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EDITORIAL

PSA SCREENING AND LOW RISK PROSTATE CANCER, WHAT´S GOING ON? ARE WE SHOOTING THE MESSENGER?

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Several recent developments in the form of publications in high impact journals and presentations at the American Urological Association (AUA) Congress and a special and very recent report from a panel of experts convened by the National Institute of Health for the purpose has rocked the international scientific community regarding diagnosis and treatment of localized prostate cancer (PC).

Since the massive introduction of the Prostate Specific Antigen (PSA) in the year 1987 (population screening programs), there was an incidence peak in the rates of diagnosis of PC, but above all at the expense of increasing the number of cases of low-risk cancer, and now 20 years later we know that only 5% of these patients will die of PC (1).

Cancer detection has been increased once PSA cut-off values decreases to indicate a biopsy, has been increased at the expense of Gleason 3 +3 (6). In 2002 over 63% of tumors that were diagnosed were Gleason 6. This increase in the diagnosis of low histological grade tumors was accompanied by a decrease in PSA levels (<10 ng / ml) (1).

In summary and detailing the roadmap followed so far, these are the different publications involved, in chronological order:

• **March/2009:** The New England Journal of Medicine published in its March issue the results of two highly anticipated studies on the role of screening in PC ("European Randomized Study of Screening for Prostate Cancer; ERSPC (2)" and "Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening (3)").

EDITORIAL

• **May/2011:** During the celebration of the American Congress of Urology in Washington DC, the first results of "VA / NCI / AHRQ CSP # 407: Prostate Cancer Intervention Versus Observation Trial (PIVOT): Main Results From a Randomized Trial Comparing Radical Prostatectomy to Watchful Waiting in Men with Clinically Localized Prostate Cancer "(4) study were presented, showing that radical prostatectomy (RP) does not increase survival compared with watchful waiting in patients at low risk.

• **October/2011:** The U.S. government agency "Agency for Healthcare Research and Quality from U.S. Department of Health and Human Services published the updated Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force (5)" These same authors published two months later a paper entitled "Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force (6)." in the journal Annals of Internal Medicine . As a main conclusion, and for the first time in its history, the Task Force does not recommend screening for men under 75 years and stated after a review of five studies that screening with PSA have not shown to decrease mortality from prostate lung cancer.

• **December/2011:** The NIH published a draft of a consensus document entitled "CONSENSUS DEVELOPMENT CONFERENCE STATEMENT: National Institutes of Health State-of-the-Science Conference: Role of Active Surveillance in the Management of Men With Localized Prostate Cancer " (1), concluding that the international scientific community has an urgent need to consider active surveillance as the first choice of treatment in patients with low risk prostate cancer (low risk defined as PSA <10 ng / ml and Gleason score ≤ 6).

That said, let's see what the situation is, and what we know.

Screening vs. no screening: Over diagnosis and Over treatment : ERSPC, PLCO and Report of the U.S. Preventive Task Force studies

The PSA-based screenings allow identifying "additional or extra " PC cases, but most trials found no statistically significant benefits in the PC specific mortality. The recent meta-analysis of randomized trials included in the Task Force5, 6 work, has not found a positive effect of screening on PC mortality. However, the two largest and higher quality trials, (ERSPC and PLCO) have reported inconsistent (2, 3).

The ERSPC trial found that performing a PSA determination every 2 to 7 years may be related to a 20% relative reduction in the risk of death from PC in a cohort of men aged 55 and 69 years (2), while the PLCO trial found no effect (3). The high rates of screening prior to the performance of PSA and the contamination in the PLCO trial control group may have reduced its ability to detect benefits, although these factors do not explain the trend toward increased risk of mortality PC-specific in the screening group.

The proportion of men in the PLCO trial that initially chose active surveillance or watchful waiting instead of treatment with curative intent was lower than in the study ERSPC 2 study (10% vs. 19%),PLCO3 evaluated a shorter screening interval (annual versus every 2 to 7 years), suggesting that screening and treatment strategies more conservative might be most effective than aggressive. Chance may also explain the apparent discrepancy between the two trials because the risk estimate overlaps.

A longer follow-up could help resolve the discrepancy, given the long latency period (10 to 15 years) that may be necessary to fully understand the effect of PSA-based screening.

The screening is associated with potential harm, including severe infections or urinary retention in approximately 1 in 200 men undergoing prostate biopsy.

It is also possible that screening involves an over diagnosis, due to the detection of low-risk PC that would not have caused morbidity or death during the life of a man, and over treatment, which exposes men to unnecessary damage. More than three-quarters of men with localized PC (about 90% of cancers detected by screening are localized) undergo treatment with radiotherapy or RP. Based on data from the ERSPC trial, it was estimated that the rate of on the screening diagnosis was as high as 50%. Thus 48 men had to be treated to prevent one single death from PC2

Pivot Trial Results: RP vs. Watchful Waiting

Before going into the details of this important study, it is important to clarify and define the concepts of ***"active surveillance (Active Surveillance)" and "watchful waiting or observation (watchful waiting)"***. Both terms have evolved over time and have not always been correctly applied.

Active surveillance as a form of treatment, consists of delaying treatment with curative intent until it becomes necessary, depending on whether a set of progression criteria of the disease appears . In the case of PC is to monitor PSA levels and perform periodic re-biopsy. By contrast, watchful waiting or observation is another way of proceeding that eludes a curative treatment until symptoms appear to require it. Somehow, it is a closer laxer monitoring.

PIVOT Study results were reported by its principal investigator Dr. Timothy J. Wilt, saying that the RP did not significantly reduce the overall rate of death from any cause or PC specific compared to active surveillance for 12 years in men with clinically localized low risk PC in PIVOT trial (4).

However, surgery appears to benefit patients with higher PSA values and those with high-risk disease.

The main results of the PIVOT trial, pending publication, offer a different approach to the RP value, of the results recently published by the Scandinavian Study Group of the PC, Nr. 4 (SPCG-4) (7), a previous PSA era showed a significant overall benefit of surgery, even in men with low risk considered tumors.

The PIVOT study (randomized controlled trial) was initiated in 1994, and included 731 men from veterans' hospitals across the United States to receive RP or watchful waiting. Inclusion criteria were: age ≤ 75 years, PC clinically localized and a PSA value of less than 50 ng/mL (4).

The average age was 67 years, and nearly a third were Afro-American. The mean and median PSA was 10.2 ng / dl and 7.8 ng / dl, respectively. Using the D'Amico risk classification approximately 43% had low risk tumors, intermediate risk 36% and 21% high risk, respectively (4).

Recruitment was completed in 2002 and followed up the patients until 2010 (with a median follow up of 10 years), determining the cumulative rates of death at specific times through an "analysis by intention to treat."

In a transverse section to 12 years, 354 of the 731 men (48.4%) had died, with an absolute reduction in mortality from all causes and cancer-specific of approximately 3% in the RP group compared with the watchful observation group . Specifically, the absolute reduction in any cause mortality cause was 2.9% (relative risk ratio (RR) of 0.88), and the absolute reduction in mortality by PC was 2.7% PC (RR, 0.63), values that were not statistically significative (4).

The effect of surgery on mortality from all causes and especially in the cancer-specific survival did not vary with age, race, self-perceived health status, or presence of comorbid conditions. There also was a significant effect of RP in mortality rates when men were classified only by their Gleason score (≤ 6 vs. 7-10) (4).

PC mortality was calculated based on risk group, which was 3% for low risk and 13% in the high risk (4).

In patients with low-risk disease, there was no absolute difference in mortality due PC between the groups of treatment, but there was a benefit of 1.4% in watchful waiting. However, in men with high-risk disease, the absolute difference was 8.4% in favor of RP.

The potential bias of the pathologist's report was evaluated, but the impact of surgery on mortality from PC in high-risk group was independent from the information of local or centralized pathologist, but not in the intermediate risk group, where the information varied depending on who was the pathologist who reported the piece.

The surgery did not reduce mortality (either all-cause or disease-specific) of patients with PSA levels less than or equal to 10, and instead showed that RP reduces both overall mortality and cancer-specific in men with PSA ≥ 10 ng / ml.

In order to compare both studies (PIVOT 4 and SPCG-4 7), it should be noted that most patients in the Scandinavian trial were diagnosed by digital rectal examination (palpable tumors) or significant symptoms of lower urinary tract obstruction. On the contrary PIVOT4 trial participants are more representative of men diagnosed and treated in the United States and Europe today, due most of them were diagnosed, only by elevated PSA levels.

This study demonstrates the deleterious effects of overtreatment. Treating 3 men with RP or 7 with radiotherapy rather than active surveillance would result in an additional case of erectile dysfunction, and treatment of about 5 men with RP rather than active surveillance would result in an additional case of urinary incontinence. Neither radiotherapy nor RP was associated with worse outcomes on most measures related to quality of life in general compared with active surveillance, suggesting that the negative effects associated with specific damage can be compensated by positive effects (perhaps related to less concern about untreated PC).

RP was also associated with perioperative mortality (30 days) (about 0.5%) and cardiovascular events (0.6% to 3%), and radiation was associated with intestinal dysfunction (4).

Expert Panel Position on the management of Low Risk PC

An independent panel convened by the National Institute of Health (NIH), has approved the use of active surveillance and thus indicating a delay in treatment for men with low risk localized PC.

The panel defined, for this review, low-risk disease with PSA <10 ng/ml and a Gleason score ≤ 6. According to this definition, it is estimated that over 100,000 men diagnosed with PC each year in the United States would be candidates for active surveillance rather than immediate treatment (1).

The PIVOT study results to be the source of reference for the expert panel's deliberations, since it is the only randomized controlled trial conducted in men only identified through PSA screening, that compare watchful waiting with radical prostatectomy.

According to the report, only 10% of men eligible for observation strategies (low-risk disease) choose this method. Probably the reasons are related to the own diagnosis of "cancer" as a general disease entity and has much to do with the form and content of doctor-patient communication, not analyzed sociocultural factors and patient's expectations (1).

For this reason, the panel also endorsed consideration of a name change to eliminate the term cancer that causes anxiety, to describe this low-risk disease, as was done with cervical intraepithelial neoplasia for the early stages of cervical neoplasia and ductal carcinoma in situ in low risk breast lesions (1).

The panel stressed the importance of patient information and the role of primary care physician, in deciding to order a first PSA to the patient.

The 14-member panel included experts in the fields of prevention and control of cancer, urology, pathology, epidemiology, genetics, transplantation, bioethics, economics, health services research, sociology, shared decision making and communication in the health field (1).

A number of questions remain open and areas where efforts should focus in the coming years to enhance and complement this strategy of active monitoring, among them the following:
- Consensus of who would be the best candidates for watchful observation
- Optimal protocol of watchful observation and possible identification as a function of known variables in the patient
- Enhance and define the best form of communication with the patient to address the issue of watchful observation
- Methods to carry out the decision process with the patient
- Criteria for inclusion / exclusion to opt for a monitoring strategy
- Short-and long-term outcomes of watchful observation

Conclusions

Briefly, the PSA-based screening is associated with the detection of a greater number of prostate cancers, but at the expense of increasing the number of low risk cases. At the same time population screening strategies have not demonstrated after 10 years a significant reduction in the numbers of PC-specific mortality. Also it has been shown that mortality associated with low-risk PC is extremely low, which leads indirectly to a high "over treatment" not without significant side effects in a large group of "over diagnosed" patients. Recent evidence shows that surgical treatment by RP has not been shown to increase survival in low risk patients, but to expose them at risk of significant side effects (sexual dysfunction and urinary incontinence). Active surveillance strategies may become short term, a new approach to many low-risk patients to delay or even prevent in many of them , an over treatment with potential deleterious effects.

Therefore, besides the respectable intellectual debate about the relevance of population screening with PSA and its socio-economic and ethical implications, perhaps the goal of scientific efforts should not focus "on the messenger" but in the message, what to do to a diagnosis of a low-risk PC, with the currently available information.

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