Urol Res (1997) 25:299–301

INVITED EDITORIAL

O. Haillot · P. Perrin

Early detection and early treatment

Received: 10 July 1996 / Accepted: 14 December 1996

"Prospective randomized trials are needed". For 10 years almost all papers about the screening, early detection and early treatment of prostate cancer have concluded with such a statement. Are early detection and early treatment possible? Are early detection and early treatment desirable? When and for which patients is early treatment necessary? Some factors are already understood even if the question cannot be answered completely.

Is early detection possible? Early detection means individual or opportunistic screening and not full-scale organization. On an individual basis for a given patient, combined use of prostate-specific antigen (PSA) and digital rectal examination (DRE) has proved to be the most efficient method (4). The drawback of individual early detection is the relatively high cost and the rate of three or four negative biopsies to one positive biopsy, especially for PSA values between 4 and 10 ng/ml. The new concept of free/total PSA ratio might be one way of increasing the specificity of PSA without loss of sensitivity, possibly leading to a decrease in the number of unnecessary biopsies when the PSA value is between 4 and 10 ng/ml [7]. It can be speculated that the free/total PSA ratio, or another improvement in PSA measurement, should in the future be the single first-line screening test, omitting DRE. This attitude would overlook the 5–10% patients with a clinically significant palpable cancer on DRE and a normal PSA value currently encountered in radical prostatectomy series. It is not known whether these patients will reach an abnormal PSA value during later serial screening and still be at a curable stage or not. If the answer is yes, these patients would not have been disadvantaged by using PSA, and/or the PSA ratio in the case of a moderately elevated PSA value, as a first-line screening test. There is currently no data to support this hypothesis.

At the present time, when a man wishes to undergo tests for early diagnosis for prostate cancer he should be offered PSA measurement and DRE provided that: (1) he is between 50 and 70–75 years old (40 years for African-Americans or in cases of familial history of prostate cancer), (2) he has a life expectancy of at least 10 years and (3) he knows, understands and accepts the risks and benefits of the screening tests.

Is screening possible? From an epidemiologic point of view, screening remains controversial even for a given target population. The aim of screening is to detect life-threatening prostate cancers at a curable stage and to cure them with appropriate treatments. Two biases may be encountered. The first is lead-time bias when, although the overall length of survival remains unchanged, screening adds a false impression of additional length of survival due to earlier diagnosis. Such a bias is possible in prostate cancer. The second is length-time bias when only less aggressive tumors are detected during serial screening. The most aggressive tumors grow to an incurable stage during the time between two consecutive screenings and are not detected at a curable stage with the screening setting. Those tumors which are detected could never have reached a life-threatening stage. Such a bias is also possible in prostate cancer screening and has never been precisely estimated.

The two consequences of lead-time and length-time biases are the diagnosis of advanced tumors at an incurable stage and the risk of overdiagnosis, defined as the diagnosis of tumors that will never progress. Diagnosis of advanced tumors is not the aim of screening but these patients will benefit from endocrine treatment, at least in terms of quality of life. The percentage of diagnosis of such tumors decreases dramatically with serial screening. Overdiagnosis occurs when clinically nonsignificant or "latent" cancers are detected by screening, leading to treatment of patients with non-life-threatening cancers. The screening series available show

O. Haillot (✉)
Department of Urology, CHU Bretonneau,
F-37044 Tours Cedex, France

P. Perrin
Department of Urology, Hôpital de l'Antiquaille,
F-69321 Lyon Cedex 05, France

a maximum rate of detection of up to 15–20% of these clinically nonsignificant cancers. In these series, the definition of such cancers is only pathological, i.e. a tumor volume less than 0.5 ml with no Gleason 4 or 5 pattern. Unfortunately, there is no agreed preoperative clinical or biological definition of an insignificant cancer. There is currently no way to predict accurately the final pathological stage or to calculate preoperatively the volume of a prostate cancer. However, in the absence of any universal magic formula, a combination of PSA density and favorable pathology results of sextant biopsies (Gleason score and quantitative analysis of systematic biopsies specimen) during precise mapping of the prostate with transrectal ultrasound would identify most patients with clinically insignificant tumors [1]. These might be managed with conservative therapy.

Moreover, overdiagnosis causes a problem only when it leads to overtreatment. The decision to treat falls in the end to the urologist who has to take into consideration not only the tumor but also the patient. The same tumor diagnosed by a single positive biopsy out of 6, with a length of 1.5 mm, Gleason 2 + 3 cancer and a PSA of 5 would, if treated, be probably considered as overtreatment at the age of 75 years but not at 60. On an individual basis, this distinction is often possible with a certain degree of subjectivity and imprecision, considering the algorithm used for selection [2]. In the National Prostatic Cancer Detection Project (NPCDP) series, a tumor considered as clinically insignificant (average lesion diameter less than 0.7 mm) was detected in 16.8% of patients but these patients were followed up and none of these insignificant tumors were recorded on final pathology reports [6].

If early detection and screening are possible, are they desirable? The two major pitfalls of screening are its cost and its real long-term efficiency in terms of decrease in mortality from prostate cancer.

The cost of screening is a very complex question. Urologists are not familiar with the mathematical models used by health economists to estimate costs. Numbers can vary widely with the criteria selected for analysis (age of the population screened, PSA as a first-line test or systematic PSA + DRE, unit cost of PSA and blood tests, clinical and pathology examinations, frequency of serial screening, use of quality of life-adjusted years). The potential side effects of extensive screening are not known, nor is the percentage of the population which could refuse or finally escape screening. Besides the cost of screening, the true cost of the treatment of diagnosed tumors has not been fully established either. For example, it has been demonstrated that length of hospital stay is the primary determinant of cost. In some United States academic centers, length of hospitalization for a radical prostatectomy is currently 4–6 days. This may not reflect the mean practice elsewhere in the United States and certainly does not reflect current practice in other countries such as Europe or Japan. Because the ultimate aim of screening is to decrease mortality from prostate cancer, the cost of screening and early treatment should be compared with the cost of palliative treatments, endocrine therapy and supportive care of cancers which become hormone resistant. The many uncertainties concerning these various costs make such comparisons highly speculative.

Long-term efficiency of screening remains controversial. Screening has been proved to detect a high percentage (70%) of so-called significant tumors at a curable stage. This is a far better percentage than in series where tumors were detected clinically. Early diagnosis permits curative treatment of localized tumors, as shown in many radical prostatectomy series with a PSA at 0 after 5 and 10 years for 70–80% of patients. There is no doubt that these patients are definitively cured. Is it enough to recommend early diagnosis and early treatment? Preliminary data from large epidemiologic studies such as the SEER program [3], showing a possible beneficial effect of treatment on prostate cancer mortality, need to be confirmed. Thirty years ago Whitmore asked "When cure is possible, is it necessary?" Observations of a long doubling time of 4 years for organ-confined tumors and watchful waiting strategies in Swedish series showed that a large percentage of patients with a small, well or moderately differentiated cancer can expect a mean survival of 10 or even 15 years. How long is the mean survival of a patient with a clinical T2 well or moderately differentiated tumor treated with a watchful waiting policy and deferred endocrine therapy? These patients are precisely those on whom urologists wish to operate, with good long-term results. However in the United States, the median life expectancy of a 68-year-old man in 1969 was 15.2 years.

In contrast to health economists, urologists think in terms of individual patients and not of the overall population. A urologist facing a patient dying of prostate cancer thinks that this patient lost a chance of a longer life some years before, when his cancer was at a curable stage. Confronted with a healthy 68-year-old patient, urologists do not like to reason as life insurance managers, betting on a statistical survival lower than the still controversial natural history of prostate cancer. Radical prostatectomy has become a popular procedure in recent years, especially in the United States, following the good results and low morbidity observed in prestigious reference institutions. It is not certain that average practice gives the same encouraging results everywhere in the world. At the same time, contemporary external radiotherapy now has a low rate of complication and long-term curative rates are very close or similar to those for radical prostatectomy.

In Europe, the ratio of prostate cancer incidence to death rate has remained stable at 2:1 for several years. In the United States, maybe due to the wide use of screening tests, this ratio is now almost 5:1 [5]. Prostate cancer is the second leading cause of cancer death in men and these patients sometimes have a very miserable end of life. We know some of the risk factors (race, family history). We have an easy pre-screening test which is not perfect but permits early diagnosis at a curable stage in

70% of cases. The price is 10–20% of nondesirable diagnoses of clinically insignificant tumors, which can be suspected in the majority of cases, and 70–80% uncomfortable and useless negative biopsies. Efficient treatments are available with inevitable side effects that must be accepted by patients before screening. The rationale for early diagnosis is ultimately based on the personal conviction that radical prostatectomy is a life–saving treatment for these patients with T1c tumors who otherwise would suffer from progression of the disease and ultimately die of prostate cancer. Organized mass screening does raise several questions. The reduction of prostate cancer mortality is the main one, but it will take at least 10 years before an answer can be provided for health policy makers. However, at the present time, is it possible for a physician not to offer the opportunity of a blood test to a man who has just retired in order to gain 5 or 10 extra years of good quality life? Is it because the only test is not perfect that it has to be rejected?

"Prospective randomized trials are needed". In terms of mass screening, this is true and such trials are currently in progress. For individual early detection, because most urologists believe they can diagnose prostate cancer at a curable stage and they have efficient treatments to cure selected patients, they generally consider that early diagnosis and early treatment are beneficial for such patients.

References

1. Goto Y, Ohori M, Arakawa A, Kattan MW, Wheeler TM, Scardino PT (1996) Distinguishing clinically important from unimportant prostate cancers before treatment: value of systematic biopsies. J Urol 156:1059
2. Humphrey PA, Keetch DW, Smith DS, Sheperd DL, Catalona WJ (1996) Prospective characterization of pathological features of prostatic carcinomas detected via serum prostate specific antigen based screening. J Urol 155:816
3. Krongrad A, Lai H, Lamm SH, Lai S (1996) Mortality in prostate cancer. J Urol 156:1084
4. Kojima M, Babaian RJ (1995) Algorithms for early detection of prostate cancer: current status of the "art". Cancer 75:1860
5. Lu-Yao GL, Greenberg ER (1994) Changes in prostate cancer incidence and treatment in USA. Lancet 343:251
6. Mettlin C, Murphy GP, Babain RJ, Chesley A, Kane RA, Littrup PJ, Mostoffi FK, Ray PS, Shanberg AE, Toi A and the investigators of the ACS-NPCDP (1996) The results of a five year early prostate cancer detection intervention. Cancer 77: 150
7. Prestigiacomo AE, Lilja H, Wolfert RL, Stamey TA (1996) A comparison of the free fraction of serum specific antigen in men with benign and cancerous prostates: the best case scenario. J Urol 156:350