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Prostate Cancer

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Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update

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Table of Contents

Introduction

In December 1995, the American Urological Association (AUA) published the *Report on the Management of Clinically Localized Prostate Cancer*.[1] The document was the culmination of six years of work by 17 clinicians and scientists and required the evaluation of 12,501 scientific publications with the detailed extraction of information from 165 papers that met the rigorous criteria of the panel of experts (Appendix 1). The Panel noted that a lack of evidence precluded specific recommendations for optimal treatment of an individual patient, which patients should be offered all treatment options, and that patient preferences should guide decision making.

Since 1995, approximately 2,600,000 men[2] in the United States have been diagnosed with prostate cancer, and nearly 375,000 men[3, 4] have lost their lives to this disease. In addition, the National Cancer Institute[4] has spent $2.1 billion on prostate cancer research and as of November 2005, approximately 28,111 scientific papers concerning prostate cancer have been published in peer-reviewed medical journals (OVID Search, December 31, 1995 to October 23, 2005; key word: prostatic neoplasms). At the same time, mortality rates from prostate cancer have been declining: 34,475 men died in 1995 compared with an estimated 30,350 in 2005.[4] Several pivotal randomized clinical trials related to prostate cancer treatment have been completed, including a chemoprevention study,[5] along with studies demonstrating prolongation of life in men with hormone-refractory metastatic disease[6, 7] and improved outcomes in men with nonmetastatic disease.[8-35] With the use of new and combined treatments, the frequency and variety of complications have differed from those previously reported. Advances have been made in prostate cancer imaging, biopsy methodology, in understanding causative factors and disease, in treatment-related quality of life and in predicting the behavior of individual tumors using risk strata.

Despite these advances, no consensus has emerged regarding the optimal treatment for the most common patient with prostate cancer: the man with clinically localized stage T1 to T2 disease with no regional lymph node or distant metastasis (T1 to T2N0-NxM0). Of the 234,460 men in the United States diagnosed with prostate cancer annually, 91% have localized disease.[36] For these men and their families, the bewildering array of information from scientific and lay sources offers no clear-cut recommendations.

Understanding this challenge for patients with newly diagnosed localized prostate cancer and the explosion in research and publications, the AUA re-impaneled the Prostate Cancer Clinical Guideline Panel (Appendix 2) for the purpose of reexamining and updating its analysis of treatment options. We herein report the results of a 5 ½-year effort to update the 1995 Guideline. The online version of this Guideline, which can be accessed at http://www.auanet.org/guidelines/, contains appendices that include additional documents used in the conduct of the analysis and the graphics detailing the Panel's findings.

Context

A contemporary man with localized prostate cancer is substantially different from the man with prostate cancer of 20 years ago. With the advent of prostate-specific antigen (PSA) screening beginning in the late 1980s and the dramatic increase in public awareness of the disease, the average new prostate cancer patient has generally undergone multiple prior PSA tests and may even have experienced one or more prior negative prostate biopsies. When the cancer is detected, it is in a substantially earlier stage, often nonpalpable clinical stage T1c with, perhaps, one to several positive biopsy cores. The typical patient usually is very familiar with his PSA history and has a history of multiple visits to either his primary care provider or urologist. The most common patient will likely have Gleason score 6 or 7 disease, reflecting the most common current grading category and the fact that contemporary uropathologists assign this score more often than in the past when this group of tumors was frequently diagnosed one or two scores lower.[37] The average patient of today also will more commonly have serum PSA levels in the 4 to 10 ng/mL range, and often in the 2.5 to 4.0 ng/mL range. In many cases, the patient's PSA history will include sufficient data to allow a prediagnosis PSA velocity or doubling time to be calculated. Generally, the treating physicians will personalize the patient's risk based on serum PSA level, highest/worst Gleason score, clinical stage, and burden of disease (either number or percent of biopsy cores with cancer).

Following diagnosis, today's patient will oftentimes be better informed and consequently request a second opinion by other physicians including other urologists or such specialists as radiation and medical oncologists. Many centers offer multidisciplinary clinics where the patient can consult with urologists, and with radiation and medical oncologists at one location. After considering the options and gathering several opinions, a patient and his family will choose

among active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy with treatment generally commencing two to three months after diagnosis. Aside from this complex decision, where the evidence basis for action has been suboptimal, patients now also are faced with subtle but important technical decisions such as choosing the type of surgery (e.g., open versus laparoscopic/robotic prostatectomy), the type of radiotherapy (e.g., conformal versus intensity modulated), the type of brachytherapy isotope, or whether a combination (e.g., brachytherapy and external beam radiotherapy) of therapies should be used. Minimal data currently are available for the following interventions: high-intensity focused ultrasound, cryotherapy, high-dose rate interstitial prostate brachytherapy, and primary hormonal therapy. Conclusions regarding outcomes of these treatments cannot be made.

It is in this very changed environment that we present the 2007 AUA Prostate Cancer Clinical Guideline Panel report.

Definitions and Terminology

The reader desiring a greater degree of information regarding the terminology used herein is directed to Appendix 3, which provides a glossary of terms important to a full understanding of the management options of localized prostate cancer.

Screening Tests

Clinically localized prostate cancer generally causes no symptoms. Slowing of the urinary stream, arising at night to void, and increased urinary frequency are common symptoms associated with aging but often are unrelated to the presence of prostate cancer. It is for this reason that early detection tests have been developed in order to identify prostate cancer while it remains confined to the prostate. The two most commonly used tests are a serum PSA level and a digital rectal examination (DRE).[38, 39]

PSA

PSA is a protein produced by cells within the prostate, and in men PSA can be measured in the blood. While higher blood PSA levels often are noted in men with prostate cancer, PSA elevation is not specific for prostate cancer. At present, a higher PSA test value is the most common reason why prostate cancer is detected in the United States.

DRE

A DRE is an examination by a physician using a gloved finger placed into the rectum to feel the surface of the prostate. The region of the prostate adjacent to the rectal wall is where tumors commonly develop; hard regions or asymmetry may indicate the presence of prostate cancer.

Prostate Biopsy

Although a higher PSA value or abnormal DRE may raise the suspicion of prostate cancer, detection requires confirmation with a prostate biopsy. At the time of biopsy, several small cores of tissue are removed from the prostate and are then examined by a pathologist to determine if cancer is present.

Tumor Characteristics

Tumor Grade

Tumor aggressiveness can be determined by the pathologist's examination of the microscopic pattern of the cancer cells. The most commonly used tumor grading system is the Gleason grading.[40, 41] This system assigns a grade for each prostate cancer from 1 (least aggressive) to 5 (most aggressive) based on the degree of architectural differentiation of the tumor. Tumors often show multiple different grade "patterns" within the prostate or even a single core biopsy. To account for this, the Gleason score is obtained by assigning a primary grade to the most predominant grade present and a secondary grade to the second most predominant grade. An exception to this is in the case where the highest (most aggressive) pattern present in a biopsy is not either the most predominant or second most predominant pattern; in this situation, the Gleason score is obtained by combining the most predominant pattern grade with the highest grade. The Gleason score is then displayed as, for example, 3+4 where 3 would be the most common pattern of tumor and 4 the second most common pattern (or highest pattern) of tumor seen in the core. Given that the individual Gleason value can range from 1 to 5, the added values (Gleason scores or "sums") can range from 1+1 to 5+5 or from 2 to 10. Generally, Gleason scores of 2 to 4 are uncommon; as a result, the majority of detected tumors range from 5 to 10.

Occasionally, if a small component of a tumor on prostatectomy is of a pattern that is higher than the two most predominant patterns, then the minor component is added as a tertiary grade to the

report (e.g., 60% pattern 3, 35% pattern 4, and 5% pattern 5 should be reported as 3+4 with tertiary grade 5).

High-Grade Cancer

With each increase in tumor score (e.g., from Gleason 5 to 6), there is an increase in tumor aggressiveness. High-grade cancer commonly refers to the most aggressive of tumors, generally Gleason scores of 8 to 10 (the most aggressive group), but also can include Gleason 7 tumors.

Tumor Stage

Tumor stage refers to the degree to which the tumor has involved the prostate gland or has spread. As with other tumors, prostate cancers that involve only a small portion of the prostate are more successfully treated than those that have extended throughout the gland. Similarly, tumors that remain confined to the prostate are also more successfully treated than those that have extended beyond the confines of the gland. Finally, tumors that have spread to sites remote to the prostate (e.g., metastatic disease in lymph nodes or bone) have the poorest outcomes. The American Joint Committee on Cancer (AJCC) has established a system of tumor staging (Appendix 4).[42]

For the purposes of this guideline, the Panel chose to only examine treatment options for the most common group of patients diagnosed today: the patient whose tumor is confined to the prostate. Using the AJCC nomenclature, these tumors are clinical stage T1 (normal DRE) or T2 (abnormal DRE but no evidence of disease beyond the confines of the prostate), N0 to Nx (no evidence of spread to regional lymph nodes or regional lymph nodes were not assessed), and M0 (no evidence of metastatic spread).

Initial Evaluation and Discussion of Treatment Options with the Patient

Standard: An assessment of the patient's life expectancy, overall health status, and tumor characteristics should be undertaken before any treatment decisions can be made.

[Based on review of the data and Panel consensus.]

Life Expectancy and Health Status

Life expectancy, rather than patient age, is a major factor to consider in treatment selection. Thus, the Panel did not specify a chronological age cutoff point for the patient to whom this Guideline applies. When a man's life expectancy is relatively long, localized prostate cancer can be a cause of morbidity and mortality. At an advanced patient age or when life expectancy is relatively short, competing hazards for mortality reduce the chance that a man will experience disease progression or die from prostate cancer (Appendix 5).[10, 43]

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 overall health status prior to deciding on an intervention: (1) overall health status influences life expectancy, and (2) overall health status may affect patient response to adverse events resulting from particular interventions. In the management of prostate cancer, urinary, sexual, and bowel functions are important to consider when choosing a therapy.

Tumor Characteristics

Tumor characteristics, including PSA level and such changes as velocity and doubling time,[44, 45] Gleason score, and tumor stage are predictive of cancer outcomes. Using PSA, Gleason score, and tumor stage, risk strata have been defined that are significantly associated with PSA recurrence and cancer-specific mortality.[46] Therefore, these risk strata have been used as the basis for the current data analysis and treatment option specifications. Because of the differences in outcome by risk group for a given treatment, the Panel opted to develop treatment recommendations based on these risk strata. The size (volume) of the prostate gland may impact the treatment choice in some situations and, thus, requires consideration prior to instituting therapy.

Risk Strata

Risk stratification schemes have been developed based on the PSA level, biopsy Gleason score, and 2002 AJCC clinical T-category that are associated with the risk of PSA failure and prostate cancer-specific mortality following radical prostatectomy, external beam radiotherapy, or

interstitial prostate brachytherapy.[47] While variations on this system exist, for the purpose of this report the following scheme was used:

- **Low risk:** PSA ≤10 ng/mL and a Gleason score of 6 or less and clinical stage T1c or T2a
- **Intermediate risk:** PSA >10 to 20 ng/mL or a Gleason score of 7 or clinical stage T2b but not qualifying for high risk
- **High risk:** PSA >20 ng/mL or a Gleason score of 8 to 10 or clinical stage T2c

Treatment Options

Watchful Waiting and Active Surveillance

The great disparity between cancer incidence and mortality indicates that many men may not benefit from definitive treatment of localized prostate cancer. Autopsy studies have shown that 60% to 70% of older men have some areas of cancer within the prostate.[48, 49] This can be compared with the 15% to 20% of men diagnosed with prostate cancer during their lifetime and with the 3% lifetime risk of death from prostate cancer.[36] Men who choose not to undergo immediate therapy may opt for continued follow-up under a program of watchful waiting or active surveillance.

Watchful waiting, as studied in randomized controlled trials (RCTs),[10, 19, 50] is based on the premise that some patients will not benefit from definitive treatment of the primary prostate cancer. The decision is made at the outset to forgo definitive treatment and to instead provide palliative treatment for local or metastatic progression if and when it occurs. Options for local palliation could include transurethral resection of the prostate or other procedures for the management of urinary tract obstruction, and hormonal therapy or radiotherapy for palliation of metastatic lesions.

In contrast to watchful waiting, a program of active surveillance is based on the premise that some, but not all, patients may benefit from treatment of their primary prostate cancer. A program of active surveillance has two goals: (1) to provide definitive treatment for men with localized cancers that are likely to progress and (2) to reduce the risk of treatment-related complications for men with cancers that are not likely to progress.

An ideal regimen for active surveillance has not been defined but could include periodic physical examination and PSA testing or periodic repeat prostate biopsies to assess for sampling error of the initial biopsy as well as for subsequent progression of tumor grade and/or volume. Active surveillance currently is under study in non-randomized trials in Canada, the United Kingdom, and the United States.[51-53] A multicenter randomized trial of active surveillance versus immediate intervention was to have opened in the United States in 2006.

Which patients are suitable candidates for active surveillance? Patients with lower risk tumors (low Gleason score, PSA level, and clinical stage) could be candidates for this treatment strategy. Several studies have shown that patients with lower grade, localized prostate cancer have a low risk for clinical progression within the first 10 to 15 years after the diagnosis.[37, 51, 54-56] Thus, this treatment strategy may be best suited for men with a shorter life expectancy. Generally, patients with high-grade tumors have a relatively poor prognosis and are not suitable for active surveillance but, as will be noted in this report, often have poor outcomes with any therapy.

Under special conditions, some patients with a longer life expectancy may opt for active surveillance as their primary management. This may include patients with very small areas of cancer in their biopsy or patients who, at the time of diagnosis, are reluctant to accept the side effects of potentially curative therapies. If the tumor shows evidence of progression (e.g., increased grade, volume, or stage) while the patient still has a reasonable life expectancy, curative treatments (e.g., surgery or radiation) can be initiated.[53] This can be a difficult clinical decision since signs of progression must be identified before the cancer evolves to a stage (or grade) where therapy is no longer curative. Currently, providing evidence-based recommendations for when to intervene in patients with a long life expectancy are not possible since markers of disease progression are poorly validated. Most reports describe a clinical strategy that includes regular PSA level measurement and DRE with a periodic repeat prostate biopsy along with an option of more active therapy if biochemical (increasing PSA) or histopathologic (increased tumor grade or volume) progression occurs.[57, 58] In this Guideline document, the Panel used the term “active surveillance” to refer to a monitoring program without initial treatment for the patient with localized cancer. As noted previously, this monitoring program and its goals may be different based on patient and tumor characteristics and thus is

distinct from watchful waiting in which a lesser degree of monitoring may be used and in which treatment is generally instituted if metastases or symptoms develop.

Interstitial Prostate Brachytherapy

Permanent interstitial prostate brachytherapy as a treatment has been performed since the 1960s.[59] Initially, patients were taken to the operating room for an open lymphadenectomy at which time they underwent placement of iodine 125 seeds. After much experience, the limitations of this technique were identified by researchers at the Memorial Sloan-Kettering Cancer Center[60] and, in the late 1980s, a transperineal approach was developed as a definitive treatment for localized prostate cancer.[61]

Patients with clinically localized prostate cancer are considered candidates for interstitial prostate brachytherapy, but practitioners differ with respect to which risk groups are offered this approach. Some practitioners will use this treatment option for low-risk disease only while others will treat both low and intermediate-risk patients.[62] Prior to initiating therapy, a transrectal ultrasound-based volume study is performed to assess prostate volume and to determine the number of needles and corresponding radioactive seeds, the isotope, and the isotope strength necessary for the procedure. The radioactive needles are implanted via a transperineal approach under guidance of transrectal ultrasound or magnetic resonance imaging. Common regimens employ 120 Gy (palladium) or 140 Gy (^{125}I) with postoperative dosimetry performed for each patient. Treatment alternatives include different isotope types in combination with hormonal therapy and/or external beam radiotherapy.[62, 63] One of the most important factors in predicting the effectiveness of an implant is implant quality. An excellent implant is defined as one in which 90% or more of the prostate gland volume receives at least 100% of the prescription dose.[64]

External Beam Radiotherapy

External beam radiotherapy has been utilized for the treatment of prostate cancer since the 1930s, with the radiation source at that time being low-energy orthovoltage equipment. Since then, technological enhancement has been significant. In the late 1960s, megavoltage irradiation with the first linear accelerators improved the ability to deliver high-radiation doses safely. Through the 1980s, inclusion of computed tomography (CT) scan-based treatment planning

improved the accuracy of treatment delivery, permitting more precise targeting of the prostate, seminal vesicles, and lymph nodes. Simultaneously, this advance facilitated better identification of the adjacent dose, limiting toxicity to structures such as the bladder, rectum, and small bowel. The CT scan-based design coupled with 3-dimensional planning allowed for the early work in radiation dose escalation. As a result of these changes in the 1980s and 1990s, radiation doses were increased safely from the then typical doses of 65 Gy to 75 to 79 Gy. In the 1990s, the advent of intensity modulation radiotherapy (IMRT) and image guidance radiotherapy either with transabdominal ultrasound or the intraprostatic placement of fiducial markers further refined treatment delivery. The resulting dose accuracy and escalation provide proven improvements in local tumor elimination and reduction in late radiation-related complications.

For men considering external beam radiotherapy, the pretreatment evaluation commonly includes, at minimum, a DRE, serum PSA level, and biopsy with Gleason histologic scoring, preferably recording the number of positive cores, the number of cores sampled, and the presence or absence of perineural invasion or tertiary grade. Radiographic staging (CT and bone scan) is recommended for patients with a Gleason score >7 or a PSA level >20 ng/mL prior to treatment. Age and general medical condition, except for exceptional circumstances, do not present an issue for a patient candidate. External beam radiotherapy is indicated as a curative treatment for prostate cancer in men who do not have a history of inflammatory bowel disease such as Crohn's disease, ulcerative colitis, or a history of prior pelvic radiotherapy.

The results of RCTs have guided the use of dose escalation and neoadjuvant or adjuvant hormonal therapy. As a result, hormonal therapy often is prescribed for men with Gleason score 7 cancer or higher or a PSA level in excess of 10 ng/mL in conjunction with standard-dose external beam radiotherapy (~70 Gy). Alternatively, dose escalation can be performed safely to 78 to 79 Gy using a 3-dimensional conformal radiation technique and at least four fields with a margin of no more than 10 mm at the prostatic rectal interface. Such techniques include a CT scan for treatment planning and either a multileaf collimator, IMRT, or proton radiotherapy using a high-energy (6 mV or higher) photon beam. For low-risk patients, the RCTs suggest a benefit of dose escalation. For patients in the intermediate-risk category, RCTs have shown either short-course hormonal therapy (~ 6 months) and standard-dose external beam radiotherapy or dose escalation (78 to 79 Gy) should be considered standard. For patients with locally

advanced or high-grade disease (Gleason score >7), RCTs have shown two to three years of post-radiation adjuvant hormonal therapy to improve survival. Follow-up at six-month intervals for five years and annually thereafter is common for the assessment of the oncological outcome.

Radical Prostatectomy

Radical prostatectomy is a surgical procedure in which the entire prostate gland and attached seminal vesicles plus the ampulla of the vas deferens are removed. Radical prostatectomy may be performed using a retropubic or perineal incision or by using a laparoscopic or robotic-assisted technique. Depending on tumor characteristics and the patient's sexual function, either nerve-sparing (to preserve erectile function) or non-nerve-sparing radical prostatectomy is commonly performed.[65] Pelvic lymphadenectomy can be performed concurrently with radical prostatectomy and is generally reserved for patients with higher risk of nodal involvement.[39]

Generally, healthy patients undergoing radical prostatectomy will be hospitalized for one to three days after surgery. Patients with significant medical illnesses or postsurgical complications may require a longer period of hospitalization. Patients are discharged from the hospital with an indwelling urethral catheter for one to two weeks to temporarily drain the bladder.

Because the entire prostate gland is removed with radical prostatectomy, the major potential benefit of this procedure is a cancer cure in patients in whom the prostate cancer is truly localized. In cases where the prostate cancer is of a high grade, when the tumor has spread outside of the prostate gland, or when the tumor is not completely excised, removing the prostate may not ensure that all the cancer is eliminated, putting the patient at risk for recurrence.

Primary Hormonal Therapy

Primary androgen deprivation therapy (ADT) may be employed with the goal of providing symptomatic control of prostate cancer for patients in whom definitive treatment with surgery or radiation is not possible or acceptable. The concept of ADT should be distinguished from the use of neoadjuvant (before radical prostatectomy or radiation therapy) or adjuvant (after radical prostatectomy or radiation therapy) hormonal therapy. Information from the CaPSURE database, a prospective, longitudinal registry of patients with all stages of prostate cancer from both community practice and academic institutions in the United States, shows that the use of primary hormonal therapy for men with localized prostate cancer has increased significantly among men

with low- and intermediate-risk disease since the 1995 AUA Guideline was published.[66] A recent report derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database found very similar results.[67]

However, published data describing the use of ADT alone as primary therapy for localized prostate cancer are either retrospective and/or do not specifically address the clinical stage T1 to T2 population discussed in this Guideline. Because of the paucity of any data, primary ADT has not been considered a "standard" treatment option for localized disease. Furthermore, there is a growing body of evidence that shows that ADT is associated with an increased risk of cardiovascular disease and diabetes.[68] Use of ADT in men who are at risk for or who are already diagnosed with heart disease and/or diabetes may negatively impact the overall health of such patients. Unfortunately, it is often these patient conditions that prompt the use of ADT rather than surgery or radiation. Therefore, the Panel consensus at the initiation of this Guideline was that primary hormonal therapy would not be included with the standard options of active surveillance/watchful waiting, surgery, or radiation therapy. The Panel recognizes that this opinion may change with time if prospective data become available.

Other Treatments

In addition to the treatment modalities described and evaluated by the Panel, a number of additional treatments as well as combinations of treatments have been used for the management of clinically localized prostate cancer. These treatments include cryotherapy,[69] high-intensity focused ultrasound, high-dose interstitial prostate brachytherapy, and combinations of treatments (e.g., external beam radiotherapy and interstitial prostate brachytherapy). Cryosurgery for the treatment of localized prostate cancer will be the topic of a forthcoming AUA best practice policy. The Panel did not include the other treatment options in the analysis and recommendations due to a combination of factors, including limited published experience and short-term follow-up as well as the similar issues that affected evaluations of other treatment options (see the "Methodology" and the "Summary of Treatment Complications" sections for an explanation of data limitations).

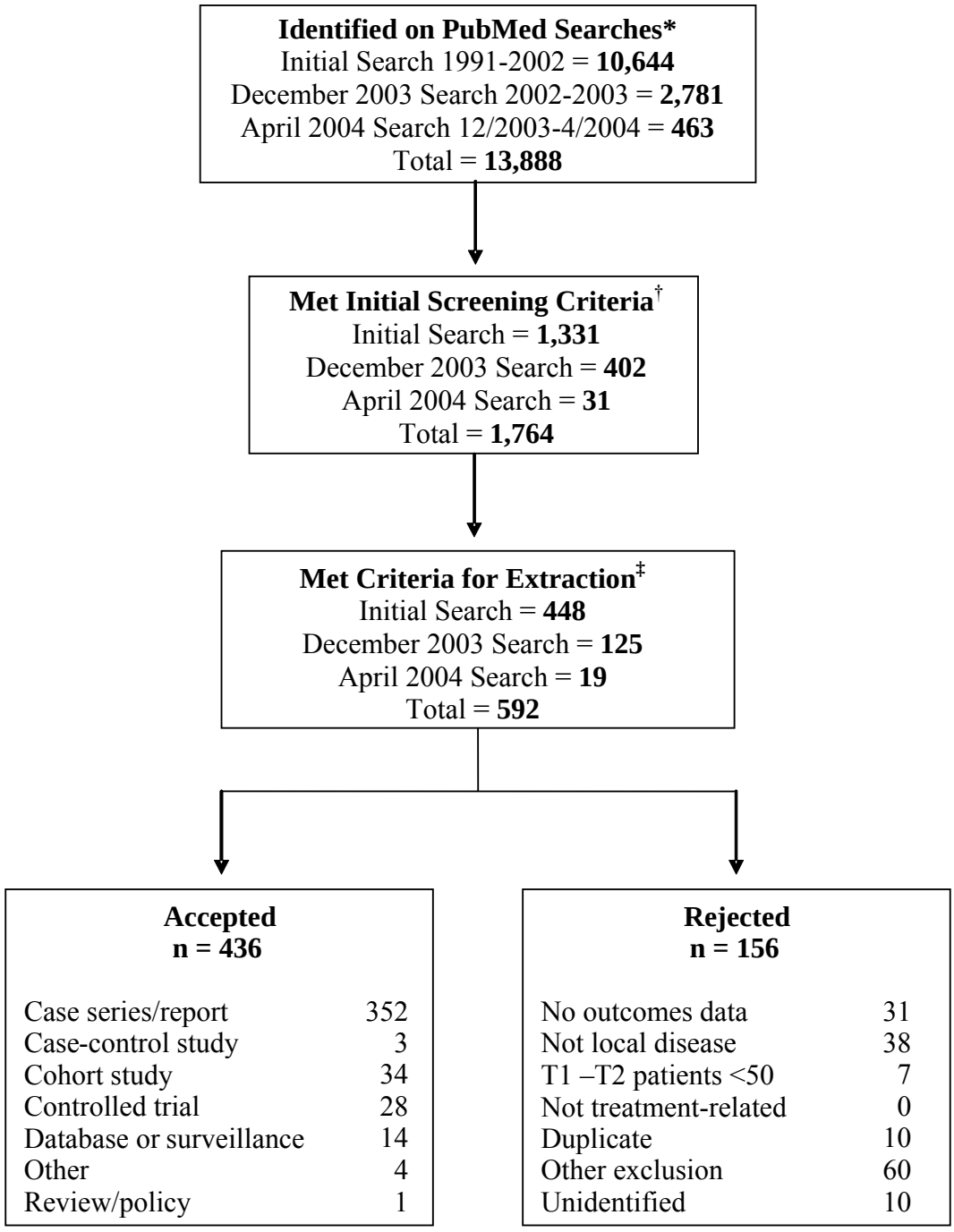
Methodology

Due to the lack of randomized studies with sufficient follow-up to accurately assess treatment impact on patient survival, the 1995 Guideline Panel (Appendix 1) was unable to achieve its primary goal of publishing summary outcomes tables that compared the available treatments for localized prostate cancer. Five years hence, with the subsequent development of measures of biochemical progression, meaningful risk categories, and patient quality-of-life measures as well as the availability of a more careful and extensive collection of outcomes data, a *Guideline Update Panel* was appointed (Appendix 2). It appeared that useful outcomes tables might be generated at this time. To that end, a two-pronged process was devised. First, the Panel began a literature search and data extraction to capture clinical treatment outcomes for patients with clinical stage T1 to T2N0M0 prostate cancer. Second, a project was begun to review the available quality-of-life measures and determine if reliable quality-of-life differences could be assessed for the alternative prostate cancer treatments. This second project ultimately was suspended due to lack of funding as well as to methodologic challenges to such an analysis and will not be reported further in this document.

Search and Data Extraction, Review, and Categorization

A series of four PubMed searches was conducted between May 2001 and April 2004 to capture articles published from 1991 through early 2004. The search terms included the MeSH Major Topics of ***prostate cancer*** and ***prostatic neoplasms*** and were limited to human subjects and to the English language. The resulting 13,888 citations and abstracts were screened for articles reporting outcomes (efficacy or side effects) of prostate cancer treatment in patients with clinical stage T1 or T2 disease (Figure 1; Appendix 6).

Figure 1. Article selection process for the 2007 Prostate Cancer Guideline Update



* Search terms were the MeSH Major Topics of prostate cancer and prostate neoplasms.
† Abstracts were screened for articles reporting outcomes (efficacy and safety) of prostate cancer treatment in patients with clinical stage T1 or T2 disease. Articles were rejected if patients with higher stage disease were included in the study and the outcomes were not stratified by stage.
‡ Articles were rejected if outcomes were not reported or stratified for early-stage patients.

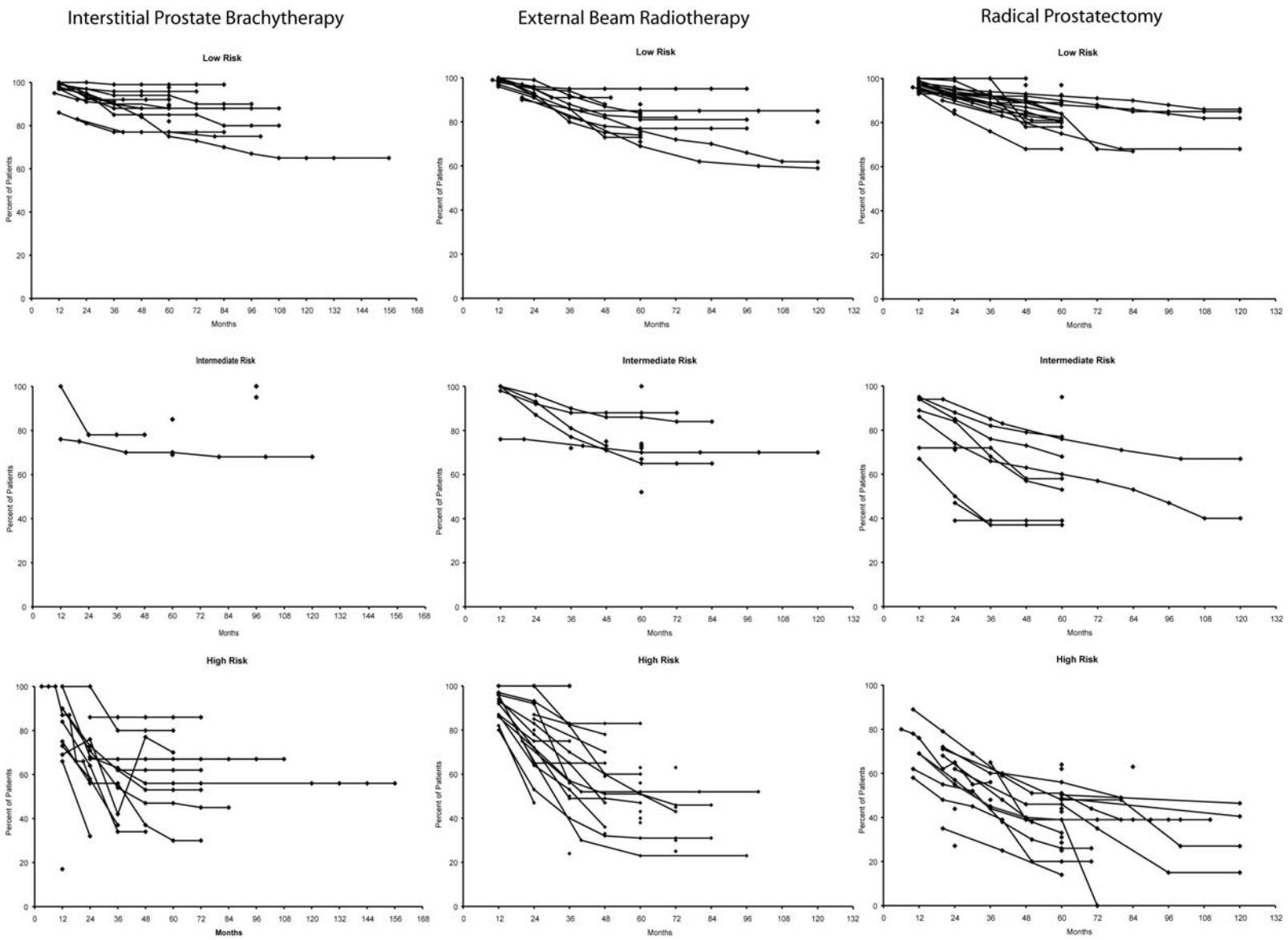
Articles were rejected if patients with higher stage disease were included in the study and the outcomes were not stratified by stage. The 592 articles meeting these inclusion criteria were retrieved for data extraction. An extraction form (Appendix 7) was developed that included patient characteristics, treatments, and outcomes data such as the definition of biochemical progression used in the study, survival, disease-free survival, and progression to invasive disease (Refer to the Glossary in Appendix 3). During the extraction process, articles again were scanned for relevance and were rejected if outcomes were not reported or stratified for clinically localized disease or if outcomes in fewer than 50 patients were reported. Detailed and repeated training of extractors was performed both by the AUA guidelines staff and consultants and by members of the Minneapolis Veterans Administration Center for Chronic Disease Outcomes Research, Cochrane Review Group in Prostate Diseases. After the data extraction from individual articles, several data quality assurance audits were performed. Double extraction of articles was not routinely performed. Weekly meetings with the data-extraction team were held to review the extraction process and to address questions. At that time, a 10% sample of articles was selected, and the extracted data, in the presence of the original article, were reevaluated by two other members, including the senior research associate and Dr. Wilt, the project director. Discrepancies and their reasons (e.g., errors of omission, commission, and interpretation) were resolved by discussion. Values that appeared to be out of bounds on any article (e.g., very low age, impossible histologic scores) were noted. Additional quality checks were performed by members of the AUA guidelines staff, consultants, and Panel members, discrepancies were noted, and feedback was provided to extractors and resolved through additional discussion and review. Upon completion, data from 592 articles were extracted and entered into a Microsoft Access© (Microsoft, Redmond, WA) database that serves as the basis for the results reported herein (Appendix 8).

The Panel met multiple times, both face-to-face and by teleconference, to review the extracted data. Attempts were made to delete reports/studies of insufficient quality (e.g., those that did not stratify patients appropriately or lacked data concerning key outcomes) and to determine which reports/studies overlapped so that duplicate data for the same patients would not be included. In addition to evidence tables, a large number of graphic displays of the extracted data were reviewed by the Panel. Displays of efficacy data were based primarily on PSA recurrence due to

the lack of long-term follow-up. The variation in definition of PSA recurrence among the studies caused considerable variation in the results as illustrated in Figure 2 and Appendix 11.

Summarizing data concerning complications presented two problems. First, methods of categorizing complications were not standardized across studies. For example, some studies reported percentages of patients with "gastrointestinal complications" while others reported separate percentages for "nausea," "vomiting," and "diarrhea." Second, not all studies reported complications by time since treatment initiation, and those that did report such information were inconsistent with regard to the time points selected.

Figure 2. Prostate-specific antigen (PSA) recurrence-free survival in patients with low-, intermediate-, and high-risk prostate cancer treated with interstitial prostate brachytherapy, external beam radiotherapy, or radical prostatectomy.*,†,‡



* Although definitions of PSA recurrence-free survival varied considerably across studies/reports,[70] all definitions were considered acceptable and the data were included in these graphs.
† Data for relevant patient groups from extracted articles are plotted on these graphs. Each article may have contributed to more than one patient group. Single points indicate groups for which data were reported at a single-time point. Points connected by lines indicate groups for which data were reported at multiple time points; analysis methods for deriving point estimates over time were variable but frequently were Kaplan-Meier estimates.
‡ Meta-analysis of combinations of data was not possible. See the discussion of data limitations in the "Methodology" section.

To resolve the first problem, the Panel reviewed all of the reported complications and collapsed those that were similar into summary categories (Appendix 10) that are used in the graphs in this document (Figures 3-5). For articles in which multiple individual complications were collapsed into a single category, the Panel assumed that there was no overlap between individual complications; thus, the percentage of patients in the summary category was the sum of the percentages for the individual complications. For example, if an article reported that 8%, 7%, and 6% of patients experienced nausea, vomiting, and diarrhea, respectively, the percentage of patients with a gastrointestinal complication would be estimated to be 21%. This method of aggregation yields upper-bound estimates of complication rates. The Panel explored the alternative of assuming complete overlap between individual complications (yielding an estimate of 8% for gastrointestinal complications in the previously described example) but concluded that such lower-bound estimates would be less useful.

To resolve the second problem (i.e., the inconsistent reporting of the times at which complications were measured), the Panel decided to disregard timing and to simply use the highest rate reported for a given complication in each study.

With these two decisions -- to use upper-bound estimates of complication rates and to use the highest rate for a complication regardless of measurement time -- the Panel elected to show the highest rates of complications occurring for each patient group in each study. As a result, estimates should consistently err on the side of overstating actual complication rates.

It is worth noting that the most difficult complications to categorize were urinary incontinence and erectile dysfunction for which there were a large number of different measures. Ultimately, the Panel elected to use consolidated measures of severity for each of these outcomes.[71, 72]

Based on the data review and subsequent identification of the data limitations detailed later in this document, meta-analysis was not deemed appropriate and further analysis and development of summary outcomes estimates were not undertaken. Thus, the present Guideline suffered the same problem as the original 1995 version: the data are still insufficient to provide adequate summary outcomes estimates for the target patient(s).

Data Limitations

Specific data limitations identified were:

1. A lack of data supporting the most important outcomes: patient survival, disease-free survival, and progression to metastatic disease.
2. The use of PSA recurrence as a measure of long-term disease control. PSA recurrence has not been shown to correlate well with longer term outcomes and has been inconsistently defined. The articles reviewed by the Panel included approximately 166 different criteria for PSA recurrence that made a comparison of treatment outcomes impossible (Appendix 11). A separate paper detailing this variation in definition of PSA recurrence is in preparation.[70] It should be noted that after the construction of the current Guideline, the American Society for Therapeutic Radiology and Oncology (ASTRO) recommended the adoption of PSA nadir + 2 ng/mL as the definition for PSA failure because it was found to be more closely associated with clinical failure (local and distant) and distant failure than the prior ASTRO definition of PSA failure.[73, 74] Therefore, future guidelines will incorporate this new definition of PSA failure.
3. The existence of few RCTs. As with the previous guideline, most of the studies were based on data from patient series. Patient selection bias could not be controlled for valid comparisons.
4. Duplication of data from articles that reported studies of the same or overlapping sets of patients that had either been reanalyzed or analyzed after additional follow-up. The Panel conducted multiple separate data extractions and analyses in an attempt to control for this rereporting of treatment series but was unable to correct for this bias due to incomplete data reporting in the individual treatment series.
5. Inconsistencies in approaches to reporting patient characteristics. Frequently, the series would report outcomes in categories of patients but these categories were rarely similar across the series. For example, outcomes of treatment in one series of patients with "low risk" disease might include a Gleason score $\leq$7, a PSA <10 ng/mL, and clinical stage T1 to T2b disease while a second series might define "low risk" as a Gleason score of $\leq$6, a PSA $\leq$10 ng/mL, and clinical stage T1 to T2a disease. Combining or contrasting outcomes with such a wide range of definitions was not possible.

6. Inconsistencies in reporting the number of patients at risk at the various follow-up times shown. Even though most studies currently report survival data using Kaplan-Meier calculations, by not including the number of patients at risk at fixed time points (e.g., five years post-surgery), it is not possible to combine weighted-like estimates across cohorts of patients.
7. Incomplete and/or inconsistent reporting of complications, most evident for the two most common complications -- erectile dysfunction and urinary incontinence. For both of these complications, a variety of outcome measures was used in the studies/reports. Unfortunately, all measures are not necessarily based on common definitions of these complications. This further jeopardizes the aggregation of these complications into incidence rates. The Panel has prepared separate analyses of the variation in reporting these complications.
8. The combination of patients with clinical stage T3 disease with those with stage T1 to T2 when reporting outcomes. As the Panel's mandate was to make recommendations for **clinically** localized prostate cancer, the inclusion of patients with T3 disease in many series made these reports nonapplicable to the target patient population for this Guideline.

The lack of and inconsistencies in the data were also, in part, due to the design and process of the data extraction. The strict inclusion criteria used to define the body of literature extracted may have caused potentially useful studies to be excluded from the analysis. For example, many radiotherapy studies reported outcomes for patients with clinical stage T1 to T3 disease. If the patients with T1/T2 disease could not be separated from those with T3 disease, this series was rejected from the extraction process because of "T3 contamination." In addition, some of the variation in outcomes may have been due to the variation in the groups examined as data were extracted by patient group based on such characteristics as stage, PSA level, and grade.

A quantitative synthesis of the results of the quality-of-life literature also was impossible due to cross-study diversity in the following:

1. Measures used to capture quality-of-life data. A wide variety of instruments has been used. While some studies use validated instruments, others use ad hoc, study-specific

measures with unknown psychometric properties. Differences in instrument content limit the ability to combine scale scores from different measures.

2. Formats of reporting quality-of-life data. Appropriate summary statistics for computing effect sizes (i.e., means and variances) are not always reported. Some investigators report scale and/or subscale means, others report median scale and/or subscale scores, and still others report only frequencies of select items.
3. The time points of follow-up assessment. Follow-up assessment points are often study-specific and vary considerably. Many retrospective series report aggregated summary scores that cover a wide range of follow-up time points.

Guideline Statement Definitions

The Panel developed guideline statements based on the limited data. As in the previous guideline, the present statements were graded with respect to the degree of flexibility in their application. Although the terminology has changed slightly, the current three levels are essentially the same as in the previous guideline. A "standard" has the least flexibility as a treatment policy; a "recommendation" has significantly more flexibility; and an "option" is even more flexible. These three levels of flexibility are defined as follows:

1. **Standard**: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) there is virtual unanimity about which intervention is preferred.
2. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.
3. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal.

Deliberations and Conclusions of the Panel

The Prostate Cancer Clinical Guideline Update Panel found wide variation in the outcomes for each treatment of prostate cancer such that it was necessary to describe most guideline statements (described later) as options. The reasons why no further treatment policies could be made were summarized previously. Nonetheless, *some* guideline statements were developed by the Panel—almost universally based on the results of RCTs, many of which were published since the publication of the 1995 Guideline. As such, the guideline statements contain several stronger treatment policies based on these RCTs. In the guideline statements, the Panel selected the term "should" when the results of one or more RCTs do apply to the patient with clinical stage T1 to T2N0M0 disease and the term "may" when the results of one or more RCTs may apply to this patient population. (For example, if an RCT showed an improvement in metastasis-free survival for surgery when compared to watchful waiting in a population of men with organ-confined prostate cancer but did not provide an analysis strictly for low-risk disease, this observation was modified by the term "may" for patients with low-risk disease.)

The collective writing efforts of the Panel members and consultants resulted in this report. After Panel approval, a draft underwent peer review by 87 individuals, including members of the Practice Guidelines Committee, the AUA Board of Directors, and external prostate cancer experts. The Guideline was modified where the Panel deemed necessary in response to comments from 27 reviewers. A final version of the report was generated and the Panel voted for approval. This version was then forwarded, in turn, for approval of the Practice Guidelines Committee and the Board of Directors.

This Guideline is published on the AUA website and printed in *The Journal of Urology*. The guideline statements are published annually in a pocket guide. This Guideline is expected to be updated when the Practice Guidelines Committee determines that additional treatments or evidence about existing treatments warrant a revision.

Future Prostate Cancer Guideline Panel Activities

Because the Panel was unable to develop guideline statements other than Options for the majority of the important decisions that patients and physicians face in the management of

clinically localized prostate cancer due to a lack of comparable data - particularly RCTs - the Panel has recommended that changes be made in the approach to prostate cancer guideline development. The Panel has recommended that this Guideline be updated regularly and that these updates be based solely on evidence from RCTs. Other data can be presented to the Guideline Panel but it is unlikely, given the experience with previous data, that treatment series will affect guideline development.

Treatment Alternatives

> **Standard: A patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, active surveillance, radiotherapy (external beam and interstitial), and radical prostatectomy. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient.**
> [Based on Panel consensus.]

When making a decision regarding treatment, patients and physicians should weigh their perception/understanding of cancer control with the potential side effects. In this Guideline, a synopsis of the results in these two domains is presented. Cancer control is presented stratified by risk group as defined previously; complications are presented stratified by treatment. It is important to recognize that as combined modality therapy has become more frequently utilized for men with high-risk disease, the rate of occurrence of complications also has increased as compared to what is reported in this Guideline for single-modality therapy.

Treatment Recommendations

Treatment of the Low-Risk Patient

> **Option: Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localized prostate cancer.**
> [Based on review of the data and Panel consensus.]

Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are all options for treatment of the low-risk patient. Study outcomes data do not provide clear-cut evidence for the superiority of any one treatment.

Standard: Patient preferences and health conditions related to urinary, sexual, and bowel function should be considered in decision making. Particular treatments have the potential to improve, to exacerbate or to have no effect on individual health conditions in these areas, making no one treatment modality preferable for all patients.

[Based on review of the data and Panel consensus.]

Standard: When counseling patients regarding treatment options, physicians should consider the following:

- **Two randomized controlled clinical trials show that higher dose radiation may decrease the risk of PSA recurrence[27, 35];**
- **Based on outcomes of one randomized controlled clinical trial, when watchful waiting and radical prostatectomy are compared, radical prostatectomy may be associated with a lower risk of cancer recurrence, cancer-related death, and improved survival.[10]**

[Based on review of the data and Panel consensus.]

Standard: Patients who are considering specific treatment options should be informed of the findings of recent high-quality clinical trials, including that:

- **For those considering external beam radiotherapy, higher dose radiation may decrease the risk of PSA recurrence[27, 35];**
- **When compared with watchful waiting, radical prostatectomy may lower the risk of cancer recurrence and improve survival.[10]**

[Based on review of the data and Panel consensus.]

Standard: For patients choosing active surveillance, the aim of the second-line therapy (curative or palliative) should be determined and follow-up tailored accordingly.

[Based on Panel consensus.]

Patients who opt not to initially treat their prostate cancers may have differing expectations. For example, some may desire to monitor the tumor carefully on a program of active surveillance that includes frequent PSA and DRE testing and with regular repeat biopsies in order to intervene the moment that there is any evidence of tumor progression. Other men may have a greater focus on current quality-of-life issues, may have little interest in intervention, and may opt for more of a watchful waiting program. The follow-up schedule for these two aims will be different with more frequent and extensive evaluations in the former and fewer in the latter.

Treatment of the Intermediate-Risk Patient

Option: Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate treatment options for the patient with intermediate-risk localized prostate cancer.
[Based on review of the data and Panel consensus.]

Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are all options for the treatment of intermediate-risk localized prostate cancer. Study outcomes data do not provide clear-cut evidence for the superiority of any one treatment.

Standard: Patient preferences and functional status with a specific focus on functional outcomes including urinary, sexual, and bowel function should be considered in decision making.
[Based on review of the data and Panel consensus.]

Standard: When counseling patients regarding treatment options, physicians should consider the following:

- **Based on outcomes of one randomized controlled clinical trial, the use of neoadjuvant and concurrent hormonal therapy for a total of six months may prolong survival in the patient who has opted for conventional dose external beam radiotherapy[14];**
- **Based on outcomes of one randomized controlled clinical trial, when watchful**

waiting and radical prostatectomy are compared, radical prostatectomy may be associated with a lower risk of cancer recurrence, cancer-related death, and improved survival[10];

- **Based on outcomes of two randomized controlled clinical trials, higher dose radiation may decrease the risk of PSA recurrence.[27, 35]**

[Based on review of the data and Panel consensus.]

Standard: Patients who are considering specific treatment options should be informed of the findings of recent high-quality clinical trials, including that:

- **For those considering external beam radiotherapy, the use of hormonal therapy combined with conventional-dose radiotherapy may prolong survival[14];**
- **When compared with watchful waiting, radical prostatectomy may lower the risk of cancer recurrence and improve survival[10];**
- **For those considering external beam radiotherapy, higher dose radiation may decrease the risk of PSA recurrence.[27, 35]**

[Based on review of the data and Panel consensus.]

Standard: For patients choosing active surveillance, the aim of the second-line therapy (curative or palliative) should be determined and follow-up tailored accordingly.

[Based on Panel consensus.]

Treatment of the High-Risk Patient

Option: Although active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are options for the management of patients with high-risk localized prostate cancer, recurrence rates are high.

[Based on review of the data.]

Standard: When counseling patients regarding treatment options, physicians should consider the following:

- **Based on outcomes of one randomized controlled clinical trial, when watchful**

waiting and radical prostatectomy are compared, radical prostatectomy may be associated with a lower risk of cancer recurrence, cancer-related death, and improved survival[10];

- **Based on results of two randomized controlled clinical trials, the use of adjuvant and concurrent hormonal therapy may prolong survival in the patient who has opted for radiotherapy.[11, 14]**

[Based on review of the data.]

Standard: High-risk patients who are considering specific treatment options should be informed of findings of recent high-quality clinical trials, including that:

- **When compared with watchful waiting, radical prostatectomy may lower the risk of cancer recurrence and improve survival[10]; and**
- **For those considering external beam radiotherapy, use of hormonal therapy combined with conventional radiotherapy may prolong survival.[11, 14]**

[Based on review of the data.]

Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and surgery remain treatment options for the patient with high-risk disease due to the lack of evidence of superiority of one therapy over another. Despite the lack of high-quality evidence of treatment benefit among these patients, a high risk of disease progression and death from disease may make active treatment a preferred option. Treatments chosen for high-risk patients (non-nerve-sparing prostatectomy, higher dose radiation, or a combination of radiation and hormonal therapy) are all associated with a high risk of erectile dysfunction.

Additional Treatment Guidelines

Recommendation: Patients with localized prostate cancer should be offered the opportunity to enroll in available clinical trials examining new forms of therapy, including combination therapies, with the goal of improved outcomes.

[Based on Panel consensus.]

The Panel feels strongly that all physicians treating patients with prostate cancer have the responsibility to inform patients of the availability of clinical trials for the management of this

disease. It will be essential for the entire medical community to participate in offering and encouraging participation in these trials in order to both advance the care for the disease as well as to provide guidance for patients who currently have few data to determine optional therapy.

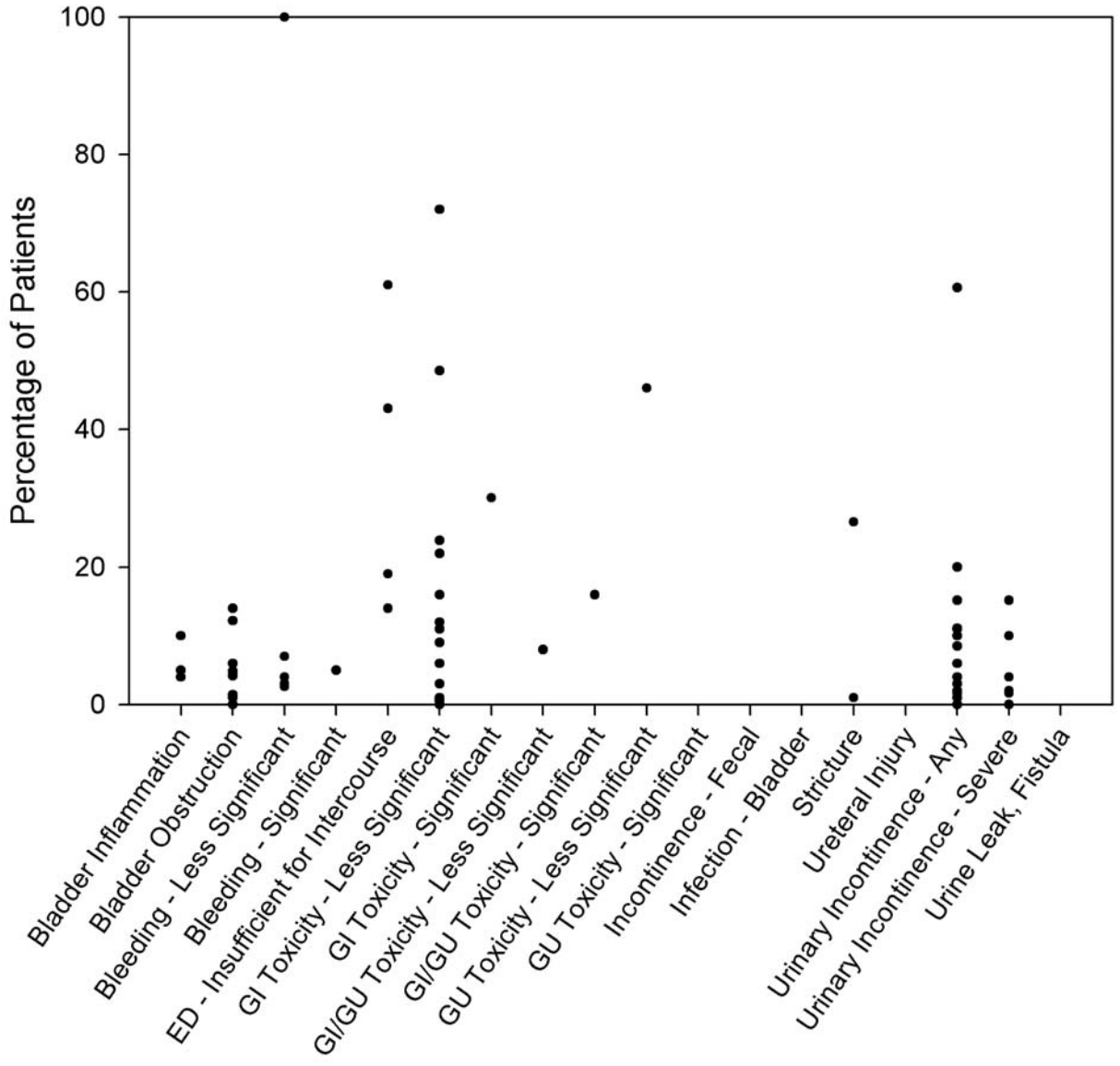
> **Recommendation: First-line hormone therapy is seldom indicated in patients with localized prostate cancer. An exception may be for the palliation of symptomatic patients with more extensive or poorly differentiated tumors whose life expectancy is too short to benefit from treatment with curative intent. The morbidities of ADT should be considered in the context of the existing comorbidities of the patient when choosing palliative ADT.**
> [Based on Panel consensus.]

Treatment Complications

Summary of Treatment Complications

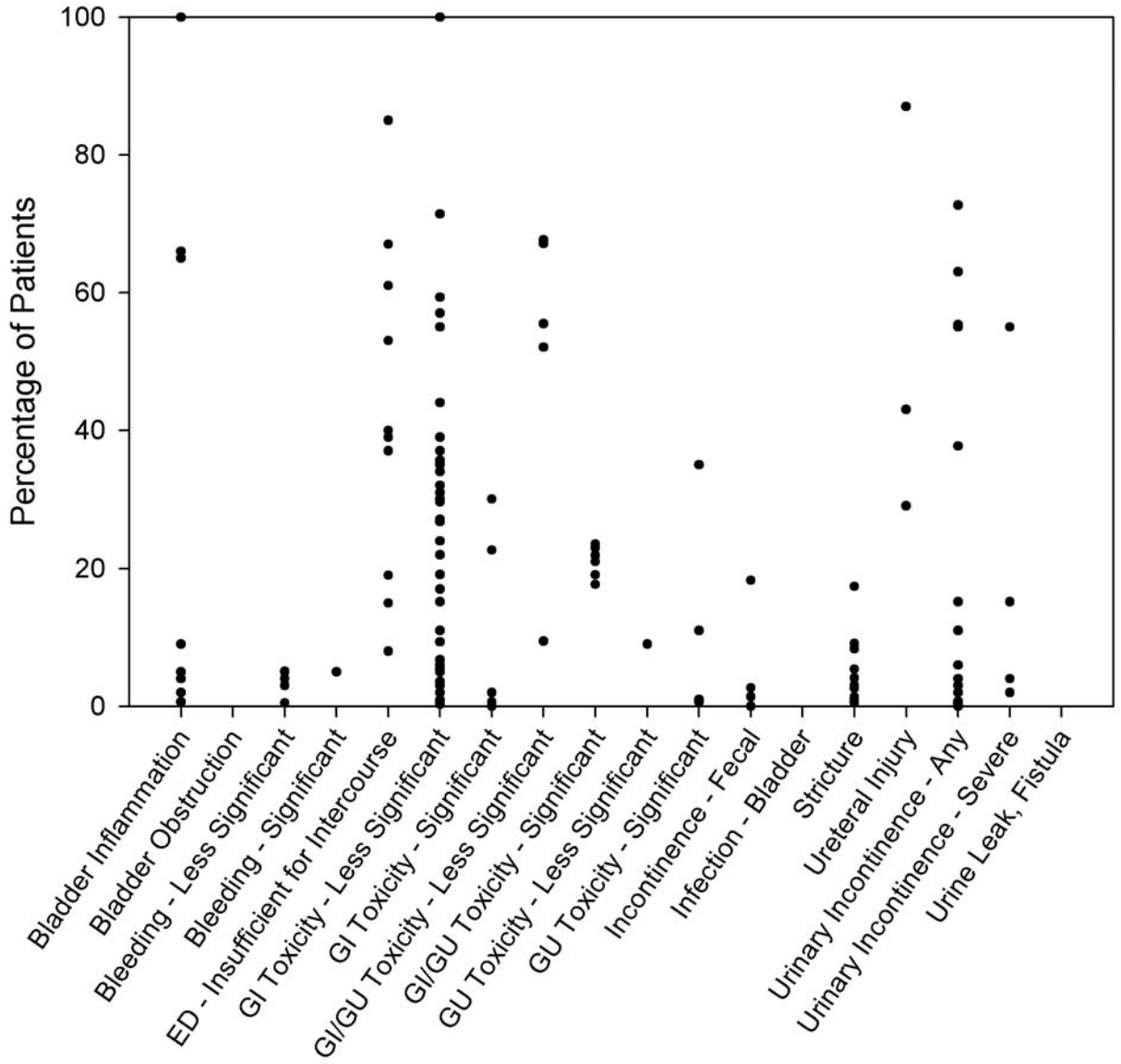
Graphic displays visually represent the rates of frequently reported complications (Figures 3-5) drawn from the interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy case series. There were too few watchful waiting or active surveillance series to warrant graphic display. As described in more detail in the "Methodology" section, because of the variation in complication reporting, similar complications were collapsed into a summary category. For studies in which the complications were collapsed, the complication rate estimate was maximized by assuming that there was no overlap between the individual reports of the complication (i.e., the percentage of patients in the summary category was the sum of the percentages for each individual report of the complication). In a series in which the complication was presented by time since treatment initiation, the Panel simply used the highest rate reported and disregarded the timing. Each circle on a graph represents one series reporting the complication. These graphs show the variability of complication rates across the reporting series reviewed by the Panel. It must be emphasized that the graphs show neither the size of each series nor the confidence interval for the indicated percentage.

Figure 3. Rate of complications reported with interstitial prostate brachytherapy*



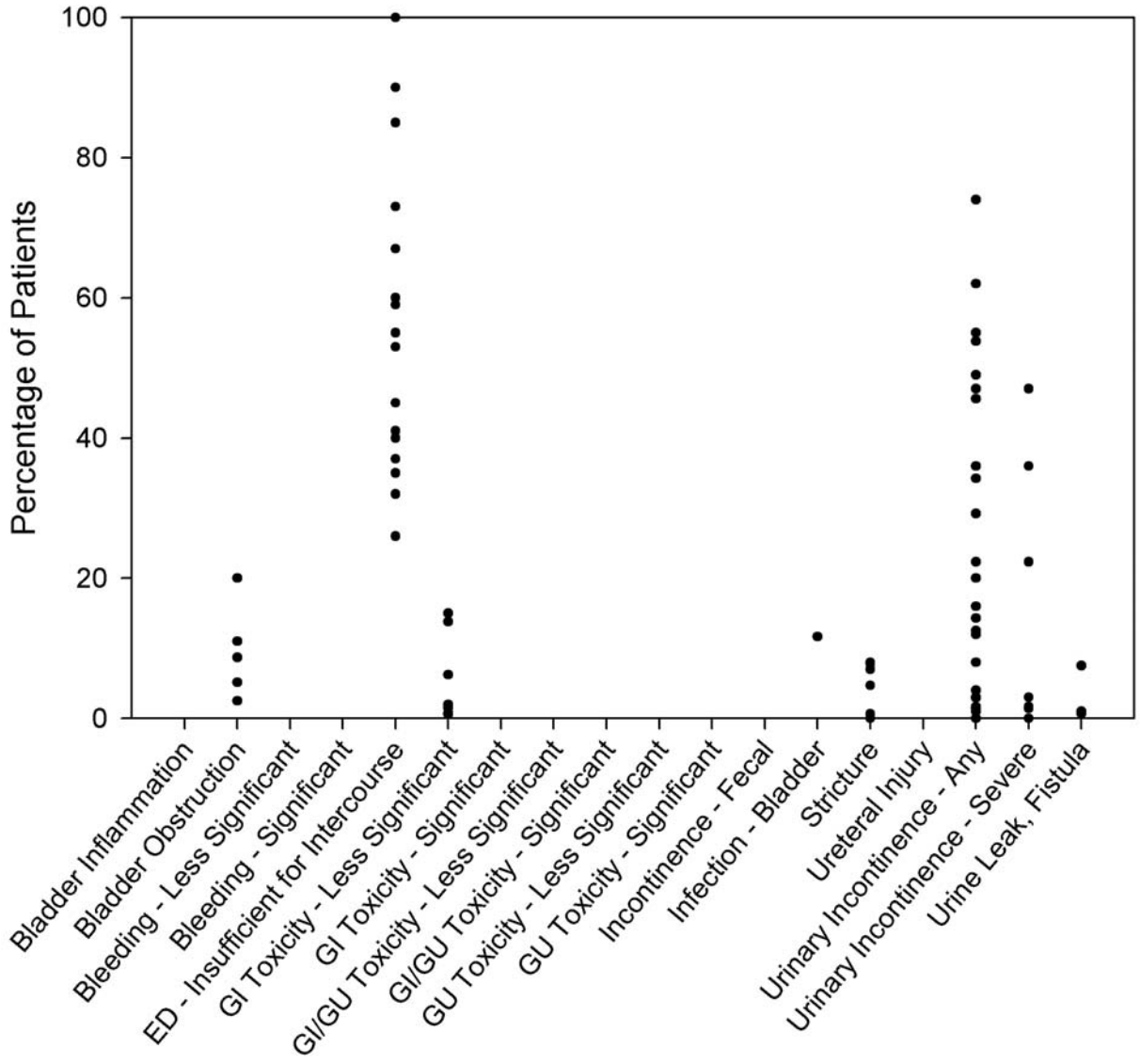
* For some complications, no data were available.
ED, erectile dysfunction; GI, gastrointestinal; GU, genitourinary.

Figure 4. Rate of complications reported with external beam radiotherapy*



* For some complications, no data were available.
ED, erectile dysfunction; GI, gastrointestinal; GU, genitourinary.

Figure 5. Rate of complications reported with radical prostatectomy*



* For some complications, no data were available.
ED, erectile dysfunction; GI, gastrointestinal; GU, genitourinary.

Some of the complications apply to all three treatment modalities, but not necessarily to the same extent. Urinary incontinence, for example, is reported by eight articles (12 patient groups with 27 individual symptom/time-data points) as a complication of interstitial prostate brachytherapy, by 10 articles (12 patient groups with 34 symptom/time-data points) as a complication of external beam radiotherapy, and by 14 articles (20 patient groups with 42 symptom/time-data points) as a complication of radical prostatectomy. To some degree, each form of therapy has its own spectrum of complications. For example, hematuria is reported in several interstitial prostate brachytherapy and external beam radiotherapy series but is not reported in any surgical series. The Panel was unable to determine that any one therapy has a more significant cumulative over-all risk of complications.

Caveats. The complications data are subject to some of the same problems as the prostate cancer outcomes data, namely: selection biases due to lack of randomization, duplication of data from separate reports of overlapping patient sets, and inconsistencies in reporting the number of at-risk patients. Other sources of bias and variability exist that are unique to the reporting of complications. These include:

1. Publication bias. The possibility exists that centers publishing their results are those with low-complication rates, a positive bias. The data also could be negatively biased since many of the series are not sufficiently recent for complication rates to reflect modern improvements in radiotherapy and surgical therapy techniques.
2. Mode of data collection. The manner in which complication data are collected is highly variable. Some series provide complications as self-reports of patients responding to standardized questionnaires regarding "quality of life." Others rely on physician reports of complications or clinical grading criteria (e.g., Radiation Therapy Oncology Group morbidity classification). Still other series provide little detail as to how the complication data were collected. The likely result is considerable variability, especially in the more subjective complications such as urinary and sexual dysfunction.
3. Definitional variability. Considerable variability exists in the definition of many complications. For example, the following definitions of incontinence were observed: "no control over urination," "any leakage of urine," "leakage of urine daily or more often," "requiring the use of protective pads," and "requiring the use of a catheter."

Proctopathy, a condition arising from radiotherapy, was indicated by a diversity of different symptoms including bowel movement frequency, tenesmus, discomfort/pain with bowel movements, and rectal bleeding.

4. Follow-up reporting variability. Many series fail to report follow-up time points at which each complication occurred or was measured. Retrospective series, in particular, often report rates corresponding to a wide interval of time. Hence, the timing of the various complications may be difficult to ascertain. Furthermore, there are far too many series that only assess complications at a single-time point. This makes defining trajectories for the most common complications impossible. Complications such as incontinence and erectile dysfunction, for instance, can fluctuate greatly as time since treatment passes. In general, single-point estimates have the potential to be highly misleading.
5. Lack of attention to patient preferences. Few series incorporate patients' subjective appraisals (or preferences) for functional states. Individual patients may appraise various complications and functional states differently throughout the course of treatment and follow-up.
6. Variability in the graphs was the result, in part, from the methods used to extract data from the articles. For some articles, multiple patient groups were reported. In several of these, complications were reported separately while in others they were reported in aggregate.

Analysis of Treatment Complications

Among the complications associated with treatments for clinically localized prostate cancer, those reported most often and with the greatest degree of variability were: incontinence and other genitourinary toxicity (i.e., irritative and obstructive urinary symptoms), hematuria, gastro-intestinal toxicity, proctopathy, and erectile dysfunction (impotence). Due to their salience, the Panel devoted special attention to these complications by highlighting findings from several of the extracted case series.

Complicating the assessment of many of these patient-centered outcomes are the changes that occur over time. For example, in the case of erectile dysfunction, early loss of erections after radical prostatectomy may be followed by later return of all or some function. Gradual physiologic loss of erections over time with active surveillance is expected, and a loss of

function over time after radiotherapy also has been described.[75] Single-point estimates of function provide overly simplistic descriptions of a complex outcome and do not incorporate patient-weighted preferences, including preferences for earlier or late function, or decision-regret measures.

Incontinence and Other Genitourinary Toxicity

The reported risk of urinary incontinence following prostate cancer therapies ranged from 3% to 74% for radical prostatectomy, 0% to 61% for interstitial prostate brachytherapy, and 0% to 73% for external beam radiotherapy (Figures 3-5). Most surgically treated men will experience transient urinary incontinence. Longitudinal follow-up data indicate that men do become more continent of urine over time, especially at one year and beyond posttreatment.[76, 77] One cross-sectional series reported rather high rates of urinary leakage for two groups of patients treated with interstitial prostate brachytherapy (one group treated with interstitial prostate brachytherapy only, the other group treated with both interstitial prostate brachytherapy and external beam radiotherapy),[78] but, in general, incontinence is less frequently observed in radiotherapy series. Incontinence is also less frequently observed in surveillance groups.[79]

The variability observed in incontinence rates likely reflects not only actual differences in the risk of incontinence among series but also differences in defining, reporting, diagnosing, and quantifying urinary incontinence. After reviewing the literature, the Panel concluded that it is not possible to make any comparisons of the risk of urinary incontinence among these forms of treatment other than to say that urinary incontinence can occur with any form of treatment for localized prostate cancer. While there may be a series in which careful assessment of urinary incontinence following a specific treatment have been made, overall there were insufficient data to provide a broad assessment of outcomes for prostate cancer management.

Other types of genitourinary toxicity have been reported in external beam radiotherapy series. Increasing irritative symptoms such as urinary frequency and urgency are common early after external beam radiotherapy but also have been shown to generally return to pretreatment levels by one and two years posttreatment.[34, 80] Obstructive symptoms such as straining and painful urination (collectively referred to as dysuria) also increase shortly after external beam radiotherapy but will return to pretreatment levels by one and two years after treatment.[34]

Hematuria appears to be uncommon (equal to or less than 5% in most series). However, it is quite common early after interstitial prostate brachytherapy implantation. In one series, 100% of men developed hematuria in the 12- to 48-hour period after the implant.[81] In this same series only 3% of these men had hematuria for up to six weeks after the implant. In another interstitial prostate brachytherapy series, only 7% of men had hematuria within 12 months of the implant.[61]

Gastrointestinal Toxicity

Bowel and other gastrointestinal problems have been reported in several radiotherapy series. Diarrhea and loose stools are common after external beam radiotherapy, typically affecting 25% to 50% of men after treatment.[34, 80, 82, 83] Some series indicate that these problems can linger for two to three years after radiotherapy in some men.[34, 83] Bowel urgency and stool frequency, problems that many older men experience prior to treatment, appear to be exacerbated by external beam radiotherapy, especially in the first year after treatment completion.[34] The Prostate Cancer Outcomes Study[75] evaluated a large group of men who underwent radical prostatectomy (n=1,156) or external beam radiotherapy (n=435) for clinically localized prostate cancer. In this study, bowel side effects were more common among men who received radiotherapy. Nonetheless, bowel symptoms also were seen among men who underwent radical prostatectomy. Studies also show that 12% to 39% of men will experience rectal pain in the year after completion of external beam radiotherapy with rates decreasing over time.[34, 82]

Proctopathy appears to be the dominant complication of interstitial prostate brachytherapy, though it does not seem to occur frequently. Symptoms of late radiation proctopathy such as rectal bleeding, rectal ulceration, tenesmus, and discomfort are reported at ≤10% in the published series.[61, 78, 84, 85] Rates of these problems increase slightly as the rectal volumes receiving the prescribed dose increase.[84] Finally, combining interstitial prostate brachytherapy with external beam radiotherapy can result in higher rates of certain complications (e.g., rectal bleeding and diarrhea) than treatment with brachytherapy alone.[78]

Erectile Dysfunction

A functional outcome of major practical interest following prostate cancer treatment is the loss of erectile function and its recovery over time. Published reports of clinical series demonstrate variability in assessing and defining erectile function that complicates assessments of risk. Based

on recent literature, it is evident that reporting of functional outcomes following prostate cancer treatment has evolved dramatically in recent years. Whereas physician reports of sexual outcome were common in the past,[86-88] validated sexual health outcome survey instruments have recently been introduced to capture patient perceptions of health outcomes following treatment.[89-92] Complicating the picture further, many reports use imprecise, outmoded terms such as "impotence," which can confound assessments of erectile function if their application implies other aspects of the male sexual response cycle, such as libido or orgasm frequency. Furthermore, certain methodological problems continue to bias results. As in 1995, studies are still difficult to interpret because of patient selection for treatment. Younger and more functional men still tend to undergo surgery. Older and less functional men still tend to receive radiotherapy. A final confounding factor of this analysis is the development of effective oral agents for the treatment of erectile dysfunction. These agents have been demonstrated to improve sexual function in some men treated for prostate cancer. Thus, in early treatment series, reported rates of erectile dysfunction may be greater than in more recent series.

Recognizing these limitations, we summarize herein the case series data on erectile dysfunction (erections insufficient for penetration or intercourse).

Erectile dysfunction rates in some surgical series are as high as 60% to 90% one or more years following treatment.[76, 79, 83, 93] Nerve-sparing procedures appear to result in preserved function for many men, though selection factors may bias the results of some of the early studies of this technique as erectile dysfunction rates were reported for only preoperatively potent men.[86, 87, 94] Among the series that include men treated with external beam radiotherapy, erectile dysfunction rates range from 0% to 85% at one year and later posttreatment.[34, 83, 93, 95, 96] Three-dimensional conformal techniques appear to result in greater preservation of erections.[95, 96] Rates of erectile dysfunction below 50% at a year or more after treatment have been commonly observed in interstitial radiation series; however, some of these series only follow initially potent men.[85, 97, 98] In one study, younger men (<60 years) were more likely to maintain erections than older men.[85] Finally, even men under watchful waiting or active surveillance will experience erectile dysfunction over time.[79, 93]

There is a definite need to consistently apply scientifically based methodology to the study of erectile function outcomes following prostate cancer treatment. In addition to the fundamental requirements of current clinical trial study design, including prospective accrual of data and documentation of pretreatment level of sexual functioning, the application of validated self-report instruments that measure sexual function should be employed.[92] Since sexual health recovery frequently continues beyond one year and extends for as long as four years following treatment, serial and sufficiently long-term assessments are invaluable.[88, 99, 100] Finally, it is important to consider other factors that can influence erectile function when reporting results (i.e., risk stratification according to nerve-sparing technique, age, partner availability, interest in sexual activity, and comorbid conditions).[86, 88, 100, 101]

Quality of Life and Treatment Decisions: A Major Patient Concern in Clinically Localized Prostate Cancer

The term "health-related quality of life" (HRQL) is typically used in the health-care arena to refer to the impact that disease and treatment have on a person's physical, emotional, and social functioning and well-being, including the impact on daily functioning.[102-106] HRQL is a patient-centered outcome and thus **must** be rated by the patient because physicians often underestimate the impact of disease and treatment on their patients' well-being.[107] HRQL is assessed by validated questionnaires and surveys administered to the patient in a standardized manner.[108] In prostate cancer, HRQL usually is divided into prostate cancer-specific and general issues. Prostate cancer-specific HRQL refers to the disease-specific sequelae of prostate cancer, including urinary, bowel, and sexual functioning. General HRQL refers to generic issues of well-being common to any medical population, including physical, role, social, emotional, and cognitive functioning, vitality/fatigue, pain, general health status, global quality of life, and life satisfaction.[109]

As stated previously in the "Methodology" section, the Panel felt it was not possible to fully extract and quantitatively synthesize the HRQL data from the selected series. Instead, the Panel has chosen to present a brief summary of the findings of two recently conducted comprehensive reviews of the HRQL literature in prostate cancer: one by Eton and Lepore,[109] the other by Penson et al.[108] Given that there is substantial conceptual overlap between the complications (as

previously reported) and the domains that define prostate cancer-specific HRQL, to reduce redundancy the Panel chose to restrict attention to the general domains of HRQL.

Most of the early studies addressing general HRQL issues (i.e., general physical function, role function, social function, emotional well-being, body pain, general health, or vitality/energy) found few differences across treatments for clinically localized disease.[109] Furthermore, early studies found no differences in general HRQL domains between treated men and untreated men (surveillance groups) or between treated men and age-matched, healthy men without prostate cancer.[110, 111] In more recent longitudinal studies, both surgery- and radiotherapy-treated men have reported some declines in role function and vitality/energy shortly after treatment—the surgically treated men reporting the most dysfunction.[112, 113] Most men in both of these treated groups, though, reportedly recovered function by one year. Following external beam radiotherapy, fatigue was commonly reported but, as long as it was temporary, did not appear to be emotionally distressing to most men.[113, 114] Men treated with interstitial prostate brachytherapy appear to have only slight declines in general HRQL.[108] Physical and functional status declines have been reported in the first few months after implant, but pretreatment levels of function are regained by most men at one year after implant.[115] A few studies have indicated certain risk factors for poor general HRQL in men after treatment for localized prostate cancer.[109] These include the presence of comorbid psychiatric conditions (i.e., prior psychiatric history, alcohol abuse, drug abuse) and the experience of pain after treatment.[116-118]

Synthesizing the findings of studies featuring quality-of-life data with those featuring treatment complications data leads to the conclusion that many men treated for clinically localized prostate cancer will experience some posttreatment problems that may impact their daily lives. Thus, there are trade-offs that must be considered and each patient needs to determine which side-effect profile is most acceptable to them when making a decision about treatment.

Randomized Controlled Trials

Introduction

In general, RCTs provide the highest level of evidence for answering research questions and developing treatment standards. Most importantly, the ability to control the influence of

potentially confounding variables, both known and unknown, allows investigators to reach conclusions that are applicable to individuals and generalized to populations. For this reason, the Panel agrees that RCTs, which address specific questions on the management of clinically localized prostate cancer, deserve special consideration.

RCTs were identified from the pool of articles generated by the Guideline Panel and from the Cochrane trials registry for prostate cancer, which was last updated on September 2, 2005. Articles selected for discussion herein were limited to studies executed as prospective RCTs that investigated the impact of interventions on treatment outcomes for localized prostate cancer. Some studies culled from the Cochrane registry did not meet the strict criteria established by the Panel but were felt to merit discussion as they provided the best available quality of evidence to answer specific research questions. These limits yielded 27 studies for incorporation into this portion of the Guideline (Tables 1-4).[8-13, 15-29, 31-35, 44, 119]

Two broad conclusions can be drawn from the review of RCTs for localized prostate cancer and will subsequently be discussed in greater detail. First, there are very few trials investigating a direct comparison of two different treatment modalities (e.g., active surveillance vs. external beam radiotherapy or external beam radiotherapy vs. radical prostatectomy). Second, there are many RCTs that investigate interventions *within* a particular treatment modality (e.g., radical prostatectomy alone vs. neoadjuvant androgen deprivation plus radical prostatectomy or different doses of radiation). As a consequence, the highest quality evidence to identify a superior treatment modality for a particular patient is lacking, but there is some high-quality evidence to support various modifications within treatment modalities.

RCTs Comparing Different Treatment Modalities

Watchful Waiting Versus Radical Prostatectomy

Given the slow progression of many localized prostate cancers, it has long been recognized that not all cases warrant intervention. Two RCTs, one in the pre-PSA era, have reported long-term follow-up of patients randomized to watchful waiting or radical prostatectomy, but the second one is not yet mature. The Veterans Administration Cooperative Urological Research Group (Table 1)[20] reported on 142 patients with clinical stage I or II adenocarcinoma of the prostate who were randomized to watchful waiting or radical prostatectomy between 1967 and 1975.[20]

This study was underpowered to detect treatment differences, and applicability of these findings to contemporary patients is limited given both stage and grade migration since the advent of PSA screening for prostate cancer.

More recently, the Scandinavian Prostate Cancer Group Study No. 4 (Table 1)[10] reported on 695 men with clinical stage T1 or T2 prostatic adenocarcinoma (comparable to current T1 to T2N0M TNM stage) who were randomized to watchful waiting (n=348) or radical prostatectomy (n=347) between 1989 and 1999. Although this trial was conducted after PSA level testing was available, only 5% of men were diagnosed by screening. Still, the distribution of serum PSA levels at the time of diagnosis more closely reflects contemporary populations in which PSA screening is widespread. After a median follow-up of 8.2 years, treatment with radical prostatectomy was associated with significantly lower risk of disease-specific mortality, overall mortality, metastatic disease, and local progression (Table 5).[10]

Table 5. Outcomes of the Scandinavian Prostate Cancer Group Study No. 4: median follow-up of 8.2 years[10]

	RP % (n)	WW % (n)	Relative risk (95% CI)	p value	Numbers needed to treat
Disease-specific mortality	9.6% (30)	14.9 % (50)	0.56 (0.36 to 0.88)	0.01	20
Overall mortality	27% (83)	32% (106)	0.74 (0.56 to 0.99)	0.04	20
Distant metastasis	15.2% (50)	25.4% (79)	0.60 (0.42 to 0.86)	0.004	10
Local progression	19.2% (64)	44.3% (149)	0.33 (0.25 to 0.44)	<0.001	4

CI, confidence interval; RP, radical prostatectomy; WW, watchful waiting.

In preplanned subset analyses, the investigators found that the reduction in risk of death from prostate cancer in those randomized to prostatectomy was more pronounced in the population of men less than 65 years of age and independent of PSA level or Gleason score at diagnosis (p=0.08 for treatment by age-group interaction). However, caution must be used in interpreting subset analyses.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT)[50] is an ongoing RCT comparing radical prostatectomy to watchful waiting in patients with clinical stage T1 or T2 disease. Initiated in 1994, accrual was slow and finally was completed with an enrollment of 731 patients in 2002. Follow-up is planned for 15 years, with overall mortality as the primary endpoint. Although findings will not be available for some time, study findings will be more applicable to contemporary patients diagnosed with localized prostate cancer.

Adjuvant Bicalutamide Therapy

The bicalutamide Early Prostate Cancer Program was a multicenter series of three international RCTs launched to assess the efficacy and tolerability of bicalutamide, either alone or in combination with radical prostatectomy, radiation therapy, or watchful waiting, in patients with clinically localized or locally advanced prostate cancer. Approximately two thirds of the patients had localized disease. This program included three separate controlled trials designed to allow for combined analysis (Table 1).[20, 33, 119] The North American trial[119] included patients who mainly opted for prostatectomy, the trial conducted in Europe[33] and other countries worldwide enrolled primarily patients receiving radiotherapy, and the Scandinavian study[20] was comprised primarily of patients choosing watchful waiting. Each study had similar endpoints, but bicalutamide treatment duration differed across the three studies. Early reports and a subsequent analysis with longer follow-up[33] have consistently demonstrated significantly improved progression-free survival with bicalutamide in the overall study population compared to placebo, but no overall survival benefit was seen. A number of subset analyses were performed based on study number, primary treatment received, clinical stage, and other factors. One analysis conducted at a median of just over five years of follow-up indicated that men with localized prostate cancer managed with watchful waiting plus bicalutamide had reduced overall survival in comparison to men managed with watchful waiting alone.[20, 33] Because the risk of a false-positive result increases with multiple statistical testing, this must be considered when evaluating the results of subset analyses. While the explanation for this difference in overall survival noted in this subgroup analysis is not readily apparent, there is some suggestion that men who are considering watchful waiting for their clinically localized prostate cancer may not benefit from the addition of bicalutamide as part of their immediate therapy.

RCTs Within Treatment Modalities

External Beam Radiotherapy

External beam radiotherapy dosage. Three recent RCTs have compared different external beam radiotherapy dosages. The first, from M. D. Anderson Hospital (Table 2),[27] compared the efficacy of 70 versus 78 Gy in 305 patients with clinical stage T1 to T3N0 prostate cancer randomized between 1993 and 1998. The primary endpoint was "freedom from failure" (FFF), which included biochemical failure defined as three successive rises in PSA level.[27] With a median follow-up of 60 months, FFF in the 78 Gy arm was 70% compared to 64% in the 70 Gy arm, representing a significant difference ($p=0.03$). The higher dose was associated with a significantly greater risk of grade 2 or higher late rectal toxicity (26% for 78 Gy versus 12% for 70 Gy; $p=0.001$). This study was performed before intensity-modulated radiotherapy and other more sophisticated computerized treatment planning were available, and the results for patients with T3 disease could not be separated from those with clinical stage T1 to T2 disease.

A similar French study, the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG) (Table 2),[9] reported early toxicity results on 306 patients with clinical stage T1 (Gleason score ≥7 or PSA ≥10 ng/mL) or T2 to T3a disease randomized between 1999 and 2002 to 70 versus 80 Gy. Data regarding treatment efficacy is not yet available, but the authors reported no significant differences in treatment toxicity between the two radiation groups. Again, patients with clinical stage T1 to T2 disease were not separable from those with T3a disease.

A multicenter RCT from Loma Linda and Massachusetts General Hospitals (Table 2)[35] reported results for 392 patients with clinical stage T1 to T2 prostate cancer randomized to 70.2 or 79.2 Gy, using a combination of photon and proton beams.[35] At five years, there was no difference in overall survival, but the higher-dose therapy conferred a 49% reduction in the risk of biochemical failure ($p<0.001$). There was no difference in the incidence of acute or late gastrointestinal or genitourinary toxicity of grade 3 or higher between these two groups. Still, both acute and late grade 2 gastrointestinal toxicity was significantly more common in the high-dose arm.

External Beam Radiotherapy Fractionation

One RCT has reported on efficacy of hypofractionation of external beam radiotherapy and one study is ongoing. The first, a multicenter Canadian study (Table 2)[25] that accrued 936 patients from 1995 to 1998, randomized men with clinical stage T1 to T2 prostate cancer to 66 Gy in 33 fractions versus 52.5 Gy in 20 fractions. The primary endpoint was biochemical and/or clinical failure, defined as three successive increases in PSA levels, clinical evidence of local or metastatic failure, commencement of hormonal therapy, or death due to prostate cancer. With a median follow-up of 5.7 years, there was no conclusive evidence for superior efficacy of either treatment regimen. Acute gastrointestinal toxicity was slightly higher in the hypofractionated arm, but there is no difference in late toxicity between the two arms. A similar RCT currently is under way in Australia with comparable findings regarding toxicity, but for which efficacy data are not yet available.[34]

The Role of Combined Therapy

Neoadjuvant Hormonal Therapy in Combination with Radical Prostatectomy

Several studies have assessed the value of neoadjuvant hormonal therapy (NHT) prior to radical prostatectomy. However, the optimal duration of treatment and the value of this intervention are not yet entirely clear. Initial results from various trials demonstrated a decrease in the rates of positive surgical margins in those men treated with NHT prior to surgery. In a study randomizing 213 men with clinical stage T1b to T2c prostate cancer to radical prostatectomy versus a 12-week course of 300 mg cyproterone acetate with subsequent surgery, Goldenberg et al. (Table 3)[16] found positive surgical margins in 64.8% of men undergoing surgery only compared to a 27.7% positive surgical margin rate in the NHT group (p=0.001). While several other groups have reached similar conclusions regarding immediate pathologic outcomes with various NHT combinations and duration,[8, 12, 15, 22, 28, 31, 32, 120, 121] it appears that NHT prior to radical prostatectomy does not impart an overall advantage in terms of biochemical recurrence rates compared to radical prostatectomy alone.[8, 21, 31, 32, 120, 121] These findings do not support the routine use of NHT prior to radical prostatectomy.

Hormonal Therapy in Combination with Radiation Therapy

In contrast to the findings of RCTs in the neoadjuvant setting, RCTs studying primary external beam radiotherapy alone or in combination with ADT have demonstrated advantages for radiation and hormonal therapy. In an RCT of 456 men, Radiation Therapy Oncology Group (Table 4)[26] 8610 demonstrated improved local control (p=0.016), time to distant metastasis (p=0.04), and cause-specific survival (p=0.05) for patients with cT2 to T4. In a subset analysis, there was a suggestion that the benefit may be seen more in patients with Gleason score of 6 or lower. Standard external beam radiotherapy with concurrent hormonal ablation that was continued for three years imparts an overall survival advantage (five-year estimates 78% vs. 62%, p=0.0002) among prostate cancer patients with clinical stage T1 to T2 with World Health Organization grade 3 tumors, or cT3 to T4N0-1M0 any grade tumors compared to radiotherapy alone.[11] Similar results have been found by Radiation Therapy Oncology Groups 8531 (Table 4)[24] and 9202 (Table 4).[17]

More recently, D'Amico et al. (Table 4)[44] reported the outcomes of 206 men with clinical stage T1b to T2bNx, PSA levels ≥10 ng/mL, or Gleason score ≥7 who were randomized to six months of androgen suppression in combination with external beam radiotherapy or radiotherapy alone. All patients were treated with 70 Gy three-dimensional conformal radiotherapy. Those in the combination arm started radiation after two months of treatment with hormonal therapy. This study demonstrated improved disease-specific (p=0.02) and overall survival (p=0.04) in the combined treatment arm with a median follow-up of 4.5 years. In addition, fewer patients required treatment for recurrence in the combination arm (p=0.002).

Other studies have aimed to define the optimal duration and timing of androgen ablation in combination with radiotherapy. Radiation Therapy Oncology Group 9413 (Table 4)[29] was a randomized 2 x 2 factorial clinical trial designed to test whether whole pelvic (WP) radiotherapy improved progression-free survival compared to prostate-only (PO) radiotherapy and whether neoadjuvant and concurrent hormonal therapy (NCHT) improved progression-free survival compared to adjuvant hormonal therapy in men receiving radiotherapy. Patients treated with WP radiotherapy had superior progression-free survival compared to PO radiotherapy (p=0.02). There was no difference in progression-free survival between the two hormonal treatment regimens. However, in order to analyze a factorial designed trial by its factors, there must be no

statistical interaction between them. In this study, there appears to be a biologic interaction between the volume radiated and timing of hormonal treatment (p=0.011 for progression-free survival). Essentially, this means that it is more appropriate for this study to be analyzed and reported as a four-arm trial. The investigators note that NCHT was beneficial in terms of progression-free survival for those receiving WP radiotherapy while the adjuvant hormonal therapy group had more favorable progression-free survival among those with PO radiotherapy.[29]

Another recently published RCT of 378 men with clinical stage T1c to T4 disease (Table 4)[13] suggests that there was no advantage of eight compared to three months of NHT prior to 66 Gy radiotherapy for men with localized prostate cancer. The five-year biochemical failure-free survival rates were 62% versus 61%, respectively (p=0.36).[13] Another smaller clinical trial from Canada (Table 4)[23] found no biochemical-free survival advantage with the addition of adjuvant hormonal ablation (n=55) versus neoadjuvant hormonal ablation (n=63) and standard radiotherapy (seven-year estimates of 69% versus 66%, respectively; p=0.60) in a mixed patient population consisting primarily of T2 but also some T3 prostate cancer patients. However, when the sample size is so small, the risk of false-positive and false-negative results is a serious concern.

In summary, many effective therapies for prostate cancer have been developed over time, but there is a paucity of high-quality evidence to favor particular treatment modalities for men with localized prostate cancer, and this evidence is not easily developed. Two examples of the latter phenomenon include the Southwest Oncology Group (SWOG) Study 8890 and the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT). SWOG 8890 attempted to compare radical prostatectomy to external beam radiotherapy with a goal of randomizing 900 to 1,000 patients. The study accrued a total of six patients in 21 months and was thereafter closed. The same accrual problem occurred with SPIRIT, an RCT comparing radical prostatectomy with permanent interstitial prostate brachytherapy in patients with clinical stage T1c or T2a disease. Despite considerable efforts and resources to recruit patients, including attempts to enroll patients in the United Kingdom, the study accrued only 56 of the total of 1,980 needed and ultimately closed within 17 months after it was initiated. From these experiences, it seems likely that some trials will never be done due in part to patient and/or physician biases.

Future Research Needs

The development of this Guideline has revealed a host of issues that the global medical community, in both academic and private practice settings, is obligated to consider and act upon. Only by doing so will the future treatment guideline development processes be successful and will better guidance be made available for patients with newly diagnosed prostate cancer. Panel members concluded that continuous updates of this guideline would only be reasonable for the inclusion of high-quality data from RCTs. Panel members were frustrated in their decision making by the poor quality of data available, generally in the form of case series, and were of the opinion that these series have added little to assist patients in deciding among treatment options. Since 1995, when the first Panel effort was completed, tens of thousands of manuscripts have been published worldwide, but a lack of randomized clinical trials and the inconsistencies in outcomes definitions, among other challenges, have resulted in little progress in furthering the development of an evidence-based guideline.

The Panel has identified a number of opportunities for investment in research, clinical trials, and reporting of results that would provide the foundation for useful updates of this evidence-based guideline:

I. Determining which prostate cancers require therapy:
    a. Markers of biological aggressiveness of prostate cancer are critical to the management of this disease with its highly variable clinical behavior in the setting of an 18% lifetime risk in the United States.[36] These biomarkers may be constitutional, behavioral, or somatic. Valuable studies of these markers will derive from studies of patients managed with active surveillance, and it will be necessary in all other patients to factor in how treatment modulates the predictive value of these biomarkers. Additional biomarkers may prove useful to predict response to therapy.
    b. Because of the potential for significant overdetection and overtreatment of prostate cancer, integrating biomarkers of aggressiveness with early detection programs is desirable. The ideal biomarker of prostate cancer detection thus would be positive in a man with potentially aggressive disease and negative in both the man without disease and in the man with disease of very low biologic risk.

c. An essential element for rapid validation of biomarkers of disease aggressiveness will be the validation of surrogate endpoints of disease progression. The most desirable endpoints on which to base disease aggressiveness are overall survival, metastasis-free survival, disease-specific survival, and risk of disease-related morbidity. Due to the time required to reach these endpoints, surrogate markers of these endpoints would accelerate the development of validated biomarkers of disease.

II. Determining the best therapy for clinically localized prostate cancer:

a. The only method to address the most important question in the treatment of prostate cancer is to increase the number of and accrual to clinical trials. These clinical trials must ask fundamental questions such as, is radical prostatectomy or interstitial prostate brachytherapy superior for the management of prostate cancer? Given the poor track record of two such studies (SPIRIT and SWOG 8890), radical change is necessary to the conduct of these clinical trials. Elements of change could include encouraging patients, physicians, funding agencies (including third-party payers), governments, and academic organizations to write RCT protocols and to participate in them. The medical community must acknowledge that the lack of RCTs precludes conclusions regarding optimal treatment and quality of life with the available therapeutic options at this time. Medical care providers, who treat patients with prostate cancer, and the patients themselves must move to an *expectation* that *patients with prostate cancer should enroll in a clinical trial*. To meet this need, trials must be available and obstacles to accrual must be eliminated.

b. It is imperative that definitions of outcomes be standardized. Among these are:

1. Biochemical (PSA) recurrence. PSA recurrence is currently only defined by ASTRO after external beam radiotherapy. A similar definition is needed for interstitial prostate brachytherapy. The Panel has developed a definition for surgery. Although a validated definition for active surveillance will require long-term studies, it also is necessary.
2. Metastasis-free survival. There is no consensus on the definition of metastasis-free survival since, for example, adenopathy above the pelvic brim could be considered M1 disease. As nodal metastases above the pelvic brim constitute M1 disease and as cross-sectional imaging often is omitted from clinical practice, a lack of standardized

follow-up protocols for imaging studies can significantly alter estimates of this endpoint.

3. Disease-specific survival. Most patients with localized prostate cancer are elderly, have comorbidities, and usually die of other diseases. Assessment of cause of death is optimally performed by a panel of experts who use pre-established rules for cause-of-death attribution. In none of the case series reviewed by this Panel was such an endpoint review panel described. Among the RCTs reviewed, only one trial described an endpoint review panel and also indicated that there were prespecified rules for attributing cause of death. Cause-of-death rules must be developed and applied consistently by endpoint review panels.
4. Complications. The Panel was concerned by the range of definitions of complications and degrees of toxicity that were reported in the published patient series. The use of the National Institutes of Health (NIH) Common Toxicity Criteria is encouraged; it is recommended that more detailed toxicity criteria be added to the NIH criteria and that these be used consistently.[122]
5. HRQL measures. With the unclear impact of therapy on the outcomes of prostate cancer and with the clear evidence of diagnosis and treatment on various system functions (e.g., urinary, sexual, and gastrointestinal), the Panel believes that each report of outcomes of therapy for prostate cancer should include appropriate measures of HRQL or patient-reported outcomes. Validated and widely used measures, with available comparative data, are highly recommended. Efficace and colleagues[123] from the European Organization of Research and Treatment of Cancer Quality of Life unit have provided a minimum set of criteria for assessing HRQL outcomes reporting in clinical trials. These can be considered "good practice" guidelines for promoting scientific rigor, clinical relevance, and usability of HRQL data. Among their more important recommendations are:
    - Stating a priori hypotheses about expected changes in HRQL.
    - Providing a rationale for using a specific HRQL measure.
    - Using only well-validated measures with psychometric properties (i.e., reliability, validity, responsiveness) reported or referenced.
    - Using adequate domains of HRQL relevant to the studied population.

- Reporting how the instrument was administered and documenting baseline compliance, specific timing of assessments, and patterns of missing HRQL data.
- Addressing clinical significance of HRQL findings (i.e., extending beyond the traditional focus on mere statistical significance by including consideration of the clinical relevance and importance of HRQL findings).

Inclusion of appropriate assessments of complications and HRQL is imperative in the clinical trial's setting because it allows patients and physicians to *directly compare* outcomes across the various treatment modalities.

c. Risk stratification has potential merit given the outcomes displayed in graphics from this analysis. Unfortunately, current methods of risk stratification do not assist patients in making a treatment decision. For example, the patient with low-risk disease does not have one clear-cut superior treatment based on RCTs but a range of options. The same is true for the patient with high-risk disease. It is recommended that a consensus be developed for a risk-stratification system that would assist patients and their physicians in treatment decision making. The strata should be based on both tumor and host characteristics and appropriate biomarkers when they become available and are validated. One possible system would include three strata: Stratum One: A prostate cancer that has low-malignant potential during the patient's life expectancy. A patient with a Stratum One tumor might thus be a candidate for active surveillance. Stratum Two: A prostate cancer for which monotherapy would have a high likelihood of disease control. Stratum Three: A prostate cancer for which monotherapy is unlikely to provide a high rate of disease control and for which multimodal therapy may be appropriate. These disease strata would facilitate both patient treatment decision making as well as the development of clinical trials.

III. Protocol design and reporting of study results:

a. The Panel feels that because of the substantial differences among disease stage, especially between clinical stage T1 to T2 and T3 to T4 disease, any future studies including both groups of subjects should report **all** data stratified by T1 to T2.

b. For groups and institutions that report on the same patient populations in multiple papers, it is strongly recommended that a **single** cohort be described, followed, and reported on, and clear reference to previous publications of the same cohort must be made. In their

review of the literature, the Panel was extremely challenged in attempting to discern if a report from a single institution described the same patients and outcomes as had been published previously in an earlier paper.

c. Many high-impact medical journals have rigorous standards for the reporting of outcomes of clinical trials. The Panel strongly encourages all medical journals that consider publishing prospective studies on prostate cancer to adopt these criteria. Examples can be found on the following websites: *Journal of the American Medical Association* at http://jama.ama-assn.org/ifora_current.dtl; *The New England Journal of Medicine* at http://authors.nejm.org/Misc/MsSubInstr.asp; and *The Journal of Urology* at http://www.jurology.com/pt/re/juro/home.htm. Appropriate editorial and biostatistical/epidemiologic support must be made available to manuscript reviewers to assist in adhering to these standards.

Acknowledgments and Disclaimers: Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update

This document was written by the Prostate Cancer Clinical Guideline Update Panel of the American Urological Association Education and Research, Inc.®, which was created in 2001. The Practice Guidelines Committee (PGC) of the AUA selected the committee chairs. Panel members were selected by the chairs. Membership of the committee included urologists with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis- or consensus-based, depending on panel processes and available data, for optimal clinical practices in the diagnosis and treatment of clinically localized prostate cancer. This document was submitted for peer review to 87 urologists and other health-care professionals. After the final revisions were made, based upon the peer-review process, the document was submitted to and approved by the Practice Guidelines Committee and the Board of Directors of the AUA. Funding of the committee was provided by the AUA. The publication also was supported by Grant Number C12/CCC323617-01 from Centers for Disease Control and Prevention. Committee members received no remuneration for their work. Each member of the committee provided a conflict-of-interest disclosure to the AUA.

This report is intended to provide medical practitioners with a consensus of principles and strategies for the treatment of clinically localized prostate cancer. The report is based on current professional literature, clinical experience, and expert opinion. It does not establish a fixed set of rules or define the legal standard of care, and it does not preempt physician judgment in individual cases.

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Table 1. Randomized, controlled trials comparing watchful waiting/placebo to other interventions *

Author	Enrollment period	Entry criteria	Intervention (n)	Results
Iversen et al.[20]	1967 to 1975	VACURG stage I or II	Radical prostatectomy plus oral placebo (n=74) vs. oral placebo (n=68)	Outcomes (median 23 years): • Overall survival, prostatectomy vs. placebo, 10.6 vs. 8 years, respectively (p=ns) • Gleason histological grade 7 to 10 vs. ≤4 (RR 5.2; p<0.001)
Bill-Axelson et al.[10]	1989 to 1999	Stage T1 (all were T1b, T1c) or T2, PSA <50 ng/mL	Radical prostatectomy (n=347) vs. watchful waiting (n=348)	10-Year outcomes (median 8.2 years) prostatectomy vs. watchful waiting, respectively: • Disease specific mortality, the primary endpoint, 9.6% vs.14.9% (RR 0.56, CI 0.36 to 0.88; p=0.01) • Overall mortality, 27.0% vs. 32.0% (RR 0.74, CI 0.56 to 0.99; p=0.04) • Distant metastasis, 15.2% vs. 25.4% (RR 0.60, CI 0.42 to 0.86; p=0.004) • Local progression, 19.2% vs. 44.5% (RR 0.33, CI 0.25 to 0.44; p<0.001)
See et al.[119]; Iversen et al.[20]	1995 to 1998	Stage T1 to T4, M0, any stage N	Bicalutamide 150 mg (n=607) vs. placebo (n=611) once daily with standard of care (radical prostatectomy, radiation therapy, or watchful waiting) until treatment failure	Outcomes (median 5.3 years): • Overall mortality, 26.9% vs. 25.9% (p=ns) • Progression-free survival improved with bicalutamide (HR 0.57, CI 0.48 to 0.68; p<0.0001)

Author	Enrollment period	Entry criteria	Intervention (n)	Results
Wirth et al.[33] This combined analysis of worldwide trials includes data reported by Iversen et al.[20]	Not reported	Stage T1b to T4, M0, any stage N (N0 in one trial)	Bicalutamide 150 mg (n=4052) vs. placebo (n=4061) once daily with standard of care (radical prostatectomy, radiotherapy, or watchful waiting)	Outcomes (median 5.4 years): • No difference in overall survival (HR 1.03, CI 0.92 to 1.15; p=0.6) • Bicalutamide improved progression-free survival (HR 0.73, CI 0.66 to 0.80; p<0.0001) • In the North American arm, no improvement in progression-free survival (HR 1.02, CI 0.83 to 1.26; p=ns)

* The information herein only summarizes the key study methods and results; please see the original papers for complete designs, results, and conclusions.

CI, 95% confidence interval; HR, hazard ratio; ns, not significant; PSA, prostate-specific antigen; RR, relative risk; VACURG, Veterans Administration Cooperative Urological Research Group.

Table 2. Randomized, controlled trials evaluating external beam radiotherapy*

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Pollack et al.[27]	1993 to 1998	Stage T1 to T3, NX/N0, M0	70 Gy (n=150) vs. 78 Gy (n=151)	6-Year outcomes (median 60 months) for 70 vs. 78 Gy, respectively: • Freedom from clinical/biochemical failure, the primary endpoint, 64% vs. 70% (p=0.03) • No difference in overall survival • Rectal complications grade 2 or higher, 12% vs. 26% (p=0.001)
Lukka et al.[25]	1995 to 1998	Stage T1 to T2, PSA ≤40 ng/mL	Non-inferiority trial comparing a long-term (66 Gy in 33 fractions over 45 days; n=470) vs. short-term (52.5 Gy in 20 fractions over 28 days; n=466) radiotherapy regimen	5-Year outcomes (median 5.7 years) for long- vs. short-term arm, respectively: • Primary endpoint: biochemical or clinical failure, 53% vs. 60% (HR 1.18 in favor of long-term arm; CI 0.99 to 1.41); the possibility of the short-term arm being inferior could not be ruled out • Grades 3 to 4 GI or GU toxicity: acute, 7.0% vs. 11.4% (4.4 difference; CI 8.1 to 0.6); late, 3.2% vs. 3.2%
Yeoh et al.[34]	1996 to 1999	Stage T1 to T2, N0, M0	Conventional (64 Gy in 32 fractions within 6.5 weeks; n=61) vs. hypofractionated (55 Gy in 20 fractions within 4 weeks, n=59) radiotherapy	4-Year outcomes (mean 44 months) for conventional vs. hypofractionated groups: • Biochemical relapse-free, 86.2% vs. 85.5% (p=ns) • No difference in GI morbidity between groups; 4 of 6 GI signs (rectal pain, mucous discharge, urgency of defecation, and rectal bleeding) were still increased at 2 years

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Zietman et al.[35]	1996 to 1999	Stage T1b to T2b, PSA levels <15 ng/mL	70.2 Gy (n=197) vs. 79.2 Gy (n=195)	5-Year outcomes (median 5.5 years), 70.2 vs. 79.2 Gy dose groups, respectively: • Primary endpoint: biochemical failure, 61.4% (CI 54.6 to 68.3) vs. 80.4% (CI 74.7 to 86.1; p<0.001) • Grade 2 acute GI morbidity, 41% vs. 57% (p=0.004), late GI morbidity, 8% vs. 17% (p=0.005) • No difference in overall survival
Beckendorf et al.[9]	1999 to 2002	Stage T2 or T3a, PSA <50 ng/mL (T1 allowed if Gleason score ≥7 or PSA ≥10 ng/mL)	70 Gy (n=153) vs. 80 Gy (n=153)	• No efficacy outcomes yet available • No difference in urinary or GI morbidity between groups

* The information herein only summarizes the key study methods and results; please see the original papers for complete designs, results, and conclusions.

CI, 95% confidence interval; GI, gastrointestinal; GU, genitourinary; Gy, gray; HR, hazard ratio; ns, not significant; PSA, prostate-specific antigen.

Table 3. Randomized controlled trials evaluating radical prostatectomy alone and in combination with neoadjuvant therapy*

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Labrie et al.[22]	Study initiated in 1988	Stage B or C	Radical prostatectomy alone (n=71) or with 3-month neoadjuvant therapy with LHRH agonist and flutamide (n=90)	Surgical outcomes: • Positive margins in 33.8% vs. 7.8% for prostatectomy alone and with neoadjuvant therapy, respectively (p=0.001)
Aus et al.[8]	1991 to 1994	Stage T1b to T3a, NX, M0	Radical prostatectomy alone (n=63) vs. 3-month neoadjuvant therapy with triptorelin 3.75 mg monthly (n=63). Cyproterone 50 mg b.i.d. was administered 1 week before and 2 weeks after first triptorelin injection	Outcomes (median 82 months), prostatectomy alone vs. with neoadjuvant therapy, respectively: • Biochemical progression-free survival 51.5% vs. 49.8% (p=ns) • Surgical outcome: positive margins, 45.5% vs. 23.6% (p=0.016)
Schulman et al.[31]	1991 to 1995	Stage T2 to T3, N0/M0, PSA <100 ng/mL	Radical prostatectomy alone (n=210) or with 3-month neoadjuvant therapy (n=192) with goserelin 3.6 mg monthly and flutamide 250 mg t.i.d.	4-Year outcomes, prostatectomy alone vs. with neoadjuvant therapy, respectively: • Primary endpoint: patients with PSA progression, 32.5% vs. 26.4% (p=ns) • Surgical outcome: pathological downstaging, 7% vs. 15% (p<0.01)
Soloway et al.[32]	1992 to 1994	Stage T2b, NX, M0, PSA <50 ng/mL	Radical prostatectomy alone (n=144) or with 3-month neoadjuvant therapy with leuprolide 7.5 mg monthly and flutamide 250 mg t.i.d. (n=138)	5-Year outcomes, prostatectomy alone vs. neoadjuvant therapy, respectively: • No biochemical recurrence after 5 years, 67.6% vs. 64.8% (p=ns) • Surgical outcome: positive margins, 48% vs. 18% (p<0.001)

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Goldenberg et al.[16]; Klotz et al.[21]	1993 to 1994	Stage T1 to T2, PSA <50 ng/mL	Radical prostatectomy alone (n=101) or with 12-week neoadjuvant therapy with cyproterone 300 mg daily (n=112)	5-Year outcomes (median 6 years), prostatectomy alone vs. with neoadjuvant therapy, respectively: • Biochemical recurrence, 33.6% vs. 37.5% (p=ns) • Overall survival, 93.9% vs. 88.4% (p=ns) Surgical outcomes: • Positive surgical margins, 64.8% vs. 27.7% (p=0.001)
Homma et al.[18]	1993 to 1995	Stage A_2, B, or C	All patients received leuprolide 3.75 mg every 28 days for 24 months and chlormadinone 100 mg daily for 3 months. Radical prostatectomy was performed prior to (n=86) or at the end (n=90) of chlormadinone therapy	5-Year outcomes for those receiving chlormadinone prior to or after prostatectomy, respectively: • Overall survival, 77% vs. 70% (p=ns) • No clinical relapse, 72% vs. 68% (p=ns) • No biochemical recurrence, 63% vs. 63% (p=ns)
Bono et al.[12]	1996 to 1999	Stage B or C (T2 to T3, N0, M0)	Radical prostatectomy alone (n=107) or with neoadjuvant bicalutamide 50 mg daily and goserelin 3.5 mg every 28 days for 3 months (n=114) or 6 months (n=82)	Surgical outcomes, prostatectomy alone and with 3 or 6 months neoadjuvant therapy, respectively: • Negative surgical margins for stage B, 48.7%, 75.6%, 81.0% (p<0.001) • Negative surgical margins for stage C, 25.9%, 64.3%, 70.8% (p<0.001)
Gleave et al.[15]	1995 to 1998	Stage T1b, T1c, or T2	Radical prostatectomy with either 3 months (n=223) or 8 months (n=234) neoadjuvant therapy with leuprolide 7.5 mg monthly and flutamide 250 mg t.i.d.	Interim outcomes, 3- and 8-month therapy, respectively: • Patients with detectable preoperative PSA, 56.7% and 24.9% (p=0.0001) • Positive surgical margins, 23% and 12% (p=0.01)

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Prezioso et al.[28]	Not reported	Stage T1a to T2b, N0, M0	Radical prostatectomy alone (n=92) or with 3-month neoadjuvant leuprolide 3.75 mg and cyproterone 300 mg weekly, 1 week prior to and 2 weeks after first leuprolide injection (n=91)	Surgical outcomes: • Positive margins in 60% and 39% of patients undergoing prostatectomy alone or with neoadjuvant therapy (p=0.01)

* The information herein only summarizes the key study methods and results; please see the original papers for complete designs, results, and conclusions.
b.i.d., twice daily; LHRH, luteinizing hormone–releasing hormone; ns, not significant; PSA, prostate-specific antigen; t.i.d., three times daily.

Table 4. Randomized controlled trials evaluating hormone therapy in combination with radiation therapy*

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Pilepich et al.[26]	1987 to 1991	Stage T2 to T4, M0, with or without pelvic lymph node involvement	Radiation alone (n=230) or with goserelin 3.6 mg every 4 weeks and flutamide 250 mg t.i.d. initiated 2 months before and continuing during radiation therapy (n=226) [RTOG protocol 8610]	8-Year outcomes (median 6.7 and 8.6 years for all and living patients, respectively) for radiation alone vs. with hormone therapy, respectively: • Primary endpoint: local failure, 42% vs. 30% (p=0.016) • Disease-free survival, 21% vs. 33% (p=0.004) • Death from prostate cancer, 31% vs. 23% (p=0.05) • Overall survival, 44% vs. 53% (p=ns)
Lawton et al.[24]	1987 to 1992	Stage T1 to T2 with regional lymph node involvement and all T3	Radiation with adjuvant goserelin 3.6 mg monthly initiated during final week (n=477) and continued indefinitely/until progression or radiation alone with goserelin initiated at relapse (n=468) [RTOG protocol 8531]	8-Year outcomes (median 5.6 and 6 years for all and living patients, respectively) for radiation with adjuvant therapy or upon relapse, respectively: • Local failure, 23% vs. 37% (p<0.0001) • Disease-free survival, 36% vs. 25% (p<0.0001) • Overall survival, 49% vs. 47% (p=ns)

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Bolla et al.[11]	1987 to 1995	Stage T1 to T2 (WHO grade 3) or T3 to T4 (any grade), M0; excludes patients with common iliac or para-aortic lymph node involvement	Radiation alone (n=208) or in combination with goserelin 3.6 mg every 4 weeks for 3 years, starting on first day of irradiation, and cyproterone 50 mg t.i.d. for 1 month, starting 1 week prior to goserelin (n=207; 65% completed study)	Outcomes (median 66 months) for radiation alone vs. with hormone therapy, respectively: • Primary endpoint: 5-year disease-free survival, 40% vs. 74% (HR 0.34, CI 0.36 to 0.73) • Overall 5-year survival, 62% vs.78% (p=0.0002) • Specific (death from prostate cancer) 5-year survival, 79% vs. 94% (p=0.0001)
Laverdiere et al.[23]	1990 to 1999	Stage T2 to T3	Compared radiation therapy with or without an LHRH antagonist and an antiandrogen Study 1: Radiation alone (n=43) or in combination with 3-month neoadjuvant (n=63) or neoadjuvant, concurrent, and adjuvant therapy, total 10 months (n=55) Study 2: Radiation with neoadjuvant and concurrent therapy, total 5 months (n=148), or neoadjuvant, concurrent, and adjuvant, total 10 months (n=148)	Study 1: 7-Year outcomes (median 5 years) for radiation alone or with 3-month or 10-month therapy, respectively: • Biochemical-free survival, 42%, 66%, 69% (p≤0.009) for comparison between radiation alone and the other 2 groups Study 2: 4-year outcomes (median 3.7 years) for 5- and 10-month therapy, respectively: • Biochemical failure, 34.7% vs. 31.8% (p=ns)

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Hanks et al.[17]	1992 to 1995	Stage T2c to T4, PSA <150 ng/mL, no involved lymph nodes in the common iliac or higher chains	All patients received goserelin 3.6 mg every 4 weeks and flutamide 250 mg t.i.d. for 2 months before and during radiation therapy. Therapy was discontinued in the short-term group (n=761) and continued for 2 years in the long-term group (n=753) [RTOG protocol 9202]	5-Year outcomes (median 5.8 years for all and 6.3 years for alive patients) for short-term vs. long-term groups, respectively: • Disease-free survival, 28.1% vs. 46.4% (p<0.0001) • Overall survival, 78.5% vs. 80.0% (p=ns) • Biochemical failure, 55.5% vs. 28.0% (p<0.0001) • Late GI toxicity grade >3, 1.2% vs. 2.6% (p=0.037)
Roach et al.[29]	1995 to 1999	Stage T1 to T4, biochemical failure 34.7% vs. 31.8% (p=ns), elevated PSA ≤100 ng/mL, at least a 15% estimated risk of lymph node involvement (T2c to T4 also eligible if Gleason score ≥6)	Patients received 4 months therapy with goserelin 3.6 mg or leuprolide 7.5 mg monthly and flutamide 250 mg t.i.d.: neoadjuvant (administered 2 months prior to and during) or adjuvant (administered immediately following) either whole pelvic or prostate-only radiation: Group 1: whole pelvic, neoadjuvant (n=322) Group 2: prostate only, neoadjuvant (n=323) Group 3: whole pelvic, adjuvant (n=322) Group 4: prostate only, adjuvant (n=325) [RTOG protocol 9413]	4-Year outcomes (median 60 months) for groups 1, 2, 3, and 4, respectively; RR (CI): • Disease progression, including death to any cause, 1.0, 1.52 (1.19 to 1.93), 1.32 (1.03 to 1.68), 1.29 (1.01 to 1.65) • Death to any cause, 1.0, 1.35 (0.87 to 2.09), 1.54 (1.00 to 2.36), and 1.21 (0.78 to 1.90) • Biochemical failure, 1.00, 1.52 (1.15 to 2.01), 1.30 (0.97 to 1.73), and 1.24 (0.92 to 1.65)

Author	Enrollment period	Entry criteria, stage	Intervention (n)	Results
Crook et al.[13]	1995 to 2001	Stage T1 to T4, M0	Radiation therapy with 3-month (n=177) or 8-month (n=184) neoadjuvant goserelin every 4 weeks and flutamide 250 mg t.i.d. initiated 2 weeks prior to goserelin	5-Year outcomes (median 44 months) for 3- and 8-month groups, respectively: • Freedom from biochemical failure, 61% vs. 62% (p=ns) • No evidence of disease, 64.2% vs. 66.3% (p=ns)
D'Amico et al.[44]	1995 to 2001	Stage T1b to T2b, Nx, M0, PSA between 10 to 40 ng/mL, Gleason score ≥7	3-Dimensional conformal radiation therapy alone (n=102) or in combination with neoadjuvant, concurrent, and adjuvant (initiated 2 months prior to and continuing through 2 months after radiation) flutamide 250 mg t.i.d.† and leuprolide 7.5 mg monthly or 22.5 mg every 3 months (n=88) or goserelin 3.6 mg monthly or 10.8 mg every 3 months (n=10)	5-Year outcomes (median 4.5 years) for radiation therapy alone or with hormone therapy, respectively: • Overall mortality, 23% vs. 12%, HR 2.07, CI 1.02 to 4.20 (p<0.05) • Prostate cancer-specific mortality, 6% vs. 0% (p=0.02) • Biochemical failure, 46% vs. 21%, HR 2.86, CI 1.69 to 4.86 (p<0.001)

* The information herein only summarizes the key study methods and results; please see the original papers for complete designs, results, and conclusions.
†The duration of flutamide treatment was not reported.

CI, 95% confidence interval; GI, gastrointestinal; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; ns, not significant; PSA, prostate-specific antigen; RR, relative risk; t.i.d., three times daily; WHO, World Health Organization.