Age-adjusted PSA-density cut off values. Can the underdiagnosis and overdiagnosis of prostate cancer (PCa) and negative prostate biopsies be reduced at no cost?

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Abstract

Introduction - Purpose: Investigation of the usefulness of age-adjusted PSA-density cut off values for performing prostate biopsies. Focus on reducing the number of biopsies and the improvement of the overdiagnosis/underdiagnosis ratio of low-risk PCa.

Material & Method: In a series of 560 consecutive patients with transrectal ultrasound (TRUS) guided biopsy, we performed a series of calculations with different PSAD cut off values and the age-adjusted PSAD cut off values proposed by the authors (PSAD ≥ 0.10 for age ≤ 69, PSAD ≥ 0.15 for age 70-75 and PSAD ≥ 0.20 for age ≥ 76).

Results: The overall diagnosis of PCa reached 41.6%. PCa was found in 10.13%, 23.48%, 53.33%, 73.16%, and a Gleason pattern of 4 or 5 was found in 6.6%, 6.46%, 20.83% and 53.24%, for PSAD values of < 0.1, ≥ 0.1 - <0.15, ≥0.15 - <0.20 and ≥ 0.20 respectively. The reduction of TRUS biopsies was calculated at 37.32% for the age-adjusted values (PSAD≥ 0.10 for age ≤ 69, PSAD ≥ 0.15 for age 70-75 and PSAD ≥ 0.20 for age ≥ 76) and at 26.42%, 50.00%, 66.07%, for PSAD cut off values of 0.1, 0.15 and 0.20 respectively. The estimated negative biopsies that could have been avoided per one non-diagnosis of low-risk PCa in men ≤ 69 years was 16 for age-adjusted values, 12.1, 8.35 and 5.75 for PSAD cut off values of 0.10, 0.15 and 0.20 respectively. The ratio of non-diagnosis of low-risk PCa under 70 years to the non-diagnosis of low-risk PCa over 75 years was 1.1 for age-adjusted values and 5.5, 6.67, 7.0, 5.6 and 4.8 for PSAD cut off values of 0.1, 0.12, 0.14, 0.15 and 0.2 respectively.

Conclusion: According to our analysis, we recommend age-adjusted PSAD cut off values. In this way, we can greatly reduce negative TRUS biopsies, the related complications and the subsequent cost of overtreatment, with only a minimal loss of low-risk PCa diagnosis, in groups with theoretically treatable disease.
Introduction
The extremely costly prostate imaging and molecular biology tests are constantly under investigation, aiming firstly to reduce overdiagnosis and overtreatment of low-risk, clinically insignificant prostate cancer in the elderly, and, secondly, to increase the early diagnosis of non-metastatic, clinically significant and localised prostate cancer in young men with a long life expectancy and potentially treatable disease. The inexpensive, extremely fast and adverse effect-free calculation of prostate specific antigen density (PSAD = PSA/Transrectal prostate size), seems lately to have been forgotten, both in literature and in everyday clinical practice, at least with regard to the selection criteria of men with an indication for performing prostate biopsy.

Material-Method
Retrospectively, in a series of consecutive patients who had undergone grey scale TRUS prostate biopsy, the diagnosis rates of PCa and the presence of a Gleason pattern of 4 or 5 were analysed based on PSAD values. We then calculated the total reduction rate in the number of biopsies and negative biopsies if various proposed published PSAD cut off values for carrying out prostate biopsies or the age-adjusted PSAD cut off values proposed by the authors (≥ 0.10 for age ≤ 69, ≥0.15 for age 70-75 and ≥0.20 for age ≥76 years) were applied. Indeed, we calculated the number of low-risk prostate cancers whose diagnosis would be missed using the proposed age-adjusted values, as well as the age distribution of these undiagnosed low-risk PCAs. We used the D’Amigo criteria for the definition of low-risk prostate cancer.

Results
The study involved 560 patients with a mean age of 67.91 (sd:8.65) years. The mean values of PSA and of the transrectally measured prostate tumour were estimated at 29.9 (sd:197.4) ng/dl and 58.02 cm3 (sd:32.84), respectively. Prostate size (Vpro) was statistically significantly reduced in men diagnosed with PCa (43.08 cm³ sd:18.04 TRUS positive vs. 68.68 cm³ sd:36.6 TRUS negative, p<0.0001). The positive prostate biopsy rates, using the criterion of its size, ranged from 71.4% for Vpro <20 cm³ to 9.9% for Vpro ≥ 80cm³ in all patients and from 66.6% for Vpro < 20 cm³ to 7.8% for Vpro ≥ 80cm³ among patients with PSA ≤ 10 ngr/dl (figure 1).

In patients with PSA ≤ 10 ngr/dl, the PCa diagnosis rate was estimated at 34.45% (n=133/386), while the diagnosis of PCa in all patients reached 41.6% (n=233/560), with a Gleason score of 6 (GS=3+3=6) in 62.7% (n=146/233) of all cancers (figure 2). The differences in the diagnosis of PCa between men aged <70 years and >75 years are presented in figure 3.

The reduction of TRUS biopsies was calculated at 37.32% if we applied the age-adjusted values (PSAD≥ 0.10 for age ≤ 69, PSAD ≥ 0.15 for age 70-75 and PSAD ≥ 0.20 for age ≥ 76) and at 26.42%, 50.00%, 66.07%, for PSAD cut off values of 0.1, 0.15 and 0.20 respectively. The reduction of negative TRUS biopsies was calculated at 53.82% for the age-adjusted values and at 40.67%, 71.56% and 84.4% for PSAD cut off values of 0.1, 0.15 and 0.20 respectively. The percentile non-diagnosis of prostate cancer (missed PCa) and low-risk prostate cancer (missed low risk PCa), by strictly applying different PSAD cut off values and its proposed age-adjusted values are shown in figure 4.

The individual non-diagnosis of low-risk PCa by age group and by different PSAD cut off values are shown in figure 5. Using PSAD cut off values of 0.15 and 0.20, 44.4% and 76.19% of low-risk PCa would be missed in men <70 years, while with the proposed age-adjusted values and a PSAD cut off of = 0.10, only 17.46% would be missed. However, using the proposed age-adjusted PSAD values would simultaneously miss low-risk PCa diagnosis in 71.43% of men ≥ 76 years, vs. only 14.28% respectively for a PSAD cut off of = 0.10.

The relative ratio between the non-diagnosis of low-risk PCa in men <70 years (“undesirable” missed low risk PCa ≤ 69 years) and the non-diagnosis of low-risk PCa in men > 75 years (“desirable” missed low risk PCa ≥76 years) for the proposed age-adjusted PSAD values and several other proposed PSAD cut off values (0.10, 0.12, 0.14, 0.15 and 0.20) are shown in figure 6.

The ratio of negative biopsies that could have been avoided at the cost of one non-diagnosis of low-risk PCa only in men ≤ 69 years (avoided negative biopsies/one missed low risk PCa ≤ 69 years) was estimat-
ed at 16 for the age-adjusted values and at 12.1, 8.35 and 5.75 for PSAD cut off values of 0.10, 0.15 and 0.20 respectively. (figure 7)

Discussion
Both in the study patients as a whole and by PSA-based subgroups, the diagnosis of PCa seems to agree with the results of other authors regarding the contribution of transrectal ultrasound-guided systematic prostate biopsies in the diagnosis of PCa. (Table 1)

In an interesting study by Verma A et al., with 521 patients, comparing total PSA, digital rectal examination of the prostate (DRE) and the free to total PSA ratio (f/t PSA), only the f/t PSA ratio was found to be a strong prognostic factor for a positive prostate biopsy. In the subsequent comparison between the f/t PSA
ratio and PSA density (PSAD), only PSAD was found to be a strong prognostic factor for PCa diagnosis. Indeed, PSAD was also a strong prognostic factor for disease aggressiveness\(^1\). In this study also, the probability of PCa diagnosis increases linearly with the increase in PSAD values. Simultaneously, a Gleason pattern of 4 or 5 was found in 6.6%, 6.46%, 20.83% and 53.24% with PSAD values of <0.1, ≤0.1 - <0.15, ≤0.15 - <0.20 and ≥0.20 respectively. In recent years, PSA density appears to play a constant and central role in the selection criteria of patients with an indication for active surveillance\(^2,3,4,5\) and the final upstaging of patients with a primary Gleason sum = 6 during transrectal prostate biopsy (TRUS Biopsy GS = 3+3), always compared with the final histopathological diagnosis after delayed radical prostatectomy\(^4\). Furthermore, in
accordance with G Agarwal et al., only a PSADensity cut off value of ≥ 0.15 was found to be significantly correlated with the future upstaging of patients with PCa and active surveillance. However, no statistically significant difference was found in the metastasis-free interval and overall survival between those who were finally treated and those who remained in active surveillance. Indeed, according to Agarwal G et al., this did not change even when comparing patients ≥70 years to patients <70 years. According to Cristea O et al., in patients with low-risk PCa, a positive DRE and PSAD of ≥0.20 advocate for immediate treatment, while an age of >70 years for active surveillance. Therefore, a great moral question has recently emerged: Why submit a man older than 70 years to a prostate biopsy with PSA ≤ 10 ng/ml, with a nega-
tive DRE and PSAD <0.15 if I then just propose that I monitor him?

The present age classification of men into groups of <70 years, 70-75 years and >75 years was conducted partly on conventional terms. We took into account however that the average life expectancy at birth for Greek men is 78.6 years (European Health Report of the World Health Organization, 2013). We also took into consideration that since 1994 there is evidence that the ten-year cancer specific survival in clinically localised low-risk PCa, without any radical treatment but only delayed androgen deprivation, reaches 87%7. Indeed, since 2012 we know that overall survival and specific 12-year prostate cancer survival do not improve by radical prostatectomy over simple surveillance in patients with low-risk localised PCa and PSA ≤ 10 ng/dl8. Therefore, of the patients with low-risk PCa and age ≥ 75 years, the vast majority will largely exceed the average expected survival without diagnosis and, mainly, without treatment for prostate cancer. Additionally, overtreatment provenly leads to a deterioration of quality of life9 and increased cost10, without any significant effect on overall survival, especially amongst very old men. However, this does not seem to be the case for young adults, even with low-risk prostate cancer. According to Godtman RA et al., it remains doubtful whether young men with a long life expectancy, even with low-risk PCa, have an indication for active surveillance11. Therefore, the diagnosis even of low-risk clinically localised PCa with a possibility of radical treatment should be the target for young adults aged <70 years, who by definition have a life expectancy of at least 15-20 years.

According to the results of this study, it appears that the reduction in the number of negative biopsies, missing low-risk PCa diagnosis in the elderly, with a minimum under-diagnosis of low-risk PCa in young men, is more effectively approached using the age-adjusted PSAD cut off values as an indication for biopsy. By definition, the lower the PSAD value we use in daily practice and the less weighted it is based on age, the more biopsies in all age groups will need to be conducted while low-risk PCa diagnosis will disproportionately increase in elderly patients, with high rates of over-diagnosis and overtreatment.

According to the results of our analysis (figure 6), it is evident that in the attempt to avoid Overdiagnosis of low-risk PCa in elderly patients, as expressed by the non-diagnosis of low-risk PCa in ages >75, at the lowest possible cost of Underdiagnosis, as expressed by the...
non-diagnosis of low-risk PCa in ages <70 with potentially treatable disease, the age-adjusted PSAD cut off values proposed by the authors achieve the most advantageous ratio. While for example with a PSAD cut off value of = 0.15 for each elderly aged > 75 where we avoid overdiagnosis of low-risk PCa we miss 5.6 patients aged <70 years with low-risk PCa, with the age-adjusted PSAD values we propose, we only miss 1.1 patients.

A limitation of the study concerns the retrospective nature of the data analysis and the lack of the prospective application of any generally accepted PSAD cut off value by all who conduct prostate biopsies in clinical practice. However, the data analysis shows that, in everyday clinical practice, the indication for a prostate biopsy in older men follows stricter criteria than for younger patients, even if only empirically. This justifies the difference in the overall diagnosis of PCa but also of low-risk PCa between men <70 and >75 years and in the mean PSA value (after exclusion of patients with PSA >100ng/dl), among men <70 years (mean PSA = 10.43, sd:12.58) and men >75 years (mean PSA = 17.05, sd: 23.04, p <005) of the study.

**Conclusion**

According to our analysis, we propose that the PSAD cut off values for prostate biopsy indications be age-adjusted. In this way, we can greatly reduce negative TRUS biopsies, the related complications and the subsequent cost of overtreatment, with only a minimal loss of low-risk PCa diagnosis, in groups with theoretically treatable disease.

**Conflicts of interest**

The authors declared no conflicts of interest.
Σκοπός: Ο σκοπός είναι η δίχως κόστος ελάττωση του ολικού αριθμού των βιοψιών του προστάτη, η ελάττωση των αρνητικών βιοψιών αλλά και η ελάττωση της διάγνωσης χαμηλού κινδύνου καρκίνου σε υπερήλικες (υπερθεραπεία) με την μικρότερη δυνατή υποδιάγνωση χαμηλού κινδύνου καρκίνου σε νεαρούς ενήλικες με δυνητικά θεραπεύσιμη νόσο.

Μέθοδος: Σε μια σειρά διαδοχικών ασθενών με διορθικά καθοδηγούμενη βιοψία του προστάτη (TRUS), πραγματοποιήσαμε μια σειρά από υπολογισμούς με διαφορετικές ελάχιστες τιμές PSAD αλλά και των προτεινόμενων ηλικιακά προσαρμοσμένων τιμών PSAD (≥ 0,10 για ηλικία ≤ 69, ≥ 0,15 για 70-75 και ≥0,20 για ≥ 76 ετών).

Αποτελέσματα: Η μείωση των TRUS βιοψιών υπολογίστηκε στο 37,32% για τις ηλικιακά προσαρμοσμένες τιμές του PSAD και στο 26,42%, 50,00%, 66,07% για ελάχιστες τιμές PSAD 0,1, 0,15 και 0,20 αντίστοιχα. Οι υπολογιζόμενες αρνητικές βιοψίες που θα μπορούσαν να έχουν αποφευχθεί ανά μια μη διάγνωση χαμηλού κινδύνου CaP σε άντρες ≤ 69 ετών, ήταν 16 για τις ηλικιακά προσαρμοσμένες τιμές, 12,1, 8,35 και 5,75 για ελάχιστες τιμές PSAD 0,10, 0,15 και 0,20 αντίστοιχα.

Συμπέρασμα: Προτείνουμε ελάχιστες τιμές PSAD ηλικιακά προσαρμοσμένες με σκοπό την μείωση των αρνητικών βιοψιών, των επιπλοκών, αλλά και του κόστους της υπερθεραπείας σε υπερήλικες με μόνο μια ελάχιστη απώλεια του χαμηλού κινδύνου PCa, στις ηλικίες με θεωρητικά θεωρητικά θεραπεύσιμη νόσο.

References

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