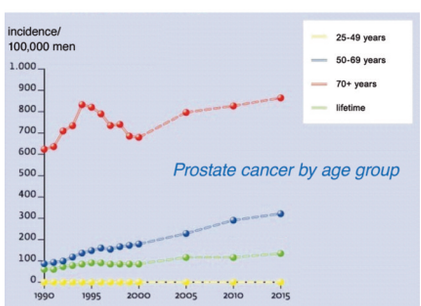
# Indolent prostate cancer and active surveillance

Prostate cancer is a remarkable disease because it can follow a very variable course in different patients. Early aggressive treatment in patients whose cancer is likely to progress slowly, if at all, causes side-effects and reduces their quality of life for no benefit. Can active surveillance avoid unnecessary treatment without missing patients whose cancers are progressing?

The incidence of prostate cancer in Europe is increasing, with figures showing that it affects 225,000 men each year. This is not only because of the aging of the European population, but also the widespread availability of prostate-specific antigen (PSA) testing, which is increasing the incidence figures in all age groups.

The European Randomised study of Screening for Prostate Cancer (ERSPC), which ran in eight countries, demonstrated the benefits of early screening. It showed that it reduces prostate cancer mortality by at




*Source: Kanker in Nederland.* KWF Kankerbestrijding (2004)

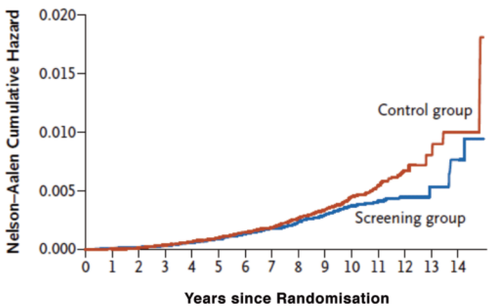
## European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss, with leading European experts, a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases. One of these will be selected for publication in each issue of *Cancer World*.

In this issue, Chris Bangma, chair of the Department of Urology at the Erasmus Medical Centre, Rotterdam, the Netherlands, reviews the role of active surveillance in managing patients with indolent prostate cancer, and considers tools that can help physicians to assess risk of progression and monitor patients over time. Daniel Helbling, from Onkozentrum Zurich, Switzerland, poses questions that explore the issue further. The presentation is summarised by Susan Mayor.

**The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do**

**REDUCTION IN DEATHS FROM SCREENING**




| No. at Risk | | | |
|---|---|---|---|
| Screening group | 65,078 | 58,902 | 20,288 |
| Control group | 80,101 | 73,534 | 23,758 |

**The ERSPC study showed screening cut prostate cancer deaths by 20%, but 48 cancers had to be diagnosed for every life saved**

*Source:* Schröder et al. (2009) Screening and prostate-cancer mortality in a radomized European study. *NEJM* 360:1320–1328. 

least 20% (FH Schröder et al, 2009). The aims of the study were: to evaluate prostate cancer mortality reduction by screening in the general population of men aged 55–74 years; to evaluate the effect of screening on quality of life; and to evaluate the sensitivity and specificity of screening instruments. Although we showed a mortality reduction, we have yet to show that quality of life is increased when men go for early screening – these results will come in future years.

The bottom line is very important, because the study demonstrated proven mortality reduction. However, the results showed that screening has to diagnose 48 men with prostate cancer and lead to them being treated in order to prevent one death from prostate cancer. This number poses a disadvantage.

The results, now at ten years of follow-up, predict that the mortality rate from prostate cancer will continue to fall in the coming years. It is likely that more men in Europe will be screened and that prostate cancer incidence will increase overall. However, screening needs to be performed at a relatively early age because, as the cumulative risk figures show, the split between the screening and control groups starts from about eight years after the randomisation. After the age of 70 years, screening is probably completely useless.

Summarising the ERSPC, it shows a significant, 20%, reduction in the relative risk of prostate cancer death for men aged 55–69 who are screened (using intention to screen analysis), which increases to a relative risk reduction of 31% after adjusting for non-compliance. The trend seen in the mortality curves suggests larger effects with longer follow-up. On the downside, healthcare providers will struggle with the high rate of overdiagnosis in screening programmes.

**LONG-TERM SIDE-EFFECTS**

| | Surgery | Brachy-therapy | External Beam |
|---|---|---|---|
| Incontinence | 5–10% | 5% | 2% |
| Erectile dysfunction | 15–90% | 10–70% | 45–85% |
| Proctitis | – | 2% | 10% |
| Micturition complaints | 1–9% | 10% | 20% |

**The choice between active treatments depends in part on balancing tumour control against side-effects**

*Source:* Erasmus MC

## TREATMENT MODALITIES

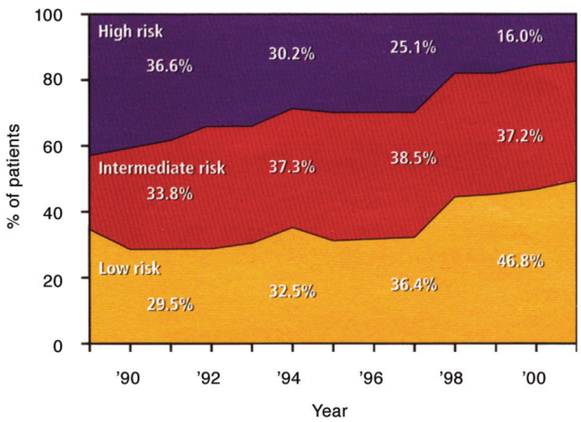
There are several treatment modalities for prostate cancer. Management options for localised prostate cancer (cancer only in the prostate) include active surveillance; brachytherapy/cyberknife; radical prostatectomy; external beam radiotherapy; high-intensity focal ultrasound (HIFU) and cryotherapy. Some of these are more invasive than others. Further modalities are: endocrine therapy, chemotherapy, vaccines, tyrosine kinase inhibitors (TKIs), watchful waiting and palliation.

All of these treatments have side-effects, which are inevitable with any treatment, but vary according to the treatment (see below). Erectile dysfunction is quite common as a side-effect, but occurs less frequently with less-invasive treatments such as brachytherapy. Incontinence is predominantly seen if the prostate cancer is removed by surgery.

It's worth adding a note of caution in interpreting these data, because they have never been challenged in a randomised study in which two or three treatments are run at the same time. Lack of uniformity in reporting side-effects can also be a problem. A man might regard himself as being incontinent, for instance, if he loses a few drops of urine, while a researcher might report incontinence only when a man needs to wear an incontinence pad.

In general, if the aim is to achieve the best tumour control with the least side-effects, then it would make sense to select the therapy according to tumour

**INCREASE IN DIAGNOSIS OF LOW-GRADE CANCERS**




As a result of increased screening, more and more men are being diagnosed with cancers that would be unlikely to cause them any problems during their lifetime

*Source:* Cooperberg et al. (2008) Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). *J Urol* 170:2415–2422, with permission from Elsevier

characteristics – for patients with smaller tumours with lower risk of metastases, and, at the other end of the spectrum, for patients dying of their tumours, treatment should be less invasive and have less side-effects.

This approach would be useful to address the large number of prostate cancer patients that will be diagnosed in the future. We cannot afford to give everybody external beam radiotherapy or a radical surgical option. It is too costly, there are too many side-effects, and side-effects will also increase costs as well as reducing quality of life. This is simply not acceptable and, therefore, we have to look for better treatments.

## Increasing diagnosis of low-risk prostate cancers

Increasing numbers of patients with low-risk tumours, with low risk for metastasis and low risk for mortality, are being detected.

There are several definitions for smaller or indolent cancers, also known as low-risk or minimal cancers. A minimal cancer can be defined according to histological terms: <0.5 ml, no Gleason 4 pattern (McNeal, Epstein). A low-risk tumour is not palpable, or just palpable, by digital rectal examination, has a low Gleason score (the sum of two scores in a pathology slide), and a PSA of less than 10–15 ng/ml.

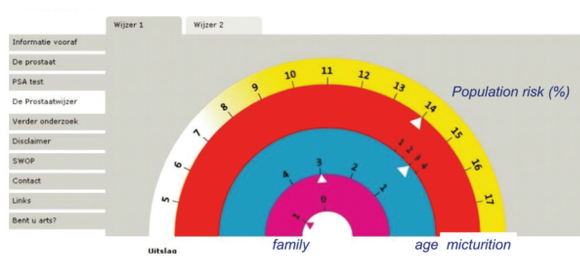
If we diagnose these low-risk types of tumour we will probably be over-diagnosing, because they are unlikely to cause any symptoms or problems during a patient's life. Low-risk tumours are diagnosed only by screening. Oncologists tend to think that the rate of indolent prostate tumours is very low, because they do not see them in the patients they treat with radical prostatectomy. This means that the rates of indolent cancers in clinical series are far lower than in population-based detection. In fact half of all prostate tumours detected by screening the general population aged between 50 and 70 years old will be small, low-risk, or completely indolent.

The fact that population-based screening will detect so many indolent cancers means it might be harmful for patients because of the anxiety it will cause them and the potential risks associated with unnecessary treatment. What can we do with these small tumours to minimise the risk? One option is active surveillance.

## Arguments for active surveillance

Active surveillance means monitoring patients carefully and delaying any invasive action until there are signs that a tumour is growing beyond the prostate and progressing to a non-curable stage. Waiting to treat until this stage means that there is still a window of opportunity in which to cure the cancer but, at the same time, it delays side-effects and, in some cases, stops the need for treatment at all. This is better for patients – improving their quality of life – as well as for healthcare systems. However, the problem is recognising growing tumours in good time so that they can be cured. How do we identify these patients and select them for extra surveillance, and determine when treatment is needed?

**PROSTATE CANCER RISK INDICATOR**




This interactive web-based tool (www.uroweb.org) enables patients and doctors to calculate the risk level of a given cancer by feeding in the relevant variables

## WHICH PATIENTS SHOULD WE SELECT FOR ACTIVE SURVEILLANCE?

We can detect quite a number of patients with indolent tumours who require active surveillance by means of clinical signs and risk-prediction algorithms. The web-based prostate cancer risk calculator, shown on page 17, can assess individual risk compared to the population risk based on the results of the ERSPC. For example, a man who has a family history of prostate cancer, is aged 60–69 and has some micturition complaints will have an individual risk of 14% compared to the population risk.

Using this type of risk calculator for indolent prostate cancer incorporates characteristics of a prostate biopsy, including the tumour size and the number of positive biopsies. For example, if only one of eight biopsies from the prostate shows cancer and if the tumour is well differentiated and of minimal length, the calculator would predict an indolent cancer in 80%–90% of cases. Once the patient and their physician know that the cancer is indolent, with a low risk of future metastasis, they can discuss management options. I would choose active surveillance for this type of patient.

**ACTIVE SURVEILLANCE SCHEDULES**

- Inclusion according to low risk criteria
- Regular 3- to 6-monthly follow-up
- Criteria for shift to invasive therapy:
  - PSA level
  - PSA doubling time
  - PSA velocity
  - PSA density
  - Repeated biopsy grade
  - Repeated biopsy number

*Source:* Erasmus MC

## ACTIVE SURVEILLANCE SCHEDULES

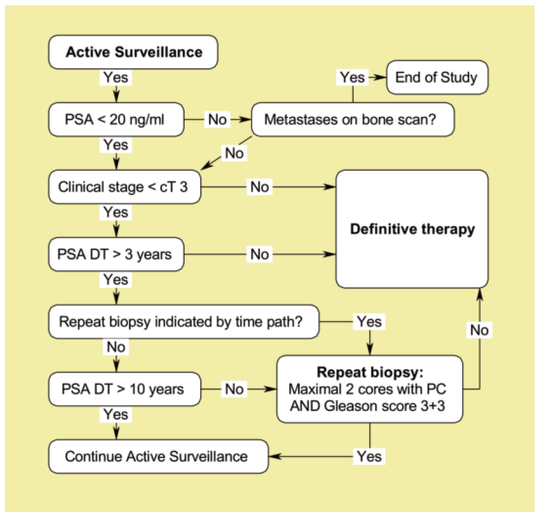
Active surveillance schedules monitor patients with low-risk cancers regularly, as often as every three months, by taking serum and seeing whether their PSA level is increasing or remaining stable. To provide additional information, active surveillance programmes use repeated biopsies, for example after one and three years, to check that the number of prostate-cancer-positive biopsies is not increasing, the grade is not decreasing, and therefore the Gleason score is not increasing, indicating a poorly differentiated cancer.

We are currently conducting a study in Europe on this, the Prostate Cancer Research International Active Surveillance (PRIAS) study, to determine whether careful monitoring enables treatment to be delayed or withheld. The trial uses a flow chart (see above) with strict criteria – for example if the PSA doubling time is getting shorter, the PSA is increasing rapidly, or repeat biopsies are showing changes – to determine when to progress to definitive therapy. The aim is to make it easier for physicians and patients to follow this approach.

The figure Analysing PSA Changes (opposite page) illustrates the graph of PSA measurements over time during the active surveillance of one patient (the black line). The green line shows a doubling time of 10 years, and the red line a doubling time of three years. If the black line is higher than the red line, this means that the PSA is increasing very quickly, which generally indicates a growing cancer. An increasing PSA can also be due to an increase in the size of the prostate gland due to benign prostatic hypertrophy, but the PSA doubling time is generally longer than in malignant disease. The analysis is complex, and we have developed a decision tree for PRIAS that incorporates a range of information, including that from PSA measurements and biopsies.

The system being used in PRIAS enables doctors to add a patient's latest PSA level to their graph, while sitting at their desk with the patient, and immediately get a new curve, together with a new recommendation of follow-up. The patient can see for himself what is happening at the same time. This system is now available in seven European languages.

**FOLLOW-UP PROTOCOL FOR THE PRIAS TRIAL**




This follow-up flowchart guides doctors and patients through the active surveillance approach, and is being used to collect evidence on the effectiveness of this strategy

*Source:* Erasmus MC

The rapid increase in the number of patients included in the PRIAS scheme shows its popularity and indicates that both physicians and patients think it is trustworthy. Approximately 1000 patients have been included over the past two and a half years, from a wide range of countries across Europe, and also Canada.

Long-term follow-up is required to prove that active surveillance is safe with regard to mortality, and that is not yet available for PRIAS. However, the ERSPC included an enormous database of 260,000 men who were screened, including 616 men from Sweden, Finland and the Netherlands who were managed conservatively. These men would have met the criteria for PRIAS, if it had been available at the time. Follow-up of these patients over 10 years shows very favourable results, with prostate-cancer-specific survival of 100% (see Survival with Conservative Management, page 20). This provides evidence that active surveillance might be a good tool for a subset of patients diagnosed with prostate cancer.

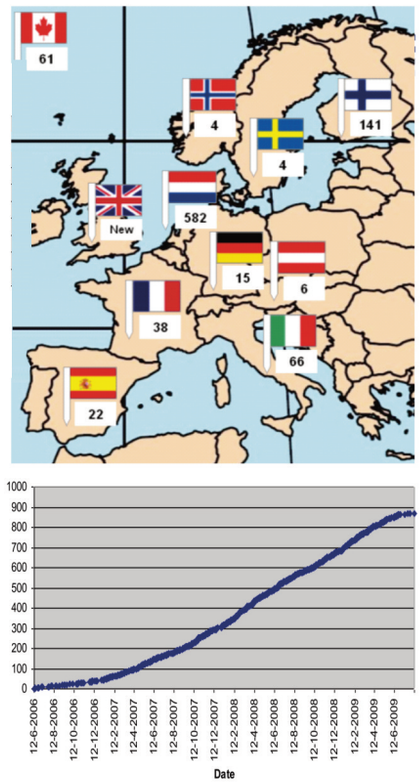
## Shifting to deferred active therapy

After two or three years of PRIAS follow-up, approximately 25% of men are given active treatment: 40% because of changes in their PSA doubling time; 40% because of changes in their biopsies, and the remainder for other reasons, including anxiety. Anxiety, in both physicians and patients, can trigger a change to active treatment, because they cannot continue with the uncertainty that a cancer may be progressing to a level where it can no longer be cured.

Overall, studies show that approximately 10%–15% of men on active surveillance, whatever their PSA or biopsies are doing, shift to some kind of invasive treatment. Quality-of-life studies in PRIAS show that most patients are very stable on all types of quality-of-life measurements during the trial. It is important to note that patients have given their informed consent prior to being included, so they understand the choice they are making. However, there is always a subset of patients that is more nervous, which can be determined in upfront psychological characteristics. In the future, it may be possible to use psychological tests before including patients in active surveillance studies.

There are other limitations to active surveillance. Several studies have shown the variability of prostate biopsies, which are very important for timely recognition of growing tumours. The procedure takes very small pieces of tissue, so taking multiple biopsies from a prostate can give results that vary quite significantly. In one study (Saudi et al. 2009), taking multiple biopsies led to an upgrading to a worse Gleason score in approximately one-third of men. This would deny the possibility of managing these men by active surveillance. Another showed that taking 20–30

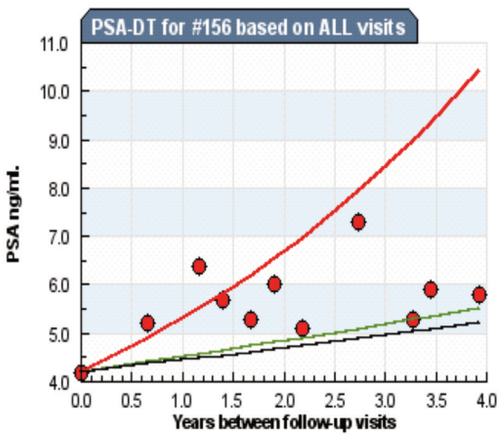
**PATIENTS IN THE PRIAS STUDY**




**Active surveillance would appear to be a popular option judging by the numbers of patients joining the PRIAS study**

*Source:* Erasmus MC

**ANALYSING PSA CHANGES**




**The rate at which a patient's PSA level rises is an important indicator of whether the cancer is growing. The doubling time (DT) for the PSA levels of patient #156 is currently slightly longer than 10 years, indicating an indolent cancer.**

*Source:* Erasmus MC

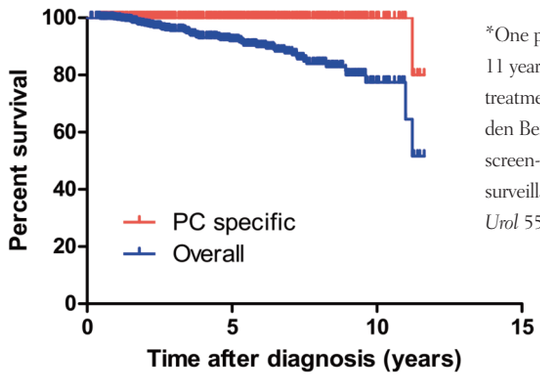
biopsies of the prostate gave an upgrading of 30%. The same study showed that the risk of downgrading was also quite high (39%–56%). These findings warn that biopsies are a crude method for determining cancer stage, so we need to find new and better methods.

## Active surveillance misses some progression towards metastasis

Several studies of active surveillance are ongoing, but it is difficult to compare them because they measure different parameters. The table below shows the number of metastases detected (highlighted area) during the follow-up of active surveillance studies. Given that this is a very low number, is it justifiable to argue that active surveillance is safe, and so to go ahead with it? I do not think so, because metastases occur very late in the disease. The lead time for screen-detected disease is ten years, and you might add another five to ten years before metastases occur. This means that it takes a long time to show the safety of active surveillance for prostate cancer in studies. For now, we have to make do with surrogate endpoints, such as the number of patients who undergo radical prostatectomy because of progression of their tumour to pT3 disease (tumour growing through the capsule of the prostate). This is not very advantageous for prognosis and, therefore, at this moment, is being used as a measure of failures in active surveillance.

We have to improve on these numbers, which lead to continued criticism of active

**SURVIVAL WITH CONSERVATIVE MANAGEMENT**




*One patient died from prostate cancer more than 11 years after diagnosis, having declined active treatment despite rising PSA levels. *Source:* Van den Bergh et al. (2009) Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. *Eur Urol* 55:1–8, with permission from Elsevier

**Retrospective 10-year survival data on 616 men who would have fulfilled the criteria for inclusion in PRIAS, and were treated conservatively, show that not one of them died from prostate cancer***

**ACTIVE SURVEILLANCE MISSES SOME PROGRESSION**

| Study, no. participants, mean follow-up | % Survival over follow-up time | Metastases analysed | % pT3 in case of radical prostatectomy | % with PSA doubling time >10 years | Conversion to invasive therapy |
|---|---|---|---|---|---|
| Klotz (2006)<br>*n* =299, 8 yrs | 99.3% Pca specific | 2/299% (N+) | 58% (14/24) | 42% | 35% |
| Parker (2005)<br>*n* =80<br>3.5 years | 100% Pca specific<br>94% overall | — | 50% (1/2) | 45% | 20% |
| Carter (2007)<br>*n* =405, 2.8 yrs<br>(range 0.4–12.5 yrs) | 98% overall | 0.5% (2) | 20% (10/49) | — | 25% after 2.2 yrs (PSA doubling time no trigger) |
| Roemeling (2007)<br>*n* =278<br>3.4 yrs | 100% Pca specific<br>90% overall | — | 1/13 (8%) | 44% | 29% after 2.5 yrs |
| Soloway (2008)<br>*n* =157<br>4 yrs | 100% Pca specific | 0% | 0/2 (0%) | Mean 13.1 yrs in no-treatment group, 3.6 yrs in treatment group | 8% |

surveillance. However, on the positive side, the overall survival curves over 10 years show that a large group of patients is benefiting from active surveillance, and this group is increasing. At the moment, the instruments available can detect indolent disease with a probability of up to 70%–80%. This can prevent at least 30% of men with screen-detected prostate cancers undergoing active treatment.

## Conclusion

The incidence of indolent tumours will increase across Europe with increasing screening for prostate cancer. Overdiagnosis by screening is unavoidable, but overtreatment can be reduced if we improve the recognition of indolent tumours and do not use invasive treatment for them.

Men can be selected for active surveillance using the tools developed in the PRIAS study. These make it simple to select patients suitable for active surveillance. Results with active surveillance are reassuring, with prostate-cancer-specific survival of 100% over 10 years.

Immediate radical prostatectomy shows identical survival and does not cure everybody. Five years after radical prostatectomy, 20% of patients have a PSA recurrence that indicates they still have cancer. Delayed prostatectomy at two years does not worsen outcomes. However, active surveillance is not safe for everyone, with around 1% showing progression to metastatic disease, and patients have to live with a slow-growing, indolent cancer. For the future, we have to find better markers for diagnosis and risk of progression, so that we can make individual assessments for patients.

## Q&A

**Daniel Helbling, from Onkozentrum Zurich, in Switzerland, hosted a question and answer session with Chris Bangma.**

**Q:** *When will the results of active surveillance studies become available?*

**A:** Final results in terms of mortality will take years. In the mean time, we have to follow this closely, looking at the study results available and trying to improve where we can with the tools we have. In one or two years, we will have new predictive tools that can be incorporated into active surveillance schemes.

At the moment, there is a lot of work with imaging. MRI scans are becoming more sensitive and ultrasound is also improving. Using these imaging techniques enables us not only to see the tumour better, but also to more accurately target the tumour with biopsy needles in order to assess whether it is worsening. We have to be on the ball and not wait until we have proven the value of active surveillance in randomised studies, but incorporate new tools into the active practice of urologists and radiologists.

**Q:** *How many biopsies are required to be sure that a patient has an indolent prostate cancer, where you can recommend watch and wait or radiotherapy?*

**A:** There is a lot of variation and nothing is standardised. Nowadays, it is generally accepted that the number of biopsies taken depends on the size of the prostate gland. For a normal gland (up to 40 ml), 8–10 biopsies are sufficient. This would increase to 10–12 for a gland of 40–60 ml, and 12–14 for a larger gland of 60 ml or greater.

**Q:** *The inclusion criteria for the PRIAS study states that the Gleason score has to be 6 or lower. We are now in an era of Gleason score inflation, with a shift towards higher scores, because they are based on definition rather than just determination. Would it be possible to accept an even higher Gleason score for active surveillance?*

**A:** This is a very important question. PRIAS was set up three years ago based on the expert opinions of world researchers in the field. The criteria include a Gleason score up to 7. Only 44 patients with Gleason scores of 7 have been included so far, but results have demonstrated that active surveillance is appropriate. Although follow-up is limited at the moment, their prostate-cancer-specific survival is 100%. This shows that patients with a Gleason score of 7 can be included, but not those with PSA levels of 20 ng/ml or four positive scores, because these extra risk factors indicate a higher risk of tumour progression that will need invasive treatment.

**Q:** *Would you use active surveillance outside the PRIAS trial as well?*

**A:** I am sure that a lot of patients are being managed in this way outside the PRIAS study. However, the great benefit of combining the data from patients in a study is that it provides better quality evidence and enables new information to be gathered. I can only advise those patients and physicians who are not currently making use of the PRIAS tool to use it. They can input data anonymously if they prefer and use the data for their own statistics. The PRIAS community will benefit from all the data being brought together in order to improve the scheme, so it is very valuable if people include their patients in it.