EDITOR'S COMMENT

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Prostate cancer screening with PSA: "Aequanimitas"

Sir William Osler, during his speech at Pennsylvania University in May, 1st, 1989, said: Gentlemen, farewell. Take with you for combat the motto of the wise old roman legislator (Antonio Pio, from Lorium in Etruria): Aequanimitas (1).

In Brazil, prostate cancer is the most frequent malignant tumor in men. In 2012, 60,180 new cases were observed, with a total mortality of 12,778 patients (2).

In the last 20 years, since the clinical introduction of prostate specific antigen screening (PSA), the incidence and mortality of metastatic prostate cancer lowered significantly. Although it not has been proved that the use of PSA was responsible for this lowering, in 1985 localized tumors in USA represented at most 58% of cases in USA; in the last few years, only 4% of patients had an initial presentation of the tumor with metastasis. Moreover, relative survival in five years increased exponentially, from 69% in the 70's to 96-99% in the present, concurrent with the general use of the exam (3-5).

But in May 2012 the United States Preventive Services Task Force (USPSTF) published a report contrary to the use of PSA for screening of prostate cancer. This recommendation received a grade "D", which meant, that, according to the panel committee opinion that was presided by a pediatrician, a family doctor and a geriatrician, existing scientific data demonstrated that there are more damages than benefits with the use of this test (6).

Recently, the American Urological Association (AUA) also published its recommendations about the use of PSA for the early detection of prostate cancer. The panel of urologists recommends the use of PSA every 2 or more years only for men from 55 to 69 years old, after a shared decision between the physician and the patient about the risks and benefits of the test. The paper states that, except for men with risk factors of prostate cancer, the routine use of PSA is not recommended for the remaining age ranges or if life expectancy is lower that 10-15 years (7).

EDITOR'S COMMENT

An ideal screening program must present several criteria:

1. Focus on diseases with impact in public health;
2. Screening of population with long life expectancy;
3. Be able to identify asymptomatic disease in a phase of its natural history liable to curative treatment;
4. Use of diagnostic tests with high specificity and sensitivity;
5. Use of non-invasive diagnostic tests, easy to apply and with low costs;
6. Use of diagnostic tests that do not detect cases with indolent clinical behavior, that lead to unnecessary treatments;
7. The treatment must be capable to modify the natural history of the disease lowering mortality;
8. The treatment must not compromise quality of life.

Since screening of prostate cancer with PSA does not meet all these criteria, it became a polemical topic. Part of controversy is due to the confusion between population screening and early diagnosis. Another part is caused by the problems related with the quality of existing studies and the analysis of the obtained results.

When health care professionals apply PSA exams in a population of asymptomatic patients, they are performing an organized population screening (or mass). This situation is quite different than of a man spontaneously consulting an urologist in his private office in order to realize an exam to verify if he has prostate cancer. In this last situation, the very own candidates are self-selected due to several reasons (familiar history of prostate cancer, partner insistence, friends influence, any urinary symptom) and this characterizes an opportunistic screening. The studied populations are not necessarily identical, since population screening is applied following an active plan, to guest people with an age range pre-defined and with pre-established frequency. In the opportunistic screening the early detection of the disease results from individual interaction and personal initiative of the patient.

Volume 39 | number 4 | July . August , 2013 | INT BRAZ J UROL

The controversy arises when the obtained information with the population screening studies with methodological problems are generalized as guidelines of medical societies in order to guide the opportunistic screening.

There are five studies about population screening of prostate cancer. Two of them are old and were realized in Quebec, Canada, and Norrköping, Sweden, with discordant results (8,9). A review of the Cochrane Library concluded that these two studies presented huge methodological limitations, preventing any proper conclusion (10).

Three other studies presented better evidence level (11-16).

The European study ERSPC [The European Prostate Cancer Screening Trial] randomized a population of 162,243 men between 55 and 69 years old, for screening with PSA (n = 81,816) or control without PSA (n = 99,184). Several medical centers participated, but the protocol was not uniform in all. Most used the value of PSA ≥ 3.0 ng/mL in order to indicate prostatic biopsy. After a median follow-up of 11 years, the screening lowered in 41% the risk of metastasis and in 20% the chance of death due to cancer (confidence levels (CI) of 95%:0.65-0.98 P = 0,004)). Among all patients submitted to biopsy, 76% presented a benign pathology, demonstrating a high level of false positive results. But 1,055 patients had to be screened and 37 were diagnosed with prostate cancer in order to prevent death by the tumor (11,12).

The North American study PLCO (Prostate Cancer Screening Trial) randomized 76,693 men aged 55 to 74 years old for screening using annual PSA and rectal digital exam (n = 38,343) or a group control for "usual urological care", that meant using their urologist criteria (n = 38,350). After 13 years of follow-up, the mortality was similar in both groups (p = not significant) (13,14). The used value of PSA that indicated biopsy was 4.0 ng/mL. The problem of this study was the control group. In the USA the "usual care" includes PSA exam, and half of the control patients were submitted to PSA compared to 85% of the randomized group. So it would not be unexpected that there was no difference between the groups. In fact, this study represents a better comparative analysis of two types of PSA screening, one more intense than the other.

Volume 39 | number 4 | July . August , 2013 | INT BRAZ J UROL

The better study, from Goteborg, Sweden, 20,000 men were randomized 1:1 for PSA screening every two years or control without PSA. Age ranged from 50 to 64 years (median = 56 years). The used PSA level for biopsy was between 3.0 to 4.0 ng/mL. After a period of follow-up of 14 years, 12.7% of patients of the screened group had a diagnosis of prostate cancer, and 8.2% of the patients of control group. There was a lowering of mortality due to prostate cancer of 40% (CI 95%: 0.17-0.64; absolute lowering of 0.9% in control group versus 0.5% in screened group). In that study, 293 patients had to be screened and 12 had a diagnosis of prostate cancer in order to lower the death by the tumor (15,16). These numbers are similar to those of breast cancer screening.

The current guidelines are based on meta-analysis (MA) of the studies that determined that there are no benefits of the screening (17-19). However, there are several factors involved in a good MA, mainly the quality of the included studies. Those of the current have important methodological problems and analyzed very heterogeneous populations. Also, a higher statistical power was given to the PCLO study than to the Sweden study, and the explanation was that 60% of the European study ERSPC included men from Goteborg.

One of the main problems with prostate cancer screening is the hyperdetection of tumor or over-diagnosis, an excess of diagnosis of clinical tumors with low significance. In the ERSPEC study, the occurrence of low risk tumors (PSA < 10 ng/mL and Gleason score ≤ 6) was almost three times higher in the screened group than in control group (11,12).

Those who criticize the use of PSA state that the only randomized study that compared radical prostatectomy versus observation in the era of PSA (PIVOT study) showed that there was no benefit of the radical surgery for the patients with low risk tumor, the majority of selected patients of screening programs [HR:1.15; CI 95%: 0.80-1.66; absolute difference after 12 years in favor of observation: 5.4% (37.2% vs. 31.8%; p=not significant)]. (20).

Moreover, the indication of prostatic biopsy according to the level of PSA has been modified over the years and contributed to the diagnosis of more low risk tumor patients (21). The analysis and interpretation of the cur-

Volume 39 | number 4 | July . August , 2013 | INT BRAZ J UROL

rent data is more complex since, besides the hyper-detection, we include the bias of time of anticipation and stage migration on the analysis of the results, artificially modifying the survival statistics.

On the other hand, there was a real lowering of the percentage of metastatic prostate cancer and the cancer-specific mortality in the last decades, coinciding with the introduction of the clinical use of PSA without any other convincing explanations (22). And the definitions that we use to classify prostate cancer came from old pathological parameters described using optical microscopy. Since until now we do not have molecular criteria to predict individual response, the interpretation of the biological behavior or "low risk or insignificant" tumors is unsafe. Opposing to the current restrictive recommendations of the use of PSA, Vickers et al. demonstrated that the level of PSA around 45 years old in patients without risk factors can provide data regarding the chance of developing more aggressive prostate cancer and death due to the tumor. Among 21,277 men from Malmo, Sweden, the authors concluded that 44% of death due to prostate cancer occurred when the PSA level was above the 10th percentile. The limit values of PSA according to age were: 45-49 years: ≥ 1.6 ng/mL; 51-55 years: ≥ 2.4 ng/mL. Men with PSA levels above these established limits present a three-time fold increase of metastatic prostate cancer in 15 years than other men and needed a more intense follow-up. To the others, more than half of the men, they suggested that three measures of PSA around 45 years old, in the beginning of the fifties and around 60 years old may be sufficient (23).

It is obvious that we need to judiciously evaluate these new proposals. Instead of accept as absolute the societies decisions, I think that we must develop our own guidelines, based on modern concepts and on the experience with our population, in order to adapt them to our reality.

For the early diagnosis of prostate cancer, as it was known by our Portuguese ancestors a long time ago, and long before Osler - not so much to the sea, not so much to the ground.

Volume 39 | number 4 | July . August , 2013 | INT BRAZ J UROL

REFERENCES

1. Osler W: Aequanimitas e outras alocuções dirigidas a estudantes de medicina, enfermeiras e àqueles que exercem a profissão médica. The Blakiston Company: Philadelphia. 3a edição. 1932; pp. 3-11.
2. Estimativa 2012 Incidência de Câncer no Brasil. Available at www.inca.gov.br/estimativa/2012/tabelaestados.asp?UF=BR.
3. Welch HG, Albertsen PC: Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. J Natl Cancer Inst. 2009; 101: 1325-9.
4. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al.: Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. Lancet Oncol. 2008; 9: 445-52.
5. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013.
6. Moyer VA; U.S. Preventive Services Task Force: Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 157: 120-34.
7. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al.: Early Detection of Prostate Cancer: AUA Guideline. J Urol. 2013; 190: 419-26.
8. Labrie F, Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, et al.: Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. Prostate. 1999; 38: 83-91.
9. Sandblom G, Varenhorst E, Löfman O, Rosell J, Carlsson P: Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol. 2004; 46: 717-23; discussion 724.
10. Ilic D, O'Connor D, Green S, Wilt T: Screening for prostate cancer: a Cochrane systematic review. Cancer Causes Control. 2007; 18: 279-85.
11. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al.: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360: 1320-8.
12. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V,et al.: Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012; 366: 981-90. Erratum in: N Engl J Med. 2012; 366: 2137.
13. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al.: Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009; 3600: 1310-9. Erratum in: N Engl J Med. 2009; 360: 1797.
14. Pinsky PF, Black A, Parnes HL, Grubb R, David Crawford E, Miller A, et al.: Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol. 2012; 36: e401-6.
15. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al.: Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010; 11: 725-32.
16. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J: Incidence of Prostate Cancer After Termination of Screening in a Population-based Randomised Screening Trial. Eur Urol. 2013; In Press.

Volume 39 | number 4 | July . August , 2013 | INT BRAZ J UROL

17. Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B,et al.: Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ. 2010; 341: c4543.
18. Roobol MJ, Carlsson S, Hugosson J: Meta-analysis finds screening for prostate cancer with PSA does not reduce prostate cancer-related or all-cause mortality but results likely due to heterogeneity - the two highest quality studies identified do find prostate cancer-related mortality reductions. Evid Based Med. 2011; 16: 20-1.
19. Ilic D, Neuberger MM, Djulbegovic M, Dahm P: Screening for prostate cancer. Cochrane Database Syst Rev. 2013; 1: CD004720.
20. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al.: Radical prostatectomy versus observation for localized prostate cancer.N Engl J Med. 2012; 367: 203-13. Erratum in: N Engl J Med. 2012; 367: 582.
21. Shekarriz B, Upadhyay J, Bianco FJ Jr, Tefilli MV, Tiguert R, Gheiler EL, et al.: Impact of preoperative serum PSA level from 0 to 10 ng/mL on pathological findings and disease-free survival after radicalprostatectomy. Prostate. 2001; 48: 136-43.
22. Ablin RJ: The United States Preventive Services Task Force recommendation against prostate-specific antigen screening--point. Cancer Epidemiol Biomarkers Prev. 2012; 21: 391-4.
23. Vickers AJ, Ulmert D, Sjoberg DD, Bennette CJ, Björk T, Gerdtsson A, et al.: Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term riskof metastasis: case-control study. BMJ. 2013; 346: f2023.

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