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REVIEW ARTICLE

When is active surveillance the appropriate treatment for prostate cancer?

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Abstract

Background. The incidence of prostate cancer has increased dramatically worldwide during the past few decades in part because of increased testing for prostate specific antigen (PSA). The aggressive use of this screening tool has resulted in the identification of many localized prostate cancers a majority of which are relatively low volume, low grade tumors. Older autopsy studies have documented that incidental prostate cancer is quite common especially in older men. The finasteride chemoprevention trial confirmed these findings. Many prostate cancers are not destined to progress to clinically significant tumors. Several case series have documented the natural history of clinically detected prostate cancer. The progression of disease identified by PSA testing is less certain. These studies uniformly show that many men with low grade tumors can survive for over two decades in the absence of treatment. Furthermore, randomized clinical trials have shown only a modest ten year survival advantage for those men undergoing either surgery or radiation. *Results*. As a consequence, men with low risk of disease progression may wish to consider active surveillance as a treatment option. To date, several case series have documented that men following an active surveillance protocol that includes regular PSA testing and periodic re-biopsy have an excellent outcome. The majority of these men have not demonstrated evidence of progression during the first decade of follow-up and among those that have the majority have undergone either surgery or radiation without compromise of their long-term outcome. Unfortunately, until better biomarkers become available, the outcome of any individual patient defies accurate prediction. *Conclusion*. Men with newly diagnosed prostate cancer must weigh the risk of disease progression against the potential efficacy and safety of treatment when making a decision whether to consider active surveillance as an appropriate treatment.

When is active surveillance the appropriate treatment for prostate cancer?

During the past three decades, the diagnosis of prostate cancer has increased substantially worldwide. The rise in incidence rates has been most dramatic in countries that have aggressively embraced testing for prostate specific antigen (PSA). In USA, for example, the annual age-adjusted prostate cancer incidence rates have almost doubled from 1980 to 2010 [1]. In 2009, over 192 000 men were told that they had prostate cancer. In the UK where PSA testing is much less widespread the incidence trends parallel those of USA, but at significantly lower numbers. Prostate cancer is diagnosed at a rate that is 2.5 times higher in USA when compared to the UK [2]. The higher incidence rates have occurred primarily among younger men where the rate ratio between USA and the UK is even higher. Among men age 45–54 years the ratio is 8.2; for men age 55–64 years the ratio is 6.7.

These numbers contrast dramatically with the number of prostate cancer deaths recorded worldwide. In 1991 over 33 000 men died from prostate cancer in USA [1]. Similar prostate cancer mortality rates were recorded in the UK. Since then there has been a steady decline in prostate cancer mortality in both countries, however the decline in USA has been significantly greater [2]. This is especially true for those men aged 75 years or over. Between 1994 and 2004 the age-adjusted prostate cancer mortality rate declined in USA by 4.17%, a rate four times higher when compared to the UK. In 2009, over 27 000 men died from prostate cancer in USA.

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Which prostate cancers are clinically significant?

The dramatic differences between prostate cancer incidence rates and mortality rates have led many researchers and clinicians to question whether all newly diagnosed prostate cancers pose a clinical threat. For prostate cancer, the ratio of incidence to mortality is now nearly 8:1. This compares with a ratio of only 1.3:1 for lung cancer and 2.1:1 for colorectal cancer. There is no universally accepted definition of clinically significant or insignificant disease, but cancer volume, clinical stage and tumor grade at diagnosis have consistently predicted long-term clinical outcome. As a consequence of widespread PSA testing, there has been a major stage shift towards localized disease. Many men are now diagnosed with low volume, low grade disease often presenting with only one or two cores positive containing Gleason 6 disease. Epstein et al. suggested four criteria to define clinically insignificant disease: tumor volume <0.5 ml, PSA density <0.15, no Gleason pattern 4 or 5 disease and the presence of less than 3 mm of tissue in a single needle core [3]. Although not prospectively validated, most clinicians believe that only tumors greater than 0.5 cm^3 are clinically significant.

Although well documented by older autopsy series, several recent publications have demonstrated that prostate cancer is a fairly common finding especially among older men. Researchers designing the finasteride chemoprevention trial estimated the prevalence of prostate cancer among men age 55–70 years to be 6% and powered the trial to detect a 25% reduction in prostate cancer [4]. After seven years of follow-up, prostate cancer was detected in 24% of men in the control group and 18% of men in the treatment group. Most of the cancers identified by this study were Gleason 6 tumors and were present in men with serum PSA levels below 4.0 ng/ml.

All prostate cancers will progress, but many prostate cancers progress at remarkably slow rates. As a consequence, competing medical hazards often play a more dominant role in patients' estimates of their long-term prognosis. Some men have aggressive disease that may benefit from early detection and intervention, but many others harbor cancers that grow slowly and never progress to clinical significance.

Several key studies have helped shape our understanding of the natural history of prostate cancer progression. Between 1989 and 2004, Johansson and colleagues published a series of four articles that documented the outcomes of untreated prostate cancer in a population based cohort of patients diagnosed with prostate cancer in Sweden [5]. No screening for prostate cancer took place during the period when this study population of 648 consecutive cases was assembled. Initially the authors found relatively low five and ten year mortality rates among men with clinically localized disease and challenged the use of aggressive initial treatment for all patients with low grade early stage prostate cancer. Long-term follow-up of the study cohort, however, suggested a rising mortality rate from prostate cancer for those men surviving 15–20 years following diagnosis.

In 1994 Chodak et al. published a report describing the results of conservative management of clinically localized prostate cancer [6]. Unlike the Johannson report, this study consisted of a pooled analysis of 828 case records from six non-randomized studies published during the decade preceding the report. Patients with poorly differentiated cancers had a significantly lower cancer-specific survival rate (34%) when compared with men who had well or moderately differentiated cancers (87%). In addition, men with poorly differentiated tumors were much more likely to develop metastases when compared to men who were diagnosed with well differentiated disease.

In 1998 and 2005, Albertsen et al. reported long-term outcomes of a competing risk analysis of 767 men diagnosed between 1971 and 1984 who were managed expectantly for clinically localized prostate cancer [7]. The results of this study are presented in Figure 1. Few men (4–7%) with Gleason 2 to 4 tumors identified by prostate biopsy had progression leading to death from prostate cancer within 20 years of diagnosis. Men with Gleason 5 and 6 tumors identified by prostate biopsy experienced a somewhat higher risk of death from prostate cancer when managed expectantly (6–11% and 18–30%, respectively). Men with Gleason scores 7 and 8–10 tumors identified by prostate biopsy experienced a very high rate of death from prostate cancer regardless of their age at diagnosis (42–70% and 60–87%, respectively). Very few of these men of any age survived more than 15 years.

Unfortunately, these studies do not reflect the impact of widespread PSA testing. Since the introduction of PSA screening, more than one million additional men have been diagnosed with prostate cancer in USA. Prior to PSA testing it was rare to diagnose prostate cancer before age 55 years. Since then there has been a dramatic increase in prostate cancer incidence among men in their late 50s and 60s and it is not uncommon to diagnose prostate cancer in men in their late 40s and early 50s. Compared to 1986, the relative incidence of prostate cancer is 1.91 times greater among men aged 60–69 years, 3.64 times greater among men aged 50–59 years and 7.23 times greater among men younger

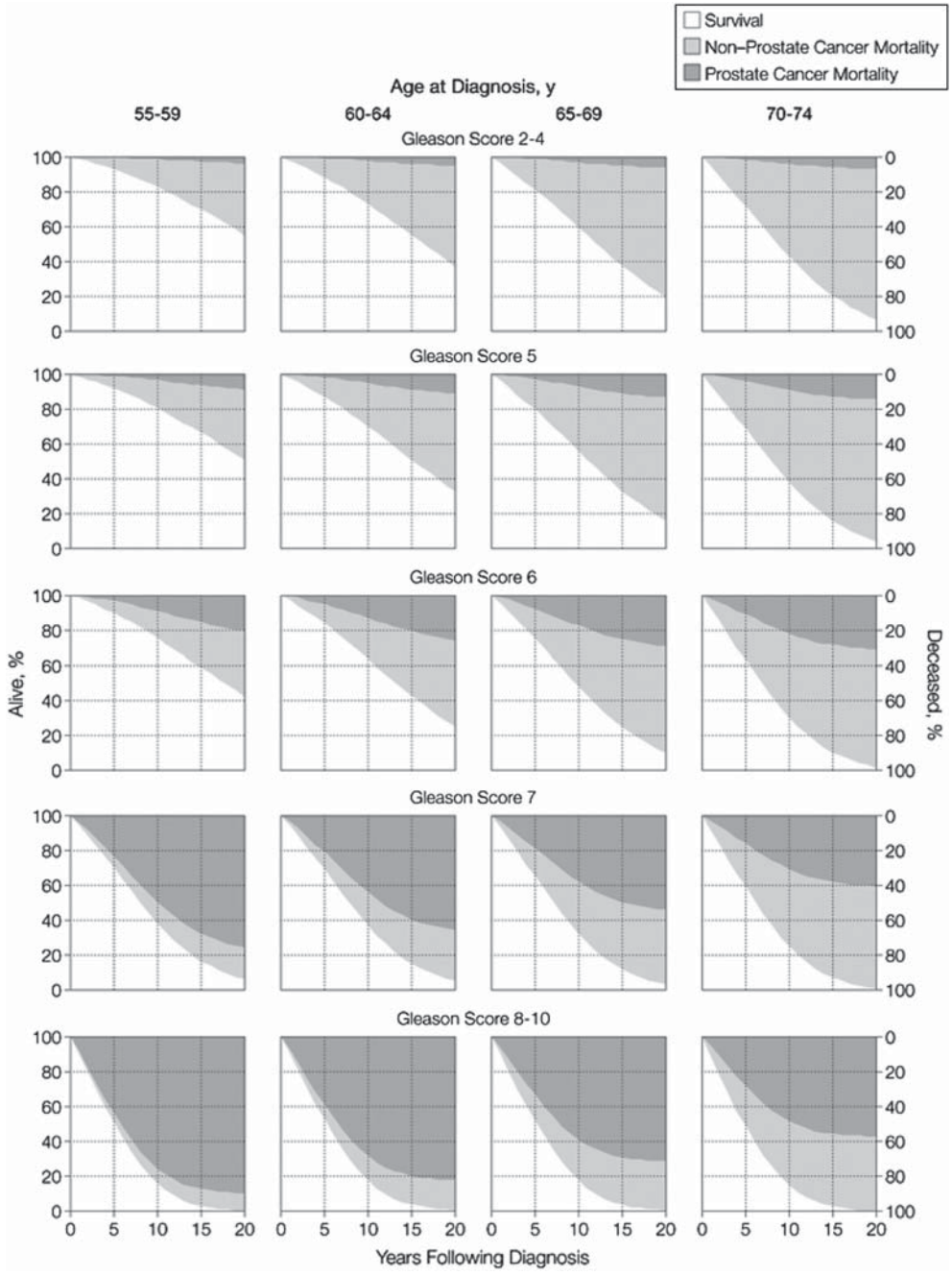

Figure 1. Survival and cumulative mortality from prostate cancer and other causes up to 20 years after diagnosis, stratified by age at diagnosis and Gleason score.

than 50 years [8]. Using computer models of incidence and mortality, Draisma et al. estimate that PSA testing has advanced the date of diagnosis by approximately 12.3 years for men age 55 years and by 6.0 years for men age 75 years [9].

Recently Grace Lu-Yao et al. explored the ten year outcomes of men over age 65 years with newly diagnosed localized prostate cancer [10]. They assembled a cohort of over 14 500 men and found that after a median follow-up of seven years most men were either alive or had died of causes other than prostate cancer (Figure 2). Ten-year prostate cancer mortality was 5.9% (95% CI, 3.6–8.2) and 6.2% (95% CI, 4.3–8.1) for men aged 66–69 years and 70–74 years, respectively, diagnosed with moderately differentiated disease. These results were much more favorable than the 15–24% mortality rates reported in the studies cited earlier. Similar improvements were observed in poorly differentiated disease. Ten-year cancer-specific mortality for T1c (screen detected) and T2 (palpable) disease was 9.8% and. 12.3%, respectively, for moderately differentiated cancer (adjusted HR = 0.63,

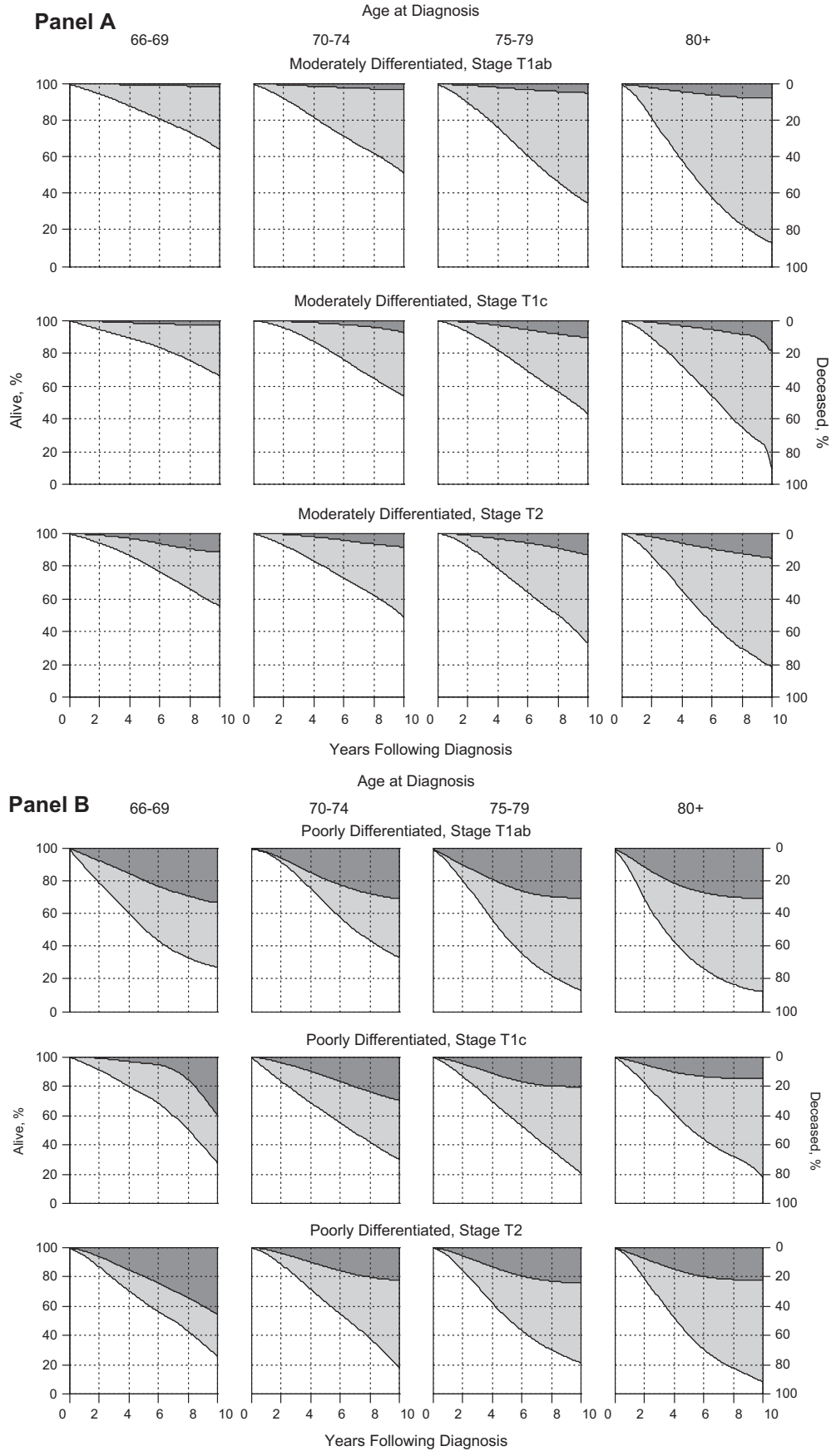

Figure 2. Competing risk of death by age at diagnosis, cancer stage, and grade. Panel A: Moderately-differentiated (Gleason 5–7) cancer. Panel B: Poorly-differentiated (Gleason 8–10) cancer.

$p < 0.001$), and 22.2% and 25.5%, respectively, for poorly differentiated cancer (adjusted HR = 0.74, $p < 0.001$). The use of chemotherapy (1.6%) and surgical or radiological intervention for spinal cord compression (0.9%) was uncommon. They concluded that contemporary men over age 65 years with screen-detected prostate cancer had survival outcomes significantly better than those in the pre-PSA era, and had a low-risk of developing cancer related complications that require palliative surgery, radiation, or chemotherapy.

Historically, tumor grade has been the most powerful predictor of clinically significant disease. When Gleason originally developed his scoring system based on lower power evaluation of glandular architecture, men were usually diagnosed following a transurethral resection, an open prostatectomy to treat obstructive urinary symptoms or a needle biopsy of a prostate nodule. Up until 2000 most pathologists used all five patterns described by Gleason, but since then many have become increasingly hesitant to grade any malignant glands lower than pattern 3. During the past decade there has been a steady inflation of Gleason scores such that all low grade tumors previously recorded as Gleason score 2–5 are now classified as Gleason score 6 and many Gleason score 6 tumors are now classified as Gleason score 7. Changes in the application of the Gleason scoring system have become so widespread that clinical outcomes are significantly improved if historical classifications are replace by contemporary classifications [11]. It is unusual for men with contemporary Gleason 6 tumors to have clinically significant progression of their disease.

Active surveillance as a treatment alternative

The rationale for selecting active surveillance over immediate surgical intervention or radiation therapy reflects the changing understanding of the risk posed by screen detected disease. Prior to the advent of PSA testing, most men presented with clinically advanced disease that often required palliative intervention. Men presenting with localized, low grade cancers frequently had slow progression of their disease and often succumbed to competing hazards [5,7]. The recent publication of results from two large randomized trials on prostate cancer screening have shown that in contemporary practice prostate cancer deaths are infrequent during the first ten years following screening and that as many as 48 men must be identified and managed to prevent one prostate cancer death [12,13].

Interest in active surveillance also reflects a greater understanding of the relative impact of intervention. Aggressive treatments make sense only if they are effective. Unfortunately, data supporting the efficacy of surgery and radiation are limited to two randomized trials both accruing men identified with prostate cancer on the basis of clinical disease rather than as a consequence of PSA testing. The Scandinavian trials of both surgery and radiation have shown that some men with localized prostate cancer live longer as a consequence of treatment, but the impact on prostate cancer mortality is modest [14,15]. At ten years, 19 men in the surgery trial and ten men in the radiation trial required treatment to prevent one prostate cancer death. Most patients participating in these trials were diagnosed on the basis of clinical findings and therefore had greater tumor volume when compared to contemporary screen detected patients. As a consequence the relative impact of treatment on contemporary patients is likely to be much less because the threat posed by clinical progression is much less.

These considerations have led clinicians at several academic medical centers to propose criteria that identify men who have a very low risk of disease progression and who may therefore want to consider a treatment strategy that defers immediate intervention in favor of a strategy that monitors disease progression and initiates treatment only when a tumor shows signs of becoming clinically significant. They have relied on concepts originally developed by Epstein to propose the following criteria: a) men who present with prostate biopsies that demonstrate prostate cancer in two cores or less, b) neither core has more than 50% involvement with disease and c) tumor histology contains no Gleason pattern 4 or 5. Active surveillance is most appropriate for men over 70 years old who have a life expectancy of 15 to 20 years or less, but can also be followed by any man who is willing to defer immediate treatment because he believes the risks associated with more aggressive treatments are not justified by the potential benefit. Active surveillance does not imply that no treatment will ever be necessary. Should additional clinical information suggest that the risk of disease progression has increased, more aggressive treatments are still available.

Several researchers have published outcomes from large observational cohorts of men who have selected active surveillance as a treatment alternative. Protocols differ slightly among institutions but usually restrict entry to men meeting the criteria outlined above. Most researchers following men on an active surveillance protocol recommend that repeat biopsies and serum PSA values be checked regularly. Protocols differ in the timing of these repeat studies. Some researchers state that a repeat biopsy should be performed within one or two months of the original positive biopsy. Others

suggest that a repeat biopsy should be performed at one year, while still others suggest that repeat biopsies can be deferred for as long as two years following the initial biopsy. Disagreement also surrounds the frequency of PSA testing. Some clinicians sample PSA every three months while others check them less frequently.

Klotz et al. recently published an update of the clinical outcomes of 450 men enrolled in an active surveillance program in Toronto [16]. After a median follow-up of 6.8 years (range 1 to 13 years) overall survival was 78.6%. The ten year prostate cancer actuarial survival was 97.2%. Most of the patients enrolled in this protocol had a low risk of disease progression. Seventeen percent of patients had Gleason 3+4=7 disease. All of the men in the latter group were older than age 70. Patients were initially followed every three months with a serum PSA level and a repeat biopsy was performed six to 12 months after the initial diagnostic biopsy and every three to four years thereafter until age 80. If the PSA doubling time was less than three years, the Gleason score increased on a repeat biopsy or there was evidence of clinical progression, patients were reclassified as having higher risk disease and were offered more aggressive therapy. After ten years of follow-up the probability of death from a competing medical condition was 18.6 times more common than prostate cancer among the patients enrolled in the study.

Six other research groups have also published their active surveillance series [17–22]. A total of 2500 patients have been enrolled and more than 200 have been followed for over ten years. All of the series rely on PSA kinetics and information obtained at repeat biopsy to identify those patients who are at a higher potential risk of disease progression. To date, the disease specific survival associated with active surveillance protocols is 99.7%.

In addition to data from case series, data from a large historical prospective cohort study also support the concept of active surveillance. Shappley et al. recently examined the consequences of deferred treatment as initial management by reviewing the outcomes of 3331 men diagnosed from 1986 to 2007 who were enrolled in the Health Professionals Follow-up Study [23]. Of these men, 342 (10.3%) initially selected no active treatment. Of these, 174 (51%) remain untreated after a mean follow-up of 7.7 years. The remainder were treated an average of 3.9 years after diagnosis. Older men and men with low risk cancer at diagnosis were more likely to defer treatment. Prostate cancer mortality did not differ among men selecting active treatment when compared to those who elected to defer treatment at the time of diagnosis.

Active surveillance, however, carries several risks. In the Klotz cohort 30% of patients have been offered more aggressive treatment because they were reclassified as having higher risk disease. Of these men, half have evidence of biochemical failure on the basis of a rising PSA. Many other patients find active surveillance disquieting. As many as one quarter of men enrolled in active surveillance programs have abandoned these programs after two years in favor of more aggressive treatment on the basis of psychological stress alone. These men have no clinical evidence of disease progression, but feel that the psychological stress of worrying about disease progression outweighs the risk of developing a complication associated with more aggressive treatment. In the SPCG-4 trial Johansson et al. reported that patients randomized to watchful waiting showed more anxiety, depression and a lower overall sense of well being when compared to those men who underwent surgery [24].

Summary

The introduction of PSA testing has dramatically increased the incidence of localized prostate cancer. Many of these newly diagnosed cancers are low volume and low grade and pose minimal threat of progression over ten years. Active surveillance is an experimental approach to managing these cases, especially for those men over age 65 years who have a life expectancy of 10–15 years. While one randomized trial has been initiated, the data supporting this approach are limited to observational cohort studies with follow-up periods of ten years or less. While not confirmed in Albertsen et al.'s observational cohort, Johannson et al. documented an increase in cancer specific mortality among men identified with palpable disease and followed beyond 15 years [5,7].

The criteria used to select and monitor men on active surveillance have not been validated. Neither PSA values nor prostate biopsies provide definitive information concerning disease progression. PSA values are known to vary widely. In a retrospective analysis of an unscreened population of 972 men with a median age of 62 years, Eastham et al. demonstrated substantial year to year variation in PSA levels [25]. Furthermore, it is unclear whether changes in Gleason score on follow-up biopsies reflect disease progression or simply reflect sampling variation. Until better biomarkers for indolent disease are identified, men considering active surveillance should carefully weigh the potential of disease progression that persists for 20 years or longer no matter how small or well differentiated the disease appears initially against the potential of complications associated with treatment that often occur shortly after the treatment has been completed.

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