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Original Article

Active surveillance for prostate cancer: a legal perspective

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Abstract: Active surveillance (AS) for prostate cancer (PCa) has become a viable management strategy for men with low-risk PCa. With AS being offered more often and more patients being included in AS studies, the aim of this paper is to describe AS from a legal perspective. What might be pitfalls in the management strategy that urologists should be aware of? In order to construct an answer to our research question, a patient from the Prostate cancer Research International: Active Surveillance (PRIAS) study will be used as an example. In the methods section, first some information on the PRIAS study is given. Then a PRIAS case will be described after which the Dutch legal framework will be set-out. Finally, the Dutch legal framework will be applied to the PRIAS case to find what would happen if that particular patient would file a complaint. On the basis of the analysis we can conclude that urologists that offer AS should be aware of the information that they provide to patients when entering AS but also during follow-up. It is furthermore important that urologists act in line with their medical professional standards. Therefore it is advised that urologists follow the progress that is made within the field of AS carefully, as the field is moving rapidly.

Keywords: Prostate cancer, active surveillance, law, informed consent, medical professional standard

Background

One of the first publications describing prostate specific antigen (PSA) as a potential biomarker for prostate cancer (PCa) was published in the 1960's [1]. In 1986 the PSA-test was approved by the American Food and Drug Association (FDA) as a test to aid in the management of patients diagnosed with PCa, and in 1994 the FDA approved the PSA-test as a diagnostic tool [2]. Since then, much progress has been made in the field of PCa detection.

With increasing evidence that PSA could be used for the early detection of PCa [3], it was in the beginning of the 90's that researchers from Belgium and the Netherlands made plans to conduct a randomized study of screening for prostate cancer [4, 5]. Pilot studies were initiated of which the most important conclusion was that a randomized controlled trial of screening for PCa in Europe seemed feasible. However, it was necessary to seek international cooperation to meet the large sample size [6]. Finally, the European Randomized study of Screening for Prostate Cancer (ERSPC) was initiated in 1994. Around the same time in the US the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial was initiated [7].

After the introduction of the PSA-test and the initiation of screening trials, the incidence of PCa in Western countries increased remarkably. Data from the American Cancer Society as well as from the European Cancer Observatory confirm this [8, 9]. Over time incidence declined; however, the incidence rates did not retain to the level that was seen before the introduction of the PSA-test as a diagnostic tool in the beginning of the 1990's. If this observation would reflect a true PCa increase, it should be accompanied by an increase in disease-specific mortality. This is however, not the case, not even today [8]. The contrary seems to be true; PCa-specific mortality declined between 1975-2010 [8, 10]. Now that the increase in incidence and mortality do not collide, another explanation for this phenomenon has to be found.

Screening for PCa has resulted in a marked stage shift; fewer men present with metastatic disease, while more men present with earlier and lower stage, lower grade and lower PSA at diagnosis [11, 12]. Although screening has shown to be effective when done in a systematic way as compared to a situation with hardly no screening [13, 14], it also causes overdiagnosis in the range of 27-56% [15, 16]. Overdiagnosis occurs when a tumor is detected that, if left unattended, would not have become clinically apparent or caused death [11, 15]. If such overdiagnosed tumors are actively treated, one speaks of overtreatment. Overdiagnosis and overtreatment are associated with harms from treatment, like incontinence and impotence, but also with a psychological burden. To date, a lot of PCa research therefore focuses on how to reduce overdiagnosis. The discovery of a biomarker that would be able to distinct aggressive from indolent PCa (a PCa that is unlikely to become symptomatic during life, also known as a low-risk or minimal cancer) would solve a large part of the overdiagnosis dilemma; however, no such biomarker is currently available.

Because most PCa's found nowadays are low-risk PCa's which have favorable characteristics and a beneficial long-term survival, active treatment is not immediately necessary [17]. It is thought that the replacement of initial active treatment with active surveillance (AS) in patients with low-risk PCa is a realistic option [17]. The aim of AS is to avoid overtreatment. With AS the tumor is closely monitored with the purpose of switching to active treatment if progression occurs. Over the past decade several AS studies have been initiated worldwide, which so far show encouraging results [18].

That AS becomes a more viable option is also recognized by many national and international urological associations. Guidelines of the European Association of Urology (EAU), the American Association of Urology (AUA), the Societé International d'Urologie (SIU), the German Urological Association (DGU) and the Dutch Urological Association (NVU) all have been updated in recent years, including AS as a management strategy for very low-risk or low-risk PCa [19-21].

Now that AS is more often offered to men with low-risk prostate cancer and more patients are included in AS studies, the aim of this paper is to describe AS from a legal perspective. With AS the chance always exists that the 'window of curability' is missed and that switching to active treatment comes too late with worse outcomes on radical prostatectomy or radiotherapy as a consequence. What would happen if a patient who was in such a situation, would file a complaint? How will such a complaint be dealt with within the Dutch legal system? What might be pitfalls in the management strategy that urologists should be aware of?

Methods

Worldwide, several AS studies have been initiated. In this paper a patient from the Prostate cancer Research International: Active Surveillance (PRIAS) study will be used as an example. First some information is given on the PRIAS study. Then a PRIAS case, patient X, will be described after which the Dutch legal framework will be set-out. Finally, we will apply the Dutch legal framework to our PRIAS case to find out what would happen if that particular patient would file a complaint.

PRIAS

PRIAS is a protocol-based, multicentre, observational study which started in December 2006. It was initiated by investigators of the Rotterdam section of the ERSPC and the Department of Urology, Erasmus University Medical Centre, Rotterdam, the Netherlands. It was designed to validate a protocol designed on currently available knowledge and if necessary adapt the management of low-risk PCa with AS. The PRIAS study is entirely web-based [17]. Currently PRIAS holds more than 4,300 patients.

PRIAS inclusion criteria are: PCa diagnosis with a PSA of $\leq$ 10.0 ng/ml; a PSA-density (PSA/prostate volume) of $<$ 0.2 ng/ml/ml; T-stage $\leq$ T2; one or two positive prostate needle-biopsy cores, with a Gleason score of $\leq 3 + 3 = 6$. The follow-up protocol includes PSA measurements every three months for the first two years and every six months thereafter. Digital rectal examination (DRE) is scheduled every six months for the first two years and once a year thereafter. Repeat biopsies are scheduled after 1, 4 and 7 years, and in case of a PSA-doubling time between 3 and 10 years, yearly repeat

biopsies are advised. Risk reclassification at repeat biopsy triggers a recommendation for active therapy and is defined as ≥ 3 positive biopsy cores and/or Gleason score > 6. A PSA-doubling time (PSADT), which can only be reliably calculated after a minimum of one baseline and four follow-up measurements, of less than three years is also used as a trigger to initiate active therapy [22]. Men entering into PRIAS all sign an informed consent.

Study protocol versus guidelines

As said, many national and international guidelines have captured AS in their guidelines [19-21].

Although AS is recognized as a reliable management strategy the inclusion criteria are not straightforward yet. Differences in the AS inclusion criteria are seen in different parts of the world and captured in the various guidelines. Furthermore, the guidelines on AS are not yet clear-cut and still leave room for interpretation and improvement. Currently, for instance, the feasibility of including multi parametric imaging (MRI) into the AS protocol is being researched. It is hypothesized that with the use of MRI the percentages of undergrading of systematic prostate biopsy and upstaging of the tumor may decline [23].

In 2013 the Movember – GAP3 project was initiated to integrate the various existing AS protocols into one straightforward, unambiguous protocol. The project started in 2014 and the results are expected within two years from now (www.movember.com).

AS in Dutch daily clinical practice

Earlier research shows that when offering AS to patients 84% of Dutch urologists follow the PRIAS protocol. Most urologists (97%) are also familiar with the NVU guideline on PCa [24]. In comparison; the PRIAS inclusion criteria are: PSA of ≤ 10.0 ng/ml; a PSA-density of < 0.2 ng/ml/ml; T-stage ≤ T2; one or two positive prostate needle-biopsy cores, with a Gleason score of ≤ 3 + 3 = 6. The NVU guideline AS inclusion criteria are: T1C-2A, Gleason score < 7, PSA < 10 ng/ml and one or two positive needle-biopsy cores.

Case description

PRIAS patient X, aged 63, is diagnosed with T2a, Gleason 6 PCa in 2 out of 12 cores in 2010. He is suitable for AS according to the PRIAS protocol and thus decides to undergo AS as an initial treatment option for his PCa. After 1 year he receives a repeat biopsy (according to protocol) which shows Gleason 6 PCa in 3 out of 12 cores. With more than 2 cores positive for PCa the protocol advises to switch to definitive treatment. In addition his PSA is rising (PSADT < 3 years) which would also be a trigger for active treatment. The patient and physician decide to ignore this advice and to continue with AS (most likely because the Gleason score is still 6, accepting the known undergrading rates of systematic prostate biopsies). One year thereafter, so two years after diagnosis, he receives another biopsy. This biopsy shows a Gleason 9 PCa in 2 out of the 12 cores. Patient discontinues AS and undergoes radical prostatectomy (RP).

One year post-surgery patient X experienced permanent erectile dysfunction, urinary incontinence and biochemical recurrence (defined as two subsequent PSA values of > 0.2 ng/ml after radical prostatectomy). The last PSA of patient X amounted to 21.6 ng/ml.

Dutch legal framework

In the Netherlands, the patient-doctor contract is regulated by the Medical Treatment Contract Act (Wet Geneeskundige Behandelingsovereenkomst, [WGBO]). The WGBO, which is part of the Dutch Civil Code, runs from article 7:446 to 7:468 Civil Code and contains the patient's core rights. According to art. 7:468 Civil Code the provisions of the WGBO are binding. Core values of the WGBO are the right of self-determination and human dignity [25].

Art. 7:446 Civil Code describes the patient-doctor contract that is realized once medical actions are performed. In the Netherlands such a patient-doctor contract is not explicitly signed, but is assumed to exist when medical actions are performed for the first time. Clauses 2 and 3 of art. 7:446 Civil Code define what medical actions are, i.e. all patient related actions that intend to cure the patient, to prevent sickness, to judge a person's health condition or providing obstetrical assistance. Nursing and caring, in certain situations, can be defined as medical actions as well.

The patient-doctor contract holds rights and obligations for both the patient and the doctor.

Doctors should provide their patients with information, they have to obtain consent from their patients before starting treatment, they have to act according to their professional standards, they have to file all patient information and give patients the right to inspect their files, they hold the oath of secrecy and only under very special circumstances can one-sidedly terminate the patient-doctor contract.

While the goal of the WGBO is patient protection, patients not only have rights. They also have obligations. On the basis of art. 7:452 Civil Code patients should provide all information that doctors need in their decision making process as well as cooperate and collaborate in effectuating the doctor-patient contract.

Art. 7:448 Civil Code mainly concerns the right of information that patients have. A doctor is obliged to provide information about the intended medical actions, treatment and the patient's current health status that is clear, relevant and adjusted to patients' educational level. It would be recommended if patients receive written information on these matters as well. Art. 7:448 Civil Code mentions the following aspects on which information should be provided: what the intended medical actions/treatment holds, risks, goal, nature and alternatives of the intended medical actions/treatment. Finally, the doctor informs the patient what all this means for their future health and the patient's perspectives. The right of information is intended to enable patients to make a well-informed decision on whether or not to provide consent on the proposed treatment. In providing the information, the doctor should be guided by what the patient should reasonably know regarding the nature and purpose of the treatment, the anticipated risks and effects, the possible alternatives and its prospects. Failing the fulfillment of this obligation raises the possibility that a patient cannot use, or only partly use, his right of self-determination which increases the risk of the patient making a choice he would not have made had he been well-informed. In case the discussed risks occur, the patient has to pose and proof that he, had he been well-informed, as a reasonably competent patient and/or due to personal circumstances would have made another choice [26-28].

Art. 7:450 Civil Code indicates that in line with the patient-doctor contract a patient's consent is needed before any medical actions are started. To overcome discussions on whether consent was provided by the patient, an option would be to have patients sign an informed consent (art. 7:451 Civil Code). Patients should only sign such an informed consent if they feel adequately informed and can take a well-considered decision to consent. If this is not the case it would result in a violation of their right of self-determination.

Art. 7:453 Civil Code requests doctors to act according to their professional medical standards. Based on these professional medical standards, a doctor is required to work according to knowledge and competences deemed familiar in their area of expertise. Professional medical standards are based on knowledge and competences a doctor should learn during their specialist-training, knowledge gained from literature, attending medical conferences, subspecialty consensus meetings, refresher courses, in-service trainings, protocols, guidelines and own experiences.

The WGBO holds the obligation that doctors should make an effort in treating their patients instead of contracting a result. Doctors are legally responsible if they have trespassed their obligation to make an effort, if they have not done their upmost best, i.e. a violation of art. 7:453 Civil Code. This is the case when a doctor has not acted in line with the professional medical standards of their specialty.

Furthermore, doctors are legally responsible if a patient foregoing medical treatment is not sufficiently informed about treatment, treatment related effects and possible alternatives. The patient has made a decision on the basis of poor information. A doctor is legally responsible for the adverse effects of that treatment in case the patient would have chosen another alternative had he received all relevant information.

On the basis of art. 7:463 Civil Code it is impossible for doctors to contractually limit or exclude their shortfalls.

A special feature of the patient-doctor contract lies in its central liability. Because patient-doctor contracts are often effectuated in hospitals where various health care workers are involved in the care process of a patient it may be difficult for the patient to hold one of them respon-

Table 1. A selection of questions included in the questionnaire sent to the experts

● How would you handle the conversation in which a patient has to choose his treatment?
● Which risks, complications and alternatives did a reasonable and reasonably competent urologist in 2010 should have discussed with patient X? Please refer to relevant literature, protocol and guidelines as much as possible.
● How often, in your experience, did patients choose AS after having provided all relevant information?
● Do you consider that the conduct of the urologist of patient X during the AS strategy between 2010-2012 at any time did not meet the standard of care that could be expected from a reasonable and reasonably competent professional? Please take into account the then prevailing medical standards.
● In case of a negligent act, please discuss the consequences for patient X?
● May the damage also have occurred when the urologist would have acted carefully? If so, please express through percentages.

sible in case a fault is made. Art. 7:462 Civil Code determines that in such situations it would suffice if the patient holds the hospital responsible.

Art. 7:462 Civil Code therefore also protects patients. The article provides an additional point of contact for patients to turn to. This may be necessary in case a doctor cannot provide sufficient recourse.

What happens when patient X from our case description holds its doctor legally responsible?

For a patient it is not easy to prove that due to the actions of his doctor damage occurred for which the doctor is liable. In principle it is up to the patient to prove this and he therefore should make use of the opinion of an independent medical expert. This expert will write a report in which he passes his judgment on the course of the illness and/or about the effect of medical treatment on the course of the illness. The patient can take this report to court and try to convince the judge - who is not medically trained - the doctor is liable for the damages occurred. The medical expert thus plays an important role; the facts and the expert's opinion are in general decisive, unless valid and compelling reasons regarding the expert's report exist.

In court, parties can request a judge to appoint an independent expert. The judge will, in consultation with the parties, appoint an expert and formulate the questions the expert must provide his judgment on. Another possibility is that the parties themselves appoint an independent expert. When parties reach agreement on who is to fulfil the role of expert as well as the key question that he should answer, then, in practice, the report of the by parties appointed expert is valued the same as the report of the expert appointed by a judge.

For this article we have asked two urologists specialized in urologic oncology (one with over 30 years of experience and one who recently completed his residency) and both working in an academic setting to act as 'experts' and to provide an expert opinion on patients' X case. The authors have set-up a questionnaire (**Table 1**) which was sent to the experts together with the patient file.

After men are diagnosed with PCa a treatment strategy has to be chosen. Which treatment options are offered, depends on the physical condition of the patient and his tumor characteristics. In case of a low-risk PCa and a good physical condition of the patient the experts would offer either AS, RP, radiotherapy (RT) or brachytherapy (BT). The urologists' preference will influence the order in which the options are discussed.

Risks and complications of AS that, according to the experts, needed to be discussed were the risk of PCa progression and the subsequent possibility of being 'too late', meaning that a second treatment will no longer be curative. Furthermore, the risks of repeated biopsies should be discussed as well as the AS follow-up scheme. The patient information brochure of the Dutch Cancer Society (KWF) says that every three to six months the urologist will perform a DRE and a PSA-test. If the course of disease stays stable over a period of two years, the frequency of the follow-up visits decreases to once a year. If the PSA increases, a yearly echo of the prostate as well as yearly prostate biop-

sies will be taken. In case of signs of tumor progression, switching to curative treatment is advised.

The experts feel that for RP it is important to discuss the perioperative risks of the operation as well as potential long term consequences. Perioperative risks of this abdominal/urological surgery are the possibility of haemorrhage, urine leakage, lymfocele, infections and thrombosis. Long term consequences that should be discussed are potential incontinence and impotence.

When discussing RT as a treatment option, it is important to discuss that besides the possibility of becoming incontinent or impotent, also radiation cystitis and proctitis can occur. This means that patients can experience radiation damage, which may cause urinary problems or fecal urgency. Side effects of BT are comparable to that of RT, although less intense.

The experts have experienced that once good information is provided, many patients (75-90%) comply with the initially advised AS protocol.

With respect to patient X, both experts feel that he was correctly included in the PRIAS protocol as he fulfilled the inclusion criteria of the study. According to the protocol patient X undergoes a repeat biopsy after 1 year. The outcomes of that biopsy showed a Gleason 6 PCa in three out of twelve cores taken. Protocol wise this was a reason to switch to curative treatment. Also his rising PSA which led to a PSADT < 3 years was a trigger to start curative treatment. It is at this moment in time that an important decision was made. The urologist and patient X decided to ignore this advice and to continue with AS. In the case of patient X it is unclear, due to the anonymity of PRIAS patients, which information was provided to the patient and how the decision was eventually made. One of the experts stated that when overlooking the case he feels that the urologist of patient X, taking into account the age of patient X, should have discouraged the decision to stay on AS. It is important to emphasize that it is the protocol's advice to switch to curative treatment and that continuation of AS comes with the risk of disease progression which might lead to metastases. If, despite the before mentioned information, the patient decides to continue AS, the urologist should emphasize that that is the patient's decision. If the urologist has not discussed these matters, the expert feels that one might speak of a negligent act for which the urologist can be blamed. However, if the urologist provided the right information and the patient decided to continue AS anyway, the doctor lived up to his professional standards.

Due to the decision to continue AS the tumor had the chance to grow. Two years after patient X's PCa diagnosis he underwent a second biopsy (this second biopsy is in line with the PRIAS protocol). This time a Gleason 9 PCa is found in two out of twelve biopsies. Patient X underwent an RP. One year post-surgery he suffers from permanent erectile dysfunction, urinary incontinence and biochemical recurrence. His last PSA amounts to 21.6 ng/ml. The question that should be answered is not whether these outcomes would have been the same had patient X been treated a year earlier, although this does seem to be the obvious question from a medical point of view, but whether the decision to continue AS after the first repeat biopsy was justified. More specifically: does the decision to continue with AS after the first repeat biopsy meet the standard of art. 7:453 Civil Code?

The experts stated that regarding the question whether the urologist has acted as could be expected from a reasonable and reasonably competent doctor (art.7:453 Civil Code) when continuing AS, it is likely that he has. Low-risk PCa is a complex disease and it is currently not possible to distinguish which low-risk cancers will become more aggressive and which will stay indolent and therefore not cause any symptoms or death of its carrier. The AS protocol has been designed to delay or avert curative treatment in men with true indolent PCa. It has been shown, however, that with the PRIAS AS protocol perhaps still too many men are advised to switch from AS to curative treatment, indicating that the protocol might still be too strict. Bul et al. [29], for example, showed that of the 446 PRIAS AS men that underwent deferred treatment after their initial biopsy, 189 men underwent RP. For 167 men (88.4%) pathology results were available. 118 cases (71%) had favorable RP results (pT2 and Gleason ≤ 3 + 4), while 49 patients (29%) experienced unfavorable results (pT3-4 and/or Gleason ≥ 4 + 3). Of the 118 cases with favorable results, 88 (75%) had been given a proto-

col-based advice to switch. Assuming that the urologist of patient X is aware of the ongoing debate surrounding low-risk PCa and AS, the experts state that deviating from the protocol in itself is tolerable. The case described enters what the expert state as 'the grey zone' for which it is not entirely clear what is the best way to handle.

Discussion

In this article we have looked at AS for PCa from a juridical point of view. As AS is a viable management strategy that is incorporated into many national and international guidelines, the authors were interested in potential pitfalls - from a juridical point of view - for urologists.

With the help of two urologists, appointed as 'experts' - as would be done in practice - we found that there are two very important aspects that need to be taken into consideration when offering AS: (1) providing that type of information to the patient on which he can base his informed consent and (2) urologists acting according to their professional standards.

According to art. 7:448 Civil Code patients have a right of information, meaning that a doctor is obliged to provide information that concerns medical actions, treatment and patients' current health status. This information should be clear to the patient, relevant and adjusted to his educational level. When offering AS it is important that urologists provide information on the risk of PCa progression and the subsequent possibility of being too late and thereby missing the window of curability. The follow-up scheme should be explained, as well as the potential risks of repeated biopsies. Furthermore, it is important that the risks and benefits of the other treatment options are explained well so that the patient can make a well-informed decision on whether or not to provide consent on the proposed treatment.

We have seen that information plays an important role throughout the entire AS period. There are various points in time during which the decision to continue or discontinue AS has to be taken. It is important, and in line with art. 7:448 and 7:450 Civil Code, to constantly inform the patient well so that he can take the decision or agree on the decision to continue/discontinue AS. We would like to advise that the discussions between the doctor and the patient are surveyed into his medical record. Men entering the PRIAS study sign an informed consent. We would like to suggest that men who are offered AS outside study environment sign informed consent as well.

Furthermore, we found that in line with art. 7:453 Civil Code urologists should act in line with their medical professional standards. Patient X was assumed well-informed and therefore the question here was whether continuation of AS was in line with art. 7:453 Civil Code. Due to the complex situation with respect to low-risk PCa, the experts stated that deviating from the protocol was tolerable. As the urologist of patient X engaged in including patients into the PRIAS study, it is likely that he is aware of the discussions surrounding low-risk PCa and AS in particular. The national and international guidelines also leave room for interpretation with respect to offering and the (dis)continuation of AS. It is, however, of upmost importance that the progress within this area of expertise is followed carefully.

Conclusion

From a juridical point of view, urologists that offer AS to their patients should be aware of the information that they provide to patients, both when entering AS and well as during follow-up. Furthermore it is important that urologists act in line with their medical professional standards. To be able to do so, it is advised that urologists follow the progress that is made within this field carefully, as the field is moving rapidly.

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