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Management of low (favourable)-risk prostate cancer

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prostate cancer; low risk; favourable risk

INTRODUCTION

Prostate cancer is a heterogeneous disease with a generally long natural history in most men. A substantial proportion of men today are diagnosed with a prostate cancer that would have remained undetected in the absence of screening (over detection), and treatment, by definition, would not improve health outcomes for these men (over treatment) [1]. The likelihood that a prostate cancer will be over treated increases as the risk profile, based in large part on cancer grade, decreases from high to low risk [2]. The management of ‘low-risk’ or ‘favourable-risk’ prostate cancer is highly controversial, with wide variation in practice patterns that are driven more by personal beliefs than evidence [3].

In this review of favourable-risk prostate cancer, I will discuss the following areas; the limitations of our current paradigm for informing patients about management options, the wide disconnect between evidence and practice patterns, the available options for management, and the opportunities that will move our field away from a ‘personal opinion’ - guided strategy to one that is more evidence based.

THE CONTROVERSY

Before the widespread use of PSA in the USA for opportunistic prostate cancer screening in the late 1980s, most men were diagnosed with disease that was too far advanced for cure. This, combined with the associated morbidity of treatments, led many patients to defer management (watchful waiting) with their physicians blessing [4]. The adoption of PSA testing in the USA in the late 1980s and early 1990s, together with ultrasound-directed needle biopsy of the prostate in men with ‘elevated’ PSA levels, resulted in a stage migration favouring early localized disease. Together with improved treatments associated with lower side-effect profiles (both surgery and radiation), increased numbers of men,

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CONFLICT OF INTEREST

None declared.

including the elderly, chose to undergo curative intervention for localized prostate cancer [5] .

There is evidence that the use of PSA for prostate cancer screening, followed by treatment of prostate cancer at an earlier stage, was responsible, at least in part, for a 30 – 40% decline in prostate cancer mortality in the USA after the adoption of PSA testing [6] . Furthermore, a randomized trial with the longest follow-up (14 years), has shown an $\approx$ 40% decline in prostate cancer mortality when comparing men who did and did not undergo PSA screening for prostate cancer [7] . However, the $\approx$ 70% increase in new cases of early stage prostate cancer that occurs with screening [8] , and the treatment of most men after a diagnosis regardless of age and risk profile [9] , has led many to question the overall health benefits of PSA screening.

In large part, the controversy over PSA screening involves the downstream effects after a diagnosis, and is the result of the enthusiasm for aggressive treatment of virtually all men who are diagnosed, regardless of their risk of being harmed by the disease [3] . For example, in the USA, two of three men between ages of 65 and 74 years with favourable-risk disease and a PSA level of < 4.0 ng/mL underwent curative intervention [10] . As a result, some have raised the question of whether PSA screening is associated with more harm than benefit [11] . The enthusiasm for treatment of favourable-risk disease has led to over treatment of prostate cancer and may have many causes; among them is the inability to risk-stratify men with certainty.

DISEASE ASSESSMENT AND STRATIFICATION OF RISK

Risk stratification of men with newly diagnosed prostate cancer is performed in an attempt to identify which patients have a disease that is or is not likely to cause harm, and thus is helpful for determining optimal management.

Numerous studies have used pretreatment variables (most commonly PSA level, tumour stage, and Gleason score), to predict the probability of Gleason score upgrading at surgery, extent of disease at surgery (surgical pathology stage), and biochemical-recurrence risk after treatment [12] . The most commonly used risk-stratification tool for selecting management for men with localized prostate cancer is based on the classification schemes of D'Amico [13] and Epstein [14] , and summarized in the National Comprehensive Cancer Network (NCCN) guidelines [15] . The D'Amico classification [13] is a tool for prediction of biochemical recurrence after treatment and stratifies patients into low-, intermediate-, and high-risk categories; while the Epstein criteria [14] have been used to further stratify men into a very low-risk category that is predictive of small-volume, low-grade cancer at surgery (Table 1) [10,13 – 15] . Together, very-low to low-risk prostate cancer describes a phenotype that could be referred to as favourable risk.

The NCCN guidelines [15] , European guidelines [16] , and Agency for Healthcare Research and Quality [17] are in general agreement that a lack of randomized trials for treatment of localized prostate cancer makes decision making difficult. This is especially true for favourable-risk prostate cancer (very low to low risk) because of the prolonged natural history of the disease, the fact that most men are diagnosed at an older age, and competing

health risks among older men making it unlikely that definitive treatment will improve overall health outcomes [18] . While there is both evidence for under treatment of high-risk disease and over treatment of favourable-risk disease [3] , high level evidence suggests that over treatment of older men with favourable-risk prostate cancer is substantial [19] , and that active surveillance is an underutilized management approach that could reduce overtreatment [7] .

As a result, guidelines for favourable-risk prostate cancer recommend that multiple options and patient preferences should be considered before deciding on a management option [15,16] (Table 1).

A limitation of current paradigms that assess disease risk is misclassification. For example, the strongest predictor of cancer-specific mortality with or without treatment of prostate cancer is grade [20,21] . Thus, grade is used in all risk-stratification tools. However, a pretreatment assessment of grade is associated with both over and under estimation of risk. Under estimation, because studies have shown upgrading rates of $\approx 25\%$ at surgery for men who are thought to harbour favourable-risk cancers on prostate biopsy [22] ; and over estimation because of grade inflation [23] . Albertson *et al* . [23] have shown that cancers that are graded as high grade today (especially Gleason score 7) were classified as low-grade cancers previously. Thus, while grade is an important marker of risk, assessment of grade can be misleading as a measure of cancer lethality; especially for the most common grades (Gleason score 6 and 3+4) assigned today.

This uncertainty with respect to risk assessment, in all likelihood, leads many physicians to recommend curative intervention because of a chance of underestimation of risk. Given the limitations of current risk-stratification schemes, and the lack of comparative effectiveness studies, it is not surprising that there would be wide variations in practice patterns of management for favourable-risk prostate cancer.

VARIATION IN PRACTICE PATTERNS

The absence of a consensus regarding the optimal management of localized prostate cancer, especially favourable-risk disease, has resulted in wide variation in practice patterns [3,24] . Radical prostatectomy (RP) has been shown to be the surgical procedure with the greatest variation by locale in the USA [3] . For the use of androgen-deprivation therapy (ADT), it has been reported that the proportion of variation attributable to the treating urologist is around 20 – 25% [25] , and that ADT use for indications that were not clear (e.g. localized disease), declined with changes in Medicare reimbursement [26] .

A more recent analysis that included data on risk profile and practice variation also suggested wide variation in practice driven by factors other than disease characteristics. The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database is a national prostate cancer registry of > 13 000 men with clinically diagnosed prostate cancer in 40 practices throughout the USA [3] . Using data from this registry, Cooperberg *et al* . [3] reported that risk profile as determined by cancer stage and grade, and PSA level, was a factor in determining management. However, the variation across practice site was substantial and not explained to a great extent by disease characteristics. For example, the

proportion of variation attributable to practice site for favourable-risk prostate cancer ranged from 21% for watchful waiting to 81% for cryoablation. These data suggest that patient and physician beliefs and preferences, rather than disease characteristics, play a large role in the choice of management. The lack of comparative effectiveness studies addressing management options for favourable-risk prostate cancer could contribute to these wide variations. An alternative explanation is the limitation of using evidence to inform practice [27], and perverse incentives that often drive physician recommendations in the USA [28].

THE DISCONNECT BETWEEN EVIDENCE AND PRACTICE

The slow prolonged natural history of favourable-risk prostate cancer, and the ease of detecting a disease with high prevalence among older men who have competing risks of mortality, leads to high rates of over treatment of prostate cancer.

NATURAL HISTORY OF FAVOURABLE-RISK PROSTATE CANCER

Albertsen *et al.* [21], were among the first investigators to chronicle the natural history of favourable-risk prostate cancers in the pre-PSA era. For men with low-grade cancers (Gleason scores of 6), the 20-year cancer-specific death rates without treatment ranged from 6% to 30% depending upon the Gleason score.

These data almost certainly over estimate 'true' cancer-specific mortality today for two reasons; the lead time afforded with PSA testing and grade migration. When compared with cancers detected without the use of PSA, PSA-detected cancers are thought to be diagnosed on average 6 – 12 years earlier depending upon patient age [29]. Further, as indicated by Albertsen *et al.* [23], many of the Gleason scores assigned as 'low grade' in the past would be re-classified today as higher grade, thus the outcomes stratified by Gleason score in the past may have been overly pessimistic. In this regard, the lethality of PSA screen-detected cancers is overestimated by earlier pre-PSA era studies that evaluated untreated men. While there are no 15 – 20-year outcomes for untreated men with favourable-risk prostate cancer diagnosed in the modern 'PSA era', 10-year outcomes of untreated men in the pre-PSA compared with the PSA era are revealing.

Lu-Yao *et al.* [2], evaluated the outcomes of conservatively managed patients in 1992 – 2002 (PSA era) and compared these outcomes with those published in the era before 1992 (pre-PSA era). They found that among those men with moderately differentiated cancers (Gleason scores 5 – 7), cancer-specific mortality for untreated men aged 65 – 74 years after 10 years was from 2% to 6% for those diagnosed from 1992 to 2002 compared with 15 – 23% for those diagnosed before 1992. In a competing risks model of hazard from prostate cancer mortality, Parker *et al.* [30] estimated the 15-year risk of prostate cancer mortality in the PSA era to be 0 – 2%, for men aged 55 – 74 years diagnosed with a Gleason score of 6 and managed conservatively. Given the low threat from favourable-risk prostate cancer without treatment, the extent to which over treatment occurs depends in part on the prevalence of the disease and treatment patterns.

HIGH PREVALENCE OF FAVOURABLE-RISK PROSTATE CANCER

The Prostate Cancer Prevention Trial (PCPT) led to an increased awareness of the high prevalence of favourable-risk prostate cancer among men with PSA levels of < 4.0 ng/mL. Thompson *et al.* [31] found that 15% of men at a median age of 69 years, with PSA levels of < 4.0 ng/mL (average PSA level $\approx$ 1.5 ng/mL), had prostate cancer on a sextant biopsy. Of those with cancer, 85% were favourable risk. In the PSA level range where many men are undergoing prostate biopsy today (2.1 – 4.0 ng/mL), prostate cancer was discovered in 25% of the men, and 80% of these were low-risk cancers. These prevalence data are consistent with the autopsy study of Haas *et al.* [32], who found that $\approx$ 30% of men at an age and PSA similar to the PCPT, had prostate cancer found on careful step sectioning of the prostate. About half of these (15%) could be detected on their *ex vivo* biopsies – a percentage similar to that found in the PCPT. Thus, the prevalence of favourable-risk disease on a prostate biopsy performed at PSA levels triggering prostate biopsies today is substantial, and has major implications for management.

Because the average age at diagnosis of prostate cancer is 67 years, and a substantial proportion of these men have favourable-risk prostate cancers with a prolonged natural history, the likelihood that curative intervention would lead to a reduction in prostate cancer mortality is small among older men with favourable-risk disease. High level evidence supports the low risk of harm without treatment from favourable-risk prostate cancer in older men, yet clinical practice does not reflect these findings.

THE EVIDENCE

The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) [19], randomly assigned 695 men with localized prostate cancer to RP or watchful waiting. In this landmark trial, patients did not have ‘screen’-detected prostate cancers and to a large extent would not be considered favourable risk by today's classification schemes (Table 2) [19]. The mean age of subjects (65 years) was similar to the average age (67 years) at diagnosis today. However, unlike most men diagnosed today, only 5% were screen detected and three of four had palpable cancers. Furthermore, about one in three men had Gleason scores of $\leq$ 7, and PSA levels were $\leq$ 10 ng/mL in almost half of the subjects. Thus, the demographics of these men were very different from men today with favourable-risk prostate cancer detected with PSA-based screening. After 12 years follow-up, the investigators showed the effectiveness of surgical treatment of prostate cancer. There was an absolute 5% and 7% significant reduction in prostate cancer deaths and metastases, respectively, associated with surgical treatment when compared with no treatment. However, as compared with men aged < 65 years, there was no overall, cancer-specific, or metastatic-free survival benefit for those men aged $\geq$ 65 years. The absence of a metastatic-free survival benefit at 12 years would suggest the probable absence of a cancer-specific survival benefit well beyond 12 years in this cohort, as metastatic disease predates prostate cancer death by years. Estimates by Parker *et al.* [30] predicted an absolute 15 year overall survival benefit for screen-detected, favourable-risk prostate cancer (Gleason $\leq$ 6) of 1 – 2% when comparing treatment with no treatment. For those men diagnosed with favourable-risk prostate cancer through PSA

screening in which there is a considerable lead time, curative intervention is unlikely to improve health for those with a < 20 year life expectancy.

What do these data tell us about the benefits of curative intervention as a management option for favourable-risk prostate cancer diagnosed today? First, the data suggest that any man with favourable-risk prostate cancer should understand that without treatment, harm from disease is unlikely in the first decade. However, progression of disease could occur in some men resulting in harm without treatment in the second decade after diagnosis and beyond. The average life expectancy of a man aged 70 years in the USA is 13 years. It has been suggested that for those in the top quartile of health, life expectancy may be 50% greater, or 19 – years for a subset of one in four men aged 70 years [33] . Perhaps for a subset of these one in four men, curative intervention might be beneficial. But for the overwhelming majority of men aged 70 years, with a favourable-risk prostate cancer, curative intervention will be associated with more harm than benefit. Thus, if one used the above data to inform the management of a favourable-risk prostate cancer diagnosed today in a man aged 70 years, one could conclude that based on the best available evidence, the optimum management for the overwhelming majority of these men should be active surveillance. Current practice would suggest a rather large disconnect between evidence and practice, at least in the USA.

CURRENT PRACTICE

In the National Cancer Institute Patterns of Care Study, a population-based evaluation, half of the men were diagnosed with favourable-risk disease in 2002 [24] . Watchful waiting, as a management option, decreased in all age groups between 1998 and 2002. Among older men, the proportion receiving surgery declined between 1998 and 2002, especially in the age range of 65 to 74 years. However, 71% of men aged 75 years with favourable-risk disease received aggressive therapy with either external beam radiotherapy or brachytherapy (Fig. 1) [24] . Watchful waiting was the management option for 12% of men with favourable-risk disease aged 65 – 74 years, and about one in five men aged 75 years with favourable-risk disease. Thus, among older men with favourable-risk disease, these data and others [9] point to *alarmingly high rates of over treatment* for prostate cancer in the USA.

In recent updates from the CAPSURE registry that evaluated > 10 000 men, 36% to 46% of men were classified as favourable-risk depending on definitions used, and of those men, 10% were managed without immediate treatment [3,34] . The trends in management show that the proportion of men managed without immediate treatment (watchful waiting or surveillance) are lower in 2004 – 2007 when compared with 1990 – 1994. This is surprising given a better understanding of the natural history of favourable-risk prostate cancer over time. Furthermore, published results from the SPCG-4 [19] should have informed clinical practice and led to reductions in curative intervention and increases in surveillance of favourable-risk prostate cancers, especially among older men.

Although surgery is the management option used least frequently among older men with favourable-risk prostate cancer, recent data show that hospital discharges for RP have increased > 50% among men aged 65 – years in the USA between 2005 and 2008,

commensurate with the adoption of robot-assisted laparoscopic RP [35] . The extent to which this increase applies to men with favourable-risk cancers is currently unknown, but probably substantial with the diffusion of robotic surgery and the advertisement of a ‘minimally’ invasive approach to RP with claims of far superior outcomes [36] .

In contrast to the high rates of over treatment of favourable-risk prostate cancer in the USA, there may be less over treatment in European countries. For example, in the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized cancer screening trial in the USA, $\approx 10\%$ of men in both arms did not undergo any immediate treatment after a diagnosis of prostate cancer [37] . In the European Randomized Study of Screening for Prostate Cancer (ERSPC) [8] , $\approx 19\%$ of the screening arm was managed with watchful waiting after a prostate cancer diagnosis; and in the Goteborg section of the ERSPC [7] , 30% of men in the screening arm diagnosed with prostate cancer were in active surveillance at the time of reporting. In the UK, ‘watchful waiting’ as a management option for favourable-risk disease increased from 0 to 39% over the period from 2000 to 2006 [38] . These data suggest that when compared with the USA, management of prostate cancer in other countries may be more evidence based.

MANAGEMENT OF FAVOURABLE-RISK PROSTATE CANCER: OPTIONS AND OUTCOMES

Today, patients with favourable-risk prostate cancer find themselves in the ‘prostate cancer treatment bazaar’ with an overwhelming choice of options [39] , a lack of evidence to support one choice over another [17] , and a resultant lack of consensus among providers that has led to marked variation in practice patterns [3] . The NCCN [15] and European guidelines [16] recommend that both curative intervention options and surveillance be discussed with newly diagnosed patients with favourable-risk (very low to low risk) prostate cancer. The primary management options include external beam radiotherapy, brachytherapy, RP, and active surveillance (Table 1). There is no evidence that any management option improves overall health outcomes when compared with another form of management for PSA screen-detected cancers [17] , although most men in the USA choose curative approaches. The lack of randomized trials and the use of intermediate endpoints in most case series, make management decisions difficult, especially for a disease with a long natural history. Patients making choices between curative management options should be made aware of differences in side-effect profiles of the various options [40] , and consider their own personal preferences. Nevertheless, in the absence of comparative effectiveness studies, factors other than those related to patient and disease will continue to heavily influence choices, and contribute to wide variations in practice for favourable-risk disease.

While high-intensity focused ultrasound and cryosurgery have been used to treat low-risk prostate cancers, long-term data to support their use in this setting is lacking [15,16] , and patients should be appropriately informed. ADT is discouraged as a primary management or as adjunctive therapy for management of favourable-risk disease because of the associated side-effects of androgen deprivation, and lack of evidence for benefit [15,16] .

For men with favourable-risk prostate cancer (very low to low risk), the pivotal post-diagnostic decision involves a choice between curative intervention and surveillance. A primary concern with a surveillance option is the underestimation of cancer grade on a prostate biopsy that could potentially compromise long-term cancer control if unrecognized in an untreated patient. Tools for selecting the 'ideal' candidates for surveillance have been published [14,41], but have the limitation of misclassification of 'risk' based on grade. Decision tools that estimate clinical endpoints (e.g. life expectancy, pathological stage, biochemical recurrence-free probability, cancer-specific survival, quality of life) have been created to help inform management decisions [42]. However, there remain limitations to accurately predicting overall life expectancy [43], and long term clinically relevant endpoints such as survival and morbidity [42].

CURATIVE INTERVENTION VS SURVEILLANCE

LOW-RISK DISEASE

Because of the uncertainty regarding the long-term risk of a prostate cancer that is found to be low grade on a prostate biopsy, a man with newly diagnosed prostate cancer must weigh the risks of harm from disease without treatment, against the risks of treatment side-effects. Both radiation therapy [44] and surgery [19] reduce prostate cancer mortality by $\approx 50\%$ a decade after diagnosis for men with non-screen-detected prostate cancers that are localized to locally advanced. Accounting for the lead time with PSA testing, results from the SPCG-4 [19] would suggest that there is minimum risk of death from prostate cancer in 10 – 15 years without treatment for a man with low-risk disease. However, given the absence of longer term data from randomized trials to show the safety of a surveillance approach, men with more than an estimated 10 – 15 year life expectancy and low-risk disease should be told that active surveillance is an experimental approach that may result in a lost opportunity for disease control. For those men who are older with associated disease comorbidity that limits the remaining years of life, active surveillance could be considered the best management [15].

A lost opportunity for effective disease control in men with low-risk disease on surveillance may occur due to the under estimation of cancer grade on prostate biopsies and/or the progression of a low-grade cancer to one of higher grade. It has been estimated that $\approx 25\%$ of men classified at diagnosis with low-risk prostate cancer will be found to have higher grade disease at surgery [22], and that 'true' disease progression from low to high grade is unusual, at least in the short term [45]. An unanswered question is the extent, if any, to which a man on surveillance who undergoes delayed intervention risks losing the opportunity for control of disease. Non-randomized data comparing men with low-risk disease who have undergone immediate vs deferred treatment, and decision analyses, have been used to inform management in the absence of randomized trials.

Statton *et al.* [46] evaluated the outcomes of men at an average age of 61 – 65 years with low-risk prostate cancers who underwent surveillance and curative intervention in a large national cancer registry. The overall 10-year prostate cancer-specific mortality was $< 3\%$ for men with low-risk disease managed initially with surveillance. The absolute difference in prostate cancer-specific mortality at 10 years for those managed with surveillance compared

with surgery was 2%. This could be compared to a 5% absolute difference in the SPCG-4 that compared no treatment with surgery [19]. The authors concluded that surveillance may be a suitable option for many men with low-risk prostate cancer, a stance that is consistent with recent guidelines [15].

An evaluation of > 3000 men with a mean age of 68 years in the Health Professionals Follow-up Study, showed that 10% of men overall deferred treatment, and that at 8 years 51% remained untreated [47]. Of those treated, on average 4 years elapsed before treatment. At a median follow-up of 8 – 9 years, there were no differences in the rates of metastatic disease or prostate cancer deaths when comparing those who deferred treatment with those who were treated initially. The prognostic risk category (low, intermediate, high) was strongly predictive of the lethal phenotype. When compared with those with low-risk disease, those with intermediate- and high-risk disease were three- and six-fold more likely to die of prostate cancer, respectively. When comparing deferred and immediate treatment, there were no differences in prostate-specific outcomes for men with low- or intermediate-risk disease. Among men with low-risk prostate cancer, prostate cancer metastases occurred in seven of 139 (5%) and 33 of 1252 (3%) of the men in the deferred and treatment groups, respectively; death from prostate cancer occurred in three of 139 (2%) and nine of 1252 (1%) of the men in the deferred and treatment groups, respectively.

In the longest prospective contemporary study of active surveillance for low- to intermediate-risk disease, Klotz *et al.* [48] followed 450 men (median age 70 years) with low- and intermediate-risk prostate cancer for a median of 7 years. In all, 17% of the subjects had a Gleason score of 3+4, 83% were Gleason 6, and 71% were considered low risk by D'Amico criteria (Table 1) [10,13 – 15]. Thus, one in three men had intermediate-risk disease. The 10-year actuarial prostate cancer-specific survival was 97%. Five deaths have occurred in this cohort between 4 and 10 years after diagnosis, and all deaths occurred in men who were re-classified as higher risk disease during follow-up. By contrast, in the SPGS-4 [19], untreated men aged > 65 years had a 12-year prostate cancer-specific survival of $\approx$ 88% that did not differ from those that underwent surgical treatment. It could be argued that deaths in the Klotz *et al.* study [48] occurred in men who had advanced disease to begin with, and that surveillance did not compromise length of life [49]. Alternatively, it could be argued that deaths occurred in men who were not good candidates for surveillance, and that earlier intervention would have prolonged life. Regardless, there is a definite, but as yet unquantifiable, long-term risk to men who choose surveillance as a management option for low-risk disease, regardless of how indolent the disease appears on a prostate biopsy.

Many centres are gaining experience with active surveillance for low-risk prostate cancers, although enrolment criteria and triggers for intervention differ. In a multi-institutional study [50] that included the University of Miami, University of British Columbia, Memorial Sloan Kettering Cancer Center, and the Cleveland Clinic, 262 patients with low-risk disease were on surveillance for a median of 29 months. The 5-year probability of remaining on surveillance was 75%, a figure that is very consistent across many studies [51,52].

Comparisons of pathological outcomes among men who undergo immediate vs delayed intervention suggest that in the short term, the window of opportunity for cure is not lost [22,53] .

Computer simulations have been used to evaluate long-term outcomes in the absence of randomized trials. Hayes *et al* . [54] conducted a decision analysis to evaluate the quality-adjusted life expectancy (QALE) of men aged 65 years managed with surveillance and curative intervention strategies (brachytherapy, surgery, external beam radiotherapy). Active surveillance was associated with the longest QALE and surgery the shortest, but the results were highly dependent on a man's preferences with respect to living with cancer and having it treated. The authors concluded that for a man aged 65 years with low-risk prostate cancer, active surveillance is a reasonable initial approach.

Liu *et al* . [55] , recently performed a decision analysis that evaluated the outcomes of men with low-risk prostate cancer managed with surveillance (the least common approach) and surgery (the most common approach), including the ratio of side-effects (cost) per additional year of life gained (incremental cost-effectiveness ratio). A man aged 67 years in average health with low-risk prostate cancer, would experience ≈ 10 years of side-effects for each additional year of life gained, under the most optimistic assumptions regarding post-surgical erectile dysfunction and incontinence. This 'cost' in terms of side-effects per year of life gained, reflects the low probability of adding years to life with surgery for most men aged > 65 years with low-risk cancer. Management options with lower side-effect profiles (e.g. focal therapy) might be associated with a lower cost.

In summary, the choice of curative intervention or active surveillance for men with low-risk prostate cancer should primarily depend on age, health status, and patient preferences with respect to living with cancer, and the possible side-effects of curative management. It is possible to explore patient preferences for living with cancer and side-effects of treatment as part of shared decision making. However, the limitations of correctly classifying a patient's long-term risk of disease progression and predicting life expectancy, together with the absence of randomized trials showing the safety of active surveillance in the long term, suggest that surveillance should be considered investigational for men who have a life expectancy that extends beyond 10 – 15 years.

VERY-LOW-RISK DISEASE

The category of very-low-risk prostate cancer is now recognised as defining a risk group that differs from the low-risk category in terms of pathological outcomes at surgery, progression risk without treatment, and recommendations for management [15,56] . The criteria for defining very-low-risk disease were first described by Epstein *et al* . [14] , among men with stage T1c (impalpable) prostate cancer (Table 1). The criteria include PSA density, which has been confirmed to be a predictor of future re-classification to a higher risk category, including high-grade disease [51,57,58] . These criteria have been used by some investigators to define a subset of men for whom surveillance may be safest.

When compared with men with low-risk disease, those with very-low-risk disease are less likely to have adverse features at the time of RP, and less likely to experience biochemical

recurrence after treatment [56,59] . For example, when comparing the outcomes of 769 men in the Johns Hopkins Active Surveillance Program, who did and did not meet the criteria for very-low-risk disease, those with very-low-risk disease were significantly less likely to be re-classified to a higher risk category and to undergo treatment [56] . In addition, the PSA-free outcomes of patients enrolled in the Johns Hopkins Active Surveillance Program who underwent delayed intervention, 80% of whom had very-low-risk disease at diagnosis [56] , appear more favourable when compared with biochemical-free outcomes of men meeting low-risk criteria who undergo delayed or immediate intervention [22,60] , although other uncontrolled factors could explain these intermediate results.

In the Toronto experience with surveillance [48] , 71% of 450 men were considered low risk by D'Amico criteria, and follow-up was available for 110 men that underwent curative intervention. The 5-year biochemical progression-free survival was 62% for those undergoing RP and 43% for those undergoing radiation. By comparison, among 192 men on surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience with very-low-risk disease, the 5-year biochemical progression-free survival was 96% for those undergoing surgery and 75% for those undergoing radiation [56] . These data suggest that carefully selected men with very-low-risk disease will have favourable outcomes when deferred treatment is required after initial management with surveillance.

Tosoian *et al* . [56] , recently reported the outcomes of 769 men in the Johns Hopkins Active Surveillance Program. The actuarial rate of biopsy re-classification to a Gleason score > 6 on annual surveillance biopsies at 10 years was 30%. In this programme, if a man had biopsy re-classification to a high-grade cancer (Gleason score > 6) and underwent surgery, the proportion with a Gleason score of 3+4 was 32% and Gleason score 4+3 was 44% on final surgical pathology. The 15-year cancer-specific mortality after surgery for men with Gleason score 3+4 and 4+3 was 4.2% to 6.5%, and 6.6% to 11%, respectively [20] in a multi-institutional study. Thus, a man with a very-low-risk prostate cancer entering an active surveillance programme who chose surgery if biopsy re-classification occurred, would have over a 10-year period, a 10% risk ($30\% \times 32\%$) of having a Gleason score 3+4 on surgical pathology and a 15-year risk of a prostate cancer death of $< 1\%$ ($10\% \times 4.2 - 6.5\%$) postoperatively; and over 10 years a 13% risk ($44\% \times 30\%$) of a Gleason score 4+3 on surgical pathology, and a 15-year risk postoperatively of a prostate cancer death of $\approx 1\%$ ($13\% \times 6.6 - 11\%$). By comparison, the 15-year risk of death from another cause for a man aged 65 years would be $\approx 40\%$ [61] . This estimate, based on biopsy re-classification triggering treatment in an active surveillance programme, and contemporary surgical outcomes by cancer grade, is consistent with modelled data from Parker *et al* . [30] . *For most men aged* 65 years with very-low-risk disease, curative intervention would appear to be unnecessary.

Although long-term data are not available to compare the outcomes of men on surveillance with very-low-risk and low-risk prostate cancer, the NCCN [15] has recommended that men with very-low-risk disease and an estimated life expectancy of < 20 years, be managed with surveillance rather than immediate curative intervention.

FUTURE

Undoubtedly, there will be improved markers of an indolent and lethal phenotype to guide management of men with newly diagnosed prostate cancer [62 – 64] , and better imaging to monitor those who choose to forego treatment of favourable-risk disease [65] . While we await these advances, trials comparing management options for localized prostate cancer will help inform the decisions regarding favourable-risk disease.

The Prostate cancer Intervention Versus Observation Trial (PIVOT) has randomized 731 men with a mean age of 67 years to surgery vs active surveillance; 43% with low-, 36% with intermediate-, and 20% with high-risk prostate cancer [66] . PIVOT, which began in 1992 will report disease specific and quality of life outcomes by disease risk profiles (low, intermediate, and high), and is nearing completion. The Prostate Testing for Cancer and Treatment (ProtecT) trial, begun in the UK in 2001 has three randomized comparison groups of men aged 50 – 69 years; conformal radiotherapy, RP, and active surveillance [67] . These trials should add to current information regarding the risks and benefits of treating men with favourable-risk prostate cancer, and hopefully move our field away from the ‘personal opinion’ -guided strategy to one that is more evidence based.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

NCCN	the National Comprehensive Cancer Network
RP	radical prostatectomy
ADT	androgen-deprivation therapy
CaPSURE	The Cancer of the Prostate Strategic Urologic Research Endeavor
PCPT	The Prostate Cancer Prevention Trial
SPCG-4	The Scandinavian Prostate Cancer Group Study 4
SEER	Surveillance, Epidemiology and End Results Program
ERSPC	the European Randomized Study of Screening for Prostate Cancer
QALE	quality-adjusted life expectancy
PIVOT	The Prostate cancer Intervention Versus Observation Trial

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'The enthusiasm for treatment of favourable-risk disease has led to over treatment of prostate cancer'

‘High level evidence supports the low risk of harm without treatment from favourable-risk prostate cancer in older men’

‘alarmingly high rates of over treatment for prostate cancer in the USA’

‘the choice of curative intervention or active surveillance for men with low-risk prostate cancer should primarily depend on age, health status, and patient preferences with respect to living with cancer, and the possible side-effects of curative management’

‘For most men aged 65 years with very-low-risk disease, curative intervention would appear to be unnecessary’

What' s known on the subject? and What does the study add?

Most men who are diagnosed with favourable-risk prostate cancer undergo some form of active intervention, despite evidence that treatment will not improve health outcomes for many. The decision to undergo treatment after diagnosis is, in part, related to the inability to precisely determine the long-term risk of harm without treatment. Nevertheless, physicians should consider patient age, overall health, and preferences for living with cancer and the potential side effects of curative treatments, before recommending a management option. This is especially important for older men, given the high level of evidence that those with low-risk disease are unlikely to accrue any benefit from curative intervention.

What is known on the subject: Over treatment of favourable-risk prostate cancer is common, especially among older men.

What does the study add: A review of the natural history of favourable-risk prostate cancer in the context of choices for management of the disease.

- The management of favourable-risk prostate cancer is controversial, and in the absence of controlled trials to inform best practice, choices are driven by personal beliefs with resultant wide variation in practice patterns.
- Men with favourable-risk prostate cancer diagnosed today often undergo treatments that will not improve overall health outcomes.
- A shared-decision approach for selecting optimal management of favourable-risk disease should account for patient age, overall health, and preferences for living with cancer and the potential side effects of curative treatments.

FIG. 1.

Age-specific percentage distribution of men with low-risk prostate cancer by type of initial management in 2002. Data from Patterns of Care Study conducted by Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute (NCI). Low risk defined as Gleason score < 7 and a PSA level of ≤ 10 ng/mL. BT (brachytherapy), EBRT (external beam radiotherapy), PADT (primary ADT), WW (watchful waiting). Adapted from Hamilton et al. [24].

TABLE 1 Prostate cancer risk stratification*

Risk profile	Criteria [†]	Approximate proportion of newly diagnosed cases [‡] , %	Management options [§]
Favourable: Very low risk	T1c Gleason score ≤6 PSA level <10 ng/mL <3 biopsy cores positive, 50% cancer in any core PSA density <0.15 ng/mL/mL	35	Active surveillance if expected life expectancy <20 years
Low risk	T1 or T2a Gleason score 2-6 PSA level <10 ng/mL		Active surveillance if expected life expectancy < 10 years Radiation (external or brachytherapy) or surgery if expected life expectancy ≥ 10 years
Intermediate	T2b - T2c or Gleason score 7 or PSA level 10-20 ng/mL	33	Active surveillance or external radiation with/without ADT with/without brachytherapy or surgery if life expectancy < 10 years Surgery or external radiation with/without ADT with/ without brachytherapy if expected life expectancy ≥ 10 years
High	T3a or Gleason score 8-10 or PSA level >20 ng/mL	32	External radiation + ADT or surgery

* From D'Amico et al. [13] and Epstein et al. [14].

[†] Adapted from Mohler J et al. [15] and based on T stage, Gleason score, PSA level, PSA density, number and percentage of biopsy cores with cancer.

[‡] Proportions from SEER of NCI as reported by Shao et al. [10].

[§] Adapted from NCCN guidelines reported by Mohler et al. [15].

TABLE 2 Cohort demographics: SPCG-4 [19]

Characteristics	Surgery (n = 347)	Watchful waiting (n = 348)
Mean age, years	65	65
%:		
Cancer detected by screening	5	5
Clinical stage T2	78	74
Biopsy Gleason score 7-10	26	30
PSA level at diagnosis, ng/mL:		
10- 20	29	27
>20	20	17