



Platinum Priority – Editorial

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Radical Prostatectomy: Yes or No? Your Culture Makes the Difference

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The selection of a tailored treatment for prostate cancer (PCa), among several alternative scenarios, depends on your urologic culture. It is the sum of technical skills, tradition, and theoretical achievements leading to the development of balanced and sensible solutions. The paper by Vickers et al. fits in such a cultural context [1]. They used data from the Scandinavian Prostate Cancer Group study 4 (SPCG-4) to develop a statistical model to determine the individualised surgical benefit, based on age and tumour characteristics, for men scheduled for radical prostatectomy (RP). In SPCG-4, 695 men aged <75 yr with clinically localised PCa and a life expectancy of >10 yr were randomly assigned to RP or watchful waiting between 1989 and 1999 [2].

Recently, SPCG-4 reached a median follow-up of 12.8 yr. Bill-Axelson et al. [3] reported a significant reduction in the rate of death from PCa and the risk of metastases in the RP group compared with the watchful waiting group. The benefit was obvious among men <65 yr and in men with low-risk tumours (ie, men with a prostate-specific antigen [PSA] level <10 ng/ml and a tumour with either a Gleason score <7 or a World Health Organisation grade of 1 in the case of tumours that were diagnosed only by cytologic assessment). Quality of life data from the same study showed that negative side effects of both RP and watchful waiting were common and that both interventions added more stress than would be seen in a background population [4].

The strengths of SPCG-4 include the randomised design (adequate randomisation and, consequently, adequate comparison of baseline characteristics of two groups: RP vs watchful waiting), the completeness and long-term follow-up (12.8 yr), and the independent and blinded evaluation of the cause of death. Unfortunately, the

recruited men had high-volume disease, the diagnosis was based mainly on symptoms (only 12% had cT1c at time of enrolment), and the confirmation of suspected PCa was obtained by a core biopsy or fine-needle aspiration—a scenario completely different from that seen in Western countries in 2012.

The Vickers et al. study [1] adds a new piece of urologic culture: “In the context of the side effects of contemporary RP, it is hard to justify surgery in Gleason 6, T1 disease and in patients much above the age of 70.” Such patients would appear more appropriate for an active surveillance (AS) program. At the other extreme, surgery seems unequivocally of benefit for patients who have Gleason 7 or 8 and stage T2 disease. It is difficult to make an evidence-based decision in patients with Gleason 6 and T2 or Gleason 7 and T1 disease, where the treatment is more of a judgement call depending on the patient’s tolerance of the consequences of surgery, such as possible urinary and sexual dysfunction, versus anxiety associated with AS.

The conclusions of Vickers et al. could become key factors for decision making in treatment of PCa, as the most important issue for patients is the trade-off between improved survival and quality of life. This consideration is particularly relevant for patients because, with current trends of testing for PSA and the lowered PSA threshold for biopsy, more and more men will be diagnosed with lower grade and stage PCa [5]. Controversy about the unproven benefit of PSA screening and its known side effects clearly have highlighted the concerns about overdiagnosis and overtreatment [6].

Raldow and colleagues recently reported an interesting analysis about the trend of curative therapies in RP [7].

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Older men with low-risk PCa have received increasingly aggressive treatment over the last decade. Use of active therapy in men with a short life expectancy (ie, <10 yr) increased by 37% from 1998 to 2007, regardless of tumour risk. During the same time, the use of curative therapy decreased slightly in men with long life expectancy. The conclusions of Vickers and co-authors [1] should change such a scenario. Recent data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) in the United States [8] showed that surgery offers no survival benefit compared with observation in men with low- and intermediate-risk disease, supporting the conclusions of Vickers et al. [1]. However, based on available data, we do not have a definitive response to this issue. Results from ongoing trials, such as the Prostate Testing for Cancer and Treatment (ProtecT) study in the United Kingdom, in which men with PSA-detected disease were randomly assigned to surgery, radiotherapy, or AS, are expected to conclude that young men with low-risk disease are overtreated with surgery because their cancer is possibly indolent.

A potential solution could come from the introduction of *focal therapy*, defined as a therapy that selectively ablates known disease while preserving existing functions, with the overall aim of minimising lifetime morbidity without compromising life expectancy [5]. In general surgery, the use of breast-sparing surgery to treat breast cancer revolutionised local control of the disease. Experience with lumpectomy shows that quality of life can be successfully integrated into the equation of cancer treatment without major loss of treatment efficacy. Some urologic groups became interested in the notion of prostate-sparing focal therapy for low-stage, low-grade PCa and several explorative studies have been listed in public registers since 2009 (eg, external-beam radiation therapy: NCT01168479; cryotherapy: NCT00928603 and NCT00774436; brachytherapy: NCT01354951, HIFU: NCT01194648, NCT01226576, NCT01094665, NCT00561262, and NCT00030277). Unfortunately, many crucial points remain unsolved, such as adequate patient selection, PCa multifocality, energy modalities, and follow-up criteria, making focal therapy far from ready to be introduced in clinical practice.

Most urologists might conclude that the use of cancer therapies should be dictated authoritatively by clinical evidence and guided by patient preferences. Urologists should explore how to incorporate both cancer characteristics and patient life expectancy into the decision-making process. Public health programmes related to the PCa outbreak (903 500 estimated new cases worldwide in 2008 [9]) need to be evaluated on whether anticipated benefits, predicted by *modelling*, are indeed happening and whether they could be cost effective. In such circumstances, modelling is likely to play an important part in the evaluation of PCa in the future because often it can be the only way to obtain an estimate of what would have happened in absence of the specific application of RP (the possible) compared with what happened in presence of RP (the actual). With good application of modelling, the urologist could estimate the real effect of RP on patients' health in circumstances in which other changes such as the

introduction of robot-assisted RP, which appears to be safer as well as more costly, are also taking place in urology [10].

Modelling has moved from an academic exercise by mathematicians to the public health field. Mathematics provides a precise quantitative language that describes the relation between variables and changes in states, and in urology we can represent mathematically the clinical course of a disease, its distribution across populations and over time, and the treatment outcome. Unfortunately, none of the indicators of model quality (model structure, parameters, and validation) guarantees that the model will produce accurate outputs. The distinction between how well a new model fits recorded data and how well a model is able to predict what will be seen remains an open issue. Following the most rigorous model-analysis standards, although necessary and requested, is not sufficient to guarantee that the model results are appropriate for each patient.

Urology medical associations and editors of urology journals need to have an active role in such a debate. The introduction of new concepts for PCa management should be part of a new rigorous culture of surgical research to reach the same levels of safety and efficacy as current standards. *European Urology* guarantees a process that excludes authoritarian practice and unilateral control while enabling a natural process of assimilation of elements in the management of PCa that shall be designated by continuous clinical research. We strongly believe that the key factor for building a new competitive urologic culture is to let new information emerge. New knowledge does not need walls, except those of universities, hospitals, and libraries.

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