)	65.9 (range: 26-92)	64.5 (range: 36-91)	70 (range: 38-90)
Number of patients	9,263	14,205	4,891	913
Number with 5-year follow-up	1,188 (13%)	1,802 (13%)	642 (13%)	400 (44%)
Number with 10-year follow-up	759 (8%)	110 (1%)	100 (2%)	46 (5%)
Number with 15-year follow-up	530 (6%)	0	0	33 (4%)
Mean follow-up	70.2 months (range: 1-372)	70.3 months (range: 1-264)	56.5 months (range: 1-219)	111.6 months (range: 3-298)
Tumor grade: well differentiated ²	23.1% (376/1,631)	41.2% (517/1,256)	38.3% (427/1,116)	62.2% (250/402)
Tumor grade: moderately well differentiated ²	56.9% (928/1,631)	40.6% (510/1,256)	51.3% (572/1,116)	34.8% (140/402)
Tumor grade: poorly differentiated ²	20% (327/1,631)	18.2% (229/1,256)	10.5% (117/1,116)	3% (12/402)
Number with PLND	83% (910/1,093)	26% (463/1,756)	87% (1,743/1,997)	0
Series published in 1960's	5	0	0	0
Series published in 1970's	6	9	2	0
Series published in 1980's	21	41	22	0
Series published in 1990's	23	23	11	6

¹ The term "series" here denotes groups of patients stratified by parameters such as primary treatment modality. One article may have more than one series. Table 2 data are from 169 series in 165 articles.

² Grading system: Categorization of degree of differentiation is based either on series reports of good, moderate or poor differentiation or on the division of Gleason sums into 2-4 (well differentiated), 5-7 (moderately well differentiated) or 8-10 (poorly differentiated).

tables for survival and tumor progression at 5, 10 and 15 years. For survival at 5, 10 and 15 years, the results are displayed graphically as well.

Summary outcomes tables

The tables indicate the range of the outcomes data reported by showing highest and lowest results reported (maximum and minimum percentages). Because combining data among series was not possible, given their variability, the panel elected not to present summary statistics (mean or median values).

The panel also decided to identify "actual" (observed, nonactuarial) data separately from actuarial data and to report them separately. Although actuarial reporting is regarded as a more reliable way to present treatment outcomes for men with localized prostate cancer, the data from series reporting "actual" data were also retained for review.

The major problem with actual reporting of outcomes is that prolonged follow-up is required to collect adequate data. Some reports include cohorts of men with a minimum of 5-, 10- or 15-year follow-up. Knowing the outcomes for each patient in a series for the entire follow-up time (5, 10 or 15 years) has the advantage that the data are indeed actual, in contrast to actuarial estimates. Unfortunately, the long-term systematic follow-up needed to accurately record these data is exceptionally difficult. Patients are often lost to follow-up or die of unknown causes, or they fail to have consistent testing or to have the data recorded so as to accurately assess disease status. Moreover, for later end points (such as 15-year disease-specific survival), the number of patients available by then is usually small, further weakening the statistical significance of the reported outcomes. For these reasons, the word "actual," when used to denote "actual" data, appears in this report in quotes.

Actuarial reporting allows earlier analysis of data sets by using all the information in the database to estimate or predict longer-term outcomes. As more patients survive to the desired end points (5, 10 and 15 years), the confidence intervals for these estimates become narrower. Such a data set is dynamic and more prospective, which eliminates some of the problems inherent in “actual” data.

A criticism of actuarial data is the inability to predict behavior of cancer for a large number of patients based on the outcomes for a few. Also, the validity of long-term patient outcomes depends in part on the number of patients available with lengthy follow-up. This type of quality assessment within actuarial data sets was rarely stated in the publications the panel reviewed during the literature search.

For both “actual” and actuarial data, the summary outcomes tables show the number of series in order to allow reviewers to estimate the degree to which the data are verifiable. The number of series, however, is not the number of independent papers or reports. As used here, “series” are groups of patients within a report stratified by parameters such as primary treatment modality or stage of disease. One report may have more than one series.

These series may be subsets of clinical stage T2 (B) disease. For instance, if a report classified outcomes within the stage B category according to clinical stage B1, B2, etc., and reported these data separately, by each substage, the panel left the data as separately recorded rather than attempting to combine outcomes. Therefore, under the broader category of stage B, there is more variability depending upon substages reported.

For Table 3 (page 25), which displays survival outcomes data, the outcomes are stratified by overall, progression-free, metastasis-free and disease-specific survival. This stratification is necessary to capture and record the major outcomes as reported. However, definitions of these survival subgroups are not standardized in the literature. The terms are used by different authors with some variability in their meaning. For this report, the panel used the following general definitions:

- **Overall survival:** Percent of men alive, irrespective of their disease status or the cause of death in those men not alive.
- **Progression-free survival:** Percent of men alive without evidence of disease progression (usually overall survival minus those men who are alive, but with progressing or recurrent disease).

- **Metastasis-free survival:** Percent of men alive without evidence of metastatic disease (overall survival minus those men who are alive, but have metastatic prostate cancer).
- **Disease-specific survival:** Percent of men who have not died from prostate malignancy (overall survival plus those men who died from causes other than prostate cancer).

For Table 4 (page 26), displaying failure/progression outcomes data, the outcomes are stratified by types of progression: local, distant, biochemical and total. Prostate cancer recurrence, or disease progression, is reported in the literature independent of survival. For the data-extraction process, the panel attempted to record the rate of progression or failure as a percentage. This percentage was either calculated or extracted from the article’s text, tables or graphs. If the percentage was calculated, it represents the number of men who experienced or were found to have progressing cancer, or were found to have new evidence of cancer after or while under the chosen therapy—as compared with the total number of men being monitored.

Progression rates were assessed at 5-, 10- and 15-year intervals. Definitions of progression are vague and vary from paper to paper. For this report, the panel defined categories of progression as follows:

- **Local:** Recurrent malignancy in the prostate or prostate bed. It may vary from tumor on random biopsies to symptomatic cancer regrowth.
- **Distant:** Radiographic evidence of cancer at sites away from the prostate area. Bone and lymph nodes are the most common. Some older studies used plain films and serum acid phosphatase to determine distant disease.
- **Biochemical:** Prostate specific antigen (PSA) at present is the most reliable means to determine prostate cancer recurrence, and contemporary reports are using PSA levels alone to define cancer recurrence. The level of PSA and rate of rise that constitute biochemical failure have not yet been defined.
- **Total:** Any evidence of local or distant or biochemical recurrence. Adding local to distant will not suffice since they may be present concurrently.

(Continues on page 32)

Table 3. Summary outcomes—Descriptive analysis of survival data

	Radical				Radiation:			
5 Year - Actuarial								
10 Year - Actual								
Metastasis Free	0				0			
Disease Specific	5	66.7%	92.0%		1	42.0%	42.0%	
10 Year - Actuarial								
Overall	7	44.4%	88.0%		11	41.4%	70.0%	
Progression Free	1	82.0%	82.0%		10	40.0%	64.0%	
Metastasis Free	0				0			
Disease Specific	3	88.5%	93.0%		3	66.1%	86.0%	
15 Year - Actual								
Overall	6	17.0%	67.0%		0			
Progression Free	5	25.0%	82.0%		0			
Metastasis Free	0				0			
Disease Specific	3	63.1%	90.0%		0			
15 Year - Actuarial								
Overall	8	22.2%	75.0%		2	31.0%	33.0%	
Progression Free	1	70.0%	70.0%		0			
Metastasis Free	0				0			
Disease Specific	5	55.0%	93.0%		0			

Table 4. Summary outcomes—Descriptive analysis of failure/progression data

	Radical Prostatectomy				Radiation External Beam				Surveillance			
	Number	Min %	Max %		Number	Min %	Max %		Number	Min %	Max %	
5 Year - Actual	3	1.8%	9.8%		7	0.0%	13.0%		0			
Local												
Distant	1	1.2%	1.2%		4	0.0%	22.0%		0			
Total	5	3.0%	12.0%		2	9.1%	20.0%		2	67.0%	85.0%	
Biochemical	0				0				0			
5 Year - Actuarial	3	2.5%	11.3%		19	0.0%	29.0%		7	7.0%	28.0%	
Local												
Distant	1	4.0%	4.0%		10	3.8%	19.5%		7	0.0%	32.0%	
Total	5	5.0%	40.0%		15	8.0%	50.0%		5	12.0%	60.0%	
Biochemical	0				1	100.0%	100.0%		0			
10 Year - Actual	0				0				0			
Local												
Distant	1	50.0%	50.0%		0				0			
Total	4	19.0%	47.0%		0				0			
Biochemical	0				0				0			
10 Year - Actuarial	2	12.0%	25.9%		9	10.0%	42.0%		1	28.0%	28.0%	
Local												
Distant	1	13.0%	13.0%		3	27.0%	32.5%		5	0.0%	56.0%	
Total	5	13.0%	80.0%		8	15.0%	60.0%		2	12.0%	50.0%	
Biochemical	0				0				0			
15 Year - Actual	2	4.0%	15.4%		0				0			
Local												
Distant	1	14.0%	14.0%		0				0			
Total	1	17.0%	17.0%		0				0			
Biochemical	0				0				0			
15 Year - Actuarial	1	22.0%	22.0%		3	17.0%	35.1%		0			
Local												
Distant	1	15.0%	15.0%		1	27.0%	27.0%		3	38.0%	64.0%	
Total	4	20.0%	100.0%		1	41.0%	41.0%		0			
Biochemical	0				0				0			

Table 5. Summary outcomes—Treatment complications

	Radical Prostatectomy		Radiation: External Beam		Radiation: Brachytherapy	
		Range		Range		Range
Perioperative death	20	0.0 %	7	0.0 %	3	0.0 %
Major bleeding	5	1.0 %	4	1.7 %	5	2.0 %
Rectal injury	10	0.0 %	3	0.5 %	2	6.3 %
Colostomy	3	0.0 %	6	0.7 %	2	0.8 %
DVT	9	0.0 %	0		3	1.8 %
Pulmonary embolus	9	0.8 %	0		7	0.1 %
Sepsis	4	0.2 %	0		1	3.1 %
Wound infection	8	1.0 %	0		9	0.6 %
Lymphocele	3	1.0 %	0		10	1.0 %
Urine leak, fistula	11	0.3 %	3	0.5 %	3	0.0 %
Edema, chronic	1	1.0 %	8	0.7 %	9	2.4 %
Cystitis	0		22	0.7 %	10	6.0 %
Incontinence (stress)	19	4.0 %	2	0.5 %	4	1.0 %
Incontinence (severe)	20	0.0 %	0		0	
Incontinence (postradiation)	0		6	0.4 %	5	1.0 %
Impotence	15	29.0 %	6	4.0 %	9	2.0 %
Bladder outlet obstruction	0		0		4	3.5 %
Bladder neck contracture	13	0.5 %	2	0.7 %	3	0.5 %
Proctitis	0		22	1.6 %	13	1.0 %
Ureteral obstruction	2	0.0 %	3	0.5 %	0	
Hematuria	1	1.5 %	7	3.0 %	4	0.1 %
Urethral stricture	5	2.0 %	21	0.4 %	5	0.6 %
Fecal incontinence	0		2	0.7 %	0	
Cardiovascular	5	0.5 %	0		1	0.8 %
Diarrhea	0		7	0.7 %	2	2.5 %
Total early	4	4.0 %	6	7.0 %	2	18.0 %
Total late	4	1.3 %	14	3.0 %	5	8.5 %

Figure 1. Overall survival: Radical prostatectomy

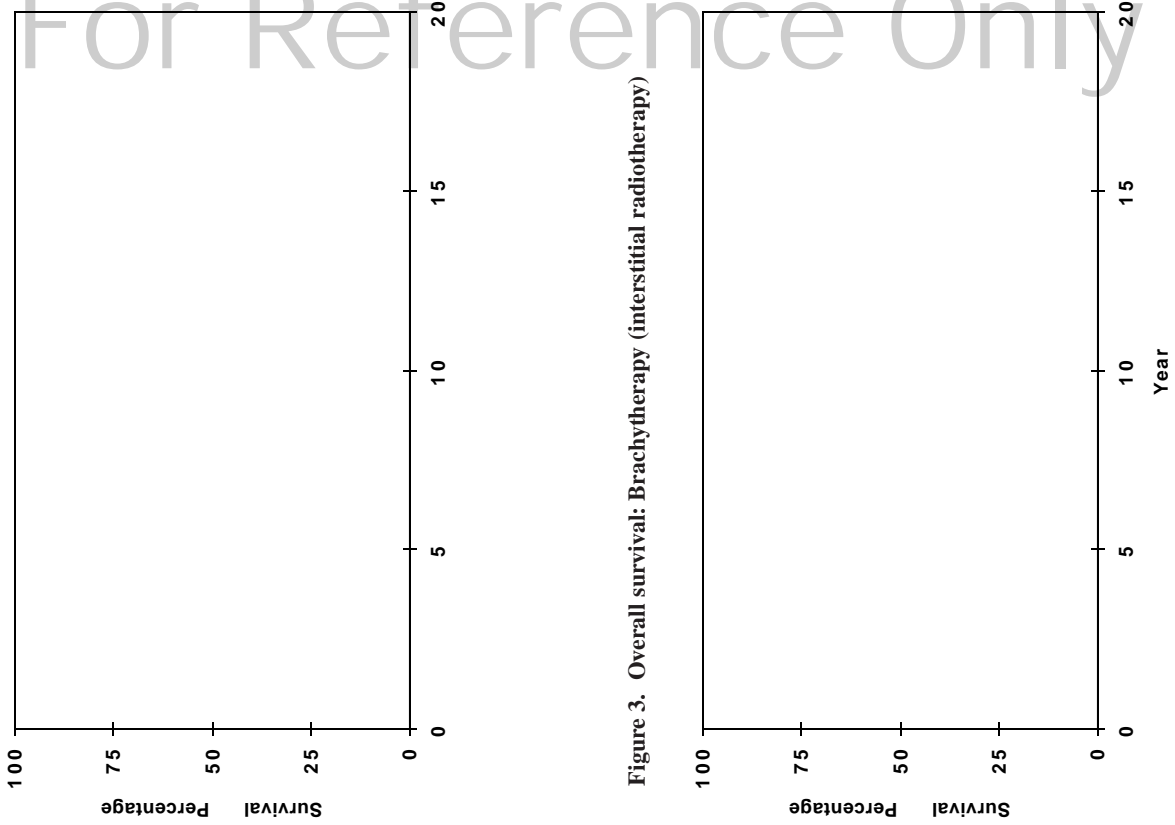


Figure 2. Overall survival: External beam radiotherapy

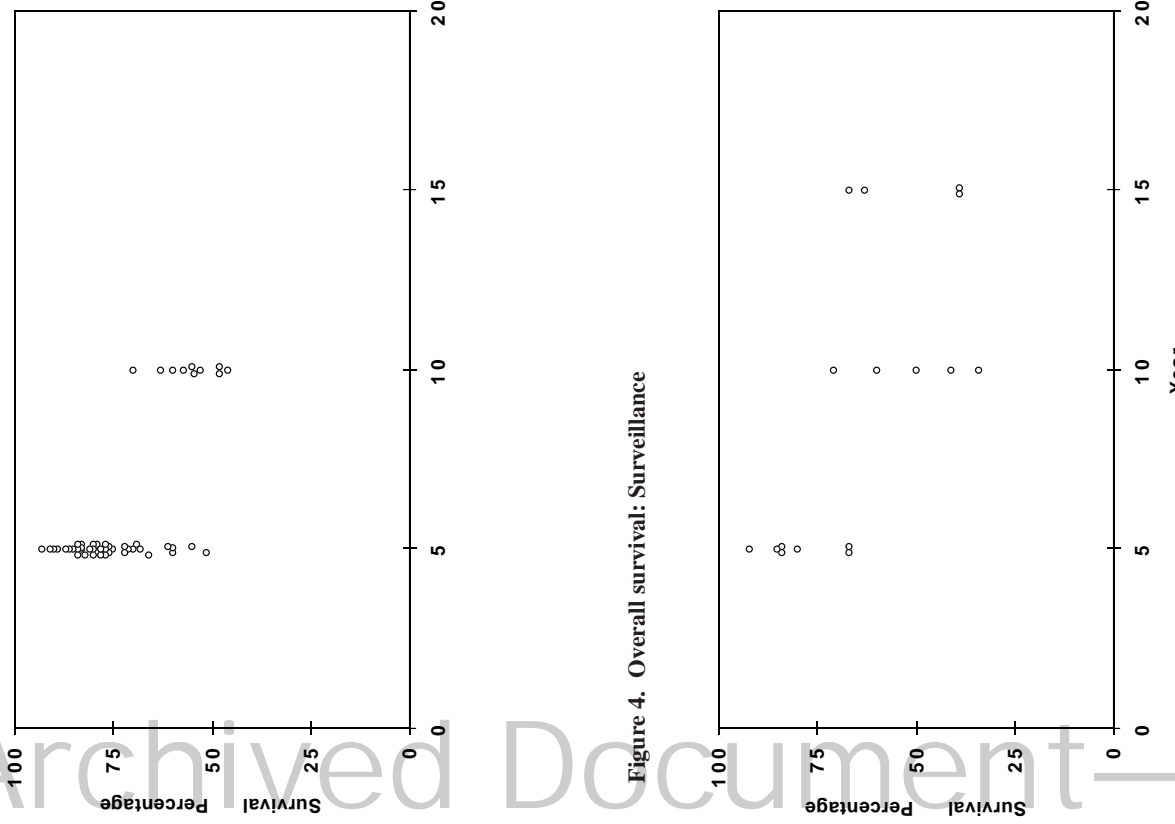


Figure 3. Overall survival: Brachytherapy (interstitial radiotherapy)

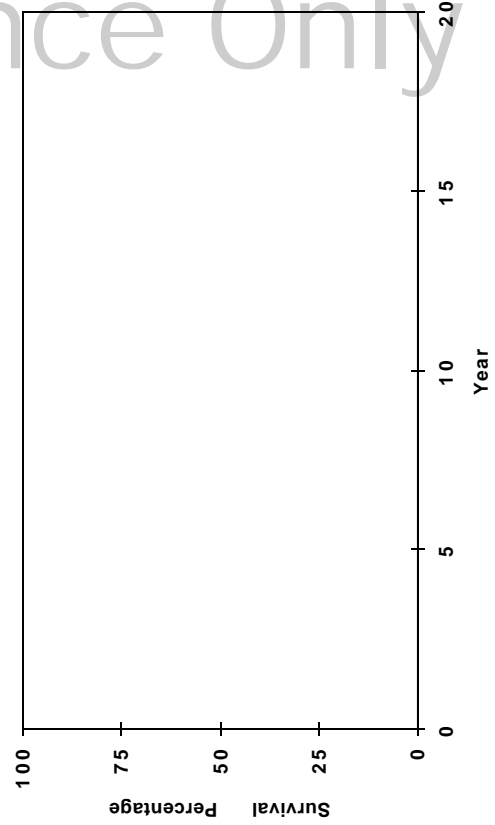


Figure 4. Overall survival: Surveillance

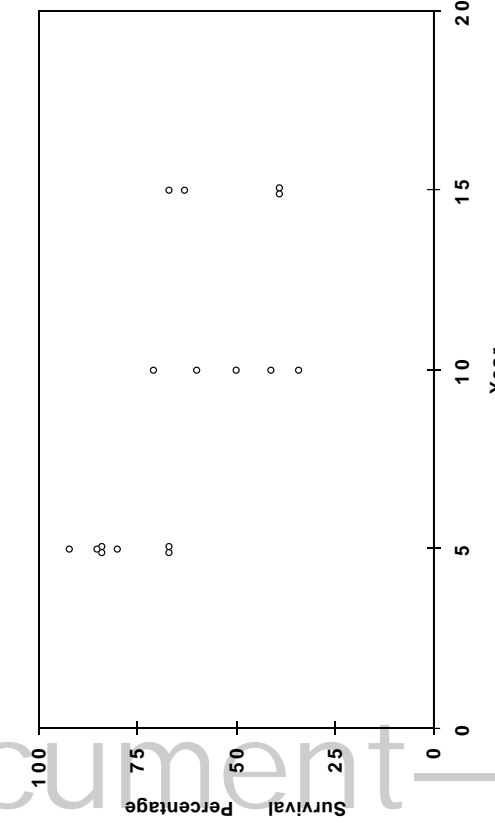


Figure 5. Progression-free survival: Radical prostatectomy

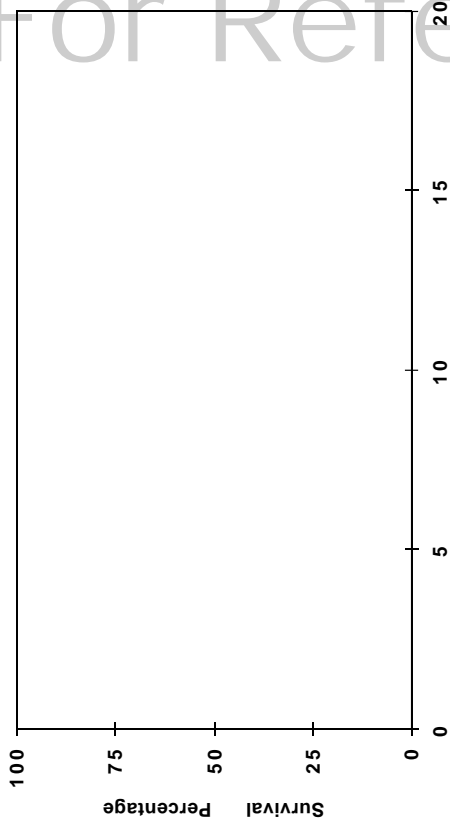


Figure 6. Progression-free survival: External beam radiotherapy

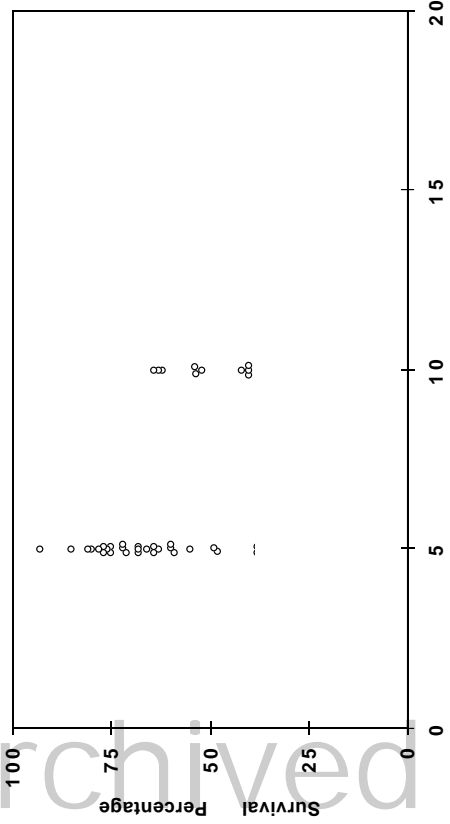


Figure 7. Progression-free survival: Brachytherapy (interstitial radiotherapy)

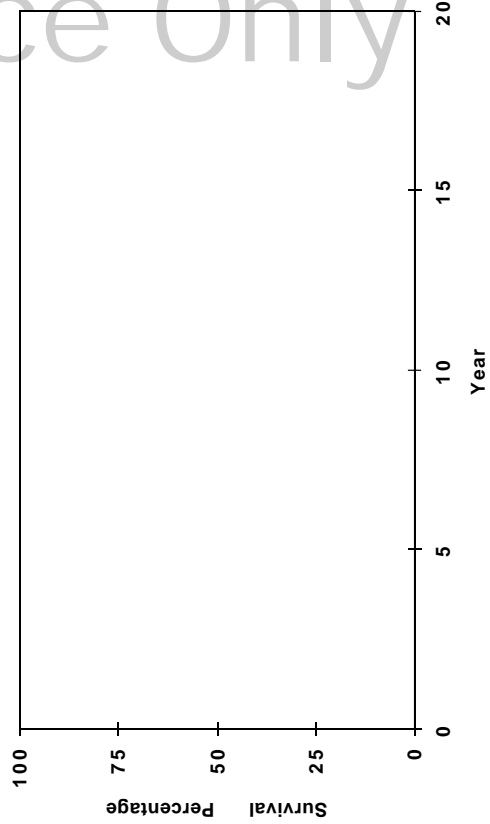


Figure 8. Progression-free survival: Surveillance

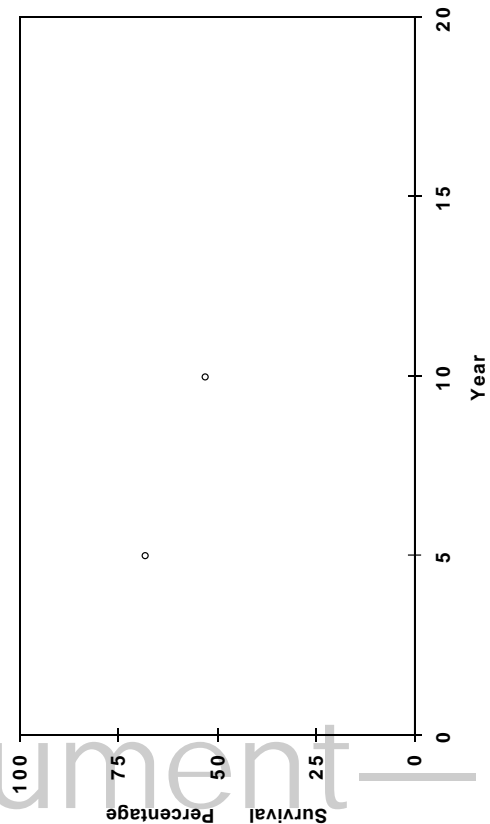


Figure 9. Metastasis-free survival: External beam radiotherapy

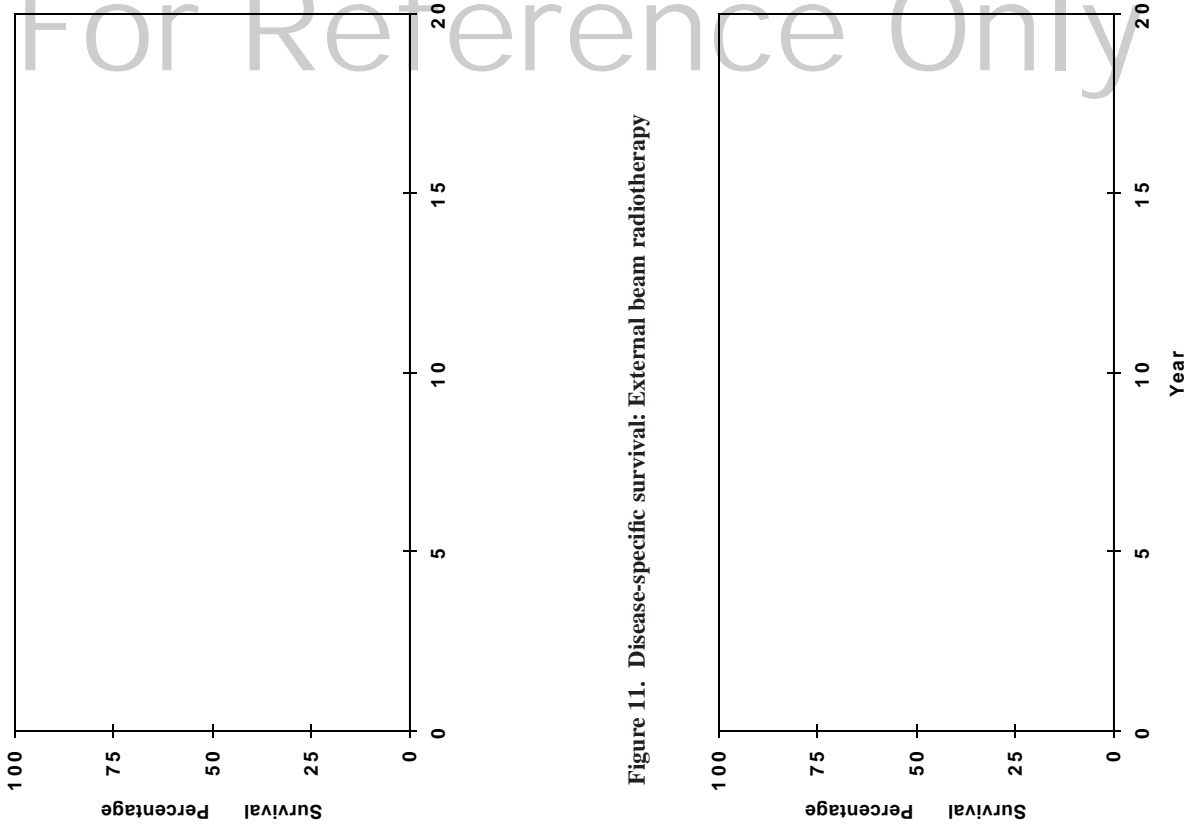


Figure 10. Disease-specific survival: Radical prostatectomy

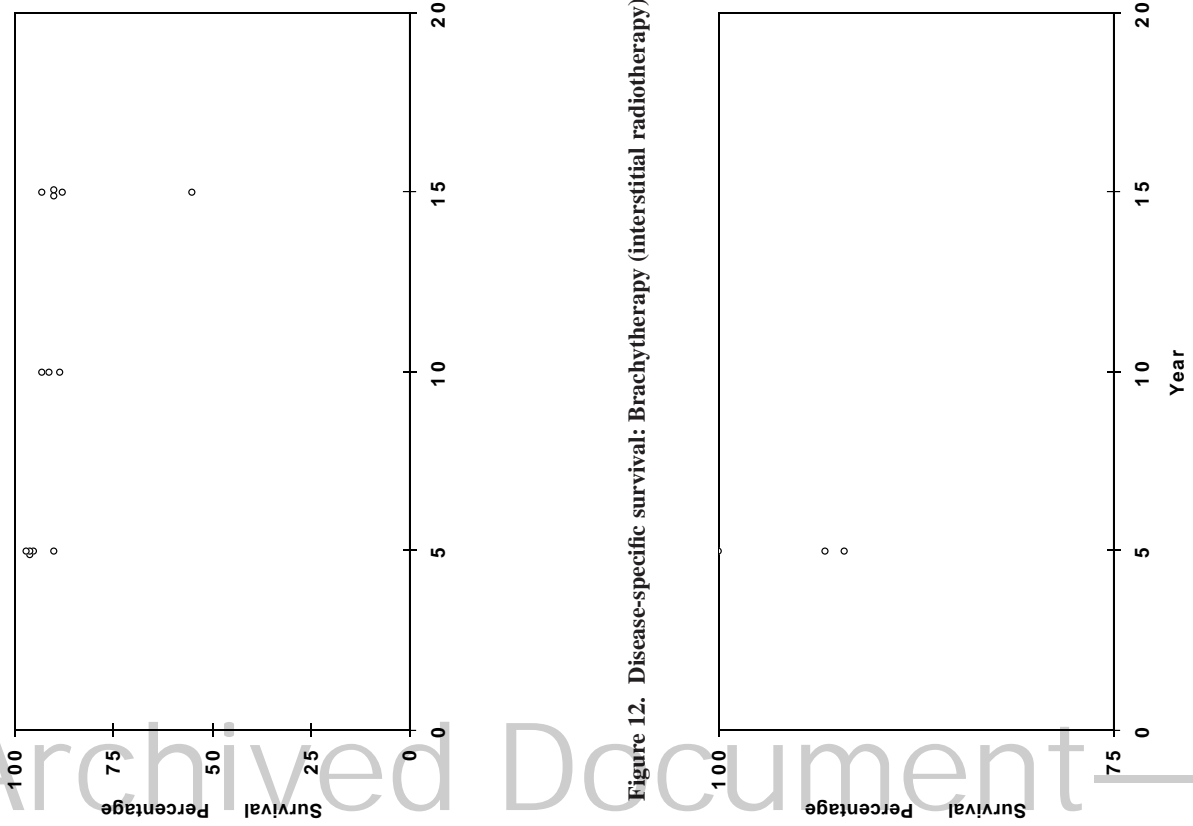


Figure 11. Disease-specific survival: External beam radiotherapy

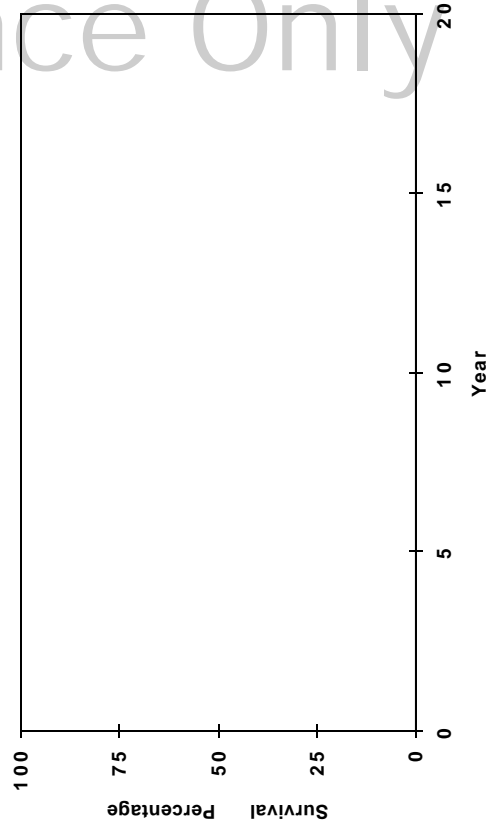


Figure 12. Disease-specific survival: Brachytherapy (interstitial radiotherapy)

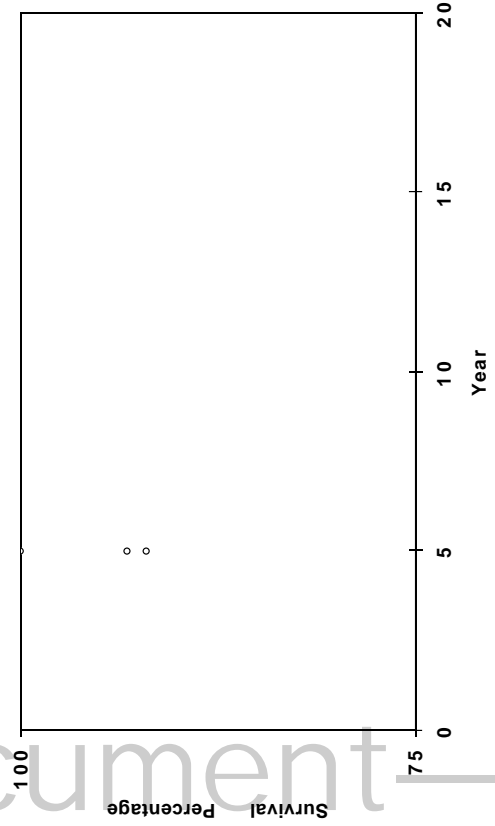


Figure 13. Disease-specific survival: Surveillance

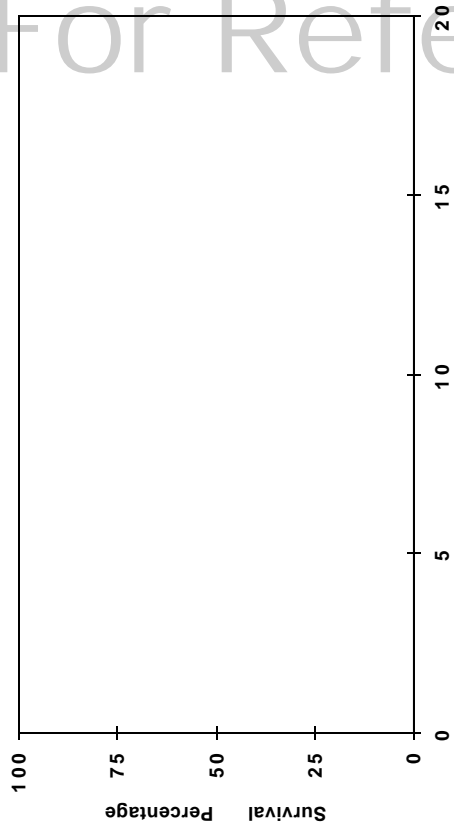


Figure 14. Complications: Radical prostatectomy

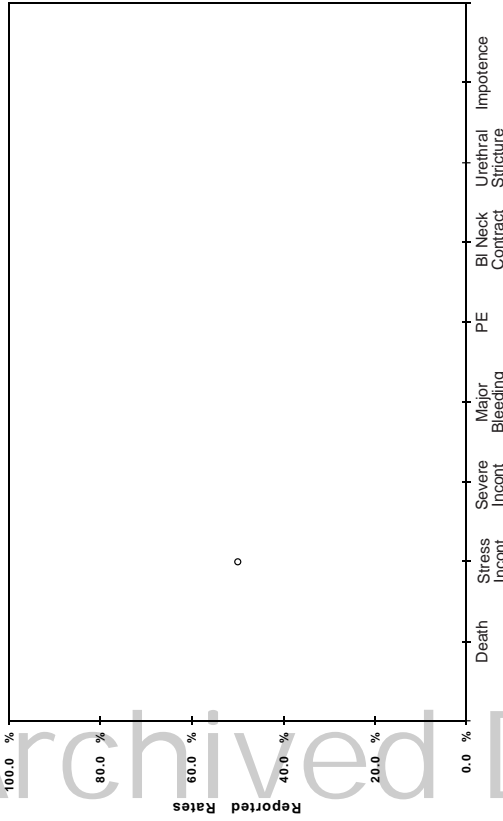


Figure 15. Complications: External beam radiotherapy

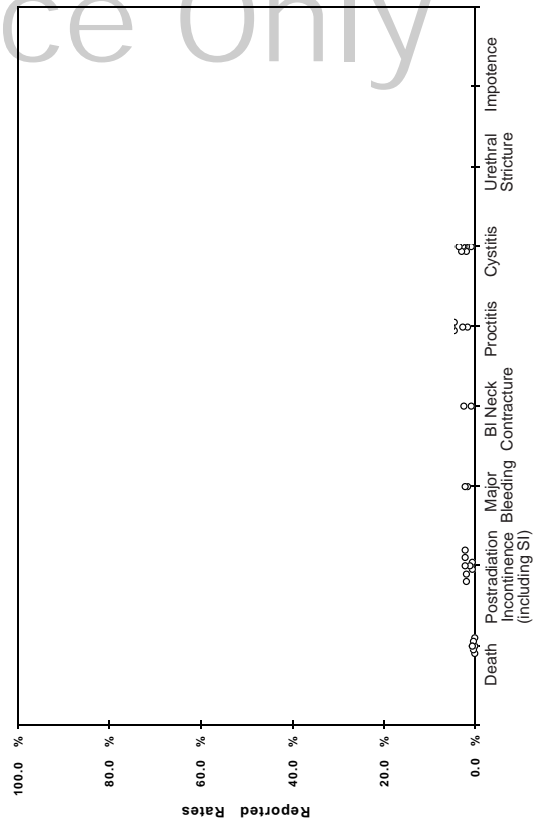
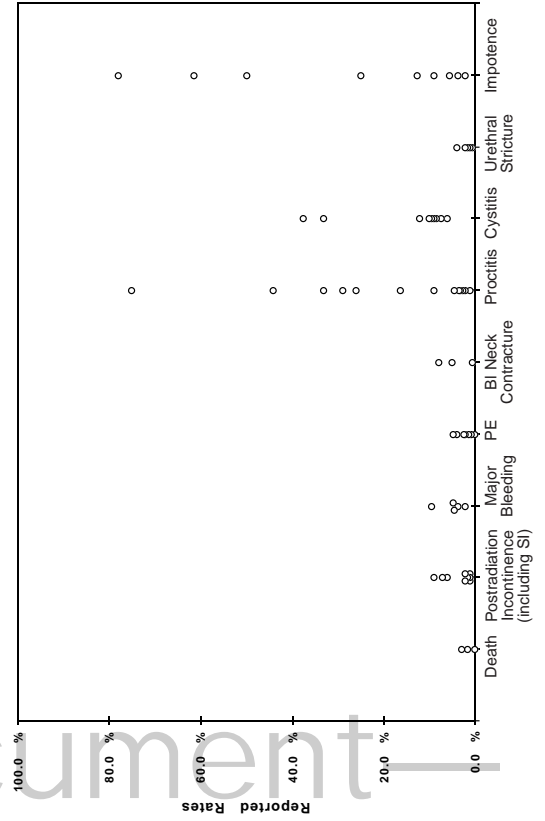


Figure 16. Complications: Brachytherapy (interstitial radiotherapy)



Circle graphs

Supplementing the tables is a graphical presentation consisting of “circle graphs” for 5-, 10- and 15-year survival (overall, progression free, metastasis free and disease specific) (see Figures 1 – 13, pages 28–31). The graphs represent actuarial data only. In each graph, the result (percentage at 5, 10 or 15 years) for one series is represented by a small circle at the corresponding point. Whereas the tables give the number of series and maximum and minimum percentages reported, the graphs also show how the reporting series are distributed over this range. It is important to note, however, that graphs do not show either the size of each series or the confidence interval for the indicated percentage.

Analysis of summary outcomes tables

The literature the panel reviewed to extract outcomes data for this report is quite heterogeneous. It covers nearly 30 years of medical history and contains data from studies representing countries in Europe, Asia, Africa and the Middle East as well in the Western Hemisphere. In part because of the heterogeneity, methods of reporting are variable—to the extent that data reported are not sufficiently comparable to provide a sound basis for estimating and comparing treatment outcomes. This is discussed at length in Chapter 1 (Methodology), earlier in this chapter (pages 22-24) and in the limitations section (page 42) of Chapter 5.

Nevertheless, results displayed in the summary outcomes tables do provide some interesting, albeit inconclusive, information regarding major outcomes of treatments for localized prostate cancer. The following analysis examines the results displayed for 5-, 10- and 15-year survival (Table 3, page 25) and for 5-, 10- and 15-year progression or recurrence/failure (Table 4, page 26).

5-year survival results

For 5-year survival, Table 3 shows that more radiotherapy series reported actuarial outcomes than reported “actual” outcomes, whereas more prostatectomy series reported “actual” numbers than reported actuarial statistics. These imbalances do not appear to be important in patients who underwent external beam radiotherapy since the “actual” and actuarial outcome results do not differ significantly. However, significant differences between “actual” and actuarial results were evident in series of pa-

tients treated with radical prostatectomy or brachytherapy.

Table 3 also shows a tendency toward excellent actuarial disease-specific 5-year survival results for all modalities. In general, the literature would appear to support the premise that, for men with localized adenocarcinoma of the prostate, disease-specific survival outcomes tend to be quite good regardless of treatment at 5 years, and that follow-up of 10 years or longer is needed to evaluate treatment efficacy with regard to preventing death due to prostate cancer.

The reported ranges between upper and lower actuarial disease-specific results (maximum and minimum percentages) are similar for each modality. External beam radiotherapy has the widest range, which probably reflects the fact that only 26 percent of patients (463/1,756) underwent a staging pelvic lymph node dissection (PLND). (See Table A-3 in Appendix A).

The proportion of patients undergoing PLND was inconsistent from series to series. The fact that few patients in the external beam radiotherapy series received PLND likely resulted in understaging. This could account for the reduced disease-specific 5-year survival rate of 63.5 percent at the low end of the range, compared with close to 90 percent at the low end for the other treatment modalities. For prostatectomy and brachytherapy, 83 percent and 87 percent of the patients, respectively, were staged with PLND before treatment (Table A-3).

In the three series reporting 89 to 99 percent disease-specific survival at 5 years for men followed by surveillance, the very good outcome may in part be due to the favorably high proportion of men with low- and moderate-grade malignancy. Only 3 percent of men treated by surveillance had high-grade tumors, compared with 20 percent, 18 percent and 10.5 percent, respectively, for the series reporting on prostatectomy, external beam radiotherapy and brachytherapy. Men under surveillance were also older at diagnosis (see Table 2 on page 23), placing them at increased risk of death from any cause (overall survival). Although age generally affects overall survival negatively, advanced age may help to explain the favorable disease-specific survival outcome for surveillance, compared to some interventional therapy groups. Older men, at greater risk of dying from “natural” causes, are at risk for a shorter time of dying from prostate malignancy.

Progression-free survival is more variable than disease-specific survival among treatment choices. In the radiation literature, a wide range of outcomes is reported. This is reflected in Table 3, in the wide ranges shown between the lowest and highest

reported results: from 32 to 93 percent for progression-free survival following treatment with external beam radiotherapy and from 38 to 90 percent after brachytherapy.

Such variability for progression-free survival is an indication of the uncertainty found in the published reports. This uncertainty is due in part to differences in intervals between follow-up and differences in defining and recording progression statistics. The definitions vary from symptomatic local disease to occult malignancy found on random posttreatment biopsy. More recently, PSA has been used to assess patients for cancer recurrence because increases in serum PSA generally predate clinical evidence of progression.

The progression-free status at 5 years for men treated with radical prostatectomy is less variable (81.9 to 92 percent actuarial, 63.6 to 91 percent “actual”) than for men managed by radiotherapy or surveillance. This is partly due to more consistent means of defining recurrence. Without the prostate in place, the variability associated with posttreatment prostate biopsy and palpable prostatic progression is reduced.

Metastasis-free survival is less subjective than progression-free survival, and outcome results would likely be more comparable between groups. However, as Table 3 shows, the treatment data available did not permit evaluation of metastasis-free survival except in a limited number of external beam radiotherapy studies.

10-year survival results

Considerably fewer papers reported 10-year survival than reported 5-year survival. In most of the papers reporting 10-year actuarial overall survival, as Table 3 makes clear, the range of outcomes was quite similar across modalities (radical prostatectomy, external beam radiotherapy and surveillance). The few modest differences may be explained by the effect of age differences.

For progression-free survival, the 10-year actuarial results appear excellent following radical prostatectomy, but only one series had extractable data. Six series reported “actual” data for radical prostatectomy. The results shown are variable (31.3 to 69 percent), the wide range reflecting the uncertainty of the data. Similar uncertainty is noted for the 10 series reporting actuarial data for 10-year progression-free survival after external beam radiotherapy (40 to 64 percent). The seven series reporting 10-year progression-free survival in men receiving brachytherapy had the greatest variability (50 to 90 percent). For men whose cancers were managed by

surveillance, only one series contained 10-year progression-free survival data. Since all patients in this series had prostate cancer that went virtually untreated, the progression-free percentage obviously depends upon how one defines “progression.” In general, the variability in 10-year outcomes illustrates the pitfalls of attempting to compare progression-free survival data from retrospective studies.

Reporting of 10-year disease-specific survival data is less subjective, as reflected in more uniform outcomes and in more closely packed data points in the graphical displays, although the latter may be more a reflection of the small number of data points (Figures 10-13, pages 30-31). The actuarial disease-specific survival results shown in Table 3 slightly favor prostatectomy (86 to 93 percent). However, the less favorable results shown for external beam radiotherapy are likely affected by clinical understaging without pelvic lymph node dissection. The favorable results for the three surveillance series may be partly due to careful selection of patients placed on the surveillance protocol. Also, because of advanced age and shorter natural life expectancy, the time these patients were at risk for dying of prostate cancer was less than that for younger men. As noted previously on page 32, this obviously affects disease-specific survival data positively, just as it affects overall survival data negatively.

15-year survival results

The 15-year overall survival data would appear uncertain following prostatectomy and surveillance, as indicated by the variable results shown in Table 3, with wide ranges between high-end and low-end (maximum and minimum) percentages. These data, however, are from a limited number of studies, and the four reported series under surveillance actually represent only two studies. Three of the four “series” are from stratified cohorts of patients within a single study (Number 9351, Appendix A, Table A-1). Stratification was based on substages of stage T2 (B) prostate cancer. The 67 percent shown as a maximum percentage for surveillance represents just the substage B1 data. For external beam radiotherapy, the relatively low overall survival results at 15 years represent data from two separate, large actuarial studies.

Both actuarial and “actual” disease-specific survival data from reports of men receiving prostatectomy indicate a high likelihood of disease-specific survival for as long as 15 years following surgery (55 to 93 percent actuarial, 63 to 90 percent “actual”).

5-year progression results

For local progression (or disease recurrence or treatment failure), the problem of inconsistent definitions invalidates most comparisons of outcome data between treatment options. In the case of prostatectomy, surprisingly few studies provide local progression outcome data that can be meaningfully extracted. The 5-year local progression rate following prostatectomy, as shown in Table 4, page 26, ranges widely from a low of 1.8 percent (“actual”) to a high of 11.3 percent (actuarial). The progression usually includes any palpable or biopsy-proven tumor in the prostatic bed or vesicourethral anastomosis.

Distant or metastatic recurrence at 5 years following prostatectomy is uncommon (1.2 to 4.0 percent). For total 5-year clinical recurrence following prostatectomy, the rate ranges from 3 to 12 percent (“actual”). For total progression, the panel excluded a subset in one of the studies (Number 9175, Table A-1). This subset consists of stage T2 (B) prostate cancer patients separated by deoxyribonucleic acid (DNA) ploidy pattern. The small population of 10 patients (4 percent) with aneuploid tumors experienced 40 percent metastatic recurrence at 5 years.

For biochemical progression, local or otherwise, the panel at the time of the literature review could find only one study with extractable data regarding PSA recurrence (Number 10790, Table A-1). This study was in the external beam radiotherapy literature. The biochemical failure rate in the study was defined as “increasing PSA after treatment.” Other definitions have been proposed, and certainly more data are needed to substantiate this definition.

For 5-year local progression following external beam radiotherapy, the actuarial rates in Table 4 range from 0 to 29 percent. The true rate is obviously uncertain, which again may be due in part to variable definitions of this outcome: symptomatic disease, palpable growth, prostate biopsy, etc.

The distant progression rate at 5 years following external beam radiotherapy is also variable and uncertain. An actuarial rate of 3.8 percent reported in one study represents a group of 26 men with clinical stage B1 and B2 disease followed both by radiation oncologists and by urologists in three different hospitals (Number 6364, Table A-1). The follow-up studies did not specify routine bone scans or serum acid phosphatase to assess distant progression. Also, the period of follow-up ranged from 6 months to 8 years (median 32 months), and the authors did not report the number of men with stage B disease who were followed for at least 5 years.

The 5-year total progression rates after external beam radiotherapy are variable as well, reflecting both varying definitions of progression and selected reporting of cohort outcomes. For brachytherapy, progression data reveal similar variability. Differing definitions of progression, technical variability and selection bias are the main reasons.

For surveillance, it can be assumed that all untreated prostate malignancies will grow, although often slowly. Therefore, progression rates on a biochemical or histologic basis are 100 percent in patients under surveillance. However, clinically important local progression during surveillance is subjectively reported among investigators. For instance, one study published a 5-year local progression rate of 65 percent (95/146) for surveillance (Number 8990, Table A-1). Progression was defined as palpable local growth of tumor, and the data were corrected to reflect cumulative probability at 5 years. By comparison, another study reported a 24 percent local progression rate, but defined local progression as “a change in local tumor category” (Number 9351, Table A-1). Distant progression rates for all studies are less subjective, as reflected by more consistent outcomes reporting in Table 4.

10-year progression results

The same problems of variability in definitions of progression, selection bias and inaccuracy in 5-year progression data are problems in data for longer follow-up. Nevertheless, it is apparent from individual reports that the incidence of disease progression/treatment failure, local or distant, does rise with time. The extracted 10-year clinical failure data reflect rates that are nearly double 5-year rates for both radical prostatectomy and external beam radiotherapy.

However, no inference can be made from the 10-year total progression/failure rates shown in Table 4. These results range too widely, reflecting highly variable and uncertain data as well as differing patient populations.

15-year progression results

Too few studies of 15-year outcomes are available to reasonably estimate failure rates. The data present in these few studies, however, indicate a stabilization of local and distant progression rates after 10 years for men treated with either radical prostatectomy or external beam radiotherapy. The rates continue to rise as expected for patients managed by surveillance. A relatively high distant failure rate is reported in three series of men treated

with brachytherapy. The three series are from the same report (Number 9879, Table A-1) and represent substages of stage T2 (B) prostate cancer. Progression/failure of 64 percent was found in men with substage B3 prostate malignancy. It is obvious that the 15-year progression data are sparse, variable and uncertain.

Treatment complications summary outcomes table and graphs

The variability in the prostate cancer treatment literature in reporting factors such as grade, stage and age of the patient—which has a confounding effect on reported data for survival and progression—has a similar confounding effect on reported data for complications from surgery or radiation treatment. The panel chose therefore to display results of the extracted data on treatment complications in the same manner as for the survival and progression data.

The complications summary outcomes table (Table 5) on page 27 lists the 25 most commonly reported complications. Under each treatment modality to which a particular complication applies, Table 5 displays the number of series reporting the complication and the lowest and highest reported frequencies of occurrence (minimum/maximum percentages). The table does not show mean or median estimates of frequency.

Graphical displays visually represent the reported frequency rates for the most important complications (Figures 14 - 16, page 31). Each circle on a graph represents one series reporting the complication. As in the graphs representing survival outcomes, these graphs are a useful supplement to Table 5 in that they show how the reporting series are distributed along the range between the minimum and maximum percentages. Again, however, it must be noted that the graphs show neither the size of each series nor the confidence interval for the indicated percentage.

It should also be noted that the data displayed in Table 5 and Figures 14–16, in addition to being subject to problems of variability mentioned previously, may be subject to publication bias. The possibility exists that those centers publishing their results are mainly centers having low complication rates. The data could also be biased in the other direction because many of the series may not be recent enough for reported complications to reflect

improvements in modern surgical and radiological techniques.

Some of the complications in Table 5 apply to all three treatment modalities, but not necessarily to the same extent. Stress incontinence, for example, is reported by 19 series as a complication of radical prostatectomy, but by only two series as a complication of external beam radiotherapy. To a considerable degree, each form of therapy has its own spectrum of complications. In an obvious example, wound infection is a potential complication of prostatectomy, but is reported by zero series under the noninvasive external beam radiotherapy. For proctitis, a potential complication of radiotherapy, Table 5 shows a zero under prostatectomy. The panel was unable to determine that any one therapy has a more significant cumulative risk of complications.

In the case of complications from external beam radiotherapy, the data shown in Table 5 may overstate the frequency of some complications following this treatment, such as proctitis and other rectal toxicity. The reason is that, in abstracting the complications data for external beam radiotherapy, the panel found very little information specific to stage T2 (B) disease. The panel faced a choice: either include only series that purely address T2 patients, in which case there would essentially be no data, or include radiotherapy series that describe complications in all stages of disease. The panel chose to include all radiotherapy series that describe toxicity in order to provide at least rough indications of risk from therapy.

However, toxicity from radiotherapy is much more likely in advanced stages of disease, because patients reported with stages T3-T4 (C) or M1 (D2) tumors are much more likely to have received radiotherapy to regional lymph nodes. Radiation to the entire pelvis and in some cases the para-aortic region is often administered in those with higher-stage disease. Moreover, these patients are often treated with significantly greater doses of radiation to significantly larger amounts of normal tissue, which markedly increases toxicity (Green, Goldberg, Goldman, et al., 1984; Lawton, Won, Pilepich, et al., 1991; Mameghan, Fisher, Mameghan, et al., 1990; Pilepich, Krall, Sause, et al., 1987; Smit, Helle, van Putten, et al., 1990).

If the panel had been able to include only the complications data for external beam treatment of stage T2 disease, the frequency rates would very likely have been less than what Table 5 shows. Patients clinically judged as having T2 disease (as a group) will generally receive a lower dose of radiation to a smaller volume of tissue.

Analysis of treatment complications summary outcomes table

Of the complications listed in Table 5 for treatments of stage T2 prostate cancer, the panel considered the most important to be perioperative death, major bleeding, pulmonary embolism, incontinence, impotence (erectile dysfunction), rectal injury, cystitis, proctitis, bladder neck contracture and urethral stricture. Most often reported are rates of death, incontinence, rectal injury and impotence. Some surgical series also comment on adverse postoperative events such as bleeding and pulmonary embolism.

A structured review of the literature (Wasson, Cushman, Bruskewitz, et al., 1993) found reported complication rates within the ranges reported in Table 5. Also, patient attitudes about the importance of such adverse events are now under active investigation. One study used standardized data collection instruments to examine patient attitudes regarding complications following radical prostatectomy (Fowler, Barry, Lu-Yao, et al., 1993). Reports by these patients indicated higher rates of stricture and incontinence than in most reported series. Moreover, complete incontinence, bladder neck contracture and stricture formation may result from additional interventions to ameliorate the original problem. Patient interviews in the Fowler study indicate that treatment of these urinary complications, with associated symptoms such as frequent urination, wetness and difficulty in voiding, is often not very successful. (Age was not related to postsurgical incontinence in this study.)

Table 5 shows that both obstruction and incontinence may be more common following surgery. Cystitis, which most often results in the symptom of urinary frequency, is a potential complication of radiotherapy. Radiotherapy is also more likely than surgery to cause bowel/rectal injury. Diarrhea associated with radiotherapy is usually transient.

With regard to the important complication of impotence (erectile dysfunction) following active treatment for prostate cancer, the reports are difficult to interpret because of patient selection. This is an instance in which a patient-related factor, age, may affect the complications data. The youngest (and presumably most potent) patients tend to undergo surgery. The oldest patients tend to receive radiotherapy. Few reports have carefully compared pretreatment and posttreatment potency. For treatment of erectile dysfunction, patients report favorably on treatment with pharmacologic erection therapy, penile implantation or vacuum devices (Fowler, Barry, Lu-Yao, et al., 1993).

With regard to perioperative mortality, death from treatment is relatively rare following external beam radiotherapy. Death following surgery, although shown to increase with age, is generally less than 1 percent in men under age 75 (Lu-Yao, McLerran, Wasson, et al., 1993).

Significant bleeding may be expected to occur following radical prostatectomy with a frequency between 1.0 and 11.5 percent. The perineal approach may have the lowest incidence of this complication. Finally, pulmonary embolism and sepsis are risks of any operative intervention. Medicare data suggest that the incidence of cardiopulmonary complications following radical prostatectomy increases to more than 7 percent in men over age 75 (Lu-Yao, McLerran, Wasson, et al., 1993).

Chapter 4: Treatment recommendations

The AUA Prostate Cancer Clinical Guidelines Panel generated its practice policy recommendations based on the outcome estimates available and on panel opinion. As explained in Chapter 1, the recommendations were graded according to three levels of flexibility based on strength of evidence and the panel's assessment of patient needs and preferences. The definitions of these three levels are repeated below from Chapter 1:

- **Standard:** A policy is 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 is considered a guideline if the health and economic outcomes of the interventions are sufficiently well-known to permit meaningful decisions and an appreciable but not unanimous majority agree on which intervention is preferred.
- **Option:** A policy is considered an option if (1) the health and economic outcomes of the interventions are not sufficiently well-known to permit meaningful decisions, (2) preferences among the outcomes are not known, (3) patients' preferences are divided among alternative interventions and/or (4) patients are indifferent about the alternative interventions.

Obviously, a standard has the least flexibility. A guideline has significantly more flexibility, and an option is the most flexible. As noted in the definitions, options can exist because of insufficient evidence or because patient preferences are divided or unknown. In the following panel recommendations, those regarding treatment choices were labeled options mostly because of insufficient evidence. None of the following panel recommendations fits the above definition of a guideline.

The standard patient

The panel's recommendations apply to the standard patient, defined as a man who has clinically localized prostate cancer (adenocarcinoma of the

prostate). For this report, the panel focused on clinical stage T2 (B) disease. Based on the opinion of the panel, recommendations may 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. For a detailed discussion of prostate cancer staging, see pages 13-15.

Recommendations: Standards

As a standard, an assessment of the patient's life expectancy, overall health status and tumor characteristics is necessary before any treatment decisions can be made.

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. (See U.S. Life Expectancy Table in Appendix C.)

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.

Tumor characteristics: The histologic grade and stage of the tumor 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 differentiat-

ed tumors which have a greater potential to be biologically aggressive and clinically significant.

As a standard, a patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, radical prostatectomy, radiotherapy and surveillance. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient.

The panel defines radical prostatectomy to include complete removal of the prostate, vasal ampullae and seminal vesicles. The panel defines radiotherapy to include external beam and/or interstitial (brachytherapy) treatments. Surveillance is 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.

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.

Recommendations: Treatment options

Options for management of localized prostate cancer include radical prostatectomy, radiotherapy and surveillance. Radiotherapy includes external beam and interstitial (brachytherapy) treatments. The panel considers these interventions to be options because data from the literature do not provide clear-cut evidence for the superiority of any one treatment. Described for each option is the patient most likely to benefit from the intervention.

Radical prostatectomy: Based on the panel's interpretation of the literature and panel opinion, the patient most likely to benefit from radical prostatectomy would have a relatively long life expectancy, no significant surgical risk factors and a preference to undergo surgery.

Radiotherapy: Based on the panel's interpretation of the literature and panel opinion, the patient most likely to benefit from radiotherapy would have a relatively long life expectancy, no significant risk factors for radiation toxicity and a preference for radiotherapy.

Surveillance: Based on the panel's interpretation of the literature and panel opinion, patients most likely to benefit from surveillance are those with a shorter life expectancy and/or a low-grade tumor.

Advantages and disadvantages of treatment options

Radical prostatectomy

The major advantage of radical (total) prostatectomy is its potential for "cure" by removing all of the tumor. "Cure" is defined as lifetime freedom from disease. Total prostatectomy in the properly selected patient will provide disease-free survival rates comparable to the expected survival in similarly aged men for up to 30 years of observation (Gibbons, Correa, Brannen, et al., 1989).

The major disadvantage is potential morbidity. Possible operative morbidity includes the following: bleeding, which can require a transfusion; difficulty with anastomosis of the bladder neck to urethra; and rectal injury. These problems will vary with the size and anatomy of the patient's pelvic organs and the experience of the surgeon. Postoperative morbidity includes problems with indwelling catheters, lymphocele, anastomotic stricture, urinary incontinence and impotence (erectile dysfunction).

With regard to impotence, some authors have reported postoperative potency rates in the 70-percent range in patients who were potent preoperatively (Catalona and Bigg, 1990). If impotence occurs after surgery (or radiotherapy or hormone therapy), what is lost is erectile function. The sensation of orgasm may remain intact. In these patients, pharmacologically induced erections (using self-administered penile injections) or use of vacuum constriction devices or penile prostheses can provide effective treatment (Lue, Carroll and Moore, 1989).

A number of articles have reported stress urinary incontinence and/or severe urinary incontinence (requiring intervention) following radical prostatectomy. The complications summary outcomes table (Table 5) on page 27 shows a reported low of 4 percent and a high of 50 percent for stress incontinence and a range from 0 percent to 15.4 percent for severe incontinence. The complications graph for prostatectomy (Figure 14, page 31) shows how the reporting series are distributed along these low-high ranges.

For mortality following radical prostatectomy, Table 5 shows a range from 0 percent to 2.1 percent. More than half the series reported 0 percent. However, the risk of death from radical prostatectomy increases with patient age and was found to be 1.4 percent in men aged 75 to 80 and 4.6 percent

for age 80 and older (Lu-Yao, McLerran, Wasson, et al., 1993).

Pulmonary embolism, in the panel's review of the literature, occurred in 0.8 percent to 7.7 percent of patients after radical prostatectomy. In a report of Medicare patients (Lu-Yao, McLerran, Wasson, et al., 1993), investigators found cardiopulmonary complications in 4 percent of men 65 to 69 years of age and in 7.4 percent of men 75 to 79 years of age. Other potential complications, such as anastomotic stricture, fistula and bowel injuries, occur infrequently.

Recent developments in the technique of radical prostatectomy may have reduced the risks of complications. Refinements in the understanding of the surgical anatomy of the prostate have made possible a more meticulous operation, improved operative visualization, reduction in blood loss and improved sexual function and urinary continence rates postoperatively.

Length of hospitalization has also been significantly reduced in many patients to 3–6 days, but the total cost for radical prostatectomy has not been well described and remains a “moving target” (Koch, Smith, Hodge, et al., 1994).

Radiotherapy

The advantage of radiotherapy (external beam radiotherapy and brachytherapy) is that it not only has a potential for cure, but is well tolerated in the majority of men when modern techniques are used. Its principal potential harms include radiation cystitis, proctitis, and erectile dysfunction. Also, because the prostate remains in place, persistence and progression of the disease may occur.

External beam radiotherapy

External beam radiotherapy can be an effective treatment in the appropriate standard patient afflicted with stage T2 prostate cancer. Notwithstanding caveats regarding survival and disease progression data (pages 32-33, 33-34), the results reported in the literature for external beam radiotherapy appear reasonably favorable. Although some selected series have reported extremely high PSA failures (noted in Hanks, 1994), others have demonstrated extremely favorable PSA control with long-term follow-up (Hanks, 1994; Hanks, Perez, Kozar, et al., 1993; Pisansky, Cha, Earle, et al., 1993).

However, an accurate characterization of the true incidence of PSA failure in an unbiased cohort is urgently needed. There is also evidence that clinical lack of local tumor progression may underestimate

the true incidence of cancer remaining in the prostate gland. Biopsies of the radiated gland have revealed persistent malignancy in at least 30 percent of patients (Kabalin, Hodge, McNeal, et al., 1989; Kaplan, Prestidge, Bagshaw, et al., 1992; Kiesling, McAninch, Goebel, et al., 1980). Recently, TRUS-guided biopsy series in selected patients suggest that the true incidence of residual cancer may be much higher than previously reported.

Regarding toxicity, external beam radiotherapy, as employed in state-of-the-art radiotherapy centers, has the advantage of having become a very well-tolerated treatment. Improvements include higher-energy radiation beams that can be more precisely focused, thus sparing larger amounts of normal tissue from therapy; improved computer technology that calculates with greater precision the absorbed dose of radiation and helps optimize treatment planning; and more sophisticated planning procedures that precisely localize both the tumor volume and normal tissues, allowing maximal sparing of normal tissues and ensuring adequate delivery of dose to the tumor.

However, there remain many potential complications. The actual incidence of erectile dysfunction for patients receiving radiotherapy (as in series of patients receiving other forms of therapy) may be underreported. Diarrhea is a potential problem for those patients who receive radiation to regional lymphatics. Other potential significant complications include rectal toxicity (proctitis, rectal ulceration, need for colostomy) as well as bladder complications (hematuria, cystitis, dysfunctional voiding).

Brachytherapy

Mature data are only available for the older retropubic brachytherapy techniques. Although problems have been reported in these mature brachytherapy series (page 18), several groups have documented reasonably satisfactory survival results. The 5-year survival data are not yet available for the newer ultrasound-guided transperineal techniques. However, as the outcomes analysis on pages 32-33 indicates, the 5-year survival results would be expected to be quite good. In general, even though sufficiently mature data are not yet available to establish superiority of the newer techniques, the panel knows of no evidence that the results from these techniques are inferior to results from the older techniques.

One clear advantage of the current brachytherapy methods is patient convenience. Several series of TRUS-guided transperineal techniques report that

the procedures are usually performed with hospital stays of 2 days or less. When permanent radionuclides are implanted, there is usually only a moderate amount of postimplantation discomfort, controlled in the overwhelming majority of patients by oral pain medications.

Disadvantages of brachytherapy can include inferior control of localized tumors. Similar to all prostate cancer treatment modalities, brachytherapy produces markedly improved local control in low-stage and low- to moderate-grade disease (Carey, Lippert, Constable, et al., 1988; Fuks, Leibel, Wallner, et al., 1991; Giles and Brady, 1986; Kuban, El-Mahdi and Schellhammer, 1989a; Morton and Peschel, 1988; Smalley and Noble, 1992).

Additionally, the importance of long-term follow-up cannot be overemphasized. Several series have reported that the mean time to local failure in brachytherapy-treated patients is in the range of 5 to 10 years (Fuks, Leibel, Wallner, et al., 1991; Kuban, El-Mahdi and Schellhammer, 1989a; Smalley and Noble, 1992). The exceedingly long time to local recurrence seen in series that have adequate follow-up emphasizes both the indolent natural history of the disease and the tentative nature of any conclusion reached in studies without follow-up of 10 to 15 years.

The ability of brachytherapy to control local disease must, therefore, be evaluated on the basis of series that have sufficient follow-up. Four different reports have compared local tumor control with brachytherapy versus control with alternative therapies. Three reported that brachytherapy produced inferior local tumor control when compared with either external beam radiotherapy or radical prostatectomy (Kuban, El-Mahdi and Schellhammer, 1989a; Morton and Peschel, 1988; Schellhammer, Whitmore, Kuban, et al., 1989; Smalley and Noble, 1992). However, differences in other factors such as patient selection, rather than the treatment itself, may explain the differences in outcomes.

With regard to complications, those reported in present brachytherapy series are remarkably heterogeneous. They include impotence (erectile dysfunction), with no convincing evidence of less risk than with external beam radiotherapy (Smalley and Noble, 1992). For the newer, TRUS-guided transperineal techniques, rates for the complications reported to date vary widely (Blasko, Ragde and Grimm, 1991; Iversen, Bak, Juul, et al., 1989).

In some stage T2 patients, higher complications have been reported for brachytherapy as compared with external beam radiotherapy. Also, patients with a previous transurethral resection or significant oth-

er uropathy have a much greater risk of developing subsequent urinary complications.

Surveillance

One advantage of surveillance therapy as a treatment option for localized carcinoma of the prostate is its low initial cost. Because most patients can be followed with DRE and PSA alone, if disease progression does not develop during the patient's lifetime, the cost of such follow-up may be very low. This advantage is dependent upon the assumption that most patients will not develop symptomatic or metastatic disease during their lifetimes. If this assumption is incorrect, the cost advantage may disappear as it has been estimated that the cost of treatment for one new case of metastatic prostate cancer is \$70,000 (Littrup, Goodman and Mettlin, 1993).

Another major advantage of surveillance for localized prostate cancer is its avoidance of morbidity associated with treatment. Most patients with newly diagnosed prostate cancer, because of the current policy of early detection and treatment, have no cancer-related symptoms at diagnosis. Surveillance would allow these men to preserve their quality of life. Conversely, radiotherapy and radical prostatectomy are associated with potential complications including erectile dysfunction, incontinence and injury to various organs from treatment (Fleming, Wasson, Albertsen, et al., 1993).

Finally, survival outcomes for at least 10 years are generally good. As summarized on page 19, available data suggest that the risk of metastatic disease and prostate cancer death in patients managed with surveillance alone is not substantially different from the risk in patients treated for "cure." A recent pooled analysis of six series of patients so treated found excellent 10-year disease-specific survivals for patients with well-differentiated and moderately well-differentiated tumors (Chodak, Thisted, Gerber, et al., 1994). On the other hand, one study reported that the majority of patients on surveillance who survive more than 10 years ultimately die of prostate cancer (Aus, Hugosson and Norlén, 1994).

Among the disadvantages of surveillance is the risk of subsequent, possibly incurable disease. In virtually every series of patients managed by surveillance, some percentage of patients was reported to have died of the disease and an additional group was reported to have suffered from disease-related morbidity. In a pooled analysis, at 10 years of follow-up, 6 percent, 6.5 percent and 42 percent of patients with well-differentiated, moderately well-

differentiated and poorly differentiated tumors, respectively, died of their disease (Chodak, Thisted, Gerber, et al., 1994). Another study reported on 61 patients with stages T1-T2 disease managed by surveillance. Of 8 who died during the period of observation, 4 died of prostate cancer (Adolfsson and Carstensen, 1991).

Then there is the risk of developing disease-related morbidity. The premise of "curative" treatment of carcinoma of the prostate is that it will prevent not only cancer-related death, but those complications related to the tumor that reduce the patient's quality of life. Patients managed with surveillance may be at a higher risk for such cancer-related morbidities. Among these complications, spinal cord compression is a major concern. This event can occur in as many as 12 percent of patients with metastatic disease and can lead to death as well as severe reductions in the patient's quality of life (Rubin, Lome and Presman, 1974). Whether intervention at the time of diagnosis might prevent such an outcome could not be predicted.

Other disease-related complications include pain, obstructive voiding symptoms, bone fracture anemia, ureteral obstruction, uremia, deep venous thrombosis and pulmonary embolism. In one paper, 26 of 223 patients followed on a program of surveillance developed metastases (Johansson, Adami, Andersson, et al., 1992). Of these 26 patients, 23 had a reduction in performance status. Of 19 patients who died of prostate cancer, their performance status decreased for more than 6 months in 12, and 13 patients required hospital care for 1 month or more prior to death. Fourteen patients in this series required hospital care for local problems due to their tumors. Of 152 patients who did not develop disease progression, 30 had mild or moderate local problems and 14 required transurethral resection of the prostate. Of 71 patients who did develop local progression, 60 had local problems (which generally disappeared after treatment with hormone therapy). Twenty-eight of these 71 had recurrent local problems during the course of their disease.

In summary, using surveillance as the primary management of patients with locally confined prostate cancer may place a number of patients at risk

for various complications related to progression of the tumor.

As pointed out on page 20, patients who elect to pursue a policy of surveillance are free to choose a "curative" intervention at any time during follow-up. However, if the goal for subsequent intervention is to time its application prior to the development of extraprostatic disease, evidence indicates that the window of opportunity is very narrow. Data from one report suggest that if serum PSA is measured during surveillance, once the value exceeds 5 ng/ml the risk exceeds 50 percent that the disease is extraprostatic (Thompson, Zeidman, Crawford, et al., 1993).

Additional treatment may be needed. In virtually every series of patients treated with surveillance for localized prostate cancer, the term "surveillance" included a variety of additional forms of treatment. Examples include a series of 122 patients (Adolfsson, Carstensen and Lowhagen, 1992). Of these, 45 percent received endocrine therapy (36 patients), external beam irradiation (12 patients), ¹²⁵I implantation (3 patients) or radical prostatectomy (4 patients). In another series, treatment for local progression was required for 23 of 120 patients (George, 1988).

It can be seen then that patients followed with surveillance may be at risk for deferring treatment to a later age and, by doing so, either deferring the side effects of treatment or, alternatively, losing the opportunity of disease control as well as undergoing invasive therapy at an age when comorbidities increase.

A major unmeasured disadvantage to a policy of surveillance is the patient's possible anxiety, his feeling that "nothing is being done about my prostate cancer." Although the patient may intellectually understand the often confusing data supporting the validity of surveillance therapy, considerable anxiety can be generated in many patients and their families by a lack of intervention. The psychological consequences of cancer risk or diagnosis awareness are well recognized, and clinicians practicing in this field are well aware of the overpowering dread that can be induced by worry about prostate cancer (Lerman, Miller, Scarborough, et al., 1991; Lerman, Rimer and Engstrom, 1991).

Chapter 5:

Literature limitations and recommendations for research

Limitations in the prostate cancer treatment literature

The explicit methodology the AUA Prostate Cancer Clinical Guidelines Panel used in its analysis for this *Report on the Management of Clinically Localized Prostate Cancer* required careful review and interpretation of published reports in the peer-reviewed literature. As discussed in Chapter 1, many articles were reviewed and most were rejected for a variety of reasons, including inaccurate reporting of data, limited time of follow-up, incomplete description of treatments utilized and poorly defined patient populations. Moreover, the studies finally selected for data extraction were not by any means free of deficiencies.

Data not based on randomized controlled trials

All the studies finally selected by the panel provided useful information, but most were case series not subjected to the rigors of a carefully performed, prospective, centrally controlled clinical trial. Many of the patient populations were “convenience samples” selected mainly because they were available in the clinical settings in which the research was conducted.

The lack of randomized, controlled trials is a problem inherent in the medical literature. Although it can be addressed and responded to, it cannot be avoided. Neither can it be dismissed. The difficulties this problem creates for developing evidence-based practice policy recommendations are especially severe with regard to localized prostate cancer. Because of the particular attributes of this disease, such as high histologic prevalence, yet variable natural history, treatment outcomes data from uncontrolled trials can be even less reliable than usual.

Insufficient data

Many of the limitations in the literature stem directly from the previously mentioned plethora of

case series and lack of randomized controlled trials. These limitations include the large gaps that exist in the literature regarding data reported. For example, many articles do not report all outcomes (such as cancer-specific survival, metastasis-free survival and tumor-free survival). There are also few data on high-grade tumors in patients managed by surveillance, or on pelvic lymph node status in patients managed by external beam radiotherapy as well as surveillance. In another very important example, many articles do not specify ages of patients notwithstanding the effect of age on survival and the significant differences in average patient age for different treatment modalities. In still another example, many articles reporting complications from treatment do not report “zero complications.” For instance, an article may not refer to incontinence in its list of treatment-related complications. Readers are left to wonder whether the complication did not occur or if it was omitted from the report.

Data variability

Data variability is one of the most frequent limitations encountered when attempting to combine evidence from multiple studies. This variability takes many forms with many causes. Variations between studies because of differences in staging methods are one example. Some articles reviewed by the panel reported outcomes according to clinical stage, others according to surgical stage. Outcomes data from these two classes of articles are not comparable.

Lymph node dissections performed for staging vary between studies. Lymphadenectomy is typically performed, but the panel could not substantiate that all procedures reported in the literature were comparable. Both extensive and limited dissections were carried out by different surgeons. In addition, although laparoscopic dissections are becoming more commonplace, they were not included in the articles selected.

Imaging studies are frequently utilized and are limited not only by the state-of-the-art technology, but by the abilities of radiologists and urologists to interpret a particular study. Laboratories vary as well. Similar studies performed in different facilities,

using different assays, could yield very different results. Urologists and radiologists also differ. It cannot be assumed that a radiation technique or surgical procedure performed by one clinician is comparable to that performed by another.

As laboratories and imaging studies vary, so do pathology reports. Controlled trials often utilize a central pathology facility, but comparing case series means comparing varied facilities. Differences exist in preparation of histologic material, especially with the current emphasis on whole mount prostate preparations. Yet, interpretations of extent of involvement and margin status are highly dependent on tissue preparation and subsequent pathologic interpretation, which makes comparisons between studies problematic. Similar variations exist in the abilities of pathologists to grade malignancies. Although standards have been established, the subjective component of these interpretations cannot be ignored.

Patient populations differ as do the methods by which patients are selected for review. For instance, some clinical reports include consecutive patients, whereas many others are based upon informal selection factors such as availability for follow-up, referral patterns and logistic concerns. Controlled studies, because of strict inclusion and exclusion criteria, may be preferable but may not be generalizable because of the carefully selected patients enrolled. Means and ranges of follow-up often vary as well. Such variations will not only have an impact on outcomes, but will influence any conclusions derived from the studies.

Because selection criteria between studies may differ, with variations in patient population, studies performed and methods of follow-up, comparisons of studies may not be reliable. A common problem with prostate cancer case series, for example, is the reporting of endocrine therapy for patients developing recurrence after surgery or radiotherapy. The timing of administration, the form of therapy utilized and the method of reporting may not be clearly detailed, thus limiting the value of the report. Controlled prospective trials, by contrast, usually specify from the outset the approach to be utilized.

Publication bias

Publication bias is a problem affecting the available data to which there may be no immediate solution. Very simply, because not all physicians publish, case-study results may not be generally repre-

sentative. Moreover, studies with negative or equivocal results are less likely to be submitted for publication and less likely to be published if submitted.

Data limitations in reflecting current techniques

The data available do not always reflect the many changes in treatment modalities that have occurred over the past two decades. For instance, early brachytherapy experience utilizing retropubic implantation techniques with ^{131}I and ^{198}Au had high failure rates. Newer methods, utilizing different isotopes (such as iridium) implanted perineally under ultrasound guidance, are being used with increasing frequency, but too few data are currently available to make efficacy comparisons.

Similarly, nerve-sparing techniques are being increasingly applied to radical prostatectomy. Yet, it must be assumed that this modification has not had any impact on survival or progression. In addition, the use of PSA to detect disease recurrence has altered the definition of treatment failure. Whether concepts regarding success and failure will now change because of the availability of this relatively reliable marker is not known. Many questions remain: Does PSA failure following radical prostatectomy or radiotherapy always indicate treatment failure? What numeric criteria should be used to establish PSA failure? What is its impact on survival?

Finally, new forms of therapy continue to evolve. Cryotherapy and other ablative techniques are being developed, but too few data are available to appropriately assess success and failure in order to make meaningful comparisons with other treatment modalities.

Recommendations for future research

Most research needs can be grouped in three categories: (1) new and better methods to diagnose and manage localized prostate cancer; (2) prospective, randomized, controlled studies of the issues concerning prostate cancer, especially controlled studies of competing treatments for the management of localized prostate cancer; and (3) studies of how prostate cancer and its treatments affect patient quality of life.

Needs for new assessment and management methods

Needs for new methods of cancer diagnosis and monitoring include a more sensitive, more specific tumor indicator. As clinically useful as serum PSA values have now become, PSA is not prostate-cancer specific. As a result, it lacks sufficient sensitivity and specificity to be the ideal screening test for prostate cancer. In addition, although serum PSA concentration correlates strongly with tumor volume ($r = 0.70$), it cannot reliably predict tumor stage on an individual basis. Moreover, PSA after androgen deprivation therapy may not always be a reliable indicator of the true tumor status because the cell's ability to express PSA is under hormonal regulation, and androgen-insensitive cells do not produce and secrete PSA to the same degree as androgen-sensitive cells. Patients with progressive disease after androgen deprivation therapy may in fact have a low or stable serum PSA concentration.

Needed also are biochemical, radiographic and/or genetic methods to reliably determine which cancers are biologically aggressive and which are clinically insignificant, so that focused treatment strategies can be developed such that treatment is initiated only in those patients with life-threatening prostate tumors.

For detecting potentially life-threatening cancers while still localized, it would be useful to have a genetic marker that can identify men likely to develop such a tumor in their lifetimes. These men could then be monitored with appropriate, comprehensive screening programs. Knowing who is at risk for developing a clinically significant prostate cancer has tremendous potential not only to increase the probability of detecting prostate cancer while still organ confined, but to markedly decrease the health care costs associated with unfocused efforts at prostate cancer detection.

Finally, with only 50 to 60 percent of newly diagnosed prostate cancers currently organ confined, there is an overwhelming need for an effective systemic therapy for this disease. At the present time, no curative treatment exists for advanced prostate cancer. None of the currently available chemotherapeutic agents is effective, and androgen deprivation therapy remains a palliative treatment for most patients. New and creative approaches, such as gene therapy, need to be pursued both at the basic science level and in prospective clinical trials.

Recommendations for randomized controlled trials

It is clear, from the discussions in this report of limitations in the prostate cancer treatment literature, that a pressing need exists for properly designed and controlled, prospective, randomized clinical trials to study effectiveness of competing treatment modalities for localized disease. In particular, randomized, 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, tumor stage, tumor 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 disease progression (including objective measures of symptoms associated with progression), risk of metastatic disease and risk of prostate cancer death.

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

- **Radical prostatectomy:** Methods of improving preoperative staging, reducing the number of patients with extraprostatic disease and reducing treatment complications; strategies to reduce the cost of the procedure; better ways to disseminate advances in surgical techniques to the urologic community; treatments for patients with pathologically proven (pT3) extraprostatic disease; and treatments for patients with evidence of serologic (PSA) failure.
- **Radiotherapy:** Ways to reduce treatment morbidity; ways to standardize 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.
- **Surveillance:** 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 localized prostate cancer.

- 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 (*e.g.*, validation of PSA failure as a surrogate for cancer survival).

Patient quality of life

Research is needed for determining how prostate cancer and its treatments affect patient quality of life. Such research would include the second topic in the foregoing list: analysis of trade-offs between survival and quality of life and how quality-of-life 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.

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 the United States. Information is now available from the Surveillance, Epidemiology and End Results Program registry, but only for a limited number of locations around the country.

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Appendix A: Data presentation

Figure A-1. Articles reviewed by year (N = 12,501)

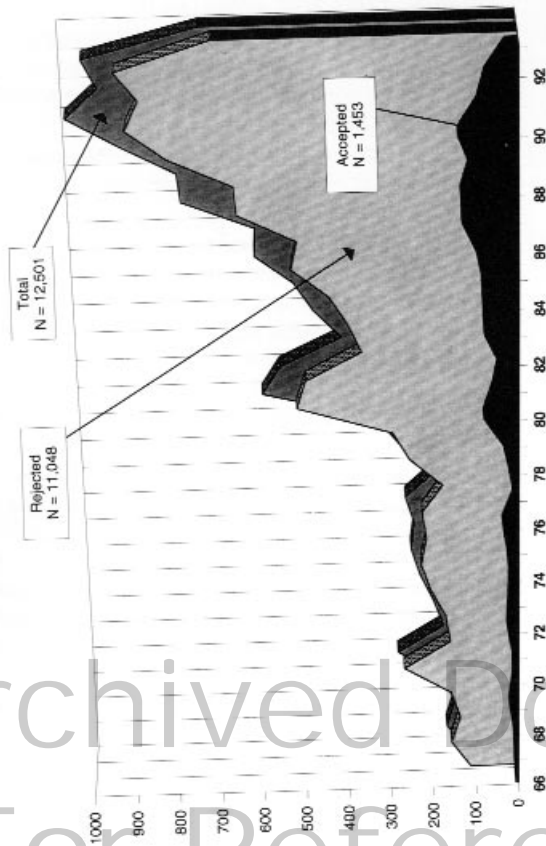
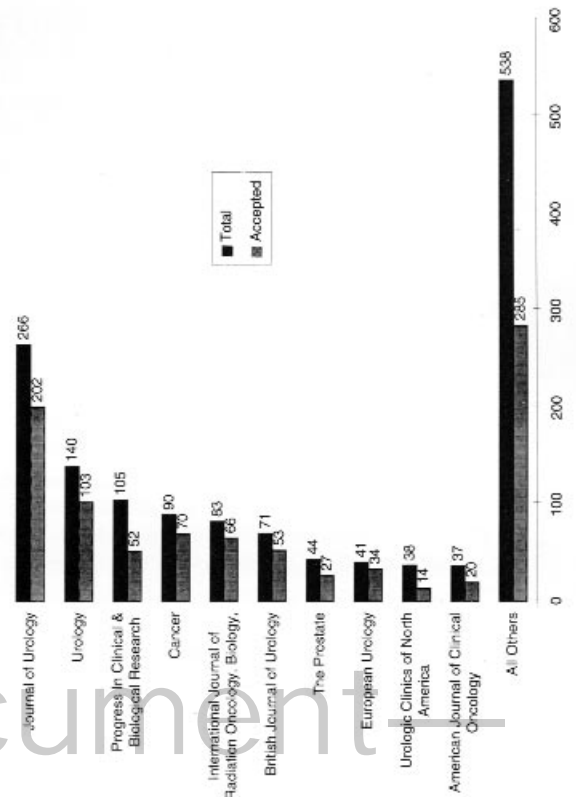


Figure A-2. Sources of articles by journal (N = 1,453)



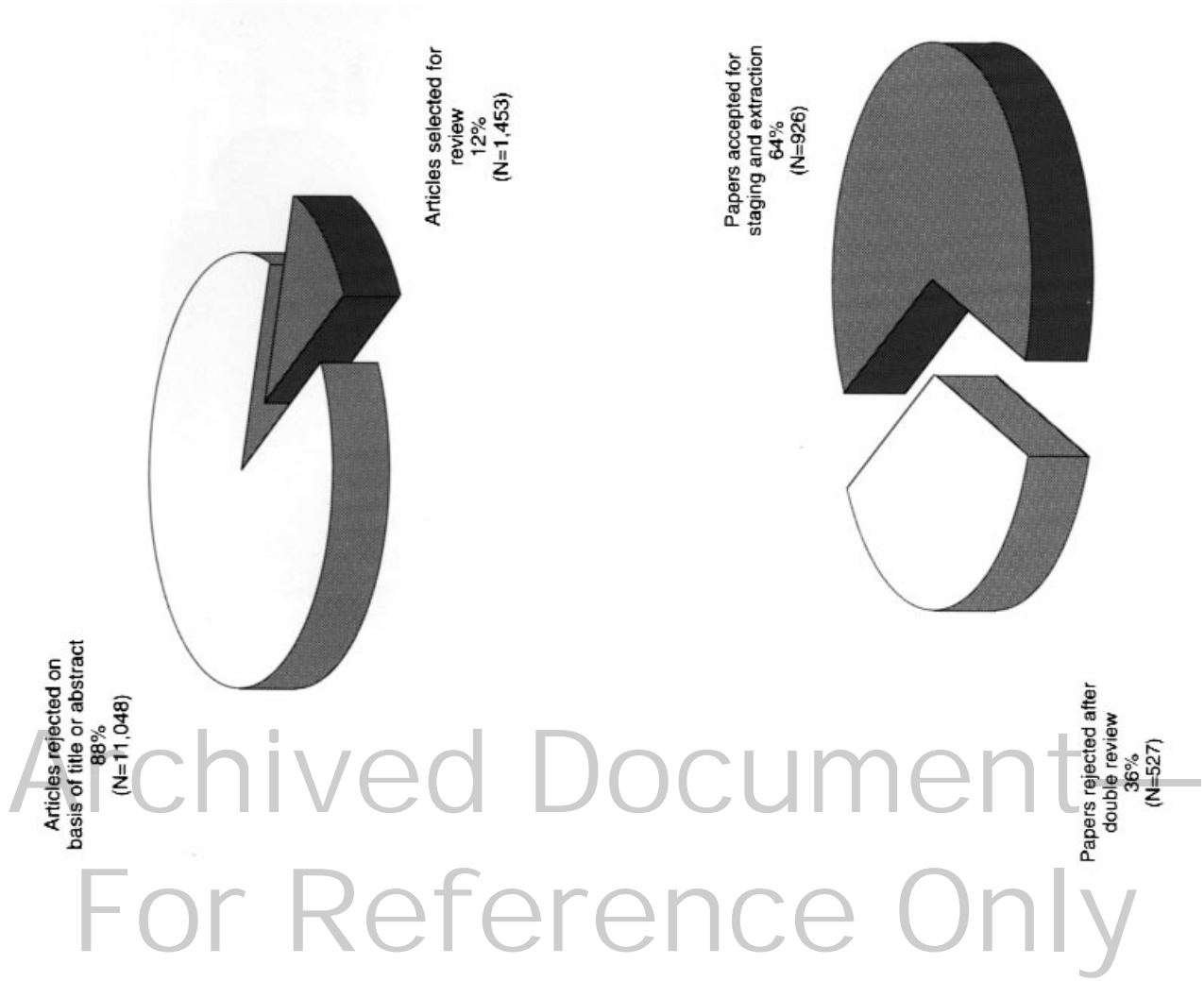


Figure A-3. Articles retrieved from MEDLINE (N = 12,501)

Figure A-4. Status of reviewed articles (N = 1,453)

Papers accepted and extracted
42%
(N=165)

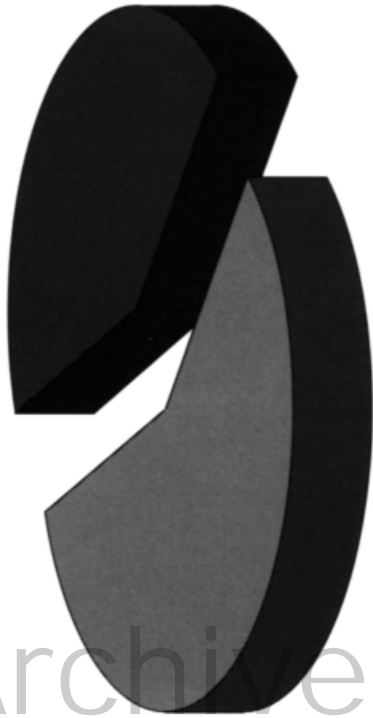


Figure A-5. Stage T2 (B) articles (N = 396)

Papers rejected at extract phase
58%
(N=231)

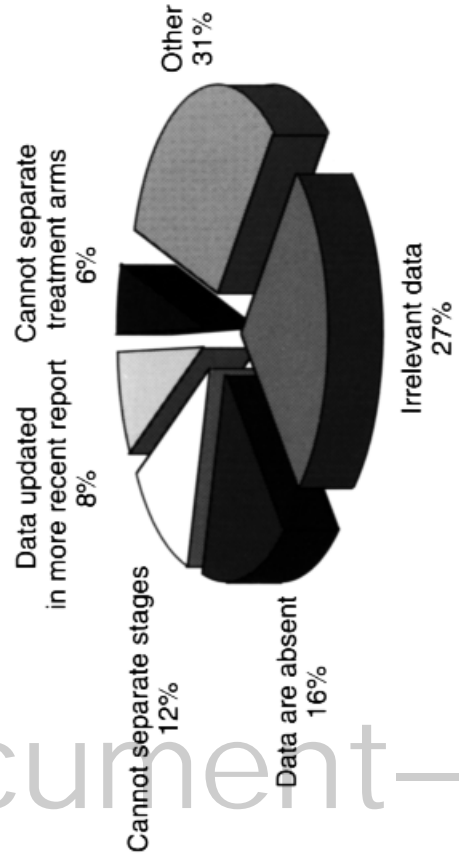


Figure A-6. Analysis of stage T2 (B) article exclusions (N = 231)

Table A-1. Bibliography by Papyrus reference number

264	California Medicine	1969	111	84-86	Total retropubic prostatectomy for carcinoma of the prostate	Hendricks, E.D., Massey, B.D., Nation, E.F., Gallup, C.A., and Massey, B.D., Jr.	Pasadena, California
308	Journal of the American Medical Association	1968	203	403-406	The palpable nodule of prostatic cancer. Results 15 years after radical excision	Jewett, H.J., Bridge, R.W., Gray, G.F., Jr., and Shelley, W.M.	The Johns Hopkins University and Hospital
342	Journal of Urology	1968	100	672-674	Twenty single nodules of prostate cancer not treated by total prostatectomy	Cook, G.B., Watson, F.R.	Ellis Fischel State Cancer Hospital and Cancer Research Center
348	Journal of Urology	1968	99	97-101	Radical perineal prostatectomy for carcinoma of the prostate: survival in 143 cases treated from 1935 to 1958	Berlin, B.B., Cornwell, P.M., Connelly, R.R., and Eisenberg, H.	Hartford Hospital (multi-site)
350	Journal of Urology	1969	102	88-90	Early prostatic cancer: long-term results with conservative treatment	Barnes, R.W., Bergman, R.T., Hadley, H.L., and Dick, A.L.	Loma Linda University (multi-site)
498	California Medicine	1967	106	372-374	Total perineal prostatectomy for carcinoma. Indications and results	Feeney, M.J., Mullenix, R.B., Prentiss, R.J., and Howe, G.E.	University of California School of Medicine (multi-site)
666	Surgical Clinics of North America	1967	47	695-706	Radical prostatectomy for carcinoma: a review and perspective	Flint, L.D., Hsiao, J.H.	Lahey Clinic
965	Cancer	1973	32	1113-1118	Radical prostatectomy in the treatment of prostatic cancer	Culp, O.S., Meyer, J.J.	Mayo Clinic and Mayo Foundation
1077	Proceedings of the National Cancer Conference	1972	7	761-767	Prostate carcinoma: external irradiation as definitive treatment	Bagshaw, M.A., Ray, G.R.	Stanford University School of Medicine
1078	Therapeutic Radiology	1973	106	407-418	Definitive radiation therapy of carcinoma of the prostate. A report on 15 years of experience	Ray, G.R., Cassidy, J.R., and Bagshaw, M.A.	Stanford University School of Medicine
1142	Urology	1973	2	643-646	Carcinoma of the prostate. Evaluation of biopsies pre- and postirradiation therapy	Longley, J.R., Pearlman, C.K., and Vermund, H.	Orange County Medical Center
1273	Journal of Urology	1972	108	604-608	Radical perineal prostatectomy: a 20-year overview	Davis, W.H., Scardino, P.L., and Carlton, F.E.	Savannah Urological Clinic
1281	Journal of Urology	1972	107	91-96	Total perineal prostatectomy for carcinoma of the prostate	Belt, E., Schroeder, F.H.	University of California Medical Center (multi-site)
1293	Journal of Urology	1972	108	944-947	Radical retropubic prostatectomy for cancer of the prostate	Hudson, H.C., Howland, R.L., Jr.	Caraway Methodist Hospital
1298	Journal of Urology	1972	107	450-453	Carcinoma of the prostate: a 15-year followup	Hanash, K.A., Utz, D.C., Cook, E.N., Taylor, W.F., and Titus, J.L.	Mayo Clinic and the Mayo School of Medicine (multi-site)
1301	Journal of Urology	1972	107	1041-1042	Carcinoma of prostate: treatment and survival with radical prostatectomy	Young, J.A., Bohne, A.W.	Henry Ford Hospital
1877	Cancer	1975	36	723-728	External beam radiation therapy of primary carcinoma of the prostate	Bagshaw, M.A., Ray, G.R., Pistenma, D.A., Castellino, R.A., and Meares, E.M., Jr.	Stanford University School of Medicine
1940	Journal of Urology	1975	113	378-379	Telecobalt therapy for prostatic cancer: rationale, results and future considerations	McLoughlin, M., Hazra, T., Schirmer, H.K.A., and Scott, W.W.	The Johns Hopkins University and Hospital
2049	Urology	1975	5	308-316	Cryosurgery for carcinoma of prostate	O'Donoghue, E.P.N., Milleman, L.A., Flocks, R.H., Culp, D.A., and Bonney, W.W.	University of Iowa Hospitals and Clinics
2426	Cancer	1977	40	1425-1433	Radiation therapy in the definitive treatment of localized carcinoma of the prostate	Perez, C.A., Bauer, W., Garza, R., and Royce, R.K.	Mallinckrodt Institute of Radiology (multi-site)
2506	Journal of Urology	1978	120	312-314	Latent residual tumor following external radiotherapy for prostate adenocarcinoma	Nachtsheim, D.A., Jr., McAninch, J.W., Stutzman, R.E., and Goebel, J.L.	Letterman Army Medical Center (multi-site)
2529	Journal of Urology	1978	120	188-190	Extended total excision of prostatic adenocarcinoma	Spaulding, J.T., Whitmore, W.F., Jr.	Memorial Sloan-Kettering Cancer Center
2661	Cancer	1981	47	1901-1910	Radical retropubic prostatectomy and pelvic lymphadenectomy for high-stage cancer of the prostate	Zincke, H., Fleming, T.R., Furlow, W.L., Myers, R.P., and Utz, D.C.	Mayo Clinic and Mayo Foundation
2690	International Journal of Radiation Oncology, Biology, Physics	1980	6	1121-1126	The adverse influence of prior transurethral resection on prognosis in carcinoma of prostate treated by radiation therapy	McGowan, D.G.	Cross Cancer Institute (multi-site)

Papyrus Reference	Journal	Year	Vol	Pages	Title	Authors	Institution
2720	Journal of Urology	1980	124	855-859	Definitive radiation therapy for prostatic carcinoma: Mayo clinic experience	Cupps, R.E., Utz, D.C., Fleming, T.R., Carson, C.C., Zincke, H., and Myers, R.P.	Mayo Clinic and Mayo Foundation
2729	Journal of Urology	1981	125	365-369	Transcocygeal 125iodine prostatic implantation for adenocarcinoma	Ambrose, S.S.	Emory University School of Medicine
2783	Urologic Clinics of North America	1980	7	623-629	The therapeutic role of pelvic lymphadenectomy in prostatic cancer	Morales, P., Golimbu, M.	New York University Medical Center
2806	Urology	1981	17	39-43	Lymphocele after pelvic lymphadenectomy for urologic cancer	Sogani, P.C., Watson, R.C., and Whitmore, W.F., Jr.	Memorial Sloan-Kettering Cancer Center
2894	International Journal of Radiation Oncology, Biology, Physics	1979	5	1957-1961	Preoperative extended field radiation with I-125 seed implant in prostatic cancer: a preliminary report of a randomized study	Charyulu, K., Block, N., and Sudarsanam, A.	University of Miami School of Medicine
3019	Urology	1979	14	555-560	Radiation therapy as definitive treatment for localized carcinoma of prostate	Jazy, F.K., Aron, B., Dettmer, C.M., and Shehata, W.M.	University of Cincinnati Medical Center (multi-site)
3050	Cancer	1979	43	1123-1127	Radiation therapy for localized prostate cancer	Taylor, W.J., Richardson, R.G., and Halfermann, M.D.	Virginia Mason Medical Center
3087	Journal of Urology	1979	121	447-451	Complications of 125iodine implantation and pelvic lymphadenectomy in the treatment of prostatic cancer	Fowler, J.E., Jr., Barzell, W., Hilaris, B.S., and Whitmore, W.F., Jr.	Memorial Sloan-Kettering Cancer Center
3195	International Journal of Radiation Oncology, Biology, Physics	1980	6	1121-1126	The adverse influence of prior transurethral resection on prognosis in carcinoma of prostate treated by radiation therapy	McGowan, D.G.	Cross Cancer Institute (multi-site)
3399	Cancer	1980	45	1906-1911	Radical surgery for prostatic cancer	Walsh, P.C., Jewett, H.J.	The Johns Hopkins University and Hospital
3401	Cancer	1980	45	1922-1928	Combined interstitial and external radiotherapy in the definitive management of carcinoma of the prostate	Guerrero, W.G., Carlton, C.E., Jr., and Hudgins, P.T.	Baylor College of Medicine (multi-site)
3480	Journal of Urology	1980	124	495-497	Radical retropubic prostatectomy after transurethral prostatic resection	Bass, R.B., Jr., Barrett, D.M.	Mayo Clinic and Mayo Foundation
3649	International Journal of Radiation Oncology, Biology, Physics	1981	7	885-890	Radical external radiotherapy for prostatic carcinoma	Beiler, D.D., Wright, D.J., and Reddy, G.N.	Geisinger Medical Center
3789	Urology	1981	17	7-11	VACURG randomized trial of radical prostatectomy for stages I and II prostatic cancer. Veterans Administration Cooperative Urological Research Group	Byar, D.P., Corle, D.K.	Clinical Diagnostic Trials Section, National Cancer Institute
3868	International Journal of Radiation Oncology, Biology, Physics	1981	7	817-819	Prophylactic pelvic girdle irradiation in the treatment of prostatic carcinoma	Hazra, T.A., Giri, S.	Virginia Commonwealth University (multi-site)
3898	Journal of Urology	1981	126	366-371	Interstitial irradiation of carcinoma of the prostate with 125iodine and simultaneous extraperitoneal pelvic lymphadenectomy in 32 patients: trials, tribulations and possible triumphs	Whitehead, E.D., Huh, S.H., Garcia, R.L., Rao, R., and Leiter, E.	Beth Israel Medical Center
3914	The Journal of the Kansas Medical Society	1981	82	278-281	Prostatic carcinoma. Treatment with I125 interstitial irradiation and pelvic lymphadenectomy	Mebust, W.K., Weigel, J.W., and Reddy, E.K.	The University of Kansas School of Medicine
4076	International Journal of Radiation Oncology, Biology, Physics	1982	8	1909-1914	Local control and survival after external irradiation for adenocarcinoma of the prostate	Rangala, N., Cox, J.D., Byhardt, R.W., Wilson, J.F., Greenberg, M., and Lopes da Conceicao, A.	The Medical College of Wisconsin (multi-site)
4106	Journal of Urology	1982	128	502-504	Radical surgery versus radiotherapy for adenocarcinoma of the prostate	Paulson, D.F., Lin, G.H., Hinshaw, W., Stephani, S., and The Uro-Oncology Research Group	Duke University Medical Center
4110	Journal of Urology	1982	128	505-509	Radiotherapy for prostatic carcinoma: post-irradiation prostatic biopsy and recurrence patterns with long-term followup	Leach, G.E., Cooper, J.F., Kagan, A.R., Snyder, R., and Forsythe, A.	Kaiser Foundation Hospital (multi-site)

4208	Urology	1982	20	591-598	125I implantation for carcinoma of prostate. Further follow-up of first 100 cases	Grossman, H.B., Bataata, M., Hilaris, B., and Whitmore, W.F., Jr.	Memorial Sloan-Kettering Cancer Center
4280	Journal of Urology	1982	127	923-927	Clinical results of early stage prostatic cancer treated by pelvic lymphadenectomy and I ¹²⁵ iodine implants	Kandzari, S.J., Belis, J.A., Kim, J.C., Gnepp, D.R., and Riley, R.S.	West Virginia University Medical Center
4285	Journal of Urology	1982	127	704-706	Radical perineal prostatectomy for clinical stage B2 carcinoma of the prostate	Elder, J.S., Jewett, H.J., and Walsh, P.C.	The Johns Hopkins University and Hospital
4287	Journal of Urology	1982	127	699-701	Preliminary observations on the results of combined I ¹²⁵ iodine seed implantation and external irradiation for carcinoma of the prostate	Ross, G., Jr., Borkon, W.D., Landry, L.J., Edwards, F.M., Weinstein, S.H., and Abadir, R.	University of Missouri School of Medicine
4345	Urology	1982	19	37-42	Cryosurgery in prostatic cancer: survival	Bonney, W.W., Fallon, B., Gerber, W.L., Hawtrey, C.E., Loening, S.A., Narayana, A.S., Platz, C.E., Rose E.F., Sall, J.C., Schmidt, J.D., and Culp, D.A.	University of Iowa (multi-site)
4383	Australian & New Zealand Journal of Surgery	1983	53	561-565	Radical radiotherapy for carcinoma of the prostate: localized and extended field treatment	Nacey, J.N.	Dunedin Hospital
4401	Cancer	1983	51	1599-1604	Protons or megavoltage X-rays as boost therapy for patients irradiated for localized prostatic carcinoma. An early phase I/II comparison	Duttenhaver, J.R., Shipley, W.U., Perrone, T., Verhey, L.J., Goitein, M., Munzenrider, J.E., Prout, G.R., Parkhurst, E.C., and Suit, H.D.	Massachusetts General Hospital (multi-site)
4639	The Canadian Journal of Surgery	1983	26	363-365	Interstitial radiotherapy for localized carcinoma of the prostate	Wilson, J.W.L., Morales, A., Bruce, A.W., and Froud, P.	Queen's University
4897	International Journal of Radiation Oncology, Biology, Physics	1984	10	1861-1867	Treatment-related morbidity in phase III RTOG studies of extended-field irradiation for carcinoma of the prostate	Pilepich, M.V., Krall, J., George, F.W., Asbell, S.O., Plenk, H.D., Johnson, R.J., Stetz, J., Zinninger, M., and Walz, B.J.	Washington University School of Medicine (multi-site)
4922	Journal of the Mississippi State Medical Association	1984	25	324-327	External beam irradiation for prostate cancer: the MBMC experience and a literature review	Reagan, M.T., Smith, R.A., and Steadham, R.E.	Mississippi Baptist Medical Center
5077	Cancer	1984	53	1857-1863	Relationship of pretreatment transurethral resection of the prostate to survival without distant metastases in patients treated with I ¹²⁵ I-implantation for localized prostatic cancer	Fowler, J.E., Jr., Fisher, H.A.G., Kaiser, D.L., and Whitmore, W.F., Jr.	Memorial Sloan-Kettering Cancer Institute
5205	The Prostate	1984	5	19-25	Carcinoma of the prostate: results of post-irradiation biopsy	Freiha, F.S., Bagshaw, M.A.	Stanford University School of Medicine
5219	Radiotherapy and Oncology	1984	1	309-315	External beam radiotherapy in cancer of the prostate. The University of Arizona experience	Aristizabal, S.A., Steinbronn, D., and Heusinkveld, R.S.	University of Arizona Health Sciences Center
5265	Cancer	1984	53	37-43	External beam irradiation of prostate cancer. Experience in 163 patients	Kurup, P., Kramer, T.S., Lee, M.S., and Phillips, R.	Rush-Presbyterian-St. Luke's Medical Center (multi-site)
5610	International Journal of Radiation Oncology, Biology, Physics	1985	11	1777-1781	Iodine-125 implants for carcinoma of the prostate	Peschel, R.E., Fogel, T.D., Kacinski, B.M., Kelly, K., and Mate, T.P.	Yale University School of Medicine
5631	Journal of Urology	1985	134	1149-1151	Nerve-sparing radical prostatectomy: extraprostatic tumor extension and preservation of erectile function	Catalona, W.J., Dresner, S.M.	Washington University School of Medicine
5642	Journal of Urology	1985	134	1140-1145	I ¹²⁵ iodine implantation for carcinoma of the prostate: 5-year survival free of disease and incidence of local failure	Schellhammer, P.F., El-Mahdi, A.E., Ladaga, L.E., and Schultheiss, T.	Eastern Virginia Medical School
5732	Urology	1985	26	1-3	Radical prostatectomy for stage A2 and B prostatic carcinoma. Operative experience	Fowler, J.E., Jr.	University of Virginia School of Medicine
5813	Urology	1985	25	228-232	Prostate cancer: experience with definitive irradiation in the aged	Green, N., Bodner, H., and Broth, E.	LAC/USC Medical Center (multi-site)
6141	Clinical Radiology	1986	37	473-477	Radical treatment of prostatic carcinoma by megavoltage X-ray therapy	Preston, C.I., Duncan, W., and Kerr, G.R.	Western General Hospital
6163	International Journal of Radiation Oncology, Biology, Physics	1986	12	1721-1727	Current conflicts in the management of prostatic cancer	Bagshaw, M.A.	Stanford University School of Medicine

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6191	Journal of Urology	1986	136	422-424	Patient survival and local recurrence rate following radical prostatectomy for prostatic carcinoma	Middleton, R.G., Smith, J.A., Jr., Melzer, R.B., and Hamilton, P.E.	University of Utah School of Medicine
6215	The Medical Journal of Australia	1986	144	624-628	High-dose radiotherapy for localized prostatic cancer: An analysis of treatment results and early complications	Kearsley, J.H.	Queensland Radium Institute (multi-site)
6331	Journal of Urology	1986	135	517-519	Prostatic carcinoma: 5-year followup of patients with surgically staged disease undergoing extended field radiation	Sause, W.T., Richards, R.S., and Plenk, H.P.	LDS Hospital (multi-site)
6344	Journal of Urology	1986	135	722-725	Preliminary observations on the results of combined temporary 192Iridium implantation and external beam irradiation for carcinoma of the prostate	Bosch, P.C., Forbes, K.A., Prassvimichai, S., Miller, J.B., Golji, H., and Martin, D.C.	Long Beach Veterans Administration Medical Center (multi-site)
6364	Urology	1986	27	10-16	Comparison of whole pelvis versus small-field radiation therapy for carcinoma of prostate	Ploysongsang, S., Aron, B.S., Shehata, W.M., Jazy, F.K., Scott, R.M., Ho, P.Y., and Morand, T.M.	Christ Hospital (multi-site)
6601	Urologic Clinics of North America	1987	14	675-684	Radiotherapy versus surgery for localized prostatic cancer	Paulson, D.F.	Duke University Medical Center
6732	Progress in Clinical & Biological Research	1987	243B	379-386	Radiotherapy of stage B2 lesions of the prostate	Bagshaw, M.A.	Stanford University School of Medicine
6813	Radiotherapy and Oncology	1987	10	7-15	Radiotherapy of prostate carcinoma: results of treatment and complications	Sack, H., Nsobuesch, H., and Stuetzer, H.	University of Cologne
6860	Anticancer Research	1987	7	395-399	Pretreatment transurethral resection of prostate cancer and disease-free survival	Natarajan, N., Mettlin, C., Murphy, G.P., and Schmidt, J.	Roswell Park Memorial Institute (multi-site)
6935	International Journal of Radiation Oncology, Biology, Physics	1987	13	499-505	A ten year follow-up of 682 patients treated for prostate cancer with radiation therapy in the United States	Hanks, G.E., Diamond, J.J., Krall, J.M., Martz, K.L., and Kramer, S.	University of Pennsylvania/Fox Chase Cancer Center (multi-site)
6937	International Journal of Radiation Oncology, Biology, Physics	1987	13	1013-1020	Prostatic carcinoma: limited field irradiation	Rounsaville, M.C., Green, J.P., Vaeth, J.M., Purdon, R.P., and Heltzel, M.M.	Children's Hospital (multi-site)
7164	International Journal of Radiation Oncology, Biology, Physics	1988	15	1307-1316	Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 7706	Asbell, S.O., Krall, J.M., Pilepich, M.V., Baerwald, H., Sause, W.T., Hanks, G.E., and Perez, C.A.	Albert Einstein Medical Center (multi-site)
7419	International Journal of Radiation Oncology, Biology, Physics	1988	15	1317-1322	Adenocarcinoma of the prostate: radioactive gold seed implant plus external irradiation	Gutierrez, A.E., Merino, O.R.	Radiation Oncology Section, St. Joseph Hospital
7519	Scandinavian Journal of Urology & Nephrology - Supplementum	1988	110	95-100	Treatment of localized prostatic cancer: Radical prostatectomy versus placebo. A 15-year follow-up	Madsen, P.O., Gravensen, P.H., Gasser, T.C., and Corle, D.K.	William S. Middleton Memorial Veterans Hospital (multi-site)
7522	Scandinavian Journal of Urology & Nephrology - Supplementum	1988	110	89-94	Radiation therapy for prostatic carcinoma	Bergman, B., Modig, H.	Departments of Urology & Andrology and Oncology, University of Umea
7644	International Journal of Radiation Oncology, Biology, Physics	1988	14	1153-1157	Iodine-125 implants versus external beam therapy for stages A2, B, and C prostate cancer	Morton, J.D., Peschel, R.E.	Yale University School of Medicine
7670	Journal of Urology	1988	139	985-988	Interstitial gold and external beam irradiation for prostate cancer	Boileau, M.A., Dowling, R.A., Gonzales, M., Handel, P.H., Benson, G.S., and Corriere, J.N., Jr.	University of Texas Medical School
7671	Journal of Urology	1988	139	989-994	Combined gold seed implantation and external radiotherapy for stage B2 or C prostate cancer	Carey, P.O., Lippert, M.C., Constable, W.C., Jones, D., and Taiton, B.M.	University of Virginia Medical School (multi-site)
7765	American Journal of Clinical Oncology	1988	11	166-171	Radiation-treated carcinoma of prostate. Comparison of survival of black and white patients by Gleason's grading system	Aziz, H., Rotman, M., Thelmo, W., Chen, P., Choi, K.N., Khil, S.U., Laungani, G.B., Brandy, M., Ayr, G., and Macchia, R.J.	State University of New York-Health Science Center at Brooklyn

7796	International Journal of Radiation Oncology, Biology, Physics	1988	14	701-709	The role of radiation therapy in stages A2 and B adenocarcinoma of the prostate	Zagars, G.K., von Eschenbach, A.C., Johnson, D.E., and Oswald, M.J.	The University of Texas M.D. Anderson Hospital (multi-site)
7832	Urology	1988	31	191-197	Radical prostatectomy. Patterns of local failure and survival in 67 patients	Schellhammer, P.F.	Eastern Virginia Medical School
8161	International Urology & Nephrology	1989	21	325-332	Experience in the treatment of localized carcinoma of the prostate by definitive external irradiation	Kuten, A., Nietzky, S., Tatcher, M., Cohen, Y., and Robinson, E.	Technion-Israel Institute of Technology (multi-site)
8182	Journal of Urology	1989	142	1262-1265	Pattern of failure after radical retropubic prostatectomy for clinically and pathologically localized adenocarcinoma of the prostate: influence of tumor deoxyribonucleic acid ploidy	Blute, M.L., Nativ, O., Zincke, H., Farrow, G.M., Thorneau, T., and Lieber, M.M.	Mayo Clinic
8257	Radiotherapy and Oncology	1989	16	1-21	Factors influencing outcome of definitive radiotherapy for localized carcinoma of the prostate	Perez, C.-A., Garcia, D., Simpson, J.R., Zivnuska, F., and Lockett, M.A.	Mallinckrodt Institute of Radiology (multi-site)
8280	Urology	1989	33	17-20	Patient selection for radical prostatectomy	Smith, J.A., Jr.	University of Utah Center for Health Sciences Christie Hospital (multi-site)
8318	British Journal of Urology	1989	63	191-195	Retrospective study of radiotherapy in early carcinoma of the prostate	Read, G., Pointon, R.C.S.	
8331	Cancer	1989	63	2468-2474	External beam radiotherapy for carcinoma of the prostate	Sagerman, R.H., Chun, H.C., King, G.A., Chung, C.T., and Dalal, P.S.	Mallinckrodt Institute of Radiology (multi-site)
8332	Cancer	1989	63	2421-2425	Prognosis in patients with local recurrence after definitive irradiation for prostatic carcinoma	Kuban, D.A., El-Mahdi, A.M., and Schellhammer, P.F.	Eastern Virginia Medical School
8333	Cancer	1989	63	2415-2420	I-125 interstitial implantation for prostate cancer. What have we learned 10 years later?	Kuban, D.A., El-Mahdi, A.M., and Schellhammer, P.F.	Eastern Virginia Medical School
8411	Journal of Urology	1989	141	82-84	Cause-specific actuarial survival analysis: a useful method for reporting survival data in men with clinically localized carcinoma of the prostate	Lepor, H., Kimball, A.W., and Walsh, P.C.	The Johns Hopkins University and Hospital
8428	Journal of Urology	1989	141	564-566	Total prostatectomy for clinically localized prostatic cancer: long-term results	Gibbons, R.P., Correa, R.J., Jr., Brannen, G.E., and Weissman, R.M.	The Virginia Mason Clinic
8493	Urology	1989	33	361-366	Prognostic significance of DNA ploidy in carcinoma of prostate	Dejter, S.W., Jr., Cunningham, R.E., Noguchi, P.D., Jones, R.V., Moul, J.W., McLeod, D.G., and Lynch, J.H.	Georgetown University Hospital (multi-site)
8615	International Journal of Radiation Oncology, Biology, Physics	1990	19	1383-1388	The role of serum prostatic acid phosphatase in the management of adenocarcinoma of the prostate with radiotherapy	Carlton, J.C., Zagars, G.K., and Oswald, M.J.	The University of Texas M.D. Anderson Cancer Center
8616	International Journal of Radiation Oncology, Biology, Physics	1990	19	1377-1382	The effect of overall treatment time on local control in patients with adenocarcinoma of the prostate treated with radiation therapy	Amdur, R.J., Parsons, J.T., Fitzgerald, L.T., and Million, R.R.	University of Florida College of Medicine
8717	Urology	1990	36	493-498	Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up	Graversen, P.H., Nielsen, K.T., Gasser, T.C., Corle, D.K., and Madsen, P.O.	Veterans Administration Hospital (multi-site)
8798	International Journal of Radiation Oncology, Biology, Physics	1990	19	561-568	Carcinoma of the prostate stage B and C: lack of influence of duration of radiotherapy on tumor control and treatment morbidity	Lai, P.P., Perez, C.A., Shapiro, S.J., and Lockett, M.A.	Mallinckrodt Institute of Radiology (multi-site)
8823	Journal of Urology	1990	144	1180-1184	Radical prostatectomy for clinical stage T1-2N0M0 prostatic adenocarcinoma: long-term results	Paulson, D.F., Moul, J.W., and Walther, P.J.	Duke University Medical Center
8827	Journal of Urology	1990	144	1420-1424	Role of nerve-sparing radical prostatectomy for clinical stage B2 prostate cancer	Bigg, S.W., Kavoussi, L.R., and Catalona, W.J.	Washington University School of Medicine University of Florida College of Medicine
8902	Radiotherapy and Oncology	1990	18	235-246	Adenocarcinoma of the prostate treated with external-beam radiation therapy: 5-year minimum follow-up	Amdur, R.J., Parsons, J.T., Fitzgerald, L.T., and Million, R.R.	
8925	Urologic Clinics of North America	1990	17	779-785	Selection of patients with stage B prostate cancer for radical prostatectomy	Middleton, R.G., Larsen, R.H.	University of Utah Center for the Health Sciences

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8990	British Journal of Urology	1990	65	611-614	The natural course of low grade, non-metastatic prostatic carcinoma	Adolfsson, J., Ronstrom, L., Carstensen, J., Lowhagen, T., and Hedlund, P.O.	Karolinska Hospital (multi-site)
9175	Archives of Surgery	1990	125	327-331	Stage B prostate adenocarcinoma. Flow cytometric nuclear DNA ploidy analysis	Montgomery, B.T., Nativ, O., Blute, M.L., Farrow, G.M., Myers, R.P., Zincke, H., Therneau, T.M., and Lieber, M.M.	Mayo Clinic
9194	International Journal of Radiation Oncology, Biology, Physics	1990	18	315-320	Bowel complications after radiotherapy for carcinoma of the prostate: the volume effect	Mameghani, H., Fisher, R., Mameghani, J., Watt, W.H., and Tynan, A.	Institute of Radiotherapy (multi-site)
9219	Urology	1990	35	223-227	Intraoperative and early complications of staging pelvic lymph node dissection in prostatic adenocarcinoma	Donohue, R.E., Mani, J.H., Whitesel, J.A., Augspurger, R.R., Williams, G., and Fauver, H.E.	University of Colorado Health Sciences Center (multi-site)
9265	Australian & New Zealand Journal of Surgery	1991	61	658-662	Radiation therapy for the management of localized prostate carcinoma	Burmeister, B.H., Probert, J.C.	Auckland Hospital
9351	Cancer	1991	67	1091-1096	Expectant management of localized prostatic cancer	Whitmore, W.F., Jr., Warner, J.A., and Thompson, I.M., Jr.	Memorial Sloan-Kettering Cancer Center
9407	Journal of Urology	1991	145	512-514	Impact of anatomical radical prostatectomy on urinary continence	Steiner, M.S., Morton, R.A., and Walsh, P.C.	The Johns Hopkins University and Hospital
9572	International Journal of Radiation Oncology, Biology, Physics	1985	11	2073-2080	Improving the therapeutic ratio of external beam irradiation for carcinoma of the prostate	Forman, J.D., Zinreich, E., Lee, D.J., Wharam, M.D., Baumgardner, R.A., and Order, S.E.	The Johns Hopkins University and Hospital
9580	Journal of Urology	1985	133	49-52	Operable prostatic carcinoma: correlations among clinical stage, pathological stage, Gleason histological score and early disease-free survival	Fowler, J.E., Jr., Mills, S.E.	University of Virginia School of Medicine
9717	Urology	1983	21	451-457	Pelvic complications after definitive treatment of prostate cancer by interstitial or external beam radiation	Schellhammer, P.F., El-Mahdi, A.M.	Eastern Virginia Medical School
9733	International Journal of Radiation Oncology, Biology, Physics	1984	10	541-548	Triple course external beam radiotherapy for carcinoma of the prostate	El-Mahdi, A.M., Turalba, C.I.C., Schellhammer, P.F., and Peoples, W.J.	Eastern Virginia Medical School/Medical Center Hospitals
9737	Journal of the National Medical Association	1984	76	61-66	External radiation therapy of localized prostatic cancer	Reddy, E.K., Giri, S., and Mansfield, C.M.	University of Kansas Medical Center (multi-site)
9879	International Journal of Radiation Oncology, Biology, Physics	1991	21	537-547	The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation	Fuks, Z., Leibel, S.A., Wallner, K.E., Begg, C.B., Fair, W.R., Anderson, L.L., Hilaris, B.S., and Whitmore, W.F.	Memorial Sloan-Kettering Cancer Center
9895	Journal of Urology	1991	145	1197-1200	Cancer control following anatomical radical prostatectomy: an interim report	Morton, R.A., Steiner, M.S., and Walsh, P.C.	The Johns Hopkins University and Hospital
9899	Journal of Urology	1991	146	798-802	Complications following external beam radiation therapy for prostate cancer: an analysis of patients treated with and without staging pelvic lymphadenectomy	Greskovich, F.J., Zagars, G.K., Sherman, N.E., and Johnson, D.E.	University of Texas M.D. Anderson Cancer Center
10039	British Journal of Urology	1992	69	183-187	Deferred treatment in clinically localised prostatic carcinoma	Adolfsson, J., Carstensen, J., and Lowhagen, T.	Karolinska Hospital (multi-site)
10076	International Journal of Radiation Oncology, Biology, Physics	1992	22	565-568	The efficacy of pharmacokinetic monitoring and dose modification of etanidazole on the incidence of neurotoxicity: results from a phase II trial of etanidazole and radiation therapy in locally advanced prostate cancer	Coleman, C.N., Buswell, L., Noll, L., Riese, N., and Rose, M.A.	Joint Center for Radiation Therapy (multi-site)
10104	Journal of Urology	1992	147	905-907	The management of rectal injury during radical retropubic prostatectomy	Borland, R.N., Walsh, P.C.	The Johns Hopkins University and Hospital
10107	Journal of Urology	1992	147	917-921	The importance of local control in the treatment of prostatic cancer	Kaplan, I.D., Prestidge, B.R., Bagshaw, M.A., and Cox, R.S.	Stanford University School of Medicine (multi-site)
10108	Journal of Urology	1992	147	888-890	Radical prostatectomy: the pros and cons of the perineal versus retropubic approach	Frazier, H.A., Robertson, J.E., and Paulson, D.F.	Duke University Medical Center

10109	Journal of Urology	1992	147	883-887	Radical retropubic prostatectomy: morbidity and quality of life. Experience with 620 consecutive cases	Leandri, P., Rossignol, G., Gautier, J.R., and Ramon, J.	Saint-Jean Languedoc-Cerou
10183	Urology	1992	39	44-47	Radical prostatectomy: OSU and affiliated hospitals' experience 1985-1989	Drago, J.R., Badalament, R.A., York, J.P., Simon, J., Riemenschneider, H., Nesbitt, J.A., and Perez, J.	Ohio State University (multi-site)
10184	Journal of the American Medical Association	1992	267	2191-2196	High 10-year survival rate in patients with early, untreated prostatic cancer	Johansson, J.E., Adami, H.O., Andersson, S.O., Bergstrom, R., Holmberg, L., Krusemo, U.B.	Orebro Medical Center Hospital (multi-site)
10251	European Urology	1993	24	1-6	Outcome of patients with untreated cancer of the prostate	Stenzl, A., Studer, U.E.	University of Berne Medical Center
10303	Scandinavian Journal of Urology & Nephrology	1993	27	219-224	Radical retropubic prostatectomy for localised prostatic carcinoma: a clinical and pathological study of 201 cases	Pedersen, K.V., Herder, A.	University Hospital
10310	Cancer	1993	72	1709-1725	Prognostic factors in prostate cancer. Analysis of 874 patients treated with radiation therapy	Zagars, G.K., von-Eschenbach, A.C., and Ayala, A.G.	The University of Texas M.D. Anderson Cancer Center
10322	Journal of Urology	1993	150	905-907	Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy	Catalona, W.J., Basler, J.W.	Washington University School of Medicine
10340	Cancer	1993	72	1291-1299	Transrectal ultrasound-guided percutaneous radical cryosurgical ablation of the prostate	Onik, G.M., Cohen, J.K., Reyes, G.D., Rubinsky, B., Chang, Z., and Baust, J.	Allegheny General Hospital (multi-site)
10369	International Journal of Radiation Oncology, Biology, Physics	1993	26	581-591	Technical and tumor-related factors affecting outcome of definitive irradiation for localized carcinoma of the prostate	Perez, C.A., Lee, H.K., Georgiou, A., Logsdon, M.D., Lai, P.P., and Lockett, M.A.	Mallinckrodt Institute of Radiology (multi-site)
10373	Urology	1993	42	13-20	Prostate-specific antigen to determine progression-free survival after radiation therapy for localized carcinoma of prostate	Schellhammer, P.F., El-Mahdi, A.M., Wright, G.L., Jr., Kolm, P., and Ragle, R.	The Center for Urologic Oncology of Eastern Virginia Medical School (multi-site)
10517	Urology	1993	41	122-126	Iodine-125 seed implants for prostatic carcinoma. Five- and ten-year follow-up	Weyrich, T.P., Kandzari, S.J., and Jain, P.R.	West Virginia University Medical Center
10550	International Journal of Radiation Oncology, Biology, Physics	1993	26	203-210	Carcinoma of the prostate: results of radical radiotherapy (1970-1985)	Duncan, W., Warde, P., Catton, C.N., Munro, A.J., Lakier, R., Gadalla, T., and Gospodarowicz, M.K.	Princess Margaret Hospital
10672	Recent Results in Cancer Research	1993	126	43-49	Radical prostatectomy for carcinoma of the prostate: long-term results	Frohmler, H.G.W., Wirth, M.P.	Urologische Klinik und Poliklinik (multi-site)
10693	International Journal of Radiation Oncology, Biology, Physics	1993	25	661-667	Short-term morbidity from CT-planned transperineal I-125 prostate implants	Arterbery, V.E., Wallner, K., Roy, J., and Fuks, Z.	Memorial Sloan-Kettering Cancer Center
10748	Journal of the National Medical Association	1993	85	109-112	Prostate cancer: results of external irradiation	Reddy, E.K., Krishnan, L., Giri, S., Evans, R.G., Mebust, W.K., and Weigel, J.W.	University of Kansas Medical Center
10790	Journal of Urology	1993	149	519-522	Prostate specific antigen after external beam radiotherapy for prostatic cancer: followup	Kaplan, I.D., Cox, R.S., and Bagshaw, M.A.	Stanford University Medical Center
11062	Scandinavian Journal of Urology & Nephrology	1992	26	231-234	Radical retropubic prostatectomy: our experience with the first 54 patients	Servoli, E., Halvorsen, O.J., Haukaas, S., and Hoisaeter, P.A.	Haukeland University Hospital
11104	Henry Ford Hospital Medical Journal	1992	40	108-110	Radical surgery in the treatment of localized carcinoma of the prostate	Telang, D.J., Miles, B.J., Farah, R.N., Littleton, R.H., Kirkemo, A.K., Peabody, J.O., Burks, D.A., Fleming, C., and Cerny, J.C.	Henry Ford Hospital
11108	European Journal of Surgical Oncology	1992	18	456-462	Radical prostatectomy for localized prostate cancer	Van-Poppel, H., Ameye, F., Oyen, R., Van-de-Voorde, W., and Baert, L.	University Hospitals of the Katholieke Universiteit
11201	International Journal of Radiation Oncology, Biology, Physics	1992	24	485-488	Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques: a reduction in acute morbidity	Sofften, E.M., Hanks, G.E., Hunt, M.A., and Epstein, B.E.	Fox Chase Cancer Center
11400	Urology	1992	40	18-26	Radiation therapy in prostate cancer: whole pelvis with prostate boost or small field to prostate?	Ploysongsang, S.S., Aron, B.S., and Shehata, W.M.	The Christ Hospital (multi-site)

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11402	Radiology	1992	184	333-339	Results of radical perineal prostatectomy with adjuvant brachytherapy	Doornbos, J.F., Hussey, D.H., Robinson, R.A., Wen, B.C., and Vigliotti, A.P.	University of Iowa College of Medicine (multi-site)
11511	International Journal of Radiation Oncology, Biology, Physics	1992	23	293-298	Comparison of pathologic and clinical evaluation of lymph nodes in prostate cancer: implications of RTOG data for patient management and trial design and stratification	Hanks, G.E., Krall, J.M., Pilepich, M.V., Asbell, S.O., Perez, C.A., Rubin, P., Sause, W.T., and Doggett, R.L.S.	Fox Chase Cancer Center (multi-site)
11645	International Journal of Radiation Oncology, Biology, Physics	1992	22	935-939	Transperineal percutaneous iridium-192 interstitial template implant of the prostate: results and complications in 321 patients	Khan, K., Thompson, W., Bush, S., and Stidley, C.	University of New Mexico Cancer Center (multi-site)
11710	Scandinavian Journal of Urology and Nephrology - Supplementum	1991	138	109-115	Long term results of ultrasonically guided implantation of 125-I seeds combined with external irradiation in localized prostatic cancer	Iversen, P., Rasmussen, F., and Holm, H.H.	Herlev Hospital (multi-site)
11850	Scandinavian Journal of Urology and Nephrology - Supplementum	1991	137	113-118	Transperineal ultrasound-guided implantation of the prostate: morbidity and complications	Blasko, J.C., Ragde, H., and Grimm, P.D.	Northwest Tumor Institute
11875	Journal of Urology	1991	146	1317-1319	Failure of open radioactive 125iodine implantation to control localized prostate cancer: a study of 41 patients	Gottesman, J.E., Tesh, D.G., and Weissman, W.D.	The Tumor Institute of the Swedish Hospital Medical Center
11936	International Journal of Radiation Oncology, Biology, Physics	1991	21	955-960	External beam irradiation versus 125 iodine implant in the definitive treatment of prostate carcinoma	Koprowski, C.D., Berkenstock, K.G., Borofski, A.M., Ziegler, J.C., Lightfoot, D.A., and Brady, L.W.	Cooper Hospital/University Medical Center (multi-site)
11939	International Journal of Radiation Oncology, Biology, Physics	1991	21	935-939	Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706	Lawton, C.A., Won, M., Pilepich, M.V., Asbell, S.O., Shipley, W.U., Hanks, G.E., Cox, J.D., Perez, C.A., Sause, W.T., Doggett, S.R., and Rubin, P.	Medical College of Wisconsin (multi-site)
11941	International Journal of Radiation Oncology, Biology, Physics	1991	21	1099-1103	Outcome for lymph node dissection negative T-1b, T-2 (A-2,B) prostate cancer treated with external beam radiation therapy in RTOG 7706	Hanks, G.E., Asbell, S., Krall, J.M., Perez, C.A., Doggett, S., Rubin, P., Sause, W., and Pilepich, M.V.	University of Pennsylvania/Fox Chase Cancer Center (multi-site)
11946	European Urology	1991	19	279-283	Radical prostatectomy for carcinoma of the prostate: long-term follow-up of 115 patients	Frohnmuller, H., Theiss, M., and Wirth, M.P.	University of Wurzburg Medical School
11972	Journal of Urology	1991	146	1040-1045	The risk of dying of prostate cancer in patients with clinically localized disease	Lerner, S.P., Seale-Hawkins, C., Carlton, C.E., Jr., and Scardino, P.T.	Baylor College of Medicine (multi-site)
12210	European Urology	1990	18	117-119	External-beam radiation for carcinoma of the prostate	Davies, A.H., Davis, H.L., Ramarakha, P., Durrant, K.D., and Fellows, G.J.	Churchill Hospital
12241	South African Medical Journal	1990	78	309-311	Radical irradiation for carcinoma of the prostate	Abbratt, R.P., Craighead, P.S., Reddi, V.B., and Sarembock, L.A.	University of Cape Town and Groote Schuur Hospital (multi-site)
12322	Urology	1990	35	377-380	Radical prostatectomy 1972-1987 single institutional experience: comparison of standard radical prostatectomy and nerve-sparing technique	Drago, J.R., Badalament, R.A., and Nesbitt, J.A.	College of Medicine, Ohio State University
12343	Journal of the National Medical Association	1990	82	181-193	Iodine-125 interstitial irradiation for localized prostate cancer	Kumar, P.P., Good, R.R., and Bartone, F.F.	University of Nebraska College of Medicine
12374	Journal of Urology	1990	143	538-544	Nerve-sparing radical prostatectomy: evaluation of results after 250 patients	Catalona, W.J., Bigg, S.W.	Washington University School of Medicine
12404	British Journal of Urology	1989	64	511-515	Early post-operative morbidity of total prostatectomy	Ritchie, A.W.S., James, K., and deKernion, J.B.	UCLA School of Medicine
12442	Journal of Urology	1989	142	1227-1229	Continence following nerve-sparing radical prostatectomy	O'Donnell, P.D., Finan, B.F.	Veterans Administration Medical Center
12539	Cancer	1989	63	2415-2420	What have we learned 10 years later?	Kuban, D.A., El-Mahdi, A.M., and Schellhammer, P.F.	Eastern Virginia Medical School

