Prostatectomy versus watchful waiting in patients with localized prostate cancer: the survival benefit can be spotted in the long run

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In the United States, prostate cancer (PCa) remains the most common non-skin malignancy in men, with an estimation of 174,650 new cases and 31,620 deaths likely to occur in 2019 (1). Nowadays, 80% of PCa is localized to the prostate at the time of diagnosis (2). Active treatment for these patients includes radical prostatectomy (RP), radiation therapy, and active surveillance in very low and low risk disease (3). At the time no definitive data exists regarding the best treatment option for localized PCa and it should be discussed with every patient on the basis of disease characteristics (4).

Historically, it has been believed that active treatment of organ confined PCa could prevent it from spreading outside of the prostate and be effective in reducing cancer mortality (5). Despite this, some data put under the spotlight that patients with localized PCa followed with expectant management carried a low mortality risk, questioning the role of active treatment (6). Holmberg *et al.* tried to clarify this aspect by designing a randomized clinical trial (RCT), the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) (7). The main endpoints were to define whether RP was superior to watchful waiting (WW) in terms of reduced cancer-specific mortality rate and of metastasis-free survival for patients with localized PCa. In a 10 year-long time period, 695 patients with clinically localized PCa were enrolled, of which 347 and 348 were randomized into the RP and the WW group, respectively. Only 53 patients (15%) belonging to the RP group refused the operation, whereas 52 patients (15%) in the WW group decided to undergo surgery at a certain point. Since this RCT was designed before the prostate-specific antigen (PSA) screening era, most cases (88%) were detected via digital rectal examination; this led to the enrollment of a consistent proportion of patients with high-risk disease. Patients eligible for this RCT were diagnosed with a localized adenocarcinoma of the prostate, less than 75 years of age, with a PSA <50 ng/mL, with more than 10 years of life expectancy, without any other malignancy and no comorbidities preventing surgery. Patients were followed-up every 6, 12, 18, 24 months after the enrollment, and then yearly until death. At a median follow-up of 6.2 years, only 31 and 16 deaths due to PCa occurred in the WW and the RP group, respectively, stressing the need of a longer follow-up period to understand the real survival benefit offered by RP for patients with localized PCa; however, men undergoing RP showed already a lower risk of metastasis (relative risk 0.63; 95% CI: 0.41–0.96; P=0.03).

Bill-Axelson *et al.* recently updated the findings of this study reporting results after 29 years from the start of the SPCG-4 (8). The endpoints were then stratified according to age at diagnosis (<65 *vs.* ≥65 years) and to some pathological features, such as extracapsular extension and Gleason score. By the end of 2017, at a median follow-up time of 23.6 years, 80% of the patients originally included in the study had died, of which 32% [181] due to PCa. There was no patient lost at follow-up. The cumulative incidence of death due to any cause and to PCa were, respectively, 72% (95% CI, 67–77%) and 20% (95% CI, 16–24%) in the RP group, 84% (95% CI, 80–88%) and 32% (95% CI, 27–37%) in the WW group. The relative risks of death from any cause and from PCa in the RP group compared

to the WW group were 0.74 (95% CI, 0.62–0.87; P<0.001) and 0.55 (95% CI, 0.41–0.74; P<0.001), respectively. On average, patients belonging to the RP group gained about 3 years of life at 23.6 years of median follow-up. The cumulative incidence of distal metastases was almost 27% (95% CI, 22–32%) in the RP group, whereas it was 17% higher (95% CI, 38–49%) in the WW group; in this regard, the relative risk of developing distant metastasis in the RP group compared to the WW group was 0.54 (95% CI, 0.42–0.70; P<0.001). In patients younger than 65 years of age, overall mortality, mortality due to PCa and risk of metastasis were respectively 15% (95% CI, 4–26%), 15% (95% CI, 5–25%) and 19% (95% CI, 8–29%) lower in the RP group than in the WW group; these results were more flattened in the subanalysis including older patients. Extracapsular extension was found in 132 (47%) of 283 specimens in the RP group; 29% and 6% of patients with and without extracapsular extension died from PCa (relative risk, 5.21; 95% CI, 2.42–11.22), respectively. Lastly, patients in the RP group with a Gleason score of 4+3 and of 8 or 9 were almost six (relative risk, 5.73; 95% CI, 1.59–20.67) and eleven (relative risk, 10.63; 95% CI, 3.03–37.30) times more likely to die form PCa, respectively, if compared to patients with a Gleason score ≤6. In this last category of patients, the number of deaths registered was low.

This study from Bill-Axelson *et al.* shows that a substantial proportion of younger patients with intermediate-high risk PCa benefitted from active treatment and had their life extended, on average, about 3 years; however, this number was calculated on the whole group of patients with localized disease, and it would have probably been higher if patients with low-risk disease would have been excluded from this computation. On the other side, patients with low-risk disease and older than 65 years old rarely die from PCa, confirming and underlying the pointlessness of creating harm with RP in this category of patients. All together, these data could help the clinician during patient counseling to undertake treatment decisions.

A few RCTs have compared RP to conservative management in localized PCa. In the pre-PSA era, Iversen *et al.* failed to show a benefit in surgery over expectant management, but their study was strongly underpowered (9). The ProtecT trial (10), which investigated the benefits in terms of survival of RP, radiation therapy and active monitoring in patients with localized PCa, detected a statistically significant superior risk of development of metastasis in the observation group rather than in the interventional arm (P=0.004), in line with the study from Bill-Axelson *et al.* However, overall and cancer specific-survival results at a 10-year median follow-up were similar in the three study groups; this difference from the SPCG-4 study could be related to the enrollment of a more uniform population of patients with less aggressive features (77% had a Gleason score 6 disease) and to the lead time bias introduced by the screening for PCa. The PIVOT trial had the same aim of the SPCG-4 and similar inclusion criteria, but RP resulted not superior to observation (11). Moreover, at a median follow-up of 13.4 years, only 9.4% of the patients studied died of PCa. These different survival outcomes could have been influenced by the evolutions in patients' selection and treatment modalities in the period in which the PIVOT trial was undergoing.

The randomized design, the length and the completeness of follow-up, and the blinded evaluation—to treatment assignments—of causes of death by an independent end-point committee constitute the strongest points of this work. Moreover, a central pathology review was performed by four expert uropathologists in two different occasions, providing reliable data on PCa features (7,12). Last, this study reports the life-long behavior of high-risk and treatment naïve PCa patients, who nowadays would instead undergo upfront intervention (3,13).

Nonetheless, this study carries some non-avoidable limitations. At the time this RCT was designed, PSA and its surrogates were not yet widely introduced into clinical practice. This aspect renders this study not adequately comparable to the current *status quo* of PCa identification and management (14). Second, biopsies were performed with the sextant technique, while patterns later introduced have been associated with a better diagnostic yield (15). Third, only the Scandinavian population has been represented in this study, despite racial disparities in terms of PCa outcomes have been reported (16,17). Therefore, the results of this study can mostly be applied to the white Caucasian population. Fourth, only two treatment modalities have been compared, even though radiotherapy represents another valuable option in localized PCa (3). Fifth, changes in surgical techniques and in treatment modalities should also be considered.

These few limitations do not reduce the value of this study, which still represents a benchmark work in the field of localized PCa. This paper especially highlights the need of a life-long follow-up to deeply understand the benefits of the different therapeutic strategies adopted for localized

PCa. To provide more definitive conclusions on this topic, further comparisons with other RCTs at final follow-up time will be needed.

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Footnote

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