Editorial

Interpretation of PIVOT findings

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The results of the long awaited Prostate Cancer Intervention versus Observation Trial (PIVOT) have been recently published in the New England Journal of Medicine (1). The primary outcome of the trial was overall survival in men treated with radical prostatectomy (RP) or observation for clinically localized prostate cancer detected with PSA screening.

Seven hundred thirty one US veterans were randomized between 1994 and 2002 to RP or observation. Mean age of the cohort was 67 years, median PSA was 7.8 ng/mL, approximately half of patients had non-palpable disease, and same proportion had Gleason score ≤7. Overall survival was 2.9% higher and cancer specific survival was 2.6% higher in surgically treated patients at the10-year median survival mark. The most prominent overall survival benefit of 12.6% was observed in patients with intermediate-risk tumors by D'Amico criteria. The likelihood of bone metastases was twice lower in the RP arm of the trial. The authors concluded that RP does not reduce significantly overall and cancer specific survival in men diagnosed with PSA screening.

Does it mean that all men with clinically localized prostate cancer should not be offered RP or should PSA screened be abandoned if active treatment does not matter? Probably not.

First, prostate cancer, even detected with PSA screening and clinically localized, is a heterogeneous disease. There is plenty of evidence that low-grade small tumors may be treated expectantly while high proportion of aggressive tumors may present as pathologically extra-prostatic disease destined to recur despite surgery, not so for the middle of the spectrum. Indeed, in PIVOT study RP was mostly beneficial in the intermediate risk tumors. Unfortunately, due to low recruitment rates the study was underpowered to detect survival differences in the clinically relevant subgroups. In the retrospect, it is apparent that at the time of study design almost two decades ago the need to focus on particular risk group may not have been that obvious. Furthermore, the control of recruitment rate is beyond researches ability.

Second, by the randomized nature of the trial not all participants complied with the intended treatment. In the RP arm 15% chose observation, 7% chose radiation and in 2% surgery was abandoned, while in the observation arm 20% received RP. The inconsistent adherence to the assigned therapy results essentially in comparing '77% surgery' to '80% observation'. It may make sense epidemiologically to avoid bias by allowing the 'intention to treat' analysis, however may not apply clinically since for a particular patient treatment choice is 100%.

Third, the presence and magnitude of competing risks is of utmost importance. Simply put, if a significant proportion of study participants dies due to other causes there is no chance to find out whether they would succumb or not to prostate cancer. PIVOT investigators applied competing risks approach to survival analysis and used overall survival as an end-point to overcome this limitation. However, it may not be sufficient if the difference between the study cohort and general population is significant. Let's see how they compare. Overall, in the PIVOT cohort other-cause mortality (OCM) was about 35% at 12 years. This is significantly higher than 14% and 30% 10- and 15-year OCM in men treated with RP as estimated from SEER data in the same time period (2). There is even more striking difference when comparing with Scandinavian population data which showed 8% OCM at 10 years or Johns Hopkins cohort with 16% OCM at 15 years (3).

It is possible that 1/3 of PIVOT participants did not achieve the 10-year life expectancy as defined by recruiting criteria because of less than optimal general health of the VA population. In this context and considering constantly improving cardiovascular mortality in US (4) it will be

difficult to extrapolate PIVOT outcomes to future radical prostatectomy candidates.

In summary, PIVOT corroborates the concept that mostly men with intermediate risk prostate cancer may benefit from radical prostatectomy and that radical prostatectomy prevents bone metastases, an important clinical end-point. Its shortcomings suggest that benefit from radical prostatectomy should be more prominent in healthier population of men not subjected to significant competing risks of other-cause mortality. As an aside, this study is an example of how an accurately designed trial may lose some of its relevance due to suboptimal accrual and changes of target population over time. Another concern is that similarly to misinterpretation of PLCO and ERSPC trials by opponents of PSA screening, PIVOT will be misused by the opponents of radical prostatectomy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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