Asian Journal of Andrology (2013) 15, 441–442

www.nature.com/aja

RESEARCH HIGHLIGHT

Screening and efficacy of radical prostatectomy

Michael Froehner

Asian Journal of Andrology (2013) **15,** 441–442; doi:10.1038/aja.2013.31; published online 15 April 2013

In a recently published study, the results of the Prostate Cancer Intervention versus Observation Trial (PIVOT) trial were compared with that of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4). The authors concluded that the discrepancy of the mortality rates between both studies may be explained by screen-related lead time and over-diagnosis. In this comment, some potential biases are discussed and the limited applicability of the results of both randomized trials to healthy candidates for radical prostatectomy is underlined.

The results of the Prostate Cancer Intervention versus Observation Trial (PIVOT)[1] raised questions on the efficacy of radical prostatectomy in men with low-risk prostate cancer. Xia and co-workers[2] used simulation modeling to determine whether the reduced absolute survival benefit in the PIVOT trial[1] compared with Scandinavian Prostate Cancer Group Study Number 4[3] may be explained by the high prevalence of screen-detected prostate cancers in the PIVOT study. The authors concluded that the discrepancy of the mortality rates between both studies may largely be explained by screen-related lead time and over-diagnosis and should not be considered as an argument against the efficacy of radical prostatectomy even in the presence of screening. The authors emphasized that there is a subset of patients that should not be treated by radical prostatectomy which needs to be identified in the future.[2]

There are further features of the PIVOT study making it appropriate to interpret the lack of survival differences in this trial with caution. With more than 30% dying of other causes by 10 years, the competing mortality rate was three times as high as usually observed in contemporary radical prostatectomy series: 10%,[4] 4%–12%[5] and 11%.[6] The PIVOT study sample obviously contained an over-proportionally large proportion of cases with a high risk of early competing mortality. This observation is particularly remarkable because it was associated with a mean age of only 67 years[1] which was not unusually high. In very healthy men selected for radical prostatectomy, even in those aged 75 or more years, the competing mortality rate within 10 years after surgery may be narrowly zero.[7]

The low statistical power to detect potential survival differences in the PIVOT trial has been emphasized.[8] It is, therefore, hardly possible to draw general conclusions from the outcome of the low-risk subgroup in the PIVOT trial. With the relatively short observation time, the small sample size and the high competing mortality rate, the lack of outcome differences is probably not suited to reassure younger and healthier patients with screen-detected prostate cancer. Currently available prognostic markers are not able to predict the course of untreated prostate cancer over decades of further life-span even if initially no high-risk features are present. The marked decrease of prostate cancer mortality in the United States since the introduction of (opportunistic) prostate-specific antigen-based screening illustrates that there is an effect of early diagnosis and active treatment on prostate cancer mortality, although randomized trials did not reveal unequivocal results so far.[8–10] It is rather the question whether the price in terms of over-diagnosis and quality of life impairment is reasonable than whether screening and active treatment are able to decrease prostate cancer mortality.

The authors discussed several limitations of their study.[2] The combination of data of different studies performed during different times in different health care systems (PIVOT and Scandinavian Prostate Cancer Group Study Number 4) is another potential limitation. It is conceivable that with a combined analysis of data also biases may be combined. In the PIVOT trial, only a small minority of initially screened patients (731 out of 13 022, i.e., 5.6%) have been eventually randomized. This figure may reflect the difficulty to recruit patients who agree to participate in such randomized trial and suggests a considerable selection process from screening to eventual trial enrollment. It is unknown in which degree this selection changed the composition of the study sample and whether the remaining screen-detected cases were still representative. It is likely that the study sample in this way was enriched by good risks. In the Scandinavian trial, a selection bias could be an explanation for the surprisingly different efficacy of radical prostatectomy in men younger and older than 65 years[11] that was in contrast to data from other studies. In a population-based cohort study that enrolled 14 516 conservatively treated patients with localized prostate cancer aged 65 years or older, the 10-year prostate cancer mortality rates did not differ after stratification by age and remained stabile even beyond an age of 80 years.[12] In the setting of the Scandinavian trial without a meaningful prevalence of prostate-specific antigen screening, patients were probably more likely to contact their doctor with lower urinary tract symptoms. Since such symptoms more frequently occur in elderly men, it is conceivable that a substantial proportion of prostate cancer in the elderly were diagnosed incidentally during workup for lower urinary tract symptoms which were not caused by the cancer itself, whereas in younger patients obstructive larger cancers which would do poorly with conservative treatment alone were more likely of being detected.[11]

Considering the potential of biases, data obtained by a combined analysis of these different randomized trials should be carefully interpreted. The resulting figures are merely

Department of Urology, University Hospital Carl Gustav Carus, Dresden University of Technology, Fetscherstrasse 74, Dresden D-01307, Germany
Correspondence: Dr M Froehner (Michael.Froehner@uniklinikum-dresden.de)

hypothesis-generating and need confirmation in further (preferably randomized) trials. Caution is particularly required when the results are applied to healthy candidates for radical prostatectomy who have a high long-term survival probability.

1 Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ *et al*. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; **367**: 203–13.
2 Xia J, Gulati R, Au M, Gore JL, Lin DW *et al*. Effects of screening on radical prostatectomy efficacy: the prostate cancer intervention versus observation trial. *J Natl Cancer Inst*; e-pub ahead of print 14 February 2013.
3 Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011; **364**: 1708–17.
4 Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ Jr, Yossepowitch O *et al*. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Clin Oncol* 2009; **27**: 4300–5.
5 Guzzo TJ, Dluzniewski P, Orosco R, Platz EA, Partin AW *et al*. Prediction of mortality after radical prostatectomy by Charlson comorbidity index. *Urology* 2010; **76**: 553–7.
6 Froehner M, Koch R, Litz RJ, Hakenberg OW, Wirth MP. Which patients are at the highest risk of dying from competing causes within 10 years after radical prostatectomy? *BJU Int* 2012; **110**: 206–10.
7 Froehner M, Koch R, Wirth M. Comorbidity and survival of patients selected for radical prostatectomy at an age of 75 years or older. *Asian J Androl* 2013; in press.
8 Thompson IM Jr, Tangen CM. Prostate cancer—uncertainty and a way forward. *N Engl J Med* 2012; **367**: 270–1.
9 Etzioni R, Gulati R, Tsodikov A, Wever EM, Penson DF *et al*. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. *Cancer* 2012; **118**: 5955–63.
10 Albertsen P. The prostate cancer conundrum revisited: further insights. *Cancer* 2012; **118**: 5724–7.
11 Froehner M, Wirth MP. Early prostate cancer—treat or watch? *N Engl J Med* 2011; **365**: 568.
12 Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y *et al*. Outcomes of localized prostate cancer following conservative management. *JAMA* 2009; **302**: 1202–9.