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Active Surveillance for Localized Prostate Cancer

A New Paradigm for Clinical Management

Second Edition

Humana Press

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Preface to Active Surveillance, Second Edition

When the first edition of this book was published, in 2012, the concept of active surveillance was very controversial. Screening enjoyed widespread public support, overdiagnosis was not acknowledged as a significant health issue, and most patients with low-grade cancer were treated radically.

The last 5 years have seen a dramatic change in the management of low-risk prostate cancer. The concept of active surveillance has become widely accepted around the world. In some constituencies, more than 90% of low-risk patients are managed conservatively. In the aftermath of the US Preventive Services Task Force level D recommendation against screening, the risks of overdiagnosis and overtreatment are now universally accepted. Indeed, just prior to the publication of this book, the USPSTF has modified their recommendation to a level C (neutral), largely reflecting the favorable impact of active surveillance on overtreatment, one of the main prior criticisms of screening for prostate cancer. The concept of active surveillance, which was first applied to prostate cancer, has now been explicitly adopted in a number of other cancer sites, particularly DCIS of the breast.

This change has meant a shift in focus. The controversy is no longer about the concept of surveillance; rather, it is about the application. There are now more than 2750 publications on the topic of active surveillance in prostate cancer, and the number is increasing logarithmically.

This textbook is unique in providing a comprehensive view of this rapidly evolving and important field. The book covers both the science and application of active surveillance. The chapters are wide ranging. The first section of the book includes chapters on the problem of overdiagnosis and overtreatment in oncology, how to screen more effectively while minimizing overdiagnosis, a provocative article on the use of fear in medicine, and a thoughtful article on the ethics and legalities of conservative management. The next section reviews the molecular events which underlie disease progression and patient selection, expanding surveillance to patients at the "margin" of low risk and improving follow-up. The lessons (and misinterpretations) of the pivotal Protect and PIVOT trials are reviewed. In the third section, the role of MRI and the use of molecular, germ line, and urine biomarkers are summarized. The next section focuses on the quality of life, decision-making, and informing patients, including how to advise them regarding lifestyle, exercise, and diet. The final section addresses the role of pharmacologic intervention to reduce progression, the update of surveillance around the world, the economics of surveillance, and outstanding research questions in the field.

The authors are a "who's who" of international prostate cancer experts. They are the most knowledgeable individuals in the world on the topics they are writing about.

Active surveillance has resulted in a significant improvement in the quality of life for hundreds of thousands of men around the world. We encourage practitioners to continue to adopt and refine the approach. Our goal is to reduce the morbidity of treatment while further reducing the mortality from prostate cancer. Our patients and their families will be appreciative.

I would like to thank my wife, Ursula Lotz, and my children, Alex and Betsy, for their inspiration and support.

Toronto, ON, Canada Laurence Klotz

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Cancer Overdiagnosis and Overtreatment

1

Laurence Klotz

Background

The diagnosis of cancer invokes fear. First recognized by the ancient Egyptians, until the modern era, cancers were diagnosed late and usually at an incurable stage. This view, of cancer as a uniformly lethal disease, has persisted. In *Dorland's Medical Dictionary* published in 1994, cancer was defined as "a neoplastic disease the natural course of which is fatal" [1]. The current issue describes cancer as "any malignant, cellular tumor, referring to neoplastic diseases in which there is a transformation of normal body cells into malignant ones" [2]. Malignant is defined as "having the properties of anaplasia, invasiveness, and metastasis; said of tumors tending to become progressively worse and to result in death." So whether it is 1900, 1994, or 2018, being diagnosed with "cancer" can portend a poor outcome and death.

This definition used to be appropriate. In the era prior to widespread imaging and testing, patients were diagnosed after they became symptomatic. Those symptoms usually occurred late in the course of the disease. In most cases patients presented with hematuria and flank mass from advanced kidney cancer, bone pain from metastatic prostate or breast cancer, hemoptysis from advanced lung cancer, or bowel obstruction from advanced colon cancer. These patients did not fare well.

Indeed, one of the first observations of clinical epidemiology in oncology was a seminal paper showing that the survival of patients with colon and lung cancer correlated more closely with whether they were diagnosed on the basis of symptoms (unfavorable), vs serendipitously after a diagnostic test (favorable), than with grade or stage [3].

The epidemiology of cancer changed dramatically with the advent and widespread implementation of new diagnostic tests, including PSA, mammography, abdominal ultrasound, and colonoscopy. These tests advanced the time of diagnosis and decreased the volume and stage at which cancers are detected. This phenomenon is termed "stage migration." Cancers are now commonly diagnosed before they would be expected to produce symptoms or manifest signs. This "lead time" is often many years. In some cases, cancers are diagnosed that otherwise would never be found and pose no threat to the life of the patient. This results in "overdiagnosis," a term that is still not in *Dorland's Medical Dictionary*!

The word "cancer" includes a wide range of conditions. At the minimum, a "cancer" is a group of cells that have an abnormal appearance. However, the natural history of these cells is extremely variable. Some are very indolent and grow slowly, if at all. Some may regress

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spontaneously. Others grow very quickly, metastasize early, and are rapidly lethal. "Cancer" is a pathological description of tissue made at a single point of time. It is not, in and of itself, a prediction about the natural history of the disease.

However, in the public mind, as in Dorland's dictionary, cancer is still a lethal disease to be eradicated, irrespective of cost and quality of life effects. This reaction can lead to overtreatment, with very significant side effects and costs. These side effects can be lifelong. While that may be warranted for a life-threatening disease, it is a tragedy when these are incurred for an insignificant entity.

Cancer Overdiagnosis

This describes a cancer that is diagnosed (usually by a screening test) that would not otherwise result in symptoms or death. Overdiagnosis occurs when the cancer is destined not to progress or because the rate of progression is so slow that the patient dies of other causes before it produces symptoms or signs. This second cause incorporates three factors: the rate of growth, the volume of cancer at the time of diagnosis, and the patient's comorbidity and competing mortality risks. In a patient with a limited life expectancy, a small cancer that grows rapidly may still be overdiagnosed. Importantly, a cancer that is overdiagnosed has all the pathological characteristics of cancer. It is not, therefore, a "false-positive" diagnosis (i.e., where a disease is falsely identified).

Cancer progression is unpredictable. Some genuine histologic cancers may never grow or spontaneously involute [4]. This is likely more prevalent than has been appreciated. Lack of VEGF may result in inability to induced neovascularity, thus dooming the cells to outgrow their blood supply [5]. Lack of telomerase may result in intrinsic cell senescence [6]. Further, host immunity may induce cancer death.

Other cancers may grow so slowly that the patient will die of another cause before it causes symptoms. A third group progresses slowly, and may lead to symptoms and death, but only after many years. The fourth group represents the classic cancer phenotype, i.e., a fast-growing, lethal cancer.

Nonprogressive or very slow-growing cancers that develop in the majority of healthy men as they age are "pseudo-diseases." Most pose no threat to the patient, notwithstanding the anxiety and other psychological effects associated with the cancer diagnosis and the risks associated with (unnecessary) treatment.

The problem is that it can be difficult to determine with confidence when a cancer diagnosis is an overdiagnosis. Overdiagnosis can only be ascertained with certainty when the patient, untreated, dies of other causes. Because one can't know this outcome with 100% confidence at diagnosis, a common response is to treat all such patients. This results in considerable costs, both financial and quality of life related. While treatment in these patients provides no benefit, it carries the risk of potentially serious adverse effects. However, an understanding of the natural history of these diseases, and the ability to stratify for risk using clinical parameters, means that overtreatment can be avoided.

Requirements for Overdiagnosis

Prevalence of Microfocal Disease

Autopsy series have shown for many years that microscopic cancers are common in people dying of unrelated causes. Prostate, breast, and thyroid cancer in particular have been identified in autopsy series, partly because these organs are small enough to permit serial sectioning of the entire organ.

Sakr reported on the analysis of 525 men dying of trauma [7]. Remarkably, 30% of men in their 30s were found to have prostate cancer. This increased linearly with age. In fact, at any age, the likelihood of harboring prostate cancer was equivalent to the patient's age as a percent (i.e., 80% of 80-year-olds). This was independent of race. Similar results, confirming the high prevalence of microfocal prostate cancer at autopsy, have been reported by others [8, 9].

Systematic examination of the thyroid at 2.5 mm intervals identified papillary carcinoma in 36% of adults in Finland. These were smaller than the slice thickness, and the authors concluded that serial sectioning would identify these lesions in close to 100% of human beings [10].

Four autopsy series which report age-related prevalence of breast cancer indicate that 7–39% of middle-aged women harbor microfocal breast cancers. This is a wide range. It may reflect differences in pathologists' willingness to call a very small lesion cancer or rigorousness of analysis of all tissue. Slice number ranged from 10 to 200 in these studies [11].

For these cancers, the likelihood of harboring foci of cancer is dramatically higher than the lifetime risk of dying of disease. Where the entire reservoir of disease is detected, the probability of overdiagnosis would be about 90% for prostate, 45–90% for breast, and 99.8% for thyroid [12].

Disease Detection

Efforts at detection are required to identify this large reservoir of microscopic cancer. The second condition is therefore an early cancer detection test.

Cancer screening refers to efforts to detect cancer in asymptomatic patients. This includes examining patients for moles or lymphadenopathy at the time of a periodic health exam, as well as PSA, mammography, or colonoscopy.

Tests unrelated to screening can also result in early cancer detection. The advent of widespread diagnostic imaging to evaluate symptoms not suggestive of cancer often leads, serendipitously, to an early cancer diagnosis. Scans of the brain, chest, abdomen, and pelvis often show abnormalities suggestive of cancer. Further, as ultrasound and CT have become more sensitive, the lesions are detected at an earlier and earlier stage. The use of CT and MRI has increased dramatically over the last 15 years [13]. Approximately 85% of asymptomatic middle-aged patients have some abnormality identified on CT of the abdomen.

Surgical procedures for benign conditions, i.e., TURP, may result in cancer detection [14]. An additional factor is the increased sensitivity of diagnostic tests. In the case of prostate cancer, this includes both a steady decrease in the PSA threshold considered abnormal and an increase in the number of cores taken. The emergence of prostate MRI early in the diagnostic algorithm of prostate cancer also poses a risk of identifying many indolent cancers.

Evidence that Early Detection Has Led to Overdiagnosis

The most powerful evidence for overdiagnosis comes from randomized screening studies. Screening results in an increase in the number of diagnosed cases, due to early detection. If all of these cases were clinically significant, the number of cases in the control group would "catch up" during long-term follow-up, as clinical disease manifested itself by symptoms (or death). A persistent gap in case number between the two groups suggests that overdiagnosis has occurred. In breast cancer, only one trial has reported long-term follow-up data on incident cancers [15]. The estimate from this study was that 24% of mammographically detected cancers were overdiagnosed [16].

Overall cancer mortality has fallen 15% in the USA since the mid-1990s. 561,400 fewer deaths have occurred between 1995 and 2005 than would be expected had previous mortality trends continued. Much of this reduction is likely due to earlier detection of many cancers. About 25% of these "avoided" deaths, or 140,300, were due to reduction in prostate cancer mortality. Screening for prostate cancer has been associated with a 40% fall in prostate cancer mortality in the USA over the last 10–15 years, from 38/100,000 in 1995 to 22/100,000 in 2006, according to 2010 statistics [17]. Screening for prostate cancer produces clear mortality reduction.

The PLCO screening trial [18] had a 22% increase in detection in the screened group. The ERSPC trial [19] found 34 additional cases per 1000 men in the screening arm, an increase of about 60%. Modeling studies have also suggested

that the risk of PSA-detected prostate cancer being "overdiagnosed" is about 67% [20].

Observational studies in a number of tumor sites also suggest frequent overdiagnosis. Japan introduced a national screening program for neuroblastoma in infants. The number of cases in the screened group increased fivefold. Based on concerns about overdiagnosis, conservative management was recommended to diagnosed patients. 100% of the 11 cancers managed this way regressed [21]; all represent cases of overdiagnosis.

Evidence of cancer overdiagnosis is clear in population studies. In cases of a true increase in the amount of cancer, rising incidence is accompanied by rising mortality rates. In case of overdiagnosis, mortality remains stable or diminishes. An example of the former is esophageal cancer [22]. Based on datasets like SEER, overdiagnosis is suggested in the cases of melanoma, thyroid, breast, prostate, and kidney cancer (Fig. 1.1). Figure 1.2 shows the rates of diagnosis of some common cancers over the last 30 years.

For thyroid cancer, the rate of diagnosis has doubled in the last 30 years, with no change in death rate. The increased new cases are confined to papillary thyroid cancer, which has the most favorable prognosis [23]. It is estimated that overdiagnosis in women accounts for 90% of thyroid cancer cases in South Korea; 70–80% in the USA, Italy, France, and Australia; and 50% in Japan, the Nordic countries, England, and Scotland [24]. In Japan, thyroid cancer incidence among screened children and adolescents was approximately 30 times as high as the national average only a few months after intensive screening programs for these age groups began in response to the 2011 nuclear accident [25]. For melanoma, the diagnosis rate has increased almost threefold, from 7.9 to 21.5 per 100,000 [26]. Most of these are localized, in situ melanomas, and their rate of diagnosis closely mirrors population skin biopsy rates. Kidney cancer rates have doubled from 7.1 to 13.4 per 100,000, reflecting the widespread utilization of ultrasound and CT imaging. A number of recent series have confirmed the indolent behavior of many kidney cancers [27, 28]. A study of the growth rate of 53 solid renal tumors, in which each tumor had at least two CT volumetric measurements 3 months apart before nephrectomy, demonstrated their variable natural history and frequent indolence [29]. Twenty-one (40%) had a volumetric doubling time of more than 2 years and seven (14%) regressed. Furthermore, slow-growing tumors were more common in the elderly. Many renal tumors thus are overdiagnosed either because they do not grow at all or because their growth is too slow for the tumor to cause symptoms before the patient dies of other causes. In the absence of systematic screening for renal cancer, the increased rate of diagnosis is

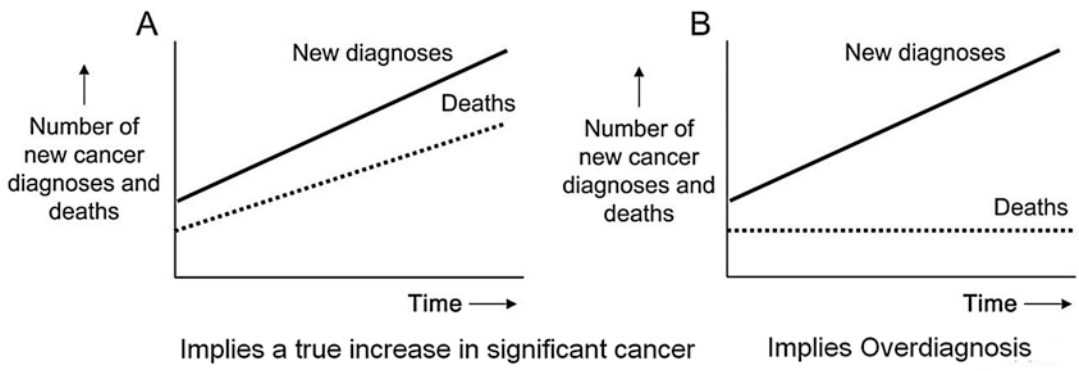

Fig. 1.1 This illustrates the difference between a true epidemic of serious disease, where a rise in incidence is paralleled by an increase in mortality, and a "pseudo-epidemic" or overdiagnosis, where the rise in incidence is not mirrored by an increase in mortality

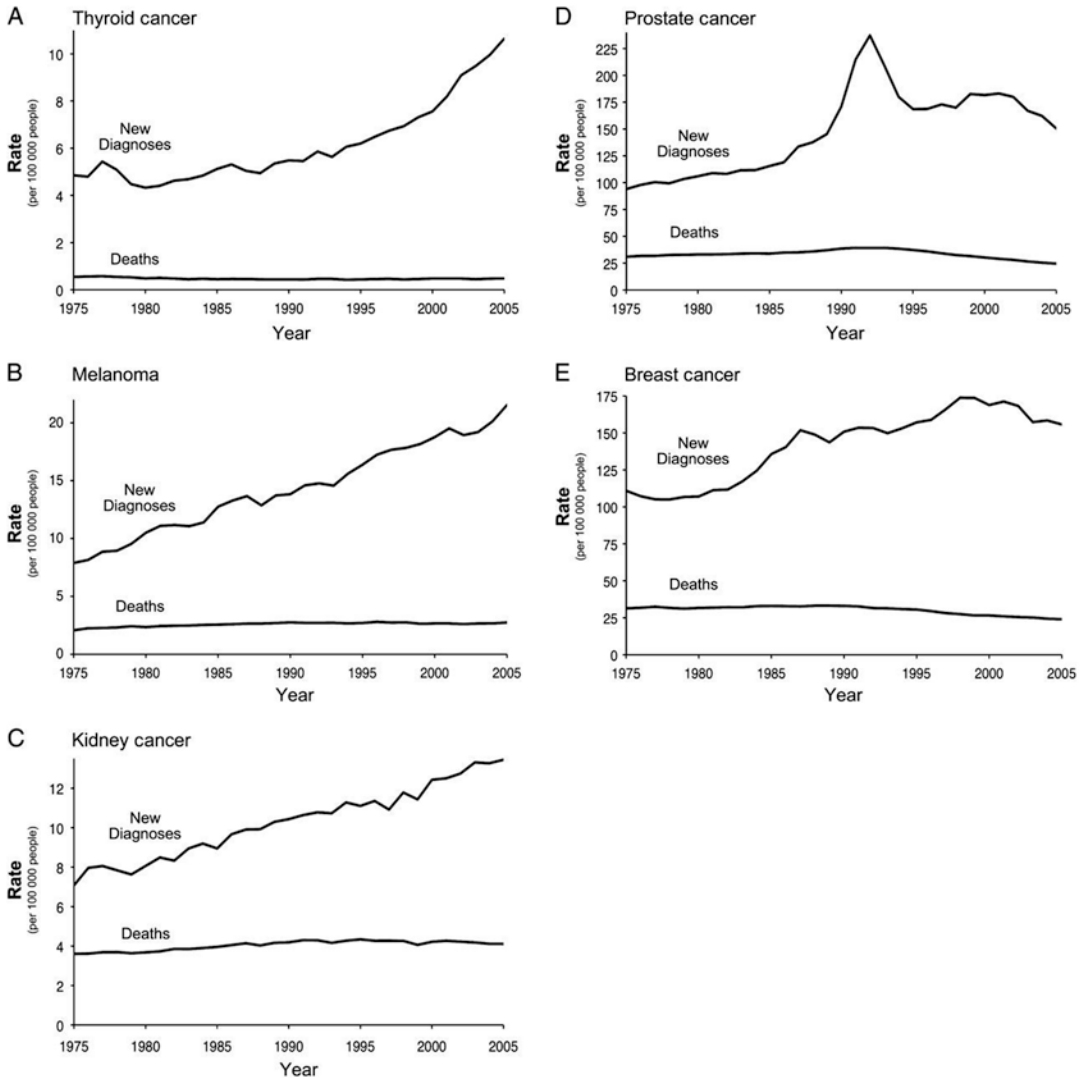

Fig. 1.2 Rate of new diagnoses and death in five cancers in the Surveillance, Epidemiology, and End Results data from 1975 to 2005 [12]. For these cancers, over 30 years between 1975 and 2005, a significant increase in age-adjusted incidence was observed, without a corresponding increase in mortality. This may reflect overdiagnosis and/or improved treatment (From Welch and Black [12]. Reprinted with permission from Oxford University Press)

likely due to the increased use of abdominal imaging.

For both breast and prostate cancer, mortality rates have decreased despite the marked increase in diagnosis. Prostate cancer mortality in the USA has fallen by about 40% since 1993, from 38.6 to 24.6 per 100,000. A similar trend has been seen in breast cancer. This decrease has multiple causes. The two most probable are the effects of early detection and improved therapy. Thus, in these two cancers, early detection is likely producing both overdiagnosis and a mortality benefit.

This is a classic benefit-harm conundrum. In prostate cancer, there appears to be an undeniable benefit of early detection, reflected by a substantial and very clinically meaningful fall in mortality. This comes at the cost of many patients being treated for each one who benefits. This overtreatment problem is a major concern.

Overdiagnosis, along with the subsequent unnecessary treatment and associated risks, is a critically important adverse effect of early cancer detection. With false-positive screening test, the adverse effects of anxiety and additional tests are short term, until the absence of cancer is confirmed. In contrast, the impact of overdiagnosis is lifelong. A cancer diagnosis may influence patients' sense of well-being, their physical and emotional health, their relationship with loved ones, and their ability to purchase health insurance.

Many have written eloquently about the medicalization of the healthy and the use of fear in overdiagnosis and overtreatment. "Today the kingdom of the well is being rapidly absorbed into the kingdom of the sick, as clinicians and health services busy themselves in ushering people across this important border in ever increasing numbers" [30]. The problem of overdiagnosis is a malady of modern medicine, not just oncology. Some argue that this problem is an inevitable but somewhat unforeseen consequence of well-meaning attempts to diagnose serious diseases at a point where they are more amenable to cure; others argue that it reflects vested medical and commercial interests in medicalizing the normal [31].

The risk of overdiagnosis and overtreatment makes informed decision-making more complex. Early treatment may help some but hurts others. This trade-off should be calculated by each individual patient based on a sophisticated understanding of the risks and benefits involved and insight into their own personal values and risk tolerance. The decision involves balancing many factors. This ideal is often not achieved.

Four strategies are warranted to improve this situation: (1) develop clinical and patient tools to support informed decisions about prevention, screening, biopsy, and treatment and offer treatments tailored to tumor biology; (2) focus on development and validation of markers that identify and differentiate significant- and minimal-risk cancers; (3) reduce treatment for minimal-risk disease; and (4) identify the highest-risk patients and target preventive interventions.

Patient education is a key solution to this problem. Patients should be adequately informed of the nature and the magnitude of the trade-offs involved. This kind of discussion is challenging for patients. Scientific illiteracy and lack of numeracy contribute to the challenge [32]. (Indeed, failure of most people to understand the nature and magnitude of risk is a major social issue and results in support for many inappropriate policies.) Patients must clearly understand the nature of the trade-off that although early treatment may offer the opportunity to reduce the risk of cancer death, it also can lead one to be treated for a "cancer" that is not destined to cause problems. These ideas are often foreign and must be presented clearly. The cancer "zeitgeist" referred to earlier in this chapter, i.e., that it is uniformly a lethal and aggressive disease, contributes to the challenge.

Quantifying overdiagnosis is often challenging. There are only a few randomized trials of prostate cancer screening and even fewer provide the needed long-term follow-up data. Nonetheless, "best guess" estimates about the magnitude of overdiagnosis are useful in decision-making. These estimates involve modeling the natural history of the cancer, the impact of early diagnosis, and competing mortality risks. It isn't clear, for example, how patient preferences are influenced by whether the number needed to treat is 12 (Hugosson Scandinavian screening study) [33] or 48 (ERSPC) [19], for each prostate cancer death avoided. Simple and transparent models with explicit assumptions and input values can be instructive.

Overdiagnosis and overtreatment generate a cycle of positive feedback for more. As the disease is more widely diagnosed, more and more people have a connection to someone, whether a family member, friend, or celebrity, who "owes their life" to early cancer detection and treatment. This is the popularity paradox of screening: The more screening causes overdiagnosis, the more people feel they owe it their life and the more popular screening becomes [34]. The problem is compounded by media reports about the dramatic improvements in survival statistics, which may

reflect nothing more than lead- and length-time effects.

Volume criteria can be used to identify candidates for conservative management. This is now widely accepted for small pulmonary nodules [35] and adrenal masses [36] detected incidentally. Identifying growth over time is another parameter that can reduce overtreatment. With lung cancer screening using CT, biopsies of small lesions are now restricted to those that grow over time [37].

Another solution is to relabel the disease with a term that doesn't include words for cancer. This was done effectively for what was formerly grade 1 papillary transitional cell carcinoma of the bladder [38, 39] and is now termed PUNLMP or papillary urothelial neoplasia of low malignant potential. It has been proposed that small-volume, Gleason 6 prostate cancer be termed "IDLE" tumors (indolent lesions of epithelial origin) [40]. This would go a long way toward reducing the problem convincing patients with a "cancer" diagnosis to remain untreated. IDLE tumors would be managed as ASAP is currently with serial PSA and repeat biopsy. However, most pathologists believe that, since low-grade prostate cancer can demonstrate local invasion, it deserves to be labeled cancer. The new grade grouping of prostate cancer is a step in this direction. Gleason 6/10, implying an intermediate grade, will now be called Group 1, reinforcing the concept of a favorable lesion [41].

The problem of overdiagnosis and overtreatment goes beyond the prostate cancer field. As physicians, we have a responsibility to recognize the phenomenon, protect our patients from it where possible, and minimize the impact in other ways. These include developing a clear definition of where it exists; describing it in simple, easily accessible terms (i.e., "too much medicine") [42]; recognizing the competing values and risks/benefits involved and developing strategies to account for these; and promoting public debate on the inherent uncertainty and limitations of health care and their implications for overdiagnosis.

Active surveillance, the focus of this book, is a major step forward in addressing this concern, not only in prostate cancer, but in many other human conditions.

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Can We Screen and Still Reduce Overdiagnosis?

2

Peter Ka-Fung Chiu and Monique J. Roobol

Autopsy Studies of Subclinical Prostate Cancer

To be able to fully grasp the potential problem of overdiagnosis, it is important to understand the natural history of prostate cancer. In a very nice overview of van der Kwast et al., different types of prostate cancer in relation to their clinical presentation and symptoms are given (Fig. 2.1) [1].

To be able to address the problem of overdiagnosis, first the proportion of indolent cancers needs to be identified. Autopsy studies of non-prostate cancer-related deaths and observational natural history studies might provide some insight into this problem. A Greek autopsy study showed that subclinical cancers were found in 13.8% (60–69 years), 30.5% (70–79 years), and 40% (80–89 years) men [2]. More recent autopsy studies showed that in 1056 White and Black men in the United States, the proportion of latent prostate cancer was as high as 44–46% (50–59 years), 68–72% (60–69 years), and 69–77% (70–79 years), with the vast majority having potentially indolent Gleason score 6 or less cancers (84–93%) [3]. These men obviously would not benefit from a diagnosis of prostate cancer in their lifetime.

Natural History of Untreated Low-Risk Prostate Cancer

Johansson et al. followed up 223 Swedish men with localized prostate cancer who were diagnosed in the pre-PSA era (1977–1984) without initial active treatment [4]. In 2004, it was reported that most observed men had an indolent course in the first 15 years, but progression and death from prostate cancer increased sharply from 15 to 20 years in those men still alive. In 2013, an updated analysis of the series was reported after 30 years of follow-up [5]. After the death of 99% of men in the cohort, it was found that only 17% of men died of prostate cancer (which means 83% died of competing causes), and prostate cancer deaths occurred mostly between 15 and 25 years from diagnosis [5].

Albertsen et al. described another cohort of 767 men (ages 55–74) diagnosed with localized prostate cancer around 1971–1984 and observed for more than 20 years [6]. At 20 years, the prostate cancer mortality rate was 30 per 1000 person-years in Gleason 6 cancer, 65 per 1000 person-years in Gleason 7 cancer, and 121 per 1000 person-years in Gleason 8–10 cancers. More than 70% of men died of other causes with Gleason score 6 at 20 years [6]. It should be noted

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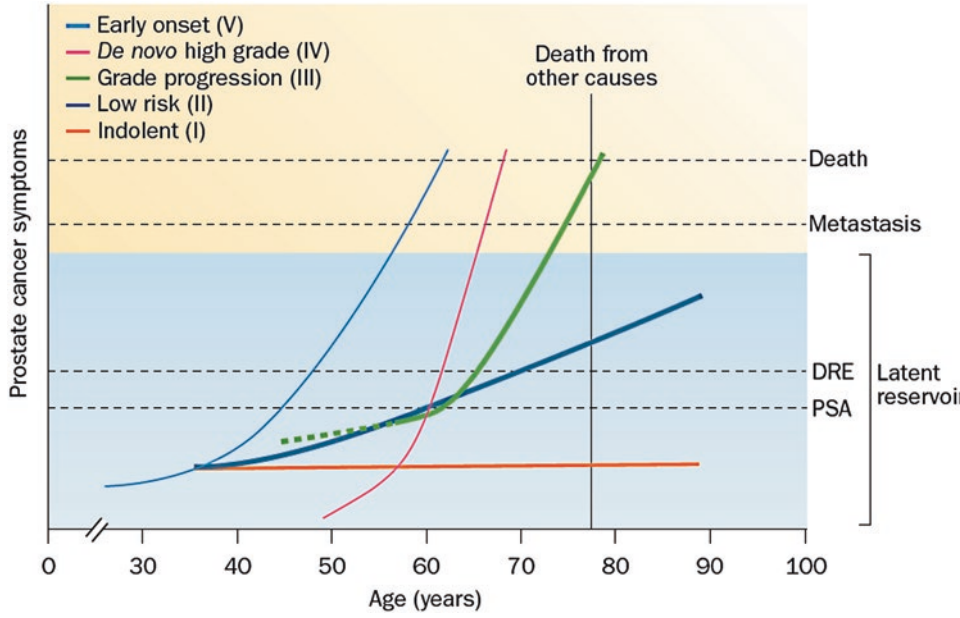

Fig. 2.1 Scheme depicting the age-related natural history of five hypothetical forms of prostate cancer (presented by the curved lines I–V) in relationship to their clinical signs and symptoms, visualizing their sojourn time in the latent reservoir (*gray-colored zone*). The X-axis represents patient age. Signs and symptoms of prostate cancer are represented by the horizontal lines. Indolent (*curve I*) and low-risk (*curve II*) cancers are thought to remain in the latent reservoir, although low-risk prostate cancer can grow in size and become PSA detectable and DRE detectable over time. When grade progression occurs in initially low-risk prostate cancers (*curve III*), these tumors can escape from the latent reservoir and become clinically detectable. It is thought that a small fraction of de novo poorly differentiated late-onset prostate cancers (*curve IV*) develop rapidly with a short sojourn time in the latent reservoir, precluding their timely detection by PSA screening. The size of the curved lines indicates their frequency in a population. A very small fraction of early-onset prostate cancers (*curve V*) with growth kinetics comparable to those of late-onset prostate cancers with grade progression (*curve III*) represent a biologically distinct subset of prostate cancers. Abbreviation: *DRE* digital rectal examination (From Van der Kwast and Roobol [1]. Used with permission, Springer Nature)

that both cohorts represented an era without PSA testing, and it is expected that most of these patients were diagnosed at a later stage as compared with prostate cancer detected nowadays. Therefore, the early localized prostate cancers that were diagnosed in more recent years might have a more indolent course than those in the natural history studies.

The control arms of the two randomized trials of surgery versus observation also provided insights in the natural history of localized prostate cancer, the Scandinavian Prostate Cancer Group 4 (SPCG4) [7] in pre-PSA era and Prostate Cancer Intervention Versus Observation Trial (PIVOT) [8] in the early PSA era. SPCG4 randomized 699 men with prostate cancer (cT1–T2) in 1989–1999 to radical prostatectomy or watchful waiting [7]. Only 5% of patients had cT1c and 75% had palpable disease (cT2) at time of diagnosis. The prostate cancer mortality in the observation group was about 20% at 15 years, and in the low-risk subgroup, the cancer mortality was only 10% at 15 years.

PIVOT randomized 731 men with prostate cancer (cT1–T2) in 1994–2002 to radical prostatectomy or observation [8]. About half of the patients had cT1c and 90% had Gleason scores 6–7. Prostate cancer mortalities of both arms were less than 20% at 15 years, and in the low-risk subgroup, the cancer mortality was less than 5% at 15 years.

In summary, localized prostate cancer shows an excellent 15-year cancer-specific survival without initial curative-intent treatment, and only

younger (<65 years old) patients might benefit from detection and radical treatment.

Estimation of the Extent of Overdiagnosis

Overdiagnosis on a population level can be estimated by either epidemiological or clinical criteria. Epidemiological studies can estimate overdiagnosis using two approaches, the so-called lead-time approach or calculating excess incidence created by active screening [9]. In clinical studies, overdiagnosis is often expressed as the number or percentage of low-risk prostate cancers that are being detected. The different approaches have a wide variable estimation of overdiagnosis and are, in addition, difficult to translate to an individual [9–11].

The ERSPC study first reported 20% reduction of prostate cancer mortality by PSA-based screening in 2009 at a median follow-up time of 9 years [12]. A 30% reduction in metastatic prostate cancer was also shown [13]. However, the excess incidence of predominantly low-risk prostate cancer cases was significant. This is expressed in the so-called numbers needed to screen and numbers needed to diagnose (in excess to a clinical situation) in order to prevent one death from prostate cancer with 1410 and 48 men, respectively. With additional follow-up, these numbers reduced to 781 and 27 men, respectively [14]. Mathematical simulation models on the basis of the Rotterdam section of ERSPC data showed that compared to a situation without screening, applying a 4-year interval and PSA-based screening algorithm from ages 55 until 70 would lead to 40% of prostate cancers detected to be overdiagnosed [15]. Three alternative screening strategies (1) screening from ages 55 to 70 with 1-year intervals, (2) screening from ages 55 to 70 with 2-year intervals, and (3) screening from ages 55 to 75 with 4-year intervals showed percentages of potentially overdiagnosed prostate cancers of 49%, 48%, and 57%, respectively [15] (Fig. 2.2).

The higher rate of overdiagnosis when screening men at higher age is confirmed by other modeling studies. Gulati et al. using a contemporary cohort of US men that modeled the effects of 35 screening strategies that vary by start and stop ages, screening intervals, and thresholds for biopsy referral concluded that less intensive screening in older men (higher PSA threshold for biopsy referral) reduces the risk for overdiagnosis [16].

This is confirmed by a recent cost-effective analysis, the Microstimulation Screening Analysis (MISCAN) model, based on ERSPC data. There it was shown that a screening algorithm with 2-year intervals between the ages 55 and 59 (3 screenings) had the best incremental cost-effective ratio [17]. However, if a better quality of life for the posttreatment period could be achieved (i.e., applying active surveillance for low-risk prostate cancer), men at older age up to 72 could also be included in a screening program [17].

Next to detecting prostate cancers that are very likely to have an indolent course based on their clinical characteristics at time of diagnosis, there is obviously another factor that is closely related to overdiagnosis, i.e., life expectancy. As is shown above, a low-risk prostate cancer at time of diagnosis can become potentially life threatening if its host lives long enough.

Finding the balance between two difficult-to-predict individual-level outcomes is needed. This balance is graphically displayed in Fig. 2.3 where it is obvious that we need to be able to predict both course of disease and life expectancy to be able to screen for prostate cancer while keeping the proven benefits and avoiding the harms.

The next sections of this chapter hence focus on who and how to screen for prostate cancer.

Who to Screen?

There are certain patient groups that have been associated with higher risks of potentially aggressive prostate cancer in population studies, and they included those with positive family history, ethnically Black men, and those with genetic predisposition to prostate cancer.

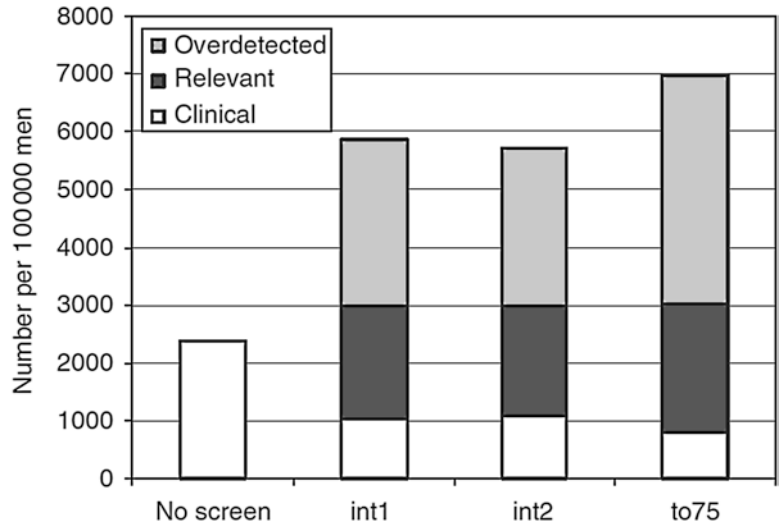

Fig. 2.2 Number of cancers detected per 100,000 men in 25 years for three screening scenarios (1-year interval ages 55–70, int1; 2-year interval ages 55–70, int2; 2 to 4-year interval ages 55–75: int4 to 75) for clinically detected cancers (interval cancers), relevant cancers (screen-detected cancers that would have given rise to clinical symptoms later in life), and overdetected cancers (screen-detected cancers that would never give rise to clinical symptoms and would not lead to death caused by prostate cancer) (From Heijnsdijk et al. [15]. Used with permission, Springer Nature)

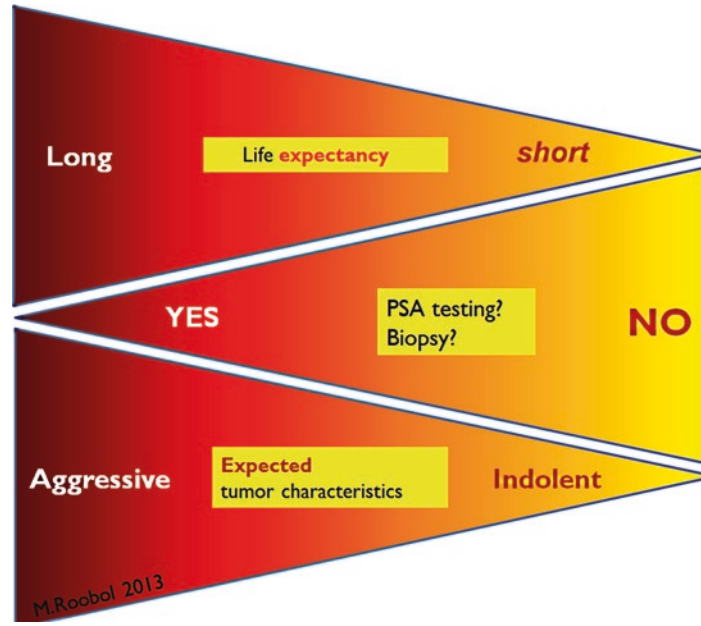

Fig. 2.3 Prostate cancer screening in association with life expectancy and disease course

Family History of Prostate Cancer

Meta-analyses on family history and prostate cancer risk demonstrated a relative risk (RR) of 2.5 in men having a lifetime risk and positive family history of prostate cancer and up to 3.5–4.4 in those with two affected first-degree relatives [18]. Those with a brother having prostate cancer had an even higher risk of prostate cancer than those with a father having prostate cancer

(RR 3.1 vs 2.4) [19]. The effect of family history was also associated with earlier disease onset (before 65 years old) (RR 2.9 vs 1.9) [20]. In the Swiss arm of the ERSPC, men with positive family history of prostate cancer had a 60% higher chance of diagnosing prostate cancer, but most of them have low-grade cancers [21].

Racial Differences on Prostate Cancer

The lifetime risk of a prostate cancer diagnosis varies in different ethnic groups. In a study in the United Kingdom (UK), the risk ranged from 13.3% in Caucasian, 29.3% in Black, to 7.9% in Asian men. The risk of dying from prostate cancer also varied from 4.2% in Caucasian, 8.7% in Black, to 2.3% in Asian men [22]. Therefore, different races had a similar diagnosis-to-death ratio of around 3:1, and Black men did not have a higher risk of dying from prostate cancer once diagnosed [22]. An earlier meta-analysis, however, showed that Black men diagnosed with prostate cancer had a 13% higher risk of prostate cancer death, which was not fully explained by comorbidity, PSA screening, or access to health care [23].

Genetic Mutations Associating with Higher Risk of Prostate Cancer

Twin studies suggested that the inherited component of prostate cancer risk is more than 40% [24]. Genome-wide association studies (GWAS) evaluated the entire genome for commonly inherited variants (>1–5% population frequency), and more than 40 prostate cancer susceptibility loci explaining approximately 25% risk were found [25]. A more recent meta-analysis of 43,303 prostate cancer men and 43,737 controls from Europe, Africa, Japan, and Latin countries has identified 23 new susceptibility loci for prostate cancer, explaining 33% of familial risks [26]. In terms of screening or early detection, it is not cost-effective to screen for all susceptible loci, and unknown whether this would provide a better harm-to-benefit ratio.

Is the Presence of a Risk Factor a License to Screen?

A study using estimates from the literature reported that screening men with a PSA level at the highest tenth percentile at 45 years old provided a better harm-to-benefit ratio compared with those with positive family history and Black race. A higher PSA at 45 years old accounted for 44% of prostate cancer deaths, while family history and Black race only accounted for 14% and 28% cancer deaths, respectively [27]. Hence, it is important to weigh both harm and benefit as equally important; in a high-risk population, there might be a larger benefit, but applying a screening approach that is not selective for potentially lethal disease, the harm may be equally increased [28].

When to Screen?

When to screen for prostate cancer is another controversial topic. It includes the starting and ending age for screening, including the so-called baseline PSA measurement at relatively young age, and the screening interval.

Starting Screening, Baseline PSA at Younger Age

A large case-control study in the Swedish population showed that a higher baseline PSA at younger age groups of 45–49 and 51–55 years was associated with higher risk of metastasis and prostate cancer deaths after a follow-up of 25 years. More than 40% of metastasis and deaths from prostate cancer occurred in men with PSA with the highest tenth percentile (>1.6 ng/ml at ages 45–49 and >2.4 ng/ml at ages 51–55) [27].

In a study investigating the PSA level of again Swedish men at the age of 60, a PSA level of <1 ng/mL was associated with only 0.5% risk of metastasis and 0.2% risk of prostate cancer death at the age of 85 [29]. In a Danish study, men with a PSA concentration of 4–10 ug/L had a sevenfold risk of prostate cancer death compared with

men with PSA <1 ug/L [30]. These data were confirmed in analyses based on the ERSPC where it is repeatedly shown that men aged 55–69 with baseline PSA levels below 1.0 ng/ml have a very low risk of prostate cancer detection, let alone dying from the disease [31, 32].

In a comparison of prostate cancer incidence and mortality between the Dutch, Swedish, and Finnish parts of ERSPC and a cohort without PSA screening (Northern Ireland), results showed that the yield of prostate cancer screening increased with the increasing baseline serum PSA level at study entry. The benefits of early detection may be small for men with a baseline serum PSA of 0–3.9 ng/mL at study entry. The number needed to investigate (NNI) to save one prostate cancer death was 24,642 in men with initial PSA <2 ng/mL, compared to NNI of 133 in men with PSA 10–20 ng/mL [33].

However, starting PSA testing at mid-age might also result in yet more testing, biopsies, and subsequent overdiagnosis. The retrospective analyses presented above, recommending, e.g., retesting intervals up to 10 years if the baseline PSA is considered low, cannot assess the effect in contemporary daily clinical practice. In an editorial by Carter et al., this lack of knowledge is clearly described. The authors question whether it is realistic to assume that a clinician will advise not to return for a PSA test within the next 10 years when the data actually show that more than half of the prostate cancer deaths in men aged 45–49 occur with a PSA of less than 1.6 ng/ml (90% of the population) [34]. So while the concept of a baseline PSA test at midlife definitely sounds appealing in retrospective analyses, the question remains whether this advice will be followed in contemporary practice.

Screening Interval

As mentioned above, in the Rotterdam section of ERSPC, men of ages 55–65 years with a baseline PSA of less than 1 ng/mL were associated with very low cancer detection after 8 years. Only 3.3% men had PSA >3 ng/mL and 0.49% cancer detection rate. As a result, an 8-year interval for screening in men with baseline PSA less than 1 ng/mL was recommended [32].

A similar conclusion was drawn on the basis of a multiethnic study in the United States. Gelfond et al. reported a 10-year prostate cancer risk of 3.4% for men (median age 58) with PSA <1 ng/mL, and among the diagnosed cancer men, 90% were of low-risk cancers. In contrast, those with PSA 3.1–10 ng/mL had a 39.0% 10-year risk of prostate cancer diagnosis. A recommendation of screening interval of 10 years or more was suggested for men with baseline PSA <1 ng/mL [35].

In comparing 2-year (Goteborg section) and 4-year (Rotterdam section) PSA-based screening in the ERSPC trial in men with ages 55–64, a 2-year screening interval reduced the incidence of advanced prostate cancer by 43% but increased the detection of low-risk prostate cancer by 46% [36]. This direct relationship between benefit and the intensity of a PSA-based screening algorithm was recently confirmed by another ERSPC analysis by Auvinen et al., where it was shown that the extent of overdiagnosis and the mortality reduction were closely associated [37]. Efforts to maximize the mortality effect by applying a PSA-based screening algorithm in all men are bound to increase overdiagnosis. The authors correctly note that this harm-to-benefit ratio might be improved by focusing on men considered to be at high risk, but how we actually can achieve that remains unclear [37].

Ending Age of Screening

In a simulation study by Ross et al., the number needed to treat (NNT) in order to prevent one cancer death increased with age. Compared with screening until age 65 (NNT 7.7), screening to 75 (NNT 12.5) and 80 (NNT 17.5) years was 2–3 times higher [38]. Zhang et al. described the optimal stopping age of PSA testing from both patients' and societal perspectives from a decision process model. Patients'

perspective was to maximize expected QALYs, while societal perspective was to maximize cost-effectiveness for QALYs. From the patients' perspective, the optimal policy was stopping PSA testing and biopsy at 76, while the estimated age was 71 from societal perspective [39].

With increasing age, the benefits of early detection reduce when deaths from other causes increase. The optimal age to stop screening is difficult to be determined. As mentioned before in the natural history studies and in the RCTs comparing surgery and watchful waiting (SPCG4 [7] and PIVOT [8]), men with life expectancy less than 10–15 years are not recommended to have any prostate cancer screening in the American and European Urological Association guidelines [40, 41].

However, due to the continuous increase in life expectancy of men, the difficulty in estimating the remaining lifetime of older men, and the availability of better treatment with fewer complications, we are now facing a changing scenario. Therefore, it would be difficult to set a rigid age to stop screening. An individual assessment with proper counseling and shared decision-making should be offered instead.

How to Screen?

Nowadays, there are better tools than PSA in screening for prostate cancer which might improve the harm-to-benefit ratio in screening. As the newer tools have better sensitivity or specificity in detecting prostate cancer, a proportion of unnecessary biopsies based solely on elevated PSA might be avoided. This could reduce both unnecessary biopsies and overdiagnosis. The most obvious way to move forward, while the 100% sensitivity and specificity lethal prostate cancer test is lacking, is to combine relevant information into prediction tools. In addition, novel imaging techniques can certainly be of aid in identifying those men that can benefit from early detection and treatment.

PSA-Based Prostate Cancer Risk Calculators

There are many risk calculators available, all having their advantages (widely externally validated, easy to use) and disadvantages (only suitable in particular settings, requiring complicated data and calculations). A meta-analysis of 6 risk calculators (out of 127 unique prediction models) included Prostataclass, Finne, Karakiewicz, Prostate Cancer Prevention Trial (PCPT), Chun, and the European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (ERSPC RC3) [42].

It showed that PCPT risk calculator did not differ from PSA testing in terms of AUC (0.66), while Prostataclass and ERSPC RC3 had the highest AUC of 0.79. The latter models doubled the sensitivity of PSA testing (44% vs 21%) while maintaining the same specificity [42].

Calibration of the models, which is important in assessing the actual predicted risk, was however poorly reported. In assessing the performance of prediction models, it was reported that both discrimination (AUC) and calibration are important [42]. Decision-analytic measures (decision curve analysis) should be reported if a model relates to clinical decisions [43].

Novel Biomarkers for Prostate Cancer Prediction

Urine PCA3

The prostate cancer antigen 3 (PCA3) is a non-coding messenger RNA found to be elevated in urine of most men with prostate cancer. A post-prostatic massage urine sample is needed for analysis. A higher PCA3 score was associated with a greater risk of prostate cancer. The discriminative ability of PCA3 was significantly better than PSA (AUC 0.76 vs 0.58) [44, 45]. However, when combined to an existing risk calculator (ERSPC RC3), there was hardly any additional predictive capability [46]. PCA3 is currently approved by US Food and Drug

Administration (FDA) in 2012 as a prostate cancer diagnostic test in men with previous negative prostate biopsy.

Urine TMPRSS2-ERG

The gene fusion TMPRSS2-ERG between transmembrane protease serine 2 (TMPRSS2) gene and the v-ets erythroblastosis virus E26 oncogene homolog (ERG) gene exists in up to 80% of prostate cancers. Urine levels of TMPRSS2-ERG correlate with clinically significant prostate cancer [47]. Adding post-DRE urine PCA3 to urine TMPRSS2-ERG further improved the prediction of prostate cancer and clinically significant prostate cancer on repeated prostate biopsies. The AUC for prostate cancer detection was 0.72, 0.65, 0.77, and 0.88 for PSA, PCA3, TMPRSS2-ERG, and combination of PCA3 and TMPRSS2-ERG, respectively [48]. This is confirmed by a larger prospective multicenter study (n = 443), in which TMPRSS2-ERG had independent additional predictive values to PCA3 and ERSPC risk calculator in predicting prostate cancer [49].

Prostate Health Index (PHI)

PSA isoform [-2]proPSA (p2PSA) was shown to be more accurate than PSA or %free PSA in predicting prostate cancer [50]. Prostate health index (PHI) was created by combining PSA, free PSA, and p2PSA in the formula (p2PSA/free PSA) × $\sqrt{}$total PSA. PHI and p2PSA had specificity 3 times of that of PSA, with best performance in the range of PSA 2–10. This could reduce unnecessary biopsies while maintain a high cancer detection rate [51]. In 2012, the FDA has approved the use of PHI and p2PSA in men older than 50 years old with a total PSA 4–10 ng/mL and normal DRE to reduce unnecessary prostate biopsies. PHI was also associated with more aggressive or clinically significant prostate cancers [52, 53]. Using a simulation model, PHI was shown to be more cost-effective than PSA-only screening [54].

Four-Kallikrein Panel (4 K)

The 4-kallikrein panel consisting of PSA, free PSA, intact PSA, and human kallikrein 2 (hK2) was shown to differentiate pathologically indolent and aggressive disease. It was shown that more than 50% of biopsies could be reduced by applying the 4K panel while missing 12% high-grade cancer and avoiding overdiagnosis of one-third of low-grade cancers [55–57].

These findings were confirmed in a large cohort of 6129 men in the Prostate Testing for Cancer and Treatment (ProtecT) study, with better AUC compared with PSA (0.82 vs 0.74). Using 6% risk of high-grade cancer as cutoff, more than 40% biopsies could be reduced while delaying diagnosis of only 10% of high-grade cancers [58].

A 4K score was created by combining the 4-kallikrein panel with age, DRE findings, and history of prior prostate biopsy and was validated to accurately identify men with high-grade prostate cancer [59]. Using the 4K score can reduce 30–58% biopsies while delaying diagnosis in less than 5% high-grade cancers. However, when combined in a multivariate prediction model, the added value is limited [46].

STHLM3

The population-based Stockholm 3 (STHLM3) study reported that the so-called STHLM3 model, which included plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, MIC1), genetic polymorphisms (232 single nucleotide polymorphisms), and clinical variables (age, family history, previous prostate biopsy, DRE), predicted Gleason 7 or above prostate cancer in a large development (n = 11130) and validation (n = 47688) cohort in Sweden. The STHLM3 model performed significantly better than PSA (AUC 0.74 vs 0.56) for Gleason 7 or above prostate cancers and could reduce 32% biopsies [60]. The issue of overdiagnosis was however not fully addressed as most prostate cancers diagnosed were still low grade, and the cost-effectiveness of such an extensive model is questionable [61].

Which Novel Biomarker for Prostate Cancer Diagnosis Should We Choose?

All of the aforementioned novel biomarkers and imaging techniques like MRI have proved to be more specific and more discriminative (in terms of AUC) than PSA and could potentially reduce a significant proportion (up to 50%) biopsies while delaying diagnosis in only a handful of clinically aggressive prostate cancers. However, there are very few head-to-head comparisons of different novel tools in terms of performance and cost-effectiveness, and the ever-increasing cost of novel tests would make screening for prostate cancer unaffordable. This creates a difficult scenario for both physicians and patients in choosing the optimal test before biopsy decisions [62]. One conclusion can be drawn from these data: combining relevant pre-biopsy information as compared to decision-making on the basis of a single PSA measurement will always help to reduce unnecessary testing and overdiagnosis.

Prostate Imaging: Multiparametric MRI of the Prostate

Conventional TRUS prostate has a poor sensitivity and specificity in identification of prostate cancers, and therefore, the main use of it is to guide prostate biopsy but not for diagnosis [63]. Recently the multiparametric MRI entered the urological diagnostic practice and is considered a promising imaging modality for the detection of prostate cancer [64]. A systematic review showed that targeted biopsy (with MRI information) had a higher detection rate of significant prostate cancer (sensitivity 0.91 vs 0.76) and a lower detection rate of insignificant cancer (sensitivity 0.44 vs 0.83) [65].

Conclusions

On the basis of natural history and screening studies, we can conclude that the risk of overdiagnosis of prostate cancer is present and considerable when applying systematic PSA-based screening in combination with random TRUS-based prostate biopsy. This should not prevent us from screening for prostate cancer, as none of us want to return to the era when many prostate cancers presented at an advanced or metastatic stage. We should aim to screen the right men (at particular high risk of aggressive prostate cancer and/or with a long life expectancy), at the right time, with the right tools. With all available knowledge, we are able to reduce the current rate of unnecessary biopsies and overdiagnosis of low-grade/low-risk prostate cancer. Adapting recommendations and guidelines is difficult but should be the way forward.

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The Role of Fear in Overdiagnosis and Overtreatment

3

Iona Heath

A Tintinnabulation of Fear

In about 1848, while writing his famous poem *The Bells*, Edgar Allan Poe invented the magnificent word 'tintinnabulation' to capture the sound of a ringing bell that lingers after the bell has been struck to mix with the sounds of succeeding bells. This chapter will argue that we now have a tintinnabulation of fear that is driving overdiagnosis and overtreatment, each fear reinforcing and interacting with the next.

There are some very dangerous synergies and they are jeopardising the great projects of medical science and medical care. Firstly there are the distinct yet overlapping fears of patients and doctors, of the bureaucrats and politicians who control the healthcare system, and of society and the culture that supports it. And secondly, there are the profits, the enormous amount of money that is made from inflating those fears, much of which is supported by good people trying to stop people dying of horrible diseases but who succumb to a dangerous degree of wishful thinking. This exists alongside and so abets the much less honourable operation of vested interest within medicine and particularly within the biotechnical and pharmaceutical industries.

Tragically, fear works to the advantage of the medical-industrial complex and, as a result, is fanned in the interests of corporate profit. The systematic medicalisation of ordinary human distress has turned into an epidemic of disease mongering, which actively inflates fear and plays on the resulting insecurity deliberately for financial gain. Fear also sells newspapers, and so many journalists, and almost all editors, play their parts willingly. Benign symptoms are portrayed as serious disease, as in irritable bowel syndrome; personal or social problems are recast as medical ones, as in much mild depression; and risks are conceptualised as diseases, as in reduced bone density or mildly raised blood pressure.

Fear increases the consumption of medical care which drives profits, and medical care itself creates more fear which is deliberately inflated by those who stand to make more profits, and so the vicious cycle rolls on.

Yet, as the great Franklin D. Roosevelt famously declared in his inauguration address in March 1933 in the depths of the Great Depression:

The Only Thing We Have to Fear Is Fear Itself

Because fear does dreadful things to people: it blights lives, it destroys health, and it drives people to make decisions and choices that are never likely to make things better.

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The Fears of Patients

In the modern secular world, symptoms of illness have become almost the only acceptable means of expressing distress and are much more commonly caused by unhappiness than by anything that medical science would recognise as disease. The attrition of belief has left little scope for finding meaning in misery, and to an ever-greater extent, medicine has expanded to fill the gap. Yet, any symptom, whatever its cause, carries a burden of fear.

Everyone is afraid of serious disease and its capacity to subvert and destroy hopes and lives, and so fear lurks, mostly unexpressed, within almost all symptoms, however, apparently trivial. The resulting paradox is that while people in the affluent world are living lives that are longer and healthier than ever before, they have become more and more fearful and worried about their health. Anxiety taints both health and life and prevents people from enjoying and using the health they have.

Patients have been made ever more aware of the pervasive nature of sinister symptoms and are constantly exhorted to be vigilant and to catch things early. Different patients may also have specific fears related to their particular symptoms, and these are sometimes exacerbated by the detail of their particular family history. And patients are also afraid that their doctors will not understand what they try to describe and that an important diagnosis will be missed or made too late through laziness, incompetence or just bad luck.

The Fears of Doctors

Doctors and other healthcare professionals share their patients' existential fears of disease and dying: they have no immunity. And doctors are also constantly afraid of making a mistake and of missing the serious diagnosis that will change a patient's life. They want, above all, not to cause harm. They are afraid of being publicly pilloried in the media. They are afraid of being subject to a serious complaint, and when things do go wrong, it is difficult to remember that the doctor will always carry a burden of guilt, feeling that they should have been able to do more – but not understanding that a feeling of responsibility is not the same as actually being responsible.

Struggling with this burden of fears, doctors, and young doctors in particular, learn to be afraid of the uncertainty that is intrinsic to medicine and indeed to any endeavour that takes general truths derived from large numbers of people and try to apply them to a succession of unique individuals. These doctors try harder and harder to be safe by ordering more tests. As a result, they find things that are nothing to do with the patient's illness and which would never cause harm if left alone. This drives overdiagnosis, too much medicine, more fear and greater profits.

The Fears of the System

The healthcare system, in the guise of its bureaucrats and politicians, is also afraid of uncertainty because uncertainty implies the necessity of professional judgement, and they distrust the innate unpredictability of this. Healthcare systems and public health are grounded in a utilitarian tradition, and as the economist Amartya Sen puts it in his magnificent book, *The Idea of Justice*:

> *The utilitarian tradition, which works toward beating every valuable thing down to some kind of allegedly homogenous magnitude of 'utility', has contributed most to this sense of security in 'counting' exactly one thing ('is there more here or less?'), and has also helped to generate the suspicion of the tractability of 'judging' combinations of many distinct good things ('is this combination more valuable or less?'). And yet any serious problem of social judgement can hardly escape accommodating pluralities of values.* [1]

Judgement in medicine has similarly tried to seek security in numbers and has too often forgotten the necessity of accommodating pluralities of values. Yet it is fear of uncertainty and of the necessity of judgement within the healthcare system that drives the contemporary obsession with counting and the ever-increasing enthusiasm for regulation and surveillance – which in turn exacerbates the fears of doctors. But as the

ancient Greeks were very aware, one cannot control probability:

> *It is a part of probability that many improbable things will happen.* [2]

The Fears of Society

So to the fears embedded in contemporary societies and cultures that prize youth, beauty and the perfect human body. The enduring universals of disease and death are an anathema. There is no place or space for the realities of death and dying or for the lonely realities of living with long-term life-changing disease or disability. Society is permeated by a protective projection of them, the sick, and us, the well.

The wishful thinking embodied in an avalanche of guidelines and protocols for both doctors and patients is used to make the chaotic and uncertain seem safe and predictable. We are led to believe that the straightjacket of an approved lifestyle combined with the highest standards of medical care will guarantee a long and happy life. Yet the unpredictable remains a daily occurrence: the young and fit still die, and the old and dissolute keep going. Health is not something that can simply be made or produced. Different people with what is apparently the same condition and in similar circumstances react differently to the same standardised treatment. All our explanations remain partial and no one is necessarily to blame.

Quackery has traded on fear for generations. Now the pharmaceutical industry prostitutes medicine for the same end. The bizarre hope of postponing death indefinitely has been suggested and assiduously promoted by those who hope to make a profit from its creation. Decades ago, philosopher and priest Ivan Illich predicted where this would lead:

> *The more time, toil and sacrifice spent by a population in producing medicine as a commodity, the larger will be the by product, namely the fallacy that society has a supply of health locked away which can be mined and marketed.* [3]

The market imperative derives from the fact that only a minority of most populations is acutely ill at any one time, whereas the majority is healthy. The healthy are however susceptible to persuasion that it is necessary for them to optimise their prognosis by undergoing screening and/or by taking preventive medication. In affluent countries, because there is now more money to be made from selling so-called 'healthcare' interventions for the healthy minority than for the sick majority, there is more pharmaceutical research in pursuit of preventive treatments than for the treatment of those who are already sick [4].

As a direct result, society spends an ever-greater amount on preventive technologies, leaving less available to treat those who are actually sick. In so doing, we shift resources from the poor and the sick to the rich and the well. This is clearly good for the medical technology and pharmaceutical industries but very bad for those funding the healthcare system, particularly as preventive technologies are much more likely to prove futile and to be overtaken by other disasters or pathologies. Overtreatment and undertreatment have become two sides of the same profit-driven coin.

Flipside Fears

This begins to hint at other, more hidden fears which are almost the flipsides of the ones already outlined. And they too afflict patients, doctors, the system and society. These flipside fears are the ones whose recognition and exploration might give us some hope of resisting the vicious cycle of fear and profit.

Flipside Fears of Patients

The flipside fears of patients include a question asked by George Eliot in her 1876 novel *Daniel Deronda*:

> *- but how to make sure that snatching from death was rescue?* [5]

In a 2010 article in the *New York Times*, writer Katy Butler describes the ruination of her elderly parents' lives by the insertion of an ill-considered pacemaker:

> *I watched them lose control of their lives to a set of perverse financial incentives — for cardiologists, hospitals and especially the manufacturers of advanced medical devices — skewed to promote maximum treatment. At a point hard to precisely define, they stopped being beneficiaries of the war on sudden death and became its victims*. [6]

At the age of 79, her father was suddenly severely disabled by a stroke which robbed him of most of his language, his mobility and his ability to care for himself. A year later he suffered a strangulated inguinal hernia, and the hospital refused to operate on him unless his wife agreed to have a pacemaker inserted because he had long-standing bradycardia and 'might die during or shortly after the operation'. He had previously declined such a pacemaker when he was competent to do so, and no one told his family about the option of temporary pacing. The pacemaker kept him alive for 6 more terrible years of worsening dementia – exemplifying bioethicist Dan Callahan's description of the Difficult Child of Medical Progress:

> *- the 1 percent of patients who consume some 21 percent of health care costs, usually succumbing gradually from multi-organ failure, illustrate the progress problem. Fifty years ago they would have died faster and, in many cases, with less suffering. We have traded off shorter lives and faster deaths for just the opposite, longer lives and slower death*. [7]

Katy Butler and her parents came to regard this as a very poor trade. But:

> *- my father's electronically managed heart — now requiring frequent monitoring, paid by Medicare — became part of the $24 billion worldwide cardiac-device industry and an indirect subsidizer of the fiscal health of American hospitals. The profit margin that manufacturers earn on cardiac devices is close to 30 percent. Cardiac procedures and diagnostics generate about 20 percent of hospital revenues and 30 percent of profits.*

Saving lives, or rather the postponement of death, makes big money, and this sort of situation is replicated everywhere.

A study published in 2008 attempted to measure the prevalence of statin use during the last 6 months of life and to determine if statin prescribing varies according to the presence of a recognisable, life-limiting condition. The researchers studied a group of patients who had died in 2004 and who were taking statins within 6 months of death. They compared those who were known to have a life-limiting condition with controls matched on number of comorbidities, age and socioeconomic status. They found that there was no significant difference in the time off statins between cases and controls and concluded that there had been a missed opportunity to reduce the therapeutic burden upon dying patients and to limit healthcare spending.

Flipside Fears of Doctors and Other Healthcare Professionals

These include a sense of the erosion of their professionalism and of respect for the necessity of judgement. They feel beleaguered by targets, by protocols and by guidelines and feel more and more constrained in their ability to adapt medical dogma to the specific needs and particular context of each individual patient:

> *Strict adherence to guidelines, for fear of risk, should not be allowed to stifle responsible, innovative practice or the patient's choice of alternative therapeutic solutions to the same problem*. [8]

But it does – every day. George Eliot recognises the wishful thinking that underpins so many of the guideline-driven conventions of contemporary medicine:

> *The truth is something different from the habitual lazy combinations begotten by our wishes*. [5]

Doctors begin to fear the possibility, even the probability, that they are doing harm while trying to do good.

Healthcare systems put enormous emphasis on screening and other preventive interventions, at least in part because there is more money to be made from the healthy majority than from the sick minority. The doctor is expected to seek out the patient rather than vice versa and, with an

implicit promise of benefit, to offer someone who is at present in good health an intervention which is expected to make their life better in the future. Unfortunately, all such interventions oblige the recipient to consider a range of possible threats to their health and are almost always associated with a degree of heightened anxiety and fear. For some people, this fear can become overwhelming and debilitating in itself. In Denis Pereira Gray's memorable image, preventive interventions stain the clear water of health with the ink of fear, and once stained the water can never be clear again. Fear cannot be taken back. The diagnosis of risk and the consequent inflation of need are not something to be undertaken lightly or unthinkingly. And doctors begin to fear that they are being used to inflate fear rather than to help contain and relieve it. The Australian sociologist Deborah Lupton writes:

> *Risk discourse is redolent with the ideologies of mortality, danger, and divine retribution. Risk, as it is used in modern society, therefore cannot be considered a neutral term*. [9]

Doctors fear that the sheer volume of risk rhetoric is more destructive than productive of health. As EM Forster recognised in his novel *Howards End*, written in 1910:

> *- she felt that those who prepared for all emergencies of life beforehand may equip themselves at the expense of joy*. [10]

An obsession with health is destructive of it. The more people are exposed to the machinations of contemporary healthcare, the more they perceive themselves to be sick and at risk, and the higher the rates of self-reported illness [11].

Doctors are also fearful of simplistic explanations and predictions and of easy promises. Take the single, apparently simple, example of inherited genetic susceptibility to an industrial toxin. The problem is that this apparently straightforward susceptibility interacts with a huge number of other factors. Effective biomedical knowledge is limited to a very few of these interactions, and thus it is impossible to make a robust prediction of the outcome. Every day, the inherent uncertainty of clinical practice familiarises the practitioner with the consistent gap between the map of medical science and the territory of human experience and suffering:

> *A map is not the territory it represents, but, if correct, it has a similar structure to the territory, which accounts for its usefulness*. [12]

It is this constantly recurring gap: between a word and its object, between a diagram and what it tries to represent, between nature and our understanding of it, between the subjective and the objective and even between Donald Schön's high ground of technical rationality and the swampy lowland of professional practice [13]:

> *This gap signals the space in which choices appear, ethics is born, democracy grows, justice evolves, secrets, lies and errors constitute communication, and human identity becomes a matter of self-delusion and composition*. [14]

To view health as the opposite of disease is a category error: health belongs to the territory and is more akin to love and hope; disease belongs to the map. The prevention of disease can never be the same as the promotion of health, and yet the two phrases are often used synonymously.

All the freedom, challenge and potential innovation of medical practice exist in this gap between the map of medical science and the territory of illness and suffering. In the gap, wisdom is more useful than information, and there is space for the exploration of:

> *- the key interests of the clinician: the exigent and difficult reality of illness as a human experience and the core relationships and tasks of clinical care*. [15]

In the relationship between doctor and patient, the doctor holds the biomedical map, and he or she has a responsibility to have studied it well. The task of both doctor and patient is to explore the usefulness and the limitations of the map in relation to the territory of the patient's illness. The social and cultural context and the life story of the patient mould the nature and experience of illness and in this way make the standardised and schematic map more or less useful. Doctors fear that the existence of the gap is misunderstood and even denied by those who organise and control our healthcare systems.

Medicine is in a mess because we have prioritised theory over practice, the disease over the experience of the patient and number over description, and we have allowed greed to play on fear at every level of healthcare.

The Flipside Fear of the System

The flipside fear of the system, and those who organise it, is first and foremost the terrifying acceleration of healthcare costs.

'EvaluatePharma' describes itself as an organisation that provides senior decision makers within the pharmaceutical industry with models of the sector from the viewpoint of the world's financial markets. According to their world preview 2014, for the first time in the pharmaceutical industry's history, the consensus forecast of worldwide prescription drug sales is set to exceed one trillion dollars, reaching $1,017bn by 2020, equating to an average growth of 5.1% per year from 2013 to 2020.

Worldwide prescription drug sales will have almost doubled in just 14 years. These profits depend entirely on us all being persuaded to take an enormous and rapidly increasing number of medications – then peeing them out into the already beleaguered environment.

Politicians and healthcare bureaucrats are also increasingly fearful of the very limited returns that they seem to be getting for the investment of enormous amounts of money. They resent the false promises of much medical research and worry about the increasing evidence of the extent of corruption within it. They are increasingly obliged to recognise that medicine delivers much less than it promises.

Take the example of screening mammography services which have cost huge amounts of money across the richer countries of the world. Yet, in February 2014, we got the results of the huge Canadian trial by Anthony Miller and colleagues following up women for 25 years and concluding that annual mammography in women aged 40–59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. And overall, 22% (106/484) of screen-detected invasive breast cancers were overdiagnosed, representing one overdiagnosed breast cancer for every 424 women who received mammography screening in the trial [16].

Screening for prostate and breast cancer in the USA has followed a similar pattern. The incidence of these cancers increased after the introduction of screening but has never returned to prescreening levels. Indeed, prostate-specific antigen testing has nearly doubled the chance that a man will be diagnosed with prostate cancer in his lifetime. The proportion of early-stage cancers has increased, but the incidence of advanced cancers has not decreased at a commensurate rate. For both cancers, screening seems to have increased the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers and therefore has not produced the anticipated reduction in cancer mortality [17].

Flipside Fears of Our Culture and Our Society

Some of these revolve around asking what is happening to children and what is happening to the old.

In America, approximately 11% of children aged between 4 and 17 years had been diagnosed with ADHD as of 2011. The percentage of children with an ADHD diagnosis continues to increase, from 7.8% in 2003 to 9.5% in 2007 and to 11.0% in 2011. Rates of ADHD diagnosis increased an average of 3% per year from 1997 to 2006 and an average of approximately 5% per year from 2003 to 2011 [18].

There is a strong association between the number of standard units of stimulant medication used to treat ADHD that is prescribed per child and the per capita GDP. ADHD appears to be a disease of rich countries, and, beyond that, the USA is a shocking outlier with very much higher rates of prescription [19]. What does this apparent overprescription mean? And what do the label and the treatment teach each affected child? They learn that they are 'not normal',

that they are not responsible for their own behaviour and that the answer to their problems comes in a bottle. I cannot think about ADHD without thinking of a boy from a large family on my patient list. His mother was physically abusive and broke one of his legs when he was a toddler. His father was granted custody and subsequently got together with a woman who already had two children of her own, and they went on to have another five children together. Increasingly desperate for attention no fewer than three boys and one girl from this family were diagnosed as having ADHD and prescribed medication. By the time I retired, the older boy had already graduated seamlessly onto street drugs, particularly cocaine.

And what is happening to our elders? As Atul Gawande put it in the New Yorker:

> *In the past few decades, medical science has rendered obsolete centuries of experience, tradition, and language about our mortality, and created a new difficulty for mankind: how to die. People die only once. They have no experience to draw upon. They need doctors and nurses who are willing to have the hard discussions and say what they have seen, who will help people prepare for what is to come—and to escape a warehoused oblivion that few really want*. [20]

Humanity has a very long tradition of eroding the present in the hope of a better future. We used to do it through religion when happiness was all too readily consigned to a distant heaven. Now we do it through healthcare, damaging the present in the hope of a better or at least a longer future. But what is the point of eking out the longest possible life if there is to be no joy in the living of it?

The great novelist Joseph Conrad evokes for me the situation within contemporary medical care:

> *- the weary succession of nights and days tainted by the obstinate clamour of sages, demanding bliss and an empty heaven, is redeemed at last by the vast silence of pain and labour, by the dumb fear and the dumb courage of men obscure, forgetful, and enduring*. [21]

And, more than 20 years ago, James McCormick who used to be the professor of general practice in Dublin explained why:

> *Health promotion ... falls far short of meeting the ethical imperatives for screening procedures, and moreover diminishes health and wastes resource. General practitioners would do better to encourage people to lead lives of modified hedonism, so that they may enjoy, in the full, the only life they are likely to have*. [22]

No one was listening then – might they begin to now?

What Can Be Done?

Zygmunt Bauman, the emeritus professor of sociology at the University of Leeds in the UK, clearly demonstrates the false certainty of some medical predictions by still being alive at the age of 90 despite his love of tobacco pipe-smoking. Bauman writes:

> *We understand now that uncertainty is not a temporary nuisance, which can be chased away through learning the rules, or surrendering to expert advice, or just doing what others do. Instead it is a permanent condition of life. We may say more - it is the very soil in which the moral self takes root and grows. Moral life is a life of continuous uncertainty, and it takes a lot of strength and resilience and an ability to withstand pressures to be a moral person*. [23]

Part of trying to address the terrible synergy of fears that I have tried to describe depends on acknowledging the extent of our uncertainty, exploring it and not disguising it by hiding behind numbers. Doctors have a terrible tendency to make sweeping assertions of what they hope will be true instead of confining themselves to what they know to be true.

As people age, it is inevitable that their expectation of life should reduce, and, exactly in parallel, their possibility of benefitting from biomedical technologies is necessarily diminished. They are experiencing what the American writer John Williams described in his great novel *Stoner* as:

> *- the slow, quiet attrition of time against imperfect flesh*. [24]

As people gradually succumb to the multimorbidity and frailty of old age, open, rational

discussions and shared and mutually responsible decisions about the point at which medicine becomes futile and wasteful are fundamentally important. Sadly, there seems to be huge reluctance among doctors and policy-makers to discuss any of this which is all too easy to understand because such discussions are often difficult and painful. Nonetheless the reluctance is regrettable especially when accusations of ageism are used to mask increasingly futile interventions that verge on cruelty. Again this situation is painfully well captured in *Stoner*:

> *Stoner had allowed himself to be poked and prodded, had let them strap him on a table, and had remained still while a huge machine hovered silently about him. It was foolishness, he knew, but he did not protest; it would have been unkind to do so. It was little enough to undergo, if it would distract them all from the knowledge they could not evade.*

The great American writer Saul Bellow seems always acutely aware of humanity's profoundest existential challenges. In his novel *Mr. Sammler's Planet* he records:

> *Seeing the singular human creature demand more when the sum of human facts could not yield more.* [25]

This applies to patients and their doctors, to the healthcare system and within our culture and society – everyone seems to want to demand more that the facts will yield. He goes on:

> *Do we always, always to the point of misery, do a thing? Persist until exhausted? Perhaps.*

And it seems to me that there is hope in that word 'perhaps'. It is the uncertainty of that 'perhaps' that lies behind the medical profession's growing determination to pay serious attention to the harms imposed on our patients by the medicalisation of ageing and death and, indeed, the medicalisation of ordinary human distress all of which have become more and more prevalent over the past 20 years.

It can never be appropriate to treat someone in their 80s in the same way as someone in their 30s, not least because the physiology of the ageing body is different, more vulnerable and more susceptible to the adverse effects of drugs. This is not ageism; it is person-centred care. When doctors fail to recognise and acknowledge existential suffering in the dying and take refuge in excessive technological interventions, patients become frightened and, no longer able to trust their doctors, may even request assisted dying. The medicalisation of life cannot be resolved by the medicalisation of death. Two technological wrongs do not make an existential right. I don't want assisted dying, but I also don't want to be fed through a tube in my stomach when I can no longer swallow.

Human society has not yet realised that Aristotle's golden mean applies to healthcare as much as to any other human endeavour or attribute. People easily understand that too little healthcare is harmful but seem to have great difficulty in grasping that too much also causes harm. It is well timed that everyone in healthcare tried to dampen rather than amplify the tintinnabulation of fear.

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4 Ethical and Legal Considerations in Active Surveillance for Prostate Cancer

Lionne D.F. Venderbos

Introduction

Active surveillance is a proper treatment option for men with low-risk prostate cancer as results from large observational active surveillance cohorts and the ProtecT study are promising in terms of disease-specific survival and metastases. After 15 years of follow-up, 1.5% of men died of prostate cancer, and 2.8% of men developed metastatic disease in the Klotz active surveillance cohort [1]. In the ProtecT study, 1.5% of men died of prostate cancer after 10 years of follow-up, while 6% developed metastases [2]. In the Johns Hopkins active surveillance cohort, the cancer-specific and metastasis-free survival were 99.9% and 99.4%, respectively, at both 10 and 15 years of follow-up [3]. The mortality rates and incidence of metastatic disease are therewith consistent with the expected mortality in favorable-risk patients managed with initial definitive intervention.

While evidence supports the inclusion of active surveillance in national and international guidelines as a treatment option for low-risk prostate cancer, and in terms of quality of life [4–7], professionals may still be hesitant to offer active surveillance as it comes with the risk of missing the window of curability – although small – and, consequently, the potential of malpractice litigation. The choice for active surveillance should, all the while, be based on the clinical characteristics of the tumor and patients' treatment preference.

In this chapter, therefore, considerations will be discussed that give insight into legal components of a potential malpractice process. By providing such an insight, we want to make professionals aware of what they can do to overcome such a process and therewith open the door to offering more active surveillance in the future. To make professionals more confident in offering active surveillance, among others, the role of information provision, the role of patient-physician communication, and the role of guidelines in offering active surveillance will be discussed.

Considerations

Information Provision and Informed Consent

Men diagnosed with low-risk prostate cancer can choose between various treatment options that are similar with respect to disease-specific survival but differ in terms of side effects [2, 8, 9]. Surgery and radiation therapy may, for instance,

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impact continence, potency, and bowel function, while active surveillance may cause anxiety and distress due to living with untreated prostate cancer [5, 10, 11]. Informing men on the advantages and disadvantages of suitable treatment options enables them to exercise their right of self-determination, i.e., to govern themselves without outside interference.

Providing treatment information to patients is the basis for informed consent. The American Cancer Society describes informed consent as a process that includes several steps, one of them being the receiving of information about the possible risks and benefits of treatment and the receiving of information about the risks and benefits of other options, including the option of not getting treated. In the United States, informed consent is an important patient right that is embedded within both national and state's law. The way information should be given may be listed in the state's laws and therefore can vary per state. In Canada doctors have a duty to treat with a reasonable degree of care, skill, and knowledge, but it also extends further and includes the obligation to provide sufficient information therewith allowing patients to make intelligent, informed, and rational decisions with respect to the proposed medical treatment [12]. The four elements required for informed consent are included in the Ontario's Health Care Consent Act: (I) consent must relate to the treatment, (II) consent must be informed, (III) consent must be given voluntarily, and (IV) consent must not have been obtained through misrepresentation or fraud. A consent is said to be informed if a person received the information about the nature of the treatment, the expected benefits of the treatment, the material risks and side effects of treatment, and the likely consequences of not having the treatment a reasonable person in the same circumstances would require in order to make a decision. If requested, additional information about one of these matters should have been received as well [12]. In England the "NHS constitution for England" contains an informed choice right, stating that patients "have the right to be given information about the test and treatment options available to them, what they involve and their risks and benefits."

In the Netherlands, the information right is embedded within the Medical Treatment Contract Act (WGBO), article 7:448 Dutch Civil Code. This article states that the physician has to provide information on the intended medical actions, treatment, and the patient's current health status. The information provided has to be clear, relevant, and adjusted to patients' educational level [13]. The information right enables patients to make a well-informed decision on whether or not to provide informed consent on starting the proposed treatment. If information is not provided in whole or in part, this may lead to the situation where a patient is not, or only partly, able to use his right of self-determination. This then may lead to the situation of the patient making a choice he would not have made, had he been well-informed upfront [13]. In addition to the information about treatment itself, in the Netherlands a discussion is ongoing on whether the physician has to provide information on how successful he has been in completing certain procedures and/or operations. The current point of view encourages an open and transparent discussion if the patient asks his physician directly, but providing the patient with statistics upfront is not necessary [14].

In Germany, patients choosing between treatment strategies have to be fully informed by their doctors as well, because only a fully informed patient can rightfully exercise his right of self-determination and provide informed consent on one of the treatment options. Providing comprehensive information entails regarding the treatment options as each other's equivalent. This is the case when, for instance, radical prostatectomy, radiotherapy, and active surveillance all likely lead to success, while the risks associated with the procedures may be different but comparable in weight. Treatment options should then be presented to the patient alike, while the physician is withholding any personal preferences that may guide the patient into a certain direction. The physician informing the patient has to be aware that recommending either one of the treatment options holds risks. The physician

may not make the treatment decision for the patient when options are equal. He may be inclined to do so but then bears the risk of being accused later on by the patient saying that the decision for active surveillance was wrong. The patient may demand compensation for his pain and suffering and because he was advised wrongly. If this occurs, the physician runs into the risk – at least from a legal perspective – that the informed consent was invalid, as it was not preceded by comprehensive and unbiased information on all treatment options. If the consent must be classified as invalid for this reason, the physician is liable for all health impairments resulting from the advised procedure – even if the side effects in itself were a consequence of medical behavior lege artis [15].

Patient-Physician Communication

Patient-physician communication is a key element in the active surveillance monitoring strategy. At the same time, communication between a patient and physician is a common source of patient dissatisfaction, and communication failures are strongly correlated with medical malpractice litigation [16–20]. Common predictors of medical malpractice claims are the physicians' inability to clearly communicate with a patient, to disclose both risks and benefits of treatments properly, and to answer patients' questions [21–23]. Levinson et al. assessed communication patterns between those physicians who did not experience malpractice litigation before and those who had previously been sued. They found that physicians who had been sued previously tended to demonstrate poorer communication skills and were less likely to start up helpful interactions with patients [23].

That good communication may avert litigation is shown in one of the worldwide active surveillance cohorts in which men whom their prostate cancer has metastasized while on active surveillance have accepted this outcome. From personal communication with the treating physician, it has become clear that he has been open to his patients from the start, explaining that it was a scientific study they were participating in with both risks and potential benefits. Open and honest communication led to transparency for both the treating physician and the patient, resulting in a good patient-physician relation in which the risks of participating in a scientific study are accepted.

There are two principles regarding communication that are important to patients: (1) the need to know and understand which demands instrumental communication from the physician (giving information and advice) and (2) the need to feel known and understood which demands affective communication from the physician (showing empathy and providing emotional support) [24]. Physicians should master certain basic communication skills as these are the basis for effective communication. And effective communication in its turn determines, to a large degree, the quality of healthcare [25]. Physicians may use the Calgary-Cambridge model to guide the patient-physician communication process. How we communicate is just as important as what we communicate [25].

How Communication Can Influence Decision-Making

How the physician communicates a prostate cancer diagnosis and the eligible treatment options can influence patient's treatment choice [26]. Scherr et al. assessed the influence of patient preferences and urologist recommendations on treatment decisions for men with clinically localized prostate cancer [27]. Before consulting with a physician, 15.2% (32/211) of patients preferred active surveillance, 35.5% (75/211) had no preference, and 49.3% (104/211) of patients preferred active treatment. Urologists recommended active surveillance in 17.5% (37/211) of the cases, in 26.5% (56/211) of cases they were neutral, and in 55.9% (118/211) they recommended active treatment. Eventually, 46% (98/211) of patients received initial active surveillance versus 54% (113/211) who received active treatment [27]. In logistic regression analysis, Scherr et al. found that receiving active treatment was primarily predicted by urologists' recommendations and that urologists' recommendations were heavily

influenced by medical factors, not by patient preferences [27]. Hoffman et al. furthermore found that for a patient diagnosed with low-risk prostate cancer in the United States, it is still likely that he receives the treatment the urologist most commonly performs [28, 29].

Shared Decision-Making

Men diagnosed with low-risk prostate cancer face a preference-sensitive decision, as no single treatment (active surveillance, radical prostatectomy, and radiation therapy) is uniformly superior in terms of survival [30]. Side effects, however, vary considerably among these treatment options. Therefore, shared decision-making is recommended by the European Urological Association (EAU), the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN). Shared decision-making refers to the process in which a patient and health professional strive to reach a healthcare choice together. High-quality shared decision-making demands that patients understand available treatment options and potential adverse outcomes of these treatments and that they have the opportunity to consider their personal values when evaluating treatment options [30]. Therefore, shared and informed decision-making are highly related, as effective shared decision-making can only be done if a patient is fully informed of the treatment options (more information on shared and informed decision-making can be found in Chap. 15).

As mentioned above, shared decision-making for low-risk prostate cancer is incorporated into several guidelines (EAU, AUA, NCCN). Furthermore, the Patient Protection and Affordable Care Act includes several sections emphasizing shared decision-making in preference-sensitive decisions [31].

Sharing a decision can be difficult. Loeb et al. examined the motivations behind physician decision-making in relation to active surveillance monitoring practices in the United States [32]. Loeb and colleagues interviewed 24 physicians, until thematic saturation was reached. Eight themes could be distinguished that explain the variation in active surveillance monitoring and reveal the motivations of physicians in offering active surveillance: (1) physician comfort with active surveillance, (2) protocol selection, (3) beliefs about the utility and quality of testing, (4) years of experience and exposure to active surveillance during training, (5) concerns about "inflicting" harm – including medicolegal concerns – (6) patient characteristics, (7) patient preferences, and (8) financial incentives [32]. Physicians stated that they try to adhere to shared decision-making and taking into consideration patient preferences. Whether a decision is truly shared, however, is dependent upon more characteristics. Recent research by the Dutch Patient Federation NPCF among 8.200 Dutch patients showed that only 37% of patients were offered more than one treatment option and were involved in the decision-making process versus 63% of patients who were offered a single treatment option or were not involved in the decision-making [33].

As said, sharing a decision can be difficult. Expert assumptions about patients' roles and responsibilities often do not reflect patients' experiences or expectations [34–37]. Still, many patients prefer to share a healthcare decision with their treating doctor, although individuals do vary in how much they wish to concern themselves with the relevant evidence [33, 37]. Decision aids may be of help in the decision-making process. In a systematic review, Durand et al. found that simulated scenarios suggested that documenting the use of decision aids or other decision support interventions in patients' notes could offer some level of medicolegal protection [21].

Guidelines

Active surveillance is incorporated into national and international guidelines as a treatment strategy for low-risk prostate cancer [38]. Physicians are advised to follow guidelines as they represent the current professional standard on which consensus was reached by a professional community. However, what is the role of such guidelines in

legal proceedings in the United States and the Netherlands?

The United States

Stimson describes what the role of guidelines is in the American legal system, in particular, in medical malpractice tort law [39]. He explains that clinical practice guidelines are formalized expert opinions and scientific data that are then used as public statements of appropriate care. These clinical practice guidelines function as a lens through which clinical decisions can be judged by non-clinicians. Clinical practice guidelines can be described as "expert-driven, evidence-based statements defining appropriate diagnosis and treatment algorithms for particular clinical problems" ([39], page 614). Clinical practice guidelines evolve over time in response to advancements in medical science and changes in both professional and societal norms.

To succeed in a medical malpractice claim in the United States, four elements must be proven by the plaintiff: (1) the physician had a duty to care, (2) that duty was breached by a deviation from the standard of care, and (3) this deviation was the direct cause (or proximate) (4) of the plaintiff's injury [39]. It is the second element – the standard of care assumption – that creates space for clinical practice guidelines to influence the court's medical malpractice analysis because it is the clinical practice guideline that informs the evidentiary foundation for the standard of care [39]. In general, clinical practice guidelines alone do not define the standard of care. In Conn v. United States (2012), the court ruled that a vague reference to a clinical practice guideline does not establish standard of care, while in Linda Pearson-Heffner v. United States (2006), it was decided that "merely alluding to general policies espoused by – in this case two – professional societies" does not constitute a standard of care [39–41]. Consensus among various existing clinical practice guidelines can help to define the standard of care as was shown in the Daberkow v. United States (2009) case [42]. Uniform consensus among clinical practice guidelines allows the court to define a standard of care. At the moment, however, such a uniform consensus guideline is not yet available for active surveillance. The Movember-GAP3 project has been initiated in 2013 to integrate the various existing active surveillance protocols into one straightforward, unambiguous protocol (see also Chap. 14). Until the results of that project are out and published, we have to work with single clinical practice guidelines, which may show similarities to some extent. In the Ellis v. Eng (2010) case, one clinical practice guideline was used to define the standard of care [43]. The American Society of Clinical Oncology (ASCO) guideline was used by both the plaintiff and the defendant's expert to argument two opposite views. The plaintiff's expert claimed that adjuvant chemotherapy was the standard of care for stage II colon cancer according to the ASCO guideline, while the defendant's expert claimed that the ASCO guideline did not require adjuvant chemotherapy. In such a case, the court is willing to engage clinical practice guidelines as the final arbiter of the standard of care [39, 43].

The Netherlands

In the Netherlands a physician and patient conclude a best effort obligation, meaning that the physician will perform care to the best of its ability. This is another type of obligation as compared to the obligation of result, where parties contract a result. Committing to produce a certain result, cure, for instance, is rather difficult, if not impossible, in a healthcare setting. In case of a best effort obligation, liability may arise if a physician has not performed to the best of its ability. According to the Medical Treatment Contract Act, the physician must observe the care of a good counselor. Therefore, a physician must act according to his professional medical standards. These standards are laid down in protocols, guidelines, standards, and the codes of conduct developed by the (urologic) profession. A physician fails when he is not performing to the best of his ability, when he – in other words – does not act in accordance with the professional standards. If such a situation occurs, the patient can come into action; he can claim honoring of obligations and dissolution of the contract or start a compensation procedure [44].

The best effort obligation concluded between a physician and patient is one that must be honored. Does the physician fail herein, and is the deficiency attributable due to fault-based or strict liability, then one speaks of a shortcoming or breach of contract. A causal link must exist between the breach of contract and the damage. When no such causal link exists, no compensation procedure can be started. In straightforward malpractice cases, a direct causal link often exists. However, in case of an information error, such a direct causal link is not necessarily present. A physician providing incorrect or incomplete information can cause damage to the patient as well. If a patient would have chosen another treatment had he been well informed, one with less risks, for instance, then a causal link can be assumed to exist [44].

Article 7:453 Civil Code indicates that the physician should observe the care of a good counselor, be responsible, and act according to his professional medical standards. Article 7:453 Civil Code is an open norm that only provides in general terms what can be expected from a "reasonably competent" and "reasonably acting" physician. What this means is more concretely stipulated in guidelines and protocols [45]. In assessing whether a physician has or has not acted rightly, the court will, in principle, look at the professional standard, as defined in the currently prevailing guidelines and protocols that apply to this individual case. A medical expert, often a colleague in the field, has a key role in a medical malpractice case, as he must decide what could be expected from the physician in terms of the provided treatment. What was at the time of acting included in the guideline?

The court will therefore start from what is included in the guidelines and protocols. The more concrete guidelines and protocols are written, the heavier the burden of proof rests on the physician may he deviate from the standard [45].

Obviously, it is legitimate to deviate from the standard if, in the specific situation of the individual patient, there is a medical reason to do so. It is very important to discuss this with the patient and then well document it into the patients' medical record, be this as accurate as possible. Note not only the selected course of action but also the rejected practice(s), preferably with a brief motivation to get an insight into the reasoning and line of thought of the physician. It is precisely this "proof" of a line of thought that a particular approach has been medically justifiable that in practice is often lacking in patients' medical records, while this can provide just the eloquence the court or expert would need [45].

Following protocols does not automatically mean you are not liable for any medical practice. Many situations may arise that proof otherwise. Conversely, not following the protocol does not automatically result in liability. There must always be a causal link between the outcome of the treatment and not having followed the guideline or protocol. Again and again the judge will take into account the specific circumstances of a case, in which the premise is that the physician in question has "acted reasonably" and is "reasonably competent" (Art. 7:453 Civil Code). Standards as laid down in guidelines and protocols are important and authoritative – because they come from the profession itself – and have a serious impact on the legal test, but they are not all determinative [45].

Discussion

Men diagnosed with low-risk prostate cancer face a preference-sensitive treatment decision. In deciding upon treatment, information provision is very important. Men choose a treatment based on the information received and subsequently provide informed consent to start treatment. Communication is an important component in that process as well as later on during follow-up. Effective communication and transparency may overcome or avert litigation, as was seen in one of the renowned active surveillance cohorts. It is therefore of upmost importance that physicians develop basic communication skills during their medical education and training and keep working on them throughout their careers. It is furthermore advised that physicians include notes in

patient records which outline their reasoning and line of thoughts in terms of offering and continuing active surveillance, so not just include what was chosen (to continue active surveillance, for instance) but also why something else was not chosen (to switch to active therapy, because clinical characteristics were still favorable). This does not have to be in extensive paragraphs; keywords can already give an insight into the reasoning of the physician.

Besides medicolegal arguments that can play a role in offering active surveillance yes or no, there may also be ethical arguments. Physicians participating in the qualitative interviews conducted by Loeb and colleagues said that they felt a tension between "over" and "under" testing patients and the desire to reduce "harm" whether through repeat biopsies vs. the risk of "missing" aggressive disease [32]. One physician furthermore stated that they are trained to do something, they are payed to do something, they are by nature doers, and active surveillance is not really part of what a surgeon is wired to do [32]. This is what you also sense in many Asian countries, where it is unacceptable to patients when "nothing" is done (as is reflected in the high use of antibiotics to dispute viruses, for instance). The percentage of low-risk prostate cancer patients choosing active surveillance in Asian countries is therefore low. While doing something is often much easier compared to doing nothing, so to say, it can be debated as the Hippocratic oath includes the "primum non nocere" principle, meaning "first, do no harm." It also raises the discussion on whether active surveillance may be classified as doing nothing, as it does entail a monitoring strategy with regular tests (prostate-specific antigen test, digital rectal examination, MRI) and prostate biopsies. Another incentive for choosing radical prostatectomy or radiotherapy over active surveillance may be a financial one. The fee for service system in the United States may influence the uptake of active surveillance there. Compared to the United States, the uptake of active surveillance in Europe and Australia is much higher [32].

To conclude, in this chapter we reviewed the components that influence whether an active surveillance patient initiates a malpractice process. By paying attention and caring for individual components of that process, such as providing well-balanced information, obtaining informed consent, communicating effectively, and taking into account patients' preferences when choosing treatment (shared decision-making), malpractice litigation may be overcome or averted. It is emphasized that whatever treatment is chosen, notes on this decision-making process have to be included in patients' records, including what was offered to patients and the physicians' thought process.

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Gleason 6 Tumors Should Still Be Labeled as Cancer

5

Angelo M. De Marzo and Jonathan I. Epstein

Introduction

In part due to changes in the grading system of prostate cancer, there has been greater recognition that relatively indolent prostate cancer is being overtreated. To mitigate against this overtreatment with its associated morbidity, there have been proposals to rename Gleason score 6 cancer (the lowest grade currently assigned) as "non-cancer." This chapter will present the issues and discuss why ultimately we are in favor of retaining designation of this tumor as adenocarcinoma yet agree that there are changes that can be made in the terminology to better reflect its prognosis which will allay patients' fear and hopefully increase the proportion of men choosing active surveillance.

Original and Modified Gleason Grading

The prostate cancer grading system currently used worldwide was developed between 1996 and 1974 by Donald Gleason, a pathologist with the Veterans Administration Cooperative Urologic Research Group [1, 2]. Two of the more prominent changes have been the disappearance of Gleason scores 2–5 from clinical practice and the tighter definition of Gleason score 6. In a study from Helpap et al. comparing grades in 1996–2000 to 2005, Gleason scores 2–4 decreased from 2.7% to 0% and Gleason score 5 decreased from 12.2% to 0.3% [3]. In Gleason's original data, patterns 1 and 2, which result in Gleason scores 2–5, were seen in 27.9% of cases [4]. In Helpap's data, Gleason score 6 decreased from 48.4% to 22.0%, with an increase of Gleason score 7 from 25.5% to 67.9% [3]. Gleason pattern 4 (which includes Gleason scores 7–8 and some of 9–10) was present in only 12.1% of Gleason's original cases [4]. The increase in Gleason score 7 tumors reflects that poorly formed glands and some cribriform glands were considered as Gleason pattern 3 in the original system yet upgraded to Gleason pattern 4 in the modified system, first in the 2005 ISUP Consensus Grading Conference [5]. In the original Gleason system, large cribriform glands that in current practice would universally be graded as pattern 4 were typically graded as Gleason pattern 3 [6, 7]. Numerous studies have demonstrated the adverse prognosis of cribriform glands [8–12]. Following these studies and the recognition that experts in prostate pathology virtually never diagnose cribriform glands as pattern 3, all cribriform patterns were accepted as Gleason pattern 4 in the 2014 ISUP Consensus Grading Conference [13].

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Improved Prognosis of Current Gleason Score 6

Gleason score 6 cancer currently has a better prognosis than in years past, referred to as the Will Rogers phenomenon, as patterns associated with more aggressive behavior have been shifted to Gleason score 7 [14]. Currently, a diagnosis of Gleason score 6 cancer at radical prostatectomy is associated with a 96% cure rate, even with the inclusion of cases with extraprostatic extension and positive margins. A pure Gleason score 6 cancer at surgery has no potential for metastatic behavior [7, 15]. Studies which show a low risk of lymph node metastases with Gleason score 3 + 3 = 6 at radical prostatectomy suffer from incomplete submission of the prostate where higher-grade cancer may not have been sampled and not applying contemporary grading criteria [16]. In the past, a diagnosis of Gleason score 6 cancer was not as predictive of a good behavior, with a higher rate of progression and some men dying of prostate cancer [7].

Alternative Non-cancerous Terminology for Gleason 6 Cancer

Some experts have questioned whether Gleason score 6 should even be called cancer given its better prognosis, proposing alternative terms such as IDLE (indolent lesion of epithelial origin) tumor because of the fear associated with the term "cancer" [17]. There are precedents for changing the name of a tumor in order to not label it as cancer. These include the use of the term "papillary urothelial neoplasm of low malignant potential (PUNLMP)" in the bladder for cases formerly designated as low-grade papillary urothelial carcinoma [18]. A low-grade adipose tissue tumor in the retroperitoneum or paratesticular region is called "well-differentiated liposarcoma" in part because of the potential to dedifferentiate [19]. A tumor with the exact same morphology and even molecular findings in the extremities is called "atypical lipomatous tumor (ALT) since in this site de-differentiation does not typically occur." Most recently, a type of papillary thyroid carcinoma has been renamed as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" [20]. These nomenclature modifications all serve to remove the label "cancer" or "sarcoma" and replace them with a more benign designation to allay patients' fears and help to prevent overtreatment.

Clinical Arguments Against Changing Gleason 6 Terminology

However, all of these entities can only be diagnosed either at specific sites (i.e., extremity for ALT) or on resections where the entire tumor has been sampled to either rule out a higher-grade component (PUNLMP) or to exclude invasive features (NIFTP). Whereas it has been demonstrated that a pure Gleason score 3 + 3 = 6 tumor lacks the capability of metastatic behavior and uncommonly extends out of the prostate, one cannot claim the same when Gleason score 3 + 3 = 6 is seen on needle biopsy. In approximately 20% of needle biopsies with Gleason score 3 + 3 = 6, there is upgrading at radical prostatectomy where the resection shows unsampled higher-grade cancer [21]. If a Gleason score 3 + 3 = 6 on needle biopsy was renamed as IDLE tumor or some other benign rebranding, it would be in error in a significant minority of cases and could lead patients to drop out of active surveillance follow-up programs as they have not been diagnosed with "cancer." In cases with Gleason score 3 + 3 = 6 on biopsy and either high serum PSA levels or extensive cancer, the disconnect by labeling these cases as not cancer is more overt, as there is an even increased likelihood of unsampled higher-grade cancer. Furthermore, how is it reconciled in Gleason score 3 + 4 = 7 or 4 + 3 = 7 cancers, where there is the potential for metastatic behavior, that the "3" refers to a benign lesion?

Morphological Arguments Against Changing Gleason 6 Terminology

Gleason score 6 cancer shares many morphological features with higher-grade prostate cancer. Gleason score 6 prostate adenocarcinoma lacks a basal cell layer, which is a hallmark of prostate

cancer regardless of grade. In contrast, with uncommon exception, benign prostate glands have a well-defined basal cell layer. Cytologically, there is a range of atypia in Gleason score 6 cancer, but some will display similar nuclear enlargement and prominent nucleoli seen in cancers of higher grade. In contrast to the circumscribed nature of tumors in other organs noted above that have been renamed as not cancer, Gleason score 3 + 3 = 6 adenocarcinomas of the prostate are infiltrative between benign prostate glands, can show perineural invasion, and can invade outside of the prostate locally.

A New Patient-Centric Simplified Prostate Cancer Grading System

Rather than change Gleason score 6 to a non-cancerous term, there needs to be a change on what patients think when they are told that they have Gleason score 6 cancer. Urologists need to reassure and educate patients on the low risk associated with Gleason score 6 cancer. In addition, pathologists need to modify how we report Gleason score 6 cancer to more accurately reflect its behavior. Contributing to this fear is that when patients are told that they have a Gleason 6 out of 10, it implies that their prognosis is intermediate, despite the fact that Gleason score 6 is the lowest grade currently assigned. We agree with Dr. Esserman, the lead author of the article proposing IDLE, where she states: "Changing the language we use to diagnose various lesions is essential to give patients confidence that they don't have to aggressively treat every finding in a scan" [17]. However, whereas her study suggests to change Gleason score 6 to a non-cancerous term, we have proposed a new grading system for prostate cancer to deal with this issue.

The deficiencies of the Gleason grading system and the need for a new simpler grading system have been outlined in detail elsewhere and are not the focus of this work [22]. Based on a series of 6462 men treated with radical prostatectomy (RP) where both the needle biopsy and RP were graded using the current modified Gleason grading system, we showed both for biopsy and for radical prostatectomy that the following Gleason Grade Groups accurately reflect prognosis: Gleason score 2–6 (Grade Group 1), Gleason score 3 + 4 = 7 (Grade Group 2), Gleason score 4 + 3 = 7 (Grade Group 3), Gleason score 8 (Grade Group 4), and Gleason score 9–10 (Grade Group 5) [23]. The new grading system used in the current study has as its underpinning the Gleason system but has significant departures from the original system with different histological criteria for Gleason patterns 3 and 4.

In a subsequent meta-analysis of over 20,000 men treated by radical prostatectomy from five institutions, Grade Groups were strongly correlated with risk of biochemical recurrence (BCR) after surgery [22]. The 5-year BCR-free survival was 97.5%, 93.1%, 78.1%, 63.6%, and 48.9% for Grade Groups 1–5, respectively (Fig. 5.1). These Grade Groups were also validated on biopsy correlating with risk of progression after radical prostatectomy and following radiation therapy. Additional studies have since been published showing the new 5 Grade Group system correlates with BCR following radiation therapy and radical prostatectomy [24–26]. The Grade Groups also correlate with prostate cancer-specific mortality following conservative therapy [27]. These new Grade Groups were formally accepted by the 2016 World Health Organization (WHO) and the College of American Pathologists (CAP) [28]. For the foreseeable future, Grade Groups would be reported alongside the Gleason score (i.e., Gleason score 3 + 3 = 6 [Grade Group 1]).

The major consequence of the new grading system relative to the issue of whether Gleason score 6 should be called cancer is that the new system addresses the issue of renaming Gleason score 6 not cancer to changing the grading system to more accurately reflect the indolent nature of Gleason score 6 prostate cancer. A Gleason score 6 out of 10 prostate cancer would in the new system be "Grade Group" 1 out of 5. Patients could be reassured that they have a Grade Group 1 tumor on biopsy that is the lowest-grade tumor possible which in most cases can be followed with active surveillance. In a recent survey of 7 focus groups with 37 prostate cancer patients from 2015 to 2016, the majority of patients (84%) agreed that it would be clearer if grades were reported on a scale of 1–5 instead of 6–10 [29]. Eighty-eight (88%)

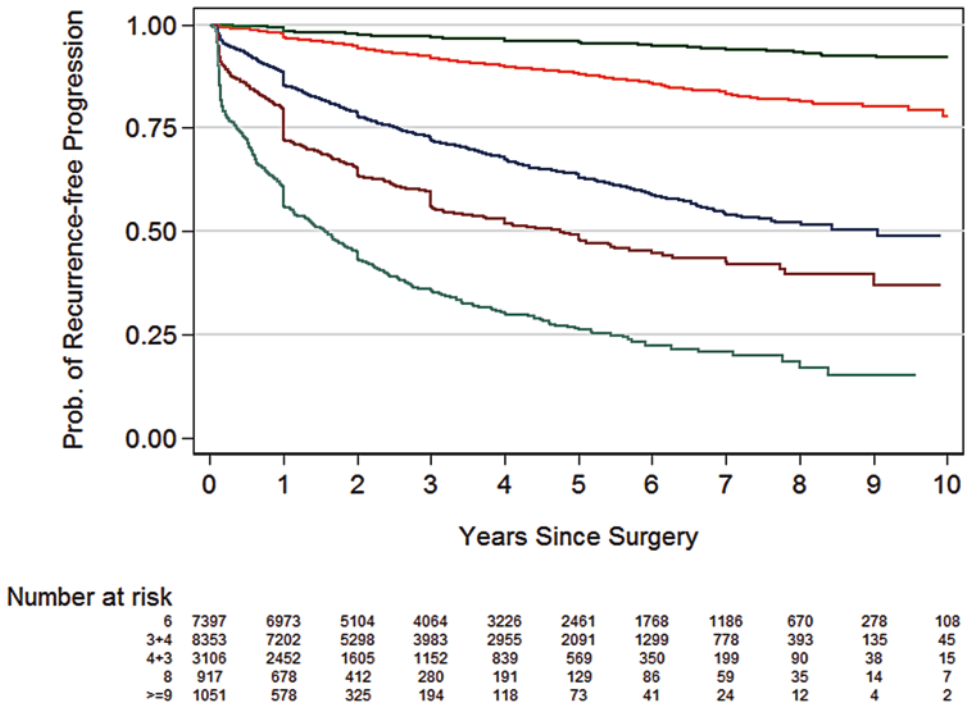

Fig. 5.1 Recurrence-free progression following radical prostatectomy stratified by prostatectomy grade. *Green line*: Gleason score 6, Grade Group 1. *Orange line*: Gleason score 3 + 4, Grade Group 2. *Dark blue line*: Gleason score 4 + 3, Grade Group 3. *Red line*: Gleason score 8, Grade Group 4. *Purple line*: Gleason score 9,10, Grade Group 5. *RFP* recurrence-free progression (From Epstein et al. [22]. Reprinted with permission from Elsevier)

would prefer to hear they have "Group 1" rather than "Gleason score 6," and 80% would feel more comfortable choosing active surveillance with "Group 1" vs. "Gleason score 6." However, follow-up is still needed with Grade Group 1 prostate cancer on biopsy as in approximately 20% of cases there is higher-grade cancer in the prostate that has not been sampled [21].

Molecular Genetics of Gleason 6 Prostate Cancer

Somatic Genetic Alterations

Molecular Subtypes of Prostate Cancer Identified by "Omics"

Over the last several years, a number of studies have characterized the molecular "taxonomy" or "landscape" of prostate cancer using high-throughput genomic analyses of hundreds of specimens, including both primary and metastatic tissue samples [30–35]. While these studies have validated many findings from prior studies, they have also provided a more comprehensive picture of "molecular subtypes" of prostate cancer and revealed a number of previously unrecognized driver genes and pathways (Fig. 5.2). For example, by profiling large number of primary and metastatic tumors, the "long tail" of prostate cancer mutations has been better identified. The long tail is characterized by the finding that a number of recurrent somatic driver mutations occur at low frequency (e.g., <5%). Interestingly, mutations within DNA repair genes (~19%), which were only partially appreciated from prior work (e.g., see [36]), occur relatively often as somatic alterations and, at least in those patients that progress to metastatic castrate-resistant disease, also occur relatively frequently in the germline (~12%) [37].

In a recent publication resulting from The Cancer Genome Atlas (TCGA) Research Network, seven major molecular subtypes of primary prostatic adenocarcinoma were identified [30] (Fig. 5.2). The first four were defined by different

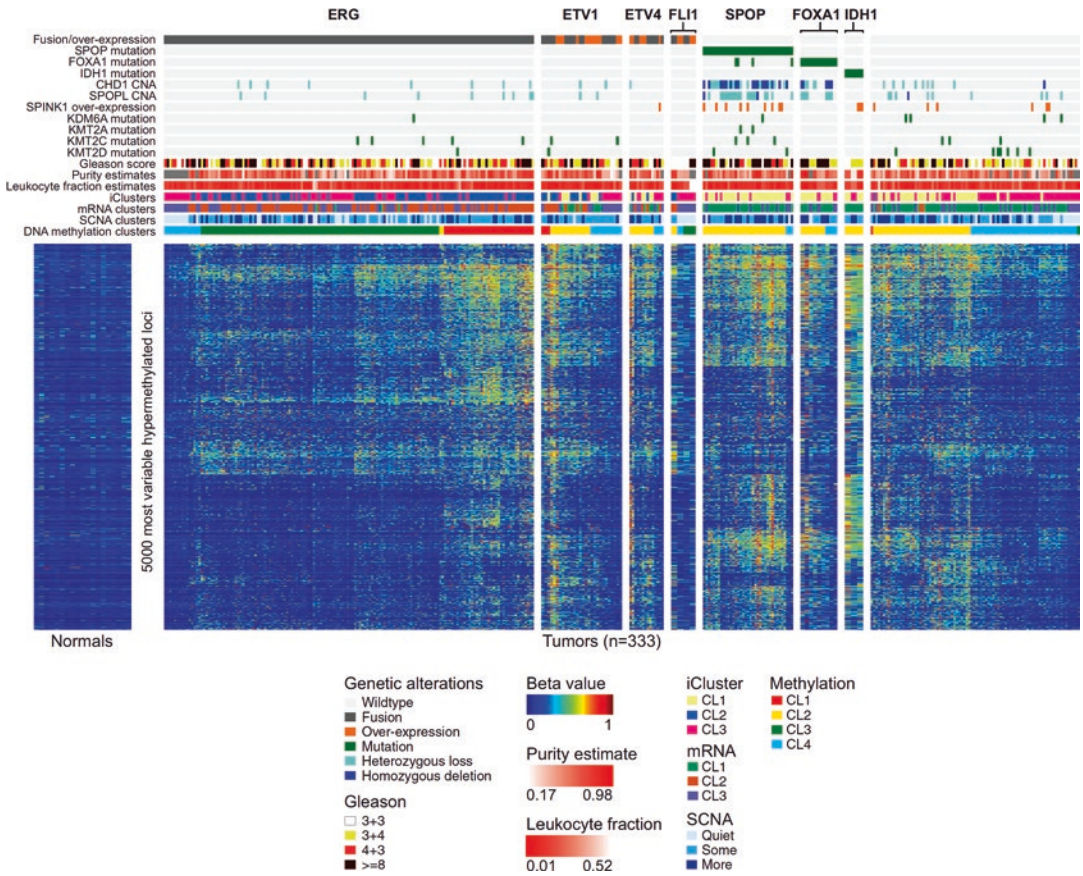

Fig. 5.2 Molecular subtypes of prostate adenocarcinoma. Somatic genetic and DNA cytosine methylation changes are shown indicating the seven major mutually exclusive subtypes of prostatic adenocarcinoma defined by the TCGA. Note that Gleason score 6 tumors are present scattered throughout all subtypes (Adapted from Cancer Genome Atlas Research Network [30], with permission from Elsevier)

ETS family gene fusions including (1) *ERG*, (2) *ETV1*, (3) *ETV4*, and (4) *FLI1*, and the remaining were defined by (5) *SPOP* mutations, (6) *FOXA1* mutations, and (7) *IDH1* mutations. Together, these subtypes encompassed 74% of all primary adenocarcinomas of the prostate with the remainder still undefined using their stratification criteria. As shown in Fig. 5.2, Gleason score 6 tumors are scattered throughout all of these subtypes indicating that Gleason score 6 tumors do not appear to arise via alterations in distinct molecular pathways from those of higher-grade lesions. When one specifically considers the first four subtypes, approximately 50% of prostatic adenocarcinomas from men of European decent harbor a clonal somatic rearrangement resulting in *ETS* family member gene fusions, with *TMPRSS2-ERG* being the most common. In terms of Gleason score and disease stage, approximately 50% of all primary prostate cancers, including tiny "insignificant" Gleason score 6 cancers at RP [38], as well as 50% of castrate-resistant lethal metastatic prostate adenocarcinomas (CRPC), have *TMPRSS2-ERG* or other *ETS*-related gene fusions [31]. Thus, the most common clonal somatic genetic alteration in prostate cancer occurs with nearly equal frequency in Gleason score 6 and higher-grade tumors. Interestingly, African American men have a lower frequency (approximately 50% of the frequency of those of European descent) of these rearrangements [39].

While the total number of overall mutations, as well as the frequency of mutations in genes encompassing the long tail, is higher in castrate-resistant metastatic prostate cancer than in primary tumor samples, considering all of the aberrations indicated above (including the long tail mutations), most somatic alterations in prostate cancer can now be clustered into major pathways (Fig. 5.3) including AR associated (*FOXA1*, *ZBTB16*, *NCOR1*, *NCOR2*), PI3 kinase pathway associated (*PIK3CA*, *PIK3CB*, *AKT1*), RAF fusions (*BRAF*, *RAF1*), WNT pathway (*APC* < *CTNNB1*, *RNF43*, *RSP02*, *ZNRF3*), DNA repair (*BRCA2*, *ATM*, *CDK12*, *MLH1*, *MSH2*), cell cycle (*RB1*, *CDKN1B*, *CDKN2A*, *CCND1*), chromatin modifiers (*KMT2C*, *KMT2D*, *KDM6A*, *CHD1*), and others (*SPOP*, *MED12*, *ZFHX3*, *ERF*, *GNAS*). Although the overall number of cases is still relatively small, when mutations in these genes occur in men with clinically localized disease, they do not tend to be highly enriched in different Gleason grade tumors and some can be found in Gleason score 6 tumors, with no apparent striking difference in the overall number of such lesions in Gleason score 6 and higher prostate tumors [30, 32, 33]. One notable exception is found in those cases that harbor *TP53* mutations or deletions. These tend to occur relatively infrequently in primary prostate tumors, but when present in such tumors, they are more common in higher-grade, higher-stage lesions [40], with a further increase seen in castrate-resistant metastatic disease [31, 35].

Other Rearrangements and Copy Number Alterations

Chromoplexy consists of a series of DNA breakage and joining events in which a number of DNA segments from different genomic locations become ligated together [32]. While not specifically addressed in the manuscript, when one examines the data, this alteration was reported to occur similarly in Gleason score 6 tumors and higher-grade prostate cancers [32, 41]. Other well-characterized and extensively documented alterations, such as deletions on chromosome 8p resulting in loss of one allele of *NKX3.1*, deletions involving *PTEN* on chromosome 10q23, and gains of 8q24/MYC, occur in Gleason score 6 lesions, albeit at a reduced

Table 1 | **Select genomic alterations and their future clinical implications**

Pathway process	Target genes	Drug development	Potential prognostic or predictive biomarkers
AR signalling	*AR*, *NCOR1/2*, *FOXA1*, *ZBTB16*, *SPOP*	N-terminal domain AR inhibitors; dual AR/GR inhibitors	AR-V7 spice variants; *AR* amplification
Cell cycle	*P53*, *MYC*, *CDKN2A*, *RB1*, *AURKA*	DNA-binding domain AR inhibitors; CDK4/6 inhibitors; AURKA inhibitors	*RB1* status; AR low/independence; *AURKA* amplification
DNA repair	*BRCA*, *ATM*, *RAD51*, *MSX2/6*, *SPOP*, *DNAPK*	PARP inhibitors, PD-L1 inhibitors	DNA repair defects
ETS fusion	*ERG*, *ETV1*	HDAC inhibitors, PARP inhibitors	*ETS* fusion status
MAPK pathway	*BRAF*, *RAF1*, *HRAS*	BRAF inhibitors; MEK inhibitors	Mutations or gene fusions
Wnt pathway	*CTNNB1*, *APC*, *ZNRF3*, *RNF43*, *RSPO2*	Porcupine inhibitors	Mutations or gene fusions
PI3K pathway	*PTEN*, *PIK3CA*, *PI3KCB*, *AKT1*	pan-PI3K and dual PI3K–mTOR inhibitors; PI3KCB inhibitors	Mutations or copy number alterations

AKT, v-akt murine thymoma viral oncogene homologue; APC, adenomatous polyposis coli; AR, androgen receptor; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BRCA, breast cancer; CTNNB1, catenin β 1; ERG, v-ets avian erythroblastosis virus E26 oncogene homologue; ETS variant 1; FOXA1, forkhead box A1; GR, glucocorticoid receptor; HDAC, histone deacetylases; HRAS, Harvey rat sarcoma viral oncogene homologue; MSX, msh homeobox; MYC, MYC proto-oncogene protein; NCOR, nuclear receptor co-repressor; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death 1 ligand 1; PIK3C, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit; PTEN, phosphatase and tensin homologue; RAD51, RAD51 recombinase; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; RB1, retinoblastoma 1; RNF43, ring finger protein 43; RSPO2, R-spondin 2; SPOP, speckle type BTB/POZ protein; ZBTB16, zinc finger and BTB domain containing 16; ZNRF3, zinc and ring finger 3.

Fig. 5.3 Major pathways associated with genomic alterations in prostate cancer. Recent whole genome profiling studies reveal that many of the mutations identified in prostate cancer can be grouped into specific pathways (Adapted from Spratt et al. [34], with permission from Nature Publishing Group)

rate compared to higher-grade and more aggressive lesions [16, 42–50]. Thus, these more traditionally examined alterations are more common in higher-grade tumors but do occur with at least some frequency in Gleason score 6. Taken together, these results suggest common molecular pathways and mechanisms for the development of a number of somatic genetic alterations between Gleason score 6 and higher-grade tumors.

Overall Percent of Genome Altered

Some types of rearrangements lead to large-scale copy number alterations with gains and losses of relatively large segments of genomic material. Such copy number alterations are common in prostate cancer [51], and a number of studies have demonstrated that copy number changes tend to increase in extent and number with grade and disease aggressiveness [32, 51–53]. Further, a subset of prostatic carcinomas, predominantly Gleason score 6 tumors, has been deemed nearly free of large-scale copy number alterations [52, 53]. These "quiet" genomes in some Gleason score 6 lesions may be molecularly distinct from other Gleason score 6 lesions and higher-grade more aggressive tumors. Nevertheless, it is also clear that at least some of the Gleason score 6 score tumors analyzed to date do show relatively large numbers of copy number alterations such that this feature alone cannot entirely separate prostate cancers by grade [32, 51–53]. Given the current evidence suggesting tumors with "quiet" genomes are likely to be nonaggressive, it is possible that in the future if a method for routine measurement of copy number could be employed clinically (e.g., using a clinical grade test in a CLIA-certified laboratory) and one could rule out the presence of any other higher-grade or separate tumor (e.g., with multiparametric MRI), then a Gleason score 6 tumor could be considered nonmalignant or premalignant if copy number alterations in such a lesion were shown to be minimal.

Somatic Epigenetic Changes

Somatic DNA methylation of the CpG island within the *GSTP1* gene occurs in approximately 90% of all prostatic adenocarcinomas, regardless of grade or stage [54]. A number of other genes are also hypermethylated frequently in prostate cancer (e.g., *APC*, *RASSF1*, *MDR1*, *EDNRB, HOXD3, TGFB2*), and although hypermethylation of some occurs more frequently in higher-grade lesions (*EDNRB, HOXD3, APC, TGFB2*) or those with biochemical recurrence (APC, *PTGS2, HOXD3, TGFB2*), most occur commonly both in Gleason score 6 and higher-grade lesions [55–57]. These results further support the overall concept of similar molecular alterations occurring in Gleason score 6 and higher-grade lesions. The finding of *IDH1* mutations in prostate cancer by the TCGA is novel, and, as in other cancers with *IDH1* and *IDH2* mutations, tumors from these patients are apparently enriched for very high numbers of somatic CpG methylation events [30]. At this time, however, there are not enough cases with *IDH1* mutations to determine whether they occur with greater or reduced frequency in Gleason score 6 tumors. When looking at the evidence from more recent genome-wide studies, it does not appear that Gleason score 6 tumors have highly distinctive somatic CpG island DNA alterations as compared with those of other Gleason scores [30, 58], although a number of CpG methylation events in specific loci do appear to add value in distinguishing lethal metastatic disease from those without biochemical progression 5 years after prostatectomy [58].

Clonal Relationships Suggest a Common Origin for Gleason Score 7 Tumor Components

Whether Gleason score progresses remains an open debate. If some higher-grade tumors can arise as a progression event from a Gleason pattern 3 lesion, then if this occurs at a non-negligible rate, it would provide an additional argument against renaming Gleason score 6 cancers as non-cancer. Recent studies examining clonal relationships between prostatic tumors that are composed of both Gleason patterns 3 and 4 indicate they are clonally linked [59, 60]. Further, in at least a few cases, it has been shown that the Gleason pattern 4 lesions harbored an additional "hit" by showing

a deletion in the *PTEN* gene, while the clonally related adjacent Gleason pattern 3 lesion did not show the *PTEN* alteration [60]. This suggests that a Gleason pattern 4 lesion can evolve from a Gleason pattern 3 tumor. This fits well with findings that *PTEN* alterations usually occur during disease progression as a subclonal molecular alteration, subsequent to *TMPRSS2-ERG* fusion, when such lesions are found together in the same tumor [32, 61–63]. While these results are compelling, this does not preclude the finding that at times it appears that high-grade prostate tumors may arise de novo in the prostate [64, 65].

RNA Expression Profiles

Using various types of large-scale gene expression profiling techniques over the last several years, a number of groups have examined the relation between gene expression profiles and Gleason grade [66–68]. While statistically significant differences have been found to be able to classify tumors of different Gleason scores using gene expression signatures and may add new prognostic information beyond GS, no specific genes or pathways have emerged that can strongly distinguish in a diagnostic sense among the different grades on an individual patient tumor basis. Hence, these methods cannot definitely classify a given tumor as indolent Gleason score 6, and none of these have been developed into a clinical grade test such that further development of these at this time does not seem practical for clinical implementation as of now. In terms of commercial activity, several companies have employed RNA expression classifiers, usually consisting of quantitative assessments of the relative RNA levels of tens to dozens of genes, to the problem of augmenting prognostic power for prediction of a number of different outcomes, independent of Gleason score (reviewed in [69]). Each of these can now be applied to clinical formalin-fixed paraffin-embedded specimens (either radical prostatectomy or biopsy as per specific clinical question being addressed), and each has shown promise in various clinical disease states to add some value to the prognostic ability of Gleason score and other standardly collected clinical-pathological parameters [69]. However, none of these can be used to determine if an individual tumor can be considered an indolent GS 6 cancer such that they could be used to help reclassify some Gleason score 6 tumors as non-cancer. Irshad et al. specifically addressed the question of identifying a gene expression signature for indolent vs. aggressive prostate cancer and were able to synthesize it down to a few protein-based IHC markers [70]. If further validated and developed into a clinical grade assay, such a test may add value in terms of this question.

Other Tissue-Based Molecular Markers

Trock et al. recently found that patients harboring pure Gleason score 6 tumors in their prostatectomy samples have a lower rate of *PTEN* loss in Gleason pattern 3 areas than patients with Gleason score 7 do in their Gleason pattern 3 regions (either 4 + 3 = 7 or 3 + 4 = 7). Further, there was also a greater rate of chromosome 8p loss and chromosome 8q24 gain in Gleason pattern 3 regions from patients with a Gleason score 7 tumor. The Gleason pattern 4 regions showed higher rates of changes at all three examined loci [71]. Lotan et al. reported that tumors that were only Gleason score 6 on biopsy that had lost PTEN by IHC had an increased rate of upgrading at prostatectomy compared to those without PTEN loss [72]. Taken together, these findings indicate that Gleason pattern 3 lesions are different molecularly depending on whether they are present in the setting of a Gleason score 6 tumor or in the setting of a Gleason score 7 tumor. These studies also suggest that appropriate molecular markers may be applied to help determine if patients with Gleason score 6 biopsies are at higher risk for harboring a previously unsampled higher-grade tumor in the prostate. Immunohistochemistry for PTEN has been extensively validated analytically and is currently employed in a number of Clinical Laboratory Improvement Amendments 1988 (CLIA) certified anatomic pathology laboratories. Another

promising tissue-based approached implemented an 8-marker multiplex immunofluorescence assay that may also prove useful in determining whether a given Gleason score 6 lesion in a needle biopsy is at risk for being associated with a poor outcome or more aggressive disease [73]. Another possible avenue may also be application of the percent of the genome with copy number alterations as mentioned above [52, 53], if this technology is further developed into a clinical grade test. Therefore, it is hoped that in the future in addition to histological grading, molecular markers along with improved imaging can be applied that will facilitate the overall determination of the aggressiveness of a given Gleason score 6 lesion and aid in the selection of patients for AS. If clinicians could be confident (e.g., ≥95%) that a given patient only harbored a Gleason score 6 lesion with molecular properties also consistent with indolent disease, then it may be appropriate to reclassify this lesion as a non-cancer.

Conclusions/Summary

There is no strong molecular evidence suggesting that Gleason score 6 as opposed to higher-grade tumors commonly arise as unique and distinct molecular subtypes, as in the case of urinary bladder cancer. In fact, a number of molecular alterations are shared between Gleason score 6 and higher-grade tumors such as *ETS* family member gene fusion events, point mutations in a number of genes, chromoplexy, and somatic CpG hypermethylation of specific genes. While some of these changes are substantially less common in Gleason score 6 tumors, they nonetheless support similar pathways of tumor development overall. Further, at least at times, it appears that Gleason pattern 3 and 4 regions within a given tumor can be clonally related and some Gleason pattern 4 lesions may evolve from Gleason pattern 3.

On a practical matter, it is possible that since a number of tissue-based biomarkers can add prognostic value beyond Gleason score, the appropriate application of such markers, along with improved imaging, can help better classify patients with an indolent Gleason score 6 tumor only. While we would not advocate changing the label of cancer for Gleason score 6 lesions at this time, these approaches may indeed facilitate the safe management of patients on active surveillance. In terms of molecular markers and the known biology of this disease, we consider overall copy number alteration burden at this time to be the most promising molecular feature that could potentially be employed to help determine if a given lesion has a "quiet" genome and could be considered indolent. Others include PTEN immunohistochemistry, commercial RNA expression signatures, and multiplex immunofluorescent assays. It should also be emphasized, however, that even if such markers or signatures are employed using validated clinical tests and such testing favors an indolent lesion, we are still left with the sampling problem in that one may have simply missed a more aggressive lesion that is present. Beyond this, even if it is clear that at a given point in time there is only a Gleason score 6 lesion (perhaps with multiparametric MRI imaging largely ruling out other higher-grade lesions) with an indolent biomarker signature, and hence one can conclude that this lesion can safely be labeled a "non-cancer," this does nont preclude the possibility that an additional clinically meaningful cancer will not develop in the future. We are concerned that if the label of cancer is removed, then many patients with Gleason score 6 tumors will be lost to follow-up. While it is not clear at present if patients with indolent Gleason score 6 tumors are at risk for developing higher-grade tumors over time, most would agree that long-term follow-up of such patients is prudent at this time.

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Risk-Based Selection for Active Surveillance

6

Jan F.M. Verbeek, Monique J. Roobol, and Ewout W. Steyerberg

Introduction

PSA screening reduces prostate cancer mortality, as reported by the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1]. The number needed to screen to prevent one case of prostate cancer (PCa) from dying from PCa is however substantial, as well as the number needed to treat to prevent one PCa death. The main drawback of PSA-guided prostate cancer screening is overdiagnosis, with estimated rates of 49–58% and related overtreatment [1]. Overdiagnosis occurs when PCa is detected by screening, while the cancer has no impact on survival (Fig. 6.1). Overdiagnosis is more likely if patients have a shorter life expectancy, due to their age or comorbidity, or if patients have a high probability of dying from other causes than PCa. The detection of clinically insignificant PCa (with low risk of disease progression) subsequently leads to overtreatment and hence unnecessary adverse effects [2]. Conservative strategies such as watchful waiting (WW) and active surveillance (AS) are needed to reduce the harms of screening by reducing overtreatment of men with a low risk of PCa progression [3]. WW is a palliative strategy usually considered for patients with a limited life expectancy with much less intense observation followed by palliative treatments for those who progress [4]. AS is a curative strategy for patients with a low risk of PCa progression with an initial period of observation, accompanied by rigorous and invasive follow-up, with delayed curative treatment for those with progression (Fig. 6.2) [5]. AS aims to avoid overtreatment. The scientific underpinning of which patients are eligible for AS is difficult, as we need to consider the risks of progression, life expectancy, and treatment effectiveness in a dynamic context. In this chapter, we first clarify the context for selection for AS qualitatively. Next, we describe the existing clinical guidelines on selection for AS. Finally, we review risk prediction models and consider how these can be used to optimize patient selection.

Patient Selection for Active Surveillance: Qualitative Considerations

The main goal of AS is to reduce overtreatment in patients with low-risk prostate cancer [6, 7]. Men with an initially low risk of PCa progression are usually considered as candidates for AS,

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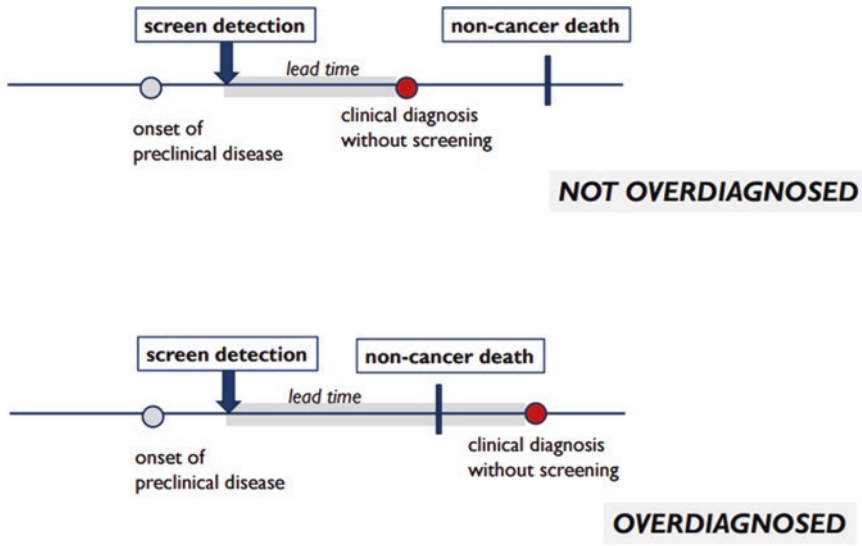


Fig. 6.1 Definition of overdiagnosis (From Etzioni [55]. Used with permission)

provided they have a reasonable life expectancy, e.g., more than 10 years. They should be distinguished from men diagnosed with a progressive prostate cancer who are more likely to die from PCa and would benefit substantially from immediate active treatment [5, 8]. On the other hand, we should not select men for AS if their lifetime risk of disease progression is very low. In these cases, watchful waiting would be the optimal treatment option. Figure 6.3 shows the timeline between diagnosis of PCa and death due to PCa or due to other causes for three exemplary patients with various absolute risks of PCa progression, based on cancer risk and life expectancy. The most beneficial strategy for the particular patient is colored green: watchful waiting [WW], active surveillance [AS], or active treatment [AT].

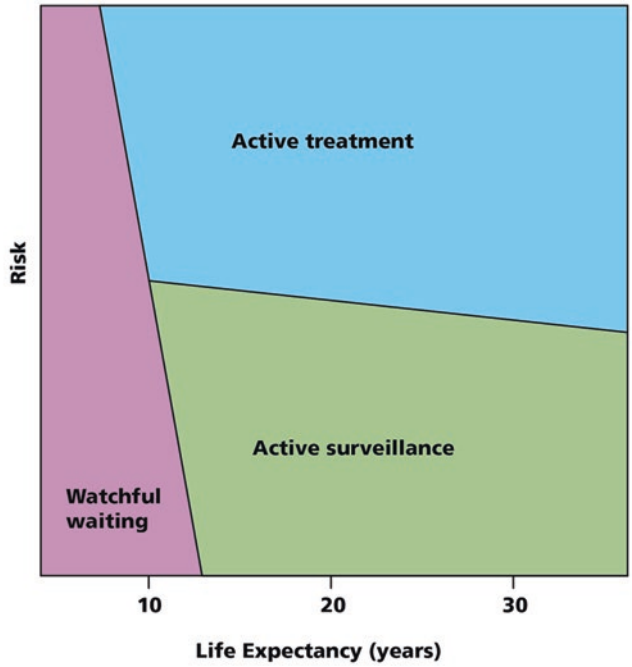
For example, patient 1A with PCa clinical stage T1cNxMx, Gleason 3 + 3 at diagnosis, and no PCa progression anticipated during his normal life span will die from other causes and not from PCa. This patient is therefore categorized as a patient with a "very low risk" of progression of PCa. WW is the optimal management in this case.

Patient 1B is an 80-year-old man with cardiovascular comorbidity and a life expectancy of less than 10 years. This patient has probably a higher chance of dying from his cardiovascular conditions than from prostate cancer even though he has a relatively high risk of progression. In his case, we expect no benefit from AS, only sustaining the negative parts of AS (e.g., prostate biopsy, risk of infection), so WW is best.

Patient 2 has a similar clinical stage T1cNxMx and Gleason 3 + 3 at diagnosis but is expected to show disease progression. If patient 2 had received WW, this progression would be missed, leading to a suboptimal treatment later on. AS would have been the preferable strategy, as disease progression would be detected on time, with PCa still in its curable stage. If thus patient received AT immediately, he would most likely be cured. The delayed treatment with AS compared to immediate AT implies that the man will sustain a better quality of life for the years before treatment.

For patient 3, diagnosed with PCa T2bNxMx and Gleason 4 + 4, AS was in fact unsuitable, because disease progression would be detected at too late a stage. This would lead to a poor clinical course compared to the situation of this patient receiving immediate AT.

An illustrative article provided an attractive analogy between the progress of disease and the speed of locomotion of turtles, rabbits, and birds [9]. In our examples, patient 1A is the turtle (very slow-growing disease and dies likely from a different cause than his prostate cancer). AT would



	Watchful waiting	Active surveillance	Active Treatment
Focus	Managing of symptoms	To delay/avoid AT	Immediate treatment
Risk of PCa progression	Very low through high in combination with short LE	Low - Intermediate	Intermediate - High
Treatment intent	Palliative	Curative	Curative
Follow-up	Patient-specific	Predefined schedule	After treatment
Life-expectancy	<10 years	>10 years	>10 years

Fig. 6.2 Association of different treatment strategies with life expectancy and risk of PCa progression. The downhill slope between AT and AS with increasing life expectancy illustrates that AT is feasible in young men. The downhill slope of WW with increasing life expectancy illustrates that the 10-year cutoff is arbitrary; a man with high risk of PCa progression with a very short life expectancy is still suitable for WW. In contrast, men with more than a 10-year life expectancy at very low risk of PCa progression may also be suitable for WW (Adapted from Bruinsma S and Nieboer D with permission. Figure 14.4 in this book)

have been unnecessary. AS would have prevented him undergoing surgical treatment, but he would still have to experience the discomfort of prostate biopsies and regular checkups during AS. Ideally, his prostate cancer would not have been detected, but now that it has been, he should receive nothing more than WW.

The other extreme is the bird; in this case the diagnosis was made too late for treatment, and the man is likely to die from prostate cancer. Finally, the rabbit represents the man with PCa who needs to be diagnosed. His risk of progression is higher than that of the turtle and could be life threatening, while the disease is still curable.

Table 6.1 summarizes the risks and benefits of the different patients on AS. Patients 2 and 3 can be considered as rabbits. Note that AT, e.g., surgery, is only immediately required for an

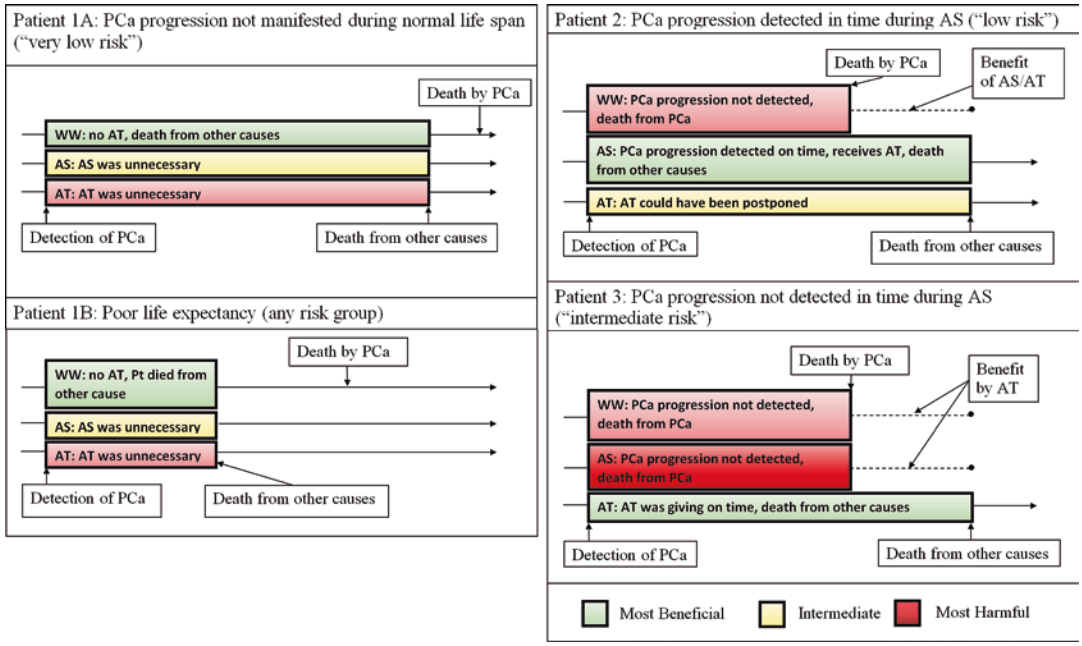


Fig. 6.3 Timelines of possible outcomes after watchful waiting (WW), active surveillance (AS), and active treatment (AT) for three exemplary patients with various risks of PCa progression. The *colored boxes* display the time between PCa diagnosis and time of death; the colors indicate the most beneficial (*green*), intermediate (*yellow*), and most harmful (*red*) treatment strategy for each specific patient

intermediate-risk or higher-risk PCa, with substantial life expectancy (patient 3), where treatment delay is anticipated to be harmful.

Patient Selection for Active Surveillance: Endpoints

Clinically relevant endpoints such as time to metastasis or disease-specific mortality should preferably be the main outcomes when deciding which treatment strategy a patient should receive [10, 11]. These endpoints imply that a long-term follow-up period of at least a decade is necessary due to the slow-growing nature of PCa [12]. A more practical endpoint is "progression of PCa" as a proxy outcome. No uniform definition of disease progression is available [12]. Progression can be defined on repeat biopsy findings, RP, or as treatment-free survival [11]. Epstein defines upgrading of the Gleason score at radical prostatectomy as disease progression [13]. Others use biochemically determined recurrence (PSA rise) or presence of distant metastasis indicated by changes in PSA, DRE, tumor grade, and tumor volume on biopsy findings or even magnetic resonance imaging [8, 13].

We note that tissue sampling errors may become apparent from repeat biopsy, often performed within 1 year after the initially positive biopsy. These are usually considered to be different from true disease progression and are labeled "reclassification" [8, 14, 15].

Comparison of Monitoring to Immediate Treatment

Findings from the recent ProtecT screening study suggest that two-thirds of the patients diagnosed with PCa may be eligible for AS [16, 17]. The ProtecT trial compared radiotherapy, surgery, and active monitoring [18]. Active monitoring is a variant between WW and AS. The study has a less restrictive entry criteria (allows inclusion of patients with GS $\geq$ 8), and the follow-up scheme

Table 6.1 Summary of harms and benefits in three different candidates for active surveillance
WW **watchful waiting,** *AS* **active surveillance,** *AT* **active treatment**

	Patient 1A / 1B		Patient 2		Patient 3	
	Very low risk, or poor life-expectancy		Low risk		Intermediate risk	
		Value		Value		Value
WW	No discomfort by biopsies, no treatment	+	Failed to detect progression on time	–	Failed to detect progression on time	–
AS	Discomfort by biopsies, no AT	+/–	Delayed discomfort and risks of AT	+	Discomfort by biopsies, no benefit of AT	– –
AT	Overtreatment	–	AT could have been postponed	+/–	Prevent progression, timely AT	+

WW: Watchful Waiting. AS: Active Surveillance. AT: Active Treatment.

is less rigorous compared to contemporary AS protocols. The ProtecT study demonstrated no survival benefit in men for the different treatment options (Table 6.2). However, the results at 10-year follow-up imply less disease progression and PCa metastases after surgery and radiotherapy compared to active monitoring. These results should be interpreted with caution since, as said, the study used an active monitoring protocol instead of a more modern AS protocol. For example the inclusion of patients with GS ≥ 8 in an active monitoring group will result in poorer outcome. Two other major randomized controlled trials have been conducted but compared surgery with WW, rather than AS. The first study is the Prostate Cancer Intervention Versus Observation Trial (PIVOT): patient enrollment started in 1994, a total of 731 patients were randomized, and 26% of the patients had GS ≥7 on initial biopsy [19]. After 12-year follow-up, the study showed no overall or PCa-specific survival benefit to RP compared to WW. On the contrary, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) had a much longer follow-up of 23 years, randomized 695 patients, and found lower disease-specific mortality for RP compared to WW [20]. Unfortunately, no analysis has yet been reported for the more typical contemporary AS candidates.

Traditional Selection for Active Surveillance

Inclusion criteria for AS patients are different between the major international AS cohorts (Table 6.3) [7, 11, 15, 21–28]. Furthermore, AS cohorts differ by protocol and in practical

Table 6.2 Main outcomes of the ProtecT trial comparing different treatment strategies

	Active monitoring $N = 545$	Surgery $N = 554$	Radiotherapy $N = 545$
PCa-specific survival – % (95% CI) at 10 years	98.8% (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)
Incidence of metastatic PCa per 1000 person-year (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)

Table 6.3 Patient- and biopsy-based inclusion criteria in different active surveillance protocols

Active surveillance protocol	Clinical stage	PSA	Gleason score	Positive cores	Core positivity (%)	PSAD (ng/dL)
PRIAS [15]	≤T2	≤10	≤3+3	≤2	–	≤0.20
Sunnybrook [21]	–	≤10[a]	≤3+3[a]	–	–	–
Royal Marsden [11]	≤T2a	–[b]	≤3+3[b]	≤50%	–	–
Johns Hopkins [22]	T1c-T2a[c]	≤10[c]	≤3+3	≤2	≤50	<0.15
UCSF [23]	≤T2a	≤10	≤3+3	≤33%	≤50	≤0.15
UM [24]	≤T2a	≤10	≤3+3	≤2	≤20	–
UC [7]	≤T2a	≤10	≤3+3	≤3	<50	–
Australian [25]	≤T2a	<10	≤3+3	<20%	<30	–
Göteborg [26]	≤T2a	≤10	≤3+3	–	–	–
MSKCC [27]	≤T2a	≤10	≤3+3	≤3	≤50	–
Japan [28]	T1c	≤20	≤3+3	≤2	≤50	–

In green, similarities between the cohorts are shown resulting in a more stringent inclusion of "low risk." The yellow color shows a wider range of criteria, which allows for a slightly higher-risk inclusion

PSAD prostate-specific antigen density; *PRIAS* Prostate Cancer Research International Active Surveillance; *UCSF* University of California, San Francisco; *UM* University of Miami; *UC* University of Copenhagen; *MSKCC* Memorial Sloan Kettering Cancer Center New York

[a]Includes Gleason ≤3 + 4 and/or PSA ≤ 20 if life expectancy ≤10 years or present comorbidities

[b]Includes patients with Gleason ≤3 + 4 if age > 65 years and PSA <15

[c]T2a only if PSA ≤10

implementation [2]. For example, the Gleason grading system changed in 2014 [29]. This means that patients included in 1995 based on the Epstein inclusion criteria could have had a higher risk than those included in the more recent cohorts. Overall, current guidelines recommend patients as being the most suitable for AS if they have pretreatment clinical stage T1(c) or T2a prostate cancer, serum PSA <10 ng/ml, a biopsy Gleason score of 6, a maximum of 2 tumor-positive biopsy core samples, and/or a maximum of 50% of cancer per core [4]. Some guidelines include statements that patients with stage T2b–T2c can also be recommended for AS. The Dutch Urology Association (DUA) guideline even recommends selecting patients with T3 for AS. Age and comorbidity are relevant, because a considerable life expectancy is important for AT, and hence AS, to show any long-term benefit. Finally, some guidelines state that patients' preference should be considered in order to reduce the dropout rate of AS patients due to anxiety [4].

Risk-Based Selection for Active Surveillance

In this section, we review studies that may improve AS risk-based selection for men with PCa using nomograms or risk calculators predicting PCa progression. Generally, the studies are similar in terms of patient's inclusion criteria, predictors, and primary outcome (Table 6.4). The primary outcome was progression, defined as upgrading of GS at radical prostatectomy, except for the Canary Prostate Active Surveillance Study which used GS upgrading on a follow-up biopsy [30]. Nomograms were constructed by logistic regression analysis. However, the Johns Hopkins AS study used a Bayesian joint model including all biopsy data during AS to improve prediction of GS ≥ 7 at RP [31]. The studies are described in more detail below.

European Randomized Study of Screening for Prostate Cancer

In a sub-study of the European Randomized Study of Screening for Prostate Cancer (ERSPC), 864 patients were evaluated with a mean follow-up of almost 9 years; the patients had undergone radical

Table 6.4 Comparison of predictive ability on the risk of prostate cancer for men potentially eligible for active surveillance

Study	No. of men	Inclusion criteria	Outcome	Predictors	AUC I 95% CI	AUC E Range
Kattan 2003 [33]	409	T1c-T2A, PSA ≤ 20, GS ≤6 on Bx, ≤50% positive cores, ≤20 mm total cancer, and at ≥40 mm benign in all cores	Tumor volume < 0.5 cc, confined to prostate and GS ≤ 6 on RP	PSA, TRUS PV, T-stage, GS, and total length of cancer in biopsy cores	0.79 (–)	0.59–0.79 [39]
Steyerberg 2007 [34]	247	Same criteria as Kattan	Same outcome as Kattan	Same predictors as Kattan	0.76 (0.70–0.82)	0.60–0.69
Ankerst 2015 [30]	859	GS ≤6, PSA ≤ 20	GS ≥7 or ≥34% positive biopsy cores on follow-up biopsy	Age, month since last biopsy, latest PSA, %positive cores, prior negative biopsy	0.72 (–)	NP
Johns Hopkins 2016 [31]	964	T1c-T2a (PSA < 10), PSAD < 0.15 ng/mL, GS ≤6, ≤2 positive biopsy cores, ≤50% positive per core	GS ≥7 on RP	Joint model: PSA, age, PV, biopsy information, RP information	0.74 (0.66–0.81)	NP
Truong 2013 [38]	431	Gleason ≤6 on biopsy and at least 10 cores	GS ≥ 7 on RP	PSA TRUS density, obesity, no. of positive cores, max. no. of cores involved	0.75 (0.69–0.82)	0.60–0.67

AUC area under curve of the receiver operator characteristic curve as a measure of the predictive model performance, *RP* radical prostatectomy, *NP* not performed

prostatectomy and 619 patients had a Gleason score of ≤6 and cT1-2 at diagnosis [32]. At radical prostatectomy, 66% of these low-risk patients still had a Gleason pattern ≤3 + 3 and ≤pT2 on final pathology. To distinguish between low-risk PCa (Gleason score ≤ 3 + 3 and ≤pT2 at radical prostatectomy) and significant PCa, a nomogram originally developed by Kattan et al. in 2003 was used. This prediction model was validated and updated by Steyerberg et al. in 2007 for use in a screening setting [33, 34]. Predictors were serum PSA, TRUS prostate volume, clinical stage, prostate biopsy Gleason score, and total amount of cancer and non-cancer tissue in biopsy cores. The performance of the model was moderate, with an area under the ROC curve between 0.60 and 0.69 at external validation [32, 35].

Canary Prostate Active Surveillance Study

The Canary Prostate Active Surveillance Study (PASS) cohort is a prospective and observational AS study. The investigators defined progression as either a Gleason score upgrade from 6 to ≥7 or an increase in percentage of cancer cores positive for cancer from <34% to ≥34% at repeat biopsy. The progression rate ranged from 10% to 30% at sequential biopsies (first, second, third biopsy), and the overall progression rate was 24% after 28 months of follow-up among 905 men [30, 36]. Noteworthy is that 55 (8%) of the 689 men without disease progression opted for active treatment. PSA, percentage of cores positive for cancer on most recent biopsy, and history of at least one prior negative biopsy were associated with progression. Together with age and number of months since last biopsy, the model had an AUC of 0.72 at internal validation [30].

Johns Hopkins

The Johns Hopkins Active Surveillance study is a cohort of men which met Epstein inclusion criteria for very low-risk PCa [31]. A total of 964 patients were included, and 195 (20%) experienced GS upgrading ≥7 on biopsy. A Bayesian joint model was constructed to predict GS ≥ 7 on RP. Using PSA and all available biopsy data gathered over time, the AUC for predictions was 0.74. This tool can be used both for inclusion criteria for men with a low risk of harboring higher-grade PCa, as well as for making predictions during AS.

The Urology Prostate Cancer Database was searched as part of another Johns Hopkins study [46]. In total, 7643 patients received RP, 5071 patients had a Gleason score of 5–6 on biopsy, and 1841 (36%) of those GS 5–6 were upgraded at RP. PSA level, maximum percentage of cancer per core, and RP weight predicted upgrade from biopsy GS 5–6 to higher GS at RP, AUC of 0.69. However, to predict progression on RP, the authors included the predictor pathology weight at RP. This risk calculator is therefore unsuitable for selecting AS patients, as we do not know the pathology weight of the prostate at the time of AS patient inclusion. PSA density may be a better alternative, given the relation between increased serum PSA levels and decreased weight with upgrading [37].

Wisconsin Risk Calculator

Truong et al. developed a prediction model for patients with Gleason 6 PCa at biopsy to predict the upgrading to Gleason ≥7 on radical prostatectomy. They assessed more than 30 predictors among 431 patients. PSA density using the US volume, obesity, number of positive cores, and maximum core involvement were included as predictors. At internal and external validation, the performance of the patient selection for AS had an AUC of 0.67 and 0.60, respectively [38, 39].

Prostate Cancer Research International Active Surveillance

The Prostate Cancer Research International Active Surveillance (PRIAS) study is a program in which men diagnosed with early prostate cancer are clinically managed by a protocol of follow-up strategy [40]. A total of 5302 men were

included across 18 countries for a 10-year follow-up time. Candidates for this program were men fit enough for curative therapy, PSA at diagnosis less than 10 ng/mL, PSA density (PSA/prostatic volume) less than 0.20, one or two biopsy cores bearing prostate cancer (using a fixed volume-dependent number of cores), Gleason score 3 + 3, and digital rectal examination-based T1c or T2 [41]. The authors evaluated the criteria used to switch to AT by assessing their ability to predict outcome on radical prostatectomy (RP) in men who stopped their adherence to AS. After 10 years of follow-up, 73% discontinued AS, mainly because of progression on biopsy, but still one-third of them had GS 3 + 3 on final RP. Multinomial logistic regression analysis was used to evaluate the predictive value of age, PSA, PSA doubling time, number of positive cores, and GS >6 on last biopsy to predict GS >6 on final RP. None of the indicators, except for GS >6 on last biopsy, were predictive and could therefore not be used as an extra predictor for risk-based selection in AS [41].

Discussion

Summary of Risk-Based Selection for Active Surveillance

Currently available prediction models and nomograms have limited predictive ability for progression, with AUC never above 0.75, reflecting limited ability to assist in a sharp selection of patients with low-risk PCa for AS. Apparently, it is difficult to make a good risk-based selection within the relatively homogeneous groups currently considered for AS. Small groups of men can be found potentially on the borders of the current selection strategies and may be candidates for WW (if very low risk) or immediate AT (if intermediate risk). Examples of possible candidates for WW may be those with very low PSA values, only 1 core with Gleason 6, PSAD <0.2. AT candidates might be patients with PSA greater than 10, and more than 2 cores with Gleason 6, and/or PSAD >0.2. Furthermore, some models still have to be externally validated prior to considering clinical implication.

For patient selection, the risk of the cancer itself needs to be combined with assessments of life expectancy and the anticipated effectiveness of treatment. Hence, a similar risk of progression might lead to AT in younger men, while it would be acceptable for AS in older men and WW in the very old. Moreover, patient preferences and anticipated anxiety should play a role.

Patients' Preference and Anxiety

Men wanting to undergo AS must be willing to attend the follow-up visits receiving biopsies and scheduled PSA testing. Without patient commitment, it is likely that they will dropout. Moreover, patients should not be included if they are anxious about biopsies or have difficulty with living with the idea of developing a possible dangerous PCa. However, not all patients are aware at the start whenever they will become anxious during follow-up. About 5–20% of the patients switch to active treatment due to patient anxiety or choice, even though they do not meet the progression triggers [42, 43].

The dropout rate during AS may be reduced by asking recently diagnosed PCa patients whether they would be anxious to undergo biopsies. In addition to the risk of progression and life expectancy, patients' preferences and anxiety should be taken into account in a situation of shared decision making. The physician might obtain an impression of the patient's self-reported health status and preferences using four simple questions [44]. This methodology is currently only usable in a general practitioner setting when PCa screening is being questioned. A similar scoring system for AS could be developed to incorporate patient preference and anxiety.

Biopsy Sampling and Specific Pathologic Findings

Biopsy sampling error partly explains the limited predictive ability of the previously mentioned nomograms and prediction models, since 30–50% of the tumors characterized as Gleason 6 on

biopsy were upgraded at radical prostatectomy [45, 46]. Therefore, a repeat biopsy shortly after the first biopsy of a low-risk PCa might improve patient selection for AS. MRI target biopsy could also potentially be a valuable addition [47].

Pathologic findings such as GS 3 + 4 = 7 with presence of cribriform or intraductal carcinoma indicate a worse disease-specific survival [48]. Men with biopsy GS 3 + 4 without this histology have similar biochemical recurrence-free survival after radical prostatectomy or radiotherapy to those with GS 6 and may be candidates for active surveillance, as long as other inclusion criteria such as PSA and tumor volume are met [49]. It is therefore recommended that pathology reports should therefore include information about the presence or absence of cribriform and intraductal carcinoma in a biopsy, to improve eligibility of men for AS and to reduce overdiagnosis [50].

Future Developments

Stronger predictors are needed to improve discriminatory performance. Imaging techniques such as MRI are currently under development, and novel biomarkers such as PHI, the 4K score, and PCA3 show promise [51–54]. Ongoing AS cohorts will mature and will provide more precise answers in the future. The Movember Foundation has initiated the Global Action Plan 3 (GAP3). This initiative supports a large centralized database, with participating centers from all around the world. Analyses from this database will support optimization of the selection of men for AS; see Chap. 14.

Conclusions

Active surveillance is a safe treatment option and should be the primary treatment strategy for low-risk PCa patients with adequate life expectancy. Occurrence of metastases or prostate-specific survival should ideally be the outcome for supporting effective risk-based selection criteria for AS patients. Optimal selection is complex, and current inclusion criteria vary substantially. Defining low risk either by simple criteria or by more refined risk-based selection models provides similar results. Future analyses with patients with longer follow-up may allow for more refined inclusion criteria, including new markers.

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7 Surveillance at the Margins: Management of High-Volume Gleason 6, PSA > 10, or Gleason 3 + 4

Laurence Klotz

Background

The theme of this book is that many patients with prostate cancer can be managed conservatively, with periodic monitoring to identify those who should be reclassified and offered treatment. The primary parameter for identifying patients at low risk of progression to metastasis is Gleason score, i.e., patients in Grade Group 1 (Gleason pattern 3). The potential benefits of conservative management are compelling and raise the obvious question: are there intermediate-risk patients who can also be safely offered surveillance as an initial management strategy? The answer is clearly yes; the challenge is to identify them accurately. The stakes are higher with intermediate-risk patients, in that the risks of progression to metastasis are greater.

The evidence to support conservative management for some intermediate-risk patients is derived from epidemiologic data, randomized trials, and prospective cohorts of such patients managed with surveillance. The limitations and risks of this approach are also derived from these studies.

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The dilemma for management of clinically localized prostate cancer emerged from the heterogeneity of this disease. Prostate cancer arises from genetically altered prostate epithelium and slowly progresses through many decades. Given the features of multifocality and tumor heterogeneity, the natural history of PCa is difficult to predict. Based on autopsy studies, men may live their natural life without having any symptom from PCa [1]. Zlotta [2] confirmed this hypothesis when prospectively comparing tissue obtained during autopsy from prostate glands on a Caucasian and Asian population. PCa was found in a similar proportion (35%) in both groups. More than 50% of cancer in the Asian group had a Gleason score 7 or greater. The natural history of this disease characterized by slow progression allows AS to be an effective management strategy. It is clear from the autopsy data that many men who harbor intermediate-risk disease (Gleason 7) are never diagnosed and therefore have "clinically insignificant" cancer.

Randomized Trials

In order to estimate the effectiveness of immediate treatment versus AS for patients with localized PCa detected by PSA, three randomized trials have been performed. The Prostate Cancer Intervention versus Observation Trial (PIVOT) randomly assigned 731 men with PCa to radical

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prostatectomy or observation. During the median follow-up of 12 years, the group treated by surgical intervention (47%) did not significantly reduce all cause or prostate cancer mortality, as compared with observation (49%) [3]. The absence of a prostate cancer mortality benefit with treatment in low risk disease was sustained with longer follow up (median 12.7 years); with intermediate risk disease there was a 14.5% prostate cancer mortality benefit with radical treatment compared to watchful waiting [4]. The second large study is the Scandinavian Prostate Cancer Group-4 randomized clinical trial. This prospective study compared radical prostatectomy versus watchful waiting (WW) in early prostate cancer. After 18 years of follow-up, overall mortality rates and prostate cancer-specific mortality were higher in patients managed with WW than in those with immediate treatment [5]. Unfortunately, neither used an AS approach with treatment if there was evidence of progression.

Lastly, the Prostate Testing for Cancer and Treatment (ProtecT) trial compared three modalities of management (active monitoring, radical prostatectomy, and external beam radiotherapy) on patients with localized PCa [6]. Patients randomized to AS had PSA monitored every 3 months during the first years and 6 months thereafter. Median follow-up was 10 years. From the 2664 patients with diagnosis of PCa, there were 17 prostate cancer-specific deaths overall (8, 5, and 4 in the AS, surgery, and radiotherapy group, respectively) demonstrating there was no significant difference in the 10-year cancer-specific survival or overall survival rates. There was a difference in metastasis rate favoring radical treatment. This likely reflects the 25% of the cohort who had intermediate- or high-risk disease, for whom conservative management is clearly associated with an increased risk of progression. Nonetheless, the lack of a mortality difference emphasizes that the majority of Gleason 7 patients are not at risk in the 10-year time frame.

Prospective Surveillance Trials

Table 7.1 lists the various selection criteria for the five largest prospective surveillance cohorts. Most groups restricted eligibility to Gleason 6, in some cases with no more than 2 cores involved and no more than 50% of any core involved. Two groups, Sunnybrook (Toronto) and Royal Marsden (London, UK), included a significant proportion of intermediate-risk patients. In the Sunnybrook surveillance cohort, 22% were intermediate risk, with Gleason <3 + 4 and/or PSA 10–20 n/ml. One third of these men were < age 70. The analysis of this group has provided some important observations. Despite close monitoring and intervention for evidence of risk progression, the 15-year prostate cancer metastasis rate was 3.7 times higher in the intermediate-risk group [12]. This increase in risk was associated almost solely with the presence of Gleason 7 cancer at initial diagnosis. Among this group, the 15-year metastasis rate was at least 20% [13]. For most clinicians and patients, that is an unacceptably

Table 7.1 Selection criteria in active surveillance patients

	Clinical stage	PSA (ng/mL)	Gleason score on biopsy	PSA density	Number of positive cores on biopsy
University of Toronto, Canada [7]	T1c/T2a	≤10–15	≤3 + 4 (1.4% of cohort were 4 + 3)	No restriction	No restriction
Multicenter European study (PRIAS) [8]	T1c/T2a	≤10	≤3 + 3 = 6	≤0.2	2
Johns Hopkins, USA [9]	T1c	NI	≤3 + 3 = 6	≤0.15	2, ≤50% core involvement
Royal Marsden [10]	≤T2	≤15	≤3 + 4	No restriction	No restriction
University of California [11]	T1 or T2a	≤10	≤3 + 3 = 6	No restriction	<33% biopsy cores

high rate of progression. In contrast, however, a recent study of intermediate risk patients on surveillance reported no increase in metastasis rate or progression compared to low risk, with up to 10 year follow up. Clearly, many intermediate risk patients are candidates; the challenge is accurate patient selection [14].

We emphasize that this experience was in the pre-MRI and biomarker era and also reflected the learning curve of active surveillance. Today, such patients would have the benefit of an MRI, with a high likelihood of identifying large-volume potentially lethal cancer and also, potentially, of a molecular biomarker to predict risk [15].

Another experience with surveillance in intermediate risk is derived from the National Prostate Cancer Register of Sweden [16] compared outcomes of 4163 intermediate-risk patients who were managed with active surveillance (23%), radical prostatectomy (52%), and radiation therapy (25%). Among patients with intermediate-risk disease, the prostate cancer mortality was 5.2% in the active surveillance group, 3.4% in the radical prostatectomy group, and 3.8% in the radiation therapy group. These figures are similar to those reported in the Sunnybrook cohort.

Because of the very favorable experience with Gleason 6 cancer, and the significantly higher rate of progression with Gleason 7 disease, most groups have now converged to a middle ground, offering surveillance to most Gleason 6 cases regardless of cancer volume and being very selective about offering it to Gleason 7 patients.

As of the publication of this document, three genetic tissue based assays summarized below have been approved by the FDA for men with prostate cancer. None of these tests have yet been validated as providing substantial benefit in the active surveillance population. However, the "sweet spot" for molecular biomarkers is the otherwise favorable risk patient with small amount of pattern 4 (Grade Group 2) on biopsy who prefers a conservative approach if possible. A low score on a validated molecular assay provides a great deal of reassurance about the safety of nonintervention.

Genomic Classifier (GC) This is a 22-marker genomic classifier (GC), based on RNA expression. GC had independent predictive value on multivariable analysis for predicting metastasis following prostatectomy, with a hazard ratio (HR) of 1.5 for each 10% increase in score, and these results were validated in two separate prostatectomy cohorts. A high score on biopsy is associated with an increased risk of metastasis (HR 1.7 for each 10% increase in score) [17, 18].

Genomic Prostate Score (GPS) This assay incorporates 12 cancer genes that represent 4 biological pathways of prostate cancer oncogenesis: the androgen receptor pathway, cellular organization, stromal response, and proliferation. A 20-point increase in the genomic prostate score (GPS) is associated with a statistically significantly increased risk of high-grade and/or non-organ-confined disease (odds ratio [OR] 1.9, 95% CI 1.3–2.9) [19, 20].

Cell Cycle Progression (CCP) This analyzes 31 cell cycle-related genes and 15 housekeeping genes by quantitative RT-PCR. The Transatlantic Prostate Group examined cell cycle progression (CCP) scores using needle biopsies of a conservatively managed prostate cancer cohort from Great Britain. In this cohort, of 349 men managed without primary treatment, the cumulative incidence of death was increased among those with CCP scores >2 (19% of the population) compared with those with lower CCP scores. Patient outcomes could not be differentiated in those with lower CCP scores. The HR of prostate cancer death was 1.7 per unit increase in CCP score. To 10 or Cancer of the Prostate Risk Assessment (CAPRA) high-risk disease [21, 22].

Evidence indicates that these genomic assays can predict indolent disease behavior despite the appearance of higher-grade cancer on biopsy. For example, a patient with Grade Group 2 (Gleason 3 + 4) PCa and a "low-risk" Oncotype DX® or Prolaris® test should have an mp-MRI to rule out any multifocal disease and can be advised to have conservative management. Future research goals will be to integrate and correlate information obtained through mp-MRI and results of genetic biomarkers.

Young age, in contrast, has not been demonstrated to be a risk factor for progression. Indeed,

the likelihood of harboring higher-grade cancer at diagnosis is lower in young men with Gleason 6 cancer. In the Sakr autopsy series, 29% of men in their 30s harbored microfocal Gleason 6 cancer [23]. Finding small amounts of low-grade cancer in a young man in no way means that he is destined to progress to significant cancer. The caveat is that they have a longer period of time to develop biologic disease progression (to higher-grade cancer). The best estimate of the likelihood of grade progression (as distinct from disease reclassification due to more accurate or repeat sampling) is 1.2–2% per year [24].

A recent study evaluated the association of age with various active surveillance endpoints [25]. Patients less than 60 years old received more surveillance biopsies per time interval. Despite the more intensive assessment, younger age was associated with a lower risk of biopsy upgrade and progression. There were no differences with respect to treatment, adverse disease, or biochemical recurrence. Younger patients should be advised that intermediate-term outcomes are not worse but that longer-term follow-up is needed. Thus, young patients can in most cases be managed conservatively but require long-term follow-up.

Exceptions are those unusual cases of young men (<50) with extensive Gleason 6 disease. These are unusual; most such patients, when diagnosed, have small-volume cancer. Extensive Gleason 6 cancer in a male under 50 may be a signal of biological instability, despite the low grade, and radical intervention may be warranted. Other clues, including PSA density, MRI, and biomarkers, should be employed to aid decision-making in this challenging circumstance.

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How Should Patients on Active Surveillance Be Followed?

8

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A Short History of Follow-Up Protocols

The first case of prostate cancer was described in 1853, and during the following century, prostate cancer was often diagnosed in a relatively late stage. This situation continued until prostate-specific antigen (PSA) testing enabled early detection in the 1990s, resulting in an increase of the incidence of localized low-grade disease [1]. During the last century, the focus was on developing palliative therapies like hormonal therapy and later also curative therapies, primarily radical prostatectomy and radiotherapy, of which the latter two became potentially curative [1–3]. The alternative to radical therapies with curative intent was watchful waiting, which meant (and still means) observing a patient's condition and offering only palliative treatment for symptomatic progression. This is offered to men whose disease has progressed to an advanced stage where curative treatment is no longer an option. However, in 1992, Jones [4] published results of a prospective study comprising patients with so-called early stage A and B prostate cancer (defined as non-palpable and palpable gland-confined tumors, respectively) who chose expectant management instead of radical treatment. The data revealed similar survival probabilities between the study cohort and the normal male population after 22 years of follow-up [4], indicating that radical treatment might not be necessary for localized prostate cancer. With the introduction of PSA for prostate cancer screening, the group of men that were detected with low-grade localized prostate cancer exploded around the mid-1990s (see Chaps. 1 and 2). Together with the high incidence rate of latent prostate cancer in autopsy studies and excellent results of conservative management of coincidentally found T1a prostate cancer, it became apparent that screen-detected patients with low-risk localized prostate cancer could also benefit from a conservative management strategy [5]. The University of Toronto group first described a prospective study cohort of low-grade localized prostate cancer patients, managed from 1995 onward with "*watchful observation* with selective delayed intervention using clinical, histologic or PSA progression as treatment indications" [6]. They subsequently termed this "active surveillance." They described that PSA-doubling time (PSA-DT) could be a useful parameter to separate biologically indolent from aggressive

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disease. The follow-up protocol of this first, and from there on named *active surveillance* (AS), cohort entailed an assessment every 3 months for the first 2 years and 6 months thereafter. At each assessment, medical history, digital rectal examination, and blood tests for PSA, prostate acid phosphatase, and serum creatinine were obtained. Patients underwent a transrectal ultrasound (TRUS) of the prostate every 6 months and systematic TRUS-guided re-biopsy at 18 months after enrollment. In addition, a bone scan was performed 1 and 2 years after enrollment with biannually repetition thereafter. PSA progression and progression of clinical or histological findings could trigger therapeutic intervention [6]. Since the publication of this first prospective study protocol, many different protocols have been applied and adjustments have been made [7].

Introduction

When it is decided to start with AS, the patient will be monitored closely by a follow-up protocol. Ideally, the only aim of a follow-up protocol would be to timely detect progression from low-risk to high-risk prostate cancer, and by that selecting those patients who would benefit from a switch to curative treatment. In practice, the follow-up protocol serves another aim since the selection of men having low-risk prostate cancer is not perfect. The protocol also has to facilitate the identification of patients who have been selected incorrectly for AS, i.e., those misclassified as having low-risk prostate cancer. Furthermore, as AS in its enterity aims to avoid the side effects of unnecessary invasive treatment, hence improving quality of life of prostate cancer patients, we should try to achieve these aims in such a way that the follow-up protocol itself does not entail unnecessary testing and is not too demanding for the patient. In this chapter, we study how, with the currently available tools, men are monitored during AS and discuss what efforts are undertaken to improve the diagnostic accuracy while minimizing the burden of follow-up.

An Overview of AS Follow-Up Protocols

There is a large variety in recommendations on how to monitor patients during AS [7]. Most follow-up protocols consist of serial risk assessments including periodic PSA tests (every 3–6 months), clinical evaluations with digital rectal examinations (DRE) (every 3–12 months), surveillance systematic TRUS-guided biopsies (every 1–3 years), and MRI with the possibility of targeting biopsies at suspicious lesions. Often a distinction can be made between methods to detect misclassification at diagnoses and methods to detect progression over time. To detect misclassification, most protocols require a confirmatory biopsy and/or MRI within 1 year after enrollment into AS. Throughout the course of follow-up, progression over time and residual misclassification are detected by subsequent scheduled or triggered risk assessments. Table 8.1 shows the most commonly used protocols. Differences between protocols are mainly based on different frequencies of assessments and different criteria used to trigger assessments. Currently, there is no consensus on the most optimal way of monitoring patients on AS.

Understanding an Active Surveillance Follow-Up Protocol

Misclassification at diagnosis and potential disease progression over time are at the basis of understanding why follow-up protocols are designed the way they are. Misclassification of AS candidates, i.e., under detection of their true Gleason grade or underestimation of their true tumor volume (by number or proportion of positive biopsy cores and/or percentage cancer involvement of any core), is the result of inaccurate diagnostic tests. On the other hand, progression over time occurs when an initial small Gleason 3 + 3 prostate cancer grows in size and progresses to Gleason $\geq$3 + 4 or when a new lesion develops, where the latter two could ultimately lead to tumor spread outside the prostate. When an assessment reveals misclassification or

Table 8.1 Follow-up protocols of several AS studies

	Risk assessment methods: frequency, timing, and triggers					
Study	PSA test (every)	DRE (every)	Confirmatory biopsy (months)	Repeated biopsies[a] (every)	Optional MRI	Triggers for biopsy and/or MRI
University of Toronto [8]	3 months[b], then 6 if PSA stable	–	<12	3–4 years	Yes	PSA-DT < 3 years[c]
Johns Hopkins University [9, 10]	6 months	6 months	<12	1 year	Yes	–
PRIAS [11]	3 months[b], then 6 and 12 months after 4 years[d]	Only at time of biopsy[d]	≤12	3 years	Yes	PSA-DT 0–10 years, >2 positive biopsy cores[d]
UCSF [12, 13]	3 months	3 months	<12	1–2 years	Yes[e]	–
MSKCC [14–16]	6 months	6 months	3	Start at 12–18 months, then 2–3 years	Yes	DRE change or sustained PSA increase
University of Miami [17]	3–4 months[b], then 6	3–4 months[b], then 6	9–12	1–2 years	–	Rise in PSA or change in DRE

PRIAS Prostate Cancer Research International Active Surveillance; *UCSF* University of California, San Francisco; *MSKCC* Memorial Sloan Kettering Cancer Center; *PSA* prostate-specific antigen; *TRUS* transrectal ultrasound; *DRE* digital rectal examinations; *PSA-DT* PSA-doubling time

[a]After confirmatory biopsy

[b]For 2 years

[c]As of 2009

[d]As of 2016

[e]Or TRUS (without biopsy) every 6–12 months

progression over time, a patient is, depending on protocol criteria, reclassified to a higher-risk prostate cancer (see Fig. 8.1). Most often, this prompts a switch to radical treatment with the intent to cure the disease and prevent further disease progression (Chap. 9).

Misclassification at Diagnosis

Mechanism

Using systematic TRUS-guided biopsy at diagnosis, as historically has been the only option until the development of MRI for prostate cancer detection, inherently results in random and/or systematic sampling error [22]. Random sampling error is caused by chance; i.e. by systematicly determining the location of the biopsy cores, they are inadvertently not taken at the location of the greatest diameter or highest grade of a lesion. Systematic sampling error means that a part of the prostate is always overlooked, for example, the anterior part because it is more difficult to adequately sample. Both ways of misclassification play a role at diagnostic systematic TRUS-guided biopsies, as most often 8–14 biopsy cores are taken randomly at different locations from mainly the peripheral zone of the prostate. In contrast, MRI-guided biopsies are taken from lesions suspicious for prostate cancer on MRI and therefore are less susceptible to sampling error but are still depending on the accurate detection of suspicious lesions on MRI (see Chaps. 10 and 11).

The Estimated Misclassification Rate

Misclassification rates in men selected for AS can be determined by using data from radical prostatectomy series in men otherwise eligible for AS. At radical prostatectomy, 33% to 45%

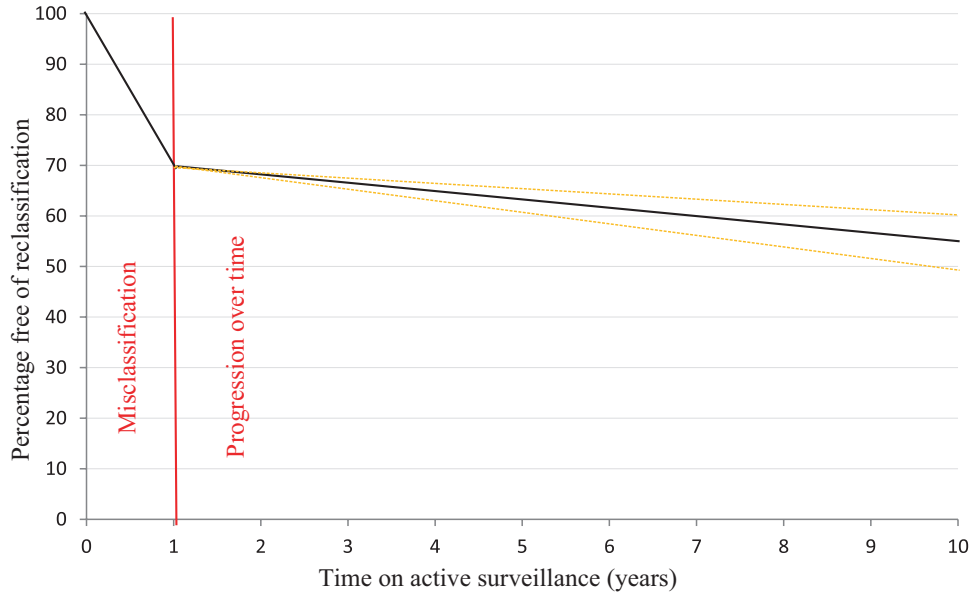

Fig. 8.1 Theoretical reclassification-free survival over time (based on 30% misclassification [18, 19] detected within the first year and 1–2% detected progression over time [20, 21])

of men who met the study inclusion criteria of six different AS protocols appeared to have stage T3 or greater or Gleason ≥7 [18]. In another radical prostatectomy study, looking at an intensively screened population [19], the rate of misclassification for three AS studies (Johns Hopkins University, University of Toronto, and "Prostate cancer Research International: Active Surveillance" (PRIAS)) ranged from 19% to 32%. On average, about one third or more of patients are misclassified after a diagnosis by systematic TRUS-guided biopsy [23] (Fig. 8.1).

Detecting Misclassification

As misclassification at diagnosis with systematic TRUS-guided biopsy is substantial (about one third of patients), reevaluation of tumor stage and grade is essential [18, 19]. To confirm the tumor stage and grade at diagnosis, the majority of AS protocols include a repeat systematic TRUS-guided biopsy within the first year. Repeating a systematic TRUS-guided biopsy ensures an appropriate number of biopsy cores are taken at the right locations and decreases the possibility of (mainly random) sampling error [24]. Currently, many AS studies have also incorporated MRI in their protocols; the diagnostic accuracy and role of MRI within AS protocols will be discussed in Chaps. 10 and 11.

Reclassification rates at confirmatory or first risk assessment vary between AS cohorts depending on how strictly patients are selected at inclusion and the reclassification criteria used. Few studies report on reclassification at confirmatory or first risk assessment separately. However, the PRIAS study showed a reclassification rate to Gleason ≥3 + 4 or high-volume prostate cancer at first systematic TRUS-guided biopsy of 24%, around 1 year after enrollment [11]. The University of Toronto showed a systematic TRUS-guided biopsy reclassification rate to Gleason ≥3 + 4 of 23%, at a median of 1.4 years after enrollment [25] (Table 8.2). Unfortunately, not all misclassified patients seem to be detected by confirmatory or first risk assessments, which can be derived from the following observations: reclassification rates (23%–27%) are lower than misclassification rates (19%–45%) as shown above, and in addition, a considerable part of reclassified patients prove to have undergone a possible unnecessary radical treatment (as will be

Table 8.2 Serial biopsy reclassification rates during active surveillance

		Repeat biopsy number[a]					
		Reclassification rate and (total number of patients)					
Study	Reclassification criteria	1	2	3	4	5	Total range
University of Toronto [25]	Histological (increased Gleason grade, e.g., ≥3 + 4)	22.9% (593)	18.4% (217)	26.7% (45)	36.4% (11)	100% (1)	22.9–100%
UCSF [37]	Histological (increased Gleason grade, e.g., ≥3 + 4)	21% (377)	22% (205)	30% (109)	29% (48)	26% (23)	21–30%
PRIAS [11]	Histological (increased Gleason grade, e.g., ≥3 + 4)	13% (3379)	13% (1077)	16% (282)	15% (68)	13% (15)	13–16%
	Volume (>2 positive cores)	18% (3379)	18% (1077)	17% (282)	16% (68)	27% (15)	18–27%
	Gleason grade and/or volume	24% (3379)	24% (1077)	25% (282)	22% (68)	33% (15)	22–33%
Total range (histology only)		13–22.9%	13–22%	16–30%	15–36.4%	13–100%	–

[a]Timing of biopsy procedures differed between studies:
University of Toronto: first biopsy at 1.4 years after enrollment, with median time between subsequent biopsies 3.1, 2.9, and 3.3 years, respectively
UCSF: median time between biopsies ranged from 12 to 16 months
PRIAS: scheduled biopsy at years 1, 3, 7, and 10 and after enrollment (if not triggered in between by a PSA-DT 0–3 years)
PRIAS Prostate Cancer Research International Active Surveillance, *UCSF* University of California, San Francisco

discussed further on in this chapter). However, anxious to avoid missing the so-called window of curability, all protocols include at least one (confirmation) systematic TRUS-guided biopsy to detect misclassified men (Table 8.1). Evidence is sparse for when the timing of a confirmatory risk assessment is optimal. The Memorial Sloan Kettering Cancer Center (MSKCC) protocol performs a confirmatory systematic TRUS-guided biopsy at 3 months after diagnosis where other protocols require this between 6 and 12 months after diagnosis (Table 8.1). It is reasonable to assume, based on studies comparing delayed and immediate radical treatment, that very few men will experience unfavorable results from extending the time between diagnoses and a confirmatory biopsy procedure, as is done in current protocols (up to 1 year) [26]. Therefore, it seems responsible to involve the patient in the decision-making and perform a confirmatory risk assessment (including MRI if available) at his convenience, somewhere within the first year after diagnosis.

Progression over Time

Estimated Progression Rate

Next to misclassification, progression over time adds to the uncertainty of the actual tumor grade and volume during follow-up. Pathologically confirmed Gleason grade ≤ 3 + 3 prostate cancer, after radical prostatectomy, has negligible potential to metastasize [27], as discussed in Chap. 5. However, in untreated patients, new lesions may develop and an initial Gleason 3 + 3 prostate cancer can progress to Gleason 3 + 4 or higher. Whether true grade progression occurs from Gleason 3 + 3 to Gleason ≥3 + 4 has long been a topic of discussion as empirical evidence is lacking. However, two modeling studies concluded that Gleason grade progression does occur over time [20, 21]. It is estimated, by modeling the outcomes of serial biopsies during AS corrected for misclassification, that the likelihood of true grade progression from a Gleason 3 + 3 to Gleason ≥3 + 4 over a period of 10 years ranges from 12% to 24%, translating to a yearly grade

progression risk of 1%–2% [21] (see Fig. 8.1). Therefore, repeated risk assessments remain essential to confirm absence of progression.

Surrogate Markers for Detecting Progression over Time

In AS protocols, several methods are used to detect progression. Some, like Gleason grade on biopsy, are a direct indication of the presence of more aggressive disease that likely needs curative treatment. Others, like PSA kinetics (PSA-DT or PSA velocity) or an increase of the number of tumor-positive biopsy cores, indirectly indicate that more aggressive disease is present. Whether these surrogate markers of disease progression should indeed trigger curative treatment depends on their direct relation with disease progression.

Prostate-Specific Antigen (PSA) Testing

PSA tests can be repeatedly performed without serious drawbacks and are performed frequently during the course of AS to monitor PSA level changes. An important factor which complicates the interpretation of PSA tests is the clinical context in which it is measured, as a rise in PSA level can be related to both benign (e.g., prostatic hyperplasia or infection) and malignant origins. According to most literature, a high PSA, PSA density, and Prostate Health Index (PHI) or fast PSA kinetics may be indicative of unfavorable prostate cancer on biopsy or radical prostatectomy [7, 28], although not all studies agree on their value for clinical decision-making [29]. As discussed in [11, 29, 30], adverse PSA kinetics should not prompt radical treatment; instead (and depending on clinical context), they should be used as a trigger for stricter follow-up (e.g., more frequent PSA measurements, an MRI, and/or TRUS biopsy). PSA density thresholds from 0.10 to 0.20 ng/ml/ml are associated with abnormalities on MRI, biopsy reclassification, and unfavorable pathologic characteristics [28, 31] where the threshold of 0.15 ng/ml/ml is most frequently used. The PHI test (a combination of total PSA, %fPSA, and proPSA) is shown to improve predicting unfavorable outcomes on biopsy and radical prostatectomy [32, 33] but is currently infrequently incorporated in AS protocols. Lastly, the frequency of PSA testing most often lies between two and four times per year, and decreasing the frequency of PSA testing after 2–4 years of stable PSA values, as progression after that time is rare, is a potential option to reduce a part of the burden of long-term AS [34].

In conclusion, it seems reasonable to assume that PSA velocity, PSA-DT, PSA density, and PHI all play a role as noninvasive predictors of underlying histological progression. However, there is no consensus on their role in clinical decision-making, which could be resolved by collaborative research and data sharing between active surveillance studies; see Chap. 14.

Digital Rectal Examination (DRE)

DRE is a relative inexpensive and easy-to-perform test, which can reveal a direct need (i.e., clinical stage > cT2) for radical treatment [11]. It is often performed during AS (4–2 times per year) with decreasing frequency over time [7] (Table 8.1). However, reclassification on the basis of DRE findings occurs infrequently (<1% of all reclassifications in the PRIAS study) [11] as can be expected after exclusion of palpable >cT2 abnormalities at time of diagnosis and the natural slow-progressing development of prostate cancer. In addition, the accuracy of DRE for detecting prostate cancer is subjective to examiner and patient factors [35]. Moreover, DRE might be experienced as an unpleasant examination. Therefore, one might consider reducing the frequency of performing a DRE further, although the tangible benefit of doing so is debatable [11].

Detecting Progression over Time

Transrectal Ultrasound (TRUS)-Guided Biopsy

Prostate biopsies after diagnosis are recommended by all AS guidelines, but the frequency and criteria at which the biopsy procedure should be repeated vary between protocols [7] (see Table 8.1). Some protocols have incorporated the use of serial MRI, which will be discussed in Chaps. 10 and 11. In the majority of protocols,

biopsy procedures are performed between every 12 months and once every 4 years, some depending on the time after enrollment on AS and/or triggers, such as PSA kinetics or DRE findings [36]. Criteria for biopsy reclassification vary as well and are based on changes in Gleason grade and/or increased tumor volume (by number of positive cores or percentage of core involvement). Reclassification rates at each subsequent systematic TRUS-guided biopsy have been published by the University of Toronto (based on Gleason grade ≥ 3 + 4); the University of California, San Francisco (UCSF) (Gleason grade ≥ 3 + 4); and the PRIAS study (Gleason grade ≥ 3 + 4 and/or >2 positive biopsy cores). The reclassification rates remained between 18% and 37% throughout the course of follow-up [11, 25, 37] (see Table 8.2). These reclassification rates are higher than should be expected from the estimated true progression rate (12%–24% during the course of 10 years) and can be explained by the remaining presence of misclassified patients or unjust reclassification criteria, as explained in the next subheading. Biopsy reclassification rates of 18%–37% also imply that the remainder (63%–82% of biopsies) were not necessary. This is crucial since prostate biopsy is associated with significant complications. Following a prostate biopsy, 25% of patients experience transient lower urinary tract symptoms (LUTS), some experience transient erectile dysfunction, and most importantly, 0.5%–6.9% of patients require hospital admission due to severe urinary tract infection and sepsis [38]. Such a biopsy complication leads to patients being less inclined to have a repeat biopsy in subsequent risk assessments during AS [39]. Furthermore, the compliance rate of patients and urologists to follow recommendations for biopsy decreases over time (from 81% in year 1 to 33% in year 10), when patients and urologist are not obliged to a strict follow-up protocol as in the PRIAS study [40].

In conclusion, not all surveillance systematic TRUS-guided biopsies result in reclassification (only 18%–37%), and not all reclassifications are clinically significant (as explained in the next subheading). In addition, the biopsy complications are not negligible, and compliance with recommended biopsies decreases over time. These findings indicate the need to improve the diagnostic accuracy of our risk assessment methods and the need to safely reduce the amount of biopsies.

Are We Truly Detecting Progression?

Both reclassification and patient requests (e.g., driven by anxiety) can lead to a switch to radical treatment. The average rate of switching to radical treatment was 8.8% per year in 26 AS cohorts [36]. Most AS cohorts show a treatment-free survival rate between 50% and 86% at 5 years, which decreases further with longer follow-up [11, 41]; see as example Fig. 8.2. However, only afterward the justification of the decision to switch to treatment can be evaluated, i.e., in case a radical prostatectomy was chosen and the pathologic outcomes are known. The aim of AS is to timely treat only those patients who need radical treatment, i.e., appear to have intermediate pathology (Gleason 3 + 4 and pT2) in their radical prostatectomy specimen. Unfortunately also favorable pathology (Gleason 6 and stage pT2) and unfavorable pathology (Gleason ≥4 + 3 or pT3 or higher) are found in radical prostatectomy specimens after AS. Patients who appear to have favorable pathology were not at risk of developing metastatic disease or prostate cancer-related death at that moment [27]. They only had a risk on true progression to Gleason ≥3 + 4 of 1%–2% per year [21]. In contrast, patients with unfavorable pathology are those who should not have commenced AS in the first place or who progressed very quickly and might have benefited of an earlier and more accurate detection and subsequent radical treatment. However, as men eligible for AS but who choose for direct radical treatment might also appear to have unfavorable pathology (i.e., were misclassified), the comparison of long-term outcomes between AS patients and men (eligible for AS but) who choose for direct radical treatment needs to be considered. Klotz et al. showed that metastatic disease and death of prostate cancer rates are similar between the University of Toronto cohort (after 15 years of follow-up) and

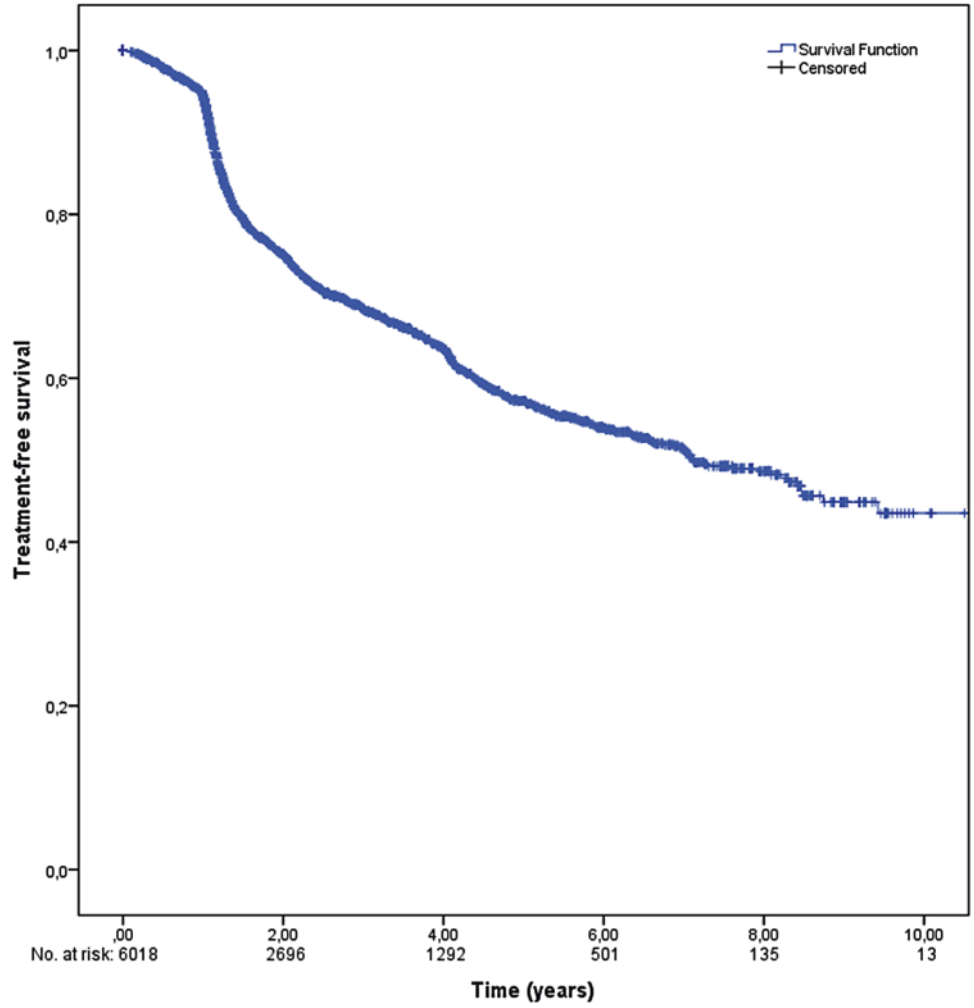

Fig. 8.2 Example of treatment-free survival during follow-up (PRIAS study – unpublished update of [43])

data from radical prostatectomy series of men otherwise eligible for AS [8].

In the PRIAS study [11], reclassification was defined as Gleason grade ≥ 3 + 4, a clinical stage higher than cT2, volume of disease (i.e., ≥2 positive biopsy cores), and until the year 2014 a PSA-DT between 0 and 3 years. By using these reclassification criteria to recommend a switch to radical treatment, 30% of reclassified patients had favorable pathologic outcomes, 34% had an intermediate pathologic outcome, and 36% had an unfavorable pathologic outcome. Interestingly, the criteria ≥2 positive biopsy cores and PSA-DT between 0 and 3 years were not predictive of intermediate or unfavorable pathologic outcomes [11]. In the Johns Hopkins University cohort [42], 31.9% of reclassified patients (defined as biopsy Gleason grade ≥ 3 + 4, PSA density ≥ 0.15 ng/ml, >2 positive cores, or >50% core positivity) had unfavorable pathologic outcome at radical prostatectomy. Again, reclassification on >2 positive biopsy cores resulted in less adverse pathology on radical prostatectomy than patients who were reclassified by Gleason grade, 23.8% versus 44.7%, respectively [42]. These findings indicate that common reclassification criteria to recommend switching to radical treatment are both

too stringent (about one third have favorable outcomes) and are not able to timely select patients with aggressive cancers (about one third has unfavorable outcomes). It seems reasonable to conclude reclassification on the basis of a volume criterion, or PSA-DT alone should not directly trigger radical treatment but instead trigger a more accurate diagnostic test (e.g., MRI) [11, 30].

What Have We Learned and What Do We Need to Know?

As shown above, misclassification occurs in about one third of patients diagnosed by systematic TRUS-guided biopsy, and not all misclassification is detected at confirmatory or first risk assessment. Although true progression rate is estimated to be 1%–2% per year, biopsy reclassification rates during follow-up remain higher (18%–37%) than can be expected. These biopsy reclassification rates also imply that the remainder of biopsies was not necessary and therefore should be avoided. Furthermore, reclassification on the basis of systematic TRUS-guided biopsy (Gleason grade and/or tumor volume) and/or fast PSA kinetics and DRE results in 14%–50% of patients to switch to radical treatment within 5 years after enrollment in AS. This switch to radical treatment, however, might have been unnecessary in one third of treated patients. Surrogate markers for tumor progression, like PSA derivatives, can be used as a trigger for further risk assessment, depending on clinical context. As the diagnostic values of PSA testing, DRE, and systematic TRUS-guided biopsy vary and the associated potential harm and burdens are substantial, and ways to optimize the use of these tests should be sought. MRI may refine the balance between accurate risk assessments and the burden of testing (Chaps. 10 and 11).

An additional way of optimizing the follow-up during AS is to enable a more individualized protocol [19, 44, 45]. Currently, AS protocols use a "one-size-fits-all" approach where follow-up tests are prescheduled, and often the frequency and timing of follow-up are not adapted to a patient's individual risk. For personalized medicine, it is necessary to differentiate patients based on their individual risk profile and be able to tailor their treatments accordingly. In addition, as personal preferences and values differ, follow-up must be tailored not only to a patient's risk profile, but also to the personal preferences of the patient. In other words, some men would accept a follow-up biopsy if the risk at reclassification is 5%, while others would not. Currently, no probabilistic-based AS protocols exist in which a comprehensive model is incorporated, which uses individual characteristics and results from predictors to help patients and their physicians determine their optimal follow-up protocol (e.g., frequency and timing of tests such as biopsy and MRI or a switch to radical treatment or watchful waiting). A first step was taken by Ankerst and colleagues, who developed a model which estimates the risk of biopsy reclassification during AS and could be used to guide decisions regarding subsequent biopsies [46]. This model will need clinical validation and, if proven useful, implementation. The additional benefit of a model-based approach is that it can be tailored to a target population and is more flexible in the sense that it can be updated relatively easily when new data or predictors become available [47, 48]. All factors we discussed above and future developments (as discussed in Chaps. 10, 11, 12, and 13) could be incorporated in such a dynamic risk prediction model to further optimize the follow-up of patients in AS, as is one of the aims of the Movember Foundation's Global Action Plan (GAP3), described in Chap. 14.

Conclusion

AS follow-up protocols are a necessity to detect tumor misclassification and progression over time within the window of curability. To delay or avoid radical treatment and its associated side effects, without compromising safety and quality of life, we should try to further improve the diagnostic accuracy, and decrease the burden, of our risk assessment methods in an individualized manner.

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Triggers for Intervention

9

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Abbreviations

AS Active surveillance
NPV Negative predictive value
PC Prostate cancer
PI-RADS Prostate Imaging Reporting and Data System
PSA-D PSA density
PSA-DT PSA doubling time
PSA-V PSA velocity

- *Some abbreviations, such as PSA, TURP,* etc., *were considered well known for the audience and thus not listed here.*

Introduction

Active surveillance (AS) is as a treatment option for patients with localized low-risk prostate cancer (PC). Contrary to watchful waiting, patients on AS are monitored in order to detect possible reclassification of the disease into clinically significant one, which would require curative intervention.

PC risk reclassification may be due to true biological progression of the disease that can occur if initially low-grade cancer cells or histologically normal cells transform into higher-grade cancer cells, as illustrated in Fig. 9.1 [1]. The rate of such true biological progression is not well known but is estimated to be 1–2% per year [2, 3].

However, more importantly, reclassification is a function of diagnostic inaccuracy, i.e., undergrading of PC initially at diagnosis. Common diagnostic measures such as transrectal ultrasound and random 12-core biopsies frequently miss high-grade cancers as well as overdiagnose insignificant cancers as illustrated in Fig. 9.2 [4].

Pre-PSA era PC was often a clinical diagnosis and based on findings in TURP specimen and referred to as "indolent" PC. Such patients were often not followed as strictly as patients in AS protocols today, and yet, excellent PC-specific survival has been reported in localized low-grade disease [5].

The PSA era is characterized by a dramatic increase in PC incidence throughout the Western world mainly due to widespread use of serum PSA for early diagnosis. PC diagnostics improved with the utilization of transrectal biopsies under ultrasound (US) guidance, replacing fine needle aspirations, and the systematic use of Gleason grading system for reporting biopsy results. Concern about potential overdiagnosis and overtreatment was soon raised [6]. Thus, there have been efforts to define clinically insignificant PC, such as the Epstein criteria [7]. These formed the basis for defining inclusion criteria and triggers for intervention in the subsequent AS cohorts and trials.

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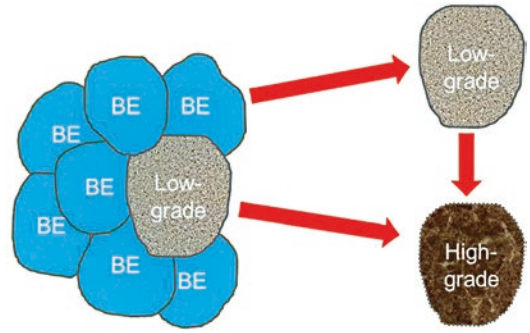


Fig. 9.1 A schematic representation of true biological progression of the disease that can occur if initially low-grade cancer cells or histologically normal cells transform into higher-grade cancer cells

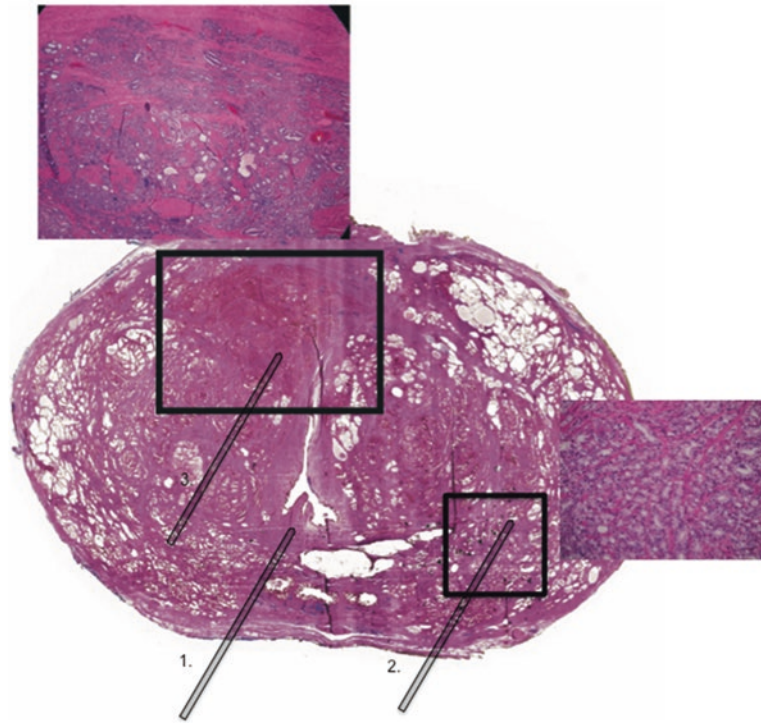


Fig. 9.2 Radical prostatectomy specimen shown with multifocal disease and three theoretical routes for TRUS-guided transrectal biopsy needle causing undergrading. *1* Needle not hitting any cancer lesions (needle 1). *2* Needle hitting clinically insignificant low-grade cancer lesion (needle 2). *3* Needle hitting a tumor but missing high-grade part of it (needle 3)

Several AS cohorts have been published, identified, and reviewed [8]. Most of the AS protocols rely on repeat biopsies to monitor the disease. The volume of the disease is generally monitored with biopsy-based surrogates, e.g., number of positive biopsies and cancer length, and PSA-based surrogates, e.g., PSA, free PSA, PSA density (PSA-D), PSA doubling time (PSA-DT), and PSA velocity (PSA-V). However, the triggers used for reclassification/progression vary remarkably between the published cohorts [8–14]. Generally, treatment is recommended if during follow-up the patient no longer meets the inclusion criteria. A summary of the triggers used in some of the well-known AS cohorts is shown in Table 9.1.

The initial reports of MRI's negative predictive value being close to 100% for clinically significant cancer seem promising in the AS setting [15]. Also, there have been noteworthy reports concerning the initial use of genetic tests to predict cancer outcome [16]. This makes it tempting to speculate that selection of patients for AS and triggers for intervention will largely rely on MRI, combined with targeted biopsies, and genetic biomarkers in

Table 9.1 Triggers for intervention in AS protocols

Cohort	Start year	Triggers for intervention
Toronto[9]	1995	GS upgrade, PSA-DT < 3 years[a]
Johns Hopkins[10]	1995	GS >6, >2 positive cores, >50% core involvement
UCSF[11]	1990	GS >6, >33% positive cores, >50% core involvement
Miami[12]	1992	GS >6, >2 positive cores, increase in core involvement
Royal Marsden[13]	2002	GS >3 + 4, >50% positive cores, PSA-V > 1
PRIAS[14]	2006	GS >6, >2 positive cores, PSA-DT < 3 years[b]

GS Gleason score
[a]Until 2008, PSA-V = PSA velocity, PSA-DT = PSA doubling time
[b]Until 2015

the future. However, the value of using MRI and genetics for surveillance in patients with PC on AS still awaits confirmation in prospective trials with sufficiently long follow-up.

Here, we take a detailed historical perspective to review the literature on triggers for intervention in PC patients on AS.

Pre-PSA Era

Before PSA became a widely accepted tool for prostate cancer (PC) diagnostics and monitoring, PC was often an incidental finding in TURP performed for obstructive urinary symptoms due to benign prostatic hyperplasia or in cystoprostatectomy performed due to bladder cancer. These PCs were considered indolent and did not usually lead to PC treatments. Instead, conservative non-standardized follow-up, if any, was exercised. Biopsies, mostly fine needle aspirations in the early era, were not routinely repeated during follow-up, and if symptomatic disease developed, endocrine treatment was initiated. This protocol with deferred palliative treatment was commonly referred to as watchful waiting.

Despite poor diagnostic work-up and quality by today's standards, as well as lack of regular follow-up and triggers in the pre-PSA era, excellent long-term survival has been reported. In a population-based study from Iceland, 100% cancer-specific survival was reported for patients with pT1a PC [5]. Additionally, in two better-known and commonly cited studies, similar findings of excellent PC-specific survival were observed for local low-grade tumors in the absence of follow-up protocol and triggers for curative intervention [17, 18]. Therefore, it may be justified to question the value of protocol-based strict follow-up, as in published contemporary AS series, for low-grade, low-stage tumors, especially considering up to 10-year lead time in PC diagnosis induced by PSA screening [19]. However, the key in AS is to correctly balance the risk of symptomatic PC against competing risks of death due to comorbidities and age, as illustrated. In this respect it is intriguing that life expectancy has increased significantly throughout the world since these famous "watchful waiting" cohorts were published. As an example, in Finland life expectancy for a man was 67.94 years in 1977, when the first patients entered Johansson's pivotal study, while it was 78.17 in the year 2014 [20]. While the more than 10-year increase in life expectancy may compensate for PSA-induced lead time, it also certainly emphasizes the importance of long-term follow-up of AS cohorts.

PSA Era

Pre-ISUP 2005

PSA was first approved by the FDA for disease follow-up after radical prostatectomy in 1986 [21]. Soon its potential as a diagnostic tool was realized, and this use was also approved by the FDA in 1994 [21]. The era is characterized by a massive increase in PC incidence due mainly to unorganized PSA-based screening, standardization of biopsies (TRUS-guided systematic biopsies), and redefined tumor grading (Gleason grading has replaced WHO grading). Two large, prospective PSA-based screening trials (ERSPC and PLCO) were launched, and it soon became evident that overdiagnoses and overtreatment were problems inherent in PSA-based diagnostics [22,

23]. This played a large role in the later recommendation of the United States Preventive Services Task Force (USPSTF) against the use of PSA screening. Eventually, efforts to differentiate clinically significant PC, i.e., those requiring treatment, from clinically insignificant PCs, i.e., those not requiring treatment, were initiated.

It is well accepted that candidates for AS are low-stage, low-grade tumors, while the roles of tumor volume and PSA in candidacy for AS are less clear. Despite a plethora of publications on "novel," RNA- or DNA-based potential biomarkers for PC, currently none are widely accepted for clinical use. Instead, tumor volume and PSA-based triggers are included in most of the published AS cohorts and guidelines.

Tumor Volume

Stamey et al. laid the basis for determining clinically insignificant PC by evaluating the incidence of PC in a consecutive series of 139 cystoprostatectomies [24]. They assumed that the pre-PSA era lifetime risk of PC (8%) would apply for the cystoprostatectomy cohort in which 55 PC index lesions were found. The number of the largest index lesions considered clinically significant stood at 11/55 (8%), clinically significant as being expected to be diagnosed during a man's lifetime in the absence of PSA. The 11 index lesions were all over 0.5 cm^3, which subsequently became the cutoff volume for clinically significant disease. In order to translate this to clinically usable criteria, as RP data is not available at diagnosis, Epstein et al. sought to look for diagnostic variables that could predict clinically insignificant versus significant PC as defined by Stamey. In a series of 157 consecutive RPs in patients with T1c disease, Epstein presented the following criteria: PSA density (PSA-D) $\leq$ 0.15, biopsy Gleason score ≤ 6, $\leq$ two positive biopsy cores, and $\leq$50% involvement of any biopsy core [7]. These two studies laid the foundation for future research on AS for patients with PC.

However, the logic in the abovementioned studies and the conclusions thereof have also been criticized. In an attempt to repeat Stamey's work in a more contemporary PSA era cystoprostatectomy cohort, Winkler et al. found 58 PCs (60%) in a series of 97 cystoprostatectomies. With the pre-PSA era assumption of 8% incidence for PC, as in the Stamey's paper, the cutoff volume for significant PC would have been 1.09 cm^3 [25]. In a following study, Wolters et al. on the other hand looked at the Rotterdam ERSPC screening cohort and concluded that 1.3 cm^3 for index tumor volume and 2.5 cm^3 for total tumor volume were more appropriate cutoff values for low-grade and low-stage PCs [26]. Importantly, all these studies merely establish general guidelines as the "one size fits all" approach does not exist in this context. The key is in the relation between tumor characteristics and competing risks of mortality, both of which are moving targets (slowly increasing aggressiveness of the tumor due to biologic progression versus shortening life expectancy due to comorbidities and increasing age during surveillance), as emphasized.

PSA Kinetics

The first papers on AS cohorts were published in 2002. In the paper by Choo et al. the early experiences from the Toronto cohort were published [27]. The authors state that the triggers used for intervention, namely, clinical, histological, and PSA progression, were arbitrarily defined, but it was concluded that PSA-DT may reflect tumor growth and predict its biological behavior. On the contrary, preliminary results of an AS cohort in the Johns Hopkins showed that PSA velocity did not correlate with disease progression, while PSA-D and free PSA did correlate [28]. They used the aforementioned triggers for progression during surveillance, which was based on yearly rebiopsies.

The rationale for using PSA kinetics as a tool to monitor PC is intuitive and was first supported by a paper in which PC tumor volume was shown to correlate with serum total PSA value [29]. However, it was later realized that over time the correlation between tumor volume and PSA has diminishes dramatically, likely due to decreasing tumor volume versus prostate volume ratio during the PSA era [30].

At the conclusion of the "early" PSA era, a candidate patient for AS was defined, triggers for

intervention started to evolve, and the role of PSA kinetics was emphasized.

Post-ISUP 2005

Characteristics of the "later" PSA era included the refinement of the Gleason grading system, continuing controversy over PSA screening, lack of support for the immediate curative treatment of low-risk PC [31, 32], start of several AS cohorts, publications of short-term AS results, and rise of MRI as an imaging tool in localized PC. Additionally, AS was finally accepted as a treatment option in most of the guidelines [33].

Gleason Grading

Gleason grading has evolved significantly over the years. Importantly, after the ISUP consensus meeting in 2005, only some of the cribriform pattern glands, those corresponding to the surrounding benign glands in size, could be considered as Gleason grade pattern 3 [34]. Ultimately, from 2010 onward the view that any size PC with cribriform architecture should be considered as Gleason grade pattern 4 has been widely adopted [35–37]. Notably, it has also been recognized that no Gleason score of 2–4 should be made on needle biopsies, a concept that had already earlier been proposed by some authors [38]. These changes in the diagnosis of Gleason scores 6 and 7 defined the so-called modified Gleason score and have resulted in disease upgrading. In other terms, a Will Rogers phenomenon has occurred in which the average aggressiveness of both Gleason score 6 and 7 subgroup cancers has decreased. Thus, both Gleason 3 + 3 and 3 + 4 PC in a surveillance biopsy today are likely to be associated with a better prognosis than they were before 2005 and 2010.

Currently, there is no evidence in the literature that definitive treatment of Gleason 6 PC prolongs survival. In fact, there is very little evidence that Gleason 6 cancer behaves like a cancer at all despite having the required histological features [39]. Also, it is difficult to find evidence from the literature for Gleason 6 PC to spread to lymph nodes, distally or to cause mortality [39, 40]. Thus, the current thinking is that Gleason 6 itself does not pose a threat to patient but is merely a risk factor for higher-risk disease. The clinical implication is that volume of Gleason 6 should not be used as the sole trigger for intervention but as a trigger for further tests to exclude co-existent higher-risk disease.

How much, if any, Gleason 3 + 4 is allowed initially or at surveillance biopsies for a man considered for AS or on AS? There is no randomized data showing survival benefit for these cancers with immediate curative treatment [31]. There is registry data suggesting that treatment consisting of a radical prostatectomy, delayed until a median of 19 months after diagnosis, did not affect the treatment outcome [41]. There is no "one size fits all" solution. The decision must be based on an individual risk assessment and is highly influenced by a patient's perception of treatment-related harms versus potential disease-related risks. Interestingly, in a recent autopsy study up to 50% of the cancers in unscreened Japanese men over 70 years of age were of Gleason 3 + 4 [42]. This suggests that especially among elderly men, Gleason 3 + 4 PC may pose only a low risk and thus be a potential candidate for AS.

PSA Kinetics Refined

Despite the fact that virtually all AS protocols incorporate PSA kinetics in their follow-up, the results are conflicting. In the PRIAS trial, PSA-DT was the second most common reason to trigger radical prostatectomy. However, in patients with PSA-DT as the sole trigger for treatment (radical prostatectomy), the surgical specimen showed favorable outcome (Gleason 3 + 3 and pT2) in almost half of the patients (46%) suggesting that PSA-DT is not specific enough (almost half the patients would undergo unnecessary treatment) [14]. Also, in the accompanying regression analysis, PSA-DT did not predict adverse pathology on RP specimen. Similarly, a report from an AS cohort from UCSF concluded that PSA-DT did not correlate with biopsy progression [43]. In the Johns Hopkins AS cohort in which treatment change is triggered only by adverse findings in yearly repeat biopsies, PSA-DT could not predict adverse rebiopsy findings while PSA-V was marginally significantly predictive ($p = 0.06$). However, no single,

usable cutoff value could be identified in ROC analysis for either PSA-DT or PSA-V [44]. Finally, Vickers et al. performed a systematic review of the literature and concluded that PSA dynamics is not a reliable trigger for treatment in early-stage PC [45]. Challenge in using PSA kinetics as a trigger in AS lies in the fact that it is not specific but prone to significant variation due to infections, interventions, medications, and other causes as illustrated in Fig. 9.3, which describes PSA fluctuations during follow-up in one selected patient. At diagnosis, this patient had two cores positive for PC (0.8 mm and 0.4 mm cancer foci). He has had three systematic scheduled rebiopsies according to the PRIAS protocol with no cancer found. Six years after the diagnosis, he had a sudden increase in PSA that was explained by recently having been ill with flu, and his PSA soon dropped to its previous level. At that time, he had his first MRI with no sign of clinically significant disease. Subsequently, 10 years after diagnosis, the patient again had a sudden rise of PSA up to almost 30ug/L which was explained by a recent episode of urinary retention. An MRI was repeated and again with no sign of clinically significant disease (Fig. 9.3).

At the conclusion of the "later" PSA era, AS was well accepted as a treatment option for low-risk prostate cancer. Lack of prospective randomized or even long-term cohort data is evident. Several national and organizational guidelines and reviews have been published [33]. In these, reclassification criteria vary remarkably (Table 9.1). Treatment is often recommended if during follow-up men no longer meet the entry criteria. Most of the guidelines recommend serial PSA measurements, DRE, and surveillance biopsies. However, controversy exists over the timing or interval of visits and the cutoffs used to trigger intervention. Generally, the value of PSA kinetics and monitoring Gleason 6 volume have been questioned as tools to trigger treatment.

MRI

Despite repeat surveillance biopsies being recommended in most of the guidelines and protocols [33], the adherence rate is poor. In the largest published AS cohort, the PRIAS trial, we recently showed that while adherence to PSA controls was excellent (91%), adherence to repeat biopsies decreased significantly over time (33% at

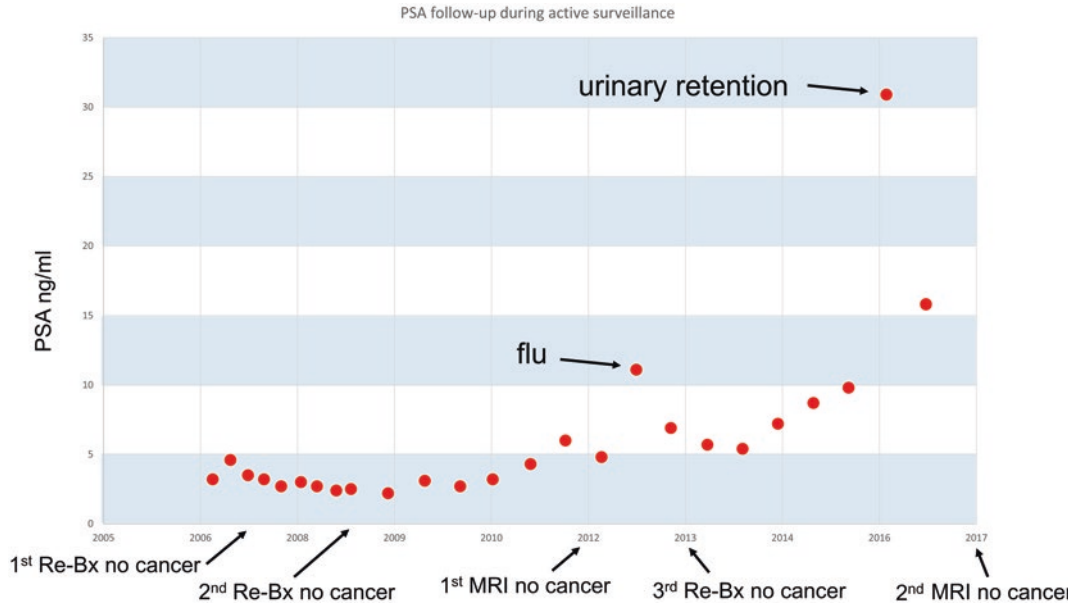


Fig. 9.3 AS patient from PRIAS trial followed for 10 years and demonstrating fluctuation in PSA. This patient had two sudden rises of PSA explained by flu and urinary retention. No PC was detected in three follow-up biopsies or two multiparametric prostate MRIs

10 years) [46]. This is likely to be caused by biopsy-related discomfort and complications [47]. Among the most feared complications are septic infections although pain, hematuria, and hematospermia are also not uncommon [48]. Furthermore, systematic, random, TRUS-guided biopsies initially miss around 30% of clinically significant cancers, while they overdetect clinically insignificant cancers (Fig. 9.2). Due to these systematic biopsy-related drawbacks, MRI has recently received a lot of attention. While the initial reports were not promising [49], the development of multiparametric MRI imaging techniques and structured reporting according to PI-RADS (Prostate Imaging Reporting and Data System) have revolutionized this use of MRI [50]. Recently, a European School of Oncology Task Force recommendation for reporting MRI in men on AS was published [51]. The aim is to standardize reporting and facilitate data collection. Ultimately, the aim is to develop criteria to distinguish true radiological disease progression during surveillance from natural variation.

Currently, the evidence for MRI comes mainly from its use in selecting patients for AS. Very high negative predictive values (NPVs), even up to 100%, have been reported for clinically significant disease [52–54]. In a recent retrospective analysis of 223 men eligible for PRIAS but undergoing immediate radical prostatectomy, the role of MRI in predicting upgrading was evaluated [53]. In a multivariate model, typical clinical variables such as age, stage, PSA, PSA density, and number of positive cores were added in addition to MRI features (PI-RADS score). The PI-RADS score was the only significant predictor, with OR of 2.72 for every unit increase in PI-RADS score. According to a recent systematic review, two-thirds of patients suitable for AS have positive MRI [54]. Positive MRI was more likely associated with upgrading in subsequent RP than negative MRI, while this was not the case for upstaging.

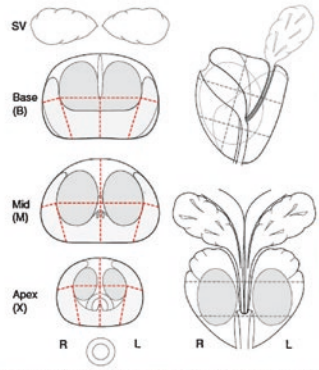
However, literature on the use of MRI as a diagnostic tool in men on AS is scarce. Nor are any MRI triggers for intervention clearly defined. While trying to define these, the following aspects have been highlighted by the PRECISE Recommendations: baseline MRI reporting must include prostate volume on T2-weighted images, the likelihood of clinically significant cancer on a 1–5 scale (either PI-RADS v1 or v2 or Likert scale) and lesion volumes (Fig. 9.4). On subsequent follow-up MRIs, in addition to parameters reported at baseline, a 1–5 scale assessment of likelihood of MRI progression should be reported (Table 9.2).

In a study by Diaz et al., the authors retrospectively looked at a cohort of 58 patients on AS (Epstein criteria) and the role of serial MRI [55]. Medial follow-up was 16.1 months and MRI progression was defined as an increase in suspicion level, largest lesion diameter, or number of lesions. Both systematic and targeted fusion biopsies were taken, and altogether 17 patients (29%) with grade progressions were detected. The authors conclude that stable surveillance MRI was strongly associated with Gleason score stability, and MRI might perhaps be used to avoid some of the surveillance biopsies, thereby reducing biopsy-related harm. However, the question is "where do we settle?" In this cohort, if patients were followed "traditionally" with systematic biopsies only, nine grade progressions would have been missed. If followed by MRI and targeted biopsies only, six grade progressions would have been missed. Therefore, the authors conclude that to maximize detection of grade progressions during surveillance, both systematic and targeted biopsies should be taken.

Felker et al. studied in a retrospective cohort of 49 patients with Gleason 6 PC on AS whether serial MRI examination could predict pathological progression [56]. MRI progression was defined as an increase in index lesion suspicion score or lesion size (doubling) or decrease in index lesion ADC of 150 mm^2 per second or more in surveillance MRI. The mean follow-up time between MRIs was 28.3 months. In one-third of the patients, the index lesion disappeared in the follow-up MRI. Pathological progression occurred in 19 patients (39%) of which systematic biopsies only would have missed nine, and fusion biopsies only would have missed seven. MRI progression added significantly to a regression model including clinical variables (PSA-D and mean cancer core length). The authors

PRECISE Case report form for men having MRI on active surveillance

Reporting radiologist		Date of scan		Date of report	
PSA		PSA date		PSA density	
Prostate volume on T2-weighted imaging		Magnet strength		Coil used	
Likelihood of clinically significant disease (1-5)*		PI-RADS 2 score (maximal)		TNM stage	
Likelihood of extraprostatic extension (T3a) (1-5)*		Likelihood of seminal vesicle invasion (T3b) (1-5)*			



Draw and number each lesion on the diagram, with the most significant lesion being number 1.

Lesion	Appeared since last scan?	Not visible	D1	D2	D3	Volume (D1 x D2 x D3 x 0.52)	Volume by planimetry	Likelihood of clinically significant disease (1-5)*	PI-RADS-2 score
1									
2									
3									

	Sequence where lesion best seen	Volume where lesion best seen	Volume on T2-weighted imaging
Lesion 1			
Lesion 2			
Lesion 3			

*Likert score of 1-5 for likelihood where 1= Very low likelihood; 2= Low likelihood 3 = Intermediate/equivocal; 4 = High likelihood ; 5 = Very high likelihood

	Date of previous MRI	Likelihood of change from previous MRI (1-5 score)	Parameter which has changed eg volume on T2W-I, visibility on DWI, Likert score or PI-RADS score, T3a or T3b disease
Lesion 1			
Lesion2			
Lesion 3			

Fig. 9.4 PRECISE task force recommendation for reporting prostate MRI in men with prostate cancer on active surveillance (From: Moore et al. [51]. Reprinted with permission from Elsevier)

conclude that stable follow-up MRI is associated with a low risk of grade progression in the setting of low PSA-D and low volume PC.

Finally, in a paper by Vos et al., the role of serial MRI in AS was studied in a cohort of 23 patients with systematic biopsies only [57]. Median follow-up time was 24.8 months and disease progression was detected in 11 (48%) and only systematic biopsies were taken. They reported sensitivity of 100% to detect disease progression but specificity of only 30%.

To conclude, current evidence for MRI mainly supports a role for as a "gate keeper," i.e., to filter higher-risk patients out of AS initially. Only a few methodologically compromised (retrospective, varying initial risk, varying definitions for progression, limited number of patients, short follow-up, non-randomized) studies evaluate the role of MRI during surveillance, and no precise recommendations for the use of MRI as a follow-up tool can be given at the moment.

Biomarkers and Genetics

Some urine-based biomarkers, mainly prostate cancer antigen 3 (PCA3) and TMPRSS2-ERG fusions, have been studied in AS. Despite promising associations to high-grade disease in the univariate setting, the results have been mostly negative in multivariate setting when commonly used clinical variables are added to the equation [58, 59] with one exception [60]. However, no data exist on these biomarkers for monitoring the disease during surveillance.

Genetic tests have also shown independent prognostic information in localized prostate cancer, and the Prolaris (Myriad Genetics Inc., Salt Lake City, Utah) and Oncotype DX (Genomic Health Inc., Redwood City, CA) assays have been approved by the FDA [61, 62]. Again, however, no data exist on serial use of these assays to monitor PC during AS. A recent study by Wei et al. looked at the intratumoral and of intertumoral genetic heterogeneity in RP specimen and its impact on the

Table 9.2 PRECISE task force recommendation for assessment of likelihood of radiologic progression in men with prostate cancer on active surveillance

Likert	Assessment of likelihood of radiologic progression	Example
1	Resolution of previous features suspicious on MRI	Previously enhancing area no longer enhances
2	Reduction in volume and/or conspicuity of previous features suspicious on MRI	Reduction in size of previously seen lesion that remains suspicious for clinically significant disease
3	Stable MRI appearance: No new focal/diffuse lesions	Either no suspicious features or all lesions stable in size and appearance
4	Significant increase in size and/or conspicuity of features suspicious for prostate cancer	Lesion becomes visible on diffusion-weighted imaging; significant increase in size of previously seen lesion
5	Definitive radiologic stage progression	Appearance of extracapsular extension, seminal vesicle involvement, lymph node involvement, or bone metastasis

From Moore et al. [51]. Reprinted with permission from Elsevier
MRI magnetic resonance imaging

above genetic assays [63]. They found considerable genetic heterogeneity among different tumor foci and between RNA- and DNA- based platforms and conclude that data generated from one single biopsy sample is not enough to guide treatment decisions. Interestingly, however, the variation in the genomic scores was lowest for the patient with the lowest Gleason grade (Gleason 3 + 4 in biopsy and RP specimen versus 4 + 3 or higher in the others).

Future

The success of AS relies on proper surveillance of the disease to trigger treatment when needed and in a timely fashion. However, in practice, there is evidence that this is not optimally executed. In particular, the adherence to follow-up biopsies is poor [46, 64]. The use of MRI will likely increase the adherence to follow-up protocols by reducing the number of biopsy sessions and biopsies per session if proven safe and feasible in prospective trials such as SPCG-17 and registry initiatives such as GAP3. Currently, genetic tests are being incorporated into prospective trials to evaluate their role as triggers for intervention during surveillance.

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MR Imaging in Prostate Tumor Volume Assessment: How Accurate?

10

Ivo G. Schoots and Theo H. van der Kwast

Introduction

Active surveillance focuses on the prevention of overtreatment by selecting patients with established features of low-risk prostate cancer [1]. Almost all eligibility criteria for active surveillance refer to a strict pathological definition of insignificant prostate cancer. The current histopathological definition of insignificant prostate cancer uses the pathological Epstein criteria, which include a prostate cancer volume of <0.5 cc, a Gleason score ≤6, no evidence of grade 4 cancer, and pathological stage pT2 [2].

The translation, in clinical terms, of this histopathological definition of insignificant prostate cancer has proven to be challenging, owing to inherent inaccuracies of biopsy diagnoses. Clinical and biopsy criteria for insignificant prostate cancer vary among various active surveillance programs, and they may include PSA level, clinical stage, Gleason score, number of positive cores, and extent of prostate cancer involvement of the biopsy [3]. For example, clinical Epstein criteria for insignificant prostate cancer are serum PSA <10 ng/ml, Gleason score ≤6, <3 positive cores, and/or a maximum of 50% of cancer per core. The latter two parameters are an indirect measure of tumor volume [4].

Most experts would now agree that Gleason score and pathological stage are the strongest determinants of the biological behavior of a prostate cancer [5]. Using the ERSPC dataset of the Rotterdam screening center, Wolters and colleagues reasoned that tumor volume correlates poorly with Gleason score (Fig. 10.1) and questioned the independent prognostic value of prostate cancer volume [7]. They argued that this 0.5 cc threshold for insignificant prostate cancer could be relaxed to a threshold of 1.3 cc for the tumor volume of the index or dominant tumor or 2.5 cc for the total tumor volume of a prostate-confined (pT2) Gleason score ≤6 prostate tumor.

The use of any definition of pathologically insignificant prostate cancer requires the examination of the entire prostate, ex vivo, since no accurate tumor volume measurement is available at this time point. In vivo, current MR imaging tools may provide an assessment of prostate cancer volume of "visible" tumors, characterized as Gleason 6 by standard and targeted biopsy findings. Tumor volume estimation of visible tumors is relevant not only to the

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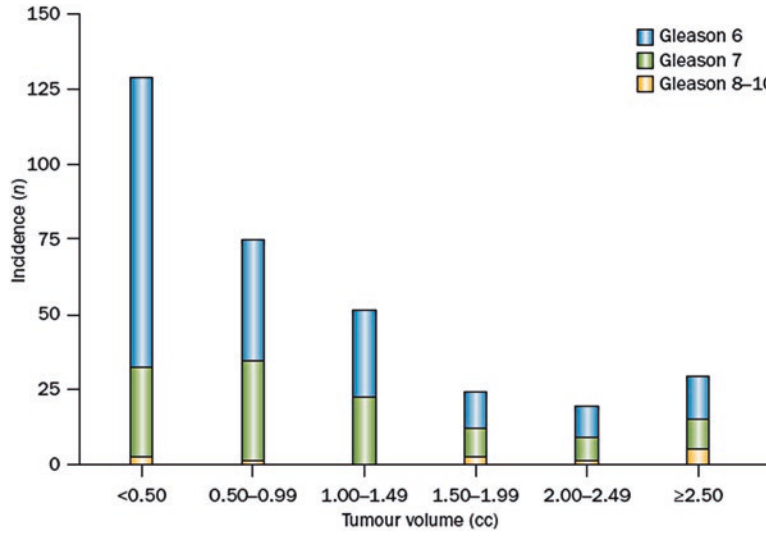

Fig. 10.1 Relationship between prostate cancer volume and Gleason score (ERSPC-Rotterdam data). The columns show the number of cases (*n*) visualizing the percentage of Gleason score 6, 7, and 8–10 for each total volume category. The different colors represent the Gleason scores (From Van der Kwast and Roobol [6])

eligibility of men for active surveillance but also for monitoring patients on active surveillance and detecting progression. Strictly monitoring these clinical and pathological characteristics over time would identify risk reclassification that would justify radical treatment [8]. If accurate assessment can be obtained by MRI, eligibility criteria could be adjusted and tumor conspicuity and tumor volume monitoring could reduce surveillance biopsies.

An unmet need is to accurately and robustly assess tumor volume in prostate cancer. In this review, we investigated the current literature focusing on the relationships between MRI volume measurements and the underlying composition of normal and malignant prostate tissue, to determine if the integration of diagnostic MR imaging would improve target delineation and volume assessment for men with prostate cancer on active surveillance.

PI-RADS Version 2 Recommendations for MRI Tumor Volume Estimation

The PI-RADS (Prostate Imaging-Reporting and Data System) standardized image acquisition and reporting is designed to be used by medical professionals in the initial evaluation of patients to assess the risk of clinically significant prostate cancer leading to biopsy and treatment [9]. The longest axis tumor diameter was more strictly introduced in the PI-RADS version 2 [10], with the cutoff of 15 mm between scores 4 and 5 on T2-weighted images. Although this PI-RADS scoring system was not designed for tumor volume assessment, some minimal requirements on tumor volume estimation were introduced, reporting the largest dimension of a suspicious finding on an axial image. If the largest dimension of a suspicious finding is on sagittal and/or coronal images, this measurement and imaging plane should also be reported. If a lesion is not clearly delineated on an axial image, the measurement on the image which best depicts the finding should be reported. If preferred, lesion volume may be determined using appropriate software, or three dimensions of lesions may be measured so that lesion volume may be calculated (max. a-p diameter × max. l-r diameter × max. c-c diameter × 0.52).

Peripheral zone lesions should be measured on apparent diffusion coefficient (ADC), reconstructed from diffusion-weighted MR images. Transition zone lesions should be measured on T2-weighted images. If lesion measurement is difficult or compromised on ADC (for peripheral

zone) or on T2-weighted images (for transition zone), measurement should be made on the sequence that shows the lesion best.

Recently, the size threshold for the highest level of suspicion (score 5) in the PI-RADS version 2 was proposed to be reduced from ≥15 mm to ≥10 mm [11], corresponding the 0.5 cc for significant prostate cancer addressed by Wolters and colleagues. However, a clear size or volume threshold on MRI remains difficult to define to discriminate significant from insignificant prostate cancer in low-grade disease. Visibility on MRI (instead of actual tumor volume) could be of additional value in discriminating significant from insignificant prostate cancer.

PRECISE Recommendations for MRI Tumor Volume Estimation

Tumor volume estimation becomes more important if MRI is used in monitoring patients on active surveillance. In particular, stable disease on clinical parameters and MRI may defer or avoid systematic prostate cancer biopsies. In an international consensus meeting, recommendations have been developed to collect data in men having MRI on active surveillance (PRECISE criteria—Prostate Cancer Radiological Estimation of Change in Sequential Evaluation) [12]. Besides data on MRI suspicion score (Likert or PI-RADS v2) and the likelihood of progression being present, the absolute size of a lesion at baseline and follow-up should be reported, addressing the importance of MRI tumor volume assessment. However, to identify tumor progression on MRI, MRI tumor volume estimation should be robust. Today, no clear recommendations on MRI tumor volume assessment are present.

Index Lesion

It is suggested that all metastatic sites in a single patient may derive from a single monoclonal precursor cell [13], indicating that a single tumor focus is responsible for tumor progression and death, despite the multifocality of prostate cancer. This focus has been labeled the index lesion and has been considered to be defined by the largest tumor focus [14–16].

Increasing data supports the validity of the index lesion as the driver of prognosis and any adverse oncologic outcome and therefore necessitates consistently localizing the index lesion in each patient. MR imaging may offer a more robust evaluation of the entire prostate that can facilitate index lesion localization.

Index lesion identification by MRI has been proven to be well associated with the largest tumor focus in histopathology analysis, with correct identification and localization of 94–98% by MRI [17, 18]. Clearly, these high percentages of correct index lesion identification may be dependent on tumor size and Gleason grade.

Intuitively, one might think that tumors grow expansively in all directions (rounded volume); however, in reality, prostate cancer may spread/diffuse through the tissue or along the prostatic border. This may hamper the volume estimation by maximum diameter measurements on imaging. Planimetric volume measurements (delineation of the tumor at each axial slide) would be most accurate; it will take significantly more time during reporting in radiological practice, and sufficient software should be available. Furthermore, for lesions best seen on DWI/ADC image sequences, a single diameter may be more reproducible than a volume because of the need to use larger voxel sizes in sequence acquisitions.

If volume on MRI could be estimated from an ellipsoid or oval tumor, the axial diameter of a 0.5 cc, 1.3 cc, and 2.5 cc tumor would be approximately ~10 mm, ~14 mm, and ~17 mm, respectively. Robustness of MRI measurements is crucial for MRI tumor volume estimation.

Prognostic Value of Tumor Volume Assessment in Radical Prostatectomies

The clinical significance of prostate cancer tumor volume in radical prostatectomy specimens is controversial [19, 20]. In univariable analysis, prostate

tumor volume is of prognostic significance, but most studies report that its prognostic significance is lost in multivariable analysis [21–25]. This may be attributed to the close correlation of tumor volume with Gleason score, T-stage, and surgical margin status of radical prostatectomy specimens. Due to the lack of independent prognostic significance, most pathologists choose not to report routinely an exact measure of tumor volume [26]. Despite this controversial issue and difficulties in accurately measuring tumor volume, pathologists agreed that some form of semiquantitative measurement of tumor volume should be reported, although no consensus was reached regarding method(s) [5].

Tumor Volume Assessment in Radical Prostatectomies

Although there are many methods available to calculate prostate tumor volume, obviously, computer-assisted image analysis systems (planimetrically) are considered the most accurate means of determining tumor volume [27]. Due to the high labor intensity, these planimetric methods are not commonly used in routine pathology practice. Alternative methods for the estimation of tumor dimensions of tumor volume (or size) rely on calculation of basic tumor dimensions [28–31]. In routine pathology laboratories, the ellipsoid formula (0.52 × length × width × height) (Fig. 10.2) may provide a close estimate of the tumor volume [31], as compared to planimetrically determined tumor volume by computer image analysis, with sensitivity and specificity of, respectively, 94% and 92% for tumor volume >0.5 cc. However, others showed the ellipsoidal method may overestimate tumor volume by approximately 30% [28, 29] and would use the formula 0.4 × length × width × height. This ellipsoid measurement is simple and reproducible and is considered appropriate for pathological tumor measurements. Nevertheless, it is not routinely applied, except in a research setting. Most clinicians do not use the measurement of cancer volume by this technique in clinical decision making, and it is not currently recommended.

MRI Signal Intensities and the Underlying Tissue Composition in Radical Prostatectomies

Relationships between MRI signal intensities and the underlying architectural prostatic tissue are complex. Langer and colleagues showed the association between specific alterations in tissue composition and MR imaging measurements [32]. They have shown that the increased per-

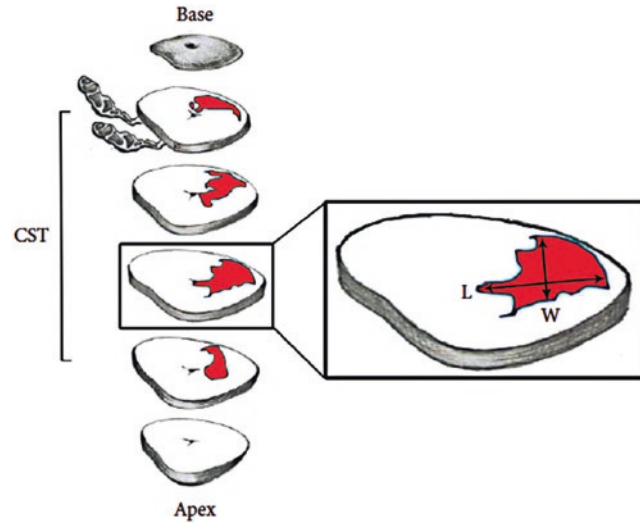

Fig. 10.2 Illustration of measurements obtained on pathological dissection. *CST* cross-sectional thickness, *L* length, *W* width (Reprinted from Perera and colleagues [31], with permission from John Wiley & Sons)

centage area of nuclei and cytoplasm, in combination with the decreased percentage area of luminal space, within equal stroma, corresponds to a decrease in T2-weighted and ADC signal intensities (Figs. 10.3 and 10.4). Furthermore, these morphological changes also correspond to the increase of the DCE-MRI volume transfer constant [K^{trans}] and decrease to the DCE-MRI extravascular extracellular volume fraction [v_e] (Figs. 10.3 and 10.4).

They also determined that the number of cellular components is significantly different between malignant and benign peripheral zone tissue, and thus these mechanisms influence prostate cancer detection with MR imaging. T2-weighted imaging is sensitive to extracellular water; ADC is sensitive to diffusion in the lumen; thus increased cellular texture corresponds to decrease in T2-weighted and ADC signal intensities. Because DCE-MRI-derived parameters are expected to be related to properties of the vasculature (rather than cellular composition), changes in cellular components occur in abnormalities associated with vascular density. Figure 10.4 shows graphically the signal intensity decays and increases of T2w, ADC, K^{trans}, and v_e, based on their published mean slopes for MRI measurements versus proportion of cellular components. Other groups have also shown this correlation between ADC and cellular density [34, 35] and between contrast MR imaging parameters and microvessel density [36] on radical prostatectomy specimen.

MRI-derived parameters are reflective of pathologically determined characteristics of prostate cancer; however, there is great overlap with benign conditions, such as benign prostate hyperplasia, inflammation, or fibrosis. For example, nucleomegaly and increased cellular density, in addition to indicating prostate can-

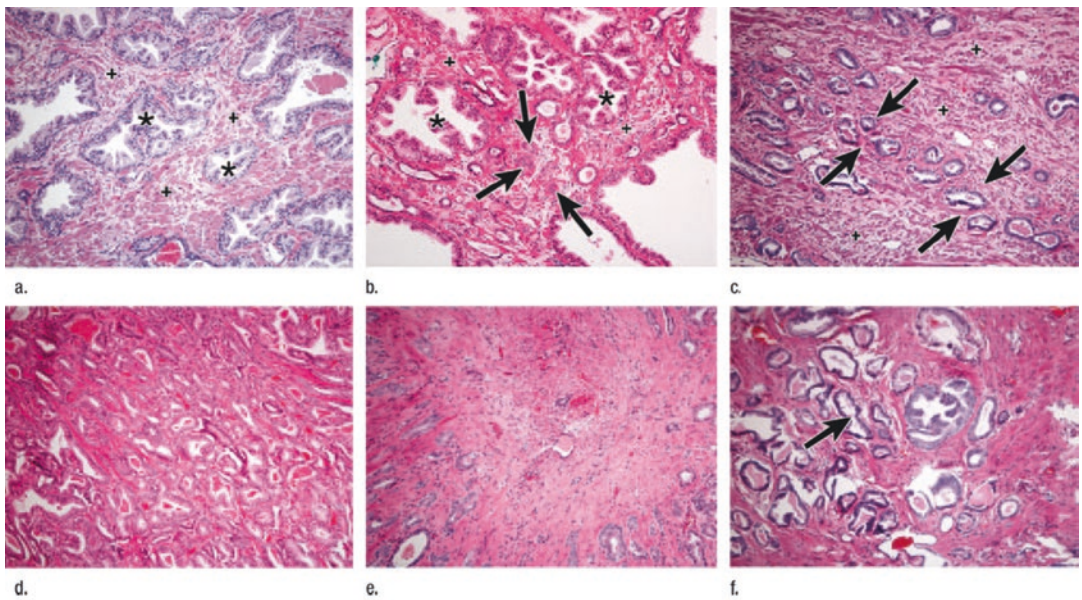

Fig. 10.3 Histologic samples from normal and malignant regions. Loose stromata are indicated with +; benign glands, with *; and malignant glands, with arrows. (**a**) Normal PZ tissue is characterized by a mixture of loose stroma and benign glands. Sparse regions in tumors consist of normal PZ tissue infiltrated by scattered malignant glands. (**b**) Malignant glands are intermixed with benign glands and loose stroma, and (**c**) a line of malignant glands traverses through otherwise normal loose stroma. (**d**–**f**) In contrast, dense regions in tumors consist of (**d**) a high proportion of malignant glands, (**e**) malignant glands mixed with desmoplastic stromata, or (**f**) dense smooth muscle tissue, uncharacteristic of normal PZ tissue and visible as solid staining. (Hematoxylin-eosin stain; magnification, ×100) (From: Langer et al. [33]. Reprinted with permission from the Radiological Society of North America (RSNA®))

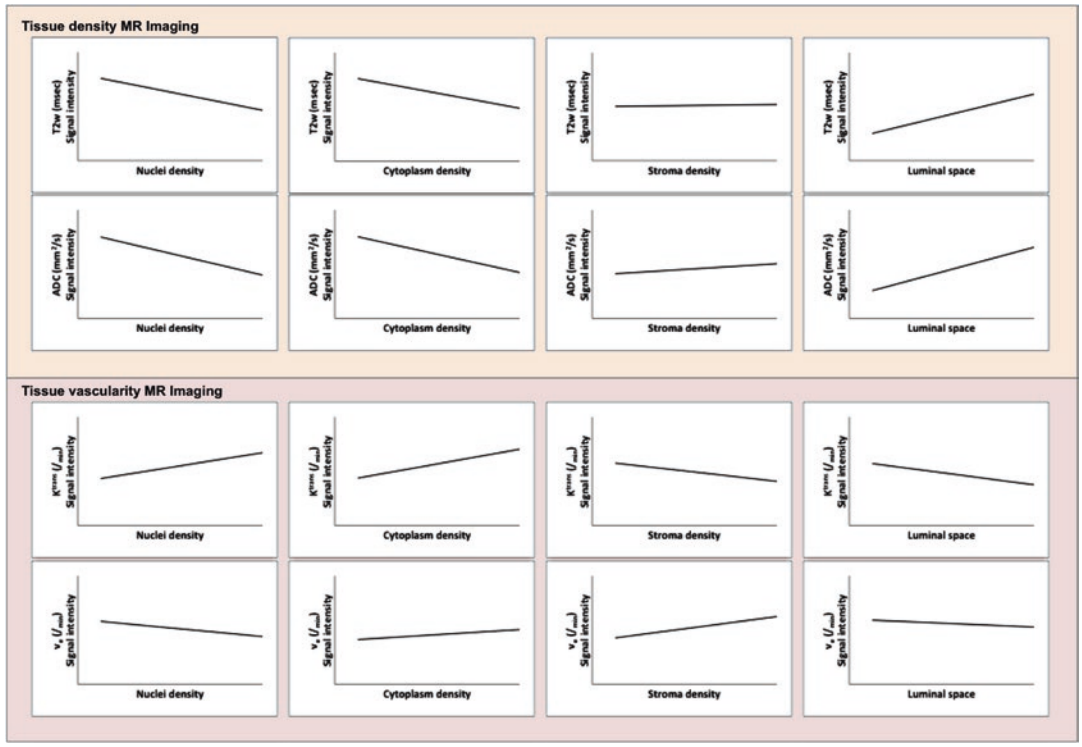

Fig. 10.4 Graphs illustrate mean slopes for MRI signal intensities versus proportion of cellular component (nuclei, cytoplasm, stroma, and luminal space) (Data from Langer and colleagues [32]; see Table 3)

cer, can also be indicative of inflammation and prostatic intraepithelial neoplasia. Luminal size can be altered in cystically dilated glands, regions of atrophy, or fibrosis. These benign abnormalities have been implicated as sources of false-positive MR imaging findings [37–40] or poor radiologic-pathologic volumetric correspondence [41].

In all such studies, MRI measurements have been determined unblinded to pathology results of prostatectomy specimen. Furthermore, in these studies, the impact on tumor detection was not investigated. In clinical practice, this detailed knowledge of tumor distribution obtained from prostatectomy specimen is of course not at hand at the time of prospective patient management. Therefore, it is the relationship between tumor detection and histopathological features that is of clinical relevance.

Visible Tumor Detection on MRI in Radical Prostatectomies

Definitely, tumor size and tumor aggressiveness may have serious impact on tumor detection on MRI. Vargas and colleagues found that the integrated PI-RADS v2 scores resulted in the correct classification of 94% (118/125) peripheral zone tumors and 95% (42/44) transition zone tumors with ≥0.5 cc on pathology with any Gleason grading [42]. This correct classification was limited for the assessment of small tumor volumes of ≤0.5 cc with Gleason ≥4 + 3. The majority of GS ≥4 + 3 tumors with volumes <0.5 cc on pathology were not detectable on MRI; MRI was only able to identify 26% (7/27) peripheral zone tumors and 20% (2/10) transition zone tumors (suspicion scores 4 and 5, PI-RADS v2). This is

not surprising: previously this group showed that lesion detectability on MRI was volume dependent and Gleason grade dependent [43]. Nonetheless, this is important to consider the limited ability of MRI to detect small lesions. This was a retrospective analysis biased by the inherent limitations of such a study design. Most likely, without the knowledge of the presence of prostate cancer, prospective studies may show even worse outcomes for MRI lesion detection of <0.5 cc. These findings have implications for the use of MR imaging in the management of patients with clinically low-risk prostate cancer, who now constitute about one-half of all patients diagnosed with prostate cancer in the Western world [44].

Bratan and colleagues found similar results [45]. They explored the tumor detection rates of peripheral and transition zone tumors on MRI as a function of histological parameters. MRI detection rates were 57–63% and 36–41% for all peripheral zone tumors and transition zone tumors, respectively, with small interobserver variation between two readers. They found an increased tumor detection rate on MRI, related to increased histology tumor volume: MRI tumor detection rates of 28%, 38%, 76%, and 96% corresponded to <0.05 cc, 0.05–0.5 cc, 0.5–2.0 cc, and >2.0 cc on planimetry histology analysis. Although the ellipsoid tumor volumes 0.05 cc, 0.5 cc, and 2.0 cc may correspond to an axial diameter on MRI of approximately 5 mm, 10 mm, and 16 mm, most likely these diameters would not always be measured on MRI, as underestimation is known when the tumor phenotype is not represented by dense tissue. Interestingly, this group also investigated the MRI tumor detection rate in relation to histological architecture. Increased MRI tumor detection rates of 35%, 40%, 62%, and 66% corresponded to lobulated, infiltrative, mixed, and dense tissue on histology analysis. Furthermore, increased MRI tumor detection rates of 38%, 76%, and 96% corresponded to increased Gleason scores 6, 7, and 8–9. From these data, we may conclude that prostate cancer location, histological volume, Gleason score, and histological architecture were independent significant predictors of tumor detection on multiparametric MRI.

Non-visible Tumor on MRI in Radical Prostatectomies

In some patients, MRI is not able to visualize an index tumor. In some studies, these tumors proved to be microscopic at histopathology with volumes almost all below the 0.2 cc [17, 46]; however, in other studies, these tumors proved to be larger than 0.2 cc [42, 45, 47]. Although patients with small tumors may be better candidates for active surveillance, irrespective of low-risk or intermediate-risk disease, non-visible tumors are not always small tumors.

Langer and colleagues showed that no significant differences in ADC or quantitative T2-weighted values were present between the surrounding normal peripheral zone tissue and the "sparse" prostate tumors, which contain a high percentage of normal peripheral zone tissue, intermixed with prostate cancer [33]. The presence of regions within prostate tumors that are intrinsically invisible by using T2-weighted and ADC-based tissue contrast may limit accurate determination of tumor volume and target definition for active surveillance but also for MRI-driven targeted biopsies or focal therapy.

Some histological characteristics are predisposed to be more visible by MRI. Rosenkrantz and colleagues described the presence of "solid tumor growth" as a key contributor to tumor detection on MRI that was present in only 58% of their investigated tumors [48]. Although there was a significant difference between the detected and missed tumors on MRI for all assessed histological features (i.e., loose stroma, desmoplastic stroma, solid tumor growth), only size, Gleason score, and the presence of solid tumor growth were independent predictors for MRI visibility on multivariate analysis. Solid tumor growth had a substantially high odds ratio (17.83) after accounting for the effects of other features, supporting the particular importance of the formation of a discrete nodule of continuous tumor growth to facilitate MRI detection. They hypoth-

esized that the inability to visualize a known tumor on MRI may indicate the absence of a distinct nodule of packed malignant glands encompassed by the tumor. In addition, desmoplastic tumor-associated stroma was present in all detected tumors, supporting the important role of stromal as well as epithelial components in tumor detection by MRI [48].

Radiologic-Pathologic Volumetric Correspondence in Radical Prostatectomies

Although MRI has the big advantage of in vivo tumor volume estimation and could therefore be valuable in diagnosis, in monitoring, and in treatment decision-making, critical analysis of the literature shows still some big hurdles to overcome.

High Range of Disagreement in Tumor Volume Estimation

Baco and colleagues indicated that the limit of agreement between MRI and histopathology tumor volume estimation of all prostate cancer lesions ranged from 147 to +135% (Fig. 10.5), which indicates clinically significant inaccuracy for MRI tumor volume estimation in clinical practice, as well as in overestimation and in underestimation [46]. Although there was a positive correlation between estimated MRI and histopathology tumor volume ($r = 0.663$, $p < 0.001$) in 135 radical prostatectomy specimens, this should be cautiously interpreted within the clinical context of high range of disagreement. These results were similar to previous results published by Turkbey in also 135 radical prostatectomies [17], Matsugasumi in 81 [49], and Mahazeri in 42 radical prostatectomies [50].

MRI Tumor Volume Underestimation in Small and Large Tumors

Le Nobin and colleagues reported significant underestimation in advanced 3 Tesla imaging and co-registration software, not only in small tumors (<1 cc) (range,133% to +85% based on T2w images) but also in large tumors (>1 cc) (range,122% to +24%) [51]. Tumor volume estimation by MRI was also underestimated in lesions with an MRI suspicion score of 4 or 5 (mean difference,45%; range, 97% to +7%) more than in lesions with suspicion score of 2 or 3 (mean difference, +2%; range, 107% to +111%). Tumor volume estimation by MRI was even underestimated in lesions with a Gleason score 7 and higher (mean difference, 39%; range, 104% to +26%), than in lesions with a Gleason score 6 (mean difference, 5%; range, 96% to +87%).

Others have also shown an overall but wide variety of underestimation of MRI and histopathology tumor volume estimation, with a large range from overestimation to underestimations between those two measurements [17, 46, 47, 52]. Overestimation could be explained by inaccuracies of imaging as well as shrinkage of the histopathological specimen due to fixation and mounting. Applying shrinkage correction (15%), however, had very little impact on the overall tumor volume agreement due to the very large standard deviations [17, 52].

The overall underestimation of tumor volume on MRI may relate to the findings of Langer and colleagues [33], which observed that prostate tumors contain regions of "sparse" malignant epithelium intermixed with mostly benign glands and stroma. These "sparse" regions were characterized as inherently invisible on MRI and posing limits on the ability to estimate full tumor volume with MRI.

MRI Tumor Volume Underestimation in High MRI Suspicion Scores and High Gleason Grading

This degree of underestimation was even more pronounced for tumors with a higher Gleason score and higher MRI suspicion score` [51]. Indeed, based on extensive previous literature showing associations between both ADC value and MRI detection with higher Gleason score, MRI would have been expected to be more reliable in estimating tumor volume for more aggres-

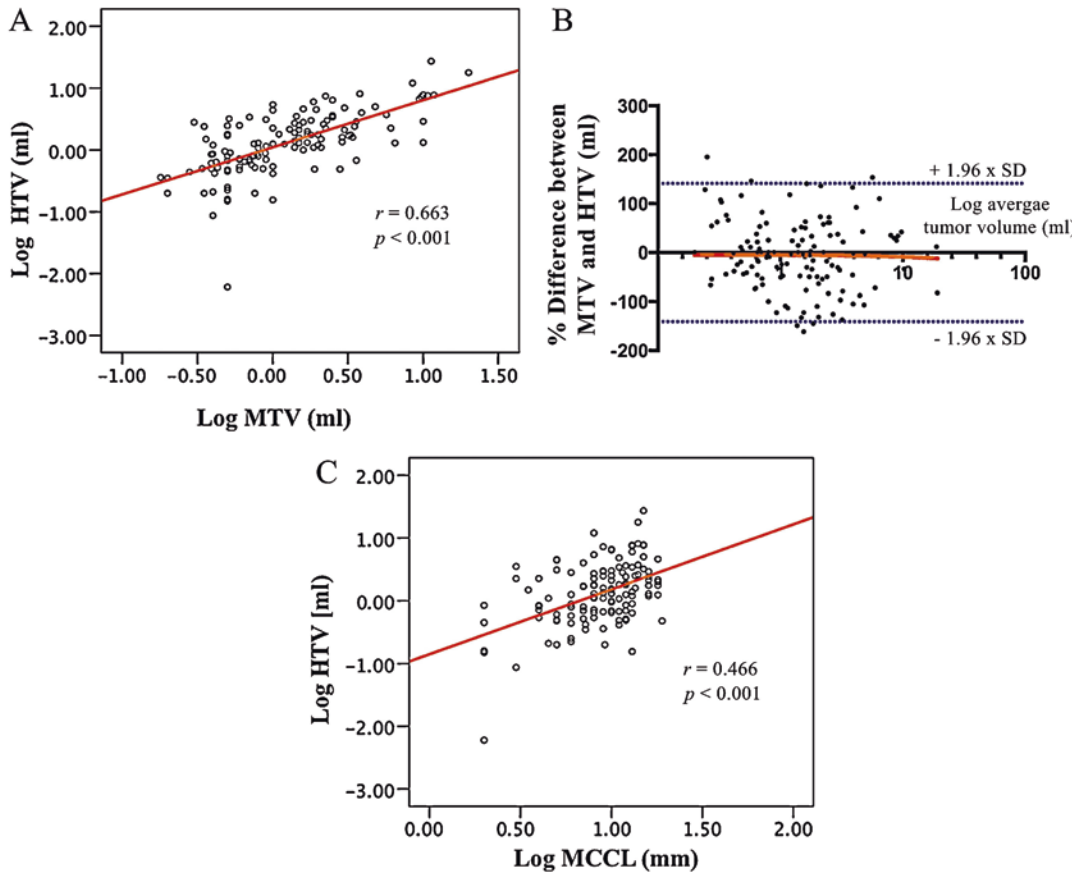

Fig. 10.5 (**a**) Scatter plot showing correlation between MRI-estimated tumor volume (MTV) and histological tumor volume (HTV) in 128 patients. The red line indicates the regression line. Data are presented on a logarithmic scale because of asymmetry. (**b**) Bland-Altman plot showing the limitation of agreement between MTV and HTV. The orange line represents the linear regression line. The percentage difference between MTV and HTV is plotted against the average tumor volume (calculated from both MTV and HTV). All values above the zero line represent overestimation of MTV, and all values below the zero line represent underestimation of MTV. The average underestimation of HTV by MRI is 5.9% (95% CI [S6.4% +18.2%]) and is constant throughout the measurement range. The limit of agreement ranges from S147 to +135%, which indicates clinically significant inaccuracy for MTV. The median (range) is 1.0 ml (0.1–20.0 ml) for MTV and 1.25 ml (0.1–27.1 ml) for HTV. (**c**) Scatter plot demonstrating correlation between the maximum cancer core length on targeted biopsy and HTV in 128 patients. The red line indicates the regression line (Reprinted from Baco and colleagues [46], with permission from Elsevier)

sive tumors. These findings, however, were based on studies focusing on the detection of prostate cancer, rather than the determination of tumor volume estimation. Others have also shown poor correlation and agreement of MRI tumor volume estimation of the higher Gleason grades with pathology tumor volume measurements [17, 52].

It could be possible that increased detection of lesions with higher Gleason score does not directly translate to improved accurate volume estimation by MRI. The radiologist's attention is mostly directed to the clear dark areas on the ADC map with low quantitative values, when estimating lesion volume of the detected tumor. This tumor volume estimation based on ADC values is also recommended by the PI-RADS version 2 guidelines for peripheral zone tumors [9]. However, this estimation may not include the more nonsolid surrounding tissue, which is most likely the more lower-grade regions on histopathology analysis, which would be less conspicuous on imaging.

Le Nobin and colleagues also speculated that lower-grade lesions, having a smaller component of solid tumor growth, will not have such a conspicuous intra-tumoral abnormality on the ADC map, leading to placement of a broader region of interest in the region of the tumor and resulting in larger volume estimates [51]. In this study, the degree of underestimation of MRI tumor volumes was more pronounced using the ADC map than using T2-weighted imaging, on which small changes in tissue could better be notified. These findings support this concept.

MRI Tumor Volume Underestimation Independent of MRI Sequence

Data on MRI tumor volume underestimation were not improved by the use of MR spectroscopy [17]. Dynamic contrast-enhanced MRI alone appeared to be inadequate for predicting histologic tumor volume [47, 53, 54]. Furthermore, Cornud and colleagues showed that no individual MRI sequence (T2w, ADC, or DCE-MRI) could accurately predict actual tumor volume [47]. In these series of 99 radical prostatectomies, again significant overestimation and underestimation rates were present. Underestimation of tumor volume occurred especially in small tumor foci (<0.5 cc). Hence, they concluded that a small tumor focus with an estimated volume of less than 0.5 cc on T2-weighted imaging should not be considered clinically insignificant. In addition to these results, adding DWI to T2-weighted imaging significantly improved the accuracy of prostate peripheral zone tumor volume measurement [50, 54]. Although the correlation coefficient improved from 0.36 to 0.60 [50], still this number presents a relatively poor positive correlation, similar to earlier mentioned results [17, 46].

Volume Estimation by MRI and MRI-Targeted Biopsies

In all previously mentioned studies, the MRI measurements of tumor volume have been determined unblinded to pathology results of prostatectomy specimen, introducing bias. In clinical practice, this detailed knowledge of tumor distribution obtained from prostatectomy specimen is of course not at hand at the time of prospective patient management. Therefore, it is the relationship between tumor detection and histopathological features within prospective patient management that is of clinical relevance.

Studies that explore the utility of defining a volume surrounding the MRI-based lesion, which could be covered by targeted biopsies of (1) the targeted lesion and (2) the surrounding tissue, are not yet available. Limited evidence is available on MRI tumor volume measurements in combination with MRI-targeted biopsies. Although we may speculate that in these studies some of the surrounding tissue has been biopsied with the 17 mm core samples, the data is inconclusive.

Baco and colleagues indicated that maximum cancer core length on targeted biopsies predicted less accurate true tumor volume on histology compared to MRI [46]. Targeted biopsies guided by elastic MR-TRUS image fusion could reliably predict the location and the primary Gleason pattern of an index tumor with 90% or greater accuracy but had limited ability to predict cancer volume, as confirmed by correlation with step-sectioned radical prostatectomy specimens.

Matsugasumi and colleagues introduced a more accurate estimation formula to predict tumor volume with vertical stretching of the MRI-estimated anterior-posterior dimension of the original MRI, in which the predictability of cancer volume significantly improved, especially for cancer volumes less than 2 cc in which the anterior-posterior diameter of the lesion likely corresponded with MR/US fusion-targeted biopsy core length (less than 17 mm) [49].

Okoro and colleagues investigated the correlation between MRI tumor volume estimation and cancer core length in MRI-targeted biopsies in men on active surveillance [55], however, without confirmation with step-sectioned radical prostatectomy specimens. Cancer core length on MRI-targeted biopsies was positively correlated with index lesion tumor volume on MRI in men on active surveillance ($R^2 = 0.31$), whereas there was no correlation seen with TRUS-guided biopsies ($R^2 = 0.00006$). Although using MRI-targeted

biopsy-derived tumor volumes may better reflect overall disease burden and may improve risk stratification among candidates for active surveillance, the positive correlation (R^2 = 0.31) was very poor.

Incorporation of accurate data for targeted biopsy-proven maximum cancer core length of the targeted lesion and surrounding tissue may facilitate prediction of histologic tumor volume or tumor diameter. Ongoing advances in precise localization of biopsy trajectories in the 3D space of the prostate will facilitate mapping of biopsy-proven cancer.

Prognostic Significance of MRI Tumor Volume Measurement in Active Surveillance

While many studies demonstrate histological differences between MRI-detected and MRI-undetected tumors as discussed in this review, a clear limitation is the absence of known clinical or prognostic significance for many of the investigated histological and MRI features. A recent systematic review on men who had radical prostatectomy despite suitability for active surveillance on TRUS-guided biopsy findings (Gleason 3 + 3 alone) showed some prognostic value of visible MRI lesions. Men with a positive preoperative MRI (visible MRI lesions with suspicion score ≥3) showed cancer upgrading in 43% (291/677) to Gleason 3 + 4 or higher by prostatectomy analysis, while men with a negative MRI had a significantly lower but still an upgrade rate of 27% (78/293) [56], showing both the strengths and limitations of MRI in monitoring men in active surveillance.

Preliminary results suggest a negative MRI is a predictor of excellent prognosis during active surveillance [57]. Small index lesions on MRI may correspond to benign lesions or indolent cancers based on grade and size [58]. If this is confirmed, an MRI with negative findings or small index tumor may allow a reduction in the need for surveillance biopsies. In addition, changes in size or conspicuity or appearance of new MRI lesion(s) may predict upgrading and trigger biopsy.

Including MRI in multivariable risk-prediction models could help in identifying men on active surveillance at risk of high-grade prostate cancer. Models to predict upgrading at repeat biopsy, using a combined approach of clinical parameters together with standard and MRI-targeted biopsies, have been published in men on active surveillance having confirmatory biopsies [59, 60]. In men on active surveillance, independent MR imaging-related risk predictors of upgrading have shown to be ADC values below 1000 mm^2/s and an MRI lesion suspicion score of 5 [61–65]. Whether the histological feature "solid tumor growth" in the study of Rosenkrantz and colleagues, as the most predictive of tumor detection on MRI [48], will be of prognostic significance is not known, and further studies are needed to evaluate the relationship between this feature, tumor progression, and clinical outcomes.

Future Perspectives

Based on the good clinical outcomes, some guidelines on active surveillance include patients with small tumor volume of intermediate risk (Gleason 7, mainly 3 + 4) (NICE [66], CCO [67]) or even patients with high risk (Gleason >7) (AUA [68]), based on the TRUS-guided biopsy findings. Reliable tumor volume estimation, whether it is by MRI and by targeted biopsies or still by standard systematic biopsies, will be more critical in these patient groups of intermediate risk and high risk.

Furthermore, there is emerging evidence that particular sub-patterns within a Gleason grade, such as cribriform architecture, may be relevant to patient outcome (Fig. 10.6) [70–73]. In Gleason grade 3 tumors (ISUP grade 1), the glands are usually small and infiltrative, but the degree of intervening stroma can vary widely, giving either a sparse or more densely packed tumor. Within Gleason grade 4, there is marked heterogeneity with respect to the tumor architecture. Gleason grade 4 now encompasses various sub-patterns, including large dilated

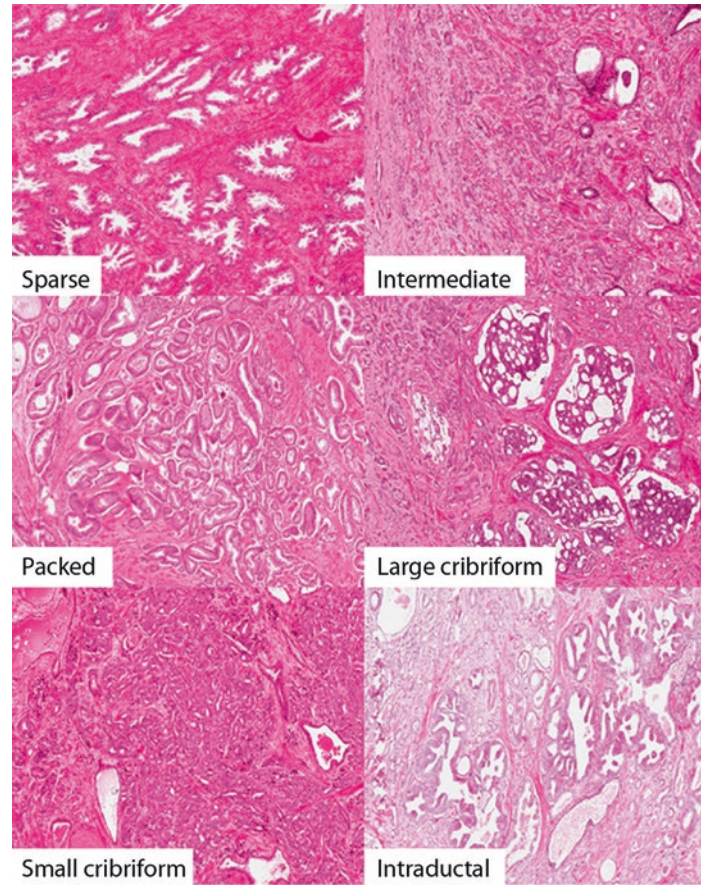

Fig. 10.6 Gleason grade sub-patterns. Representative images of the sub-patterns of Gleason grade 3 (sparse, intermediate, and packed) and Gleason grade 4 (large cribriform, small cribriform, and intraductal). All sections were stained with hematoxylin and eosin (Reprinted from Downes and colleagues [69], with permission from Elsevier)

glands filled with abundant epithelium (large cribriform), small infiltrative poorly formed glands, glandular fusion, and mucinous tumors. Given the variety of histologic patterns, differing MRI characteristics may be observed on T2-weighted imaging [69] and other sequences. Knowledge of the relationship between MRI signal and Gleason grade sub-pattern could facilitate accurate contouring of heterogeneous tumors on MRI, facilitating targeted biopsy or lesion monitoring in men on active surveillance patients.

Conclusion

MRI tumor volume estimates of known prostate tumors by histopathology analysis of prostatectomy specimen tend to substantially underestimate actual index tumor volumes, with a wide variability in underestimation to overestimation across individual cases, irrespective of actual tumor size. The underestimation may be more pronounced for tumors with a higher Gleason score and higher MRI suspicion score. Combined T2-weighted and DWI/ADC imaging significantly improved the accuracy of tumor volume measurement, but a relatively low positive correlation remained. Caution is therefore required for the clinical application of MRI tumor volume measurements. Significant tumor volume misjudgment by the use of MRI has implications for guidance of physicians and patients in risk assessment, candidate selection for active surveillance, or choice of treatment of prostate cancer.

Distinctions in Gleason scores and other histological features that are predictive of long-term outcomes may eventually be appreciable on MR images and contribute substantially to patient treatment management. Better insight regarding tumor

phenotyping by accurate co-registration of MR images to histopathology of prostate specimen may be useful in applying prospective MRI findings towards improving determinations of prognosis and appropriateness of surveillance, as well as to guide targeted biopsy and therapy procedures.

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Can MRI Replace Biopsy in Men on Surveillance?

11

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Introduction

Before the introduction of active surveillance for men with low- and intermediate-risk prostate cancer, most men fit for active treatment were treated by either radical prostatectomy or radical radiotherapy. Both of these approaches can result in significant morbidity, whilst a number of studies have questioned the presumption that radical treatment is invariably associated with a benefit in prostate cancer-specific mortality [1, 2]. The intention of active surveillance is to minimize the morbidity of treating prostate cancer whilst preserving oncological efficacy, by avoiding or deferring treatment in a group of men, whilst offering appropriate treatment in a timely manner to those who are more likely to benefit [3].

Current protocols for active surveillance based on digital rectal examination (DRE), prostate-specific antigen (PSA) and transrectal ultrasound (TRUS) biopsy can have problems related to classification errors at the start of active surveillance and ongoing imprecision in monitoring tumour size and grade [4].

Currently, PSA kinetics are used as a guide to identify patients at higher risk of pathological upgrading and in some centres as a trigger for active treatment, whilst others would only use a PSA trigger for reassessment of the patient, including repeat biopsy. In a study of PSA kinetics in a large cohort of men on active surveillance by Loblaw et al. [5], false-positive PSA triggers (such as doubling time <3 years or PSA velocity >2 ng/year) occurred in 50% of stable untreated patients, none of whom progressed, required treatment or died of prostate cancer. In a systematic review by Vickers et al. [6], it has been shown that PSA kinetics, apart from the absolute value of PSA, have no independent predictive value in localized prostate cancer.

It is known that systematic TRUS biopsy can miss a substantial proportion of significant prostate cancer [7, 8]. If men have been diagnosed using standard transrectal sampling, then rebiopsy can overcome the random error associated with this (e.g. missing a smaller cancer in the peripheral zone by chance) but is less likely to overcome the systematic error due to undersampling of anterior, apical and midline tumours.

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There is a growing body of evidence that using multiparametric magnetic resonance imaging (mpMRI) to target the initial or follow-up biopsy improves the accuracy of classification and may overcome these sampling errors [9].

This chapter will look at the use of mpMRI when compared to biopsy in men with prostate cancer who choose to adopt a surveillance strategy and the potential role of mpMRI as a surveillance tool to reduce the need for repeat biopsy.

Multiparametric MRI

Multiparametric MRI (mpMRI) refers to the use of multiple anatomical and functional imaging parameters read in conjunction with one another. It usually includes T1- and T2-weighted sequences, diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE). Initially, spectroscopy was also included, but this technique is now less favoured.

T1-weighted sequences are very useful to detect post-biopsy haemorrhage, as blood will show as high signal (brighter); in the early post-biopsy period, this could mimic the avid uptake of contrast agent typical of prostate cancer and lead to both under- and overestimation of tumour volume. On T2-weighted imaging, prostate cancer commonly returns as low signal (darker). DWI assesses the diffusivity (i.e. the free movement) of water molecules within a tissue. In prostate cancer, the movement of water is more restricted than the surrounding tissues, due to the disorganized cellular structure; this will result in a higher signal (brighter) on long *b*-value sequences and a lower signal (darker) on the reconstructed apparent diffusion coefficient (ADC) map.

Restricted diffusion (i.e. lower ADC values) correlates with higher Gleason grade tumours in men on active surveillance [10].

DCE refers to the intravenous administration of a specific contrast agent, most commonly gadolinium. An important aspect is the rapid acquisition of the post-contrast sequences, to allow detection of early contrast uptake. Prostate cancer is usually characterized by a steep wash-in/washout curve, due to its disorganized vascularity. The curve typically shows rapid wash-in and, due to leaky vasculature, rapid washout.

Active Surveillance Protocols

To date, there is no universal consensus on the inclusion criteria for men on active surveillance. Different protocols have been established which determine eligibility based on PSA, DRE and TRUS-guided biopsy results. Differences lie in Gleason score, PSA thresholds or on the definition of clinically significant cancer. Some series recommend active surveillance for men with Gleason 3 + 4 disease in which the component of pattern 4 is small (<10%) [11], whereas the majority include only men with Gleason 3 + 3 [12].

MpMRI has gained popularity in the management of men on active surveillance, with 71% of clinical users of prostate MRI using it in men on active surveillance, in a recent survey [13]. MpMRI is recommended by the UK National Institute for Health and Care Excellence at the start of active surveillance and is also deemed suitable for repeat assessment in men during follow-up [14]. MpMRI offers the potential to identify men with clinically significant disease which was missed or under-sampled at first assessment and is particularly important in men on active surveillance to confirm the absence of large-volume, high-grade cancer in the anterior gland. The negative predictive value of mpMRI for ruling out clinically significant disease has reported values of greater than 90% in men on active surveillance [15].

Reporting of Prostate MpMRI in the Diagnostic Setting

The likelihood of prostate cancer on mpMRI is commonly assessed using the Prostate Imaging Reporting and Data System (PI-RADS), which has been recently updated to PI-RADS version 2.0 [16]. This classification is based on specific

features on each sequence used in mpMRI, in order to standardize the reporting and the likelihood of significant prostate cancer on a scale that is reproducible.

The prostate is divided into discrete anatomical regions, and a 1–5 score is given according to explicit criteria. DWI is considered the dominant sequence to evaluate the peripheral zone, whilst T2-weighted imaging is the dominant sequence for the transition zone. An overall score (1–5) is then assigned to describe the likelihood of clinically significant cancer on MRI. The ability of PI-RADS to assess the likelihood of prostate cancer has been demonstrated in a recent meta-analysis [17]. However, some centres use a less didactic Likert score, where the radiologist reports the likelihood of clinically significant disease on a scale of 1–5 where 1 and 2 are unlikely, 3 is equivocal and 4 and 5 are increasingly likely [18]. The Likert score allows more scope for the radiologists' overall impression to dominate the final score, rather than a summation of each sequence, and there is debate about whether Likert or PI-RADS has better performance characteristics. Whichever is used, the score is compared to histological assessment, to assess the performance characteristics of mpMRI in a particular patient population.

Using the MRI Data to Target the Biopsies

There are three techniques of mpMRI guidance currently available for registering the MRI images seen in the diagnostic mpMRI scan to the image seen at the time of biopsy. The simplest method using a standard TRUS biopsy probe is simply to review the prostate mpMRI images and to use 'visual registration' and anatomical landmarks seen on mpMRI and ultrasound to transfer the mpMRI information to a location seen on ultrasound. The option of software-assisted registration (often known as *fusion*) is also available. This requires an experienced radiologist to contour the prostate and the lesion of interest on mpMRI and for this to be uploaded to the software tool. The biopsy operator then contours the prostate on the ultrasound images at the time of the biopsy, and the software adds the lesion contour to the real-time ultrasound image. The third approach is to use an interventional mpMRI scanner (often of lower magnet strength than a diagnostic scanner) and to match the diagnostic and interventional images to identify the biopsy target.

MpMRI Findings in Men Suitable for Active Surveillance

There are two sources of histological verification of mpMRI data which are of interest in men on active surveillance. The first comes from radical prostatectomy specimens (whole-mount histopathology) in men who had an mpMRI prior to surgery, in the setting of having initial biopsies suitable for active surveillance. A recent review [9] has reported ten studies that evaluated radical prostatectomy data of men who were deemed histologically eligible for active surveillance and had undergone preoperative mpMRI. Data synthesis showed that the likelihood of a positive mpMRI preoperatively was 73% (963/1326). Upgrading occurred in 43% (291/677) of cases, which was higher than the 27% (78/293) for patients with a negative mpMRI preoperatively. The denominators differ for these data because not all groups included all data for upgrading. These results indicate that it is more likely for upgrading to occur when there is a lesion visible on mpMRI. Upstaging occurred in 10% (54/557) of positive mpMRI cases, which is similar to the 8% (16/194) in patients with a negative mpMRI.

The second source of evidence comes from repeat biopsy in men who had mpMRI, following an initial biopsy suitable for active surveillance. The same review [9] identified seven papers on this topic, and data synthesis showed that 70% of men (340/488) had a positive mpMRI, of whom 39% were subsequently reclassified due to targeting of MRI lesions.

In another study, the upgrading seen with MRI-targeted biopsy after initial low-risk tumour on first biopsy was in the order of 30% [19], similar to the upgrading seen between standard biopsy

and radical prostatectomy in men with low-risk disease [20]. MRI-targeted biopsy is more likely to give a more accurate picture of the maximum burden of disease than standard biopsy, with little upgrading between MRI-targeted biopsy and radical prostatectomy [21].

MRI and Targeted Biopsies in Men on Active Surveillance

De Visschere et al. have recently led a review [22] showing that in men with normal findings on mpMRI (i.e. PI-RADS overall assessment score 1 or 2), the risk of having a clinically significant prostate cancer is very low; the negative predictive values range between 63% and 91% for prostate cancer of any grade and from 92% to 100% for clinically significant prostate cancer (depending on the definition of clinically significant disease used) in low-risk men (PSA < 10, normal DRE, no family history). Furthermore, despite the risk of missing some lesions, the majority of missed tumours on mpMRI were low grade and organ confined [23]. This high negative predictive value has led some centres to use mpMRI as a way to reduce the need for repeat biopsy in men on active surveillance.

When a confirmatory biopsy (i.e. the first biopsy after initial diagnostic biopsies with features suitable for active surveillance) is considered, an mpMRI prior to this can be assessed for evidence of concordance with the initial biopsy. For those men with a discordant mpMRI (defined in one study as showing a lesion >1 cm), the risk of upgrading on targeted biopsy was 77% (10 of 13 men, with the remainder having similar histological findings to the baseline biopsy) [24]. One of the confounders of lesion size on mpMRI can be the presence of inflammation around a low-grade cancer. Therefore, it is important to conduct an MRI-targeted biopsy of any lesions to assess whether they reflect higher tumour burden than seen at the original biopsy or a low-volume tumour with some surrounding inflammation, particularly in the post-biopsy setting.

The concept of 'risk inflation' with an MRI-targeted approach is important to bear in mind. Traditional risk calculators are based on biopsies which are intended to systematically sample the prostate. Therefore, the presence of two or more positive cores would suggest that cancer is of a significant enough volume to be deemed clinically significant disease. However, when the biopsy strategy aims to oversample an area at high risk, then the number of cores positive does not have the same implication [25]. It makes sense therefore to use the maximum Gleason grade and maximum cancer core length as the sole determinants of tumour burden in targeted biopsies.

Hu and colleagues [26] identified 113 men on active surveillance who met the Epstein criteria (Gleason score 6 or less, 2 or fewer cores positive and 50% or less of any core) and subsequently underwent confirmatory targeted biopsy using software-assisted registration. The authors concluded that taking multiple cores from a reliable mpMRI target increases the probability of finding more than two positive cores (36%); in other words, upgrading beyond the Epstein criteria is a frequent finding with targeted biopsy. These results suggest that an increased number of Gleason 6 cancer should not exclude men from active surveillance and that the Epstein criteria should be re-evaluated in this scenario, in order to account for the risk inflation due to targeted biopsy.

The relationship between software-assisted MRI-targeted biopsy and Gleason score in men on active surveillance has been reported in a cohort of 245 men undergoing confirmatory biopsy [27]. Twenty-six percent of men with a diagnosis of Gleason 6 disease based on conventional TRUS biopsies were upgraded to GS $\geq$ 7 on subsequent software-assisted biopsy, suggesting that this biopsy technique can improve detection of higher-grade cancer.

Definition of Radiological Progression in Men on Active Surveillance

There is little dispute that mpMRI and subsequent targeted biopsy after an initial diagnosis of low-grade prostate cancer are helpful in identifying higher-grade disease in some men. This is generally accepted as reclassification rather than

progression, when there has been a short time interval between the original and MRI-targeted biopsy. The role of mpMRI in identifying true radiological progression (which is presumed to be related to pathological progression) is less well defined at present [9]. There is initial evidence that men with a visible lesion on mpMRI are more likely to show radiological progression than those with no visible lesion at baseline [28].

When assessing changes on mpMRI, it is imperative to first define radiological progression in this context. The Response Evaluation Criteria in Solid Tumours (RECIST) criteria are deemed unsuitable for men on active surveillance, as the criteria in the current RECIST 1.1 [29] use one-dimensional aspects for volume measurements and a lesion must be a minimum of 10 mm in maximal dimension before it is considered assessable [30, 31]. For men with localized prostate cancer, a 1 cm diameter lesion is likely to contain significant Gleason pattern 4 and be unsuitable for active surveillance in a man who is fit enough for radical treatment.

Radiological progression in men on active surveillance can be defined as either an increase in the size or change in the intensity of a lesion noted at baseline or the appearance of a new lesion during follow-up. These definitions can be in terms of size (measured on T2-weighted sequences or DCE images) or radiological characteristics, such as conspicuity (i.e. the measure of the difference between a lesion and the surrounding areas in the prostate). Although radiological progression is defined on radiological criteria alone, it is usually confirmed with repeat targeted biopsy to establish that it is correlated with histological progression either in terms of the grade or burden of disease. There are currently no specific thresholds established for either radiologically significant disease or radiological progression. Once data are established in this area, it is likely that thresholds will be set for each (Fig. 11.1 and Fig. 11.2).

Currently, different groups are using different parameters. Morgan et al. [32] defined progression as cases that progressed to radical treatment, rather than according to radiological or histopathological criteria alone. The difficulty here is that it can lead to a circular argument, if the clinician is aware of the mpMRI changes and moved to offer radical treatment because of the change on mpMRI.

The National Institute of Health (NIH) group used change in size of a lesion, change in appearance of a lesion and appearance of a new lesion to define radiological and found that when all three characteristics were present, then the rate of pathological progression from International Society of Urological Pathologist (ISUP) grades 1–2 or 2–3 [33] was 100%, compared to 33.3% when only one characteristic was seen [34].

A panel of experts, convened by the European School of Oncology, has recently published the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) guidelines [35], in order to facilitate robust data collection of mpMRI in active surveillance. Using these guidelines in reporting mpMRI at baseline and follow-up in men on active surveillance will allow assessment of the natural history of mpMRI findings in men on active surveillance. The PRECISE recommendations include a score for the likelihood of change between a baseline and follow-up mpMRI. If widely used, the data derived from the application of these guidelines would facilitate the determination of thresholds that identify radiological significant disease and important radiological changes on mpMRI [35].

Nassiri et al. [36] analysed 259 men on active surveillance (196 with Gleason score 3 + 3 and 63 with Gleason score 3 + 4) who were diagnosed by MRI/US fusion-guided biopsy and who underwent subsequent fusion biopsy for as long as 4 years of active surveillance. The primary endpoint of the study was to determine the rate of upgrading to Gleason score $\geq$ 4 + 3 using targeted biopsy. The authors concluded that 63% of men with Gleason score 3 + 4 had upgraded by the third year of active surveillance, compared with 18% of men with Gleason score 3 + 3 at entry ($p < 0.01$). Interestingly, 97% of all upgrades (32/33) occurred within an mpMRI-visible lesion ($n = 21$) or a tracked site ($n = 11$). This suggests that the use of software-assisted biopsy, especially when tracking an mpMRI-visible lesion, could be of great help in the detection of potentially aggressive cancer during active surveillance.

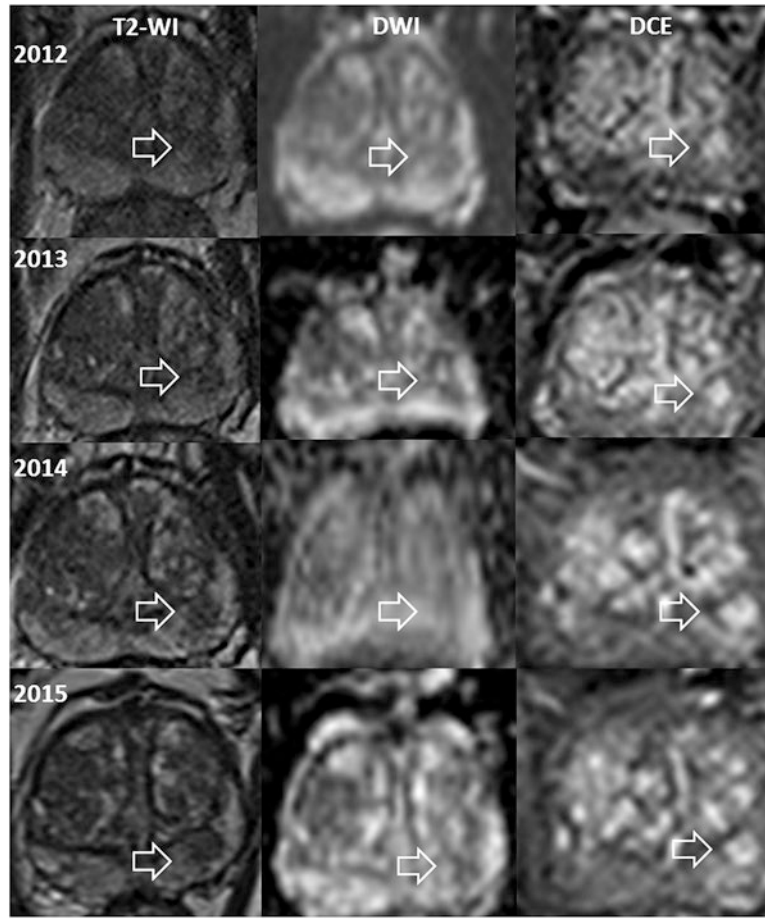

Fig. 11.1 Man on active surveillance for prostate cancer (Gleason 3 + 3) diagnosed in 2010 4 cores of a TRUS standard 12-core biopsy (4 mm maximum cancer core length). The mpMRI scans show a left-sided peripheral zone lesion (arrows) characterized by low signal intensity on T2-weighted imaging, restricted diffusion in the ADC map and focal enhancement on dynamic contrast-enhanced sequences. The lesion did not show significant progression on mpMRI and this man is still on active surveillance

Cost Implications of MRI to Inform Active Surveillance

The cost of mpMRI on active surveillance is often a factor in its use in a routine setting. Although the cost in some health care systems is high, it can be offset against the cost savings generated by delaying or avoiding surgery or other treatments. Gordon and colleagues [37] have evaluated the cost-effectiveness of mpMRI to diagnose prostate cancer and direct all low-risk patients to active surveillance. They developed a cohort model in three different scenarios (i.e. (i) no mpMRI but only active surveillance, (ii) mpMRI *and* active surveillance in a biopsy-naïve population and (iii) mpMRI and increased active surveillance uptake) and concluded that mpMRI *and* active surveillance in men with low-risk prostate cancer are strongly cost-effective (likelihood of 86.9%). For every 1000 men suspected of prostate cancer, using mpMRI could avoid 340 biopsies, detect an additional 20 significant cancers and detect 10 fewer insignificant cancers. However, this only addresses the use of a single mpMRI scan prior to first biopsy and not the use of follow-up mpMRI whilst on active surveillance. This would require an additional evaluation, in light of whether other tests (e.g. routine rebiopsy) could be omitted.

Conclusion

There is good evidence to support the use of mpMRI in men with an initial biopsy suitable for active surveillance, and to target any lesions seen on mpMRI, often in conjunction with a confirmatory systematic biopsy.

MpMRI may offer an opportunity to follow men on active surveillance without the need of

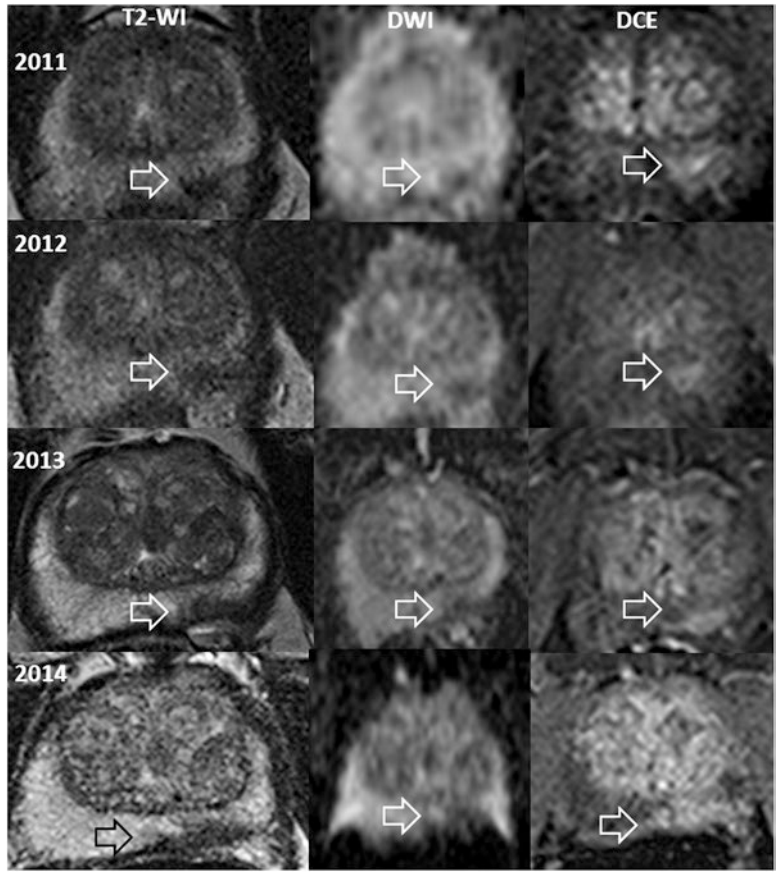

Fig. 11.2 Man on active surveillance for prostate cancer (Gleason 3 + 3) diagnosed in 2003 on TRUS biopsy in up to 3 mm of 3/22 cores. The mpMRI scans show a left-sided peripheral zone lesion between the apex and mid-gland (arrows) abutting the prostatic capsule characterized by low signal intensity on T2-weighted imaging, restricted diffusion in the ADC map and focal enhancement on dynamic contrast-enhanced sequences. The lesion did not show significant progression on mpMRI until 2014, when the T2-weighted images suggest a slow progression of the lesion (likely T3a disease). Subsequent biopsy demonstrated overall Gleason score 3 + 4, with maximal Gleason 4 + 3 in five out of nine cores. This man underwent radical prostatectomy confirming Gleason 4 + 3 and T3a disease at left posterior surgical margin

performing further biopsies, in the absence of signs of progression. Although mpMRI is of interest for the monitoring of men on active surveillance, robust data from prospective studies are needed before widespread adoption of mpMRI can replace repeat biopsies.

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Tissue-Based Markers for Risk Prediction

12

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Introduction

Molecular risk assessment via tissue-based assays (gene expression profile and/or proteomic tests) in the evaluation of prostate cancer represents a growing armamentarium with rapidly evolving data that suggests these tools might help clinicians more accurately choose the right treatment for the right patient at the right time. Patient selection for surveillance (i.e., no definitive local therapy or delay of definitive local therapy) represents an unmet need for increased accuracy of risk assessment, a gap that both available molecular risk profiling tests and further research and development are seeking to bridge. Historically, treatment selection indicated which definitive therapy was chosen (prostatectomy, radiotherapy, etc.) and did not include active monitoring of a newly diagnosed patient. The relative long-term safety of AS in patients selected on clinical criteria has been reported [1, 2]. The molecular tests detailed herein have been more recently assessed with respect to the similar, but not entirely equivalent, clinical question: which individual derives treatment benefit [3–5]? These tests provide an answer by enabling management decisions based on the biologic potential of an individual patient's tumor. This precision medicine approach to disease management is in early stages but likely represents a paradigm shift that will gain ground in the future. Indeed, molecular tests are included in the discussion of risk stratification in the latest edition of the NCCN prostate cancer guidelines [6]. Accurate assessment of patients' suitability for active surveillance is important at the population level as well. 180,890 cases of prostate cancer will be diagnosed in 2016 [7]. Recent analyses show the proportion of these cancers that are low risk and/or Gleason ≤6 that ranges from 22 to 50% [8, 9], the majority of whom are likely candidates for AS. However, an estimated 50–70% of newly diagnosed patients will still undergo definitive therapy, highlighting the need to expand AS programs. This chapter reviews the development of tissue-based risk prediction markers and rationale and data supporting their use during the counseling of patients regarding AS. We also posit specific ways in which initial and serial testing might be of value to patients who are managed on AS for increasing lengths of time. Additional preclinical, tissue-based molecular data supporting the importance of increased use and further refinement of current tissue-based markers is discussed as well.

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Clinically Available Tissue-Based Biomarker Assays

Genomic Prostate Score: Development, Clinical Validation, and Clinical Utility

The genomic prostate score (GPS) (Oncotype DX; Genomic Health, Redwood City, California) is derived from the relative expression of 17 genes involved in major tumorigenesis pathways prospectively selected for their predictive value with regard to clinical disease recurrence, cancer-specific mortality, and adverse pathology at prostatectomy independent of the Gleason grade of the sampled tissue [10]. The individual gene expression levels are measured as described previously in a minimum sample of 1 mm of tumor and combined algorithmically into the GPS [10]. Using the patient's initial NCCN risk group categorization as a reference, the GPS results in a reported percentage likelihood of favorable pathology which can be significantly higher or lower than that initially predicted by the NCCN risk group clinical parameters.

Men eligible for AS based on clinical criteria, but who instead underwent early prostatectomy, were analyzed in the initial clinical validation study. Consideration of significant clinical covariates in this cohort did not diminish the ability of GPS to predict high-grade and/or non-organ-confined pathology. The odds ratio (OR) for each 20-point increase in GPS adjusted for continuous Cancer of the Prostate Risk Assessment (CAPRA) score was 2.1 (95% CI 1.4–3.2); adjusted for NCCN risk group, the OR was 1.9 (95% CI 1.3–2.8), and adjusted for age, PSA, clinical stage, and biopsy Gleason score, the OR was 1.9 (95% CI 1.2–28). These data powerfully illustrate that GPS adds additional clinically meaningful predictive value to previously validated multivariable risk stratification tools [5]. GPS was also predictive of time to biochemical recurrence and adverse pathology at prostatectomy after adjusting for NCCN risk group in an additional validation study which importantly included more African-American men than the initial studies [11].

Preliminary analysis of the initial 4,000 commercially run assays demonstrated a change in risk classification in 25.2% of patients with pre-assigned NCCN risk. 36.9% of low-risk patients were relabeled as very low risk, and 11.3% of low-risk patients were relabeled as low intermediate [12]. The low-risk category encompassed the largest proportion of reassigned patients, thus representing the highest yield target population for additional clinically meaningful data. Additionally, a retrospective review of GPS use in private practice clinics revealed a 24% absolute increase in active surveillance after GPS scores were used in clinical decision making [13]; and a prospective clinical utility study reported a 10% absolute increase in AS after institution of GPS [14]. A subsequent prospective evaluation of the GPS reported a cutoff point for likelihood of favorable pathology at 76% that performed the best, correctly classifying 91.2% of patients with a sensitivity of 95.7% and specificity of 81.8% with an AUC of 0.95 [15]. The authors thus recommended definitive treatment for those patients whose results fell below this cutoff.

Cell Cycle Progression Score: Development, Clinical Validation, and Clinical Utility

The cell cycle progression (CCP) score (Prolaris; Myriad Genetics, Salt Lake City, Utah) is derived from an algorithmic analysis of the expression levels of 46 genes highly correlated with prostate tumor cell proliferation in 2–4 mm of tumor tissue [16]. In contrast to GPS, its initial development did not account for tumor heterogeneity or biopsy sampling error [16]. Subsequent retrospective studies have, however, demonstrated conserved predictive value for risk of metastases and/or disease-specific survival in a biopsy-based setting, despite differences in methodology [3, 17].

A meta-analysis of the CCP score literature demonstrated its predictive value for disease-specific survival (pooled hazard ratio (HR) of 2.08) as well as biochemical recurrence (pooled

HR of 1.63) [18]. The CCP score has also been combined with the CAPRA in order to form an even more robust predictor of death from prostate cancer (clinical cell cycle risk (CCR) score). In a distinct cohort of 761 men with clinically localized prostate cancer, the CCP score and the CCR score hazard ratio for death from prostate cancer for one unit change of the score was 2.08 (95% CI 1.76–2.46) and 2.17 (95% CI 1.83–2.57) [19].

Using these scores as continuous risk variables in clinical encounters with patients sometimes adds more complexity, rather than clarity to the discussion. Thus, preliminary data attempting to define a CCR cutoff of ≤0.8 below which active surveillance is safe is a potentially useful concept. This cutoff was evaluated in two retrospective cohorts in which 10-year prostate cancer mortality was 3.2% at the threshold. In a commercially tested cohort, 36% of patients qualified for AS on clinical parameters alone, which increased to 60% when the CCR threshold was employed [20]. The CCP score has also been shown to improve upon clinical predictive models [21] and add value in real-life clinical decision making. In surveys of ordering physicians, 32–65% of cases demonstrated a change in intended treatment after using the CCP score [22, 23].

ProMark: Development and Clinical Utility

ProMark (Metamark Genetics, Waltham, Massachusetts) is a protein quantification profile [24] that shares similar principles to GPS and CCP in development and application. In the initial biopsy simulation study, it was comprised of 12 proteomic biomarkers which were demonstrated to predict for aggressive disease and lethal outcome while accounting for biopsy sampling error. This was achieved by creating biopsy simulation tissue microarrays (TMA) from areas of highest and lowest Gleason pattern in prostatectomy sample tissue blocks from a cohort of 380 patients. The final predictive model was then tested in both of these tissue microarrays separately. The area under the curve for disease aggressiveness was 0.72 (0.64–0.79) for the low TMA and 0.70 (0.62–0.77) for the high TMA. The areas under the curve were similarly concordant between high and low TMA for lethal outcome [4]. In a subsequent blinded validation study of an 8-biomarker assay derived from the initial markers, ProMark improved upon clinical risk stratification tools. At a risk score ≤0.33, the likelihood of favorable pathology (surgical Gleason score ≤3 + 4 and organ-confined disease ≤T2) for NCCN very low-risk and low-risk groups was 95 and 81.5%, respectively, compared to 80.3 and 63.8% using the clinical criteria alone. A similar improvement upon D'Amico low-risk criteria was seen as well [25].

Examination of the use of ProMark in an early experience of 293 patient samples demonstrated that the distribution of ProMark scores closely resembled expected frequencies in the low-, intermediate-, and high-risk categories [26]. Additionally, a simulation model developed by Roth et al. did demonstrate that the use of this assay with regard to treatment decisions in patients with Gleason Grade Group 1 and 2 cancers resulted in 0.04 more quality-adjusted life years and a $700 cost savings [27].

Decipher Postop: Initial Development and Validation

Decipher is a genomic classifier (GC) comprised of 22 coding and noncoding RNAs. It was developed by modeling differential RNA expression in a cohort in which a third of the patients had early clinical metastasis after biochemical recurrence and rapidly validated in a more modern clinical cohort similarly enriched for patients with high-risk features at prostatectomy [28, 29]. These initial studies and several subsequent analyses have reconfirmed Decipher's ability to add meaningful predictive value of pertinent clinical outcomes in high-risk patients undergoing local therapy. Thus, while not directly applicable to the active surveillance eligible patient, they provide a reference framework for the robustness of the test to predict a tumor's biologic potential independent of clinical risk factors and is reviewed briefly

here. Cooperberg et al. applied CAPRA-S risk assessment to the initial Mayo high-risk post-prostatectomy clinical validation cohort to demonstrate that Decipher re-classified as low to intermediate risk 49 of 82 patients initially classified as high risk based on CAPRA-S score alone [30]. Ross et al. reported the application of Decipher to a natural history cohort of 356 men who underwent RP and received no additional treatment until the time of metastasis [31]. Decipher was an independent prognosticator of metastasis in multivariable analysis and with a *c*-index of 0.76 and was similar to that of the CAPRA-S risk model. However, when combined with CAPRA-S, it raised the *c*-index to 0.87. Klein et al. reported similar predictive value for Decipher with a *c*-index of 0.77 in a cohort of 169 node-negative post-prostatectomy patients managed without adjuvant therapy who experienced rapid metastasis at a median of 2.3 years [32]. Additionally, when applied to a cohort of patients treated with adjuvant radiation post-prostatectomy, Decipher demonstrated there was no difference in metastasis rates among patients with low GC score (<0.4); however, in patients with higher GC scores (≥0.4), there was a four-fold increase in 5-year metastasis in patients treated with salvage versus adjuvant radiation [33].

Decipher Biopsy: Clinical Development

While the initial Decipher development and validation studies were performed on radical prostatectomy specimens and thus now are referred to as *Decipher postop*, the test has recently been moved into the biopsy space as reported by an initial study of 57 patients where it was shown to predict 10-year metastasis risk post-radical prostatectomy on the initial biopsy specimens [34]. The Decipher test plus the National Comprehensive Care Network (NCCN) model had a *c*-index of 0.88 (95% CI 0.77–96) compared to the *c*-index of NCCN alone which was 0.75 (95% CI 0.64–0.87). Decipher was the only significant predictor of metastasis when adjusting for other important covariates: age, preoperative PSA, and biopsy Gleason score (hazard ratio per 10% increase in Decipher score = 1.72, 95% CI 1.07–2.81, $p = 0.02$). Further studies with larger sample sizes are needed to validate these findings. This study also did not specifically address an active surveillance setting (i.e., all patients in this study underwent subsequent prostatectomy). However, similar to the other molecular tests which have been more extensively studied in this arena, it appears that its most robust clinical potential for active surveillance is the ability to reclassify clinically intermediate-risk patients into a lower-risk category. No NCCN low-risk patient in this study developed metastasis. Of the 27 NCCN intermediate-risk patients, 13 were reclassified as Decipher low risk and none of these patients developed metastasis either, whereas 43% of the NCCN intermediate-risk patients were classified as either Decipher intermediate or highly developed metastases. This type of analysis, if replicated in a conservatively managed cohort, may allow the test to aid safe expansion of active surveillance to the portion of clinical low- or intermediate-risk patients who otherwise might undergo treatment.

Decipher: Clinical Utility

Clinical utility studies utilizing Decipher biopsy have yet to be reported, as the test was just recently made available. However, Decipher postop has been repeatedly shown to result in significant changes in clinical management [35–37]. Given its powerful prognostic value, a similar result for Decipher biopsy could be expected.

Practical Application of Molecular Risk Profiling to Active Surveillance

The contemporary active surveillance cohorts are highly informative regarding the overall safety of this management strategy. They cannot, however, determine whether a singular case of disease-specific mortality is a direct consequence of surveillance-induced treatment delay abrogating

their chance for cure. We cannot know if these patients were still destined to die from their disease if they had been subjected to immediate treatment upon diagnosis [38]. Data presented by Auffenberg and colleagues suggests that it may be the latter [39]. They found that with median follow-up of 506 days, men undergoing initial surveillance followed by delayed prostatectomy were no more likely to have positive margins, extraprostatic extension, seminal vesicle invasion, or lymph node metastases. More definitive results may come with further follow-up. Meanwhile, the available data on the added predictive value of molecular risk tests compared to the clinical entry criteria alone used in currently maturing AS series suggests it may be possible to reduce an already low long-term disease-specific mortality risk even further or to maintain this acceptably low mortality risk while increasing numbers of AS patients. Molecular risk profiling should be used to more accurately identify, and remove from AS eligibility, men who harbor known risk factors for increased disease-specific mortality that were missed by clinical criteria alone.

There is no available prospective, randomized data that definitively demonstrates which, if any, of these tests outperform current clinical risk stratification in a contemporary AS cohort, nor is there head to head comparison data. They each have been evaluated with regard to slightly varied clinical endpoints (Table 12.1). A multiarm prospective trial of patients choosing AS, randomized to either a molecular profiling test or clinical risk stratification alone to decide final AS eligibility, could more definitively answer some of these unknowns. However, these studies would require lengthy follow-up to examine clinically meaningful endpoints during which time it is likely that interim technological advances would supplant the test versions used during trial enrollment. Additionally, while the clinical utility studies for these tests have demonstrated change in management based on their results, the impact of these changes on long-term individual outcomes is unknown.

The advent of tissue-based molecular risk assessment has also underscored some shortcomings of histopathological tissue examination.

Table 12.1 Commercially available tissue-based molecular risk prediction tests that may help improve accuracy of patient risk stratification for active surveillance selection

Company/test name	Molecular type	Primary endpoints
Prolaris – cell cycle progression	Gene expression (RNA quantification)	Risk of biochemical recurrence, metastasis, and disease-specific mortality
Genome DX – Decipher biopsy	Gene expression (RNA quantification)	Risk of metastasis
Genomic Health Oncotype DX – GPS	Gene expression (RNA quantification)	Adverse pathology: primary Gleason pattern 4 or any pattern 5 and/or non-organ-confined disease (T3), risk of BCR
Metamark – ProMark	Protein quantification	Adverse pathology: Gleason ≥4 + 3 and/or non-organ-confined disease (T3a, T3b, N1, or M1)

Concordance among pathologists in Gleason grading and practices of reporting cancer quantity widely varies, complicating the delivery of uniform and accurate prognostication for patients and clinicians considering active surveillance [40, 41]. Low interobserver reproducibility when differentiating tangentially sectioned Gleason pattern 3 from poorly formed glands of Gleason pattern 4 on needle biopsy has been seen in active surveillance cohorts [42, 43]. This pathologic uncertainty between Gleason 6 and 7 cancer could account in part for the wide distribution of molecular risk scores in individual clinical risk categories (i.e., a NCCN low-risk patient has a 77% average probability of favorable pathology at prostatectomy, but a genomic prostate score

might give that same patient up to an 86% probability of favorable pathology). Additionally, Gleason 6 cancers are likely now more biologically homogenous, and Gleason 7 cancers more heterogeneous, due to the ongoing Gleason grade migration resulting from the change in grading methodology in 2005 [44–46]. A small portion of AS patients may also receive different treatment recommendations at follow-up biopsy based on the definition of histopathological progression used [47].

Validated molecular risk assessment tests provide an easily exportable, consistent level of objectivity, independent of local pathologic expertise, potentially rendering an even greater increase in prognostic precision than previously reported in cohorts undergoing centralized pathologic review. Their use can also potentially mitigate some of the inter-patient variability that is introduced by variable pathologic interpretation. This added knowledge is particularly helpful in more confidently recommending AS to some patients with Gleason 7 cancer with molecular risk scores that indicate low likelihood of adverse pathology as well as providing additional peace of mind to a patient with very low risk Gleason 6 cancer choosing AS.

Adaptable Active Surveillance Follow-Up with Molecular Risk Assessment

There is currently a range of reported follow-up biopsy intervals of patients on AS, with no available data supporting the use of one frequency over another and no reports regarding the safety of modifying follow-up intervals based on clinical risk factors.

Prospective data regarding stability of individual patients' molecular risk scores over time is also lacking; however, important inferences can be made from the clinical validation studies that may help encourage individual tailoring of AS follow-up schedules. In addition to the ability of ProMark and GPS to predict the initial presence of adverse pathology, Decipher biopsy predicts a 10-year metastasis risk after prostatectomy. GPS and CCP score boasts 15-year follow-up data with regard to risk of clinical recurrence (GPS) and metastasis-free survival (CCP) [3, 5]. Applied as prospective selection criteria for an AS cohort, the hypothesis is that patients with the lowest likelihood of adverse pathology would also likely have the most stable molecular risk scores over time, intuitively demonstrating the possibility for decreased frequency of monitoring without sacrificing mortality benefit.

In patients that have molecular risk stratification at the time of initial diagnosis which demonstrates a low likelihood of adverse pathology, a longer interval to re-biopsy or conversion to a watchful waiting protocol could be considered [48]. Conversely, in patients with a higher likelihood of adverse pathology, a shorter interval to re-biopsy or a more confident decision for immediate treatment may be made. While this rationale is based on robust retrospective follow-up data, definitive support for this strategy would come in the form of randomization of patients to more intensive or less intensive follow-up based on their molecular risk profile. Molecular risk profiling adds prognostic precision to known clinical parameters; it does not replace them. Clinicians must still exercise judgment regarding factors of patient life expectancy, comorbidity, and patient desire when using a molecular risk score to help plan the frequency of follow-up in an individualized AS protocol (Fig. 12.1).

Molecular Markers in "Insignificant" Cancer

Recent results from large active surveillance cohorts suggest that some patients with otherwise classified "insignificant" cancer, and some that fulfill additional stringent clinical selection criteria, still have a risk of metastasis and death [1, 2, 50]. In the Sunnybrook experience, the initial Gleason score of the 15 patients who died from prostate cancer is not specified; however, it does report that 16 of 28 patients (66%) who developed metastatic disease had Gleason ≤6 cancer and 7 of them fulfilled Epstein criteria. The average patient in this cohort was almost 68 years

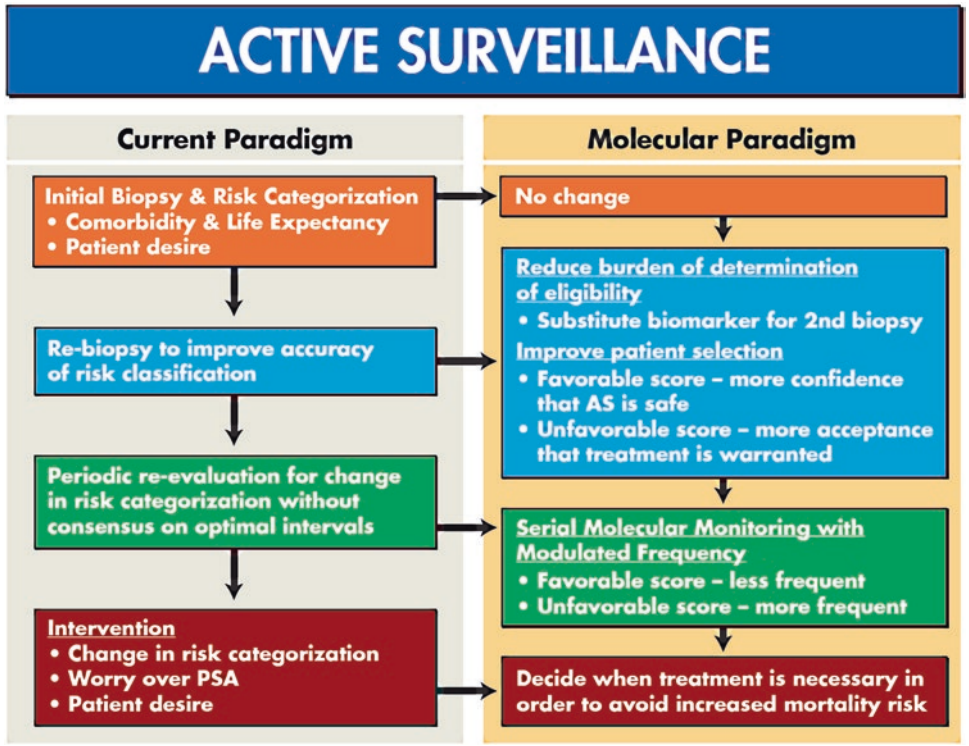

Fig. 12.1 Individualized AS protocol using molecular risk assessment (From: Reichard et al. [49]. Reprinted with permission from John Wiley and Sons)

old; thus, one might estimate as this cohort is enriched with younger patients, this risk may increase further [1]. In the Hopkins experience, there were 2 prostate cancer deaths per 100 person-years in the very low-risk patient group ($n = 926$) and 3 additional low-risk patients with lymph node or distant metastasis per 100 person-years [2]. In the ProtecT Study Group's comparison of monitoring, surgery, or radiotherapy for localized prostate cancer, metastases developed in men in the active monitoring arm at a rate of 6.3 events per 1000 person-years during 10 years of follow-up. This was substantially higher than patients treated with surgery or radiation. Additionally, there were eight prostate cancer deaths in men with Gleason 6 cancer at initial diagnosis across all three trial arms [50].

Gleason pattern 3 cancers are molecularly more benign than their Gleason pattern 4 and 5 counterparts. This is not unexpected given the strong prognostic value of Gleason score alone and the overwhelmingly positive outcomes of the contemporary active surveillance cohorts previously discussed. There are also, however, several studies that suggest there are some Gleason pattern 3 cancers that have molecular characteristics of more aggressive disease. This is also not unexpected as there are still patients with low-risk disease from these active surveillance cohorts who develop metastasis and/or die of prostate cancer. A closer look at the molecular characteristics of these potential outliers is warranted in order to push the area under the curve for prediction of negative outcomes in patients evaluated for active surveillance as close to 1 as possible. It is likely that the Gleason 6 cancers with adverse molecular features de-differentiate prior to metastasizing, since there are virtually no well documented cases of pure, surgically confirmed Gleason 6 that have metastasized.

Analysis of 340 Gleason 6 prostate cancers using the Decipher genomic classifier revealed high-risk and intermediate-risk scores in 7 and 13% of patients, respectively [51]. Thus, 25

patients had a seven times higher risk of metastasis, and 43 patients had a two times higher risk of metastasis than the remaining 276 patients in this cohort. All tumors were rereviewed by expert genitourinary pathologists using the ISUP 2005 Gleason grading criteria. While there was a significant proportion of pattern 4 disease identified upon rereview, examining the prospective cohort patients specifically, there was no statistically significant difference between the Decipher scores of those upgraded and those that were not. It is still unclear whether aggressive behaviour of the small minority of Gleason 6 cancers with adverse genetic features is generally due to co-existent occult higher grade cancer, or due to de-differentiation of Gleason 6 cancer. Both are possible.

Polson and colleagues reported that the TMPRSS2/ERG gene fusion (a critical and likely early factor in prostate cancer pathogenesis) is present and expressed at the transcriptional and translational levels in the stem cell compartment from primary human prostate cancers, including 3 of 5 analyzed Gleason 3 + 3 = 6 cancers [52]. This is significant given the possibility that the cancer stem cell population potentially drives the process of metastasis as well as therapy resistance, leading to recurrence and relapse. Additionally, 10–20% of Gleason 6 cancers demonstrate loss of important tumor suppressor genes such as PTEN [53, 54]. The significance of PTEN loss is clearly demonstrated in an animal model in which the combination of PTEN loss and MYC activation is sufficient to lead to genomic instability and lethal metastatic disease [55].

Evidence for a biological field effect in prostate cancer is demonstrated by the predictive value of the presence of PTEN loss, MYC/8q gain, and LPL/8p loss on Gleason pattern 3 biopsies for the presence of un-sampled Gleason pattern 4 cancer. In other words, the presence of these markers in a Gleason pattern 3 core makes it much more likely to have come from a prostate that harbors Gleason pattern 4, suggesting that molecular changes of tumor aggressiveness are present before histologic changes occur. This demonstrates yet again that biologically important markers for adverse pathology are found in Gleason pattern 3 cancer [56]. Testing for PTEN deletion and TMPRSS2/ERG fusion on biopsy tissue is commercially available through Metamark Genetics, Waltham, Massachusetts.

An analysis of biopsy-based genomic and microenvironmental indices to predict 5-year risk of biochemical recurrence (BCR) after local therapy revealed that several individual Gleason 6 tumors had a higher percentage of genome alteration as measured by copy number variation than some Gleason ≥8 tumors with significant overlap in the genomic instability of Gleason 3 + 3 = 6 and higher-grade tumors [57]. Percentage of genome alteration carries strong prognostic value independent from clinical covariates. Every 1% increase imparts a 5–8% decrease in 5-year post-local therapy biochemical recurrence-free survival [57]. Interestingly, among the low- and intermediate-risk prostatectomy cohort, the risk signature was more strongly predictive of biochemical relapse than clinical variables. 89% (95% CI 85–96) of good prognosis (PGA ≤7.49) patients were free from BCR at 5 years compared to 58% (35–96) of poor prognosis (PGA >7.49) patients.

There is data suggesting that the multiple tumor foci detected in patients with prostate cancer have independent origins. However, whole-genome sequencing of multiple metastatic sites from several patients' primary tumors demonstrated a common clonal origin containing 40–90% of the total mutations and the majority of driver mutations. The implication is that widespread metastases originate commonly from only one of many tumor foci – a foci potentially small enough to be easily missed under normal pathological examination, regardless of its grade [58].

An in-depth analysis of the genetic phylogeny of multifocal prostate cancer in three separate cases identified multiple independent clonal expansions of cells in both neoplastic and morphologically normal prostate tissue [59]. This is important since the mutations defining the clonal expansion of morphological normal tissue were the same as those in cancer. There were large numbers of mutations shared among foci of Gleason 6 and 7 cancer, as well as a smaller but significant number of shared mutations in the adjacent normal tissue.

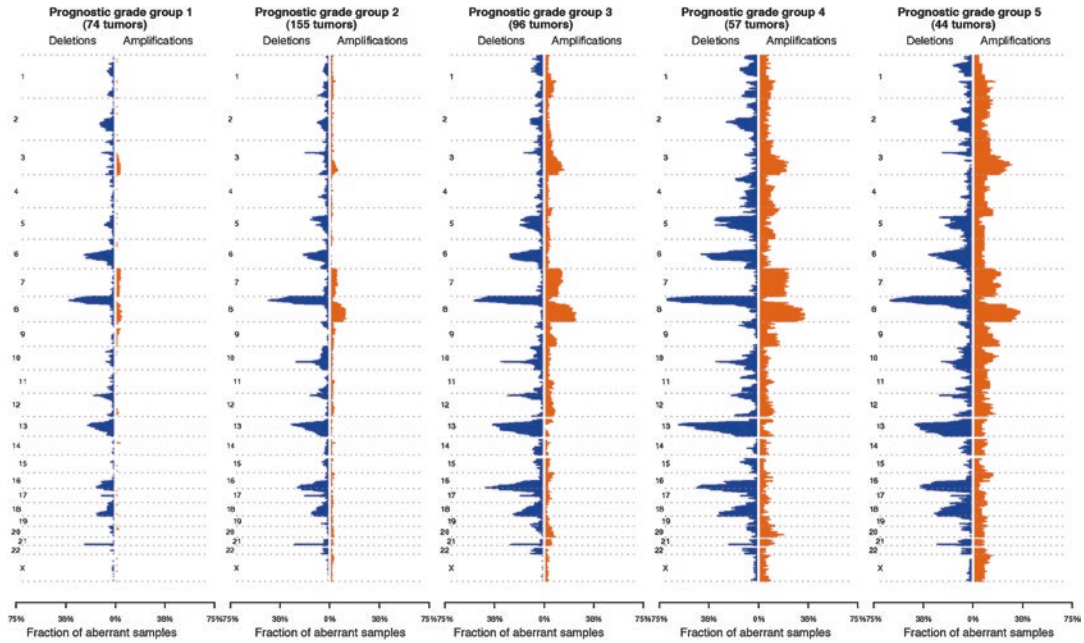

Fig. 12.2 Landscape of somatic copy alterations from 426 prostate cancer cases by prognostic grade group 1–5. Note the same pattern of deletions/amplifications remains across grade groups; only a fraction changes (From: Rubin et al. [60]. Reprinted with permission from Elsevier)

In describing the genomic correlates to the new grade 1–5 prognostic groups for prostate cancer, Rubin et al. demonstrate that Gleason 6 cancers harbor similar mutations to higher-grade cancers, albeit at a lower frequency [60]. The molecular profile of some low-grade tumors looks remarkably similar to those more frequently found in higher-grade cancer (Fig. 12.2).

Finally, the overexpression of long noncoding RNA SChLAP1, an independent predictor of lethal prostate cancer, was found in 4 of 165 Gleason $\leq$6 cancers and present in 11 of 334 Gleason 3 + 4 cancers [61].

The plausibility of genetic alterations characteristic of aggressive and even lethal prostate cancer lurking in tissue that lacks the morphologic changes necessary to garner a histologic classification equaling the seriousness of its underlying molecular perturbations has been thoroughly demonstrated (Table 12.2). The implications of these findings are such that clinicians should not fall into the temptation of a one-size-fits-all approach with regard to active surveillance. While current tissue-based molecular risk assessment is an improvement on clinical risk assessment, it is an incremental improvement that is not a panacea. Continued development and integration of molecular tumor analysis with pathological grading/staging is important to achieve the most accurate prognostic information possible. Further progress may come by combining molecular tests into algorithmic formulas in order to reliably detect patients who may currently meet all active surveillance eligibility criteria but may in fact still harbor disease that warrants treatment.

Conclusion

Utilizing clinical staging and risk prognostication methods, AS has rendered very positive results, with a variety of studies demonstrating cancer-specific survival rates at or near 100%. However, these studies have captured only a small portion of the number of men who are potential AS candidates. Future improvement in screening tests will hopefully obviate the need for drastic

Table 12.2 A variety of approaches that have shown a percentage of Gleason 6 tumors have molecular features of more aggressive disease

Gleason 6 characteristics	Clinical outcome	Molecular markers	Reference
6% rate of metastasis or death despite aggressive therapy	Risk of metastasis or death	Oncotype DX	Klein et al. [5]
7% of Gl 6 cancers with high-risk scores	Five-year metastasis risk	Decipher	Klein et al. [34]
Significant overlap of risk scores in Gl 6 cancer vs. higher grades	Five-year metastasis risk	Decipher	Klein et al. [32]
Harbored by some Gl 6 tumors	Lethal prostate cancer	SChLAP1 overexpression	Mehra et al. [61]
Significant overlap between Gl 6 and higher-grade tumors	Five-year risk of biochemical recurrence	Copy number variation, tumor hypoxia	Lalonde et al. [57]
Harbored by many Gl 6 tumors	n/a	TMPRSS2/ERG fusion	Polson et al. [52]
Harbored by many Gl 6 tumors	n/a	PTEN loss	Lotan et al. [53]
Harbored by many Gl 6 tumors	Lethal metastatic disease	PTEN loss and MYC activation	Hubbard et al. [55]
Large number of shared mutations among normal tissue, Gl 6, and Gl 7 cancer in the same prostate	n/a	Genome-wide DNA sequencing	Cooper et al. [59]
Biomarker alteration in Gl 3 glands, much more common in Gl 7 tumors	Potential for validation to predict upgrading at prostatectomy/select for active surveillance	PTEN loss, MYC/8q gain, and LPL/8p loss	Trock et al. [56]
Similar loci of copy number alterations to higher-grade groups	Correlation of genomic instability with grade groups	Somatic copy number alterations	Rubin et al. [60]

increases in AS numbers; however, overdiagnosis will unlikely be reduced to nil in the foreseeable future. To safely increase the number of patients who are managed with AS, the negative predictive value of whichever combination of clinical nomogram and molecular risk profiling is used must be high enough so that the cancer-specific survival rates of patients who are managed with AS do not fall below those who are immediately treated. This is especially salient due to the decreasing average age of the AS patient [62]. Tissue-based molecular risk profiling can help improve risk stratification for patients being evaluated for and subsequently followed on AS while potentially mitigating some of the associated clinical and psychological burden.

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13 International AS Registry: The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance Initiative

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Context and Rationale

In recent years, active surveillance has evolved from an experimental protocol to a broadly accepted—in fact, preferred—management strategy for men diagnosed with low-risk prostate cancer [1]. At present, two prospective active surveillance studies have reported long-term outcomes of men with favorable-risk prostate cancer [2, 3]. Both studies show that active surveillance for favorable-risk prostate cancer is feasible and seems sufficiently safe with regard to clinical disease progression at 10 years and beyond. Nevertheless, numerous questions remain, including who are the ideal candidates for active surveillance and what is the best follow-up protocol. The use of many different active surveillance protocols has been reported in the literature [4]. The inclusion criteria and follow-up protocols to identify disease progression have not yet been standardized, and various parameters are taken into account when recruiting or monitoring patients [5]. Clearly, there is a need for a worldwide consensus regarding the optimal criteria and protocols for active surveillance including the possibility of regional variations. A single set of guidelines are needed in order to

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reduce variations within geographical areas in clinical practice and to optimize clinical decision-making. As with everything else, there are trade-offs [6]. Very strict selection criteria reduce misclassification but greatly decrease the number of men eligible for active surveillance [6, 7]. Multiple repeat biopsies provide histologic verification of grade stability but increase the risk of biopsy-related complications [6]. With the additional confirmation that active surveillance is durable and safe, the next step is to optimize its use through more comparative data on patient selection and testing protocols [6]. With this in mind, the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) project was initiated.

The Movember Foundation [8]

The Movember Foundation is a global charity with a vision to change the face of men's health and a commitment to ensure that men live happier, healthier, and longer lives

. Since 2003, millions have joined the men's health movement, raising in excess of AUD $730 million and funding over 1,000 projects in 21 countries focusing on prostate cancer, testicular cancer, and suicide prevention. The Movember Foundation invests in initiatives that deepen the worldwide knowledge of prostate cancer through [8]:

- Biomedical research
- Trialing and implementing ways to improve the lives of men with prostate cancer from diagnosis through treatment, decision-making, active recovery, and well-being
- Raising awareness and ensuring that prostate cancer is a public priority
- Educating men on when and how to take action
- Creating a new posttreatment care pathway that will help men living with prostate cancer to access care and support that enhance their quality of life
- Investing in national prostate cancer clinical registries to provide population insights and an understanding of how to improve health outcomes for men throughout their prostate cancer journey

An Innovative Global Approach

The Movember Foundation believes that team-based research, performed across borders with a strong collaborative mind-set, avoiding duplication of work, can deliver innovation and knowledge sharing that leads to an acceleration of results that benefit men diagnosed and living with prostate cancer today. This has led to the realization of the Global Action Plan (GAP), a key initiative undertaken directly by the Movember Foundation. By bringing together over 350 international researchers, GAP facilitates a new and unprecedented level of global research collaboration, not previously seen within the prostate cancer community. There are seven GAP projects focusing on the following areas: the Global Prostate Cancer Biomarker Initiative (GAP1), Imaging in Advanced Prostate Cancer (GAP2), Active Surveillance for Low-Risk Prostate Cancer (GAP3), Exercise and Metabolic Health in Advanced Prostate Cancer (GAP4), Testicular Cancer Translational Research Project (GAP5), Oligometastatic Prostate Cancer Initiative (GAP6), and Psychosocial and Peer Support for Testicular Cancer Project (GAP7) (Fig. 13.1).

Fig. 13.1 Global research collaboration

The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Initiative

The Movember Foundation has committed EUR €2.4 million to the Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative to construct the largest centralized prostate cancer active surveillance database to date, comprising the majority of the world's active surveillance patient data. This will help create a global consensus on the selection and monitoring of men with low-risk prostate cancer and will reduce the number switching to active therapy within 1 year after the start of the active surveillance protocol and has the potential to improve their quality of life [9]. Overall milestones include worldwide consensus guidelines on active surveillance and a worldwide web-based platform on active surveillance with information and guidelines on active surveillance as an acknowledged treatment option for prostate cancer.

Outcome from GAP3 for Patients and Clinicians

The analysis of the data collected will allow clinicians to better select men that are eligible for active surveillance [10]. This will provide a safer option for men choosing to delay or avoid the potential side effects such as erectile dysfunction and incontinence that can be incurred by treatments such as surgery and radiation therapy. New guidelines will be created to allow clinicians to be able to more confidently identify men suitable for active surveillance and to also better determine when a man's prostate cancer has progressed and therefore requires active treatment. This will provide reassurance to men that they have made the most informed treatment decision for their type of disease [10].

Methods

Who Is Involved?

Requirements for the participation in GAP3 include, among others, ethical approval for sharing digital patient data in a centralized global database and an active registry of active surveillance patients over the last 2 years or more, including at least 50 patients included annually. The global initiative has brought together a vast wealth of clinical and research experience in prostate cancer research and clinical practice with all partners from around the world benefiting from each other's data, resources, and expertise to

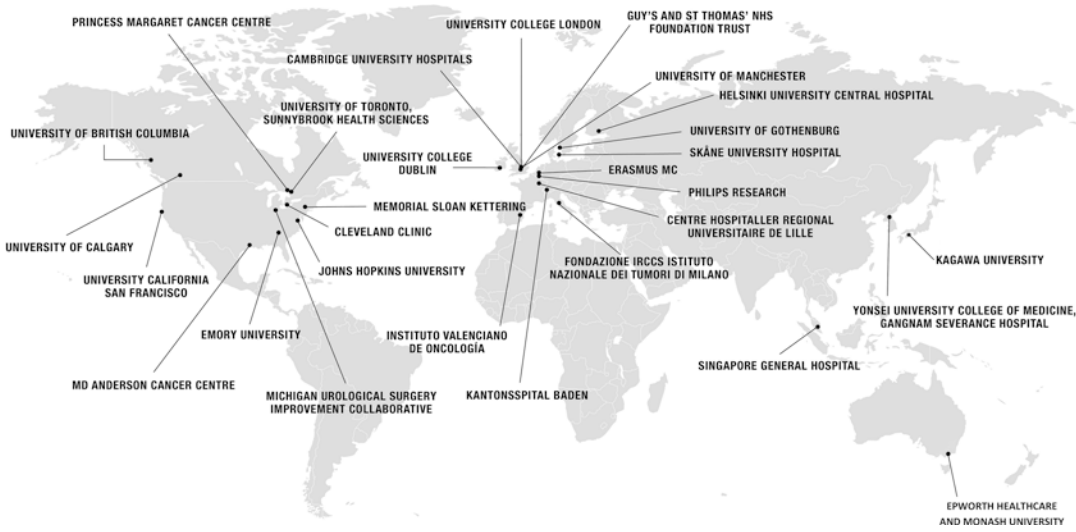

Fig. 13.2 Participating centers GAP3

provide better outcomes for their patients. To date, GAP3 has united as many as 30 institutions, hospitals, and research centers from the USA, Canada, Australia, Singapore, Japan, Korea, the UK, Ireland, the Netherlands, France, Sweden, Finland, Switzerland, Italy, and Spain. This global network is still expanding since the initiative is open for other eligible centers to join as well. Figure 13.2 provides an overview of the institutions that are currently participating in GAP3.

In total, the original GAP3 project will take two and a half years to complete. In the *first phase* of the project, the global database will be created by combining existing active surveillance databases worldwide. The *second phase* will involve the development of a consensus guideline on active surveillance.

Phase 1: Design of the Global Database

Clinical Research Questions

What is a man's risk on having event X (symptoms from metastases or prostate cancer death) when he starts following active surveillance? And what are the risks of side effects of a particular treatment (e.g., urinary dysfunction, bowel dysfunction, and erectile dysfunction) and loss of quality of life? The decision to pursue active surveillance is entirely the man's, but it is the urologist's responsibility to make sure that the man fully understands all the benefits and risks of active surveillance, as well as the benefits and risks of other treatment options available [11]. In order to assist both clinicians and patients in this critically important treatment-related decision-making process, there are a number of questions which will be addressed:

1. What is the common definition of low-risk prostate cancer?
2. How can we establish the diagnosis of a low-risk prostate cancer?
3. What is the role of comorbidity/life expectancy?
4. What are the best monitoring tools and at which frequency should these be used?
5. What should trigger the switch from active surveillance toward watchful waiting?
6. What should define the switch from active surveillance toward active treatment?
7. How best to evaluate the efficacy of active surveillance?

These unresolved issues in active surveillance for prostate cancer require further study and are identified by the GAP3 clinical experts as the key questions of the global initiative.

Content GAP3 Database

What is the most informative data needed to answer these research questions? To achieve a consensus on the design and contents of the global active surveillance database, there was a need for a minimal definition of the GAP3 codebook. A consensus has been reached on the codebook of the GAP3 database among the clinical investigators. The codebook of the global database consists of four sections: inclusion, follow-up, before diagnosis, and end of active surveillance. At time of inclusion, the consortium is interested in recording host characteristics (e.g., age, BMI, race, ethnicity, marital status, educational level, life expectancy, comorbidities/overall health status, etc.) and tumor characteristics (e.g., clinical stage, PSA, biopsy Gleason score, PSA density, number of positive cores, maximum extent cancer per core, etc.). During follow-up, information is gathered on, e.g., PSA, PSA kinetics (PSADT, PSAV), T-stage by DRE, biopsy characteristics, and MRI findings. PSA before diagnosis is also registered. With regard to the end of active surveillance, an inventory is made of, e.g., the reasons for stopping active surveillance, type of metastasis, type of treatment, and cause of death. As a next step, an inventory on available data has been made, including potential markers, imaging, QOL data, and others.

Construction of the Central Database [12]

Based on the consensus contents of a global active surveillance database, Philips Research has constructed the GAP3 database. The IT infrastructure of the global database is based on the tranSMART prostate cancer instance of the TraIT IT infrastructure developed by Philips within the Dutch CTMM-TraIT (http://www.ctmm-trait.nl) and CTMM-PCMM (http://www.ctmm.nl/en/projecten/kanker/pcmm?set_language=en) projects. This infrastructure offers support for collecting and combining the various large, longitudinal datasets from the participating institutes (Fig. 13.3). Transfer of these datasets takes place using the Secure Data Transfer (SDT) tool provided by Philips. The clinical data has been gathered using a global data model, specifically designed to contain all the data items needed by the statisticians to answer the research questions defined by the principal investigators at the start of the project. During this process, several issues arose, such as low data quality and incompatibility of the local data models with the global data model. These issues were solved using quality check software and data mapping software that were developed in-house. The global dataset can be browsed through the web-based tranSMART platform, which is only accessible for a selected group of statisticians. tranSMART supports a number of statistical analyses, such as survival analysis, logistic regression, and correlation analysis, and can incorporate genomic data and imaging metadata as well. The tranSMART instance is connected to RStudio [13] to enable the statisticians to execute their own R [14] scripts on the database, in a secure and reproducible manner.

Other Activities in Phase 1

For quality control of the biopsy Gleason scores used for inclusion of patients for active surveillance and for decision-making during follow-up, a centralized pathology review of approximately 5% of the biopsies by virtual microscopy is currently conducted. It concerns a random selection of 5% of confirmatory biopsies of the active surveillance population of each of the participating centers included in GAP3. The hematoxylin-eosin-stained biopsy slides will be reviewed for Gleason score (primary and secondary GS) and the biopsy core length. In addition, data is collected on the maximum number of cores per cassette and the extent of carcinoma and the total core length. The results will be taken into account in the final statistical analysis. Expected improvements for patient care include the standardization of pathology grading of prostate cancers diagnosed on biopsies, the development of a quality parameter for prostate biopsy core length, and improved selection of men entering an active surveillance program.

Although described broadly as a management option for low-risk prostate cancer patients, there is a semantic heterogeneity in the literature and guidelines on active surveillance. For instance,

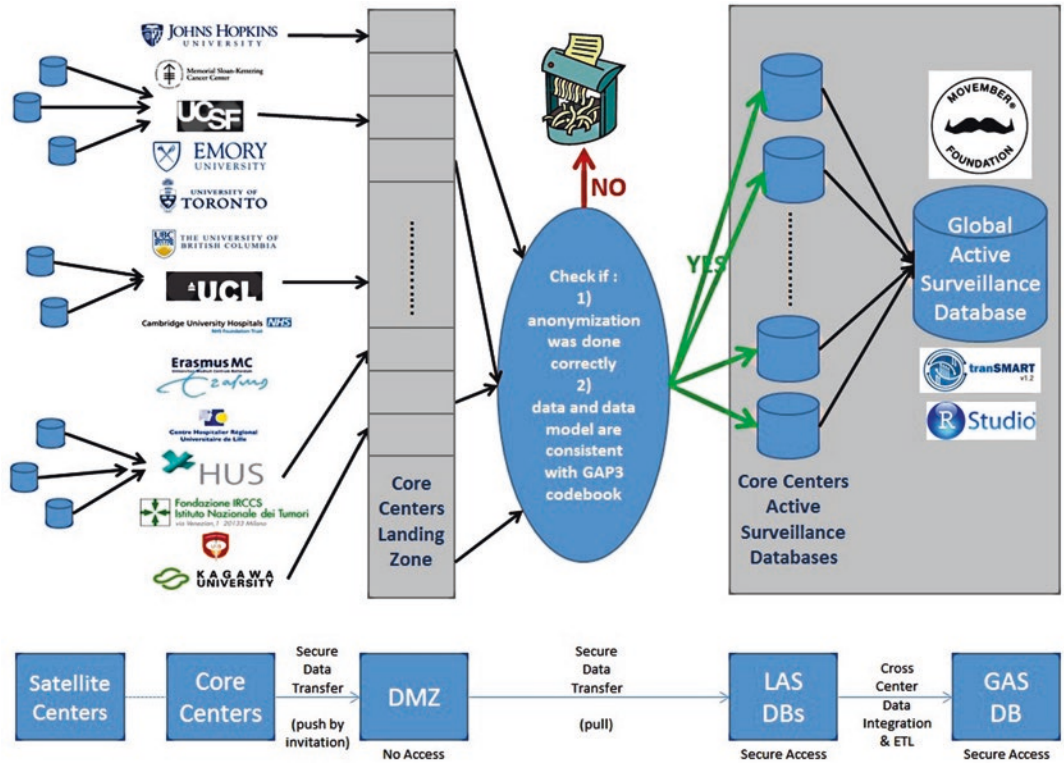

Fig. 13.3 The dataflow from the participating centers to the global database (*The overview of satellite centers is not exhaustive). *DMZ* demilitarized zone; *LAS DBs* local active surveillance databases; *GAS DB* global active surveillance database; *ETL* extract, transform, load

the specific definitions of the terms *active surveillance* and *watchful waiting* (*WW*) are inconsistent in the published literature and can elicit significant confusion. Further, various definitions of low-risk prostate cancer exist in these guidelines, as specified by different combinations of clinical criteria including clinical and pathological characteristics. Also, definitions of disease reclassification and progression differ among published guidelines, and multiple criteria for the initiation of curative treatment are proposed. Problems resulting from the use of ambiguous language include hindered clinical decision-making, particularly in multidisciplinary collaborations, and limited opportunities for research [15]. Further, it has raised a barrier that hampers exchange of knowledge within and between fundamental domains of research and research groups [16]. An important step toward global consensus was therefore to define some sort of "new (but uniform) Active Surveillance language." Consensus definitions were derived using a modified Delphi method in which a panel of leading prostate cancer specialists in the field participated [17].

Phase 2: The Development of a Consensus Guideline on Active Surveillance

Publication on Active Surveillance Guideline Consensus

The aim of the GAP3 initiative is to create a global consensus on selecting and monitoring men with low-risk prostate cancer. As a first action, the project leaders started with the development of a guideline consensus on active surveillance based on a review of the current guidelines available around the world. Existing

guidelines on active surveillance for clinically insignificant prostate cancer were systematically reviewed to provide a comprehensive view of the recommendations regarding patient selection, monitoring during active surveillance, and disease progression [18].

Statistical Analysis of the Global Database

The consensus-based guidelines will be adapted based on the outcomes of the statistical analysis of the database. A brief description of the statistical analyses plan is provided below.

A conceptual framework was developed to identify which patients are most suitable for active surveillance, relating life expectancy, risk, and treatment choice (Fig. 13.4). If the patient's life expectancy is relatively short, watchful waiting is the preferable option. If the patient's life expectancy is relatively long, and the risk of adverse outcomes due to prostate cancer is relatively high, immediate treatment is preferred. Active surveillance is suitable for men with a relatively long life expectancy and low risk of adverse outcomes. The adverse side effects of treatment are avoided, and if disease progression occurs, curative treatment may still be initiated. The key challenge here is to reasonably weigh the harms and benefits of all treatment options and identify the preferred treatment option for a patient.

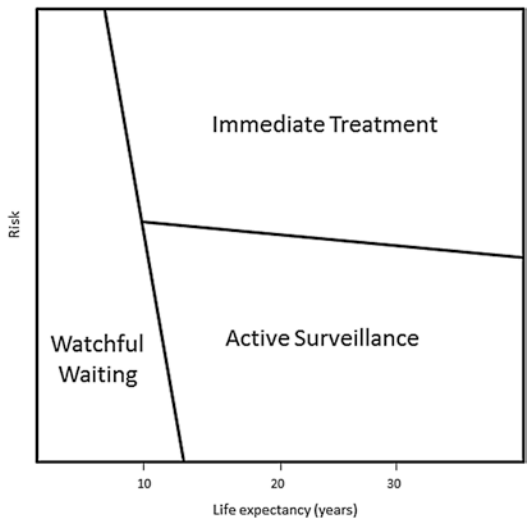

Fig. 13.4 Conceptual framework to identify patients suitable for active surveillance

Two possible end points are relevant for selecting patients that are fit for active surveillance, namely, reclassification (i.e., disease progression after 1 year) and progression (i.e., disease progression after 4 years). To identify patients who leave active surveillance within 1 year of commencing active surveillance, prediction models will be constructed to estimate the probability that a patient moves off the active surveillance protocol within 1 year. A similar approach will be followed when predicting the risk of leaving active surveillance after 4 years, using cox or logistic regression models. Performance measures used to assess the resulting models are discrimination, calibration, and clinical usefulness. Specific attention is needed for dealing with different patient cohorts. Final presentation of models will focus on risk stratification to categorize patients by likelihood of stopping active surveillance, and this will be compared to currently used stratification schemes.

To gain more insight in the best criteria for monitoring patients on active surveillance, different follow-up schedules will be compared to the most intensive follow-up schedule and examined according to how many biopsies would be avoided versus how many progressions would be detected at a later time point. This has previously been studied by Kates et al. [19], who compared the Johns Hopkins and Prostate Cancer Research International Active Surveillance (PRIAS) protocols. Furthermore, the compliance rate of patients to the guidelines in each study will be compared. Different prediction models have been developed to predict the probability of detection of upgrading at biopsy (Ankerst et al. [20]; Sooriakumaran et al. [21]; Coley et al. [22]). Validation of these models will be performed in the GAP3 database. Subsequently, dynamic risk prediction models will be created that update the risk predictions as new data becomes available using joint models [23].

We furthermore need to establish what should trigger the switch from active surveillance toward active treatment and what should trigger

the switch from active surveillance toward watchful waiting. The first step is to describe the current criteria for switching from active surveillance toward active treatment. These criteria can then be used to define relevant end points and develop statistical prediction models predicting the risk of meeting these criteria. These prediction models can be either static or dynamic models, i.e., based on baseline data only, or incorporate information gathered during active surveillance, such as PSA and biopsy results. Also, the different criteria in the available cohorts for switching from active surveillance to watchful waiting will be described. In the current cohorts, these criteria are typically defined as the moment the life expectancy is below a prespecified threshold. Using the estimates of life expectancy from a previous step, we can provide more detailed estimates of life expectancy for patients on active surveillance, which may be used to define the moment of switching from active surveillance to watchful waiting.

Based on the outcomes of these statistical analyses, consensus guidelines on active surveillance will be generated in discussion between clinicians and other stakeholders.

Web-Based Active Surveillance Platform

As a next step, an online platform will be created in collaboration with the Movember Foundation. This worldwide active surveillance platform will provide access to the active surveillance guidelines which will be available in various languages. In addition, the worldwide active surveillance platform will provide information on active surveillance as an acknowledged treatment option, current active surveillance initiatives and collaborations, and the latest (prostate cancer research) news and events and will offer suggestions for lifestyle changes (such as improving nutrition, reducing stress, and getting more exercise). The GAP3 outcomes will be complementary to other activities funded by the Movember Foundation, such as the GAP1 initiative on biomarkers, GAP4 project on prostate cancer exercise and metabolic health, and Movember's prostate cancer survivorship support program, TrueNTH.

Results

Currently Available Guidelines [18]

As a first action, the project leaders started with the development of a guideline consensus on active surveillance based on a review of the current guidelines available around the world. To date, 16 guidelines [4, 24–38] have been published to assist both clinicians and patients in critically important treatment-related decision-making, which include criteria for enrollment of patients in AS programs and their subsequent management. According to recommendations contained in all guidelines, AS is primarily recommended for patients with low-risk tumors. Some guidelines have taken the position that AS could be an appropriate management strategy for patients with intermediate- or high-risk disease.

Summary of Eligibility Criteria [18]

Multiple criteria have been proposed for identifying patients with prostate cancer who have a favorable prognosis and are, therefore, candidates for active surveillance. Most available international guidelines recommend clinical risk stratification based on patients' tumor stage, serum PSA level, Gleason score, and estimated tumor volume as the primary means of refining patient selection. PSAD, the minimum number of prostate biopsy cores acquired, the patient's life expectancy, the presence of comorbidities, and the patient's preferences have been advanced by some but have not, thus far, been universally adopted as risk stratification tools. Although many variations in risk stratification schemes currently exist, guidelines predominantly recommend that the most suitable patients for active surveillance are those with pretreatment clinical stage T1(c) or T2a prostate cancer, serum PSA

<10 ng/ml, a biopsy Gleason score of 6 or less, a maximum of one or two tumor-positive biopsy core samples, and/or a maximum of 50% of cancer per core.

Summary of Surveillance Type and Frequency [18]

Following initiation of active surveillance, most guidelines recommend serial measurement of serum PSA levels, digital rectal examination, and surveillance biopsy sampling in order to identify pathological progression. However, many uncertainties remain surrounding the optimal timing of these surveillance strategies. PSA kinetics and MRI are less frequently recommended as methods to identify whether or not a patients' cancer has progressed.

Summary of Switching Criteria [18]

Several guidelines do not include any criteria on switching from active surveillance to definitive therapy. Definitions of disease reclassification and progression differ between guidelines, and multiple criteria for initiation of treatment are proposed. Some guidelines advocate the initiation of curative treatment if progression to a higher-grade tumor (mainly described as Gleason pattern 4 or 5) is observed or if an increase in the number of tumor-positive biopsy cores (>2 of a recommended minimum of 10 cores) or an increase in the extent of cancer per core sample (to >50% of cancer per tumor-positive core) is detected on the analysis of surveillance biopsy samples. Clinical progression detected during DRE (although currently not clearly defined), a serum PSADT of <3 years, or a change in patient preference is also regularly described as risk reclassification criteria, leading to initiation of definitive treatment.

Despite the ample availability of guidelines on active surveillance for patients with prostate cancer, consensus on inclusion criteria, surveillance schedules, and intervention thresholds is currently lacking. The future of active surveillance and its uptake as a management modality will depend on better patient selection and validated monitoring schedules to improve the identification of disease progression. Combining existing evidence and gathering more long-term evidence are needed in order to derive a broadly supported guideline to reduce variation in clinical practice and to optimize clinical decision-making. This is where the GAP3 initiative can make a significant contribution.

Semantics [17]

To reach international consensus on the definitions of terms related to active surveillance, a modified Delphi method was used in which a panel of 12 leading prostate cancer specialists from Australasia, Europe, the UK, Canada, and the USA participated. An iterative three-round sequence of online questionnaires which addressed 61 individual items was filled out by each panel member. Consensus was considered to be reached if ≥70% of the experts agreed on a definition. To facilitate a common understanding among all experts involved and resolve potential ambiguities, a face-to-face consensus meeting was held between the Delphi rounds. In the end, 100% ($N = 61$) of the survey items achieved formal consensus.

In order to help clinicians, researchers, and patients to gain an understanding of the specific active surveillance terminology, a glossary of terms has been developed. In this glossary, active surveillance is defined as a monitoring strategy for patients with prostate cancer with the aim of avoiding or deferring curative treatment. Watchful waiting is described by the experts as the management of patients with a limited life expectancy, where palliative treatment (without curative intent) is initiated if symptoms develop. Low-risk prostate cancer is considered to be a prostate cancer with a low risk of progression on repeat biopsy (i.e., an increase in Gleason score or more cores positive for cancer) and with a good prognosis. Reclassification has been defined as a change in risk group as a result of reevaluation of clinical or pathological parameters, unlikely to be due to actual changes in cancer biology. According to the expert panel, "progression" is a broad term indicating worsening of the disease, based on an increase in grade or extent of

disease after a follow-up period, unrelated to resampling. For all terms and definitions, the following link is available: (http://www.nature.com/nrurol/journal/v14/n5/fig_tab/nrurol.2017.26_T1.html) [17].

Agreement between international experts has been reached on relevant terms and subsequent definitions in active surveillance for patients with localized prostate cancer. The glossary of terms is intended to provide a generic outline of the domain of active surveillance and is designed to create common terminology for the profession and to capture the essence of active surveillance for others. The standard terminology may support multidisciplinary communication, reduce variation in clinical practice, and optimize clinical decision-making. The glossary of terms will form the basis for all communication within the GAP3 consortium and will facilitate the retrieval of relevant data, information, and (exchange of) knowledge.

Content of the GAP3 Database: Descriptives [39]

The database has a significant amount of highly informative patient data which provides the research teams with a wealth of information about active surveillance for low-risk prostate cancer. The Movember active surveillance database currently contains datasets of 15,101 patients from 25 centers.

At time of diagnosis, median age was 65 yr (IQR 60-70); median PSA was 5.4 ng/ml (IQR 4.0–7.3); median PSA density was 0.12 ng/ml (IQR 0.09–0.17); and median prostate volume was 43 cc (IQR 33–59). Most men had a clinical stage T1 (72%), a biopsy Gleason score of 6 (89%), one tumor-positive biopsy core (60%) and no comorbidity (66%).

Men on AS had a median follow-up time of 2.2 years (IQR 1.0–4.5). Maximum follow-up time was 21.3 years. After 5, 10, and 15 years of follow-up, respectively, 58%, 39% and 23% of men were still on AS; 23%, 30% and 36% discontinued due to protocol-based progression (Fig. 13.5).

The project is currently in its analysis phase. Publication on consensus guidelines in a peer-reviewed journal is aimed for in 2019 and will be made available to patients by publication on the Movember website in various languages after this date.

Dissemination of Guidelines

The development and publication of a global clinical practice guideline are only the first steps in the process to improve patient care [18]. There are a number of opportunities to consider as to how to most effectively translate the knowledge generated through the GAP3 project into action that benefits men. Focus should be on the adoption of the guidelines into clinical practice, assuming the evidence underpinning the guidelines is sufficiently strong. The adoption of the guidelines into clinical practice can be influenced by integrating the GAP3 guidelines for prostate cancer clinical quality registries (national, state, or hospital based) and clinical professional education programs (e.g., prostate cancer UK health professional program) and dissemination at major meetings. In the longer term, there is an opportunity to influence patient decision-making by leveraging/strengthening existing relevant decision support applications using the GAP3 data, facilitating education of the GAP3 clinical guidelines in key patient education materials, and undertaking media campaigns in selected countries to promote the GAP3 guidelines.

Future Plans

The GAP3 project is finished under its current project plan in February 2017. Additional funding has been committed by the Movember Foundation to support the conclusion of the current GAP3 project and to provide sustainability of the GAP3 database over the medium-long term (from March 2017 until February 2019). By maintaining the current database and updating the clinical data annually, continuous information

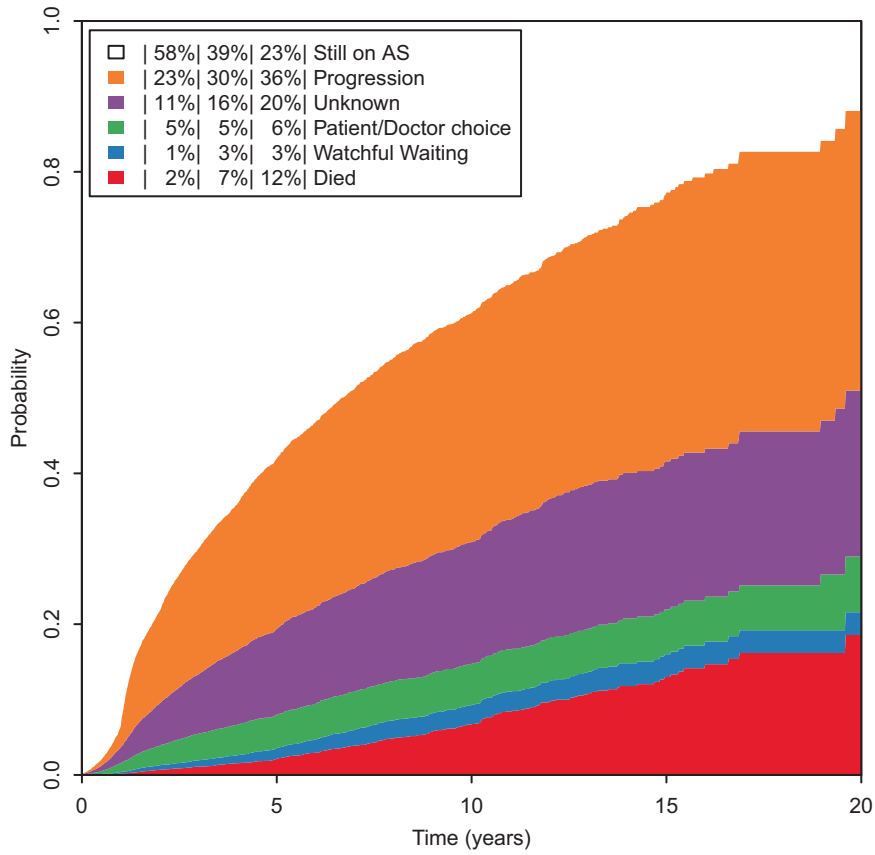

Fig. 13.5 Discontinuation of active surveillance over time. *Progression* = clinical and pathological progression, clinical progression, other PSA kinetics, pathological progression, PSA progression (PSADT < 3 years), or radiological progression

will be provided for the web-based active surveillance platform (e.g., epidemiologic data, information on active surveillance as a treatment option, current initiatives and cooperation, suggestions for lifestyle changes, etc.).

There is a growing evidence that the current strategies for active surveillance are safe for the large majority of patients, but there is still room for improvements regarding patient inclusion and monitoring in order to include more men with low-risk tumors, reduce unnecessary biopsies, and therefore improve overall quality of life. MRI is regarded by experts globally as an essential and increasingly important technology for the future management of active surveillance. During the course of the GAP3 project, it has become apparent that there is an urgent need to assess the value of MRI with respect to lesion definition and changes over time. The current patient series lack sufficient volume to be analyzed appropriately, and therefore the need to combine these data in a database is of pivotal importance. This also holds true for genomic testing, the role of which within active surveillance needs further research, as well as the role of quality of life in the decision to initially pursue active surveillance rather than active treatment. There are high expectations that the worldwide GAP3 database, if sustained and adjusted to these anticipated analyses, will be a powerful decision-making tool. Therefore, new patients will be added to the GAP3 database for which MRI data is available.

To exploit the available data as best as possible, the global database will be accessible for

research projects over the medium-long term after majority approval by the clinical research partners (not in an open access format, but in collaborative projects). Collaborative activities will be employed within the GAP3 consortium and with relevant external partners.

Concluding Summary

In summary, active surveillance is evolving into a well-accepted management strategy for appropriately selected men. Unless the overdiagnosis of indolent prostate cancer is reduced by alternative diagnostic strategies, active surveillance will continue to play an important role. The GAP3 initiative will make significant contributions to this field of research by offering standard, evidence-based guidelines [18]. Clinicians will be able to use these guidelines to more confidently identify men that are suitable for active surveillance and to also decide whose prostate cancer has progressed and will, therefore, require treatment. Such guidelines will provide reassurance to men that they have made the best treatment choice for their type of disease [18]. Longer follow-up, achieved by ongoing commitment of GAP3 participating centers, and the evaluation of sophisticated imaging and new biomarkers, will result in more valuable data and eventually in better patient outcomes.

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Better-Informed Decision-Making to Optimize Patient Selection

14

Lara Bellardita, Paola Dordoni, Letizia De Luca, Julia Paola Menichetti Delor, and Riccardo Valdagni

Introduction

It probably happened to everyone, when visiting a city, to find those panels that say "You are here!" with a well-marked exclamation point indicated on a map. The information per se may not be as useful as one could think. Knowing where we are is definitively something we need to know, but that is only the starting point. We will then need to figure out how we want to continue the visit of the city, and we will make decisions based on what we are interested into: we may want to wander around the old city centre or discover the more modern district and probably avoid the dodgy neighbourhoods. Some travellers like to simply get lost and let themselves be surprised by what the place has to offer, but at some point everyone needs to know where they are and how to proceed.

We definitively need information to experience a satisfactory journey. When travelling, we get maps at the airport info point or at the hotel concierge. We buy guides, reporting historical and cultural information as well as useful, practical tips on where to sleep, eat and shop. We enquire locals regarding places where they usually go. We ask questions, require directions and look for advices. That of course may change from person to person, as each one of us is a traveller with his or her own unique demands, expectations and features.

Shouldn't we expect at least something similar from men when they enter the unknown territory of cancer? Cancer is somehow still a "taboo" word which throws men and their loved ones into the medical labyrinth, of which they have no knowledge or understanding [1]. The land is stranger and threatening and no map or direction is immediately available.

When men are diagnosed with potentially low-volume and non-aggressive prostate cancer (PCa), they start a complex journey into an unusual territory. They deal with the opportunity of choosing among multiple therapeutic/observational strategies that differ in terms of clinical and personal costs and benefits. They may, at least initially, feel lost and disoriented navigating the stranger territory of disease. When active surveillance (AS) is a viable option offered by clinicians, men and their families may perceive initially as a counterintuitive one saying "You have cancer but you do not necessarily need to treat it immediately (and possibly will never need to)". In order to optimize patient selection, men might need support in seeing things

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from a different perspective and go beyond the traditional scenario of "cancer = treatment" ("as soon as possible!").

Supporting men and their families in the treatment/AS decision-making (DM) process can be challenging and time-consuming. This chapter aims to present an overview of the factors that influence the DM process when AS comes into play and to suggest strategies and tools that can facilitate the communication process between physicians and men diagnosed with potentially non-aggressive PCa, thus improving patient selection in AS. We will discuss AS DM based on existing literature and our 10 years of experience within a multidisciplinary setting, where psychologists collaborate with physicians and patients throughout the whole DM process [2, 3].

How Do Patients Choose? Treatment/AS-Related DM

The information "you are here" could be useful for a traveller at the starting point, but that information does not guide him throughout the travel. Patients who are offered active treatment and AS options have to figure out where they want to go and how they want to proceed in order to make an aware choice. For men who start the journey into the unknown and frightening territory of cancer, coming up with a decision that is fully more satisfactory than another is a complex process. The acceptance of the prostate cancer diagnosis often represents the very first milestone. Men who are generally in good health suddenly and unexpectedly become oncology patients. As a matter of fact, the prostate-specific antigen (PSA) test that eventually triggered a biopsy is often prescribed without providing men adequate information on what it really measures and what could be the scenarios emerging from the detection of PSA levels that are considered out of the normal range [4–6]. The following steps imply understanding the nature of their disease and facing the unexpected possibility of being offered more than one option, including AS when feasible based on specific criteria. Men may enter a phase of *decisional conflict*, i.e. they feel uncertain about the course of action to be taken as choice among competing options involves risk, loss and challenges to personal values [7]. DM about cancer treatment has been defined as a "simple matter: choose the option that prolongs life most" ([8], p. 1). When the patient has more than one option, and such options are equivalent in prolonging his life, then the direction would be "choose the one that maximizes quality of life" (ibidem). But while men can immediately see very clearly that AS is the choice that will likely protect their quality of life by avoiding treatment side effects, the first assumption is not equally straightforward (i.e. they may feel uncertain about AS efficacy in terms of survival) [9].

Literature on DM in men with low-risk localized PCa has shown high levels of decision-related distress at the time of diagnosis [8, 10, 11]. As a matter of fact, disease-related DM is complex, and "the right" – or "one-size-fits-all" – decision does not exist. DM in men with PCa who are offered AS could be particularly challenging because it implies the subjective assessment of complex – somewhat still uncertain – medical information which is, on top of everything, often provided in a "foreign" language, i.e. the medical jargon.

Making decisions – above all when health is at stake – is often a demanding process. People process information – and act – according to their own subjective assessment. Furthermore, choices are often constructed in the moment of the DM process, based on patient's available emotional, cognitive and interpersonal resources [12]. People are guided by how they frame the options when making decisions; the adopted frame is based on their own previous experiences, the related emotions and the value they put on the consequences of each options [13]. Moreover, the frame could be influenced by social norms, routines and personal characteristics.

Scholars have been trying for some time to gain more insight on the DM in low-risk PCa. Categorizations of factors influencing treatment considerations and attitudes have been proposed.

In order to provide a guide for a better understanding of the complex DM process patients

go through, we summed previous categorizations derived from DM literature and represented the main findings in Fig. 14.1. The assumption is that DM is a long-term process starting from the moment of the diagnosis. All throughout the process, patient's characteristics, other people and external events can affect the evolution of the DM process. Some of patients' characteristics (i.e. education) are constant during the whole process and represent what we can define their "background" (the patients' pre-existing baggage). We then distinguish between "internal factors" and "external factors". The combination of these factors at a cognitive level (e.g. ratio between losses and gains of each option) and at an emotional level (fears and expectations) leads to the final decision.

Patients' Backgrounds

As previous studies demonstrated [14, 15], patients have personal characteristics that may impact on the treatment DM process. Demographic, psychosocial and clinical variables may affect patient's final decision. Personality traits such as neuroticism can impact on patients' perspectives [16]. On the contrary, optimistic traits and high resilience have been associated with low emotional distress [17]. Together with personality, personal attitudes towards life and stressful events, as well as age, can influence treatment DM [16, 18, 19]. Findings on younger men highlighted higher anxiety levels at the moment of diagnosis [20]. Younger men may be more exposed to the decisional dilemma of facing death-related anxiety vs the desire to

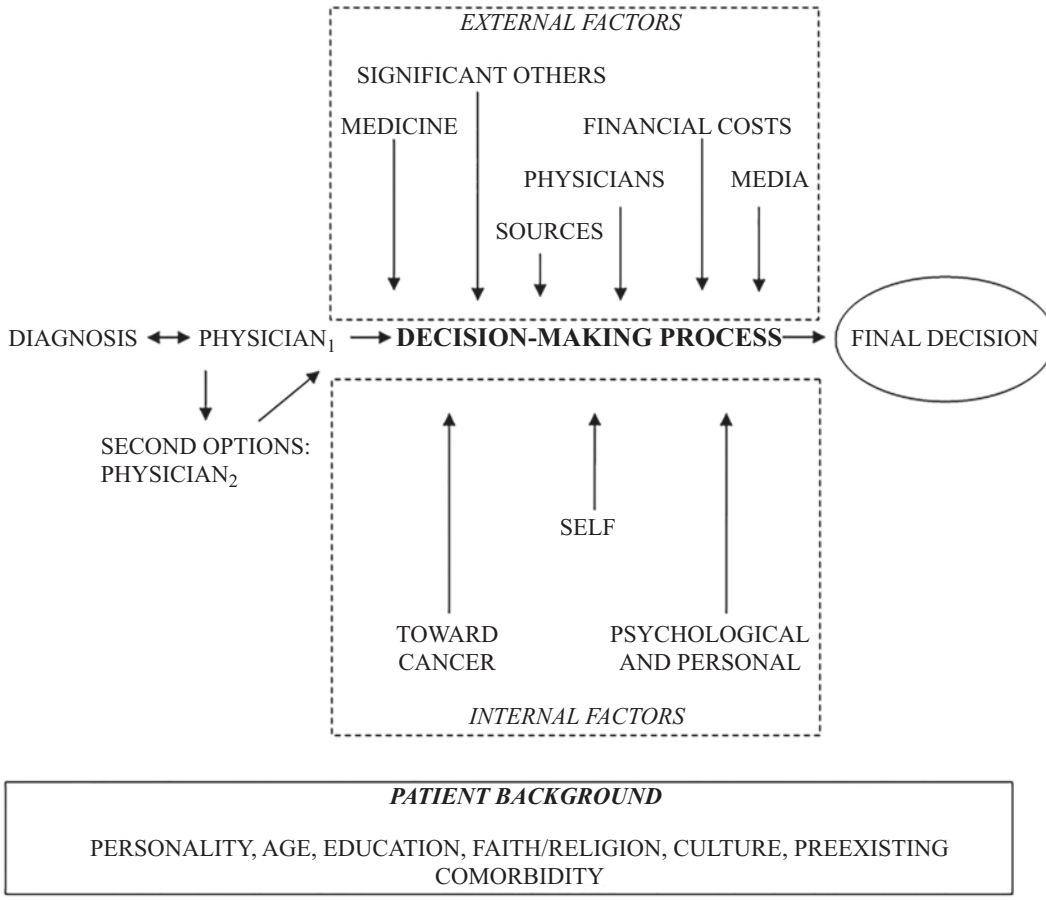

Fig. 14.1 Low-risk prostate cancer DM

protect their quality of life [21]. A further demographic variable that has been discussed in literature is education. Highly educated men were reported as seeking second opinions and having a harder time selecting the treatment especially when specialist's information and recommendations differed [16], whereas less educated men are usually more inclined to assume a passive DM style [18].

Scarce research addressed faith/religion and cultural differences in treatment DM [16, 19]. Faith and religion may act as support in treatment DM process as coping with uncertainty-related distress. Research on differences based on ethnicity showed that men with African-American background were found to report less trust in the healthcare system, which may influence their treatment DM process. Other studies showed that Hispanics, Asian and Latinos were more likely to prefer surgery [19, 22].

Finally, pre-existing medical conditions (such as cardiovascular disease, diabetes or cancer) were reported as crucial variables when deciding for treatment/AS. Some researchers [18, 23] reported that medical conditions did not affect patients' perception of seriousness of their cancer; however, given the paucity of literature on this aspect, more understanding on how the presence of comorbidities influences men's attitude towards AS is needed.

Internal Factors

Patients' values and personal beliefs regarding cancer are important factors influencing treatment DM [24]. When patients consider cancer a sort of *slow-moving turtle* ([18], p. 91), they are more oriented towards AS. On the other hand, men whose belief is that cancer should be removed would be more likely to prefer an active treatment [25, 26] and to more often switch from AS to active treatment [27]. Patients' perceptions of some medical aspects, for instance, specific antigen velocity [27, 28], can make the difference between choosing for an active treatment vs AS; indeed, patients after diagnosis of low-risk PCa often search for scientific evidences [29], and men who consider only surgery may have different perceptions of treatment efficacy than men who consider also other treatment options [19].

Together with personal beliefs, men's attitudes and expectations towards cancer can be precursors of treatment DM process. Patients create their own scenario of cancer when they receive the diagnosis. Assuming, correctly or not, that their physicians objectively explain all the treatment options and the related efficacy, patients may not necessarily develop accurate expectations and may create a personal perception of treatment security and side effects [16, 24]. Men's perceptions of side effects and the extent to which they value a specific aspect of functioning are important components of the DM process too. Moreover, patients may have attitudes towards physicians such as trusting – or not trusting – doctors based on a number of previous experiences, which will make them rely on some experts rather than others [16].

The role of emotions and psychological factors in treatment DM has been discussed. The opportunity to choose treatment/AS may represent an actual burden [19] which affects the DM process itself [30]. Anxiety is a key factor from the moment PCa is diagnosed and in the whole DM process [31]. Literature results in decision-related distress and PCa treatment decisions are not consistent. Some studies reported a relationship between specific treatment and distress, with outcomes such as decision regret when distress is higher [32] and satisfaction with the choice when distress is lower [33]. Conversely, other studies showed no relationship between decision-related distress and treatment options [11]. Finally, some studies revealed the role of anxiety in predicting the decision of patients to move from AS to active treatment [27].

Another important personal factor influencing treatment DM is the fear of uncertainty. According to some authors, this factor is probably the one that mostly accounted for selecting treatment/AS – despite the potential of treatment side effects [34]. The desire to take action in the face of cancer threat can motivate patients in choosing an active treatment over AS; in particular, sur-

gery is viewed as the most aggressive treatment against the threat of cancer [25].

Finally, the way patients deal with the cancer diagnosis may have an impact on the treatment DM process. Attempting to take control of the decision, seeking information and searching for social support are common strategies through which patients positively cope with the diagnosis [16, 18]. Seeking information is one of the most used coping strategies when patients are in need of reassurance [35]. Men with PCa diagnosis who sought information (written information and the Internet) about treatment options ended their search only once the final AS decision was taken [18].

External Factors

Patients may perceive and/or receive "external pressure" from family, physicians, peers, other survivors' experiences and anecdotal experience [11, 16, 18, 19, 29]. Even though a portion of patients prefers not to reveal to others their health status and they prefer their cancer diagnosis to be a secret [18], most men are likely to seek information and suggestions from friends; indeed, vicarious experiences and other people's beliefs play a strong sway over men's final decisions [16]. Differences in treatment orientation may vary based on men's marital status with married/living with partner, men being more oriented to consider only surgery [19]. In particular for younger men, their wives preferred the surgery option. Wives and partners are often described by patients as information gatherers and supporters [16]; some studies highlighted that wives and family pressures extensively influenced patients' DM [36] so that men who were oriented to AS "went back" and decided to have active treatment. There is strong agreement in the literature about the central role of physicians and specialists in the DM process. One of the main sources of information for patients is the physician and there is the risk that *to a hammer everything looks like a nail* and that physicians carry with them a bias determined by their own field of speciality when describing treatment options. A lack of knowledge regarding AS may prevent also physicians including it among the options. A multidisciplinary approach [10, 37, 38] is likely to limit such bias as patients have the opportunity to discuss treatment options with different specialists at the same time. Physicians' points of view on treatment options, the way in which physicians describe diagnosis and treatment options and physicians' recommendations are all elements that significantly influence patients' choice. Physicians' professionalism, expertise, reputation and research profiles may help patients perceive a sense of security and confidence in physicians' recommendations [18], sometimes putting on the background men's own priorities and needs. Most research reports that a small number of men with localized PCa are presented with the option of AS [16, 18, 19, 23, 29, 39]. Physicians may influence patients by directly recommending one option over another, or men could be influenced by physicians' description of treatments. For example, a surgery-oriented urologist may mention AS but then emphasize that the impotence side effect could be avoided by a competent surgeon and that remedies are available to face treatment-related sexual dysfunctions [16]. A recent work [40] highlighted the importance of the messages that physicians give to patients. Specialists who straightforwardly describe observational options as a reasonable alternative can help patients in considering AS.

The agreement among different physicians can influence the DM process; in case of lack of agreement and inconsistencies between different clinical consultations, patients can feel a sense of non-control, anxiety and confusion.

Informal sources of information such as media and the Internet represent important external factors that have an impact on the AS decision. Patients want to be informed; hence, they could arrive at the first visit after diagnosis with all of the information they gathered on the web, TV, newspapers and magazines. The Health Information National Trends Survey data [41] portrayed a shift in the ways in which patients consume health and medical information, with more and more patients looking for information online before talking with their

physicians [42]. Younger men (age 65 or younger) are more likely to engage in web-based search for answers to their doubts [43]. However, older patients may be supported by their family members in searching on the Internet. Patients use many sites to access different types of information. The advantages of the Internet searches are that men can find help in dealing with the diagnosis, taking charge of the DM process and reducing anxiety [44, 45]. The other side of the coin is that men could also gather misleading information from media [45, 46]. It would be helpful to examine in-depth the impact of Internet-gathered information on the decision to select AS.

Finally, it should be considered that in some countries, where the access to care is not provided by the national health care system, treatment financial costs may influence treatment/AS DM [19].

Why (and Why Not) Do Patients Choose AS?

For men who are offered the option of AS, further variables come into play and the DM process can be more challenging. Some factors can represent important levers for patients to choose AS, and some others can hinder the choice of AS. Keeping in mind both the main motivations leading patients to choose AS and the main obstacles and barriers can be crucial in order to overcome selection biases and support an aware choice [47].

Even though the healthcare staff seems to have an often obvious rational underlying the selection to join an AS protocol, patients and their families may have the sensation of "not treating" [48] a life-threatening illness during a first and more treatable stage, which may appear a highly unreasonable choice [24]. First of all, personality and personal attitudes towards illness and feeling of uncertainty can be a very relevant reason why men not choose AS: men may think "wait and see" is not their typical way of fixing problems [29]. The idea of not acting immediately to try to eradicate what is still referred to as the "evil", the "dangerous killer" [49], or that one is sitting on the "crater of a volcano", can effectively trigger feelings of intense anxiety, particularly linked to the reality of living with such a disease, the consequent uncertainty of the outcome as well as a strong sense of lack of control [50]. Van den Bergh et al. [51] found that the most frequent reported disadvantage of AS was the risk of disease progression; patients reported negative feelings in losing control over their treatment decisions, distress and desire for a more active participation in disease management. Uncertainty and fear of cancer could also be the major reasons that lead patients to drop out from AS [52].

Risk perception is another component of the internal set of characteristics that impact the DM process; the term "risk perception" refers to the patients' representation of the potential harm of their cancer in the future. Unfortunately, to the best of our knowledge up until now, studies on this issue are few. From our clinical experience in a multidisciplinary care team, patients' risk perception seems to be a crucial factor guiding DM. While from clinicians' perception the communication of a 3 + 3 Gleason pattern score and the opportunity of AS should be reassuring for the patient and his family, on their side patients may still create a scenario where developing metastases could occur from one day to another.

Demographic characteristics could represent further barriers to the adherence to AS protocol. Patients' age has been discussed as a relevant reason why men not choose AS [53]. Typically, physicians recommend active treatment to younger patients. However, younger patients are likely to be the ones mostly advocating to be active members of treatment DM process given their extended life expectancy. For this reason, decision to join or not to join AS should be extensively discussed with them [54].

Another barrier that should draw clinicians' attention is the family system; family members can be very influential in treatment DM, as by far most patients consult with their spouses or significant others before making treatment choice

[55, 56]. It is not unusual for some patients to report pressure from family members to pursue a more aggressive treatment, leading to the exclusion of AS as a viable option [57].

The experience of other cancer patients is an important reason to exclude AS; anecdotal and others' experiences could elicit fear of cancer and of its consequences.

Last but definitely not the least, physicians play a key role in guiding patients' treatment DM and, in turn, in patients' final decision [58]; in particular, physicians' recommendation is often identified as one of the most important factors driving the DM process against AS protocol [18, 26, 53, 59]. Physicians should present unbiased information in their discussion with patients as a significant proportion of AS candidate could be denied access to this option solely because of their physician's attitude towards it [60] and because of a general lack of medical support [61]. A hurried and inaccurate flow of information between the doctor and patient is therefore likely to affect access to AS. Few patients opt for AS because the physicians recommended it as the best option for them [18]. Nevertheless, a study from Gorin et al. [60] on men on AS showed that physicians' influence was the greatest contributor (73%) to patients' decision to elect the treatment, followed by avoiding incontinence consequences (48%) and erectile dysfunction (44%). Patients who elect AS are mostly motivated by the desire to maintain their quality of life and delay the potential effects of active treatments [18, 24, 51, 62].

In summary, receiving a cancer diagnosis may catapult patients in a state of urgency, driving them to request rapid and concrete interventions; this scenario is also typical in case of low-risk PCa diagnosis despite the lack of a significant threat for survival. Basically "staying with the uncertainty" means "taking a risk for the future", and in case patients do not receive enough support and reassurance, fear can guide the decision.

We conclude that there are both internal and external reasons why men choose and not choose AS; interventions are needed to prevent bias from external pressures and to support psychological distress related to treatment/AS DM, thus overcoming the barriers to AS.

How to Overcome Barriers to AS

Important barriers can hinder the patients' choice of AS – as demonstrated by the low uptake of AS among potentially eligible men [37, 63–65] – and can consequently reduce the possibility for patients to select AS even when it would be a suitable choice reflecting the patient's preferences. As a result, patients risk making an unaware and uninformed choice, which is often an unsatisfactory choice. This can lead to difficulties in driving the selected choice forward and, consequently, to poor health outcomes. Following these premises, it is evident how overcoming barriers to patients' selection of AS can be of vital importance for patients to travel to the chosen treatment option at best and for healthcare systems to reduce costs of improper use of services [66].

How can barriers to AS be overcome? How can patient selection in AS be optimized? Sustaining PCa patients' ability to make an aware and informed choice and making patients main actors of the process of DM needs that patients are properly equipped – first of all, with regard to information given – and that a shared decision-making (SDM) process is supported by healthcare professionals. The selection of the optimal treatment strategy implies two main assumptions, i.e. informing patients about the multiple reasonable available options and thoroughly discussing options while taking into consideration their own preferences and values [12]. The benefits of similar efforts can be very important. In fact, literature showed that better-informed patients tend to improve preference for no active treatments [67] and applying a SDM process allows even more fair and ethical choices to be sustained [68, 69].

Give a Map: Better Information, Better Equipment to Optimize Patients' Choices

It is impossible to choose an option, if one does not know that there is an option and that this option is reasonable [40]. Receiving and understanding the complex information about treatment options and outcomes is a necessary condition

for patient participation in the treatment decision process [70]. Patients desire this information; they need to know how to care for themselves and for their health [71]. Furthermore, if patients are not informed, they will be unable to assess "what is important to them" and so to establish informed preferences [72]. Establishing informed preferences and taking a shared decision is a multiphased journey which necessarily starts from making patients aware of what is happening to them and of what they can do to handle the situation.

The clinical encounter is a critical and pivotal event in this sense [72, 73]. The first goal of this encounter is to provide patients with information on what is happening to them. Starting from what patients know can facilitate defining where they are, which information they already have and whether these are correct [72]. And yet, the information "you are here" is useful but not enough to get the patient to make an aware choice. Patients should be given a "map". Thereafter, a clear and balanced presentation of relevant, reliable and evidence-based information should be assured. First of all, information concerning the care process should be provided. Second, all the treatment options should be explored and presented. This is an important moment to make AS a reasonable option and reduce the potential biased imbalance for AS [40]. Finally, patients need to be informed on all the relevant advantages and risks of each option. Disease-related outcomes are in first line, but also information on sexual, psychosocial and lifestyle changes are important for patients [54, 61, 71].

As previously highlighted, it is important to consider that the clinical encounter is not the one and only place for information exchanges: patients seek information also in other moments and from different additional sources [73]. If properly supported and reliable, that information can be an important supplement able to enhance patients' skills in managing the clinical encounter and the disease's turning points as best as they can. Indeed, providing information in different alternative formats can make relevant health messages more effective [74]. Educational activities and health information-seeking behaviours before and after the clinical visit have been proved to improve participation levels in treatment DM and psychological autonomy [73]. Last but not least, receiving information from additional sources has been demonstrated to make the choice of AS more trodden [73], confirming the key role of different health information in fostering a fair and aware choice.

The Role of Decision Aids (DAs)

Throughout the years, several aids have been developed to allow low-risk PCa patients making an informed choice [75–79]. These tools are specifically developed to support the DM pathway – particularly, the low-risk PCa patients one [77] – with the advantages of being equitable, evidence-based and not biased. Reviews of these aids [76–80] reveal that summarizing information is the main function generally covered. As showed above, providing reliable and balanced information is a necessary condition for DM. DAs might help ensuring that patients will receive clear, well-structured and complete information on PCa and treatment options. Booklets or leaflets, Internet pages managed by advocacy associations or web sites and informative videos or DVDs have been developed with this aim, and evidences suggest that they can increase patients' knowledge and accurate risk perception [79]. However, evidence on aids for informational purposes only are limited [81], as DM does not end with providing information. Decision aids can help further catalyze the DM process since they can provide an additional pivotal function: summarizing pros and cons of the different options and helping patients weigh them based on their preferences and values. Similar tools generally include preference or value clarification exercises or guided steps for treatment decisions, which can help eliciting the patient's lens and can help patients making value-based choice. Examples of tools including a value elicitation component are those based upon the Ottawa Decision Support Framework [89]. These are evidence-based, take-home, self-administered tools aimed at increasing the likelihood that patients' decisions are based

on better knowledge, realistic expectations and personal values through simple-to-follow tasks and exercises [80, 82]. Similar tools including value clarification exercises can have further positive consequences on man's well-being. Indeed, they can help in lowering the decisional conflict related to feeling uninformed and unclear about one's values, with a consequent decrease of anxiety and uncertainty [79, 80]. Even more, they can help patients taking a proactive role in the DM process [79, 80], improving the rates of patients choosing an option congruent with their values. Finally, they can improve communication with healthcare professionals [83]. More complex and detailed DAs, including both informational and decisional support, have thus been proved to be more effective than those supporting only information [83]. Even more, reviews revealed that not all of the aids discussed AS [37]. Up-to-date DAs have often given little attention to AS [84], and there is still a need for new DAs that highlight AS as a reasonable option. For example, narrative framing (i.e. providing key messages to propose AS as an acceptable choice) is suggested as a useful technique to be included in DAs to sustain the reasoned adoption of AS in clinical practice and to reduce the imbalance for overtreatment [75, 85]. The advantages of DAs for DM can be huge. However, to date some limitations in DA development and delivery may hinder the opportunity of these tools to allow an informed DM to be realized. Scholars must develop a new generation of decision support interventions addressing both the informational and the preference-support aims, including AS as a reasonable option, systematically developed, methodologically sound and consistent with the international guidelines (i.e. the International Patient Decision Aid Standards) [79]. Furthermore, barriers to implementation in clinical practice of such tools need to be urgently overcome, and there is a need for studies aimed at understanding how to best implement those tools in clinical practice [79].

Patients and clinicians can take advantage of DAs, i.e. tools that have been developed in order to provide clear, well-structured and complete information on PCa. Booklets, Internet pages managed by advocacy associations and informative videos, they can all increase patients' knowledge [86]. DAs that include explicit values clarification exercises improve informed and value-based choices with positive consequences in terms of lowering the decisional conflict and increasing the levels of engagement and the rates of patients choosing an option that is congruent with their values [83].

Co-drive: Decision-Making Is a Double-Deck Call

Educating the patient and fully informing him about the different treatment options and outcomes is surely a first essential step to ensure that decision is taken on responsibility of the patient and that all the options are equally considered [67]. However, this is not enough to guarantee that patients are engaged in the DM process and that they would make an informed, individualized and reasoned decision based on their realistic values and preferences. Only informing patients is not enough; we need to consider patients' personal interpretation of decisions. This statement is supported by literature on DAs and also by that on SDM [66, 83]. Considering patients' values and preferences is particularly important in the context of low-risk PCa where decisions are highly preference sensitive. Listening to the patient's voice can thus allow patients making "the best choice for them". Patient values about the pros and cons of the different treatment options need to be elicited, explicitly understood and incorporated into decisions. Furthermore, since perceptions of outcomes are shaped by how patients perceive themselves in that specific life moment, personal factors need to be considered too [73]. This means considering patients as persons who are the main actors of their care and communicating with them not only about medical factors but also about personal ones. "Where would you like to go?" and "How can I help you get there?" are metaphorically the questions that should be addressed. Finally, it is important to consider that the option of AS starts out with disadvantages because of the conventional wisdom that cancer

needs an urgent treatment and that delaying it can put the patient at risk [40]. In this sense, patients' values and expectations for care need to be explored and balanced in a direction that is aligned with the evidence-based guidelines for low-risk PCa treatment. This means that a personal appraisal of information about treatment choices requires not only supporting but also guiding. Patients need a co-driver. DAs can support this co-driving, but they cannot replace it. Patients need someone expert (i.e. the physician) who will work in tandem with them and share the responsibility of both offering and requesting information in order to reach a SDM process [68]. Serving as a co-driver for patients necessarily means shifting from a paternalistic paradigm where the physician makes decisions and then informs the patient (paternalistic model) to a new approach to care where patients are considered partners in the care management and in the DM process [87]. This means not only that an informed decision should be reached by patients (informed model) but that this decision is shared and discussed in a journey where healthcare professionals colead with the patient [88]. In the SDM process, professionals – as well as the wider network of the patient – collaboratively work with the patient throughout the different steps of the DM process (i.e. information exchanges, preferences' elicitation, deliberation about treatment, final decision) to make the deliberation process a success and, thus, to arrive to a shared informed decision [88, 89]. They recursively share information, jointly participate in the DM and agree in a course of action that incorporates the patient's informed personal preferences [90, 91]. All the involved actors work towards reaching an agreement, and all have an investment and engagement in the decision. The resulting SDM process is thus iterative and recursive and allows moving from an initial preference guided by patients' lay values and expectations to a patient's expert and informed preference. Co-driving with patients in the SDM process is thus a good deal. There are some real questions that could be useful to effectively guide patients to reach a shared informed decision (e.g. "Which benefits and harms matter most to you?" or "Who can support and advise you in making a choice?"). Figure 14.2 reports a toolkit of questions that we have been using to support AS DM and that we developed based on four main areas of the SDM process as based on the Ottawa Decision Support Framework [89] (i.e. identify the decision and the different options, identify pros and cons of the different options, weigh pros and cons of the different options, identify needs for support in DM).

But why should a similar process be adopted? Literature evidences show that there are huge benefits to adopting SDM in clinical practice.

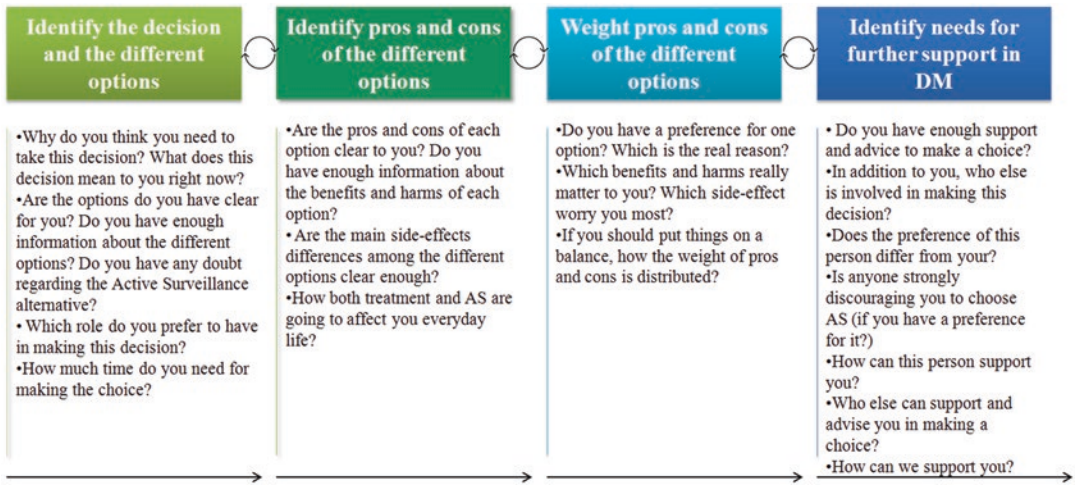

Fig. 14.2 Treatment vs AS DM: Questions to engage patients in a SDM process

SDM has indeed the potential to reduce overtreatment and to sustain more fair and ethical choices [68, 69], as well as to improve patient satisfaction and health outcomes [92]. SDM is currently considered paramount from an ethical perspective to begin with and a way of enhancing patient engagement and activation [93]. Not surprisingly considering these findings, SDM is being included in different healthcare policies and guidelines for PCa as hallmark of good clinical practice (i.e. American Urological Association, American Cancer Society and the US Preventive Services Task Force) [90, 91]. It is however still difficult to effectively apply it in practice. Patients more and more want to play an active role in the DM and desire to collaborate with professionals [71, 94–97]. Professionals, in turn, need to be engaged in a similar effort and should be trained to recognize the value of SDM [94–96].

Shared Decision-Making: Better if Multidisciplinary

Objective evidence and patient preference guide treatment decisions in low-risk PCa, but specialists' bias guide them too [37, 60]. Particularly where evidence does not strongly support a single clearly superior option, simultaneously meeting the different specialists can help ensuring that specialty bias is avoided. For these reasons, multidisciplinary team care has been increasingly incorporated into PCa clinical practice [2, 98]. In multidisciplinary team care, visits are managed by different specialists (e.g. surgeon, radiation oncologist, medical oncologist, psychologist) who work in chorus to afford patients the opportunity to discuss the different options in an interactive fashion and to make informed decisions consistent with their goals of care [38]. In similar clinical encounters, power roles are reorganized in a more balanced and democratic way, and patient centeredness is ensured [99]. As such, multidisciplinary SDM in PCa management has been proved to overcome clinicians' preferences and bias and thus improve selection of AS among patients [37]. High satisfaction rates of patients are reported in studies exploring the adoption of this approach as well as enhanced outcomes and reduction of treatment regret [100].

SDM is a double-deck journey which involves on one side a multidisciplinary care team and on the other side a patient. No man is an island. Patients are surrounded by significant others (i.e. family members and friends), who can play a central role in the treatment DM process. Others' opinions could introduce complexity in this process; for instance, wives of patients with low-risk PCa have been often perceived as an external pressure on the treatment decision [16]. In one study exploring the relationship between the patient's preferred role in treatment DM and the searched advice, men who assumed a collaborative role rated the advice from their partners as more important compared to men who assumed either an active or passive role [54]. This signifies that SDM implies considering that also family plays an important role.

Why and How: Training Physicians for SDM?

The management of low-risk nonaggressive PCA urges clinicians to adopt a SDM procedure and to go beyond the old paternalistic model associated with the idea of patient as a totally passive subject, subordinated to the figure of a prevailing and self-ruling physician, solely responsible for making treatment decisions [101]. There is the need and the opportunity for a new concept of patient and care, based on engagement, shared responsibility, interdependency and mutual exchange. Treatments should occur only after a patient is thoroughly informed about the implications of the choice and has agreed to the procedure on the basis of such comprehensive information [102].

While academic medicine embraces the construct of SDM as a clinical ideal [102], there are still many issues regarding the implementation of such approach in day-to-day clinical practice. In fact, there are still many studies highlighting the influence that physicians play in defining the outcomes of the DM process related to PCa [18, 26, 53, 59]. However, specialists involved in PCa

management should pay special attention to the actual involvement of patients and stimulate them towards the understanding of the most important factors in relation to the DM process, in order to effectively advise them about the most appropriate treatment options.

SDM implies four requisites [103]:

1. At a minimum level, both the physician and patient are involved in the treatment DM process.
2. Both the physician and patient share information with each other.
3. Both the physician and the patient take steps to participate in the DM process by expressing treatment preferences.
4. A treatment decision is made and both the physician and patient agree on the treatment to implement. Each component emphasizes the central role of communication skills.

Communication between doctor and patient represents the heart of medical practice, with therapeutic alliance being the basis for information exchange leading to adequate diagnosis and treatment plan. Effective communication helps improve patients' knowledge about their disease and thus supports a higher compliance to the treatment, optimizes time management and reduces the risk of care staff burnout [104]. Conversely, a deficiency in this ability represents the basis of considerable number of problems, such as non-adherence to treatment, dissatisfaction with care, lack of recognition of psychosocial needs and physicians' frustration [105]. Communication in the medical field has always been a very sensitive and complex issue; doctors often prefer to concentrate their resources solely on the technical aspects of care, neglecting the management of relational aspects. Some professionals may feel threatened by the growing empowerment of patients [106], even in relation to current medical crisis and due to the general difficulty of sharing information with an increasingly sceptical public, currently equipped with more or less appropriate tools to search and collect information and draw to conclusions. The medical approach based on a limited dialogue with patients allows the doctor to avoid having to deal with the profound emotional reaction that may arise when a cancer diagnosis is communicated [107]. Furthermore, physicians are often reluctant to disclose information that are relevant to face uncertain choices (especially in cases where these choices involve trade-offs among risk, disability and death) [108]. Leaving a patient without much chance to express himself could represent a defence of the physician's psychological integrity.

Most often physicians get a large amount of technical training, but they lack the opportunity to build communication and interpersonal skills, which are often considered pertaining to personal characteristics and individual sensibility rather than actual competencies that can be learned and/or refined. Some research studies have also indicated that physicians themselves acknowledge a gap in communication skills training particularly in managing emotional and behavioural reactions of patients [109, 110]. Nowadays courses are offered as continuous learning opportunities, but more often than not the focus is on how to deliver information and bad news and rarely entails the ability to engage patients and involve them as main characters on the stage of the DM process.

Researchers have been investigating the effectiveness of communication skills training programs designed for physicians [111–113], especially the improvement of their communication skills over time, the increase of the emotional depth of their interviews and the increase of physician empathic expression during patient interactions also in the long term [114].

Despite the centrality of this issue, little knowledge is currently available on the acceptance and effects of SDM physicians' training programs. Clinicians' general tendency is to positively welcome SDM training [115]. Bieber et al. [116], starting from the hypothesis that SDM can be a potential solution to improve interaction between physicians and fibromyalgia patients, found that specific SDM communication training program could actually be effective in teaching physicians to perform SDM and that it reduces frustration in patients. Interestingly, the study highlighted that physicians with per-

sonality characteristics clashing with the SDM concept (such as being too domineering or too hostile) benefited most from the training.

Tinsel et al. [117] demonstrated the positive effects of SDM physicians' training also for patients' activation, in order to facilitate their empowerment and improve control of some physical parameters.

In the oncologic field, Harter et al. [118] highlighted that when physicians improve their competence in SDM by appropriate training, their patients suffer less anxiety and depression; this could be particularly true for AS where a "co-constructed" choice of enrolling in an observational program very likely represents a protective factor for patients' psychological well-being and quality of life [24, 119].

Conclusions

Supporting men towards an aware choice of AS that is based on relevant elements rather than on unclear and unaware pressures (including external recommendations, intrinsic characteristics of the specific treatment, personal impressions, previous belief, economic considerations, etc.) requires medical teams taking into account the importance of a thorough and truly shared discussion about specific characteristics, evidence of efficacy and risk of complications of each therapy, as well as more subjective factors that can influence a patient's choice [30].

In order to improve selection in AS, "informed" DM should be considered the minimum requirement but cannot be considered enough. The information "you are here", i.e. a brief, limited description of the stage of the disease and partial explanation of the available options, is useful but not sufficient to accompany the patient in making an aware choice regarding AS. Patients need a "map", i.e. comprehensive and balanced information concerning all the available options and their potential side effects that should be supported by the use of DA tools [120]. Additionally, rather than just providing information, physicians and medical staff should ask questions focused on the patient's priorities, fears, values and preferences, such as "Where would you like to go" and "How can I help you get there?".

When it comes to making health-related choices, pure "rational" thinking is an illusion. Assessing and processing information is costly and we prefer to save time and energy [121, 122]. We mostly rely on previous experiences and "sense of guts". While this is more often than not an effective and efficient strategy, the complexity of treatment/AS DM after the diagnosis of low-risk potentially nonaggressive PCa needs the risk of bias (both from the patient and the physician side) to be accounted for. Talking out and through issues in a relationship based on trust, and weighing the trade-offs of all the different options allows patients to make an informed and SDM that will safeguard all the actors involved from future regret.

Nonetheless, up-to-date DAs have often been given little attention to AS [84]. What's the use of a map if it was never updated? And even if you have updated, good, reliable maps, they may not be enough for you to find your actual desired point of arrival. You may be reading the map upside down, and if you travel alone, no one is going to point that out. Or you may be travelling with someone who wants to go a different way, and you cannot come to an agreement on which road is the one you want and should take.

It is by now largely agreed upon that a patient's choice of AS strongly reflects physicians' preferences [123, 124]. What can be done then? Physicians should become *co-drivers*, i.e. to work in partnership with patients and share the responsibility of both offering and requesting information in order to reach a SDM process. In car rallies a "co-driver" is the navigator, whose job is to navigate, by reading off a set of pace notes to the driver. The co-driver tells the driver what *lies ahead*, *where to turn*, *the severity of the turn* and *what obstacles to look out for*.

Physicians should serve as navigators [125], by supporting patients and their families in actively engaging in the DM process and in the

care path. If AS is coherent with where the patient would like to go, it is necessary to support the choice over time with proper clinical and non-clinical interventions such as clearly defined, understandable follow-up schedule as well as psycho-educational interventions (i.e. conferences for patients, and offers to patients and spouses of psychological support for AS-related anxiety).

How can patients be effectively engaged in a SDM process that suits their cultural, cognitive and emotional situation? Physicians should work against the natural impulse to tell the patient what to do [126]. Rather, they need to ask to which extent a patient is ready to make decisions: Do they have enough knowledge and understanding? Are they aware of values and priorities? Do they have enough family and social support in order to finalize their decision?

While patients need to adopt a different perspective when looking at physicians' option of "living with an untreated cancer", clinicians will need to change their own perspective on patients, including accepting and reinforcing the active contribution that men themselves and their families can bring to the DM process as "subject matter experts" of their own priorities as far as overall quality of life.

Key Summary Points

- *Active surveillance is a journey not (only) a destination*. The decision-making (DM) process faced by low-risk PCa patients when considering active surveillance (AS) is a complex journey influenced by many individual and contextual factors; clinicians should know how these factors work in order to overcome those hindering AS.
- *How do patients travel?* All throughout the process, patient's characteristics (i.e. education) combine with some "internal factors" (i.e. values) and "external factors" (i.e. external pressure). The combination of these factors at a cognitive level (e.g. ratio between losses and gains of each option) and emotional level (fears and expectations) leads to the final decision.
- *What are the milestones of the journey?* Two main essential aspects should be employed in order to effectively manage the DM process in order to improve AS selection: provide proper information and engage patients and their families in a shared, responsible DM process. Clinicians need to work collaboratively within a multidisciplinary setting throughout the different steps of the DM process to enhance the deliberation process.
- *Use a compass*. Decision aids (DAs) can catalyse the multidisciplinary informed SDM process by providing clear and reliable information and by helping patients weigh pros and cons of the different options based on their preferences and values.
- *A new journey for physicians.* Learning and practicing a multidisciplinary SDM culture is a new challenge for professionals as well as for patients. Training programs could teach why and how to implement a culture of SDM and how to effectively communicate options and evidences in order to optimize patient selection in AS.

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How Does QoL Compare Between Surveillance and Active Treatment?

15

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Abbreviations

AS	Active surveillance
BAI	Beck Anxiety Inventory
BDI	Beck Distress Inventory
BHS	Beck Hopelessness Inventory
BT	Brachytherapy
EORTC-QLQ-C30	The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30
EPIC	Expanded Prostate Cancer Index Composite
FC	Focal cryoablation
HRQOL	Health-related quality of life
IIEF	International index of erectile function
IPSS	International prostate symptom score
IQR	Interquartile range
MAX-PC	Memorial anxiety scale for prostate cancer
PCa	Prostate cancer
QoL	Quality of life
RARP	Robot-assisted radical prostatectomy
RP	Radical prostatectomy
RT	Radiotherapy
SHIM	Sexual Health Inventory for Men
STAI	State trait anxiety inventory

Introduction

A growing body of evidence from observational cohort studies has led to AS increasingly being considered safe in terms of PCa-specific mortality and increasingly being included in treatment guidelines [1–4]. This results in yet another treatment option for men with early PCa.

Long term survival data from randomized trials comparing PCa therapies including active surveillance (AS) are not yet available. Observational data, and 10 year data from randomized trials, suggest that survival rates for prostatectomy (RP), radiotherapy (RT), and AS for men with early PCa are similar [5–8]. The availability of various medically reasonable treatment options combined with roughly similar survival rates and differences in types and rates of side effects make treatment selection for early PCa a preference-sensitive decision [9]. In preference-sensitive

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decisions, there is no best strategy, since either the evidence on the benefit–harm ratio is insufficient or the ratio depends on (patients') values [9]. In such situations shared decision-making is increasingly considered as the preferred mode of reaching a decision about which treatment option to aim for. We refer to Chap. 14 for a description of shared decision-making. In making a treatment choice, especially in the case of preference-sensitive decisions, the quality of life (QoL) effects of the various treatment options provide crucial information, both for patients and healthcare providers. In this chapter we aim at providing that information.

QoL refers to the general well-being of persons or groups. In this chapter we focus on health-related quality of life (HRQOL), which refers to the health aspects of QoL [10]. HRQOL is considered "to reflect the impact of disease and treatment on disability and daily functioning" [10]. We distinguish two types of QoL effects in relation to PCa diagnosis, treatment, and side effects:

1. Effects on prostate-specific function and bother
2. Effects on anxiety and distress

In the following paragraphs, a comprehensive overview is provided on recent relevant findings relating to these two types of QoL effects.

Associations of AS with Prostate-Specific Function and Bother

With AS the morbidity of immediate curative treatment strategies may be delayed or overcome. AS, although less invasive than RP and RT, does however involve regular biopsies, which carry some risk [11]. The number of biopsies patients under go depends on the AS strategy followed, but a mean of 2–3 in the first 2 years is not uncommon [12–14], with increasing follow-up leading to additional biopsies. It has been hypothesized that biopsies may affect urinary and sexual function because of the invasiveness of the procedure. Recent research has assessed the prevalence of effects of biopsies on urinary and sexual function and how these functions in men on AS compared to the urinary and sexual function of men that underwent direct curative treatment.

AS Compared to Curative Treatment

In a study by Jeldres and colleagues, disease-specific QoL of men diagnosed with low-risk PCa who chose RP or AS was assessed using the EPIC [15]. In this longitudinal study, prostate-specific functions were assessed at baseline (immediately before or after biopsy) and at 3, 6, 9, 12, 18, 24, and 36 months. Two hundred and twenty eight men underwent RP, while 77 were managed with AS. At diagnosis the mean age of men in the RP group was 58 years and for AS patients 65 years. The baseline measurement revealed significantly lower sexual function and bother scores for the AS group as compared to the RP group (sexual function, 51 (SD 26) vs. 62 (SD 22), $p = 0.002$; sexual bother, 70 (SD 29) vs. 79 (SD 29), $p = 0.03$). No significant differences were seen regarding urinary function and bother at baseline. During the entire follow-up period, sexual function and bother scores were lower for the RP group than for the AS group. RP had a bigger impact on sexual function and bother than AS; 3 months after treatment, RP baseline scores were reduced by half. However, 6 months after treatment, scores improved, and they stabilized by 2 years, but all the while remained significantly lower than those for AS patients at 3 years of follow-up. Overall, after 3 years of follow-up, sexual function decreased in men on AS from 51 to 50 and in men on RP from 62 to 40. At all time points, the RP group was much more bothered by their loss of sexual function than the AS group. The RP group reported significantly poorer urinary function at all follow-up time points than the AS group. Between 3 and 12 months after surgery, urinary function scores recovered in the RP cohort, but remained lower than those of the AS cohort. Overall, after 3 years of follow-up, urinary function decreased in men on AS from 93 to 90. In the RP group, urinary function scores decreased from 95 to 50 3 months after surgery

and then increased to 80 after 3 years of follow-up. The RP cohort reported significantly lower urinary bother scores than the AS cohort, 3 to 12 months after surgery, but scores recovered and were equivalent to the AS scores at 2 and 3 years follow-up. In the RP group, changes in sexual function, sexual bother, and urinary function were clinically relevant. The authors concluded that AS is a feasible option in terms of postponing the morbidity associated with RP.

Van den Bergh and colleagues explored whether undergoing robot-assisted RP (RARP) after an initial AS strategy had an additional unfavorable effect as compared to men who directly choose RARP [16]. The AS group consisted of 29 patients (mean age 62.3 years) and the direct-RARP group of 363 (mean age 60.7 years). An average of 15.4 months was spent on AS before men were operated. Measured through the EORTC-QLQ-PR25, preoperatively, the AS group experienced good urinary function, was sexually active (5.3/8), and had good sexual function (14.4/16). Preoperatively, men who choose direct RARP had more urinary symptoms (11.2 vs. 10.6, $p = 0.342$), were less sexually active as compared to the AS group (4.4 vs. 5.3, $p = 0.001$), and experienced somewhat worse sexual functioning (13.3 vs. 14.4, $p = 0.029$). Following RARP, the QoL scores of most domains deteriorated in the AS-RARP group, with significant unfavorable changes for the PR-25 sexual activity and sexual functioning scales as well as the IIEF-15 score. Similar results were found when comparing the pre- and postoperative scores within the direct-RARP group. Changes in the sexual activity and function and erectile function scores were not only statistically significant but also clinically relevant. The postoperative scores of the AS-RARP and direct-RARP groups were very similar, suggesting that the AS group experienced worse QoL after RARP than initially when they were still on AS.

In the UK, Watson and colleagues explored ongoing symptoms in treated PCa patients [17]. Men diagnosed 9–24 months previously and whose condition was considered stable were invited to self-complete a single QoL questionnaire. Of the 493 invited participants, 316 filled out and returned the questionnaire (response rate 64.1%). The EPIC-26 was used, with higher scores indicating better function. One hundred and fifteen patients underwent surgery (37%), 117 radiotherapy (37%), 17 brachytherapy (5%), 36 hormone therapy (11%), and 43 AS (14%). The sexual domain summary score was lowest for men that underwent RT with adjuvant HT (median 12.5, IQR 4–17) and highest for men on AS (median 57, IQR 13–88). The urinary domain summary score was lowest for the surgery group (median 86, IQR 67–100) and highest for the RT and HT groups (median 100, IQR RT 79–100, and HT 86–100). Men on AS had a median domain score of 93.8 (IQR 86–100). Unfortunately, cancer characteristics for the various treatment groups were not outlined by the authors which hindered the interpretation of the differences in reported scores. The same holds for demographic characteristics, such as age.

In a much smaller study cohort, De Cerqueira and colleagues compared the erectile and voiding functions of patients undergoing focal cryoablation (FC, $n = 10$), brachytherapy (BT) ($n = 9$), or AS ($n = 11$) using the IIEF-5 and the IPSS [18]. The mean age of men in the FC group was 62.9 years (SD 6.87), 58.0 (SD 10.8) for the BT group, and 71.9 (SD 8.13) for the AS group. Men in the AS group were significantly older ($p < 0.001$). The IPSS score of 7 for the FC group indicated no to mild symptoms, while the scores of the BT group (17.1) and the AS group (12.45) indicated moderate symptoms ($p = 0.0223$). Regarding erectile dysfunction (IIEF-5), the FC group reported a score of 15.3, the BT group 14.4, and the AS group 13.2, all indicating mild to moderate erectile dysfunction ($p = 0.98$).

In a Dutch study by Van den Bergh and colleagues, the sexual function of 266 men with localized PCa either on AS ($n = 129$) RP ($n = 67$) or RT ($n = 70$) was assessed [19]. Ten items on sexual functioning were completed at two different time points after diagnosis (AS) or start of treatment (RP or RT) (6 and 12–18 months). The mean age of the AS group was 64.9 years, for the RP group 62.1 years and 68.1 years for the RT group. (65–68% of the AS group, 35–36% of the RP group, and 36–37% of the RT group

reported to be sexually active). Of these sexually active men, 44–51% of the men in the AS group, 96% of the men in the RP group, and 73–76% of men in the RT group had problems getting or keeping an erection. Of the sexually inactive men, 20–30% of the AS group, 86–91% of the RP group, and 56–60% of the RT group reported to be inactive because of erectile dysfunction. Multivariable analysis showed that these differences were significant, except for the AS versus RT comparison.

Finally, Pham and colleagues evaluated prostate-specific function using the EPIC in men on AS (n = 89) as compared to men who were followed after a negative prostate needle biopsy (non-cancer comparison group, n = 420) [20], with mean ages of 64 (SD 8) and 61 (SD 8), respectively. Prostate-specific function was assessed at biopsy, which served as baseline, and then annually for up to 3 years. Scores between groups were very similar at all time points. Sexual function and bother as well as urinary function and bother scores were very comparable to those found in the literature [21], reflecting acceptable sexual function (EPIC score 50–55) and bother (EPIC score 65–70) and good urinary function (EPIC score 90–95).

The above observational studies indicate that men who chose AS experience better sexual and urinary function in the short and intermediate term as compared to men who are directly curatively treated. Men choosing an AS strategy and initially averting treatment-related morbidity who switch to RP in a later stage do not seem to experience worse prostate-specific function as compared to men who underwent initial RP.

Studies Reporting on AS Only

Three observational AS studies explored whether prostate biopsies impacted men's prostate-specific function [22–24]. Hilton and colleagues used the Sexual Health Inventory for Men (SHIM) to test whether erectile function decreases with the number of biopsies experienced [22]. Cross-sectional analyses were done in 427 men who evaluated their erectile function after they underwent at least one prostate biopsy. Longitudinal analyses were performed in 220/427 men who had undergone at least 2 biopsies. This group included 70 men who underwent 3 or more biopsies. The median age of men on AS was 61 years (IQR 57–66). In the total cohort of 427 men, 1398 evaluations of erectile function were provided after up to 9 biopsies per man. Analyses revealed no association between erectile function and increasing biopsy exposure, after adjusting for age, sexual activity status, clinical stage, and diagnostic period [22]. Pearce and colleagues assessed prostate-specific function through the sexual function subscale of the EPIC-26 and the AUA-symptom index (AUA-SI) to measure the impact of lower urinary tract symptoms over a 4-week period [23]. EPIC-26 and AUA-SI scores were compared at baseline and at 6, 12, 18, and 24 months. One hundred and ninety five men on AS were included in this study with a mean age of 66.5 years (SD 6.8). Ninety-seven percent of men enrolled into the AS program had 1–2 prostate biopsies with a mean of 12.4 (SD 1.5) cores per biopsy. At baseline, the mean EPIC-26 sexual function score was 61.4 (SD 30.4), which decreased to 53.9 (SD 30.7) after 24 months of follow-up. The AUA-SI score remained quite stable throughout the follow-up period at a value of 6.9–7.7. Multivariable analysis showed that older age, unemployment, and a history of diabetes, CAD, or hypertension were predictors for significantly lower EPIC-26 sexual function scores. According to the authors, anxiety, AUA-SI, number of biopsies, and total cores taken did not predict sexual dysfunction [23]. Parker and colleagues also used the EPIC to measure urinary and sexual function [24]. In a total of 180 men on AS with a mean age of 67.2 (SD 8.9, range 40–87), urinary summary scores were quite stable over six time points, from 86.8 immediately after enrollment to 86.9 after 30 months of follow-up. The sexual summary score reported after enrollment was 59.5, gradually decreasing to 52.4 after 30 months of follow-up. Time turned out to be a significant predictor of the sexual summary score (p = 0.047), and age was significantly associated with the sexual

summary score ($p < 0.001$). The authors found that the number of experienced prostate biopsies had no bearing on sexual function scores [24].

Opposite to the outcomes of Hilton et al., Pearce et al., and Parker et al. [22–24], Fujita and colleagues reported that serial prostate biopsies did appear to adversely affect erectile function of men with PCa on AS but that it did not affect lower urinary tract symptoms [12]. The authors used the SHIM and IPSS to measure prostate-specific function at protocol entry and at a cross-sectional point in 2008. One hundred and fifty-two men on AS were included for baseline and follow-up SHIM analyses and 123 for baseline and follow-up IPSS analyses. On average men underwent 1.1 (SD 0.4) biopsies before entering the protocol. After entry into the study, men for the SHIM analysis underwent on average 2.3 (SD 1.9, range 0–8) biopsies and men for the IPSS analysis 2.3 (SD 2.0, range 0–11) biopsies. Mean ages in the two analysis cohorts were 68.7 (SD 6.1) and 68.1 (SD 6.1). Analyses revealed that the number of biopsies was associated with a decrease in SHIM score ($p = 0.04$) and that a history of three or more biopsies was associated with a greater decrease in SHIM score than seen after ≤2 biopsies ($p = 0.02$). In multivariable analysis only biopsy number was associated with a decreasing SHIM score ($p = 0.02$), and not age, prostate volume, or PSA. Men without preexisting erectile dysfunction (so a protocol entry score of 22–25) experienced steeper decreases in their SHIM scores as compared to men with mild to moderate erectile dysfunction at protocol entry ($p = 0.06$). The authors found no correlation between the number of biopsies and the IPSS scores of men on AS.

Three of the four studies reporting on the association between prostate biopsies and potential erectile dysfunction or urinary incontinence did not find such an association [22–24], and one did find an association [12]. As AS cohorts will mature further with more patients undergoing repeat protocol biopsies, this association needs to be further explored, when a larger share of men in ongoing AS studies have experienced more biopsies (≥3 or more).

Associations of AS with Anxiety and Distress

AS has been increasingly advocated as an alternative to curative treatment for men with low-risk PCa [25]. The functional benefits resulting from the noninvasive nature of AS, and its potential to reduce overtreatment, have increased the acceptance of this treatment method over the past years [26–28]. However, concerns about the psychosocial impact of AS have been expressed, as early studies have indicated increased levels of anxiety and distress that accompany living with untreated cancer in PCa patients on AS [29]. Currently, a growing body of research has been conducted on the effects of AS on QoL and how this compares to the effects of curative treatment options.

AS Compared to Curative Treatment

In the Netherlands, van den Bergh and colleagues examined the impact of deferred robot-assisted radical prostatectomy (AS-RARP) as compared to direct RARP [16]. One group initially spent a median of 15.4 months on AS ($n = 29$) before undergoing RARP; the other group directly chose RARP ($n = 363$) and received treatment after a median of 3.3 months. Main reasons for undergoing RARP after initially opting for AS were repeat biopsy risk classification (45% of men initially on AS) and PSA progression (38% of men initially on AS). Experienced distress was the reason for quitting AS in two men (7% of men initially on AS) of the AS group. QoL was assessed using the EORTC-QLQ-C30 directly after diagnosis and every 6 months after treatment or during AS. In this study, preoperative and postoperative scores were compared within and between groups. Significant changes in emotional function over time were found in both groups (79.4 preoperative to 90.7 postoperative, $p = 0.004$ in the AS-RARP group versus 76.1 preoperative to 87.0 postoperative, $p < 0.001$ in the direct-RARP group), with higher scores indicating better function. The reassuring effect of RARP on anxiety and distress was thought to be of influence in these findings. Both preoperative

and postoperative scores on emotional functioning were slightly higher in men that delayed treatment for more than 12 months, but these differences were not significant. Additionally, both groups experienced high levels of social function preoperatively (95.4/100 AS-RARP and 93.0/100 direct-RARP, $p = 0.347$). However, social functioning significantly decreased in the direct-RARP group ($p < 0.001$) but not in the AS-RARP group ($p = 0.117$) [16]. Overall, QoL was more favorable in the AS-RARP group compared to the direct-RARP group preoperatively (83.0 vs. 77.6, $p = 0.043$). Postoperatively, QoL was similar in both groups (81.5 vs. 77.8, $p = 0.368$).

De Cerqueira and colleagues compared QoL measures in 30 low-risk PCa patients undergoing FC ($n = 10$), BT, ($n = 9$), and AS ($n = 11$) [18]. Anxiety (BAI, Beck Anxiety Inventory), hopelessness (BHS, Beck Hopelessness Inventory), depression (BDI, Beck Distress Inventory), and mental health (SF-36 Mental Health) were assessed by cross-sectional surveys distributed between 12 and 24 months after diagnosis (AS group) or treatment (FC and BT group). Men in the AS group were significantly older ($p < 0.001$). Men on AS reported the highest levels of hopelessness (mean 4.81, SD 2.71) versus men on FC (mean 3.00, SD 3.43) and BT (mean 1.77, SD 1.48). Scores in the AS group indicated mild hopelessness and differed significantly from the scores indicating minimum hopelessness in the other two groups ($p = 0.03$). This effect was possibly influenced by the significantly higher mean age in the AS group ($p = 0.0014$), as hopelessness was weakly to moderately correlated with age. Anxiety and depression scores did not differ between groups ($p = 0.68$ and $p = 0.49$). However, average anxiety scores in AS patients indicated a mild form of anxiety, compared to minimal anxiety in the other groups. Minimal distress was experienced in all groups. Finally, mental health scores were comparable between groups ($p = 0.49$) and ranged from 75.27 in the AS group to 82.80 in the FC group. De Cerqueira and colleagues suggest that AS is often perceived as living with "untreated" cancer and may therefore cause feelings of uncertainty and distress [18].

Van den Bergh and colleagues studied sexual function in men with low-risk PCa and compared men on AS ($n = 129$) to men that underwent RP (67) or RT ($n = 70$) [19]. Participants, Dutch PCa patients diagnosed through PCa screening, completed two questionnaires on QoL. The first survey was conducted within 6 months after diagnosis (AS group) or treatment (RP and RT group); the second survey was administered within 12–18 months after diagnosis or treatment. Patients on AS showed more favorable characteristics due to strict inclusion criteria regarding, for instance, maximum Gleason score, but these were controlled for in the multivariable analysis. Over 90 percent of men who quit AS during the study period did so because of reclassification of the disease. The SF-12 mental component summary (MCS), CES-D, and STAI-6 were used to assess psychological QoL. While men on AS reported significantly more anxiety then men on curative treatment (STAI, $p = 0.002$) in the first survey, they reported significantly less depression (CES-D, $p = 0.010$). Both groups of patients remained well below the clinical thresholds for clinical anxiety and depression. Patients on AS and patients on curative treatment reported similar mental QoL (SF-MCS). The second survey showed similar scores for both groups on mental health and anxiety, with decreased experienced anxiety in both groups. Finally, depression scores remained significantly more favorable in the AS group as compared to curative treatment ($p = 0.026$) at the second assessment [19].

Finally, Pham and colleagues compared QoL between men with low-risk PCa on AS ($n = 89$) and men who were followed after a negative prostate needle biopsy ($n = 420$, non-cancer group) [20]. QoL was assessed with the SF-36 (MCS) at baseline before biopsy and after 12, 24, and 36 months. In total, 12 men on AS (13%) switched to active therapy after a median of 25 months. Additionally, seven men without cancer at baseline developed PCa after a median of 35 months. No differences in QoL were found between men on AS and the non-cancer comparison group, except for a slightly stronger decrease in mental health in men on AS between baseline and 36 months ($p = 0.048$). However, this

decrease did not show to be of clinical importance, and scores at 36 months did no longer differ significantly between groups [20].

Studies Reporting on AS Only

Three longitudinal studies evaluated the impact of AS on psychosocial QoL in men with low-risk PCa. Pearce and colleagues assessed PCa-specific anxiety (MAX-PC), examining PCa anxiety, PSA anxiety, and fear of recurrence [23]. A total of 195 men were included in the study, and measures were assessed at baseline, 6, 12, 18, and 24 months. Over the total study period, a significant decline in total PCa-specific anxiety ($p = 0.03$) and PCa anxiety subscale scores ($p < 0.0001$) was found. However, the relevance of the changes found between baseline and 24 months follow-up was clinically modest. PSA anxiety and fear of recurrence did not show any significant changes ($p = 0.83$ and $p = 0.62$, respectively) [23]. Parker and colleagues explored relationships between illness uncertainty, anxiety, fear of cancer progression, and QoL in men with low-risk PCa on AS in the USA [24]. Questionnaires were distributed among 180 men diagnosed within the past 6 months (baseline) and were repeated every 6 months for a period of 2.5 years. Forty-four percent of men were followed ≥2 years and 71% for ≥1 year. Seventeen percent of the respondents left the study cohort due to disease reclassification. Illness uncertainty (MUIS) significantly decreased between 12 months and 2.5 years ($p < 0.0001$). The length of follow-up was negatively associated with anxiety (STAI), with significantly lower anxiety scores reported at 18 months and 2.5 years than at baseline ($p = 0.009$). However, referring to Chipman et al. [30], the authors conclude that the findings may perhaps not be clinically significant, as scores on general QoL (SF-12 MCS) and fear of disease progression (MAX-PC) were found to be predicted by uncertainty and anxiety but remained stable over time (all p values >0.10). Age was negatively associated with QoL ($p < 0.0001$) [24]. Another longitudinal study on anxiety and distress in men on AS was conducted by Venderbos and colleagues [31]. This prospective study was conducted among Dutch participants of the PRIAS study, which were diagnosed with PCa within 6 months prior to study entry. The population consisted of men on AS ($n = 150$) with a mean age of 64.6 years. Questionnaires were distributed at 0–6, 9, and 18 months after diagnosis of PCa, and participation rates were 86%, 90%, and 96%, respectively. The questionnaires assessed decisional conflict (DCS), depression (CES-D), PCa-specific anxiety (MAX-PC), and self-estimated risk of disease progression. Of the men initially included in the study, 6 switched AS for active treatment due to anxiety and distress (5%) and 36 due to reclassification or disease progression (28%) between 0 and 18 months. Mean scores for all measures remained below clinical thresholds at 0, 9, and 18 months, indicating good mental health. Average scores on decisional conflict, depression, PCa-specific anxiety, and self-estimated risk of disease progression did not change between 0, 9, and 18 months. Generic anxiety (STAI-6) and fear of disease progression significantly decreased between 0, 9, and 18 months. However, the clinical relevance of these findings was modest. Of the 26 men who reported STAI-6 scores >44 at baseline (indicating clinical anxiety), 8 men became less anxious (and remained on AS), 6 remained anxious (but remained on AS), 10 quit AS due to disease progression or reclassification, and 2 quit AS due to their anxiety. An additional four men who were not highly anxious at baseline quit AS due to anxiety. Overall, however, mean scores for anxiety (STAI-6) remained below the clinical threshold at all measurements [31].

Watts and colleagues evaluated the existence of anxiety and depression among men with PCa on AS in the UK [32]. Postal surveys assessed anxiety and depression with the Hospital Anxiety and Depression Scales (HADS, range 0–21). The high response rate of 73% resulted in a study population of 313 patients on AS, with a mean age of 70.5 years. Additionally, the study sample reported an average HADS anxiety score of 4.84; scores of 23.3% (73 men) indicated clinical anxiety. A significantly higher prevalence of anxiety

was found among divorced men, indicating a correlation between anxiety and relational status. The mean HADS depression score for the study sample was 3.29; scores of 12.5% (39 men) were higher than 8, indicating clinical depression [32].

Another observational study conducted in Australia by Anderson and colleagues explored anxiety among men with low-risk PCa on AS [33]. In total, 260 men were invited to complete a single questionnaire, and the response rate was 33% (86 patients). Non-responders had been on AS significantly shorter than responders, and the included study population had a mean age of 65.7 years. Levels of general state anxiety (HADS-A) and trait anxiety (STAI-T) were normal for most men in the study sample (86% and 77%, respectively). Fear of recurrence was low in 79/86 responders (92%). Levels of disease-specific anxiety (MAX-PC) were low for 75 /86 men (87%). Anxiety related to PSA testing was low among all but one participant (99%). Overall, the level of HRQOL (FACT-P) was high in the sample, compared to clinical data [34]. Trait anxiety and fear of recurrence were correlated to cancer-related HRQOL (FACT-P), and higher levels of trait anxiety and fear of recurrence predicted lower HRQOL scores in this study population. Of the total study population, 23 men quit AS due to clinical progression of the disease, and 4 quit by choice. These four men showed lower levels of general state anxiety (HADS-A) but higher levels of PCa-specific anxiety (MAX-PC) and fear of recurrence compared to the total study population. However, statistical significance of these differences cannot be assessed due to the small number of patients. Men who quit AS did so after a median of 6 months on AS [33].

Finally, in a study by Berger and colleagues in the USA, characteristics of men from the John Hopkins active surveillance cohort were assessed [35]. The study population consisted of 584 men on AS, 311 men who left AS due to disease reclassification, and 103 men who left AS by choice. Men leaving AS by choice were younger than those continuing AS. Additionally, a lower proportion of men in this group had PSA levels <4 ng/mL at baseline. Multinomial logistic regression found younger age predicted self-elected leaving of AS, with more 40–60-year-olds choosing to leave AS than men over 70. Additionally PSA levels were correlated to choosing to leave AS, with men with higher levels (4–10 ng/mL) leaving AS significantly more often than men with lower levels (<4 ng/mL). Qualitative interviews were conducted among 14 men that choose to leave AS and 7 men that were recommended to leave AS due to disease reclassification. Both groups gave similar reasons of joining and leaving AS. Main themes for those joining AS were a low statistical risk of death by PCa and avoiding aggressive treatment. Fear of cancer, both by the patients and their loved ones, was a reason to switch from AS to curative treatment. Additionally, patients leaving AS indicated a preference for being treated at a younger age and an intolerability of the uncertainties that accompany the monitoring in AS. Some men also used AS to delay treatment instead of completely avoiding treatment.

The studies described above show similar psychological QoL in men on AS and men on curative treatments. However, one small study suggested that patients on AS experienced more hopelessness and anxiety than men on FT and BT [18]. Slightly higher levels of anxiety have been found among AS patients shortly after diagnosis, but the anxiety levels decreased significantly after curative treatment [16]. These findings indicate that living with untreated cancer may increase experienced distress. However, multiple studies reported high levels of social and emotional functioning in patients on AS [16, 19]. Other studies have also found similar levels of mental health in men on AS and men on curative treatment or even men without cancer [18–20]. Additionally, the majority of low-risk PCa patients on AS showed low levels of anxiety and fear of recurrence [23, 31, 33], and the overall QoL was found to be high [31, 33]. Moreover, psychological QoL has been found to improve over time, with anxiety scores decreasing to similar levels of that in men on curative treatment [20]. A positive correlation was found between length of time on AS and QoL [24]. Reasons for quitting AS were mostly related to reclassification or progression of the disease, and only a lim-

ited number of men on AS quit due to distress or anxiety [19, 31, 33]. These men tended to be younger than the average AS man [35]. Accordingly, men who select AS tend to be older than those who choose for active treatment [18].

Conclusion

Our summary of recent relevant literature on AS and QoL shows an absence of associations between prostate biopsies and erectile dysfunction and urinary incontinence in three of four identified studies. Studies reporting on anxiety and distress in relation to AS tend to report that men are doing well. It remains important to realize that these findings relate to men who opted for AS themselves. The described samples are all self-selected, and currently available data originate from observational studies. The results of the first randomized study into this topic are expected to be published in the next few years.

The long-term data on QoL of AS men that now become available confirm the short-term picture: the majority of men who opt for AS generally tend to report low levels of anxiety and good, or even better, prostate -specific function than men who were actively treated for PCa. The QoL of AS men is comparable or even better than that of men without PCa. This is important information for patients who need to make a treatment choice and for physicians who need to inform and support their patients in selecting the treatment that is right for them.

We emphasize a few other points. We acknowledge a paucity of long-term data, especially in cohorts of older people. Disentangling late effects of treatment from effects of aging on, for instance, physical function is challenging. Therefore, we recommend including reference groups without PCa in cross-sectional studies, with longitudinal follow up as well. Including such a longitudinal reference group will provide the opportunity to explore to what extent sexual and urinary function loss is related to age and to what extent it might be related to experiencing biopsies. Inclusion of a longitudinal reference group will provide a longitudinal picture of "normal" aging and will enable a better interpretation of the long-term functioning of patients, in this case of men who opted for AS.

A second issue is the rate of men who quit AS on their own accord. In the studies that we described, the rate of men that quit AS due to nonmedical reasons ranged from 7% to 15% [16, 31, 33]. Other studies also describe varying rates. Bokhorst and colleagues reported on 5302 men who followed the PRIAS protocol [1]. Of these men, 1768 switched to curative treatment up until the end of follow-date of November 2015. Of this group, 177/1768 (10%) did so due to anxiety [1]. Klotz et al. also reported on the long-term follow-up of their AS cohort [4]. Of the 993 participants reported on in their paper, 267 underwent curative treatment. Patient preference was a reason in 16 participants who discontinued AS (6%) [4]. Finally, in their systematic review, Simpkin et al. summarize factors that determine change from AS to curative treatment [36]. They found that in the 17 studies who provided reasons of change to curative treatment, on average 20% discontinued AS because of patient choice or anxiety (95% CI 14–27%) [36]. We conclude that the percentages of men quitting AS due to anxiety differs substantially. Also, switching to curative treatment means that men leave the AS cohort, which often leads to QoL no longer being assessed. Therefore, we cannot assess whether the switch to curative treatment indeed resulted in lower levels of anxiety. We therefore recommend the continuation of QoL assessments of men who initially opt for AS but later opt for active treatment.

A third issue is the appropriateness of AS with respect to age. Several studies have indicated that AS is more appropriate for older men, as these men tend to be more prone to treatment-related complications such as impotence and incontinence [37, 38]. Additionally, an American study on men's motives for quitting AS ($n = 21$) found that many of the interviewed men feared living with "untreated cancer" and therefore preferred curative treatment [39]. Moreover, these men indicated that AS had been more acceptable to them if they had been older (e.g., 60 or 75 years old); they now felt healthy and wished to cure the cancer so that it was over and done with, and they

Table 15.1 Details of studies into prostate cancer-specific function and bother

Authors, journal, year	Country	Study design	Therapies and number of participants per study group	Measures	Number of measurements
AS compared to curative treatment					
1. Jeldres et al., *cancer*, 2015 [15]	USA	Longitudinal	AS $n = 77$, RP $n = 228$	EPIC	Baseline (before or after biopsy), 3, 6, 9, 12, 18, 24, and 36 months
2. Van den Bergh et al., *Scand J Urol*, 2014 [16]	The Netherlands	Observational	AS robot-assisted RP $n = 29$, Robot-assisted RP $n = 363$	EORTC-QLQ-PR25, IIEF-15, ICIQ-SF	One preoperative and one postoperative
3. Watson et al., *BJUI*, 2015 [17]	UK	Cross-sectional	Surgery $n = 115$, RT $n = 36$, RT with adjuvant HT $n = 81$, primary HT $n = 36$, AS $n = 43$	EPIC-26	One between 9 and 24 months after diagnosis
4. De Cerqueira et al., *Eur J cancer care*, 2015 [18]	Brazil	Cross-sectional	Focal cryotherapy $n = 10$, brachytherapy $n = 9$, AS $n = 11$	IPSS	One between ≥12 or ≤24 months of diagnosis or treatment follow-up
5. Van den Bergh et al., *BJUI*, 2012 [19]	The Netherlands	Longitudinal	AS n = 129, RP $n = 67$, RT $n = 70$	10 items on sexual function	AS, 6 and 18 months after diagnosis; RP&RT, 6 and 12 months after start of treatment
6. Pham et al., J *Urology*, 2016 [20]	USA	Longitudinal	Non-cancer $n = 420$, AS $n = 89$	EPIC	Baseline (before or after biopsy), 12, 24, and 36 months
Single AS studies					
7. Hilton et al., *J Urology*, 2012 [22]	USA	Longitudinal	AS one biopsy $n = 427$, AS two biopsies $n = 220$, AS three biopsies $n = 70$	SHIM	Every 6 months
8 Pearce et al., *sexual medicine*, 2015 [23]	USA	Longitudinal	AS $n = 195$	EPIC, AUA-SI	Baseline, 6, 12, 18, and 24 months
9. Parker et al., *BJUI*, 2016 [24]	USA	Longitudinal	AS $n = 180$	EPIC	Time of enrollment and then every 6 months for up to 30 months
10. Fujita et al., *J Urology*, 2009 [12]	USA	Observational	AS $n = 152$	SHIM, IPSS	Baseline and one measurement in March 2008

Table 15.2 Details of studies into anxiety and distress

Authors, journal, year	Country	Study design	Therapies and number of patients per study group	Measures	Number and timing of measurements
AS compared to curative treatment					
Van den Bergh et al., *Scand J Urol*, 2014 [16]	The Netherlands	Observational	AS robot-assisted RP $n = 29$, robot-assisted RP $n = 363$	EORTC-QLQ-C30	One preoperative and one postoperative
De Cerqueira et al., *Eur J cancer care*, 2015 [18]	Brazil	Cross-sectional	Focal cryotherapy $n = 10$, brachytherapy $n = 9$, AS $n = 11$	BAI, BDI, BHS, SF-36 MH	One between ≥12 or ≤24 months of diagnosis or treatment follow-up
Van den Bergh et al., *BJUI*, 2012 [19]	The Netherlands	Longitudinal	AS $n = 129$, RP $n = 67$, RT $n = 70$	SF-12, (MCS), CES-D, STAI-6	AS: 6 and 18 months after diagnosis; RP&RT: 6 and 12 months after start of treatment
Pham et al., *J Urology*, 2016 [20]	USA	Longitudinal	Non-cancer $n = 420$, AS $n = 89$	SF-36	Baseline (before or after biopsy), 12, 24, and 36 months
Single AS studies					
Pearce et al., *Sexual Medicine*, 2015 [23]	USA	Longitudinal	AS $n = 195$	AUA-SI, MAX-PC	Baseline (before or after biopsy), 12, 24, and 36 months
Parker et al., *BJUI*, 2016 [24]	USA	Longitudinal	AS $n = 180$	MUIS-STAI, SF-12, fear of disease progression/recurrence with subscale MAX-PC	Time of enrollment and then every 6 months for up to 30 months
Venderbos et al., *Psycho-oncology*, 2015 [31]	The Netherlands	Longitudinal	AS $n = 129$	MAX-PC, STAI-6, CES-D	Baseline (<6 months after diagnosis), and after 9 an 18 months
Watts et al., *BMJ Open,* 2015 [32]	UK	Cross-sectional	AS $n = 313$	HADS-A, HADS-D	One
Anderson et al., *BJUI*, 2014 [33]	Australia	Cross-sectional	$N = 86$	HADS, STAI, MAX-PC, FACT-P	One
Berger et al., *Patient*, 2014 [35]	USA	Cross-sectional	AS $n = 1159$	Average time on AS, reasons for leaving AS.	One

no longer needed to think about it. Finally, doctor's recommendations also seem to play a role in (not) choosing AS in this younger group [39]. On the other hand, one could argue that, given the low PCa-specific mortality in AS groups [1, 3, 4], AS may be particularly beneficial for those with longer life expectancies, since they may have more years to enjoy normal erectile, voiding, and bowel function.

In this chapter we provided an extensive overview of recent findings on AS and quality of life. We hope this overview will support the process of selecting the right treatment for men with low-risk prostate cancer (Tables 15.1 and 15.2).

Conflict of Interest The authors have nothing to disclose.

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16 The Potential Benefits of Diet and Physical Activity Among Active Surveillance Patients with Low-Burden Prostate Cancer

Stacey A. Kenfield, David Tat, and June M. Chan

Introduction

With prostate-specific antigen (PSA) screening, a large proportion (25–80%) of current prostate cancer diagnoses in the USA may be indolent disease that would not cause morbidity if left undiagnosed and untreated [1–4]. Overtreatment remains a challenging problem to the extent that prostate cancer therapies are associated with morbidity and adverse effects on health-related quality of life (HRQOL) [5, 6].

In the last decade, accumulating data indicate that *active surveillance* is a safe management strategy for men diagnosed initially with low-burden prostate cancer (e.g., early-stage, low-grade, low-volume prostate cancer), and consequently the usage of active surveillance has increased nationwide [7–9]. Active surveillance includes careful monitoring of PSA kinetics and serial biopsies with intervention based on these parameters.

Men electing active surveillance may have the most to gain from lifestyle modifications that reduce risk of progression given that they are not pursuing active treatment. Our team recently reviewed the role of diet and lifestyle factors and the risk of prostate cancer progression and death [10]. In this chapter, we provide an updated summary derived from that report and highlight topics that may be especially relevant to men on active surveillance. In particular, we focus on summarizing the more recent epidemiologic literature on modifiable post-diagnostic risk factors for prostate cancer progression, with specific mention of studies that address active surveillance, although such data remain limited. Further evidence that lifestyle factors after diagnosis may offer benefit to men opting for active surveillance comes from studies of broader populations of men with prostate cancer (including those opting for treatment) focused on biochemical and clinical outcomes (e.g., PSA recurrence, metastasis, prostate cancer death). It should be considered, though, that risk factors for localized progression within the prostate among men opting for active surveillance may be different than progression of micrometastatic cells that have escaped the prostate (and remain after surgical removal of/radiation to the prostate gland) given the different

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mechanisms involved in each process. Thus, while it is reasonable to glean knowledge from the general literature on men with prostate cancer, there is a need for additional studies among men on active surveillance.

Obesity

There is a reasonably strong and consistent body of evidence indicating that obesity (either before or at the time of diagnosis) is associated with greater risk of prostate cancer progression and prostate cancer-specific mortality, independent of diet, physical activity, or clinical factors [11–23]. For example, among 2546 men diagnosed with localized prostate cancer, a 1 unit increase in prediagnostic BMI was associated with ~10% increase in risk of prostate cancer-specific mortality, and BMI ≥ 30 was associated with a nearly twofold increased risk of prostate cancer-specific death (RR = 1.95; 95% CI:1.17, 3.23) [13]. BMI at diagnosis has also been positively associated with worse clinical presentation at diagnosis [15, 20, 22] and greater risk of prostate cancer recurrence or progression [16, 19, 21–23]. A recent meta-analysis of six studies in prostate cancer patients estimated that a 5 kg/m^2 increase in BMI significantly increased risk of prostate cancer-specific mortality by 20% and biochemical recurrence by 21% [24]. A per 0.1-unit-higher waist/hip ratio (WHR) was associated with a 21% increased risk of advanced prostate cancer [25], and two studies reported that men in the highest vs. lowest quintile of WHR had a 27% increased risk of aggressive prostate cancer [26] and a 58% increased risk of metastatic prostate cancer [27]. Cohort studies have also reported that adulthood weight gain is associated with increased risk of advanced [28], high-grade [28], and fatal prostate cancer [29] and an increased risk of recurrence and shorter time to biochemical failure among men with prostate cancer who underwent prostatectomy [17, 30]. There are limited data suggesting that the positive association between obesity and risk of more aggressive prostate cancer is stronger among African American men than Caucasians [20].

Physical Activity

In contrast to obesity, exercise and healthy body size may reduce prostate cancer progression and prostate cancer-specific death by having a pleiotropic effect on energy metabolism, inflammation, oxidative stress, and AR signaling pathways [11, 31–35]. Accumulating evidence from prospective cohort studies suggests that physical activity, specifically vigorous activity (i.e., activities that require an energy expenditure six or more times the resting metabolic rate, such as jogging or bicycling), is associated with reduced risk of advanced [33, 36, 37], aggressive [32], and fatal prostate cancer [34, 36].

Our group was the first to report on physical activity *after* diagnosis in relation to prostate cancer-specific mortality and total mortality [35]. In the Health Professionals Follow-Up Study (HPFS), we reported that 3+ h per week of vigorous activity after diagnosis vs. <1 h per week was significantly inversely associated with total mortality and associated with a 61% reduction in risk of prostate cancer-specific mortality (HR = 0.39; 95% CI: 0.18, 0.84; *p*-trend: 0.03). We observed a trend toward similar results in CaPSURE™ (Cancer of the Prostate Strategic Urologic Research Endeavor) where we examined risk of prostate cancer progression, primarily measured by PSA rise and undergoing secondary treatment [31]. These results were particularly compelling as there was less potential for reverse causation, as physical symptoms of prostate cancer progression that may cause a decrease in physical activity are unlikely to precede biochemical recurrence.

Additionally, in both studies, we observed a potential benefit of brisk walking after prostate cancer diagnosis. Men with prostate cancer who walked 7+ h per week at a brisk pace had a 56% reduced risk of prostate cancer-specific mortality compared to men who walked <7 h per week at an easy pace (HPFS: HR = 0.44; 95% CI: 0.17, 1.15). Likewise, men with prostate cancer who walked 3+ h per week at a brisk pace after diagnosis had a 57% reduced risk of prostate cancer progression compared to men who walked <3 h at an easy pace (CaPSURE™: HR = 0.43; 95%

CI: 0.21, 0.91). More recently, it was reported that in a distinct cohort of ~830 Canadian men with prostate cancer and up to 17 years of follow-up, post-diagnosis recreational physical activity was associated with ~45% reduced risk of prostate cancer death [38].

Together, these findings suggest that physical activity, including more vigorous activity and brisk walking, may delay or deter prostate cancer development, progression, or death. While these results are not specific to active surveillance patients, our team is currently following up on these studies by examining the effect of a personalized aerobic exercise program on prostate tumor biology, among men opting for active surveillance. This trial is currently open for enrollment in the San Francisco Bay Area (please see Table 16.1 for more details).

Smoking

Accumulating evidence suggests that smoking may increase risk of aggressive prostate cancer and prostate cancer-specific mortality. The US Surgeon General found the evidence "suggestive" that smoking contributes to a higher prostate cancer mortality rate [39], in agreement with a 2014 meta-analysis of 51 articles reporting that smoking was associated with a 24% increased risk of prostate cancer death (RR = 1.24; 95% CI: 1.18, 1.31) and a statistically significant dose-response (RR = 1.20 for 20 cigarettes per day). The population attributable risk was 6.7% and 9.5% for cigarette smoking and prostate cancer death in the USA and Europe, respectively, corresponding to more than 10,000 prostate cancer-related deaths annually in the two regions combined [40]. A more recent 2015 NEJM-published, pooled analysis of five US cohort studies by Carter et al. found that current smokers experienced a 40% increased risk of death compared to those who had never smoked (RR = 1.4; 95% CI: 1.2, 1.7) [41]. Several studies reported that smoking is associated with more aggressive disease at diagnosis, defined as higher stage or tumor grade [42–44], and the relation between smoking and cancer progression, defined as biochemical recurrence [5, 45], metastasis [46], and hormone refractory prostate cancer [47], is suggestively positive. Concern remains that some or all of the observed associations may be due to delayed diagnosis and treatment among smokers.

In 2011, with 22 years of follow-up and a large number of outcomes (524 prostate cancer-specific deaths and 878 biochemical recurrences), we examined smoking at the time of prostate cancer diagnosis and prostate cancer-specific mortality and biochemical recurrence in the HPFS. Current smoking was associated with a 61% increased risk of prostate cancer-specific mortality (HR = 1.61; 95% CI: 1.11, 2.32) and a 61% increased risk of biochemical recurrence (HR = 1.61; 95% CI: 1.16, 2.22) [48]. Even after adjusting for changes in grade and stage secondary to smoking, estimates for current smoking were as follows: prostate cancer-specific mortality (HR = 1.38; 95% CI: 0.94, 2.03) and biochemical recurrence (HR = 1.47; 95% CI: 1.06, 2.04). Further adjustment for treatment did not significantly change these estimates. In a separate analysis to evaluate potential bias from any difference in screening behavior between smokers and nonsmokers, we included only men diagnosed from 1994, after PSA screening had become well established. In that analysis, we further adjusted for screening intensity as reflected in the proportion of 2-year periods in which a participant reported at least one PSA screen, dichotomizing at 50%. The estimates for smoking were even stronger after adjustment for PSA screening intensity: prostate cancer-specific mortality (HR = 2.12; 95% CI: 1.18, 3.79) and biochemical recurrence HR = 2.02; 95% CI: 1.30, 3.13). If the association between smoking and prostate cancer-specific mortality and recurrence resulted from delayed diagnosis, we would have expected to see an attenuation of the association. Thus, the observed positive associations between current smoking and risk of prostate cancer mortality or recurrence were likely *not* due to this potential bias.

In this same report, a greater number of pack-years were associated with an increased risk of prostate cancer-specific mortality, but not bio-

Table 16.1 Selected active or completed lifestyle trials in men with prostate cancer (PC) on active surveillance (AS)[a] pending[b] published studies

Name of trial (NCT No.)	Start	Subjects	Inclusion criteria	Intervention	Outcomes (*primary*, secondary, tertiary)
Feasibility Study on a Nordic Lifestyle Intervention Trial Among Men With Prostate Cancer (NCT01300104)	Feb 2011	24 Danish men	Biopsy-proven PC within 2 years, Gleason ≤6, PSA ≤10 ng/ml	Prescribed vigorous exercise ≥3× 45 min/week, whole grain rye (170–180 g/day)	*Feasibility*, PC progression (PSA and biopsy), insulin sensitivity/secretion, metabolic profile, inflammation, quality of life
Diet in Altering Disease Progression in Patients With Prostate Cancer on Active Surveillance (NCT01238172)	Jan 2011	464 men	Biopsy-proven PC within 2 years, clinical stage ≤T2a, no distant metastasis (no M1), <25% of biopsy cores with cancer	Dietary education and telephone counseling sessions for 24 months	*Clinical progression*, time to progression, time to treatment, anxiety (PC related), quality of life, dietary recall
Effect of Sulforaphane on Prostate CAncer PrEvention (NCT01950143)	Aug 2013	78 men	Low/intermediate PC, BMI between 19.5 and 35 kg/m^2	Standard broccoli soup, Beneforté broccoli soup, or Beneforté extra broccoli soup for 12 months	*Global gene expression in prostatic tissue*, metabolite concentration in prostatic tissue
Active Surveillance Exercise Clinical Trial (NCT02435472)	May 2016	Estimated 150 men	Biopsy-proven localized PC, clinical stage <T3, PSA ≤10 ng/ml	4–5 home-based walking sessions/week at 55–75% individual exercise capacity	*Genomic signature changes (3 a priori genomic classifiers)*, mRNA expression patterns, anxiety (general and PC-specific), adherence
Exercise Training as a Novel Primary Therapy for Men With Localised Prostate Cancer (NCT02409212)	May 2015	Estimated 50 men	Biopsy-proven low/intermediate PC, Gleason ≤3 + 4, PSA ≤20 ng/ml, clinical/diagnostic evaluation in past 12 months, life expectancy ≥10 years	Supervised and independent aerobic exercise sessions for 12 months with bimonthly counseling	*Feasibility by rate of recruitment*, adherence
Low-Fat Diet and Fish Oil in Men on Active Surveillance for Prostate Cancer (NCT02176902)	Nov 2014	Estimated 100 men	Biopsy-proven PC, clinical stage ≤T2c, Gleason <3 + 4, PSA <20 ng/ml	4 fish oil capsules/day for 1 year with dietary counseling and low-fat diet guidelines	*Proliferation index (Ki67) in prostatic tissue*; other tissue markers/biomarkers of proliferation/progression, cell cycle progression; serum PSA, GPR120 gene expression, adherence
Diet and Exercise Program in Promoting Weight Loss and Improving Health in Patients With Low- or Low-Intermediate-Risk Prostate Cancer (NCT02454517)	May 2016	Estimated 200 men	Biopsy-proven low/intermediate PC, Gleason ≤3 + 4, PSA <20 ng/ml, BMI ≥25 kg/m^2	Diabetes prevention program intervention with specific diet and 16x 30–60 min exercise sessions over 24 weeks	*Change in expression of insulin receptor (IGF-1R)*, *fasting C-peptide*, *insulin*, *IGF-1, IGF-BP3*, *adiponectin levels*; *protein kinase B on PC epithelial cells*; *fasting glucose levels*; *sustainability of beneficial changes*; adverse pathology; quality of life

Cholecalciferol Supplement in Treating Patients With Localized Prostate Cancer Undergoing Observation (NCT00887432)	April 2009	Estimated 100 men	Biopsy-proven PC, ECOG status ≤1, most recent 25(OH) D3 levels <40 ng/ml within 3 months of study, no history of PC treatment	PO cholecalciferol daily for 9 months followed by 3 month washout, then 9 months placebo; the reverse is also implemented in the second arm	PSA response, PSA dynamics/change, toxicity, relationship between CYP24, 27B1, and SNPs and serum 25-OH(D) in response to supplementation
CAPSAICIN Trial: Assessing Capsaicin as a Chemopreventive Agent for Prostate Cancer (NCT02037464)	Jan 2014	Estimated 100 men	Biopsy-proven PC, clinical stage ≤T2b, Gleason <6, PSA <10 ng/ml, recent PC biopsy	One capsaicin supplement capsule 2× daily	*Biomarker changes (ki67 and p27)*, PSA kinetics, tumor grade, additional biomarkers of apoptosis, TRP-V1, and TRP-V6
Molecular Mechanisms of Dutasteride and Dietary Interventions to Prevent Prostate Cancer and Reduce Its Progression (NCT01653925)	Nov 2010	120 men	Low-risk PC	5 dietary consultations over 12 months to encourage omega-3 intake and low-fat diet; 6 months into trial, add 5α-reductase inhibitor for 6 months	*Lipid metabolism from blood and prostatic microenvironment*, gene expression profile, estrogen/androgen metabolism, utility of urine-based PC markers (PCA3)
Web-based Lifestyle Trial Among Men With Prostate Cancer: Prostate 8 (NCT02470936)	June 2015	Estimated 76 men; AS and post-RP	Biopsy-proven nonmetastatic PC with diagnosis >=2010; clinical stage ≤T3a; if treated, must be >3 months prior to enrollment; ≤4 of 8 healthy behaviors on questionnaire	Web-based, personalized lifestyle program with diet and exercise recommendations and online tools; Fitbit with online community access; and behavior-reinforcing text messages	*Health behavior changes*; *task self-efficacy*, *intervention acceptability*; change in physical activity, plasma vitamin E, lycopene, blood pressure, fasting glucose, cholesterol, HbA1c, CRP, waist circumference, weight, BMI, anxiety (general and PC-specific), depression, quality of life

[a]All participants are under active surveillance unless otherwise specified
[b]Trials above have no associated results to our knowledge at time of chapter submission (10/2016)
[c]Information directly from clinicaltrials.gov

chemical recurrence. Compared to current smokers, men who quit smoking more than 10 years ago had prostate cancer mortality risk similar to those who had never smoked. Additionally, the study by Rieken et al. supports these findings and reported a similar risk of biochemical recurrence for long-term quitters of 10 or more years compared to those who were never smokers (HR = 0.96; 95% CI: 0.68, 1.37) [49].

Overall, the literature on smoking and prostate cancer suggests that smoking may promote the development of more aggressive disease and increase prostate cancer recurrence and prostate cancer-specific mortality. Quitting smoking may reduce risk of progression or death from prostate cancer as well as lowering the risk of nearly all chronic diseases.

Dietary Factors

There are several different aspects of diet that may contribute to prostate cancer progression. Below, we review vegetables, grains, and soy; meat, fat, and animal products; coffee and tea; and nutritional supplements. For each topic, we briefly summarize the epidemiologic literature with a focus on effects of the food or nutrient after diagnosis.

Vegetables, Grains, and Soy

Vegetables are a rich source of vitamins, minerals, and phytochemicals, some of which may be beneficial in reducing risk of prostate cancer development or progression. While there are some inconsistencies, data generally suggest that lycopene/lycopene-rich foods (e.g., *tomatoes*) [50], *cruciferous vegetables* [51], and *soy/soy-based foods* [10] may reduce the risk of developing prostate cancer, in particular more aggressive disease.

Only limited studies have examined post-diagnostic intake of vegetables and the risk of prostate cancer progression. Our team observed that post-diagnosis intake of tomato sauce (but not fresh tomatoes) and cruciferous vegetables was associated with marked reductions in the risk of recurrence among men initially diagnosed with localized prostate cancer [10, 52, 53], although data were not entirely consistent across studies.

In a post hoc exploratory analysis of 41 men with localized prostate cancer enrolled in a randomized controlled trial in Norway, subjects receiving ~30 mg of lycopene per day for 25 days from tomato-containing products had a PSA decrease of 0.23 μg/L as compared to the control group that experienced a 0.45 μg/L increase ($P = 0.02$) [54]. Landberg et al. conducted a small randomized crossover trial of 24 men with untreated prostate cancer who consumed 6 weeks of a diet plentiful in rye whole grains/bran then 6 weeks of a refined wheat-based diet, with a 2-week washout period in between [55]. Seven men dropped out, leaving 17 men with complete data for analysis. The authors reported that the rye whole grain and bran diet vs. refined wheat diet were associated with lower levels of urinary C-peptide and plasma insulin and PSA [55]. While compelling, it should be noted that these types of results come from small trials, and further research is warranted to understand the biological effects of these foods and nutrients on prostate cancer etiology and progression.

In unaffected men, several studies have focused specifically on the potential protective benefits of *soy* on risk of developing prostate cancer. A recent meta-analysis of five cohort and nine case-control studies reported a 26% reduction of prostate cancer risk for consumption of soy food (RR = 0.74, 95% CI: 0.63, 0.89; $P = 0.01$), specifically for consumption of non-fermented soy food (e.g., tofu and soy milk) (RR = 0.70, 95% CI: 0.56, 0.88; $P = 0.01$) and not for fermented soy foods (e.g., miso and natto) (RR = 1.02, 95% CI: 0.73, 1.42; $P = 0.92$) [56]. Some data suggest that results may be limited to or stronger among Asian populations as opposed to Western populations [56] or may depend on genetic variants in estrogen receptor [57, 58]. In prostate cancer patients, the evidence on soy and its effect on PSA levels have been inconsistent; some studies have reported favorable effects while others reported no effects [59–61]. This

heterogeneity was recently summarized in a 2015 review [62].

Several studies that examined soy among patients electing active surveillance also had mixed results [63–66]. While not directly relevant to men on active surveillance, there are some data from men initially treated for their prostate cancer showing a potential beneficial effect of soy, though data are also inconsistent. Studies have examined the relation between PSA rise and use of soy products as a supplemental therapy [67] or as a secondary treatment for recurring prostate cancer [68, 69]. Ahmad et al. conducted a randomized placebo-controlled trial observing soy supplements alone and PSA rise [67]. Patients with localized prostate cancer who were scheduled to receive radiation therapy enrolled to receive 200 mg/day soy isoflavone supplements or a placebo for 6 months in conjunction with radiation treatment [67]. After radiation treatment, the soy supplement group had a greater reduction in median PSA value than the placebo group (76% vs. 59% reduction in median PSA value, respectively). In another randomized placebo-controlled trial, soy isoflavone supplement treatment before radical prostatectomy was associated with lower inflammatory mRNA and protein expression levels and increased cell cycle progression inhibitor *p21* mRNA expression levels in prostatectomy specimens [70]. In contrast to these compelling findings, in a double-blinded RCT of ~177 men with high prognostic risk prostate cancer managed by surgery, 2 years of daily supplementation with soy protein isolate led to no difference in the occurrence of biochemical failure compared to placebo (calcium caseinate) [61].

Meat, Fat, and Animal Products

Fairly consistent evidence suggests that greater intake of processed meat (including processed red meat or processed poultry) elevates the risk of developing prostate cancer [71, 72], including more advanced disease or aggressive disease [73–76]. Potential biologic mechanisms may involve fat, nitrites and nitrates contained in processed meat, or carcinogenic heterocyclic amines (HA) formed during cooking at high temperatures. The World Health Organization recently classified processed meat as a human carcinogen and red meat as a "probable" carcinogen. While one systematic review and meta-analysis reported a general null association between red meat and prostate cancer risk [71], the WHO report mentioned specifically a body of evidence indicating positive associations between red meat and risk of developing advanced prostate cancer [72]. Limited (and not entirely consistent) data suggest that fish may be a healthy alternative to red or processed meat for men with prostate cancer [52, 77, 78]. Omega-3 fatty acids, found in fish, are actively being studied for the primary prevention of cancer and cardiovascular disease (NCT01169259).

Poultry intake (prior to diagnosis) was recently shown to be inversely associated with risk of developing advanced and fatal prostate cancer in a pooled analysis of 15 cohort studies [79]; specific types of poultry or cooking methods were not specifically evaluated. Egg consumption during adulthood may increase risk of developing aggressive prostate cancer. The same pooled analysis reported that participants who ate about one half an egg or more per day had a 14% increased risk of advanced and 14% increased risk of fatal prostate cancer compared to those with very low egg intake [79]. In the HPFS, we reported a statistically significant 81% increased risk of developing lethal prostate cancer among men consuming 2.5 or greater eggs per week compared to those consuming less than half an egg per week [80].

Studies on meat or animal product intake among men on active surveillance have not been reported to the best of our knowledge. However, a few studies have focused on the associations of post-diagnostic meat (including poultry), fat, or animal product intake and risk of prostate cancer progression, and a few clinical trials are examining comprehensive lifestyle changes, including vegetarian diet, among men on active surveillance (see below, multiple lifestyle changes). Among men diagnosed with localized prostate cancer in CaPSURE™, men with the

highest intakes of poultry with skin had a 2.3-fold increased risk (HR = 2.26; 95% CI: 1.36, 3.76 comparing highest to lowest quintile) of prostate cancer recurrence/progression compared to those with the lowest intake [77]. This could be due to higher heterocyclic amine content or the cooking method used in chicken eaten with skin vs. without the skin. We observed a more modest nonsignificant increased risk of poultry intake with skin in the HPFS adjusted for pre-diagnosis intake [80]. Skinless poultry was not associated with progression in either study. In CaPSURE™, men in the highest quintile of egg intake had a twofold increased risk of prostate cancer progression compared to those in the lowest quintile (HR = 2.02; 95% CI: 1.10, 3.72) [77], while no association was observed for egg intake after diagnosis and lethal prostate cancer in the HPFS, which accounted for pre-diagnosis intake [80]. The increased risk observed in CaPSURE™ could be attributed in part to egg consumption prior to diagnosis, which could not be accounted for in this analysis. More studies are needed to substantiate these observations.

Processed red meat was associated with an elevated but nonsignificant increased risk of prostate cancer progression in both CaPSURE™ and HPFS [77, 80]. Saturated fat consumption, most often from meat, has been implicated in prostate cancer progression [81]. Strom et al. observed a twofold increase in risk of biochemical recurrence (HR = 1.95; 95% CI: 1.19, 3.19) associated with greater saturated fat consumption among 390 men who underwent radical prostatectomy for organ-confined prostate cancer at diagnosis [82]. In 2015, we analyzed data from the Physicians' Health Study and reported that men consuming 5% more of their daily calories from saturated fat and 5% less of their daily calories from carbohydrates had a 2.8-fold increased risk of prostate cancer-specific mortality (HR 2.78; 95% CI: 1.01, 7.64, $P = 0.05$). Those consuming 10% more of their daily calories from vegetable fats and 10% less of their calories from carbohydrates reduced their risk of overall mortality by a third (HR = 0.67; 95% CI: 0.47, 0.96, $P = 0.03$) [83].

Dairy intake and higher calcium intake (greater than the recommended dietary allowance of ~1000 mg/day) have generally been associated with a small to moderate increase in the risk of developing prostate cancer [10, 84]. Data on post-diagnostic intake of dairy are limited, but suggest that higher dairy intake after diagnosis may be associated with an increased risk of developing fatal prostate cancer and that intake of high-fat dairy in particular may be detrimental. For example, among ~3900 men initially diagnosed with localized prostate cancer, consumption of whole milk (but not low-fat milk) was associated with a twofold greater risk of progression to lethal disease [85]. Among 926 men initially diagnosed with nonmetastatic prostate cancer in the Physicians' Health Study, consuming ≥3 vs. <1 servings/day of dairy was associated with 2.4-fold increased risk of prostate cancer death; of note, in this study, while this positive association was stronger for high-fat dairy, there remained a positive association for low-fat dairy as well [86].

Coffee and Tea

A few studies have reported that pre-diagnostic coffee consumption is associated with a significant reduction in the risk of developing high-grade or lethal prostate cancer [87, 88]. One study of 47,911 men observed a 60% reduction in the risk of lethal prostate cancer for men in the highest (≥6 cups per day) vs. lowest categories of coffee consumption [88]. The results were similar for caffeinated and decaffeinated coffee and may be due to coffee's antioxidant effects [89]. Those findings were supported by some, but not all, subsequent studies, as well as meta-analyses [90, 91]. There are no studies to date about post-diagnostic coffee intake and risk of progression of prostate cancer; however, one study by Geybels et al. among men diagnosed with prostate cancer found that drinking ≥4 cups per day of coffee vs. ≤1 cup/week (measured 2 years before diagnosis) was associated with a 59% reduced risk of prostate cancer recurrence/progression (HR = 0.41, 95% CI: 0.20–0.81; p-trend = 0.01) [92]. Because

the data are limited in men with prostate cancer, the evidence is not strong enough to recommend that nondrinkers take up coffee to lower their risk of prostate cancer progression. However, coffee may improve overall health and is associated with lower risk of a number of illnesses, including gallbladder disease, diabetes, Parkinson's disease, and overall death, so it may be beneficial to maintain intake for prevention of other health conditions if already a coffee drinker.

Several epidemiologic studies, mostly in Asian populations, suggest that tea consumption may possibly be associated with a reduced risk of prostate cancer [93]; however, a recent meta-analysis of observational studies reported no overall association for tea consumption and prostate cancer, with a suggestive benefit seen only in case-control studies, which are prone to substantial bias [94]. Another meta-analysis found green (but not black) tea consumption to be beneficial, but again, the benefit was only observed in the less reliable case-control studies [95]. Some clinical trials of tea extracts have yielded promising initial results [96, 97], but not all [98] for chemoprevention. Further studies of tea, and especially trials of tea extracts in prostate cancer patients, are warranted. Given the limited evidence, the data are insufficient to recommend taking up consumption of tea to reduce risk of prostate cancer progression.

Nutritional Supplements

Currently, several large professional bodies generally do not recommend the usage of nutritional supplements to prevent cancer or cancer progression [99, 100]. Rather, in the American Cancer Society 2012 summary on Nutrition and Physical Activity Guidelines for Cancer Survivors, Rock et al. state: "Evidence from both observational studies and clinical trials suggests that dietary supplements are unlikely to improve prognosis or overall survival after the diagnosis of cancer, and may actually increase mortality" [99].

One exception may be vitamin D, as it has recently been reported that many older adults are vitamin D deficient [101, 102]. Vitamin D is actively being studied for primary prevention of total cancer and cardiovascular disease as part of the NCI-funded VITAL trial (NCT01169259), slated to release results in late 2017. In the interim, men should have their levels checked by their doctor before taking a vitamin D supplement.

Since our last summary, further data have emerged indicating the need for tailoring when it comes to nutritional supplementation. Individuals may have different needs depending on their treatments, other conditions, or status with regard to particular nutrients. Also, there have been several cautionary tales indicating that more is not always better [103, 104], and an individual's baseline level of a particular nutrient or his genetics may influence how his body responds to supplementation [103, 105–108] with regard to cancer outcomes. For example, in the HPFS, among ~4400 men initially diagnosed with non-metastatic prostate cancer, those who consumed 140 or more μg/day of supplemental selenium after diagnosis had a 2.6-fold increased risk of prostate cancer death [103] compared to nonusers. An earlier placebo-controlled trial among men on active surveillance randomized to placebo, 200 ug/day or 800 ug/day of high-selenium yeast for 6 months, reported no difference in PSA velocity between groups; however, those in the highest quartile of baseline selenium and supplemented with 800 ug/day of selenium had a higher PSA velocity compared to placebo [109]. Such findings underline the need for caution when considering using vitamins or supplements, as it is possible that not all vitamin usage is benign or beneficial. Therefore, it is recommended that cancer survivors review their usage of nutritional supplements with their physicians, as individuals may require different supplements throughout the different phases of their cancer management or due to other comorbidities or conditions.

Taken together, men with prostate cancer should focus on consuming a varied diet rich in vegetables, whole grains, skinless poultry, and fish and avoid processed meats rather than focus on consuming any specific vitamins or supplement.

Multiple Lifestyle Changes

As cancer has multiple causes, it is reasonable to assume that disparate lifestyle factors may work together to reduce or delay the risk of progression. We previously investigated the combined effect of six lifestyle factors and the risk of developing metastatic or fatal prostate cancer, among ~42,000 men from the HPFS (576 lethal prostate cancer events observed). The six factors investigated were BMI <30 kg/m^2, not smoking or quitted more than 10 years ago, engaging in ≥3 h of vigorous physical activity weekly or ≥7 h of brisk walking, and consuming ≥1 serving fatty fish, ≥7 servings of tomatoes, and <3 servings of processed meat per week. Men who followed five to six factors had about a 68% decreased risk of developing lethal prostate cancer compared to those following zero to one factor [110]. These results examined *pre-diagnostic* lifestyle habits and the risk of developing lethal prostate cancer but may still be relevant to men on active surveillance who have not received treatment or had their prostate glands removed (i.e., men who are similar to the general population aside from having received a diagnosis). We saw similar results when applying the six-factor score to the Physicians' Health Study [110].

There are several open clinical trials examining lifestyle interventions, several of which are summarized in Table 16.1. Studies chosen for the table focused on men on active surveillance and pending published studies. Of note, the Men's Eating and Living trial (MEAL) is a multisite national phase III randomized clinical trial testing the hypothesis that a high vegetable diet reduces the risk of disease progression in prostate cancer patients on active surveillance. MEAL is funded by the Department of Defense, the National Cancer Institute, and the Prostate Cancer Foundation. The accrual goals were met (n ~ 464), and the trial is in an active follow-up phase, with results anticipated in 2018. For further details, see NCT01238172 on clinicaltrials.gov.

In the Active Surveillance Exercise Trial, we are examining the effects of a 16-week tailored home-based aerobic exercise program (vs. usual care) on prostate tumor biology among men opting for active surveillance. All eligible and consenting men will undergo a thorough baseline cardiopulmonary fitness evaluation; be asked to donate blood, urine, and archived tumor tissue from a recent biopsy; and complete surveys. Those randomly assigned to the intervention arm will receive a 16-week exercise program tailored to their baseline level of fitness and designed to increase their cardiopulmonary fitness level safely and gradually. Men are provided with heart rate monitors (chest strap or watch based) to help meet heart rate goals during each prescribed exercise session. We will examine post-intervention biopsy samples to evaluate changes in prostate tumor biomarkers. This study is open to all men opting for active surveillance for their prostate cancer in the San Francisco Bay Area. For further details see NCT02435472 on clinicaltrials.gov.

The Prostate 8 study is a web-based intervention evaluating whether a tailored lifestyle report + interactive patient website + Fitbits help men with localized prostate cancer opting for active surveillance or surgery adopt healthy habits, compared to usual care. The study is being conducted at the University of California, San Francisco. The website is designed to promote the adoption of eight healthy habits, selected based on data that these lifestyle factors decrease the risk of prostate cancer progression. Men are randomly assigned to the multicomponent intervention vs. usual care for 12 weeks, and primary outcomes are feasibility and acceptance; secondary outcomes include changes in anthropometric metrics, blood levels of antioxidants, self-reported diet, exercise habits, and quality of life. The accrual goals were met (n ~ 76) and results are expected in Fall 2017. Please see NCT02470936 on clinicaltrials.gov for more information.

The Prostate Cancer: Evidence of Exercise and Nutrition Trial *(PrEvENT)* is a cohort and randomized controlled trial of post-diagnostic men scheduled for RP evaluating the effect of physical activity and dietary interventions on post-prostatectomy outcomes. Specific dietary interventions that will be observed include

Table 16.2 Organizations that provide downloadable patient recommendations for cancer, nutrition, and lifestyle

Organization	Web Address
The American Cancer Society	http://www.cancer.org/Healthy/EatHealthyGetActive/index http://www.cancer.org/healthy/informationforhealthcareprofessionals/acsguidelines/nupaguidelinesforcancersurvivors
The Prostate Cancer Foundation	https://www.pcf.org/wp-content/uploads/2016/10/PCF_HW_Guide2017.pdf http://www.pcf.org/site/c.leJRIROrEpH/b.5814067/k.2BBE/Prostate_Cancer_Guides_and_Books.htm
World Cancer Research Fund Report International	http://www.wcrf.org/int/research-we-fund/cancer-prevention-recommendations/cancer-survivors

lycopene-containing foods, plant-based diets, dairy products, and soy milk. Prior to RP, participating men are put in cohorts and tissue and baseline markers are collected. Following RP, men participating in the trial are randomized to one of six experimental conditions, each with a specified level of exercise and dietary intervention. These men will then be followed at 3 months and 6 months post-randomization.

To further explore the potential benefits of exercise, it is worth noting that the Movember Foundation recently funded a phase III clinical trial examining the effects of 24 months of high-intensity aerobic + resistance exercise vs. usual care on overall survival; secondary outcomes include progression, symptomatic skeletal-related events, circulating metabolic biomarkers, physical function, and quality of life. This study aims to recruit 866 men worldwide, including at least 8 sites in North America. Please see NCT02730338 on clinicaltrials.gov for more information.

Conclusions

While data remain limited with regard to lifestyle risk factors among men on active surveillance, current data suggest that it would be prudent for men with prostate cancer to consider the following recommendations:

- Participate in regular physical activity, including brisk walking and more vigorous activity if possible.
- Stop smoking.
- Eat more vegetables, including cooked tomatoes and cruciferous vegetables.
- Limit meat consumption, especially processed meats and poultry with skin.
- If eating meat, try fish and skinless poultry.
- Limit saturated fat (e.g., poultry with skin, high-fat dairy).
- Review the usage of specific vitamins or nutritional supplements with your physician.

Several organizations have also compiled patient-friendly material based on available scientific evidence (Table 16.2). These reports, readily available on the Internet, contain sensible recommendations, similar to that provided above.

Future Directions

Further studies of complementary approaches for managing men on active surveillance are warranted. The MEAL trial is currently in active follow-up phase and will address the critical question of whether increasing vegetable, whole grain, and legume intake delays biological progression or initiation of treatment among men on active surveillance. The Active Surveillance Exercise Trial is open in the San Francisco Bay Area and will examine the potential benefits of exercise on prostate tumor biology and other systemic markers of biological progression. Since our last update, progress has been made in launching several studies that will evaluate the biological and clinical impact of lifestyle interventions. However, we purport that further research, including randomized clinical trials and implementation studies examining the usage of health technology, is warranted to determine how best to support men in adopting healthy habits after a diagnosis of prostate cancer. It is also a public health priority for healthcare providers, employers, and insurance companies to develop better policies and systems that support patients with cancer in making healthy lifestyle changes to maximize their quality of life and survival.

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17 Is There a Role for Pharmacologic Manipulation to Prevent Progression in Men on Active Surveillance? The Role of 5-ARIs, Statins, and Metformin

Roy Mano and David Margel

Introduction

Traditional treatments for Pca, such as surgery or radiation, are associated with significant adverse events and can negatively affect the quality of life of patients and their families [1–3]. Low-risk prostate cancer may be treated with active surveillance since randomized trials have failed to show a beneficial impact of immediate radical treatment on survival [4]. The negative effects of treatment combined with potentially long latency of the disease, late age of onset, and high prevalence make prostate cancer an ideal target for primary and secondary disease prevention. Several medications have been evaluated as potential agents for prostate cancer prevention including 5-α(alpha)-reductase inhibitors (5-ARI), statins, and metformin. Herein we describe possible mechanisms through which these medications act to inhibit prostate cancer development and progression and focus on their role in secondary prevention of low-risk prostate cancer.

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5-α(alpha)-Reductase Inhibitors (5-ARI)

The rationale for the specific use of 5-ARIs as chemopreventive agents is based on the androgenic nature of prostate cancer and the uniform absence of prostate cancer among men with congenital deficiency of 5α(alpha)-reductase [5]. The enzyme 5α-reductase resides in prostatic tissue and converts circulating testosterone to localized dihydrotestosterone (DHT), a more potent agonist of androgen receptors in prostatic cells. 5α(alpha)-reductase has two isoforms: type II 5α(alpha)-reductase is the isoform common in benign prostatic tissue; type I predominates in localized prostate cancer [6]. Finasteride is a selective inhibitor of the type II enzyme, while dutasteride inhibits both isoforms [7]. The decreased levels of DHT induced by 5-ARIs may inhibit prostate cancer development and progression, thus providing the rationale for its role as a chemopreventive agent.

Statins

Statin medication effectively lowers serum cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [8]. The chemopreventive role of statins for prostate cancer may be the result of

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cholesterol-mediated and non-cholesterol-mediated pathways [8].

Discrete portions of the cell membrane consisting of cholesterol-rich domains termed "lipid rafts" play a central role in intracellular signaling [9]. These membrane rafts may promote prostate cancer development and progression via androgen receptor, epidermal growth factor receptor, and luteinizing hormone receptor pathways [8]. In a xenograft model of LNCaP cells, inhibition of cholesterol synthesis decreased the cholesterol content in lipid rafts, attenuated AKT signaling, and induced tumor cell apoptosis [10]. In addition, cholesterol serves as a precursor for androgen production; thus, lowering cholesterol levels may lower androgen levels. However, observational studies have not supported the association between statin use and reduced androgen levels [11].

Statins may also directly affect cancer cells, independent of cholesterol levels, and may inhibit prostate cancer growth by exerting proapoptotic, anti-inflammatory, and anti-angiogenic effects [12].

Metformin

Metformin reduces hepatic glucose production, increases insulin sensitivity, increases glucose use by peripheral tissues, and thus decreases the blood glucose levels in patients with type 2 diabetes mellitus [13]. Metformin exerts its antineoplastic properties in multiple pathways including AMP-activated protein kinase-dependent and kinase-independent pathways, alteration of insulin and insulin-like growth factor signaling, and suppression of androgen signaling [13].

AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase that regulates cellular energy metabolism. AMPK suppression has been associated with the activation of tumor growth pathways, including the mammalian target of rapamycin (mTOR) pathway. Metformin activates AMPK and thus decreases mTOR signaling which decreases protein and fatty acid synthesis and inhibits cell proliferation [14]. Furthermore, the suppression of de novo lipogenesis is directly responsible for AMPK-mediated inhibition of prostate cancer growth [15]. Multiple AMPK-independent mechanisms, including the reduction of cAMP levels which inhibits protein kinase A activity and blocks glucagon-dependent glucose production, have also been associated with the treatment of diabetes mellitus and the antineoplastic properties of metformin [16].

Insulin, insulin growth factor (IGF) 1, and IGF 2 act to promote tumorigenesis by binding to the insulin receptor and activating the PI3K/AKT/mTOR pathway leading to abnormal cell proliferation, inhibition of apoptosis, and carcinogenesis [13]. Furthermore, hyperglycemia aids tumor growth since tumor cells are highly reliant on aerobic glycolysis to generate energy (the Warburg effect). Metformin inhibits gluconeogenesis and decreases circulating glucose and insulin levels thus opposing the tumorigenic effects of hyperinsulinemia and hyperglycemia [17].

Metformin reduces the activity of cyclin D1 which has been shown to be a central regulator in androgen-dependent transcription and cell cycle progression of prostate cancer cells [18]. In addition, metformin may disrupt androgen signaling by directly acting against androgen receptor pathways. These antiandrogenic effects may act against the development and progression of prostate cancer.

Preventive Medicine

Preventive medicine or preventive care refers to measures taken to prevent diseases (or injuries), rather than curing them or treating their symptoms. Preventive medicine strategies are typically described as taking place at the primary, secondary, and tertiary levels:

1. *Primary prevention* strategies intend to avoid the development of disease.
2. *Secondary prevention* strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.
3. *Tertiary prevention* aims to reduce the negative impact of established disease by restoring function and reducing disease-related complications.

The Role of 5-ARIs, Statins, and Metformin in Primary Prevention of Prostate Cancer

There are two positive large randomized controlled studies demonstrating the effect of 5-ARIs in primary prevention of prostate cancer [19, 20]. The Prostate Cancer Prevention Trial (PCPT) reported a 24.8% relative reduction (95% CI 18.6–30.6, $p < 0.001$) in the risk of prostate cancer in patients receiving finasteride over the 7-year study period [19]. Similarly, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial reported a relative reduction of 22.8% (95% CI 15.2–29.8, $p < 0.001$) in prostate cancer events over the 4-year study period [20]. However, in both studies, there was an increased likelihood of developing high-grade tumors when 5-ARIs were given as preventive agents to healthy men, which led the Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) to recommend against prostate cancer chemoprevention labeling for the 5α(alpha)-reductase inhibitors finasteride (Proscar) and dutasteride (Avodart). Therefore, a more appealing strategy would be to use 5-ARIs to delay progression in those men already diagnosed with prostate cancer.

Most clinical data evaluating the effect of statins on the development and progression of prostate cancer are based on observational studies utilizing large databases or meta-analyses of statin randomized control trials. Since these studies were focused on cardiovascular outcomes, they were underpowered to evaluate the true effect of statins on prostate cancer, and most studies did not detect a significant effect [21]. Farwell et al. performed a large observational study comparing men receiving statins to those receiving antihypertensive medication. In this cohort, statin users were 31% less likely (HR 0.69, 95% CI 0.52–0.9) to be diagnosed with prostate cancer, and increased levels of cholesterol were associated with a higher incidence of prostate cancer (HR 1.02, 95% CI 1–1.05). This association was more prominent for high-grade tumors [22]. Other large cohort observational studies did not demonstrate an association between statin use and prostate cancer incidence or grade [23–25].

Conflicting results exist in observational studies evaluating the association between treatment with metformin and prostate cancer risk. In a large retrospective cohort study, no association was demonstrated between metformin use and the risk of prostate cancer (OR 1.03, 95% CI 0.96–1.1), regardless of cancer grade and method of diagnosis [26]. Contrary to these findings, in a case control study base on the Danish Cancer Registry, metformin users had a decreased risk of developing prostate cancer compared with never users (OR 0.84, 95% CI 0.74–0.96) [27].

5-ARIs in Secondary Prevention

Several studies, including one RCT, have examined the role of 5-ARIs to prevent progression in men with low-risk, localized prostate cancer followed by active surveillance [28–32]. In their initial single-institution, retrospective cohort study, Finelli et al. compared 70 men started on a 5-ARI at variable time points after their diagnostic biopsy to 218 men who were not treated with 5-ARI while on active surveillance for low-risk prostate cancer. Progression was defined as GS >6, maximal core involvement >50%, or >3 positive cores on follow-up biopsy. At a median follow-up of 38.5 months, men treated with 5-ARI experienced lower rates of progression (18.6% vs. 36.7%; $p = 0.004$) and were less likely to abandon active surveillance (20% vs. 37.6%; $p = 0.006$). These findings remained significant on multivariate analysis [28]. The study was criticized for not relating to the use of 5-ARI as a time-dependent covariate, thus potentially overestimating its benefit [33]. In a subsequent reanalysis using a Cox proportional hazards model with time-dependent covariates, lack of 5-ARI treatment continued to be associated with pathological progression (HR 4.55, 95% CI 1.61–12.5, $p = 0.004$) [29]. Contrary to these findings, Ross et al. reported a retrospective study of 587 men enrolled to an active surveillance program, 47 of whom received 5-ARI during surveillance. The main study outcome was progression on surveillance biopsy, and the use of 5-ARI was treated as a time-dependent covariate. On univariate analysis, progression occurred in 17%

of 5-ARI users compared to 31% of nonusers ($p = 0.04$). However, the significance of the association was lost on multivariable analysis when adjusting for age, α-blocker use, PSA level, %free PSA, PSA density, prostate volume, and number/percent biopsy core involvement at diagnosis [30]. Finally, Shelton et al. reported on 82 men with very low-risk prostate cancer and benign prostatic hyperplasia who were followed with active surveillance and received 1 year of treatment with 5-ARI. At their first restaging biopsy, 54% of men had no evidence of prostate cancer, 21% continued to have very low-risk prostate cancer, 20% progressed to low-risk prostate cancer, and 5% to intermediate-risk prostate cancer (Gleason score 7). During 3 years of follow-up, most patients (57/82, 70%) maintained very low-risk prostate cancer or had negative surveillance biopsies; thus, the authors concluded that 5-ARI treatment for patients on active surveillance for very low-risk prostate cancer is a safe treatment option. Furthermore, 5-ARI therapy increases the sensitivity of prostate-specific antigen and can aid in targeting biopsies [31].

The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial is the only phase III RCT to evaluate the safety and efficacy of 5-ARIs in secondary prevention in men with low-risk prostate cancer followed by active surveillance. In this randomized, double-blind, placebo-controlled trial, men aged 48–82 who had low-volume Gleason score 5–6 prostate cancer, PSA ≤10 ng/ml, and were followed by active surveillance were randomized to receive once daily dutasteride 0.5 mg/day ($n = 147$) or matching placebo ($n = 155$). The total follow-up was 3 years, with 12-core biopsy samples obtained at 18 and 36 months. The primary end point was time to disease progression. This was a composite outcome defined as the earliest of the following events: receipt of primary therapy for prostate cancer (e.g., prostatectomy, radiation, hormonal therapy) or pathologic progression (≥4 cores involved, ≥50% of any core involved, or any Gleason score ≥7). Secondary end points included improving anxiety, quality of life (QOL), and urinary symptoms in men undergoing active surveillance. At 3 years of follow-up, 54/144 men (38%) in the dutasteride group had disease progression compared to 70/145 men (48%) in the control group, (HR 0.62, 95% CI 0.43–0.89, $p = 0.009$). Subjects treated with dutasteride were more likely to have no cancer detected on follow-up biopsies (23% in the placebo arm vs. 36% in the dutasteride arm, $p = 0.024$). The main difference between the two groups was a reduction in number of cores involved a nd extent of core involvement by Gleason 6 cancer in the dutasteride group compared to placebo, perhaps reflecting the known cytoreduction effect of the drug. Importantly, Gleason score 8 cancer was detected in the final biopsy in two men in the dutasteride group and three controls, and no case of Gleason score 9–10 cancer was noted on the final biopsy. Based on the memorial anxiety scale for prostate cancer (MAX-PC), overall prostate cancer anxiety assessment remained almost constant for controls and decreased for patients who received dutasteride throughout the study. Specifically, patients at the dutasteride group reported a significantly lower fear of recurrence. Overall rates of adverse events did not differ significantly between dutasteride and placebo. Sexual adverse events and breast-related disorders were apparent in 35 men (24%) receiving dutasteride and 23 men (15%) in the placebo group; however, this difference was not statistically significant. Likewise, no difference was noted in cardiovascular complications. The authors conclude that among men followed for prostate cancer with active surveillance, dutasteride may delay the time for cancer progression and decrease prostate cancer-related anxiety. Therefore, dutasteride may provide a useful adjunct to active surveillance [32]. A limitation of the REDEEM study is that a reduction of volume of Gleason 6 disease with dutasteride was the main difference between the two arms. Since dutasteride reduces prostate epithelial cell volume, this is not surprising. Whether this will translate into a meaningful biological difference remains unce rtain.

Statins in Secondary Prevention

In a large population-based study, Yu et al. identified 11,772 men with newly diagnosed nonmetastatic prostate cancer and reported that the post-diagnostic use of statins was associated with a decreased risk of prostate cancer mortality (HR 0.76, 95% CI 0.66–0.88) and all-cause mortality [34]. Multiple studies have specifically evaluated the role of statins in secondary prevention after radical prostatectomy and curative radiation therapy for localized prostate cancer [21].

Reports regarding the association between postoperative statin use and prostate cancer recurrence after surgery are inconsistent. While one study reported that post radical prostatectomy statin use was associated with a significant 36% reduction in the risk of biochemical recurrence [35], other studies failed to find an association between statin use and biochemical recurrence [36–38]. On the contrary, studies evaluating the effect of statin use on the incidence of prostate cancer recurrence after curative radiation therapy have shown a significant improvement in freedom from biochemical failure [21]. The exact difference between postradiation and postsurgery effect is not known.

The REALITY trial is a prospective study of the use of red yeast rice (RYR) to prevent progression among men with low-risk prostate cancer [39]. RYR is a naturally produced substance that inhibits cholesterol synthesis, has a similar structure as lovastatin, and competes favorably with lovastatin, pravastatin, and simvastatin in terms of lipid-lowering potency [40]. Furthermore, a commercial RYR product was evaluated in a large randomized, placebo-controlled trial which included patients with a previous myocardial infarction. In this study RYR significantly reduced lipid levels, especially LDL, and appeared to have a favorable impact on cardiovascular end points including nonfatal myocardial infarction and death from cardiovascular disease. Moreover, cancer-related mortality and overall mortality were significantly reduced in patients receiving RYR [41]. Furthermore, intact RYR has a direct effect on LNCaP cells and may favorably inhibit androgen-dependent and androgen-independent prostate cancer growth, which can translate into an inhibition of prostate cancer proliferation and progression [42]. This inhibitory effect was observed in prostate cancer xenograft models following treatment with RYR [43].

In the REALITY study, men with localized low-risk prostate cancer on active surveillance will receive 3600 mg of RYR daily, with an estimated reduction of 20–35% in LDL cholesterol levels. Patients will be followed with the aim to evaluate whether lipid-lowering medication may have a beneficial effect in secondary prevention of low-risk, localized, prostate cancer [39]. Results of this study may eventually support the role of statins as secondary prevention agents in men with low-risk prostate cancer on active surveillance.

Metformin in Secondary Prevention

The role of metformin for secondary prevention of prostate cancer has been studied with conflicting results. In a group of 3873 patients with incident diabetes diagnosed with prostate cancer, the cumulative duration of metformin treatment after cancer diagnosis was associated with a significant decreased risk of disease-specific and all-cause mortality in a dose-dependent fashion [44]. Similarly, in a group of patients with localized prostate cancer treated with external beam radiation therapy, rates of 10-year prostate cancer-specific mortality were significantly lower in patients receiving metformin when compared to diabetic patients who did not receive metformin (2.7% vs. 21.9%, respectively, $p \leq 0.001$). Furthermore, metformin may decrease the development of castrate-resistant prostate cancer in patients experiencing biochemical failure [45]. Other studies failed to show a decreased risk of cancer-specific or all-cause mortality in patients with nonmetastatic prostate cancer and a history of treated type 2 diabetes mellitus [46] nor a beneficial effect of metformin on biochemical recurrence after radical prostatectomy for clinically localized prostate cancer [47, 48]. In a recent

report, Mayer et al. retrospectively evaluated the effect of metformin use together with docetaxel when treating diabetic patients with castration-resistant prostate cancer. The use of metformin did not improve cancer-specific survival or overall survival in this setting [49].

To date, no randomized study evaluated the role of metformin in secondary prevention of very low-risk prostate cancer. The Metformin Active Surveillance Trial (MAST), which is currently recruiting, is a phase III, randomized, double-blind, placebo-controlled trial that will evaluate whether metformin can delay time to progression in men on expectant management for low-risk prostate cancer compared to placebo. An estimated total of 408 men will be enrolled during the study period. Inclusion criteria include men aged >18 and <80 years with biopsy-proven localized prostate cancer choosing expectant management as their primary treatment. The diagnostic biopsy will include at least ten cores and performed ≤6 months of screening. Patients will have <3 positive cores, <50% of any one core positive, Gleason score ≤6, clinical stage T1c-T2a, and a serum PSA ≤10 prior to biopsy. Estimated life expectancy of participants will be >5 years, and their hemoglobin A1c levels <6.5%. Exclusion criteria include past treatment for prostate cancer, use of antiandrogenic medication, diagnosis of diabetes mellitus, prior exposure to metformin, or a contraindication for metformin treatment. The intervention arm will receive a 1 month run-in of metformin 850 mg daily after which they will receive metformin 850 mg twice daily for 35 months, for a total treatment period of 3 years. The primary outcome will be time to progression defined as the earliest of either primary therapy for prostate cancer or pathological progression (more than three cores involved, >50% of core involved, Gleason pattern >3). Additional secondary outcomes will include changes in disease-related patient anxiety as evaluated with the MAX-PC score and changes from baseline in decisional satisfaction and decisional conflict as measured by the decisional regret scale. In addition, treatment safety and adverse events will be determined [50].

Discussion

The concept of prevention was popularized by Benjamin Franklin, whose aphorism – "an ounce of prevention is worth a pound of cure" – has withstood the test of time. 5-ARIs are may play a role in cancer prevention. However, the associated loss of libido induced by 5 ARIs and concerns about the potential for upgrading has limited their role in primary prevention. These concerns have also diminished enthusiasm for their role as secondary prevention agents in men on surveillance. In men on 5 ARIs for whom the indication is BPH/LUTS, a diagnosis of low grade prostate cancer need not influence the BPH treatment decision, and in fact a dual benefit in terms of also reducing the risk of disease progression is plausible.

Despite a sound scientific rationale for the use of metformin and statins for prostate cancer prevention, clinical data are conflicting, and there are currently no RCTs to support their role in secondary prevention. Ongoing trials should shed light on their potential for secondary prevention in low-risk prostate cancer patients.

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18 The Update of Active Surveillance Around the World: Utilization and Outcomes

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Active surveillance (AS) involves deferring initial treatment and instead performing serial monitoring of prostate cancer to identify later evidence of reclassification and offer selective delayed management. Dissociating diagnosis from treatment is important to reduce the downstream harms of screening [1], and follow-up studies of AS have demonstrated that this is a safe option for men with favorable disease, demonstrating a low risk of prostate cancer metastasis or death within 10–15 years [2, 3]. AS is considered a standard management option in current guidelines. For example, the American Society of Clinical Oncology (ASCO) recently endorsed guidelines from the Cancer Care Ontario (CCO) stating that AS is the recommended management option for most patients with low-risk prostate cancer and may also be offered to selected patients with low-volume intermediate-risk disease [4]. This chapter explores the utilization of AS throughout the world and summarizes clinical outcomes reported in the literature.

Utilization

In past decades, AS was vastly underutilized, with only 10% of low-risk patients in the United States Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry managed expectantly in 2004–2006 [5]. Based on registry data from 2010 to 2013, however, Cooperberg and Carroll recently reported that 40% of low-risk cases were managed expectantly in the contemporary setting [6]. Among men >75, the rate of AS in this population was 76% during this time period. The New Hampshire Cancer Registry similarly showed uptake of AS by 42% of low-risk patients in 2011 [7].

Disparate results were reported among 91,556 men in the National Cancer Data Base diagnosed with low-risk prostate cancer from 2010 to 2013 [8]. In this population, only 12% underwent expectant management. Overall, it is clear that there continues to be significant variation in the uptake of AS across American practice sites. A collaborative registry from Michigan reported that overall 49% of low-risk patients diagnosed in 2012–2013 were managed by AS [9]. However, this varied significantly across practices from 27% to 80%.

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Several studies have attempted to further characterize the underlying reason for such variability. Hoffman et al. reported that physician factors accounted for a greater proportion of the variation in use of observational management than patient and cancer-specific factors [10]. Specifically, the diagnosing urologist accounted for 16% of the variation, while patient and tumor characteristics accounted for only 8%. Patients whose cancer was diagnosed by urologists who treated prostate cancer were more likely to receive up-front treatments offered by that urologist. Lester-Coll et al. reported that patients evaluated at academic centers were 2.7 times more likely to receive expectant management compared to community centers [8]. However, even within the Veterans Health Administration, Filson et al. reported significant variability in use of expectant management across facilities [11].

Cher et al. convened a panel of physicians to explore decision-making about AS in greater detail using hypothetical clinical scenarios [12]. Patients with low-volume Gleason 6 disease were considered highly appropriate for AS. For scenarios with high-volume Gleason 6 or low-volume Gleason 3 + 4 disease, prostate-specific antigen (PSA) density, race, and life expectancy were considered significant factors in the decision-making process regarding appropriateness of AS.

Globally, multiple studies have reported a reduction in the proportion of patients with low-risk disease undergoing radical prostatectomy over time [13, 14]. Meanwhile, an increasing number of patients are choosing AS. Nationwide Swedish data showed that utilization of AS increased from 57% to 91% in very low-risk patients and from 40% to 74% for low-risk cancers from 2009 to 2014 [15]. Overall, 19% of men with intermediate-risk disease chose active surveillance in 2014, but this proportion was higher among certain subsets of patients within this population. For example, among patients with Gleason 6 disease who were considered intermediate risk by virtue of a PSA level from 10 to 20 ng/ml, 53% chose AS, while AS utilization was lower for men with Gleason 3 + 4 disease.

In the Victoria Cancer Registry in Australia, 66% of low-risk patients were managed by active surveillance in 2013 [16]. A Canadian multidisciplinary clinic reported that 59% of low-risk and 16% of low-intermediate-risk patients chose AS [17]. Overall, these data are encouraging by demonstrating a reduction in the overtreatment of low-risk prostate cancer and expanding use of AS.

Outcomes

Outcomes have recently been published from several institutional AS cohorts. This wealth of emerging data, however, must be interpreted with caution in light of its limitations. Given that AS has only recently been more widely accepted and endorsed [4, 18, 19], only a minority of men managed with contemporary AS have been followed over the long term (≥10 years). This point is particularly relevant in light of the prolonged time course from diagnosis to metastasis or death in the setting of low- to intermediate-risk prostate cancer (PCa) [20–22]. Furthermore, AS has traditionally been offered to older men with limited life expectancy [23]; therefore, evidence of its effectiveness in younger men remains limited. Nonetheless, the practice of active surveillance has grown in both scope and sophistication since its introduction more than 20 years ago [23, 24], and data describing its use have similarly expanded.

Initiation of two large, prospectively designed AS programs in 1995 set the course for subsequent study of the approach [23, 24]. Reports from Johns Hopkins University and Sunnybrook Health Sciences Centre in 2002 provided preliminary data based on the 7-year AS experience, with reports of long-term outcomes emerging in 2015 as these cohorts matured [2, 3]. Since the launch of these programs, a number of institutions worldwide have followed suit and added compelling results on the effectiveness of AS in the early to intermediate term (<10 years) [25–31]. Overall, pertinent clinical outcomes after AS have been reported in 10,395 men across 9 published single- and multi-institutional AS cohorts with follow-up data [2, 3, 25–31].

Notably, there is currently no “universal” approach to AS. We have previously described the relationship between the nature of AS protocols

and the risks and outcomes associated with this strategy [32]. As expected, the outcomes observed in AS programs appear to depend on the nature of a given program, including its criteria for selection, monitoring, and triggers for intervention. Therefore, meaningful interpretation of patient outcomes requires an understanding of each program's patient population and approach to management.

Johns Hopkins University (Baltimore, Maryland, USA)

The Johns Hopkins approach to AS was based on the work of Epstein and colleagues, which specified clinical and pathologic criteria associated with small volume, clinically insignificant PCa [33]. Specifically, the authors reported that men with PSA density less than 0.15 ng/ml/cc, Gleason score ≤6, two or fewer positive biopsy cores, and ≤50% involvement of any core with cancer were demonstrated at prostatectomy to have organ-confined, low-grade tumors of ≤0.5 cc in approximately 80% of cases. At the same time, failing to meet these criteria was associated with larger, non-organ-confined, high-grade cancers in approximately 80% of cases. The predictive accuracy of the Epstein criteria was subsequently confirmed in a prospective study [34], and these metrics of clinically insignificant cancer have been adopted as part of the National Comprehensive Cancer Network (NCCN) definition of very low-risk (VLR) prostate cancer [18].

Accordingly, the AS experience at JHU has primarily aimed to enroll men with VLR cancer and therefore offers some of the more stringent criteria for inclusion. At last report, 71% of men enrolled in AS at JHU met VLR criteria, and 29% met low-risk (LR) criteria (clinical stage ≤T2a, PSA <10 ng/ml, and Gleason score ≤6); no men with intermediate-risk PCa have been included in the JHU cohort [2]. Furthermore, the JHU program includes intensive monitoring (Table 18.1). Patients undergo PSA testing and clinical exam every 6 months and have traditionally undergone yearly prostate biopsy in most cases. Intervention is recommended in all men who fail to meet the initial enrollment criteria during follow-up.

Table 18.1 AS protocol at Johns Hopkins University

Enrollment criteria	PSAD <0.15, clinical stage T1c, Gleason score ≤6, ≤2 positive cores, and ≤50% involvement of any core (preferred); or PSA <10, clinical stage ≤T2a, and Gleason score ≤6
Monitoring	PSA + DRE every 6 months; prostate biopsy every 1 year
Triggers for intervention	Failure to meet enrollment criteria

Outcomes from JHU were most recently reported in 2015 and described 1298 men of median age 66 years [2]. Median follow-up of the cohort was 5.0 years, with 650 men followed for at least 5 years and 184 men followed for at least 10 years. The cumulative incidence of definitive treatment with radical prostatectomy or radiotherapy was 50% at 10 years and 57% at 15 years. Freedom from metastasis was 99.4% at both 10 and 15 years, and prostate cancer-specific survival was 99.9% at both 10 and 15 years.

Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada)

Also initiated in 1995 and first reporting outcomes in 2002 [24], the Sunnybrook experience provides a substantial volume of information regarding the longer-term outcomes of AS. In contrast to the JHU program, inclusion in AS at Sunnybrook has been more permissive. Prior to 2000, patients with Gleason score ≤3 + 4 and serum PSA ≤15 ng/ml were eligible for AS. Since 2000 those criteria have been modified to permit AS for GS ≤3 + 4 and PSA 10–20 ng/ml only in men with life expectancy less than 10 years (Table 18.2). Monitoring at Sunnybrook has consisted of PSA testing every 3–6 months, initial confirmatory biopsy within 1 year of diagnosis, and subsequent biopsies every 3–4 years. Intervention is recommended upon Gleason score upgrading, and, prior to 2008, in cases of PSA doubling time (PSADT) less than 3 years. Based on evidence that PSA kinetics are not reliable predictors of reclassification [35, 36], the program has since considered short PSADT an indi-

Table 18.2 AS protocol at Sunnybrook Health Sciences Centre

Enrollment criteria	Gleason score ≤6 and PSA ≤10 (low risk) or Gleason score ≤3 + 4 and PSA ≤20 if life expectancy ≤10 years (intermediate risk)
Monitoring	PSA every 3–6 months; biopsy within 1 year then every 3–4 years
Triggers for intervention	Gleason score upgrading; prior to 2008, also included PSADT <3 years

Table 18.3 Active surveillance in the Göteborg screening trial

Enrollment criteria	No curative treatment for PCa within 6 months of diagnosis
Monitoring	PSA every 3–6 months; biopsy within 12 months if cancer volume <2 mm, otherwise every 2–3 years in the absence of worrisome findings
Triggers for intervention	PSA progression, increased Gleason score, increased cancer volume, or clinical progression

cator for further evaluation rather than immediate intervention.

Last reported in 2015, outcomes from Sunnybrook are based on 993 men with a median follow-up of 6.4 years; 206 men were followed for more than 10 years and 50 men for more than 15 years [3]. Notably, 21% of the cohort had intermediate-risk cancer, including 13% with Gleason score ≥7. The cumulative incidence of treatment was 36% at 10 years and 45% at 15 years. During follow-up, 28 men (2.8%) developed metastatic disease, and 15 men (1.5%) died of PCa. Prostate cancer-specific survival was 98.1% at 10 years and 94.3% at 15 years.

Active Surveillance in the Göteborg Screening Trial (Göteborg, Sweden)

The AS experience in Göteborg differs from JHU and Sunnybrook most notably in how the cohort was derived. As reported in 2016 [25], this study population was composed of men diagnosed with PCa based on the Göteborg screening trial, which has been described in detail previously [37]. Importantly, management with AS was not determined based on strict inclusion criteria, but rather the use of AS was classified retrospectively in men with very low-, low-, and intermediate-risk disease who did not undergo curative treatment within 6 months of diagnosis. Similarly, the monitoring protocol was not prospectively defined, but surveillance has generally included PSA testing every 3–6 months. Early rebiopsy (≤12 months) was not standard in the cohort but was typically performed in men with limited cancer volume (<2 mm) at diagnosis to confirm suitability for AS. Additional surveillance biopsies were generally performed every 2–3 years in the absence of other worrisome findings (Table 18.3).

Ultimately, the 474 patient cohorts captured a relatively wide distribution of baseline risk categorization, as it was composed of 51% VLR cancers, 27% LR cancers, and 22% intermediate-risk cancers. Median overall follow-up was 8.0 years, with 181 men followed for more than 10 years and 31 for more than 15 years. The 10- and 15-year rates of treatment were 53% and 66%, respectively. Metastasis-free survival was 99% at 10 years and 93% at 15 years. A total of six men died of PCa, with associated cancer-specific survival rates of 99.5% at 10 years and 96% at 15 years. Notably, there were no deaths among men with very low-risk prostate cancer.

Prostate Cancer Research International Active Surveillance (PRIAS)

The PRIAS study was initiated in 2006 and represents a departure from the conventional, single-institution approach to AS [38]. In contrast, PRIAS includes participants from academic, nonacademic, and private practices derived from over 150 centers across 18 countries. Patient data are prospectively entered through the PRIAS website, allowing for efficient provision of recommendations and data collection across several sites. Initial patient selection criteria included clinical stage ≤T2c, PSA ≤10 ng/ml, PSAD <0.20 ng/ml/cc, Gleason score ≤6, ≤2 positive biopsy cores, and fitness for curative treatment (Table 18.4). In recent years, these criteria have been adapted to include select Gleason score 3 + 4 = 7 patients and to accommodate changes in practice secondary to the use of

Table 18.4 AS protocol in Prostate Cancer Research International Active Surveillance (PRIAS)

Enrollment criteria	Clinical stage ≤T2c, PSA ≤10 ng/ml, PSAD <0.20 ng/ml/cc, Gleason score ≤ 6, and ≤2 positive biopsy cores (or ≤15% of total cores positive); or Gleason score 3 + 4 = 7, ≤ 2 positive biopsy cores, ≤10% cancer involvement in any core, and age ≥70; all patients must be fit for curative treatment
Monitoring	PSA every 3–6 months; DRE every 6–12 months; scheduled biopsy at years 1, 4, 7, and 10, with additional biopsies recommended if PSADT <10 years
Triggers for intervention	Gleason score >6, >2 positive biopsy cores, or clinical stage >T2

saturation or magnetic resonance imaging (MRI)-guided biopsies [26]. The initial 2 years of follow-up include PSA testing every 3 months and DRE every 6 months, and subsequent monitoring includes PSA testing every 6 months and DRE every 1 year. Surveillance biopsies are scheduled at years 1, 4, 7, and 10 from diagnosis; additional interval biopsies are recommended if PSADT is <10 years. Active treatment is recommended upon detection of Gleason score >6, more than two positive biopsy cores, or clinical stage >T2.

As a relatively young study with an innovative, online approach for widely capturing data, PRIAS has reported on 5302 men, of which 3379 underwent at least one surveillance biopsy and 622 were followed for >5 years. At 5 and 10 years of follow-up, 48% and 27% of the cohort remained on AS, respectively. During follow-up, 30 men underwent biochemical recurrence (BCR) after prostatectomy or radiotherapy, 10 developed local recurrences, 8 developed metastatic disease, and 1 man died of PCa. Given the low event rate and limited follow-up, the authors reported a composite endpoint including BCR, local recurrence, metastasis, and PCa death. Cumulative incidence of this outcome was 2% at 5 years and 6% at 10 years following diagnosis.

University of California, San Francisco (UCSF; San Francisco, California, USA)

UCSF has prospectively collected clinical data in men diagnosed with PCa who did not undergo active treatment for at least 6 months for many years [27]. This active surveillance cohort has evolved with time in terms of patient inclusion and monitoring criteria. As of 2015, strict inclusion criteria included serum PSA ≤10 ng/ml, clinical stage T1/2, biopsy Gleason score ≤6, ≤33% of biopsy cores positive, and ≤50% cancer involvement of any core (Table 18.5). Recommended monitoring has included PSA testing every 3 months, transrectal ultrasound (TRUS) every 6 months, and an initial confirmatory biopsy within 12 months of diagnosis. Subsequent prostate biopsies have been recommended every 1–2 years according to clinical risk. Indications for treatment include biopsy, Cancer of the Prostate Risk Assessment (CAPRA) risk, or clinical stage reclassification.

Clinical data were reported in 2015. A total of 810 men consented to study inclusion and had accrued at least 6 months of follow-up, of which 556 (69%) met inclusion criteria. Over a median follow-up of 60 months, including over 200 men with at least 7.5 years of follow-up, the authors observed metastatic disease in only 1 man (0.12%) and prostate cancer death in none. Five-year treatment-free survival was 60%. Additional time-specific outcomes were not reported.

Royal Marsden (London, England, UK)

In 2002, the Royal Marsden Hospital in the United Kingdom (UK) began prospectively collecting data on men managed with AS [39]. This program differs from others in that it selectively

Table 18.5 AS protocol at University of California, San Francisco (UCSF)

Enrollment criteria	PSA ≤10 ng/ml, clinical stage T1/2, biopsy Gleason score ≤6, ≤33% of biopsy cores positive, and ≤50% cancer involvement of any core
Monitoring	PSA every 3 months; TRUS every 6 months; biopsy within 12 months then every 1–2 years based on clinical risk
Triggers for intervention	Biopsy reclassification (Gleason score >6, >33% of biopsy cores positive, >50% cancer involvement of any core), CAPRA risk reclassification, or clinical stage reclassification

excludes very young men and the elderly by restricting eligibility to men aged 50–80 years. Enrollment criteria include clinical stage T1/T2, PSA <15 ng/ml, Gleason score ≤6, and no more than 50% of overall biopsy cores positive (Table 18.6) [28]. Men who presented with Gleason score 3 + 4 were in some cases also enrolled if they were older than age 65. The inclusion criteria for Royal Marsden are relatively permissive in some regards; for example, there is not a specific threshold for exclusion based on elevated PSAD or high involvement of cancer within a positive biopsy core. During surveillance, PSA and DRE are performed every 3 months in year 1, every 4 months in year 2, and every 6 months thereafter; biopsies are performed approximately every 2 years. Intervention for treatment is recommended if the PSA velocity (PSAV) exceeds 1 ng/ml per year or if adverse histology is detected on repeat biopsy, defined as Gleason score ≥4 + 3 or the presence of cancer in more than 50% of biopsy cores obtained.

As of 2013, the Royal Marsden experience included 471 men (median age 66 years) managed with AS for a median follow-up time of 5.7 years. Of these, 383 (81.3%) were classified as low risk, while the remaining 88 (18.7%) were intermediate risk. Within the cohort, 33 men (7.0%) were diagnosed with Gleason score 3 + 4 disease. Analysis of intermediate-term outcomes from this cohort demonstrated 2- and 5-year treatment-free survival rates of 89% and 70%, respectively. The rate of adverse histology at these same time points was 6% and 22%, respectively. While rates of metastatic disease were not reported, there were two (0.4%) deaths attributed to prostate cancer over the entire follow-up period.

Table 18.6 AS protocol at Royal Marsden

Enrollment criteria	Age 50–80, clinical stage T1/T2, PSA <15 ng/ml, Gleason score ≤6 (or 3 + 4 if age > 65), and ≤50% total biopsy cores positive
Monitoring	PSA and DRE every 3 months for year 1, every 4 months for year 2, then every 6 months; biopsy every 2 years
Triggers for intervention	PSAV >1 ng/ml/year, Gleason score ≥4 + 3, or >50% positive biopsy cores

Additional Cohorts

As the concept of active surveillance has taken hold, numerous institutions from around the world have followed suit in reporting their respective experiences. Three additional cohorts have contributed to the literature describing outcomes over the shorter term (median follow-up <5 years).

St. Vincent's Prostate Cancer Centre (Sydney, Australia)

The St. Vincent's experience was initiated in 1998, with AS reserved for men with clinical stage <T2b, PSA <10 ng/ml, Gleason score ≤6, <20% of cores with cancer, and <30% cancer involvement of any positive core (Table 18.7) [29]. However, the program has also allowed for the inclusion of men with up to two higher-risk features, including age <55 years, PSA >10 ng/ml, clinical stage ≥T2b, small-volume Gleason score 3 + 4, >20% of cores with cancer, or >30% cancer involvement of any positive core. These patients were followed using PSA measurements every 3 months for 3 years and every 6 months thereafter, DRE every 6 months for 3 years and every year thereafter, and biopsies at 1 year, 2–3 years, and every 3–5 years thereafter. Intervention is recommended if there is a new diagnosis of Gleason pattern 4 cancer or, in select patients with small-volume Gleason score 3 + 4 disease, an increasing proportion of Gleason pattern 4. Other triggers for intervention include PSADT <3 years, PSAV >0.75 ng/ml, clinical

Table 18.7 AS protocol at St. Vincent's Prostate Cancer Centre

Enrollment criteria	Clinical stage <T2b, PSA <10 ng/ml, Gleason score ≤6, <20% positive biopsy cores, and <30% cancer involvement of any positive core (preferred); see text for detailed higher-risk criteria
Monitoring	PSA every 3–6 months; DRE every 6–12 months; biopsy at 1 year, 2–3 years, then every 3–5 years
Triggers for intervention	New presence or increasing proportion of Gleason pattern 4, PSADT <3 years, PSAV >0.75 ng/ml, clinical stage ≥T2b, >20% positive biopsy cores, or >40% involvement of any positive core

Table 18.8 AS protocol at University of Copenhagen

Enrollment criteria	Clinical stage ≤T2a, PSA ≤10 ng/ml, Gleason score ≤6, ≤3 positive biopsy cores, and <50% cancer involvement of any positive core
Monitoring	PSA and DRE every 3 months; rebiopsy 1 year after diagnosis
Triggers for intervention	Clinical stage ≥T2b, PSADT <5 years, Gleason score ≥7, or number of positive biopsy cores >3

stage ≥T2b, >20% of biopsy cores positive, or >40% involvement of any positive core.

From 1998 to 2012, St. Vincent's followed 650 men over a median follow-up time of 4.6 years. Treatment-free survival rates at 1, 3, and 5 years were 92%, 68%, and 57%, respectively. Overall, 245 (37.7%) men underwent radical treatment and 7 (1.1%) experienced BCR. At the time of median follow-up, the BCR-free, metastasis-free, and prostate cancer-specific survival rates were 99%, 100%, and 100%, respectively.

University of Copenhagen (Copenhagen, Denmark)

At the University of Copenhagen, AS has been offered since 2002 to individuals who meet strict selection criteria [30]. This population includes men with clinical stage ≤T2a, PSA ≤10 ng/ml, Gleason score ≤6, ≤3 positive biopsy cores, and <50% cancer involvement of any positive core (Table 18.8). Patients have been followed with PSA and DRE every 3 months and a rebiopsy performed 1 year after diagnosis. Conversations about switching to treatment were initiated if clinical stage is ≥T2b, PSADT is <5 years, Gleason score is ≥7, or the number of positive biopsy cores is >3.

From 2002 to 2011, the program included 167 men (median age 65 years) followed for a median of 3.4 years. During this time frame, 59 patients (35.3%) discontinued active surveillance, with 47 (28.1%) demonstrating progression of disease. They estimated the 5-year probability of remaining on active surveillance to be 60%. Biochemical recurrence, metastasis, and prostate cancer-specific mortality rates were not reported.

Table 18.9 AS protocol at University of Miami

Enrollment criteria	Clinical stage T1/T2, Gleason score ≤6, PSA ≤10, ≤2 positive biopsy cores, and ≤20% cancer involvement of any core
Monitoring	PSA and DRE every 3–4 months for the first 2 years, then every 6 months; biopsy at 9–12 months, then every year unless earlier biopsy is warranted
Triggers for intervention	Gleason score ≥7, >2 positive biopsy cores, or increase in tumor volume

University of Miami (Miami, Florida, USA)

The University of Miami began offering AS in 1992 to men with stage T1/T2 disease, Gleason score ≤6, PSA ≤10, ≤2 positive biopsy cores, and ≤20% cancer involvement of any positive core (Table 18.9) [31]. Each patient was followed with PSA and DRE every 3–4 months for the first 2 years and every 6 months thereafter. The study protocol was modified in 2000 to include a prostate biopsy at 9–12 months from diagnosis and every year thereafter, with additional biopsies recommended with a substantial rise in PSA or changes in DRE. Curative treatment was recommended for Gleason score ≥7, >2 positive biopsy cores, or an increase in tumor volume.

As last reported in 2010, a total of 230 men with a median age of 64 years were followed for a median of 2.7 years. Of these 230 individuals, 32 (14%) underwent treatment, and none experienced BCR. While the metastasis rate was not reported, no man in this cohort has died from prostate cancer.

Summary of Outcomes

In early 2016, we reviewed the protocols and outcomes from nine major AS programs which previously reported pertinent outcomes over a reasonable follow-up interval [32]. At the time, these programs included 7552 men, with median age ranging from 63 to 68 years and median follow-up from 1.6 to 6.4 years. In the interval since that review, additional data have emerged

Table 18.10 Outcomes from AS programs with 5-year median follow-up (2010–2016)

			Treated				Metastasis/MFS			Cancer death/CSS		
Program	*N*	*Follow-up**	*N (%)*	*5-year*	*10-year*	*15-year*	*N (%)*	*10-year MFS*	*15-year MFS*	*N (%)*	*10-year CSS*	*15-year CSS*
Johns Hopkins (2)	1298	5.0	471 (36%)	37%	50%	57%	5 (0.4%)	99.4%	99.4%	2 (0.15%)	99.9%	99.9%
Sunnybrook (3)	993	6.4	267 (27%)	24.3%	36.5%	45.0%	28 (2.8%)	–	–	15 (1.5%)	98.1%	94.3%
Göteborg (25)	474	8.0	202 (43%)	–	53%[a]	66%[b]	–	99%	93%	6 (1.3%)	99.5%	96%
UCSF (27)	810	5.0	348 (43%)	40%[c]	–	–	1 (0.12%)	–	–	0 (0%)	100%	100%
Royal Marsden (28)	471	5.7	145 (31%)	30%	–	–	–	–	–	2 (0.4%)	–	–

CSS, cancer-specific survival; *MFS*, metastasis-free survival

*Median (years)

[a]Reported as 47% treatment-free survival

[b]Reported as 34% treatment-free survival

[c]Reported as 60% treatment-free survival

from the Göteborg trial and PRIAS programs [25, 26]. A contemporary assessment of these programs now includes 10,395 patients, with median follow-up times ranging from 3.4 to 8.0 years in eight of nine programs. Perhaps more importantly, an increasing number of men are reaching 10 and 15 year milestones.

Selected overall and time-specific outcomes from AS programs with intermediate and longer-term follow-up (median ≥5 years) are listed in Table 18.10. At 10 years from diagnosis, approximately one-third to one-half of men electing AS will have undergone treatment. This finding emphasizes the underlying philosophy of the contemporary AS paradigm – not to eliminate treatment altogether but to eliminate treatment in those men who demonstrate truly insignificant disease while safely delaying treatment in others. As illustrated throughout the chapter, outcomes of AS are encouraging to date. With additional men now followed for 10 years and longer, 10-year prostate cancer-specific survival ranges from 98.1% to 100%. As additional findings are reported in the coming years, the utility of AS over the long term will become even clearer.

Conclusions

The use of active surveillance has undeniably expanded in recent years, both in North America and abroad. With additional intermediate and long-term data, it is increasingly clear that AS is a safe and beneficial approach for most men with very low- and low-risk cancers. Still, the use of AS varies substantially within these populations, reflecting differences in risk tolerance and philosophy amongst practitioners.

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Tissue Preservation: Active Surveillance and Focal Therapy as Complimentary Strategies

19

Juan Gómez Rivas and Mark Emberton

Background

The following chapter contains a summary of the differences and areas of overlap between the two main prostate preserving strategies that exist for patients with low- to moderate-risk prostate cancer, namely, active surveillance and focal therapy. Our overriding view is that the two strategies overlap to a considerable degree. As a result, they do not appear as mutually exclusive strategies. Instead, the two appear as complimentary strategies that can be adopted in sequence to each other as part of a risk-adjusted care programme. This welcome and beneficial convergence is set to continue, and to become the most important revolution in early prostate cancer management in the last 50 years as clinicians emerge from the era of blindness to tumour location to an image based approach.

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Common Ground

Active surveillance (AS) and focal therapy (FT) – directing therapy to the cancer (plus a margin) rather than to the entire prostate – share considerable common ground. Both embrace as a core belief that, given an acceptable oncological risk, men, on balance, would prefer to keep their prostates rather than surrender them to willing surgeons or radiotherapists. Clinicians recommending the tissue-preserving strategies of AS and FT do so in the hope of mitigating some of the harms associated with overdiagnosis and the resulting overtreatment. While we can't reverse a diagnosis if one is given to a patient, what we can do is offer the newly diagnosed man a pathway that is associated with reduced levels of side effects by adopting a policy of tissue preservation when it is both possible and sensible to do.

Strategy One

Active surveillance offers a holding strategy; 'You do have prostate cancer Mr. Smith, but we are pretty sure that it's an unimportant one. I think it is unlikely to affect you if we leave it alone. Let's keep an eye on it and treat if it shows signs of change'.

Strategy Two

Focal therapy offers a risk reduction strategy; 'You do have prostate cancer Mr. Jones. We have

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located what we believe to be the worse of it. We should be able to treat the cancer and at the same time preserve most of your prostate'.

In essence the two overlap considerably; however, one is backloaded, the other front- loaded. Both seek to derive a group of low-risk men who can safely avoid radical therapy at the whole-gland level. Active surveillance typically does this by reviewing the status of low risk over time by exposing the patient to an imperfect test (systematic biopsy) although MRI and MRI-guided biopsies are correcting this imprecision. On each round of testing, some men are reclassified as exceeding the upper threshold of risk and exit AS – usually by being offered whole-gland radical therapy [1]. On each round, as more men exit, we end up with a group of men enriched with low-risk status given that they have been deemed free of 'progression' due to their lack of histological reclassification.

The clinician offering focal therapy, because his or her need defines the topography of the disease, needs to establish the location, extent and risk (by virtue of grade and maximum cancer core length) up front as these three attributes inform the conduct of the therapy. Precision is required, on the one hand, to rule in clinically important cancer within the field of therapy (high specificity). It is also required to rule out clinically important cancer within the volume of tissue that is to be spared (high sensitivity). It should be of little surprise that our traditional diagnostic tests are not up to the job. Instead, the focal therapist has to embrace a sampling strategy that can fulfil both these requirements.

The challenges that face the clinician who recommends a tissue-preserving strategy differ significantly from those that present to the whole-gland therapist. The whole-gland therapist at the most basic level requires, as a minimum, a prostate cancer diagnosis. One millimetre of Gleason 3 plus 3 historically, was sufficient to proceed. In many centres, the presence of pattern 4 is the minimum threshold for treatment. The imprecision of the risk attribution is not of any great concern to the prostatectomist, nor is it to the radiation oncologist planning the patient's IMRT, for instance, as the treatment for organ-confined disease is independent of burden, grade and location of the cancer. In a sense, everyone gets the same because the target is the prostate, not the cancer. Surgeons have known there will be upgrading from biopsy pathological status to that derived by whole mount section for many years. The degree of upgrading is an inverse measure of the accuracy of their risk stratification system.

The clinician advocating AS requires a bit more information than the whole-gland therapist as a prostate-preserving strategy will fail to 'mop up' any excess disease that might have been overlooked initially. So, as well as a lower threshold – the patient does need to have a prostate cancer diagnosis – the application of a higher disease threshold is also required in AS. Put another way, what is the worst disease that this man has? Here, we have a problem. Standard TRUS-guided biopsies, because of an inherent imprecision that results from both systematic and random error, can reliably only ever give us information on the lower threshold. In other words the product of TRUS biopsy in terms of pathology output nearly always gives us the minimum amount of disease that might be present, not the maximum. This occurs because prostate cancers, within the diagnostic spectrum that concerns us, tend to occupy about 1/30th of the volume of the prostate. The usual biopsy strategy rarely samples more than 0.5% of the prostate volume. As a result, a direct hit of a tumour focus is a rare event. Because either a miss or a glancing blow is more likely than a direct hit, it is the norm that both maximum cancer core length and Gleason pattern will be under-represented on an initial set of biopsies compared to what is truly there. Therefore, defining the upper limit of disease has proved difficult with the standard diagnostic PSA/biopsy pathway. The strategy that has tended to be applied as a form of correction to this widely recognized sampling deficiency is a reapplication of TRUS-guided biopsy. Some AS protocols advocate a verification biopsy at entry. In other words, the patient's low-risk status needs to be upheld beyond a second set of biopsies for the patient to be permitted entry. This strategy, though widely adopted, makes little sense given the poor reli-

ability of TRUS biopsy when applied over time – an attribute exploited by both REDUCE and REDEEM studies [2, 3]. When coupled with the sensitivity of about 20–30% of TRUS biopsy for clinically significant disease – the target condition we are seeking to rule out – the strategy is unlikely to be an efficient one.

If a qualification re-biopsy is not a requirement, most clinicians will recommend a re-biopsy sooner rather than later, usually within the first year or two. The same limitations apply to a deferred biopsy as they do to an immediate 'verification' biopsy. Trans-rectal ultrasound biopsy does not have the specification to rule out clinically important disease of whatever definition. The reasons are technical but relate to the systematic under sampling of certain parts of the prostate (some parts are never reached) but also to the divergent sampling strategy (midline to lateral) that the technique employs. For a very good, but rather technical, essay on these issues, please refer to Kepner's treatment of this [4].

The reapplication of the TRUS biopsy at given time points, in most AS protocols, deserves some attention. Obviously, a test does not improve in terms of its overall accuracy just because it is reapplied. Reapplication of the test will serve to reduce some of the random error inherent in the parts of the prostate routinely reached by the biopsy strategy. Systematic error will not be affected, unless a different needle deployment is used or the prostate is rendered smaller and therefore more accessible to the same needles, as, for example, by exposure to a 5-alpha reductase inhibitor. The reduction in random error will be most evident within the peripheral zone of the gland. Two things might happen as a result, assuming that the original placement of the needles has been adequate and assuming that no new cancers have arisen, nor has any progression of existing ones resulted in the interval. The first is to stumble across pre-existing small cancer foci that could have easily been missed on the first round. The second is to hit a pre-existing cancer more directly and as a result obtain a different spectrum of Gleason pattern. Given the floor effect of Gleason 3 + 3, the only difference that can be derived is an escalation of risk by an upgrading of the Gleason pattern even when no real change has occurred. Maximum cancer core length can go in either direction provided that the first biopsy contained more than 1 mm of disease. If the patient starts with just 1 mm of disease, it is hard to get less than this.

The deferring of the verification biopsy in the way that is traditionally done in AS to the impartial onlooker makes little sense. Low-risk cancers shouldn't change very often, and if they do it should be over a very long time frame. If this is the case, why then plan biopsies at 1–3-year intervals in the manner that is commonly done in AS protocols. The planning of interval biopsy imposes two ideas that are both insecure. The first is that TRUS biopsy is a 'good' test at ruling in clinically significant disease if it is indeed present. It is not. The second, probably a spurious idea, which is communicated by this policy, is that if we wait, even a short period of time in prostate cancer terms, the cancer – that was previously deemed to be low risk – may indeed transform into a more aggressive one, and if it does we can identify it.

A major drawback in the application of TRUS biopsy during the follow-up of patients in AS is low compliance and infectious complications. Since compliance with follow-up is essential for the oncological safety of AS, strategies are needed to reduce unnecessary biopsies. mpMRI is increasingly used in men on active surveillance and could help to select those men who need a repeat biopsy. An mpMRI ± target biopsy strategy could reduce the number of follow-up biopsies by omitting TRUS biopsies in the absence of suspicious lesions (one third of men on AS) and potentially even mpMRI target biopsy in the absence of radiological progression of a known lesion [5].

One last issue that has not been discussed too much relates to the intensity of the biopsy regimen over time. The norm in surveillance, whether intended or not, is to diminish the intensity of follow-up over time. This is often patient led but usually condoned by the treating physician. It is likely however that the probability of progression, if it indeed occurs, increases with time as the patient gets older. It is likely that the safest

period is the period soon after diagnosis and/or reclassification.

What Do We Learn from the ProtecT Trial?

ProtecT, which aims to evaluate the effectiveness, cost-effectiveness and acceptability of treatments for men with localized prostate cancer, was a randomized controlled trial which ran from 1999 to 2009 and which screened around 82,429 men for PSA. A total of 2664 men were found to have prostate cancer, with 1643 randomized to active surveillance, radical prostatectomy or radiation therapy.

The results show that death from prostate cancer in patients during the study remained low at a median of 10 years of follow-up, at approximately 1%, irrespective of the treatment assigned. All-cause mortality was also low, at approximately 10%. The rate of disease progression among men assigned to prostatectomy or radiotherapy was less than half the rate among men assigned to active monitoring ($P < 0.001$ for the overall comparison), as was the rate of metastatic disease ($P = 0.004$ for the overall comparison). These differences show the effectiveness of immediate radical treatments over active monitoring, but they have not translated into significant differences, nor have they ruled out equivalence in disease-specific or all-cause mortality. Due to the natural history of prostate cancer, longer-term follow-up is necessary. The majority of men who were randomly assigned to active monitoring (88%) accepted their treatment assignment, but a quarter of them received radical treatment within 3 years after their initial assignment and over half by 10 years; at the end of the study, 44% of the patients who were assigned to active monitoring did not receive radical treatment and avoided side effects.

One lesson learned from the ProtecT trial is that classical risk categories do not help in clinical decision-making. Experts state that contemporary risk categories based on PSA, Gleason score and clinical stage appear insufficient to reliably predict progression in individuals with clinically localized PSA-detected PCa after a median 10 years of follow-up. Decision making is enhanced by incorporating more information from the biopsy, including number of cores and the maximum and total cancer length.

The ProtecT trial concluded that men with newly diagnosed, localized prostate cancer need to consider the critical trade-off between the short-term and long-term effects of radical treatments on urinary, bowel and sexual function and the higher risks of disease progression with active monitoring, as well as the effect of each of these options on quality of life [6].

Active Surveillance, Focal Therapy and the Future

Fortunately, much of what we do for men at risk of prostate cancer and those who have been diagnosed with prostate cancer is set to change. The key ingredient that has been missing so far is tumour location. Imagine treating kidney, breast or liver cancer without a sense of where the tumour is located. It would be impossible. It is humbling and rather worrying to think that we diagnose and treat prostate cancer without knowledge or tumour location or indeed extent. If we don't know where the cancer is, we have to seek it out, through our process of blind and partially random biopsy. If the patient does indeed have prostate cancer identified, treatment has to be directed at the organ because we truly do not know where the cancer resides.

The Diagnostic Pathway Is Set to Change

Two things have changed. The first is imaging in the form of mpMRI. The second is image-guided biopsy. For this process to work, the imaging, as in all other solid organ cancers, is being done prior to the biopsy. This has two consequences. The first is that some men, probably about a third, are able to avoid a biopsy despite their elevated PSA. This is based on the high sensitivity (80–90%), negative predictive value (90–95%) and

low negative likelihood ratio (0.1–0.2) of mpMRI for clinically significant disease that has now been demonstrated in numerous studies [7, 8]. If this performance proves sufficiently reassuring to men with a high PSA, and more importantly, to their urologists, it is reasonable to assume that some men will choose to defer the biopsy. However, the precise prevalence of normal MRIs in men at risk is not yet known. Until it is we can only guess what proportion of men might safely defer or avoid a biopsy. About a third of men diagnosed with Gleason 6 prostate cancer based on systematic biopsy will have a 'normal' MRI. These normal MRIs will be overrepresented with men who have low-volume microscopic foci of well-differentiated prostate cancer.

In contrast, men who on MRI are shown to have lesions (low signal on T2; and/or early enhancement and washout on dynamic contrast; and/or low coefficients on diffusion weighted imaging) will proceed to an image-guided biopsy. Numerous studies demonstrate high sensitivities and positive predictive values for clinically important prostate cancer (80–90%) when imaging is used to inform the sampling strategy [9]. This compares very favourably with our current practice standard, TRUS biopsy, that has been associated with a sensitivity for clinically important prostate cancer in the order of 30%.

In a recent meta-analysis, a large variability in reported negative predictive values (NPV) was observed. Many factors, such as differences in mpMRI protocols, definition of negative mpMRI or biopsy protocols, can explain this variability. However, two major causes of variability must be pointed out. First, the cancer prevalence is highly variable, ranging at patient level from 13% to 74.7% for overall prostate cancer and from 13.7% to 50.9% for clinical significant prostate cancer. This variability was observed in both the biopsy-naive and the repeat biopsy setting. As NPV depends on prevalence, this had a major impact on reported NPV. Second, the definition of clinical significant prostate cancer differs from one series to another, and differences of up to 21% could be observed in NPV when different definitions of csPCa were used in the same dataset [10].

In a recent retrospective study of 514 patients, mpMRI NPV for Gleason 7 cancers was 91% when the PSA density was 0.2 ng/ml/ml and only 71% when the PSA density was >0.2 ng/ml/ml (p = 0.003) [11]. In another series of 288 biopsy-naive patients, no csPCa (Gleason score 7 or maximum cancer core length 4 mm) was found in 44 patients with a PSA density of <0.15 ng/ml/ml and a PI-RADS v2 score of <3/5 [12].

Correlation with radical prostatectomy specimens has demonstrated that mpMRI has excellent sensitivity in detecting prostate cancer with a Gleason score of 7 [13, 14]. As a result, prostate mpMRI is increasingly used in patients with a suspicion of PCa to localize abnormal areas before biopsy. A large body of literature has shown that targeted biopsies of suspicious lesions seen on mpMRI improved the detection of clinically significant prostate cancer, at least in the repeat biopsy setting. Current recommendations are that an mpMRI is performed before repeat biopsy to allow TBx of suspicious lesions in addition to standard biopsies [15, 16].

Image-guided biopsy has two principal effects. The proportion of men with clinically significant disease, as determined by our current definitions, is rising significantly. At the same time the proportion of men with clinically insignificant disease is decreasing. We might, on face value, welcome these two outputs of image-guided biopsy, given that they will be achieved with fewer men biopsied overall and with fewer needle deployments – compared to the practice standard – in those that are biopsied.

The PROMIS study evaluated the diagnostic accuracy of mpMRI and TRUS biopsy against an accurate reference test in biopsy-naive men with a suspicion of prostate cancer. It is the largest registered trial to date of the population at risk, in which the conduct and reporting of each test was standardized and done blind to the other test results. PROMIS represents level 1b evidence for assessment of diagnostic accuracy. The main findings suggest that if mpMRI was used as a triage test, one-quarter of men might safely avoid prostate biopsy. The high NPV is reassuring in that a negative mpMRI result

implies a high probability of no clinically significant cancer. Further, overdiagnosis of clinically insignificant cancers might be reduced, while detection of clinically significant cancers improved compared with the standard of TRUS biopsy for all men. The lower specificity and positive predictive value of mpMRI shows that a biopsy, with the needles deployed based on the mpMRI findings, is still needed in those men with a suspicious mpMRI. PROMIS concludes that TRUS biopsy performs poorly as a diagnostic test for clinically significant prostate cancer and mpMRI, used as a triage test before first prostate biopsy, could identify a quarter of men who might safely avoid an unnecessary biopsy and might improve the detection of clinically significant cancer [17].

Our standard definitions of risk are based on a random sampling process that is blind to location. When the prostate is sampled in such a way, a direct hit of a cancerous lesion is a very rare event. TRUS biopsy systematically under-represents both grade and burden – hence the upgrading or reclassification that we are so used to. Because image-guided sampling does indeed induce a direct hit more often than it does not, maximum cancer core lengths are typically and sometimes frighteningly long even for a lesion that is deemed to be small. For instance, a 0.5 cc lesion – Stamey's volume threshold for significance – will often generate a maximum cancer core length of 10–12 mm, amounting to 70% or 80% of the core. Thus, the patient remains low risk by applying a common sense approach. However, he would no longer be labelled low risk if any of the commonly used risk stratification systems in widespread use today were applied. With the increased precision, we will have to introduce new definitions of risk that are more appropriate to a targeted strategy.

We have proposed such a model based on both volume and grade that has been validated through a process of simulation against a radical prostatectomy cohort [18]. The risk stratification system is collectively exhaustive and mutually exclusive to three definitions of risk and is simply displayed and communicated as a traffic light system (Fig. 19.1). Green disease is that disease that we might consider inconsequential which a 51-year-old patient has a 40–50% chance of harbouring, according to the postmortem series. It is limited to small foci of exclusive Gleason pattern 3.

Yellow disease represents a tumour focus greater than 0.2 cc but less than 0.5 cc as predicted by the maximum cancer core length that is greater than or equal to 4 mm. Alternatively, any secondary pattern 4 in a lower burden of cancer would trigger a status of yellow disease. Yellow disease is typically indeterminate. I don't think anyone today, hand on heart, can predict which way it will go. In the older man, an agreement to watch it might be reasonable. In the younger man, treatment might be more sensible, until that is we know the true biological potential of such lesions.

Red disease, characterized as it is by longer cancer core lengths (>/=6 mm) and/or by dominant Gleason pattern 4 in a smaller lesion, is the type of disease that most of us would want to treat. Red disease meets or exceeds the threshold for lesions of 0.5 cc volume.

It has to be said that all these definitions are very conservative. They need to be at this stage if they are going to be adopted. Recent reports from the European Prostate Cancer Screening study suggest that provided tumour volumes remain on the lesser side of 1.3 cc and are populated exclusively by Gleason pattern 3 that men have little to worry about [19].

The Current Role of Biomarkers and Genomics in the Diagnostic Pathway

Screening, overdiagnosis and overtreatment are current topics of debate and intense investigation in prostate cancer, and there are some cases where mpMRI is not conclusive or not helpful (young patients, indeterminate lesions). Biomarkers are an alternative in the diagnostic pathway of prostate cancer. The ideal prostate cancer biomarker would be capable of distinguishing prostate cancer from benign prostate conditions and differentiating between aggressive and indolent tumours.

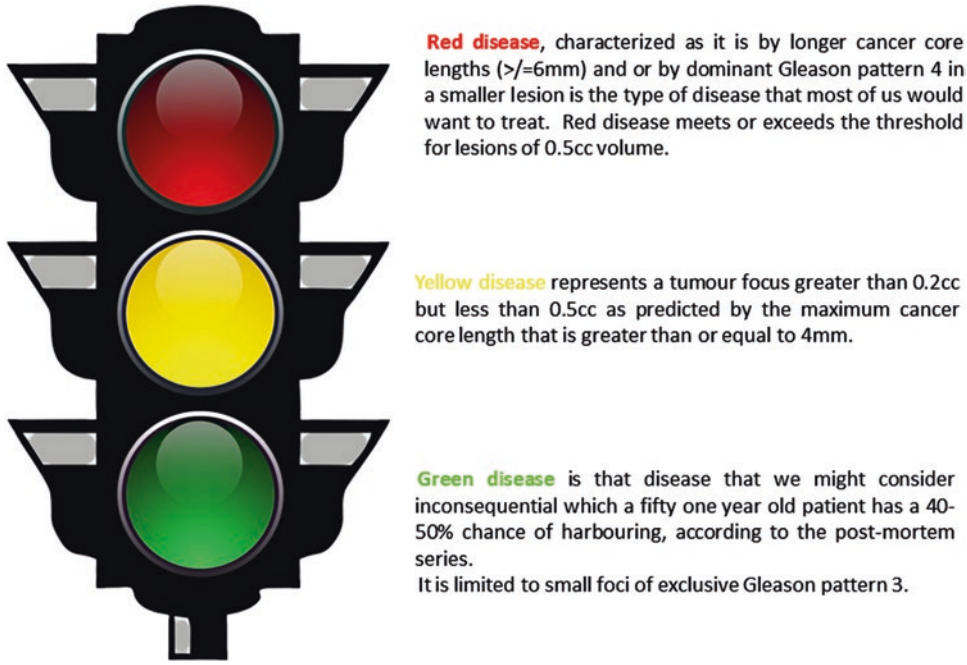

Fig. 19.1 New risk definitions in prostate cancer. Traffic light system

Sampling errors inherent with the random tissue collection of the biopsy procedure result in a false-negative rate of approximately 25%. This imprecision poses a diagnostic dilemma, often resulting in multiple repeat biopsies from the fear of missed cancer in men with persistent risk factors, resulting in added morbidity and cost. Although diminishing rates of cancers are detected during these invasive repeat procedures, a high rate of clinically significant (i.e., a Gleason score ≥7) cancer is still on the second, third and fourth or more biopsies (65%, 53% and 52%, respectively). Molecular testing is another option to help identify occult cancer in this situation [20].

Prostate Health Index (PHI) is a blood test that combines the relative concentrations of three different PSA forms, total PSA, free PSA and [−2]proPSA, using a mathematical formula: ([−2]proPSA/free PSA) × $\sqrt{}$PSA. The 2016 National Comprehensive Cancer Network guidelines offer PHI as option to increase specificity before initial or repeat biopsy, and it has regulatory approval in more than 50 countries [21, 22].

PHI has been consistently shown to outperform PSA to distinguish malignant and benign prostate conditions in men with a PSA level >2 and/or suspicious DRE. Several studies have demonstrated that PHI significantly improves prostate cancer detection in high-risk cases and also predicts the aggressiveness of disease. In the clinic, PHI is less expensive than other test like the 4K score or PCA3 and does not require a physician to conduct a digital rectal examination, making it logistically attractive for both clinicians and patients [20].

In a recent study combining PHI and mpMRI in men requiring a repeat biopsy, the potential value of the PHI in the context of image-guided repeat biopsies was explored. In this study adding PHI to mpMRI improved overall and significant cancer prediction (AUC 0.71 and 0.75) compared to mpMRI + PSA alone (AUC 0.64 and 0.69, respectively). At a threshold of ≥35, PHI + mpMRI demonstrated a negative predictive value (NPV) of 0.97 for excluding significant tumours. In mpMRI negative men, the PHI again improved prediction of significant cancers, AUC

0.76 vs 0.63 (mpMRI + PSA). Using a PHI ≥35, only 1/21 significant cancers was missed, and 31/73 (42%) men are potentially spared a re-biopsy (NPV of 0.97, sensitivity 0.95). In this way, the authors proposed PHI adds predictive performance to image-guided detection of clinically significant cancers and has value in determining the need for re-biopsy in men with a negative mpMRI [23].

Prostate cancer antigen 3 (PCA3) score measures the ratio of PSA3 and PSA mRNA in the urine after vigorous DRE using transcription-mediated amplification. Although PCA3 can be offered to patients with a previous negative biopsy, the best threshold value for repeat biopsy is controversial. In addition, its relationship to cancer aggressiveness is subject to debate and generally inferior to other markers [24].

The 4K score is a risk calculator for the detection of PCa on the biopsy based on a 4-kallikrein panel combined with the patient age, DRE and biopsy history. The 4-kallikrein panel includes total PSA, fPSA, iPSA and hK2, a kallikrein with high homology with PSA. The 4K score is associated with an improvement of 8–10% in predicting biopsy-confirmed PCa, indicating that the use of the 4K score could potentially reduce the number of prostate biopsies currently conducted by an estimated 48–56% [25].

ConfirmMDx® is a methylation assay that measures changes in methylation in benign tissue in order to identify peritumour regions adjacent a missed cancer (termed the 'halo effect'). This test evaluates methylation patterns of three genes: glutathione Stransferase pi 1 (GSTP1), adenomatous polyposis coli (APC) and Ras association (RalGDS/AF6) domain family member 1 (RASSF1) [26].

Investigators in the MATLOC study specifically examined the ConfirmMDX® test by running this assay on core prostate biopsy samples from men with prior negative biopsy. After adjusting for patient characteristics, the assay was a significant predictor of repeat biopsy outcome on multivariate analysis (OR 3.17; 95% CI 1.81–5.53) with a negative predictive value of 90%. A subsequent study of 350 American men demonstrated a negative predictive value of 88%, and ConfirmMDx was the most significant independent predictor of finding prostate cancer in repeat biopsy samples (OR 2.69; CI 95% 1.60–4.51) [27].

The Prostate Core Mitomic Test™ is another field effect laboratory test that is based upon detection of a single 3.4 kb mitochondrial DNA deletion. An early study involves a cohort of 183 men including those with benign, malignant or premalignant biopsy samples, with a reported AUC of 0.87 in the validation phase of this study.

In a follow-up study of 101 patients undergoing repeat biopsy procedures, 20 were found to have prostate cancer within 1 year of the initial biopsy; analysis of biopsy samples for prostate cancer using the PCMT was associated with a sensitivity and specificity of 84% and 54%, respectively, a negative predictive value of 91% and an AUC of 0.75 (34). Larger validation studies are required before the widespread use of this assay can be recommended [28, 29].

A Convergence of Pathways

Much of what we have written above is evidence based. Advances in imaging and targeted biopsy have improved the ability to differentiate intermediate and high-grade cancers from indolent ones. It is here that things get difficult. Remember, fewer men are biopsied overall. Those that are biopsied are more likely to have significant disease by current and possibly by modern criteria – that is what the radiological phenotype confers. Fewer men exit this process with a label of clinically insignificant prostate cancer. Surely a good thing as the label brings with it little clinical utility if it is a correct attribution. The reduction in insignificant prostate cancer diagnoses is the product of two processes. The first is that fewer men are biopsied overall. And second, that biopsies moves from random towards a more targeted sampling in those men with lesions on MRI. If, however, urologists insist on random sampling, possibly in addition to targeted sampling, the rates of clinically insignificant disease will rise, but will still be less than they are currently.

It follows therefore that with fewer men diagnosed overall and fewer men labelled with clinically insignificant prostate cancer (green disease), there should be a reduction in the requirement for AS in the future. The only thing that will challenge this is a reappraisal of our notion of risk. In all AS protocols, there are many men that exceed our upper threshold; we just don't know about them. It just may be that yellow disease might be perfectly acceptable to watch in some men because we can be 95% sure that no red disease is present concurrently. This new precision should give us confidence. We just need the data, but this will take time to mature. Even red disease might be acceptable in some men especially if it augmented with information on biology. The deep sequencing of these lesions – possible only through representative pathology – it is hoped will assist in the more refined classification of the more 'aggressive' lesions.

So what of focal therapy? Focal therapy, by definition, has always required a target. Well-characterized and precise targets will be the product of the new imaging-based pathway. It is possible that the question of focal therapy may come up much sooner than it currently does; at present it usually requires the patient to raise the issue himself. The reason for it coming to the forefront rather earlier in the pathway is that the patient and the treating physician will be faced with information on location very early – in fact before the biopsy. This, as it does today (when available), triggers discussion – often initiated by the patient – of whether it is absolutely necessary to treat all of that normal tissue.

The ability to better determine cancer grade and extent has led to a renewed interest in partial gland ablation treatments such as FT, whereby only the area of the prostate harbouring clinically significant disease is treated, sparing collateral structures and resulting in less morbidity than a whole-gland approach. FT would be an ideal approach for localized small-volume cancers of intermediate or high grade if they could be accurately targeted and treated completely, leaving areas of indolent cancer that do not pose a biological threat to be actively monitored with AS [30]. Conceptually, if detected early enough and treated effectively, this approach would alter the long-term risk of disease progression. The key to this approach is patient selection; this strategy has a greater likelihood of success when applied to an individual with a suitable disease burden. The rate of technological and biological advances has outpaced the ability to accrue meaningful data regarding the best patient selection criteria.

In a recent expert panel consensus, the theme of treating an intermediate or high-grade lesion was explored, while leaving low-grade cancer to be monitored with AS, thus downgrading the patient back into the AS pool. On the basis of the expert panel findings, a Gleason 3 + 4 lesion, when it can be completely ablated, appears to be the best candidate for FT. However, the lack of consensus regarding possible application of FT to cancers $\geq$4 + 4 suggests reluctance in extending the role of FT to high-grade cancers. Regarding residual cancer to be monitored with AS, the expert panel is challenged by the broad spectrum of opinions when details were requested. While there was a strong consensus that some kind of systematic biopsy was necessary to assess the mpMRI negative portion of the gland before ablating a biopsy-proven mpMRI-suspicious lesion, the view on biopsy density ranged from 12 core biopsy to 1 core per ml of gland, with the only unanimity being that 8 or 10 cores are insufficient. Similarly, the wide range of opinions on acceptable untreated cancer resulted in the consensus statement adopting the lowest common denominator of opinion that only a small volume of untreated Gleason 3 + 3 was acceptable. Further scientific study and long-term data will be necessary to influence opinion on these topics [31].

Also, genomic tools have been developed with the purpose of stratifying patients after the prostate cancer diagnosis in order to help urologist to personalize therapies and follow-up schemes and may play a role in guiding patient selection for FT vs AS. These are reviewed elsewhere in this book [32].

Prostate FT is a field with constant evolution both in technological application and understanding of biological processes. Patient selection is the cornerstone in any FT strategy.

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The Economics of Active Surveillance for Prostate Cancer

20

Robert B. Lurvey and Marc A. Dall'Era

Introduction

Over the last decade, society has made tectonic, if long anticipated, shifts toward how it regulates and allocates healthcare resources. Many of the legislative changes for more access to healthcare suggest a shift in social values, including the shift from healthcare as a luxury commodity to a universal right. These shifts will come to redefine our understanding of the economics of healthcare. That is to say, these shifts will redefine our understanding of how society produces, consumes, and manages healthcare resources. Ultimately, the variables that impact how society produces, consumes, and allocates healthcare resources must be identified, defined, and understood to help any discussion of our healthcare values and to inevitably guide treatment decisions by urologists.

Given the many decision points in the diagnosis and management of prostate cancer, prostate cancer offers many angles for economic understanding. Of the treatment and diagnosis points in prostate cancer, active surveillance (AS) is a prime subject for discussion of economics, given its multiple algorithm options, evolving costs, and criteria for use. As the healthcare markets shift, to continue to deliver the best overall care for the patient while recognizing the impact economics have on patient and payer decision-making, the urologist must understand the economics of both disease and treatment.

In the first part of this chapter, we discuss the high-cost burden of prostate cancer. In light of recent studies showing patient decision-making is impacted by cost, we then review studies analyzing the costs of prostate cancer treatment, particularly active surveillance. We review studies both in the United States (US) and globally. Next, we review the ever-changing algorithms for AS, recognizing that it is increasingly embraced and utilized in men with low-risk disease and new technologies and efficiencies in computing have moved advanced imaging and novel biomarkers into mainstream of AS algorithms across the globe [1]. There remains no globally accepted protocol for AS, and we will discuss current strategies and consider how recent regulatory changes in the United States health marketplace may affect the economics of AS. We will also address utilization of potentially costly tests in this paradigm. Finally, we discuss the limitations of our current understanding of the economics of prostate cancer. In particular, we discuss how current studies have focused on a single variable, financial cost, at the expense of understanding other cost variables including time cost and risk

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tolerance which are also involved in patient and practitioner decision-making.

Cumulative Cost of Prostate Cancer to the Healthcare System Is High

The global financial burden of prostate cancer is substantial and likely to increase in the coming decades [2]. The mere prevalence of prostate cancer is a driving force of its cost burden. Prostate cancer remains the most common cancer in men, with 1.4 million incident cases and over 290,000 deaths from prostate cancer in 2013, and was the most incident cancer in men in 104 of 188 countries for which data are available [3]. Additionally, costs will likely increase with increasing diagnosis and survivability of prostate cancer.

Although each individual case of prostate cancer may not incur a particularly high cost, given the incidence and prevalence of prostate cancer, the cumulative cost to healthcare systems is high. For the task of estimating and discussing costs, cancer care can be divided temporally into an initial phase (first 12 months after diagnosis), continuing care phase, and end-of-life phase (last 12 months of life). All men diagnosed with prostate cancer will accrue costs attributed to cancer treatment during the initial phase of their disease, and many will experience a prolonged continuing care phase as they are successfully treated and followed. A relative minority of patients will progress to die from prostate cancer and accrue costs during the end-of-life phase. Congruent with the natural history of prostate cancer, Skolarus et al. found that within Medicare beneficiaries, the initial phase of care accounted for the highest costs to the individual followed by the continuing care phase [4]. For the individual, continuing care expenditures exceeded those of initial care after 8 years [4]. For a healthcare system, the majority of prostate cancer patients will be in the continuing phase of the disease as the median age for diagnosis is approximately 65 years old, with a greater than 93% cancer-specific survival at 15 years [5]. Ultimately, nearly 47% of prostate cancer spending, therefore, is in the continuing phase of care [2]. As survivability increases and PSA screening detects earlier cancers, the continuing phase will be extended, and the overall economic burden of prostate cancer will make it one of the most expensive cancer types for society [2].

These increases are not limited to the US market with a third-party payer system. For example, Japan, a country with universal single-payer insurance, is predicted to experience a 150 times increase in spending on prostate cancer in the next 10 years [6]. In addition, although the impact of changing PSA utilization in the United States led to dramatic decreased incidence of localized disease, prostate cancer incidence is still expected to increase worldwide as other countries adopt traditionally "Western" lifestyles and screening practices. Globally, prostate cancer is largely a disease of the wealthy, with 57% of the cases occurring in economically advantaged countries in 2013 [7]. Between 1990 and 2013, age-standardized incident rates increased by 63% in these countries and by 135% in developing or traditionally impoverished nations thus closing the diagnosis gap [7]. Finally, rapid assimilation of advanced technologies and novel therapies for prostate cancer will also contribute to this increase in future costs of care despite unclear or only modest benefits [8].

Cost of Each Treatment

For 2010, across all phases of care, the costs of prostate cancer care in the United States were estimated at $11.9 billion [9]. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CapSure) show that prostate cancer-related costs within the initial phase vary from $2586 for traditional watchful waiting to $24,000 for external beam radiation therapy [10]. Proton beam therapy exceeds these costs considerably with expected mean costs of $63,000 at 15 years [11].

A similar study on French men with prostate cancer demonstrated highest initial treatment costs associated with radiation therapy [12]. Charges associated with radical prostatectomy on average are $7,300 per case compared to $46,900

for external beam radiation therapy [13]. With a lack of clear evidence for which treatment modality provides superior outcomes, data suggest that radical prostatectomy may be the more cost-effective initial local treatment for prostate cancer [14]. Costs associated with ongoing management for prostate cancer across all phases of care must be calculated differently as they accrue and perhaps change over time. Several studies show that traditional watchful waiting (WW) is associated with the lowest average annual costs as only a fraction of men progress to metastatic disease and receive androgen deprivation therapy [10, 15]. In contrast to WW, AS involves close observation for early signs of disease progression when treatment with curative intent can still be offered and thus will accrue more costs during the ongoing care phase. With AS, opposed to WW, patients undergo more intense follow-up integrating frequent PSA measurement, regular physical exams, and repeat prostate biopsy, thus accruing greater costs over time [16].

For localized, low-risk prostate cancer, there is a lack of level 1 evidence comparing the cost-effectiveness of different treatment modalities. Fewer studies compare the economic burden of treating men with early-stage prostate cancer, and the associated costs of care are often overlooked as government or third-party payers shoulder the brunt of the expenses. Aizer et al. estimated the costs associated with overtreatment of low-risk prostate cancer by comparing men with <10-year estimated life expectancy (for which there is no evidence of a survival advantage with local treatment) [17]. They showed that 67% of low-risk men were overtreated with prostate-directed local therapy despite lack of survival benefit [17]. Compared with no active treatment within 1 year, men undergoing radical prostatectomy or radiation therapy accrued additional median per-patient cost of over $18,000. It is increasingly important for health policy makers, physicians, and patients to study and integrate direct, indirect, and out-of-pocket expenses when making treatment decisions. In the current and anticipated global healthcare environment, analyzing economic endpoints for prostate cancer is critical with particular attention to the relationship between costs and patient outcomes.

Treatment Choice in Prostate Cancer Is Cost Sensitive

Although there are few studies on the real costs associated with AS, the existing studies are limited to only cost analyses, but not economic decisions. In the simplest studies, this approach only identifies the cheapest approach to managing men with AS. In more complex studies, this assumes the patient is a "rational actor," choosing the approach that gives them the most life expectancy for the least cost. Many of these models relied on Markov analyses, which depend on the Markovian assumption that the probability of any event is independent of individual patient characteristics or choice. Yet, research in economic theory has evolved with the growth of behavioral economics. In essence, this suggests that patients will choose the path offering the least risk and healing closest to the status quo [18]. Patients also categorize options or activities as either risky or safe when making treatment decisions [18]. For example, a patient may categorize AS as entailing just "a follow-up visit" (safe) or may categorize it as "watching the cancer" (dangerous). Conversely, surgery may be viewed as dangerous in certain circumstances or through the framing of surgery as "robotic" may be considered safe (new technology and "minimally invasive"). True economic analyses, therefore, regarding AS are complex, and to date, little research has been done within the realm of patient decision-making under an economic framework.

This will become more important under healthcare systems where patients may share greater portions of costs than before, and there is some evidence of sensitivity to cost in patient decision-making at the population level [19]. Weiner et al. correlated the rate of active treatment for new diagnosis of prostate cancer from the SEER database against both the rate of economic growth as measured by the S&P 500 index, inflation, and average income [19]. Ultimately,

more patients chose conservative management during recessionary periods, when patients presumably had less health insurance and were required to pay more of the costs associated with prostate cancer treatment [19]. Their study only covered a 2-year period, however, and given the indolent nature of prostate cancer, they may have instead witnessed patients deferring care rather than choosing true active surveillance.

Comparative Costs of Active Surveillance for Prostate Cancer

Expenses associated with prostate cancer management after diagnosis and during the initial phase of care are substantial yet highly variable due to multiple treatment strategies available with no clear data on comparative effectiveness. Costs associated with treatment will also vary inter- and intranationally according to healthcare delivery systems and sources of payment. All of these factors must be considered when interpreting data from prostate cancer economic studies. PSA-based prostate cancer screening in the United States remains controversial, with the US Preventive Services Task Force (USPSTF) recommendation against widespread screening efforts in 2012. This came in large part from the over-detection and overtreatment of indolent disease. Roth et al. showed that from an economic perspective, PSA screening can be cost-effective, primarily when AS is utilized for men with low-risk disease as many men may never require cost-intensive therapies [20].

There are several important considerations to make when analyzing the expenditures associated with AS for low-risk prostate cancer. Economic analyses are dependent upon methods used to measure expenditures and which variables are included in the estimate. Discrepancies exist between hospital or physician charges, for example, and what is actually reimbursed or paid by patients or third-party payers. Costs associated with AS are sensitive to the surveillance paradigm followed such as how often repeat prostate biopsy is performed, frequency of patient visits, and utilization of novel technologies. Cumulative costs also depend on the number of men exiting surveillance or progressing and requiring additional treatment over time.

Keegan et al. used Markov simulation modeling to estimate direct costs accrued over time for men on active surveillances while accounting for men transitioning to other therapies [21]. The direct costs of prostate cancer treatments were estimated by US Medicare reimbursement schedules for these services. The models simulate a theoretical cohort of men initially managed with AS and then followed for 10 years, accounting for the proportion of men who receive secondary therapy over time for disease progression or personal choice. The percentage of men leaving AS each year and the specific mix of secondary therapies selected was estimated from literature [22]. These total costs were then compared to the direct costs associated with other standard-of-care prostate therapies. These data show that under the assumptions inherent to the model, AS is economically advantageous over other immediate therapies for low-risk prostate cancer. Individual patients starting AS and progressing to other treatment over time may ultimately accrue higher healthcare costs. The economic advantages associated with AS, however, are realized as the majority of men remain untreated over the course of the study (5–10 years).

Utilizing a similar Markov model, Dragomir et al. performed a cost comparison analysis for men with low-risk prostate cancer with the Canadian healthcare system [23]. This analysis went a step further, including the effect of competing mortality and cancer recurrence in the estimates. The model assumed 22% of men received additional treatment by the end of 5 years while 17.3% of men have died while on surveillance. After 10 years, the AS program resulted in an overall cost savings of $99.5 million compared with immediate treatment for all men [23]. In similarity to the analysis by Keegan et al., this savings is realized by the fact that 57.2% of men were still on surveillance at 10 years and did not undergo additional, costly treatments and 17% of the cohort died from other

causes. A separate analysis focusing on the Canadian healthcare system also showed AS resulted in lower costs and greater quality-adjusted life years for low-risk disease than active treatments [24].

Prostate biopsy is the highest expenditure for men on AS, and increasing the frequency of prostate biopsy will reduce the cost-effectiveness of this approach. In the analysis by Keegan et al., yearly surveillance biopsy reduced the average simulated cost at 10 years by $4951 per patient [21]. With every other year, biopsy costs exceed those of up-front brachytherapy by year 9 and approached costs of prostatectomy at 10 years. Newer technologies including imaging and biomarkers that may decrease or eliminate the need for repeat prostate biopsies may therefore translate into both quality of life and economic advantages for men on AS.

As demonstrated in these studies, the comparative cost-effectiveness of AS is also strongly sensitive to the proportion of men exiting AS each year and receiving other therapies as well as the costs of these additional therapies. In the model by Keegan et al., a sensitivity analysis predicted lower 5-year costs with AS as long as fewer than 70% exit AS in any given year and at least 12% of men remain on AS at year 5. At year 10, at least 15% of men must remain on surveillance to maintain an economic advantage. The 15-year model performed by Dragomir et al. estimated $7,000–$8,000 per-patient cost reduction with AS with 16.5% of men receiving additional treatment and 24.3% remaining on AS. These estimates are reasonable based on published figures from AS series; however, as longer-term studies mature, it is unclear if these estimates will be accurate [25]. The contemporary AS series reported by Klotz et al. with one of the longest follow-up periods estimates that 55% of men remain on AS without treatment at 15 years [26]. The cumulative incidence of treatment at 15 years in the Johns Hopkins series, however, was 57%, which may effect cost savings estimates with longer-term follow-up [27]. The comparative costs of AS and various initial treatments for prostate cancer at 5 years from these analyses are summarized in Table 20.1.

Novel Imaging and Biomarker Integration into AS

Novel biomarkers and advanced imaging with multiparametric magnetic resonance imaging (mp-MRI) are rapidly being developed and integrated into clinical practice for men with low-risk prostate cancer. No economic analyses incorporate mp-MRI or novel biomarkers for AS, both associated with increased up-front costs during the initial phase of cancer care. These tests may add considerable expense and should be the focus of future cost-effectiveness studies. Two scenarios where these technologies may prove cost-effective are by improving patient selection, thus decreasing additional treatment over time, and by reducing the need for repeat prostate biopsies; however, these remain to be shown.

A 31-gene expression assay (Prolaris®) and a 17-gene expression panel (Oncotype DX®) are both marketed toward selecting patients for AS, but cost ~$3000–$4000 USD. These assays may still prove cost-effective if they prove to increase the number of men who choose AS (thus deferring more expensive initial treatments) while reliably selecting men up front who are less likely to progress over time. Albala et al. demonstrated increased utilization of AS after Oncotype DX testing with decreased utilization of both prostatectomy and radiation therapy by 10 and 14%, respectively [28]. Despite additional up-front costs associated with the assay, this resulted in a net per-patient savings of $2286 USD.

Mp-MRI has emerged as the modality of choice for prostate cancer imaging and particularly for selecting men for AS and possibly following them for disease progression. This imaging modality integrated with technology for targeted prostate biopsy may improve patient selection, by detecting clinically significant tumors earlier in the disease process when curative therapy may be recommended. The costs associated with MRI are much more variable between hospitals and health systems than the abovementioned biomarkers. MRI costs also have more potential to decrease over time as equipment become more efficient and less expensive. Although not studied in the setting of AS,

Table 20.1 Comparative costs of active surveillance and various treatments for prostate cancer at 5 years

Treatment	5-year costs, US model (Keegan et al.)	5-year costs, Canada model (Dragomir et al.)	Est. lifetime costs, Canada model (Sanyal et al.)
Active surveillance	$16,699	$2,991	$18,452
Radical prostatectomy	$29,862	$8,357	$23,830
EBRT	$55,681	$12,879	$29,465
EBRT/ADT	$59,381	$15,062	*
Brachytherapy	$23,717	$9,073	$24,927
ADT	$47,055	$28,338	*

mp-MRI is predicted to be cost-effective to select men with elevated PSA for prostate biopsy [29]. Diaz et al. utilized serial mp-MRI for men on AS and demonstrated a relatively high negative predictive value of 80% for changes in Gleason grade, suggesting that this may also substitute for costly surveillance prostate biopsies [30].

Evolving Physician Payment Reform: The Impact on Active Surveillance

Both public and private healthcare payment systems are evolving with improved emphases on cost containment, quality of care, and efficiency. These reforms are rapidly moving away from the traditional fee-for-service model toward a global or episodic payment structure. The Affordable Care Act (ACA) represents the largest change to the US healthcare market in a generation. The ACA represents such a tremendous change to health policy when the *Journal of the American Medical Association* published a report by Barack Obama on the act's impact, the only one ever written by a sitting president [31]. Though many of the changes of the ACA are still to be defined through the regulatory process, without question the ACA presents an overhaul of the reimbursement structure that may eventually impact the economics of the AS [32].

First, and most significantly, the ACA will shift from a fee-based reimbursement to a value-based reimbursement [33]. In this new paradigm, both reimbursements will also be tied to "quality" metrics. As one might expect, the quality metrics possible in AS versus active treatment that are distinctly different may be difficult to define. For example, one would expect a quality metric assessing blood transfusion and readmission after prostatectomy to impose a higher penalty than urinary retention after a surveillance biopsy. Moreover, in this paradigm, it has yet to be determined how AS payment would be determined. In the current model, a patient visit is paid as a patient visit. But in a value-based model, the physician could theoretically be paid a capitated annual fee per AS patient instead of a fee-per-visit, ultimately allowing providers to choose how they wish to arrange their surveillance algorithm. In most AS cost models, the greatest overall expense value is in patient contact-included prostate biopsies and PSA testing, with pathology and ultrasound being a much smaller portion of the expense [33, 34]. In the coming years, the regulatory framework will need to define how physicians are reimbursed for performing AS as well as which metrics these payments are associated with.

Second, the ACA has increased reimbursement rates to primary care physicians and further encourages the deployment of more primary care physicians [33]. This shift in economic value may encourage more aspects of the surveillance to be performed by primary care physicians or even allied healthcare professionals such as nurse practitioners or physician assistants, with the specialist only involved for more invasive testing or treatment.

As stated before, the ACA also represents a cultural shift away from fee-for-service and toward payment for value. This shift is further reflected in the Medicare Reform and CHIP Reauthorization Act (MACRA) of 2015. Though

limited only to Medicare beneficiaries in the United States, MACRA aims to change how the US government pays for healthcare services with a focus on quality over quantity, in other words, a focus on rewarding "value." MACRA moves physicians into the Merit-Based Incentive Payment System, where physicians are rewarded for meeting certain "value" targets. Physicians can also opt to be paid under a standard bundled payment system. One model of dealing with these new payment methods would be the Oncology Care Model [35]. This bundles all the costs associated with a single cancer type and redistributes them among the multiple players in a patient's care.

Ultimately, as AS evolves into more refined risk stratification, the question of what constitutes a quality metric in the surveillance paradigm will grow. For example, some quality metrics are straightforward such as prophylactic antibiotic use before prostate biopsy or adequate sampling with 10–12 cores. But if a patient based on privately purchased proprietary genomics tests wants to go to a biannual instead of annual biopsy schedule, would his physician be penalized? This chapter does not seek to answer these regulatory quandaries based on social values. Instead, we pose these questions to evolve the conversation to further recognize that as social values shift, the individual decisions on AS will change.

Limitations

Important limitations exist when interpreting these data from simulation. Long-term implications of treatment with any modality including AS are not considered including later recurrences, complications from treatment, or future medical costs. Infectious complications and hospitalizations from prostate biopsy, however rare, will add to the financial burden of AS; however, it is unclear if infectious complications are higher for men undergoing repeat biopsies [36]. Most studies rely on Medicare reimbursement or payer fee schedules to help build their models. Out-of-pocket costs, estimated to range from $5576 for radical prostatectomy to $2010 for radiation therapy, are primarily the burden of the patient yet contribute to the overall costs of treating prostate cancer [37]. Higher physical functional status after prostate cancer treatment associates with lower out-of-pocket costs and therefore may be lower with AS than the other therapies [37]. More specifically, improved urinary and sexual functional domains are associated with better overall functional status and thus translate into lower indirect costs.

Moreover, indirect costs including lost productivity or early mortality were not considered. Patient travel costs, for example, are not insubstantial, and many countries have moved toward consolidating specialty care visits to help reduce travel time. These changes would carry over to a high patient contact protocol such as AS for prostate cancer [38].

In addition to the indirect costs, few studies have incorporated "benefit" into the cost analysis. Hayes et al. performed a similar analysis as Keegan et al., but included quality-adjusted life expectancy into their formula for outcomes [39]. Despite including indirect costs, they still found that AS and WW were cheaper than active treatment over a lifetime. They also noted that WW yielded longer quality-adjusted life expectancy than AS for less cost, but that this benefit was lost when the chance of progression on AS went down to 15% [39]. Overall, AS at that level was $15,000 more expensive than WW for two additional quality-adjusted life expectancy months.

Lastly, many of the economic analyses were based on North American (United States and Canada) healthcare models and may not be applicable globally.

Conclusions

Prostate cancer care can incur substantial costs at all stages of disease and will continue to rise in the new millennium. AS offers patients the opportunity to defer aggressive treatment until felt necessary. Longer-term risks with this approach appear low, and deferred treatment does not appear to compromise the chance for

cure [26]. AS appears to reduce prostate cancer healthcare expenditures by limiting costly therapies to those likely to benefit the most from aggressive treatment. As long-term data from AS clinical trials becomes available, the true cost-effectiveness of this approach can be measured along with the impact of novel technologies including MRI and gene-based biomarkers.

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Research Questions in Active Surveillance

21

Laurence Klotz

Introduction

The controversies and unanswered questions in this field have moved from concept to application. Given the enormous amount of data from randomized trials (PIVOT, Protect) and prospective series of conservative management reviewed in this book, no informed individual would argue that the principle of conservative management for low-risk disease is misplaced. The questions are now related to who, how, when, and what. The main areas of uncertainty are outlined in this chapter. They cover a broad swath of current research in prostate cancer.

What Are the Molecular Events that Signal "Progression" of Low-Grade Disease?

For example, PTEN deletion has been identified as a key step in the progression of prostate cancer and is present in about 10% of Gleason 6 cancers. However, this deletion on its own may not be sufficient to induce a metastatic phenotype. For example, recent studies s uggest Myc amplification in conjunction with PTEN deletion induces genomic i nstability and metastatic Pca [1]. We are just at the beginning of learning which genetic and epigenetic aberrations alter the behavior of prostate cancer cells. Many other tantalizing mechanisms have recently been identified; for example, the effect of circulating exosomes containing biologically active molecules, i.e., mRNA, shed by more aggressive cancer cells and incorporated into low-grade cells resulting in more aggressive behavior [2]. Another priority is determining whether patients with certain known germ line mutations, for example, BRCA1 or BRCA2, are candidates for surveillance. BRCA mutations confer marked genetic instability, and recent studies indicate that the mutational load of localized prostate cancer resembles that of CRPC, making these patients poor candidates for conservative management [3]. We will learn much more about how these aberrant genetic pathways interact over the next decade.

How to Optimally Identify the "Wolves in Sheep's Clothing"

As described previously, the Achilles heel of active surveillance is the misattribution of low risk based on systematic biopsies showing low-grade cancer in the 25–30% of patients who harbor a higher-grade cancer that was missed due to

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sampling. The increased use of MRI will address this substantially but not completely. We know much better today how to use baseline parameters to identify the patient at risk (PSA density, extent of core involvement, race, etc.). The use of MRI and molecular biomarkers is further refining this. Nomograms incorporating MRI and/or biomarker findings to predict the risk of coexistent higher-grade cancer are needed urgently. Sorting out how to use these tests optimally will require further research. For example, how best to manage the patient who has a Pirads 4 lesion whose targeted biopsy shows Gleason 6 cancer is unclear at present. Does the presence of restricted diffusion mean he has a biologically more aggressive cancer despite being Gleason 6? Was a higher-grade cancer missed, or does it signify nothing? The role of a genetic biomarker in this setting seems obvious, but there is little data on this situation. The field of radiomics, i.e., the molecular events associated with restricted diffusion and other MR abnormalities associated with cancer, is in its infancy. Similarly, what is the best strategy for a patient with microfocal Gleason 6 cancer whose Prolaris or Oncotype Dx assay reveals a mildly elevated risk score? MRI with targeted biopsy also likely plays a role in this setting but there is little data. How to integrate MRI and biomarkers into treatment decision-making is a major research priority.

Which Intermediate-Risk Patients Are Candidates for Surveillance?

Recent data, described in this book, indicates that the approach to surveillance, based on PSA and serial biopsy, is imperfect for Gleason 7 patients. Despite close monitoring and selective delayed intervention, 20% or more of these patients progress to metastasis by 15 years. Yet the glass is also half full; 80% remained free of mets. Obviously, therefore, many intermediate-risk patients are candidates for surveillance; the key is to identify those with indolent disease accurately. Further studies using molecular biomarkers and MRI to select these patients are warranted.

Once patients have been selected for surveillance, a host of research questions present themselves.

What Interventions (Diet, Exercise, Micronutrients, and Pharmacologic Agents) Are Warranted to Reduce the Risk of Biological Progression?

This is a fruitful and important area for research. Many ongoing studies are evaluating the role of exercise, dietary modification, and naturally occurring micronutrients in men on surveillance (Table 21.1). These patients are followed for many years; they are motivated; and a great deal of evidence suggests that prostate cancer progression is amenable to modification by dietary or other influences. Specific questions include the role of exercise, weight loss, reduction of animal protein or carbohydrate in the diet, and the use of natural dietary micronutrients, including pomegranate, capsaicin, lycopene, etc. A host of other compounds have been suggested as being useful in the surveillance setting, so-called holistic surveillance.

There is also a great deal of interest in the use of common drugs with metabolic or cardiovascular benefits, particularly statins and diabetic medications, i.e., metformin. Clinical intervention trials testing these agents are warranted.

What Is the Most Efficient and Cost-Effective Way to Follow Patients Longitudinally? Is Serial Biopsy Still Required and in Whom? Can Risk Stratification Allow Some Patients to Minimize the Burden of Follow-Up?

This is both a quality of life and economic question. An unmet need in the field is excessive reliance on serial biopsy. Can MRI, if negative, replace systematic biopsy, and can targeted biopsy alone (i.e., 2–4 cores) replace the 12–14 core systematic approach? Can patients with a

Table 21.1 Ongoing or completed lifestyle studies in active surveillance

Name	*N*	Intervention	Outcome
Nordic lifestyle 2011	24	Vigorous exercise > = 3 ×/week, rye	PCa progression
Diet in PCa 2011	464	Dietary education and telephone counseling × 2 years	Clinical progression, TTP
Sulforaphane 2013	78	Broccoli soup (3 versions)	Gene expression
AS exercise 2016	150	4–5/week home walking	Genetic signature changes
Exercise training 2015	50	Supervised/independent aerobic exercise × 12 months	Feasibility, adherence
Low-fat diet, fish oil 2014	100	Fish oil caps × 1 year, low-fat diet	Ki-67 in PCa tissue
Diet/exercise 2015	200	Diet, 16 1 h exercise over 24 week	IGF, adiponectin, etc.
Cholecalciferol 2009	100	Cholecal. × 9 month	PSA kinetics
Capsaicin 2014	100	Capsaicin 1 tab bid	Gene expression
Dutasteride, diet 2010	120	5 consultations, omega 3, 5ARI	Lipids, genes, PCA3
Web-based lifestyle 2009	76	Web-based diet, exercise	Behavioral changes, BMI

negative molecular biomarker avoid or reduce the frequency of biopsies? Is the negative predictive value of a negative MRI sufficiently high that a biopsy can be safely avoided, and how does the NPV vary according to patient risk? Aside from discontinuing surveillance because of short-life expectancy, are there patients whose disease is so predictably indolent that no further follow-up is required despite a 15–20-year life expectancy? How do we identify these?

Many national policy groups have recommended against PSA screening, largely due to the risks of overdetection and overtreatment. Can the widespread adoption of surveillance for low-risk disease rehabilitate prostate cancer screening and satisfy policy makers and methodologists that the benefits outweigh the risks at an acceptable cost? This will require modeling studies based on recent data.

Summary

In summary, research is warranted at the molecular, epigenetic, epidemiological, radiologic, and clinical trial levels.

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