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Editorial – referring to the article published on pp. 366–374 of this issue

Do We Need the Final Results of the ERSPC Trial?

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The oncologic community eagerly awaits the final results of the two important international screening studies for prostate cancer (Prostate, Lung Colorectal and Ovary [PLCO] and European Randomized Study of Screening for Prostate Cancer [ERSPC]). In the report by de Vries et al. in the current issue of the journal [1], the investigators of the ERSPC trial publish for the first time results regarding overall and disease-specific survival in the screening arm of the Rotterdam section of the trial compared to historical controls.

The 1014 patients with prostate cancer detected by screening are compared with a control group from the Dutch cancer registry of the same region. After a median follow-up of 5 yr, only 20 patients (2%) had died from prostate cancer. The comparison with the control group of patients diagnosed with prostate cancer between 1996 and 1998 reveals a difference of 15.6% in favour of the screened population. Of importance, this control group is not at all identical with the ERSPC control group. However, the 97.7% rate of disease-free survival of the 1014 patients is in line with the currently published rates in patients with localised disease [2].

The authors conclude that patients within a screening program have a higher overall survival, which is not surprising because the patients see physicians more frequently. They further conclude that patients with screening-detected cancers are most unlikely to die from prostate cancer within 5 yr. This again is not surprising because the ERSPC investigators have already stated that the rate of favourable tumours within screening-detected

cancers is much higher compared to the control group [3]. Therefore, this effect is completely explained by lead-time bias. Their last conclusion is that due to the limited number of prostate cancer deaths because of the high numbers of favourable cancers, the final evaluation of the ERSPC program may take longer than 10 yr. This, of course, is disappointing for the urologic community.

This conclusion describes the problems of a trial that started randomisation in 1993 and finished enrolment in 1999. Within this time period, the 5-yr disease-specific survival rates of prostate cancer patients had improved significantly. This is nicely shown in Fig. 2B of the article [1] in the current issue. From an approximately 70% disease-free survival (DFS) rate in the population 1988–1991, this percentage increased to 82% DFS for the population 1996–1998 and 88% in the population diagnosed at the end of the enrolment (1999–2001). The DFS of the ERSPC control group is not revealed yet for obvious reasons, but the main problem will be that there is an increasing contamination of the control group by prostate-specific antigen (PSA) testing from the early 1990s to 2000. In the final years of the enrolment, the control group certainly did not differ from the screened group as it did 6 yr before. This may diminish the difference in DFS rates. The second problem may be the high rate of detection of favourable tumours by screening as described earlier [3,4]. The third problem is the high rate of treatment in patients who may be candidates for active surveillance. At the time when the trial started, only a few patients were offered active

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surveillance. After the publication of the Canadian group regarding the favourable results of surveillance, this treatment strategy emerged [5]. Nearly one third of patients in this ERSPC group with screening-detected cancers would have been candidates for active surveillance [6]. However, 90% of patients chose active treatment with a somewhat higher chance of side-effects. For example, of the 20 patients who have died from prostate cancer in this publication, 4 died after radical prostatectomy but 2 of these 4 died perioperatively. Seventeen of 20 patients who died from prostate cancer had high-risk features. Only 10% ($n = 100$) of patients voted for watchful waiting. Therefore, the changing treatment options in the last 5 yr will certainly become a problem in the interpretation of the ERSPC trial results. If the trial fails to show a superiority of screening in terms of mortality, people will argue that in recent years many had an opportunistic screening (currently an estimated 7%). If the trial shows the superiority of screening in terms of mortality, people will argue whether a rigorous active surveillance strategy instead of a mere control group would be the easiest solution for the problem and that this strategy had been underused during the time of enrolment. With an even longer follow-up, the problems will not disappear.

Of importance, this trial delivers repeatedly valuable information on the changes of prostate cancer management in the 1990s with strong implications for treatment. Before the final results will be published, this trial yields results that influence treatment decisions of today, for example, baseline PSA, frequency of PSA values to exclude progression, and cut-off levels of PSA. Nearly all patients who are in danger of dying from prostate cancer within 5 yr have Gleason 4 + 4 or higher differentiation, only 15% of patients with favourable parameters and active surveillance need deferred treatment, and thus the overall disease-specific survival at 5 yr currently is nearly 100% [2]. Screening or not is mainly a health policy issue. For most men, an early PSA value at the age 40–45 yr is important [7]. With standardisation in the diagnosis and implementation of active surveillance, most of the important problems appear in the patients with locally advanced or metastatic disease. During the last years the number of patients with the primary diagnosis of a metastatic

prostate cancer has decreased. Thus, at the time when the screening results are available, the potential screening population will have changed with most of the men already knowing their PSA value and acting accordingly. The ERSPC trial has already provided the uro-oncologic community with such valuable information that the planned publication should not be delayed. Remember the Holmberg data that were derived from a completely different staging era when the diagnosis by transurethral resection was common [8]? At the time of publication this time lag certainly influenced the interpretation of the results in terms of translation to the current clinical situation. This should be kept in mind if the conclusion is drawn that the final results of the screening trials will take longer than expected.

References

- [1] de Vries SH, Postma R, Raaijmakers R, et al. Overall and disease-specific survival of patients with screen-detected prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. *Eur Urol* 2007;51:366–74.
- [2] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin* 2006;56:106–30.
- [3] Roemeling S, Roobol MJ, Gosselaar C, Schroder FH. Biochemical progression rates in the screen arm compared to the control arm of the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Prostate* 2006;66:1076–81.
- [4] Postma R, van Leenders AGJLH, Roobol MJ, Schröder FH, van der Kwast TH. Tumour features in the control and screening arm of a randomized trial of prostate cancer. *Eur Urol* 2006;50:70–5.
- [5] Klotz L. Active surveillance for prostate cancer: for whom? *J Clin Oncol* 2005;23:8165–9 (review).
- [6] Roemeling S, Roobol MJ, Postma R, et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *Eur Urol* 2006;50:475–82.
- [7] Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology* 2006;67:316–20.
- [8] Bill-Axelsson A, Holmberg L, Ruutu M, et al., Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977–84.