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Comparison of three guidelines for screening, diagnosis and staging of prostate cancer in the USA and Europe

Abstract

Background: Prostate cancer is the most frequent malignancy for males. The recommendations of guidelines for screening and diagnosis play an important role in the clinical practice of many urologists. However, there are several discrepancies between these guidelines that have not been evaluated.

Methods: The European Association of Urology (Europe), the National Comprehensive Cancer Network (USA), and the American Urological Association (USA) guidelines were examined analyzing the agreements and discrepancies between each guideline.

Results: There are many agreements and discrepancies between each guideline, namely: 1) Age for the initiation of PSA screening, including patients at high risk: discrepancies 2) Age to stop screening: discrepancies 3) Evaluation of germline risk variants in patients at high risk, especially BCRA2 mutation: discrepancies 4) Additional tests to avoid unnecessary biopsies: agreement. 5) Indication to perform a first prostate biopsy: discrepancies. 6) Systematic biopsy cannot be ignored in the first biopsy: agreement. 7) From a negative biopsy it is necessary to perform an mpMRI to increase the detection of lesions: agreement 8) Risk stratification: discrepancies. 9) Clinical stratification: discrepancies.

Conclusion: A unanimity of criteria is necessary in the three guidelines. Nevertheless, each guide must also take into account certain social and economic situations. Our proposal is the establishment of common minimum criteria that must be met in the diagnostic process for all affected men in our societies.

Keywords: prostate cancer, guideline, comparison, diagnosis, screening, staging

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Background

Currently, prostate cancer (PCa) is the second most prevalent neoplasm in the male population worldwide, with an estimated incidence of 1,414,259 new cases and a mortality of 375,304 patients in 2018.[1] According to the data from the National Health Institute, in the United States of America, the number of new PCa cases was 109.5 per 100,000 men per year and mortality was 19.2 per 100,000 men per year (rates are adjusted for age 2012-2016). It is estimated that in 2017 there were 3,170,339 men living with PCa in the United States.[2] In Europe, the incidence is 214 cases per 100,000 men, exceeding that of lung or colorectal tumors.[3] To help professionals in their management, the PCa clinical guidelines are developed based on evidence in the published literature and are created by experts in each field, considering the reality and clinical conditions in each region and/or country in order to standardize medical care. This allows observing discrepancies between clinical guidelines according to the regions where they are implemented. The aim of this study was to compare these guidelines for the diagnosis and staging of PCa from the European Association of Urology (EAU, Europe), the National Comprehensive Cancer Network (NCCN, USA), and the American Urological Association (AUA, USA.), highlighting and analyzing both the agreements and discrepancies between each.

Methods

The guidelines included were: EAU Guidelines on Prostate Cancer 2020 imply recommendations for the European Association for Nuclear Medicine (EANM),[4] the European Society for Radiotherapy and Oncology (ESTRO), the European Society for Urogenital Oncology (ESUR) and the International Society of Geriatric Oncology (SIOG); from the NCCN Guidelines on Prostate Cancer V3.2020,[5] NCCN Guidelines for the Early Detection of Prostate Cancer 2.2020,[6] AUA Guidelines, Clinically Localized Prostate Cancer: AUA/American Society for Radiation Oncology (ASTRO)/Society for Urologic Oncology (SUO) Guidelines,[7] early detection of prostate cancer: AUA 2019.[8] The guides were accessed on the organizations' websites. The outcome measures were the agreements and discrepancies between the guidelines for each specific topic of diagnosis and staging in prostate cancer, and the results are presented in the different sections.

Results

The analysis shows considerable agreement between the different clinical guidelines, but we will also observe disagreements between the different chapters: screening, prostate biopsy, risk stratification, and clinical staging.

Screening

The EAU guide does not recommend population screening, but rather an individualized strategy based on risk, with information on the pros and cons of diagnosis and possible treatment: a) PSA determination in men over 50 years of age, b) PSA determination in men over 45 years of age if they are African descent or have a family history of prostate cancer, c) PSA determination in men over 40 years of age if they are BRCA2 carriers. It also proposes follow-up with

determination of a new PSA every two years in patients younger than 40 years with a PSA>1 ng/mL or those younger than 60 years with PSA>2 ng/mL, or postpone to 8 years if they are not within this at-risk group, advising to interrupt the early diagnosis program in patients according to their general condition and/or life expectancy <15 years.[4] The NCCN guidelines also advocate an individualized approach rather than a population-based one, and recommend initiating screening of patients older than 45 years of age who are well informed about the risks and benefits. They suggest to repeat PSA every 2-4 years in patients with PSA <1ng/mL or every 1-2 years if the PSA is between 1 and 3 ng/mL. They also propose to discontinue follow-up in men >60 years with PSA <1ng/mL or >75 years with PSA <3 ng/mL. In the case of African-American men or patients with a BRCA 1 or 2 mutation, they recommend follow-up from the age of 40 years with annual PSA.[6] The AUA recommends to not perform routine PSA in patients younger than 40 years of age, older than 70 years of age, or with a life expectancy of less than 10-15 years. For the rest of the age groups, it advises making shared decisions with adequate information on risks and benefits before the patient undergoes a PSA determination. They suggest a new PSA every 2 years, this interval being individualizable based on the patient's risk.[8] They support urging these patients to interrupt prostate cancer screening when they have a PSA below 4 ng/mL, due to the low possibility of cancer-specific mortality rate (1%) (Table 1).

Table 1

Guideline	EAU	NCCN	AUA
Age of onset	> 50 years > 45 years if African descent > 45 years with a family history. > 40 years with BCRA2 +	> 45 years > 40 years in African Americans or BRCA1/BRCA2 +	> 55 years > 40 years in high-risk patients
Screening timing	PSA >1 ng/mL in <40 years or PSA >2 ng/mL in <60 years: Apply for PSA every 2 years PSA <1 ng/mL in <40 years or PSA <2 ng/mL in <60 years: Apply for PSA every 8 years	General population: - PSA <1ng/mL every 2-4 years - PSA 1-3 ng/mL every 1-2 years African American or BRCA1/BRCA2 +: every 1 year	Request PSA every 2 years depending on the outcome
Screening interruption	Interrupt if life expectancy <15 years	Interrupt in >60 years with PSA <1ng/mL or >75 years with PSA <3 ng/mL	Interrupt if life expectancy <10-15 years or >70 years with PSA <4 ng/mL

Evaluation of germline risk variants

For the correct performance of prostate cancer screening, it is necessary to know the genetic load of our patients. For this reason, the latest update of the 2020 EAU guideline recognizes the strong relationship between the mutation in the BRCA2 gene and the presence of metastatic or early-onset prostate cancer.[9] Patients at risk for BCRA2 mutation are people with multiple breast cancers in the family, two or more primary types of BRCA2-related cancers in a single family member, male breast cancer, and Ashkenazi Jews. The AUA guide recommends genetic counseling (genetic testing for BRCA2) to families with high-risk localized prostate cancer and a family history of specific cancers (breast, ovarian, pancreas, gastrointestinal tumors, and lymphomas).[9] The NCCN guidelines recognize the association of prostate cancer with the hereditary syndrome of breast and ovarian cancer (secondary to germline mutations of DNA repair genes) and Lynch syndrome, in approximately 11% of patients.[10-12] For the determination of germline gene mutations, the following genes must be studied: MLH1, MSH2, MSH6, and PMS2, as well as the homologous recombination genes BRCA2, BRCA1, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2. Therefore, in patients with pathological anatomy of intraductal carcinoma, they suggest extending the genetic study with: BRCA1, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2. A summary of this section is presented in Table 2.

Table 2

Guideline	EAU	NCCN	AUA
BRCA2 application in patients at risk of mutation	+	+	+
High-risk, very high-risk prostate cancer; localized or metastatic prostate cancer	-	+	+
Prostate cancer with intraductal histology	-	+	-

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Additional determinations

These tests can be in serum by detecting kallikreins (PHI and 4K score), in urine with detection of substances such as PCA3, TMPRSS2-ERG, and exosomes secreted by prostate tumor cells (Progensa, MiPS , ExoDx, and SelectMDX), and finally by tissue analysis (ConfirmMDX). The three guides comment that they help us increase the specificity of PSA, however with certain nuances depending on the determinations. The AUA does not assess any of these tests; on the contrary, the NCCN and the EAU highlight the following markers (although the EAU recommends them with a weak degree). See Table 3.

Table 3

	EAU	NCCN	AUA
Progensa (FDA approved)	Determine whether to repeat a biopsy after a previous negative biopsy. It is not cost-effective.	Approved to decide whether to repeat biopsy in patients >50 years of age with >1 negative biopsy.	They do not issue a recommendation. Helps with the decision of new biopsies.
SelectMDX	Estimate the risk of high-risk prostate cancer. It is not cost-effective.	Experimental Use	
MiPS	Experimental use	Experimental use	
ExoDx	Experimental use	Alternative to prostate biopsy (1st or subsequent)	
4K	Determine whether to repeat biopsy after a negative previous biopsy.	Alternative to prostate biopsy (1st or subsequent). But it has no exact cut-off point.	
PHI (Aprobado por FDA)	Determine whether to repeat a biopsy after a previous negative biopsy. It is not cost-effective.	Alternative to prostate biopsy (1st or subsequent)	
ConfirmMDX	Not recommended for routine use.	Determine whether to repeat a biopsy after a previous negative biopsy.	

- **PHI test:** It combines free and total PSA with a PSA isoform called proPSA (p2PSA).[13] It correlates with the grade of the tumor. Several studies have shown that this method is twice as sensitive as the percentage of free PSA in detecting prostate cancer in patients with PSA between 2 and 10 ng/ml.[14] Other studies show that it can predict aggressiveness, and therefore be useful in clinical examination.[15] The NCCN approves its use in patients with PSA 4-10ng/ml.
- **4K:** It combines the determination of free, intact and total PSA, together with kallikrein-like peptidase 2 (hK2), in addition to age, digital rectal examination, and biopsy. The NCCN proposes it for patients prior to a first or subsequent biopsy, with a high risk of PCa, despite not having an optimal cut-off point. The European guideline does not clearly pronounce any of these determinations, even though some multicenter studies have shown that both PHI and 4K exceed the ratio between free/total PSA, achieving clinically significant detection in men with PSA between 2-10 ng.[16] Neither has proven to be superior to the other.[17]
- **Progensa test:** It is based on the detection of PCA3 in urine. For EAU, the indication of the test is to determine if a biopsy should be repeated after a negative result, but its clinical efficacy for early diagnosis remains uncertain.[18] The NCCN has approved it to decide when repeating a biopsy would be advisable in which patients older than 50 years with >1 negative biopsy.
- **MiPS:** It combines the detection of TMPRSS2-ERG in urine, together with PCA3 and serum PSA, resulting in an improvement in the detection of prostate cancer.[19] In this regard, both the NCCN and the EAU coincide and consider it exclusively experimental.
- **ExoDx prostate:** it is based on the detection of PCA3 and ERG in exosomes of prostate cells in urine. It reduces the number of unnecessary biopsies by 27% compared to current procedures. While the EUA considers it, at least for the moment, an experimental method, the NCCN considers it an option in patients in whom it is planned to perform a prostate biopsy, either first or successive.
- **SelectMDx:** it is based on the isolation of microRNA in urine, in this case HOXC6 and DLX1. The presence of microRNA provides an estimate of the risk of finding prostate cancer in the biopsy, as well as the presence of high-risk cancer in a re-biopsy.[20] The NCCN considers it an exclusively experimental method at the moment. The EAU does not establish a firm position on the matter, but includes it as a technique.
- **ConfirmMDx:** It starts from the concept that benign tissue near a cancer focus shows epigenetic alterations and quantifies the level of methylation of promoter regions of three genes in benign prostate tissue (GSTP1, APC and RASF1). A multicenter study found an NPV of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men.[21] The NCCN approves it to decide whether to repeat a biopsy, in contrast to the EAU, which does not recommend it, and advocates the use of mpMRI.

Indication to perform a first prostate biopsy

The EAU guidelines recommend performing a prostate biopsy in the event of abnormalities in PSA (2-10 ng/mL), digital rectal examination, and/or imaging tests such as mpMRI and risk calculators. The patient's age, comorbidities, and the consequences of possible therapies should also be considered and discussed before indicating

a biopsy.[22] Limited and isolated elevation of PSA should not be an indication for immediate biopsy. The need to perform a seminal gland biopsy is not well defined by the authors of the European guidelines, although they recognize that with a PSA >15ng/dl, the risk of tumor invasion is 20-25%.[23] The NCCN guidelines recommend that after analyzing the clinical history and risk factors, patients should be managed based on their age and PSA value. Patients who are under screening have to be classified according to their age:

Between 45 and 75 years of age and a PSA greater than 3ng/dL, the following should be done: repeat the PSA at 6-12 months, digital rectal examination, assess for possible BPH, and use specific markers.

Over 75 years of age, we must assess their life expectancy and determine PSA only in healthy patients and in those without previous PSA. The PSA value for performing a biopsy in these patients would rise to 4ng/dL. A biopsy by rectal examination will be indicated only when it is very suspicious.

The AUA guideline does not establish a cut-off point for PSA. Still, it acknowledges that in the intervention group of the ERSPC trial, performing a biopsy in patients with a PSA above 3ng/ml was associated with a reduction in prostate cancer mortality in men from 55 to 69 years of age compared to the control group (not screened).[24,25] However, the AUA consensus believes that the urologist should consider all the factors that lead to an increase in PSA, being able to postpone the biopsy according to the volume of the prostate, age, and inflammation. All of this allows us to delay the biopsy, with PSA levels above 3-4 ng/ml being acceptable. We must bear in mind that the PSA is not a dichotomous test, but a dynamic test that indicates the risk of aggressive cancer. On the other hand, the AUA guidelines conclude that the use of calculators has not shown to be helpful in predicting the risk of prostate cancer. In patients who wish to be evaluated beyond 70 years of age, the risk/benefit must be more carefully assessed. It is recommended to increase the cut-off threshold to perform a prostate biopsy to a PSA> 10 ng/ml. This decision is based on data from the PIVOT study. With a mean age of 67 years at diagnosis, the patients who obtained an increase in survival from all causes, after treatment compared to observation, were those with a PSA greater than 10 ng/dl.[26] A summary is seen in Table 4.

Table 4

Guideline	EAU	NCCN	AUA
Middle-aged patients	- PSA 2-10 ng/dl *, in conjunction with calculators/MRI	Between 45 - 75 years of age:	> 40 years of age:
	- PSA >10 ng/dl	- PSA >3 ng/dl, repeat it in 6-12 months, with prostate volumetric study	- Assess each case individually, it is not a dichotomous variable
	* Confirmation: 2 determinations separated by weeks		(PSA >3 ng/dL)
		> 40 years of age in African Americans or BRCA 1/2 positive:	
		- PSA >3 ng/dl	
Elderly patients	No specification	> 75 years of age with PSA >4 ng/mL, assessing life expectancy and comorbidity	> 70 years PSA >10 ng/dL, assessing life expectancy and comorbidity

Use of mpMRI in the management of prostate cancer

The three guidelines analyze the results of the main studies carried out in recent years on the usefulness of Multiparametric Magnetic Resonance (mpMRI) for the detection of prostate cancer: MRI-FIRST, PRECISION, and 4M.[27-29] The three studies conclude that MRI increases the amount of clinically significant cancer (ISUP> 2), posing a useful tool to perform prior to the first biopsy and thus to avoid unnecessary biopsies in low-risk patients (Table 5).

Table 5

	EAU	NCCN	AUA
	++	+/-	+
MRI ¨naive¨ patients	Strong recommendation justified by meta-analysis	Recommendation only in experienced centers. Cost-effectiveness not valued	Weak recommendation, it increases clinically significant prostate cancer diagnosis
MRI in second biopsies	Strong recommendation justified by prospective studies	Strong recommendation justified by prospective studies	Strong recommendation justified by prospective studies
Systematic and/or cognitive biopsy/ fusion	"Naive": perform both	"Naive": perform both	"Naive": perform both
	Second: it can only be done as cognitive/ software fusion.	Second: it can only be done as cognitive/ software fusion.	Second: perform both

"Naive" patients: In those who have not had a previous biopsy, the EAU guide parts from the Cochrane meta-analysis where we found a sensitivity of 95% (95% CI: 0.87-0.99) for tumors with an ISUP grade >3.[30] However, the NCCN guidelines comment that since mpMRI is a good option in naive patients. It must be taken into account that the studies on which these review data are based, they are carried out in high-performance centers, so the results cannot be fully extrapolated and even if their cost-effectiveness has not been proven. Finally, the AUA guide establishes a weak recommendation for its extended use, for the same reasons that the NCCN.

Patients in successive biopsies: The three guidelines advise to perform a mpMRI to increase the detection of lesions.

Systematic or directed biopsy: The AUA guide insists on the need to perform both due to the possibility of losing patients; however, the EAU and NCCN recommend performing a directed prostate biopsy in second biopsies, provided that qualified and experienced radiologists are available due to the great variability between radiologists. In this directed biopsy, no differences were seen between cognitive or fusion biopsy by experienced people.[31]

Stratification according to risk

The EAU stratifies the risk groups considering mainly the D´Amico classification that takes into account the PSA grade, the Gleason score, and the extension of the main tumor (cT).[32] It suggests dividing the intermediate risk group into two groups as low intermediate risk (ISUP 2) and high intermediate risk (ISUP 3). On the other hand, we have the NCCN and AUA risk classifications, which increase the D´Amico criteria. They subcategorize the low-risk group into two as very low and low risk, and the intermediate risk group into two as favorable and unfavorable intermediate risk.

The **very low risk group** is defined by Epstein et al.[33]: 2 or less positive cores, at most one third of the total (<34 %), with <50 % involved, ISUP 1 (GS 3 + 3), and a density PSA <0.15 ng/ml/cc. We found a difference between the NCCN and the AUA. The AUA includes clinical stage T2a within a very low risk, while the NCCN only includes T1. In the **intermediate risk group,** the EAU guideline includes only cT2b, but the AUA and NCCN guidelines also include cT2c. According to the NCCN consensus panel, to be considered a **favorable intermediate-risk patient**, it is mandatory to have an ISUP Grade 1 or 2 and have more than 50% negative biopsy cores. If the patient is ISUP Grade 3 or has >50% positive biopsy cores, they are considered in the **unfavorable intermediate-risk** category. The AUA guideline chose not to include the percentage of positive biopsy cores in the subcategorization. In **the high-risk group**, the NCCN guideline makes a division considering very high-risk patients with a primary Gleason pattern of 5 or more than 4 cores with cT3b or higher, with an ISUP grade of 4 or 5. Both the AUA and the EAU are similar in this regard (Table 6).

Table 6

LOW RISK				
EAU	**NCCN/ AUA**			
· PSA <10ng/ml and	**VERY LOW RISK**	**LOW RISK**		
· ISUP 1 and	· cT1 (and cT2a in AUA) and	· PSA <10ng/ml and		
· cT1-T2a	· ISUP 1 and	· ISUP 1 and		
	· PSA <10 ng/ml and	· cT1-T2a		
	· ≤2 affected cores (<34% of the total) and ≤50% in each core, and			
	· PSA density <0.15 ng/mL/cc			
INTERMEDIATE RISK				
EAU	**NCCN**		**AUA**	
· PSA 10-20ng/ml or · ISUP 2-3 or	1. It does not have high or very high-grade criteria, and one or more intermediate risk factors (IRF):		· PSA 10-20ng/ml or	
·T2b-c		· ISUP 2-3 or		
· cT2b	· ISUP 2 or 3		· cT2b-c	
	· PSA 10-20ng/mL			
	Favorable	**Unfavorable**	**Favorable**	**Unfavorable**
· 1 FRI and	· 2 o 3 FRI and/or	· ISUPU 1 (with PSA 10-20ng/ml) or	· ISUP 2 (with PSA 10-20ng/ml or stage T2b-c) or	
· ISUP 1 or 2 and	· ISUP 3 and/or	· ISUP 2 (with PSA <10ng/ml)	· ISUP 3 (with PSA < 20ng/ml)	
	· <50% positive cores	· ≥50% positive cores		
HIGH RISK				
EAU	**NCCN**		**AUA**	
· PSA >20ng/ml or · ISUP 4-5 or	**HIGH**	**VERY HIGH**	· PSA >20 ng/ml or	
·T3a or	· T3b-T4 or	· ISUP 4-5 or		
· cT2c	· ISUP 4-5 or	· Primary pattern 5 or	· ≥T3	
2. Locally advanced if cT3-4 or cN + (any PSA and ISUP)	· PSA >20ng/mL	· > 4 cores with ISUP 4 or 5		
			*T3 is considered locally advanced	

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Clinical staging

When comparing the EAU, NCCN and AUA guidelines, we observed that to assess the local extension of PCa, the main tools are digital rectal examination and PSA. Other imaging techniques are used as complementary remote staging tests, as shown in Table 7.

Table 7

LOW RISK				
EUA	**NCCN/AUA**			
Do not use tests for staging *	**Very Low**	**Low**		
	Not indicated	Not indicated		
INTERMEDIATE RISK				
EUA	**NCCN**		**AUA**	
In ISUP> 3, at least one abdominal-pelvic CT scan and one bone scan	**Favorable**	**Unfavorable**	**Favorable**	**Unfavorable**
	· Scintigraphy NOT recommended · Pelvic +/- abdominal imaging ** test if nomogram predicts> 10% possibility of nodal involvement	· Scintigraphy if T2 and PSA> 10 ng/ml · Pelvic +/- abdominal imaging ** test if nomogram predicts> 10% possibility of nodal involvement	Not indicated	Consider bone scan and CT/MRI
HIGH RISK				
EUA	**NCCN**		**AUA**	
Abdominal-pelvic image and bone scan	**High**	**Very High**	Bone scan and CT/MRI	
	Bone scintigraphy. Pelvic +/- abdominal imaging	Bone scintigraphy. Pelvic +/- abdominal imaging * test if nomogram predicts >10% possibility of nodal involvement		
	* test if nomogram predicts >10% possibility of nodal involvement			

Discussion

Our main objective in this article was to analyze the agreements and differences between the main clinical guidelines to promote a unification of criteria in future consensus. Therefore, it was based on a narrative review of the most frequently consulted available guides. The guidelines are based on solid scientific evidence supported mostly by clinical trials, thus considered the "gold standard," but they present notable disagreements that could be due to different factors. The great pressure that public health systems are subjected to is well known, especially in the field of cancer diagnosis, where costs have increased in recent years. Also, not every system supports that pressure in the same way. Mariotto et al.,[34] estimate that the healthcare cost associated with oncological pathology in the USA was 183 billion dollars in 2015 and that it will increase in the coming years by 34%, reaching 246 billion dollars. Prostate cancer detracts from this budget a significant percentage, since is the most frequent male neoplasm, and it will increase of 46% is estimated in the coming years.[34]

Population screening: Carrying out population screening for prostate cancer, as we well know, is a highly controversial topic around the world. There are no established protocols but each of the groups recommends different guidelines to follow. Callender et al.,[35] found that offering screening to men at higher risk could potentially reduce overdiagnosis and improve the benefit-harm ratio and cost-effectiveness of a prostate cancer screening program. Offering screening to men with an absolute risk threshold of 4% to 7% could lead to higher QALY/QUALY (Quality of Life-Adjusted Year of Life), lower costs, and a reduction from 32.1% to 56.7% in overdiagnosis compared to age-only screening. The EAU guidelines propose an individualized approach that establishes a joint screening based on risk and age, starting at 55 years and with intervals of 2 or 8 years depending on the risk that the patient has. Likewise, in high-risk patients, PSA is considered at 40 years of age.

Evaluation of germline risk variants: Another novel and controversial issue is the need for a genetic evaluation in patients with a high suspicion of mutation in genes of the tumor process. Studies over the past five years have found pathogenic germline variants in 12 to 17% of men with prostate cancer and these changes can affect everything from the treatment options available to them to management strategies used for other members of the same family.[36] The IMPACT study made clear the relationship of high-risk or early-onset prostate cancer with the mutation of the BCRA2 tumor suppressor gene. For this reason, the study of the BCRA2 gene in patients with a high suspicion of mutation is highly recommended, and if positive, the patient should be referred to specialized centers due to the great impact, not only in prostate cancer but also because of the propensity that leads to the appearance of other types of tumors.[9]

Additional tests to avoid unnecessary biopsies: It is clear that additional tests on serum and urine can help obtain more conclusive data. However, the different guidelines analyzed suggest a low cost-effectiveness. Therefore, its use is relegated to the field of clinical studies because its strength of recommendation is weak in assessing the risk of PCa in asymptomatic patients (EAU).[18]

Diagnostic imaging: Regarding the performance of mpMRI for the characterization of local extension, it is evident that the use of this technique is currently widespread in most of our hospitals. Even so, the presence of specialized radiologists trained in this technique is essential to carry it out. According to several studies, there is still a high variability between readers when evaluating this test. Muller

et al. analyzed the observations of 5 untrained radiologists, who obtained in the diagnosis of the grade according to PIRADSv2 a kappa concordance index of only 0.46,[38] whereas according to the AIAG manual, for the existence of a good concordance, a minimum value of 0.75 is necessary.[39] However, in other studies such as Greer et al. who analyzed the results of expert radiologists, this kappa value increases to 0.86.[40] In the same study, it is observed that when detecting naive patients with prostate cancer, the sensitivity is different depending on the experience of the radiologist. Thus, we observe that radiologists with more experience observed PIRADS 4 lesions with an average sensitivity of 60% for all lesions versus 49% by inexperienced radiologists (P<0.001). The average sensitivity to detect lesions with ISUP>1 was 90 % for experienced radiologists versus 79% for professionals with moderate experience. For this reason, it is important to know the experience of our radiologists when performing mpMRI on naive patients as the first diagnostic step and to train specialized radiologists to reduce subjectivity in the interpretation of results. We must also consider the economic impact of MRI in all patients with suspected prostate cancer. On a positive note, the EAU guideline states in the section "Other Considerations: Reproducibility of multiparametric magnetic resonance imaging" that "Despite the use of the PIRADSv2 scoring system, the reproducibility between MPMR readers it is still moderate at best." This assertion has been recently supported by the work of Westphalen et al.,[41] who evaluated 3449 of 5082 lesions on mpMRI. Biopsy results showed 1698 cancers with GS greater than or equal to 3+4 (International Society for Urological Pathology grade group ≥2) in 2082 men. In all centers, the estimated Positive Predictive Value was 35% (95% confidence interval [CI]: 27%, 43%) for a PI-RADS score greater than or equal to 3 and 49% (95% CI: 40%, 58%) for a PI-RADS score greater than or equal to 4. They concluded that the positive predictive value of mpMRI was low and varied widely between centers

Risk stratification

When it comes to risk stratification, the AUA and NCCN guidelines carry out a detailed division that is oriented in a very practical way for clinical utility in making subsequent therapeutic decisions. This implies significant cost savings in staging tests:

Low risk: They incorporate the concept of very low risk for patients who are candidates for active surveillance, allowing them to be differentiated from other patients who would be candidates for active therapy. It is very important to understand that continuous advances in imaging with biopsies aimed at suspicious areas in addition to systematic biopsy will lead to a purification of the concept of non-significant cancer and therefore to vary this classification.

Intermediate risk: Both North American guidelines clearly assume favorable and unfavorable sub-classifications according to different patient factors. This allows, on the one hand, to save on staging tests with low power of sensitivity, such as bone scintigraphy, in patients with intermediate risk and a favorable prognosis, and on the other hand, to concentrate resources on those that are unfavorable. Unfortunately, the European guide barely mentions these sub-classifications.

High risk: Practically, the AUA and EAU guidelines do not establish a subclassification in this group because there is no impact on the management of the patient, although there is for their prognosis. The NCCN guidelines propose a sub-classification.

Social reflection and the diagnosis of prostate cancer

It is disturbing to see a lack of unanimity when analyzing these 3 prostate cancer detection guidelines generated in the countries within the highest quartile of Human Development Index (HDI) on the planet according to the Human 2019 Development Report of the United Nations Development Program (UNDP), published on December 9th, 2019 and compiled based on estimates from 2018.[42] Also, we must ask ourselves about the causes that these differences originate from in healthcare in the face of a topic as prevalent as it is specific in the world's male population. Well, if it is striking that a man in this case is treated with differences in the 62 countries with the highest Human Development Index in the world, we cannot even imagine what happens in the other 171 countries that are in quartiles 2 (very high HDI), 3 (medium HDI), and 4 (low HDI). One of the essential points is the difference that the health systems make. Assuming that, at present, all health systems face great challenges of different kinds (financial problems, increased demand for health services, and scarcity of available resources) that make adequate care unsustainable. The different guidelines must establish minimum common criteria that must be met in the diagnostic process of prostate cancer for all affected men in our societies.

Conclusion

The analysis of the three guidelines has revealed the disagreements between them regarding the management and diagnosis of prostate cancer. A unanimity of criteria would be necessary; however, the realization of each guide takes into account their social and economic situations. Our proposal is the establishment of common minimum criteria that must be met in the diagnostic process of prostate cancer for all affected men in our societies.

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Authors' contributions

All the authors had contributed to conception and design, acquisition of data, or analysis and interpretation of data. Also they had revised it critically for important intellectual content and they had approved the final version to be published.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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