

Review

Early Prostate Cancer: Prevention, Treatment Modalities, and Quality of Life IssuesJ.W. Moul^{a,*}, J. Anderson^b, D.F. Penson^c, L.H. Klotz^d, M.S. Soloway^e, C.C. Schulman^f^aCenter for Prostate Disease Research, Uniformed Services University of the Health Sciences, 1530 E. Jefferson St., Rockville, MD 20852, USA^bRoyal Hallamshire Hospital, Sheffield, UK^cUniversity of Washington School of Medicine, Seattle, WA, USA^dSunnybrook Health Science Center, Toronto, Ontario, Canada^eUniversity of Miami School of Medicine, Miami, FL, USA^fDepartment of Urology, Erasme Hospital, University Clinics of Brussels, Brussels, Belgium

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Abstract

Our understanding of the screening, prevention and treatment of early prostate cancer is improving. This is a result of new data from clinical trials and the incorporation of efficacy measures based on risk assessment and quality of life (QoL). This review aims to examine completed and ongoing clinical trials that address issues in early prostate cancer, including screening, prevention, treatment, and QoL. Prostate-specific antigen (PSA) testing has a crucial and evolving role in detecting primary prostate cancer, evaluating prevention interventions and assessing the effectiveness of treatment. Questions remain about the optimal PSA parameters appropriate for primary screening and for diagnosing relapse. Emerging and established data provide evidence that early intervention with hormone therapy, either as immediate or adjuvant therapy, delays progression in prostate cancer patients with intermediate or poor prognosis. The impact of therapeutic modality on QoL has become better characterized, as QoL instruments have been developed, validated and applied.

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1. Introduction

Prostate cancer is the most common cancer in men in Western countries and is the second leading cause of cancer death [1]. In 2002, there were an estimated 189,000 new cases of prostate cancer in the USA, with 30,200 deaths caused by the disease [2]. Prostate-specific antigen (PSA) testing has led to prostate cancer being detected at earlier stages and in younger men than was previously the case. Many men are asymptomatic and physically and sexually active at diagnosis. In addition, more patients are being treated by curative procedures [3,4]. These trends have led to increasing

numbers of patients undergoing prostate cancer management for longer periods of time.

However, a levelling in the rate of diagnosis of prostate cancer has occurred in recent years [2]. In addition, a recent analysis found that, on average, pre-treatment PSA level fell by a rate of 0.8% per year between 1988 and 1997 [5]. This is an especially encouraging trend that is greatest in African Americans, in whom significant downward shifts in the clinical stage and pathologic grade of prostate cancer have also occurred [5,6].

Management options for clinically localized prostate cancer include radical prostatectomy, radiotherapy and watchful waiting. Potentially curative procedures are normally offered to men with a life expectancy of ≥ 10 years [7]. In addition, adjuvant therapy in the form of androgen deprivation has been shown to improve survival when given during, and for 3 years after,

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¹ The opinions and assertions contained herein are the private view of the author and are not to be construed as the reflective views of the US Army or the US Department of Defense.

radiotherapy [8,9] and there is increasing evidence that hormone therapy for prostate cancer patients with intermediate or poor prognosis delays disease progression [10–12].

This article reviews ongoing and completed trials that address issues in early prostate cancer screening, prevention and treatment, and examines the impact of treatment on health-related quality of life (QoL).

2. Prostate cancer screening

Two large trials are ongoing to investigate whether screening by digital rectal examination (DRE) plus PSA testing can reduce mortality from prostate cancer.

The European Randomised study of Screening for Prostate Cancer (ERSPC) trial is enrolling men aged 55–67 years and, to date, has recruited 163,126 men. Three-year results from 60,211 Finnish men in the ERSPC trial show that screening is acceptable for the target population, with a 69% participation rate [13–15]. Men with a PSA level of ≥ 4.0 ng/ml were referred for DRE, transrectal ultrasound, and biopsy, while men with a PSA level of 3.0–3.9 ng/ml were offered DRE alone. The overall disease detection rate was 2.6%, ranging from 1% in men aged 55 years to 5% in those aged 67 years. The detection rates for Gleason scores 2–6 and 7–10 cancers were 2.1% and 0.4%, respectively.

The Prostate, Lung, Colorectal and Ovarian (PLCO) trial aims to enrol 150,000 American men aged 55–75 years, with a 13-year follow-up period [16]. A study of 32,486 men from the core age group (55–69 years) found 3362 men (10%) with a serum PSA level of ≥ 4 ng/ml; this PSA level was used as a cut-off for biopsy, which was performed in 84% of cases. An additional 6% of men were referred for further assessment based on other criteria [13]. Both the ERSPC and PLCO trials have the power to show definitive results during 2005–2008.

There is a substantial period of time during which most curable disease can be detected. This provides a rationale for less frequent prostate cancer screening [17]. PSA data recently became available from a study of 27,863 men aged 55–74 years participating in the PLCO trial, of whom 55% had initial PSA levels < 2 ng/ml [18]. Over 98% of men with a PSA level < 1 ng/ml at baseline still had a PSA level < 4 ng/ml after 4 years of annual PSA testing, and over 98% of men with a baseline PSA level of 1–2 ng/ml had a PSA level of < 4 ng/ml after 1 year. This report therefore recommends PSA testing every 5 years and every 2 years for men with baseline PSA levels of < 1 ng/ml and 1–2 ng/ml, respectively.

3. Primary prevention strategies

Although chemoprevention is already well established in areas such as cardiovascular disease and breast cancer, it is a relatively unproven concept for prostate cancer. It is important to distinguish between primary prevention, which reduces cancer incidence, and secondary prevention, which delays cancer progression. The slow natural history of prostate cancer necessitates that trials of prevention should be large and long term [19]. Stratification of patients into risk groups (based on criteria such as PSA level, Gleason score, and pathologic stage) is valuable to allow conclusions to be generated.

Preliminary data for selenium and vitamin E indicate that their use in the primary prevention of prostate cancer warrants further study. In a placebo-controlled study of selenium supplementation for cancer prevention in 974 men with a history of skin carcinoma, secondary endpoint analyses showed that supplemental selenium (200 μ g/day selenized yeast) was associated with a significant reduction in prostate cancer risk of 63% compared with placebo ($p = 0.002$), at a mean follow-up time of 2.5 years [20]. The placebo-controlled Finnish α -Tocopherol, Beta-Carotene Cancer Prevention Study examined the effect of 50 mg α -tocopherol (a form of vitamin E) and beta-carotene, separately or together, on prostate cancer risk in 29,133 male smokers [21]. At a median follow-up of 6.1 years, mortality from prostate cancer was 41% lower (95% confidence interval [CI] –65%, –1%) among men who received 50 mg α -tocopherol compared with those who did not. Results from the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT), involving over 32,000 men, are expected in 2012 [22].

Data for other possible risk factors, such as a low-fat diet, stress, and vitamin D are also encouraging, although studies to-date have not been large or conclusive [23,24]. Herbal therapies such as PC SPES and SPES [25,26] have gained popularity as alternatives to conventional hormonal ablation in patients with a rising PSA level after primary therapy, as a result of the perceived benefits of using natural products and the proven clinical response in causing a reduction in PSA level. However, in February 2002, following safety concerns after the discovery of undeclared prescription drug ingredients in PC SPES and SPES (warfarin and alprazolam, respectively), the manufacturers recalled the drugs in the USA.

An ongoing Phase III, randomized, double-blind, placebo-controlled trial of finasteride (5 mg/day) for the primary prevention of prostate cancer (the Prostate Cancer Prevention Trial) includes 18,882 men and will

close in 2003 (results are expected during 2004–2005) [27]. Trials of cyclo-oxygenase inhibition in prostate cancer using Cox-2 inhibitors are also underway [28].

Trials in the prevention of precursor lesions, such as prostatic intraepithelial neoplasia (PIN), are another valuable approach to primary prevention. Several cooperative group trials of PIN prevention are underway.

4. Treatment of early prostate cancer

Current treatment options for early prostate cancer include radical prostatectomy, radiotherapy, hormone therapy (androgen ablation) and watchful waiting. For younger patients with T1 or T2 disease, radical prostatectomy is currently the most common treatment choice, followed by radiotherapy and watchful waiting. However, the use of androgen deprivation therapy as primary treatment, neoadjuvant therapy for patients planning radiotherapy, adjuvant therapy, or as therapy for biochemical recurrence following radical prostatectomy or radiotherapy is growing in intermediate- and high-risk groups [29,30].

A controlled trial comparing radical prostatectomy with watchful waiting showed no difference in survival after 23 years' follow-up [31]. However, this study was relatively small ($n = 142$) and was conducted before PSA testing had an impact on the diagnosis and management of prostate cancer. Recently, data from the Scandinavian Prostatic Cancer Group (SPCG-4), on radical prostatectomy versus watchful waiting in 695 patients with T1b, T1c, or T2 prostate cancer became available [32]. During a median follow-up of 6.2 years, 62 men in the watchful waiting group and 53 in the radical prostatectomy group died ($p = 0.31$). In all, 31/348 (8.9%) deaths amongst those patients assigned to watchful waiting and 16/347 (4.6%) deaths amongst those assigned to radical prostatectomy were due to prostate cancer (relative hazard, 0.50; 95% CI 0.27, 0.91; $p = 0.02$). Patients assigned to surgery had a lower relative risk of distant metastases than men assigned to watchful waiting (relative hazard, 0.63; 95% CI 0.41, 0.96). The investigators concluded that radical prostatectomy significantly reduced disease-specific mortality, but in this relatively short follow-up period there was no significant difference between surgery and watchful waiting in terms of overall survival.

Several other trials of watchful waiting are ongoing. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is comparing the effects of radical prostatectomy and watchful waiting on survival and QoL in 1050 men aged <75 years with clinically localized prostate cancer [33]. The European Organi-

sation for Research and Treatment of Cancer (EORTC) study 30991, a randomized Phase III step-up study on initial antiandrogen monotherapy in comparison with watchful waiting in asymptomatic (T1–3, any Gleason score, N0 or NxM0) prostate cancer patients without local treatment of curative intent, opened in 2001 and aims to recruit 1266 men.

For low-risk prostate cancer, survival differences may be difficult to demonstrate within the confines of manageable cohort size and study duration. In that context, trials that include QoL as an important secondary endpoint (e.g. PIVOT) may generate quality-adjusted survival rates that would affect decision-making. Modern trials often include endpoints based on biochemical progression or disease progression. These include PSA doubling time (e.g. in a post-radical prostatectomy setting, ≥ 2 years, with a minimum PSA level of 0.5 ng/ml), or a progression of 1–2 Gleason scores, or local progression.

Ongoing randomized trials comparing active treatment modalities in early prostate cancer are shown in Table 1. Preliminary data are available from the Canadian Urologic Oncology Group trial, CUOG-P-95A, and the bicalutamide ('Casodex'²) Early Prostate Cancer (EPC) program. CUOG-P-95A is comparing 3 months of neoadjuvant hormone therapy (leuprolide plus flutamide) with 8 months of the same therapy before radical prostatectomy in 547 patients [35,36]. Serum PSA levels decreased by 89% (to 0.12 $\mu\text{g/l}$) after 3 months' therapy, with a further 53% decrease (to 0.056 $\mu\text{g/l}$) between 3 to 8 months' therapy. Presurgical PSA nadir levels were <0.1 $\mu\text{g/l}$ in 35% of patients in the 3-month group compared with 73% of patients in the 8-month group, and >0.3 $\mu\text{g/l}$ in 37% and 10% of patients, respectively.

The ongoing bicalutamide EPC program, the largest prostate cancer intervention trial in history, compared the non-steroidal antiandrogen bicalutamide (150 mg/day), plus standard care (radical prostatectomy, radiotherapy or watchful waiting) with placebo plus standard care in 8113 patients with localized or locally advanced prostate cancer [10,11,34,38]. The study consisted of three randomized, double-blind, placebo-controlled trials, conducted in separate geographic regions: North America (Trial 23; $n = 3293$), Europe, South Africa, Israel, Australia and Mexico (Trial 24; $n = 3603$), and Scandinavia (Trial 25; $n = 1218$). At the first analysis scheduled in the protocol, conducted after a median of 3 years' follow-up, survival data were immature, with 6% overall mortality and <2% of patients dying of prostate cancer. However, overall data show a 42% reduction

² 'Casodex' is a trademark of the AstraZeneca group of companies.

Table 1

Ongoing randomized trials comparing active treatment modalities in early prostate cancer

Trial	Design	n	Endpoints included [references]
Bicalutamide EPC program	Bicalutamide 150 mg/day plus standard care (RP, RT, WW) compared with placebo plus standard care	8113	Overall survival, disease-free survival [10,34]
ACOSOG SPIRIT	RP versus BT in patients with Gleason score 6, PSA <10 ng/ml, T1c or T2a disease	1890	Overall survival, QoL
RTOG 99-02	Androgen ablation, RT +/- chemotherapy with acetazolamide, etoposide and estramustine for localized high-risk prostate cancer	1440	Overall survival, biochemical control, local control, disease-free survival
EORTC 30943	Immediate versus deferred hormone therapy in patients with elevated PSA level after definitive treatment for localized prostate cancer	1166	Overall survival, disease-free survival, QoL, cost effectiveness
EORTC 22961	RT + 6 months maximal androgen blockade then LHRHa (30 months) versus no further treatment	966	Overall and disease-free survival, disease-free interval, local regional control, toxicity, QoL
RTOG 96-01	RT +/- bicalutamide 150 mg (for 2 years) in patients with rising PSA level following radical prostatectomy	810	Overall survival, second PSA-based progression, time to distant failure, and disease-specific survival
MRC/SWOG/NCIC PR07	Hormone therapy plus radical radiotherapy versus hormone therapy alone in non-metastatic prostate cancer	650	Overall survival, disease progression and symptomatic local control
CUOG-P-95A	3 versus 8 months of neoadjuvant hormone therapy	547	PSA-free survival [35,36]
NCI ECOG: E-97077, MDA-ID-97077, NCI-T97-0069	12 months of total androgen blockade after RP for T1–2, M0, high-risk patients	496	Disease-free survival at 5 years [37]

ACOSOG SPIRIT: American College of Surgeons Oncology Group Surgical Prostatectomy versus Interstitial Radiation Intervention Trial; BT: brachytherapy; CUOG: Canadian Urologic Oncology Group; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; EPC: Early Prostate Cancer; LHRHa: Luteinizing hormone-releasing hormone; MDA: MD Anderson; MRC: Medical Research Council; NCI: National Cancer Institute; NCIC: National Cancer Institute of Canada; PSA: prostate-specific antigen; QoL: quality of life; RP: radical prostatectomy; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; WW: watchful waiting.

in the risk of objective progression (Fig. 1); 13.8% versus 9.0% [10]. The reduced risk of disease progression was observed in both localized and locally advanced disease. There was also a 33% reduction in the risk of bone metastasis (7.9% versus 5.3%), and a 59% reduction in the risk of PSA progression (33% versus 17%) with bicalutamide 150 mg compared with

standard care alone [10,34,38]. Exploratory subgroup analyses showed that a reduction in objective progression occurred irrespective of the type of standard care (Fig. 2) [39]. The tolerability of bicalutamide is closely related to its pharmacology, with gynaecomastia and breast pain being the most common adverse events. These adverse events were mild-to-moderate in >90%

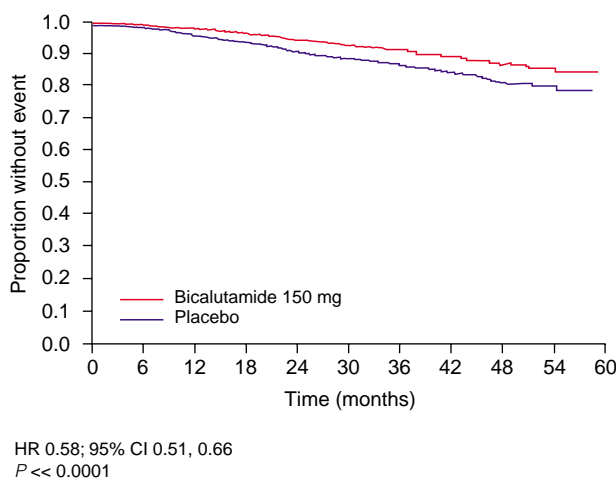


Fig. 1. Kaplan–Meier curve showing time to objective progression (progression-free survival; confirmed by bone scan, magnetic resonance imaging, ultrasound, or computed tomography scan) in the bicalutamide EPC program [10].

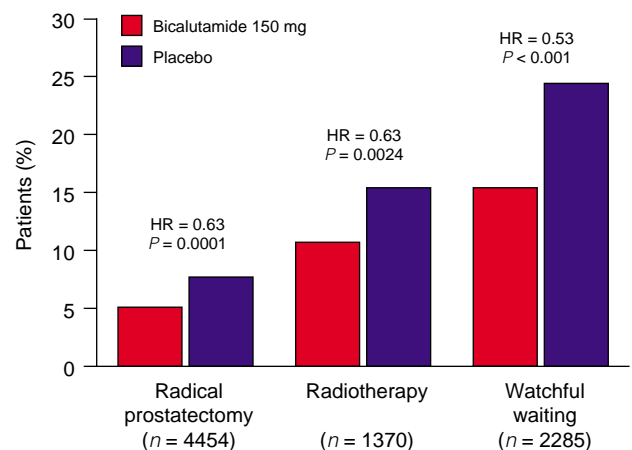


Fig. 2. Percentage of patients with objective disease progression (confirmed by bone scan, magnetic resonance imaging, ultrasound, or computed tomography scan) following radical prostatectomy, radiotherapy or watchful waiting in the bicalutamide EPC program [39].

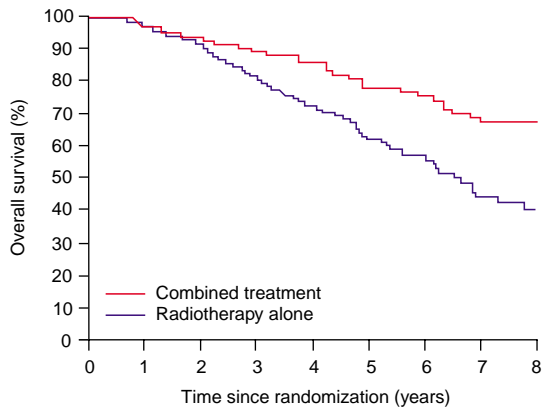


Fig. 3. Kaplan–Meier estimate of overall survival in men with locally advanced disease (M0) who had received radiotherapy and immediate or deferred goserelin (EORTC 22863) [8]. Overall survival rate at 5 years was 78% (95% CI 72%, 84%) for the combined-treatment group and 62% (95% CI 52%, 72%) for the group treated only with radiotherapy ($p = 0.0002$).

of cases. This study must be interpreted with caution, as the data are immature, and since early treatment with bicalutamide could reduce the duration of response to androgen ablation in a post-progression setting. Longer follow-up will determine whether the reduced risk of disease progression will translate into a survival benefit.

4.1. Early versus deferred hormone therapy?

Studies in rat prostate cancer models support the use of immediate hormone therapy, which is most effective in terms of survival when initiated at the time of, or early after, tumor implantation [40,41]. For patients with locally advanced prostate cancer who receive radiotherapy, several prospective, randomized, controlled, multicenter trials have indicated that adjuvant hormone therapy (goserelin [‘Zoladex’³] or orchiectomy) extends progression-free survival and may also improve overall survival in some patients [8,9,42–45] (Fig. 3). Although data on the use of adjuvant hormone therapy after radical prostatectomy are currently more limited, results from two studies support this approach in patients with an unfavorable prognosis [46,47] (Fig. 4).

Supporting the case for early intervention in the adjuvant setting, recent data show benefits with androgen deprivation therapy, in terms of: reduced PSA levels; reduced tumor volume; improved margin status; pathologic down-staging; and reduced risk of progression [10,38]. In a small study of immediate versus deferred hormone therapy for prostate cancer patients not suitable for local treatment of curative intent, median time to disease progression was 2.8 years longer for patients receiving early hormone therapy, although this study found no difference in the overall

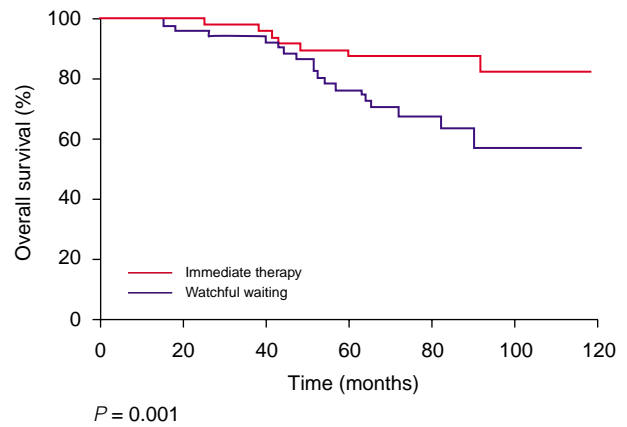


Fig. 4. Kaplan–Meier estimate of overall survival in men with lymph node metastases at radical prostatectomy randomized to adjuvant hormone therapy or watchful waiting [46].

pain-free interval after orchiectomy, and maximum pain levels and performance status were the same in both groups [48]. Taken together, the evidence provides a rational basis for the early initiation of hormone therapy. However, the question of exactly how early to treat is unanswered. Several nomograms, equations and tables for risk stratification for localized prostate cancer have been developed, taking into account several prognostic factors such as a PSA level, Gleason score, and clinical or pathologic stage [49,50].

5. Defining biochemical failure after treatment for early prostate cancer

Management of patients with a rising PSA level after radical prostatectomy or radiotherapy is a common problem [29,50–52].

5.1. Radical prostatectomy

For patients who have undergone radical prostatectomy, biochemical failure is broadly defined as a post-operative elevation of the PSA level. However, the PSA level threshold used to define biochemical failure has not yet been standardized. Amling et al. [53] investigated the effect of using various PSA cut-off levels for defining biochemical progression in 2782 men with clinically localized prostate cancer (cT1–T2) who had undergone radical prostatectomy. Based on results from this study, it was proposed that a PSA cut-off level of ≥ 0.4 ng/ml may be the most appropriate definition of biochemical failure after radical prostatectomy. In the authors’ experience, the most common cut-off level used in clinical practice is ≥ 0.2 ng/ml. In the Mayo series, 51% of patients with a PSA < 0.2 ng/ml did not

³ ‘Zoladex’ is a trademark of the AstraZeneca group of companies.

experience a continued rise in PSA level over 3 years [53]. In such patients, benign prostate glands at the margin may account for some of the detectable PSA level, and further studies are warranted to investigate this important observation. It seems sensible to adopt the Amling definition (a PSA level of ≥ 0.4 ng/ml) as the standard until further evidence becomes available.

5.2. Radiotherapy

The American Society for Therapeutic Radiology and Oncology (ASTRO) defined biochemical failure after radiotherapy as three consecutive rises in PSA level after post-treatment PSA nadir is achieved [54]. Although this definition is widely used, it does have limitations including an inability to define “cure”. Using data from 688 patients treated with radiotherapy, Taylor et al. [55] evaluated the sensitivity and specificity of several modifications to the ASTRO definition. They found that a requirement for the final PSA level in a series of consecutive rises to be >1.5 ng/ml increased the specificity of biochemical failure and that, for a fixed specificity, defining biochemical failure based on two consecutive rises or the slope over the previous year, could increase the sensitivity by up to approximately 20% and lead to slightly earlier detection compared with the ASTRO definition. Investigating two different modifications to the ASTRO definition in a series of 1373 patients treated with external-beam radiotherapy, Kattan and colleagues found that estimates of recurrence rates were improved by early censoring of patients with rising PSA levels who had not yet met the failure criteria, and by counting cumulative rather than consecutive rises in PSA levels [56].

In the brachytherapy setting, biochemical failure is also defined according to the ASTRO consensus [57]. However, PSA bounce is common in patients who undergo brachytherapy [58] and may confound the diagnosis of biochemical recurrence. Nevertheless, if a patient has three consecutive rises in PSA level, this is generally considered “real” and cannot usually be attributed to bounce. In patients who experience PSA bounce, a course of antibiotics or non-steroidal anti-inflammatory drugs may determine if infection or inflammation is contributing to the rise in PSA level, although this approach has not yet been fully studied. An interesting recent study compared the ASTRO criteria with the PSA cut-off level of 0.2 ng/ml as definitions of biochemical failure in 591 men who received iodine-125 implantation, followed by external-beam radiotherapy [59]. A significantly greater percentage of men had disease recurrence by a PSA cut-off level of 0.2 ng/ml than by ASTRO criteria, and therefore, these authors suggested that a PSA cut-off

level of 0.2 ng/ml should be adopted as the standard for all curative treatments for localized prostate cancer.

5.3. Hormone therapy

5.3.1. Primary therapy

Biochemical recurrence after primary hormone therapy should be defined as three rising PSA levels at least 2 weeks apart. However, with ultrasensitive PSA assays, caution is required regarding small rises in PSA level over time [60,61]. If the patient is receiving combined androgen blockade, the antiandrogen should be withdrawn once recurrence is suspected. The patient should then be observed for at least 4 weeks if previously on flutamide and 8 weeks if previously on bicalutamide [62].

5.3.2. Neoadjuvant or adjuvant therapy

At present, there is no definition of biochemical relapse in patients who receive either neoadjuvant or adjuvant hormone therapy in conjunction with primary therapy. This issue will be addressed at the next ASTRO Consensus Development Conference, and will be the focus of much attention over the next couple of years. A recent study showed that the median time to recovery of serum testosterone to above castrate levels was 11 months following neoadjuvant hormone therapy (median duration 5 months) prior to radiotherapy [63]. Therefore, measurement of testosterone concentrations is important when interpreting post-treatment PSA levels.

5.4. Watchful waiting

The rubric of watchful waiting encompasses two radically different approaches to patient management. Historically, it meant monitoring patients for symptoms and clinical progression only, and intervening with androgen deprivation therapy upon symptomatic progression. More recently, an approach better described as “active surveillance” has been described. This involves close monitoring of PSA and local extent of disease, with active intervention for the subset of patients who demonstrate progression [64]. A further set of biopsies may be helpful to monitor tumor grade and to estimate tumor volume. The definition of PSA progression in patients on active surveillance is variable. Some clinicians use the ASTRO definition of three consecutive rises in PSA level, although this is limited in that untreated prostate cancer will usually result in a rising PSA level. Other clinicians become concerned when a PSA level of 20 ng/ml is reached, because of the associated risk of clinical metastases, while others rely on PSA velocity or rate of change. Klotz et al. [65] have reported that the median PSA

doubling time in favourable risk prostate cancer is 10.1 years. A PSA doubling time of <3 years identifies 20% of such patients as “rapid risers”, most of whom are still amenable to curative intervention. The remaining 80% appear to have relatively indolent disease.

6. QoL issues

When making treatment choices in early prostate cancer, patients must weigh the benefits, such as delay in time to progression and increased time without pain, against adverse events that may affect QoL. Health-related QoL encompasses the physical, emotional and social wellbeing of the patient and will be influenced by the psychologic and physical effects of the disease, as well as its treatment [66,67]. The psychological effects of being diagnosed with prostate cancer, even when asymptomatic, may have a measurable impact on QoL. The components of QoL often thought as being of most concern to patients with prostate cancer are impotence and incontinence. Treatment choice surveys show that only a minority of men are willing to accept a treatment that has a >50% risk of impotence [68], and that men will often accept a certain degree of reduced life expectancy in return for maintained potency [69,70]. Therefore, for treatments with similar outcomes in terms of survival or time to progression, a QoL tool that includes measures of both impotence and incontinence is an important endpoint to consider.

QoL issues become more important as therapies become more widely used, for longer durations, and in patients with fewer symptoms. Watchful waiting avoids the immediate harmful side effects of early intervention, but an impact on QoL is often experienced by men with untreated prostate cancer, in the form of troublesome local and systemic symptoms that affect their daily routine [71]. Radical prostatectomy may be associated with a loss of sexual function and incontinence, and radiotherapy may be associated with a loss of sexual function and gastrointestinal side effects [72,73]. Hormone therapies vary with respect to their side-effect profiles but, overall, QoL may be influenced by effects on physical and sexual activity, sexual interest, anemia, bone mineral density, gynecostasia, and breast pain [74,75].

Several generic, health-related QoL tools are used to measure both “function” and “bother” in patients with prostate cancer. The Medical Outcomes Study Group Short-Form Health Survey (SF-36) [76] is probably the “gold standard” generic tool. However, cancer-targeted instruments such as the Cancer Rehabilitation Evaluation System (CARES) Short Form, the Functional

Assessment of Cancer Therapy-General (FACT-G) form, and the EORTC QoL questionnaire (EORTC QLQ-C30) have been found to be more sensitive to relevant changes in men treated for local prostate cancer [66,77–79]. Some tools designed to assess the existence and severity of sexual problems, such as the Golombok Rust Inventory of Sexual Satisfaction (GRISS) [80], have been used in studies in prostate cancer treatment involving antiandrogen therapy [81–83].

Several questionnaires have been designed specifically for prostate cancer, although they differ in content and emphasis. The validated Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a supplemental prostate-targeted module used with the FACT-G tool, and addresses weight loss, appetite, and urinary and erectile difficulties in a 12-item scale [84,85]. The University of California, Los Angeles Prostate Cancer Index (UCLA PCI) is a validated 20-item questionnaire that quantifies 6 separate domains: urinary function, urinary bother, sexual function, sexual bother, bowel function, and bowel bother [79,86,87]. The prostate cancer module of the EORTC QLQ-C30, a 20-item questionnaire covering bowel, urinary, and sexuality symptoms, has been validated in men with localized [88,89] and metastatic [90] prostate cancer.

In the Prostate Cancer Outcomes Study (PCOS), based in six geographically distinct areas of the USA, a modified survey that included certain items from the UCLA PCI was being systematically used to assess the impact of primary treatment on QoL. Lower rates of impotence in groups of men who had nerve-sparing versus non-nerve-sparing radical prostatectomy, and significantly lower rates of potency and continence in older versus younger patients who had undergone radical prostatectomy, were characterized [91]. Using the same tool in a different group of patients from the PCOS, men taking luteinizing hormone-releasing hormone (LHRH) agonists as primary therapy fared worse in several domains (e.g. significantly more breast swelling) compared with men who had been surgically castrated, although similar rates of sexual function were seen [92]. When comparing androgen deprivation (castration) with no therapy in patients with newly diagnosed prostate cancer, significantly higher rates of impotence and reduced vitality were found in the former group who, despite this, were significantly more likely to be satisfied with their treatment decision than the latter group [93]. So far, QoL data from the PCOS are only available for 1–2 years out of a planned 5-year follow-up. Five-year results will be reported in 2003. A more comprehensive tool has been created by expanding the UCLA-PCI to include a hormonal domain with specific questions on

breast tenderness and gynecomastia, both of which are side effects of all currently available non-steroidal antiandrogens, to form the Expanded Prostate Index Composite (EPIC) [94–97].

Bicalutamide monotherapy has been shown to offer improved health-related QoL compared with castration in patients with locally advanced non-metastatic disease (M0). Using a brief, self-administered, patient questionnaire covering 10 domains of health-related QoL (general health perceptions, pain, emotional well-being, vitality, social functioning, physical capacity, sexual interest, sexual functioning, activity limitation, and bed disability) [98], data from two large studies showed that bicalutamide was favored in 8 out of 9 evaluable dimensions, and was statistically significant for sexual interest ($p = 0.029$) and physical capacity ($p = 0.046$), suggesting that this treatment may benefit patients with early disease [81,99].

In the Scandinavian trial (SPCG-6) of the ongoing bicalutamide EPC program, sexual function was assessed using the GRISS [80]. Sexual frequency was retained in 63.5% of the bicalutamide 150 mg group and in 78.0% of the standard care alone group, and sexual function was retained in 74.9% and 85.0% of patients, respectively.

In early prostate cancer, where many patients are asymptomatic, gynecomastia and breast pain due to androgen deprivation causes considerable bother to some patients. This problem is greater with antiandrogens used as monotherapy than with androgen deprivation. In the bicalutamide EPC program, the main side effects of bicalutamide 150 mg were gynecomastia plus breast pain (53%), breast pain alone (20%), and gynecomastia alone (13%), though these were mild-to-moderate in >90% of cases. Withdrawals due to breast pain and/or gynecomastia were 15.6% in the bicalutamide 150 mg group, compared with 0.7% in the standard care alone group [38], although withdrawals due to objective disease progression were 2.6% and 9.3% in the two groups, respectively [10]. Withdrawal rates due to breast pain and/or gynecomastia were higher in the US trial (in which most patients were receiving curative treatment) than in the Scandinavian trial (in which most patients were

undergoing watchful waiting and were, on average, older), despite similar rates of side effects, suggesting that patients in the former group are less willing to accept this form of side effect when they have already received potentially curative treatment. These side effects are reversible if therapy is withdrawn within a few months of the onset of symptoms. Although no data are available on the reversibility of long-term bicalutamide-induced gynecomastia, there are limited data from studies of gynecomastia due to other causes showing that the risk of irreversibility increases with the duration of the gynecomastia [97,100]. Studies evaluating hormone therapy and radiotherapy in the prophylaxis and/or treatment of gynecomastia and breast pain in men receiving bicalutamide are ongoing [96]. Prophylactic irradiation of the breasts has been shown to significantly reduce the incidence and severity of bicalutamide-related gynecomastia [101]. In future trials of antiandrogen therapy in early prostate cancer, it may be desirable to assess QoL using a tool (such as EPIC) that evaluates the patient's perception of breast tenderness and gynecomastia.

7. Conclusions

Trials are ongoing to address issues in early prostate cancer, including optimal screening strategies, the potential of primary prevention, the most effective treatment modalities (either as single or combined therapy), the benefits of early versus deferred hormone therapy, the PSA-based definition of biochemical failure, and the importance of QoL as an endpoint in clinical trials. Data on the efficacy of prevention will emerge as current studies mature. In the meantime, considerable data already exist that show benefits with early intervention in prostate cancer. Early results of the bicalutamide EPC program support a role for antiandrogens in the adjuvant setting. QoL is an important endpoint in trials conducted in patients with early prostate cancer, and future trials of antiandrogen therapy should include assessment of QoL parameters, including sexual function, bowel and urinary function, and gynecomastia and breast tenderness.

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