ACTIVE SURVEILLANCE: AN INDIVIDUALIZED APPROACH TO EARLY PROSTATE CANCER

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Up to 80% of men with PSA screen-detected prostate cancer are over-diagnosed, i.e. their cancer would never have become symptomatic [1]. Over-diagnosis would not matter if treatment had no morbidity; it would be acceptable to treat all cases, including those destined never to cause symptoms, if treatment was problem-free. However, while radical treatment for prostate cancer may or may not improve a man's longevity, it can certainly have a major effect on his lifestyle. Ideally, such intervention should be restricted to those who need it. Active surveillance aims to individualize the management of early prostate cancer by selecting only those men with significant cancers for curative treatment. Patients are closely monitored using serum PSA levels and repeat prostate biopsies. The choice between radical treatment and continued observation is based on evidence of disease progression during this initial monitoring. Active surveillance must be distinguished from watchful waiting, which for decades has described a policy of observation with the use of palliative treatment for symptomatic progression. Or in other words, to emphasize the differences between these contrasting approaches, whereas watchful waiting involves relatively lax observation with late, palliative treatment for those who develop symptoms of progressive disease, active surveillance involves close monitoring with early, radical treatment in those with evidence of significant biochemical or histological progression.

Although active surveillance of one form or another has been widely used on an *ad hoc* basis, the concept was formally described for the first time in 2001 by Choo *et al.* [2]. In that study, eligibility was restricted to men with clinical stage T1b-T2b disease with a Gleason score of ≤7 and an initial PSA level of ≤15 ng/mL. Men were followed every 3 months for the first 2 years and then 6-monthly, with a DRE and PSA testing at each visit. A repeat biopsy was taken at 18 months. Indications for radical treatment were: PSA progression, defined as a PSA doubling time of <2 years; histological progression, defined as upgrading to a Gleason score of ≥8 on re-biopsy; or clinical progression. The latest update of this study [3] included data on 206 men, with a median initial PSA level of 6.5 ng/mL. At a median follow-up of 29 months, 48 men had received radical treatment, four had died from unrelated causes and 154 remained on observation. Of the 48 men who had radical treatment, 29 met the criteria for disease progression, while the other 19 elected to have treatment without having met the criteria. Experience at the Royal Marsden is similarly encouraging; between 1993 and 2001, 80 men with early prostate cancer were managed using active surveillance at the Royal Marsden. To date, 10 have received radical treatment, three have died from unrelated causes and 67 continue on observation. No patient has developed metastatic disease and none has died from prostate cancer. Interestingly, the median PSA doubling time in the Marsden series is up to 14 years, suggesting an indolent course of disease in most cases. The long-term efficacy of an active surveillance policy is being compared with immediate radical treatment in the ProtecT trial.

Ongoing studies seek to define an optimum active surveillance protocol. For example, the variation in the findings between initial and repeat biopsies within the first few years of surveillance seem to reflect the limitations of sampling, rather than tumour progression [4,5]. There is therefore an argument for an extensive initial biopsy with, e.g. 12 cores, to minimize sampling error, with repeat biopsies taken less frequently than every 2 years. A prospective study of active surveillance at the Royal Marsden, supported by the NCRI Prostate Cancer Collaborative, is using monthly PSA levels and will address the optimum frequency of PSA testing, and the number of observations needed to estimate PSA doubling time.

The choice of the PSA doubling-time threshold used as an indication for intervention is somewhat arbitrary. A lower threshold will spare more men the morbidity of radical treatment, but might adversely affect long-term survival. However, a longer threshold doubling time, while it may be safer in terms of cancer control, will increase the burden of treatment side-effects. The Royal Marsden policy is to use an individualized threshold for each patient, depending on absolute PSA level and life expectancy, and assuming that low-grade prostate cancer seldom becomes symptomatic before the PSA level reaches 50 ng/mL. For example, a man with a PSA level of 6 ng/mL needs three PSA doublings before his PSA will reach 50 ng/mL. So if his life expectancy were 20 years, then radical treatment would be indicated if his PSA doubling time was shorter than ≈7 years. However, if his life-expectancy were 30 years, then a doubling time threshold of 10 years would be more appropriate.

The true value of active surveillance may prove to be not just as an attractive alternative to immediate radical treatment, but as a step towards a whole new paradigm for managing prostate cancer. Prostate cancer prevention trials, e.g. SELECT, typically require tens of thousands of healthy subjects followed for many years. An alternative, and arguably more appropriate, approach would be to study the prevention of clinically significant disease in men with PSA screen-detected cancers managed by active surveillance. This type of secondary prevention study could be completed far more rapidly, and with fewer patients than a traditional primary prevention study. A placebo-controlled, randomized trial of selenium supplementation at the Royal Marsden will test the feasibility of this approach.

In summary, active surveillance is an attractive approach to managing early prostate cancer, which may spare men the side-effects of treatment without compromising survival. Ongoing studies seek to optimize the active surveillance protocol. Chemoprevention studies in men on active surveillance may lead to a new treatment paradigm for early prostate cancer, aiming not to eradicate the disease, but to alter its natural history.

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