Editorial

The prostate cancer management dilemma: is it time to start a new era?

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Introduction

Prostate cancer is one of the most common lethal cancers in men in the developed countries. In the USA, it is estimated to affect 161,360 men (19% of all the newly diagnosed cancers) with an estimated mortality of 26,730 men (8% of all cancer deaths) in 2017. This renders it the most commonly diagnosed cancer and the third most common cause of cancer death in the USA in 2017 (1). Prostate cancer is an unique malignancy in that most of patients die with and not because of it (2). The optimal management strategy for localized prostate cancer is still controversial. The ongoing war between early active treatment in the form of radical prostatectomy (RP) or external beam radiotherapy and deferred management in the form of watchful waiting started long time ago (3-6). Despite this long ongoing war, there are few randomized controlled trials (RCTs) concerned with this influential issue because of the difficulty in organizing such studies. The most important RCTs are Veteran's Administration Cooperative Urological Research Group (VACURG) (6), Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) (7), The Prostate Testing for Cancer and Treatment (ProtecT) (8), and Prostate Cancer Intervention Versus Observation Trial (PIVOT) (5).

Defenders of each treatment modality have their rational reasons; for instance, early active treatment provides the advantages of tumor eradication, but it carries the risk of associated morbidity and mortality. On the other hand, expectant management is associated with less morbidity but it is not concerned with tumor eradication and, therefore, carries the risk of disease metastasis or progression and cancer-related death (3).

PIVOT

Recently, Wilt *et al.* (5), published the results of the extended follow up of the PIVOT. In this trial, 731 patients with localized prostate cancer were randomized in two treatment groups either RP (n=364) or observation (n=367). Patients were followed-up for 19.5 years (median 12.7 years). The study's primary outcome was all-cause mortality and the main secondary outcome was prostate-cancer mortality. All-causes mortality occurred in 61.3% (95% CI, 56.2–66.1) in RP group and 66.8% (95% CI, 61.8–71.4) in the observation group [relative risk (RR) 0.92, 95% CI, 0.82–1.02]. All-causes mortality was lower with surgery than observation but the difference was not significant (hazard ratio, 0.84; 95% CI, 0.70–1.01; P=0.06). On the other hand, prostate cancer death occurred in 7.4% (95% CI, 5.2–10.6) and 11.4 % (95% CI, 8.6–15.1) in the RP and the observation groups respectively (RR 0.65, 95% CI, 0.41–1.03). Interestingly, the prostate-cancer mortality was also lower with surgery than observation but not significantly lower (hazard ratio, 0.63; 95% CI, 0.39–1.02; P=0.06) (5).

Wilt *et al.* (5), stated that despite the differences in mortality rates favoring surgery over observation after long follow-up (19.5 years), it is still insignificant statistically. Furthermore, surgery showed better results regarding the frequencies of disease progression and treatment. On the other hand, observation was better as regards long-term erectile and continence function.

This study brings to mind a very crucial question; can we shift localized prostate cancer patients from RP to observational management? There are some points to consider before answering this question.

Concerns about the PIVOT

Statistical power

No doubt that the PIVOT trial is one of the largest RCTs (731 patients) comparing between RP and observation in the management of localized prostate cancer; however, there are some concerns regarding the PIVOT. The first concern is that the survival rates in between the two groups may not be as dramatic as it seems to be as the PIVOT trial did not meet their pre-set enrollment target (2,000 patients) and, therefore, their statistical power to detect significant difference in their primary endpoint may be limited. This is proved by the wide confidence interval around the all-cause mortality and prostate-cancer mortality (3,5,9).

Generalizability

Moreover, Dalela *et al.* (10), studied the generalizability of the PIVOT results where they analyzed the characteristics of prostate cancer patients managed by either RP or observation within the national cancer database (NCDB) in between 2004 and 2014. All the patients who did not meet the inclusion criteria of the PIVOT trial were excluded. Overall, 355,366 patients met the inclusion criteria (294, 109 patients 83% undergone RP and 61,257 patients 17% were treated by observation). After analyzing and comparing the characteristics of the 355,366 patients within the NCDB with those of the PIVOT, they assumed that the PIVOT sample of patients may not be truly randomized and that their baseline characteristics and treatment selection significantly differed from the planned source population. Barbosa *et al.* (11), supported these results, by analyzing 35,954 patients from the Veteran Affairs hospitals (the same source of the patients of the PIVOT trial) in nearly the same period of the PIVOT trial (1994–2001) showing significantly better overall survival for men in their cohort than those of the PIVOT trial, raising concerns about the validity and generalizability of PIVOT.

Ten years survival

Furthermore, there are some concerns regarding the 10 years-survival rate of the PIVOT patients, because all-causes mortality appeared to be quite high (48%). This raises concerns regarding the life-expectancy of the PIVOT patients and their ability to benefit a long-term survival after definitive treatment (9).

Other RCTs

Finally, the PIVOT authors stated that their results are comparable to the results of ProtecT and SPCG-4. However, PIVOT should not be compared to ProtecT as the PIVOT compares between RP versus observation while ProtecT studies the active monitoring. On the other hand, the SPCG-4 showed a significant absolute reduction in the rate of overall deaths, cancer-related deaths and metastasis in the RP group compared with the observation group with extended follow-up (up to 23.2 years) and this reduction was more significant in patients younger than 65 years (7). The different results between the two trials in spite of the similar number of patients (695 in SPCG-4 versus 731 in PIVOT) may be due to the difference in the clinical stage (T1c patients 50% in the PIVOT versus 12% for the SPCG-4) and mean PSA (7.8 ng/mL in PIVOT versus 13 ng/mL in SPCG-4) (9).

Retrospective cohorts

The lack of RCTs concerned with the comparative evaluation of different treatment modalities of localized prostate cancer yielded the observational retrospective cohorts of great importance as a primary source of information (12). Likewise, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) guidance and Cochrane Collaboration and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group offered tentative support to the dependence on observational studies as a source of information in case of absence of sufficient evidence from RCTs (13-16). Several retrospective cohort studies stated that RP has a favorable survival outcome compared to observation (2,17-19).

Guidelines

Furthermore, most guidelines recommend watchful waiting for low-risk prostate cancer patients. For example, the European Association of Urology (EAU) guidelines recommend watchful

waiting for patients not eligible for curative treatment with short life expectancy, while they recommend RP in patients with low- and intermediate-risk disease and life expectancy more than 10 years (20). While the American Urological Association (AUA) guidelines recommend RP for intermediate and high risk localized prostate cancer patients and recommend active surveillance for very low-risk patients (21).

Localized prostate cancer overtreatment

We cannot neglect that there is overtreatment of localized prostate cancer and we think that the PIVOT results emphasize this problem either directly or indirectly. The introduction of prostate-specific antigen (PSA) resulted in an increase in the rate of early diagnosis of prostate cancer. This early diagnosis has resulted in an increase in the rate of unnecessary treatment especially in the elderly population with life expectancy less than 10 years. Observation is recommended for those elderly patients with low-risk prostate cancer, however, only 20–35% of them actually choose observation as their initial therapy (22). This overtreatment problem is associated with increased medical costs and increased surgical adverse effects like urinary incontinence and erectile dysfunction (22).

Moreover, Hager *et al.* (23), studied the treatment modalities for low-risk prostate cancer in the USA and Germany between 2004 and 2011, and they stated that RP was performed in 36.1% and 66.2% in the USA and Germany respectively. On the other hand, observation including primary androgen deprivation therapy (ADT) was used in 24.2% versus 16.2% in the USA and Germany respectively. In Germany, Observation alone was used in 12.2%. Throughout the years of the study, RP decreased in the USA from 37.1% to 34.2%, while it remains stable in Germany at 66.2%. Nonetheless, observation with ADT increased in the USA from 18.0% to 33.2%, while in Germany, it was stable until 2009 when it started to increase from 15.2% to 19.4%. These results show that there is already a shift towards better patient selection criteria for each treatment modality (23).

Conclusions

Finally, the PIVOT trial is an important trial with high evidence level; however, it should direct us towards a better selection of patients undergoing RP rather than rushing towards observation. We should not underestimate RP role in the management of localized prostate cancer. More studies are needed to identify which patient will benefit from RP.

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