Epidemiology and Diagnostics of Prostate Cancer During COVID-19 Pandemic

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Background: Prostate cancer (PCa) is the second most common cancer in the male population and represents a major health problem, especially in developed countries, where older men are more prevalent in the general population. Analyzing recent data for European countries, the incidence is highest in Northern and Western Europe (>200 per 100,000), while the rate is lower in Eastern and Southern Europe, but shows a continuous increase. Globally, about 450,000 Europeans are diagnosed with prostate cancer each year, and prostate cancer was the second most common cause of cancer-related deaths in 2018, when it was the cause of death for 107,000 men in Europe. Global data for BiH indicate that PCa is the second most common cancer in the male population, or the third leading cause of death in men due to cancer. Objective: The aim of this study was to analyze (PCa) how PCa screening is the most controversial topic regarding statements described in the urological literature searching most important biomedical on-line databases. Methods: Authors used descriptive method for this systematic study based on the published literature, summarized through meta-analysis, to show that screening was associated with an increase in PCa diagnosis. Results and Discussion: Most of authors written about this topic and concluded that the greater detection of localized and less advanced PCa disease, but without benefits in the field of PCa “specific survival” and “overall survival”, “overdiagnosis” and “overtreatment”, leading to recommendations against systematic population screening in all countries, including Europe. The main diagnostic tools for diagnosing PCa are digitorectal examination (DRE), serum specific antigen concentration (PSA), transrectal ultrasonography (TRUS) and mp MRI, and the definitive diagnosis is based on pathohistological verification of cancer in prostate biopsy specimens or operative specimen. The indication for biopsy should be determined based on PSA levels and/or suspected DRE, depending on age, potential comorbidities and therapeutic consequences, and the indication for repeated biopsy is an increase or persistently elevated PSA, suspected DRE, “atypical small acinar proliferation” (ASAP), extensive high grade “prostatic intraepithelial neoplasia” (PIN) and positive multiparametric MRI of the prostate (PI-RADS ≥3). Conclusion: PCa volume assessment is based on DRE and PSA with the addition of multiparametric MRI, bone scan and CT, although there are new imaging modalities, such as PET/CT scan and Diffusion-weighted whole-body MRI. However, the cost-effectiveness of these new approaches needs to be further assessed. Given that COVID-19 has imposed other priorities on all health systems, we hope that the diagnosis of clinically significant prostate cancer and adequate treatment is not questionable at this time.

Keywords: prostate cancer, DRE, PSA, TRUS, prostate biopsy, CT, MRI, skeletal scintigraphy.
1. INTRODUCTION

Nothing. Early detection of prostate cancer (PCa) using prostate-specific antigen (PSA) and prostate biopsy have been shown to reduce PCa mortality (1–3). However, PSA testing and the use of systemic transrectal ultrasound-guided biopsies (TRUSGB) have low specificity, resulting in unnecessary biopsies, pre-diagnosis of PCa, and potentially over-treatment (1). In contrast, systematic biopsy can also lead to a false negative biopsy result or misclassification of the tumor, so that a clinically significant tumor may remain undetected (4, 5). Magnetic resonance imaging (MRI) followed by targeted biopsies reduces unnecessary biopsies and over-diagnosis of clinically insignificant (indolent) PCa, and thus reduces over-treatment of PCa (4, 6-8). On the other hand, active patient monitoring also reduces PCa over-treatment. International clinical guidelines provide precise guidelines for the diagnostic evaluation of patients, and PSA screening has been synonymous with PCa overdiagnosis and therapy for many years. The fact that the decline in mortality caused by PCa is stagnant, and that it is on the rise again in some countries, has led to a loud thinking that it is time to change the recommendations made by the European Commission for PCa screening (9).

2. EPIDEMIOLOGY

According to the latest data, Prostate Cancer is on the rise, and is the most frequent cancer in Europe with important consequences for healthcare systems. Every year, around 450,000 European men are diagnosed with Prostate Cancer. It has overtaken colorectal cancer, and is now the second commonest cause of male cancer death. Prostate Cancer killed 107,000 men in Europe in 2018 and thus, is not an indolent disease, killing more men than breast cancer kills women. It is a chronic disease that causes many emotional and social problems for patients and their families. Prostate Cancer is on the rise, and is the most frequent cancer in Europe with important consequences for healthcare systems. Every year, around 450,000 European men are diagnosed with Prostate Cancer. It has overtaken colorectal cancer, and is now the second commonest cause of male cancer death. Prostate Cancer killed 107,000 men in Europe in 2018 and thus, is not an indolent disease, killing more men than breast cancer kills women. It is a chronic disease that causes many emotional and social problems for patients and their families (9). EAU adopted as official document: “White paper on prostate cancer. Recommendations for the EU Cancer Plan to tackle Prostate Cancer” (16).

And according to data related to 2012, prostate cancer was the most common cancer of age-adjusted men, aged 65–74 years, with a mean age of 66 years (10). On the other hand, looking at the entire male population, PCa was the second cancer diagnosed in men, with an estimate that it was diagnosed in 1.1 million men worldwide in 2012, and accounted for 15% of all cancers diagnosed (11). Autopsy studies show that the prevalence of PCa up to 4 decades of age is about 5% (CI: 3-8%), and from 80 years of age 59% (48-71%) (12). In general, the incidence of PCa in the world varies by geographical region, and is highest in Australia and New Zealand, North America, and Western and Northern Europe, mostly due to more aggressive use of the PSA test, as well as the older age of the male population, in those spaces. The incidence is low in East and South-Central Asia, while in Eastern and Southern Europe, where it was also lower, it began to show a continuous increase (11, 13). According to EUCAN data from 2012, Norway (193/100,000) and France (187.5/100,000) have the highest age-standardized incidence rates, followed by Moldova (30.5/100,000) and Albania (24.8/100,000) (14).

According to GLOBOCAN data from 2012, PCa is the second most common cancer of the male population in Bosnia and Herzegovina, and the third leading cause of death from cancer in the entire male population (12). According to the data for public health of Republika Srpska, the total number of new cases of PCa in Republika Srpska in 2011 was 247 men, and the incidence was significantly higher in men older than 65 compared to men younger than 45-65 years, and was 122/100,000 men in the age-adjusted group, which is less than the European average of 96/100,000. According to the same data Globocan 2012, in BiH the incidence in the age-standardized male population for PCa was 44/100,000, with a rate of mortality 45/100,000, while in the EU the incidence was 96/100,000, and the mortality rate was 19/100,000. According to the same data, lower rates than BiH were only in Ukraine, Moldova and Albania. Of the total number of newly diagnosed PCa patients at the UCC RS in Banja Luka, at the time of diagnosis, 59% had advanced or metastatic disease.

In terms of survival, there is still a difference in survival between men in Eastern Europe and others in the rest of Europe. According to EUCAN data from 2012, the European average mortality rate is 16.3/100,000 (14). Over the previous decade, the 5-year relative survival rate for PCa was on the rise, from 73.4% between 1999 and 2001 up to 83.4% in the period 2005-2007 (15). The latest data globally indicate that mortality is stagnant, but in some countries, mortality is rising again, as is the case in the UK.

With the expected increase in the duration of life, and the incidence of PCa, it is expected that the economic burden of the disease in Europe will increase significantly. The total economic cost in 2018 for PCa in Europe was about 9 billion euros, with a higher proportion of PCa during care in the first year after diagnosis, which was about 5.8 billion (16).

3. PROSTATE CANCER PRECURSORS

Prostatic intraepithelial neoplasia (PIN) and atypical small acinus proliferation (ASAP) are considered precursors of prostate cancer (10). PIN consists of benign prostatic acinuses or ducts with cytologically atypical cells and is classified into Low-Grade PIN and High-Grade PIN (HGPIN) (17). Evidence that HGPIN is a precursor to some prostate cancers is the size and number of HGPIN foci in adenocarcinoma patients compared to those without cancer, and HGPIN levels increase, more multifocal cancers occur.
Further, biomarkers and molecular changes in HGPIN show similarity to cancer (17).

However, a presence of PIN is not necessary for cancer to develop. LGPINs, especially those present in the transition zone, are not closely related to HGPIN (17).

ASAP presents a higher risk histology than PIN for prostate cancer (10). The probability of prostate cancer after recognizing ASAP is 40-50% (17).

4. PROSTATE ADENOCARCINOMA

The most common prostate cancer is adenocarcinoma and it represents more than 95% of prostate cancers. 60-70% of prostate adenocarcinomas originate from the peripheral zone, 10-20% from the transitional zone and 5-10% from the central zone. In cases when it occurs in the peripheral zone, most typically occur on the back of the prostate, where it can often be palpated by digitorectal examination.

For the prognosis of prostate cancer, it is important to determine the degree of differentiation of the tumor itself and the degree of disease progression. The Gleason system is the most commonly used grading system for PCa (10). The degree of differentiation of the tumor (degree) depends on the ratio of the size of the nucleus to the cytoplasm, hyperchromasia of the nucleus, the number of mitoses and changes in the structure of prostate tissue. PCa has a heterogeneous degree of cell differentiation within tumor tissue. For that reason, the definitive degree of PCa differentiation, the so-called The Gleason score is determined by transrectal biopsy of the prostate under ultrasound control, transurethral electroresection or after radical surgery. The most prominent pathological changes are observed in cancer samples, and they are given numbers; primary degree for change represented in more than 50% of the sample and secondary degree for change represented in less than 50% and at least 5% of the sample (10, 17, 18). 1 denotes well-differentiated carcinoma, and 5 denotes poorly differentiated or anaplastic carcinoma. The values are then added together, and the final Gleason score can have a value of 2-10. The Gleason score between 5 and 10 has the most diagnosed PCa, and the prognosis of cancer depends on it. Cancers with values of 2-4 are rarely diagnosed and are considered weakly aggressive, 5-6 mildly aggressive, 7 suggests that the cancer is moderately aggressive, and Gleason score 8-10 indicates highly aggressive cancer (19). A total Gleason score of 6 (3+3) is considered a relatively indolent disease. In the differentiation of moderate from high-grade tumor, the primary Gleason pattern is the most important determinant of biological risk. Thus, within the Gleason score of 7, tumors labeled 4 + 3 are much more aggressive than 3 + 4 (10, 17).

In 2014, the International Society of Urological Pathology ranked PCa grades from 1 to 5 in such a way that GS 2-6 represents ISUP grade 1, GS 7 (3+4) ISUP grade 2, GS 7 (4+3) ISUP grade 3, GS 8 (4+4 or 3+5 or 5+3) as ISUP grade 4 and GS 9-10 as ISUP grade 5.

Age at the time of diagnosis is also recognized as a prognostic indicator. High-grade or locally advanced PCa in younger men are often more aggressive than when present in older men. The hereditary form of prostate adenocarcinoma usually manifests itself 6-7 years earlier than the sporadic form of the disease (20). The clinician’s task is not only to diagnose PCa, but also to distinguish between aggressive and indolent disease. Therefore, screening programs should use the most significant risk factors to more accurately identify men who are more likely to have an occult disease and thus allow physicians to thoughtfully test those patients who would benefit most from detecting the disease (21).

5. DIAGNOSTIC EVALUATION

5.1. Symptoms

The symptoms caused by PCa are not specific, i.e., the same symptoms are present in benign prostate enlargement and chronic prostatitis. In the early stages of the disease, most patients do not have symptoms of the lower urinary tract, and when they appear, they are present as symptoms of filling (more frequent urges to urinate, urgent urges to urinate, nocturnal urges to urinate) or symptoms of urination. weak and intermittent jet, terminal dripping, feeling of incomplete bladder emptying). Locally advanced adenocarcinoma due to infiltration of the bladder trigonum can cause ureteral obstruction and consequent hydronephrosis with an increase in nitrogenous substances, and invasion of seminal vesicles can cause hematospermia or decreased ejaculate volume (10, 17).

The metastatic stage of the disease may be clinically manifested by bone pain and/or pathological fractures due to expansive osteoblastic lesions, secondary anemia, edema of the lower extremities due to lymphatic obstruction, paraneoplastic syndrome associated with visceral metastases (brain, liver, coccygeal dysplasia), as a result of sepsis caused by uroobstruction, and even paralysis as a consequence of metastases in the spinal column and compression of the spinal cord. For these reasons, early detection is considered necessary, with the aim of identifying adenocarcinoma limited to the prostate (10, 17, 22).

The main diagnostic tools for diagnosis are DRE, serum PSA concentration and transrectal ultrasonography (TRUS) and TRUS biopsy, and the definitive diagnosis is based on pathohistological verification of adenocarcinoma in prostate biopsy specimens or surgical specimen (10, 17, 22).

5.2. Digitorectal examination

Digitorectal examination (DRE) is the first test in the diagnosis and assessment of local prevalence of prostate cancer due to its simplicity and possibility of wide application. Most prostate cancers, since they are localized in the peripheral zone of the prostate, can be detected by DRE, when the volume is about 2 ml or more. Cancers located in the central and transitional zones of the prostate cannot be diagnosed by DRE, which is a disadvantage of this examination. In about 18% of all patients, PCa is detected only by suspected DRE, independent of PSA levels. Suspect DRE in patients with PSA greater than 2 ng/mL.
has a positive predictive value of 5-30%. Suspected (abnormal) DRE is a strong indicator for prostate biopsy as well as for higher PCa aggressiveness and should be an indication for prostate biopsy (23).

5.3 PSA testing

The PSA measurement represented a revolutionary advance in setting up a PCa diagnosis. It was discovered in 1979, and its clinical application emerged in the late 1980s and 1990s when it evolved as an invaluable tool for determining the need for prostate biopsy, and then, after PCa diagnosis, for risk stratification and for monitoring the clinical response, for the selected treatment modality (2, 3). PSA is kallikrein, which is produced by prostate epithelial cells, and is organ-specific, not cancer-specific. Under normal circumstances, only small amounts of PSA circulate in serum in free and bound form (10, 18). Serum levels may be increased due to benign prostate enlargement (BPE), prostatitis, and other nonmalignant conditions, but it is closely associated with localized and advanced PCa (18). PSA, as an independent variable, is a better predictor of cancer than the suspected signs of DRE or TRUS.

Serum PSA levels of up to 4 ng/mL are generally used as cut-off values for "normal" and "abnormal" (18). PSA is not an ideal tumor marker. 20-40% of patients with prostate-restricted adenocarcinoma have a PSA value of less than 4.0 ng/mL, while a positive predictive value (PPV) of serum PSA at 4-10 ng/mL is only 20-30% (2, 3). At a serum PSA value greater than 10 ng/mL, PPV increases to 72% (10). In light of all this, reference ranges of PSA depending on age/ethnicity have been proposed (10). However, the results of the PCPT study, which included prostate biopsy regardless of PSA value, showed that there is no PSA level below which the risk of PCa drops to zero (24). The value of PSA therefore indicates the continuity of risk, i.e., the higher the PSA, the higher the risk of PCa (25).

There are several modifications of serum PSA levels that may improve PSA specificity in early PCa detection. These modifications include PSA density, PSA density of the transition zone, age-specific reference range, and PSA molecular forms. However, these derivatives and PSA isoforms, such as (cPSA-i.e., complex PSA), proPSA (precursor isoforms of PSA), BPSA (benign PSA), iPSA (intact PSA) have limited benefit in routine clinical practice and are therefore not included in European Association guidelines (26). Index F/TPSA is a concept widely used in clinical practice to improve the distinction of benign prostate enlargement (BPE) from PCa. This ratio is used to stratify PCa risk for men who have a PSA level of 4-10 ng/mL and a negative DRE. In a prospective multicenter study, PCA was found on biopsy in 56% of men with f/ tPSA <0.25 ng/mL, and only in 8% of men with f/ tPSA >0.25 (25). Nevertheless, this test must be taken with caution, as several pre-analytical and clinical factors may influence f/ tPSA, such as fPSA instability, very large prostate volume, and test variables. For example, fPSA is unstable at a temperature of 4 degrees Celsius, but also at room temperature. In addition, the characteristics of the test itself can vary, and concomitant BPE in large prostate can result in a dilution effect. Otherwise, f/tPSA should not be used clinically if tPSA >10 ng/mL during monitoring with known and detected PCa.

There are two methods of measuring PSA over time: PSA velocity (PSAV) and PSA doubling time (PSADT). PSAV is defined as the absolute annual increase in serum PSA, and PSADT measures the exponential increase in serum PSA over time, reflecting relative changes. These two concepts may be prognostic agents in patients treated for PCa, but have limited value and use in the diagnosis of PCa. Prospective studies have shown that these measurements do not provide additional information compared to PSA itself (26). Prostate Cancer Gene 3 (PCA3) is a new marker, detected in urine sediment after prostate massage by DRE (27, 28). The price of the "Progens" PCA3 urine test is now commercially available. The PCA3 test is superior to total PSA and the percentage of free PSA in the detection of PCa in men with elevated PSA. The PCA3 test can be used with PSA as well as with other clonic risk factors in the nomogram as a diagnostic tool to decide on a first or repeat biopsy. The PCA3 score increases with "prostate cancer volume". The presence of elevated PCA3 in urine has PPV for the presence of cancer on prostate biopsy with an accuracy of 74.6% and is particularly useful in the assessment of men with previous negative prostate biopsy and an increase in PSA (10). The main indication for the use of the PCA3 urine test could therefore be in determining when prostate rebiopsy is required after the initial negative biopsy, but in this regard, the "cost-effectiveness" aspect should be considered.

5.4. Prostate biopsy

The indication for biopsy should be determined based on PSA levels and/or suspected DRE. The patient's age (life expectancy), potential comorbidities, and therapeutic consequences should also be considered (29, 30).

The first elevated PSA level should not promptly indicate a hasty biopsy. PSA levels should be repeated after several weeks with the same test under standard conditions (no ejaculation, no manipulations such as catheterization, cystoscopy, or TUR, and no urinary tract infection) in the same diagnostic laboratory, using the same PSA test method. The standard for performing prostate biopsy is ultrasound-guided biopsy, and although the transrectal approach is used for most biopsies, some urologists prefer to use the perineal approach. The detection rate of PCa in perineal biopsies is comparable to the transrectal approach (31, 32). An ultrasound-guided perineal approach is a useful alternative in special situations, i.e., after rectal amputation. Prostate biopsy is performed through the peripheral zone of the prostate with possible additional samples of any abnormal zone detected by DRE/TRUS (29, 30). Traditionally, 6 samples were taken along the parasagittal line between the lateral edges and the middle of the prostate in the area of the prostate apex, middle part of the prostate and prostate base bilaterally (29, 30). However, several studies have shown that taking more than 10 samples from more lateral direct peripheral biopsies increases the PCa detection rate by 14-20% com-
pared to sextant biopsy, and now the position of most uro-
logical associations is to take sextant biopsies from each
lobe of the prostate, i.e., a total of 12 biopsy specimens,
which has become the most widely accepted method in re-
cent times (29, 30). Although a small number of PCa origi-
nate from the transitional zone, biopsy and transitional
zone slightly increased the overall detection of PCa, when
a more extensive prostate biopsy is undertaken (29, 30).
The Vienna nomogram suggests a sampling minimum
of 8–18 depending on the patient’s age, prostate volume,
and PSA value of 2–10 ng/mL to ensure 90% PCa detection
safety. However, most initial biopsy studies show that a
further increase in biopsy samples taken >12-14 or a sat-
uration pattern does not bring significant benefit and
does not contribute to the percentage of positive biop-
sies. From the aspect of saturation prostate biopsy, some
studies have reported that the incidence of PCa detected
with saturation repeat biopsy (more than 20 samples) is
between 30% to 43% and depends on the number of sam-
ples taken during previous biopsies (33). In special situa-
tions, a saturating biopsy may be done with a transperi-
neal approach. This can be detected by an additional 38%
of PCa, but the incidence of urinary retention is high (10%)
and this deficiency reduces its clinical application (34).

Prostatic samples taken from different locations are
sent to the laboratory in separate vials and should be
processed in separate cassettes. Before processing, the
number of samples from the vials and the length of each
sample should be recorded. There is a significant corre-
lation between prostate tissue sample and PCa detection
rate. To optimize the detection of malignant lesions, sam-
ples should be cut at three levels.

5.5. Repeated biopsy
Indications for repeated prostate biopsy are an increase
or persistently elevated PSA, suspected DRE, ASAP, ex-
tensive PIN (multiple biopsy specimens and sites), and a
positive multiparametric MRI finding.

High grade PIN, as an isolated finding is not considered
as an indication for repeated biopsy. Extensive PIN, or
PIN in multiple biopsy sites, may be a reason for early re-
peat biopsy, because the risk of PCa increases. If clinical
suspicion of PCa persists despite negative biopsies, MRI
may be useful in examining the possibility of anterior lo-
calization of PCa, followed by TRUS or MRI-guided biopsy
of the suspected area, and a positive multiparametric
MRI finding (35).

5.6 “Imaging” (transrectal ultrasonography / multi-
parametric MRI of the prostate)
Transrectal ultrasound (TRUS) is the standard for di-
agnostic evaluation, and transrectal ultrasound-guided
prostate biopsy (TRUSGB) is the standard for prostate
biopsy (Figure 1). However, TRUSGB has its limitations.
First, clinically insignificant (indolent) PCa are unneces-
sarily detected. Second, many men undergo TRUSGB and
do not have a PCa. TRUSGB have complications, such as in-
fecions and bleeding, which also leads to increased treat-
ment costs (36). Third, clinically significant PCa may re-
main undetected. Fourth, the observed risk stratification
errors lead to errors in the selec-
tion of the therapeutic modality
for patients undergoing active
surveillance for presumed low-
risk PCa.

Multiparametric MRI (mpMRI)
relative to TRUSGB, reduces the
detection of insignificant PCa,
while increasing the detection
of clinically significant PCa (37–
39). Selective localization of clini-
cally significant PCa allows MR-
directed biopsy and therefore
fewer biopsy specimens are re-
quired (Figure 2). This improved
the diagnostic evaluation for men
with suspected PCa. If mpMRI is
unsuccessful, hasty TRUSGB can
be avoided (40, 41). Numerous
multicenter randomized studies
have confirmed the superiority
of mpMRI and MR-direct biopsies
over TRUSGB (42–47). Given the
limitations present in these studies, a prospective mul-
ticenter study compared mpMRI + MRGB directly versus
TRUSGB in men with suspected PCa and concluded that MRI versus TRUSGB resulted in identical detection of clinically significant PCa, with no significant clinical significance. insignificant (indolent) PCa. In that high-quality study, almost half of the men did not have MRI suspicious signs on PCa, which is more than in other studies. Failure to perform TRUSGB resulted in the loss of only 4% of clinically significant PCa, so patients may benefit from MRI, because biopsy can be avoided in half of men with indolent PCa detection without compromising the detection of clinically significant PSA, as well as the required smaller number biopsy specimens for diagnosis (48). In any case, we must remember that in diagnosing PCa, after DRE and PSA have been performed, no imaging modality (TRUS/ mpMRI) can shift the prostate biopsy and the pathohistological diagnosis it provides. The requirement for optimal assessment ranged from “extant” to extended biopsy and from extended to saturation biopsy, with the goal of reducing random sample bias and improving disease staging. The next step certainly represents the use of a targeted biopsy into the suspect zone seen in multi-parametric magnetic resonance imaging. The technique of these targeted biopsies predominantly detects “higher grade PCa” while losing “low-grade areas”.

5.7. Clinical “staging”

In clinical staging, PCa volume assessment was based on DRE and PSA with the addition of mpMRI, skeletal scintigraphy (bone scan) and CT. The TNM classification is used to determine the extent of the disease. The TNM system is an abbreviation where T is used to evaluate the extent of the primary tumor, N is used to express the involvement of lymph nodes, while M indicates the existence of the spread of the disease to distant parts of the body. Assessing the prevalence of PCa by TNM system before treatment is called “clinical” TNM classification of prostate cancer, as opposed to possible postoperative assessment of the stage of the disease by microscopic analysis of tissue and is called “pathohistological” (p) TNM classification of prostate cancer. The pTNM classification differs from the TNM classification for clinical stages T1c and T2 substages. All pathohistologically confirmed PCa after radical prostatectomy, which are “organ-confined”, are classified as pathological stage T2, and currently the Union for International Cancer Control (UICC) no longer lists pT2 substages. Transrectal ultrasound (TRUS) and mpMRI are indicated in T-staging. In the assessment of nodal status (N), the use of CT and MRI, Choline PET/CT and/or prostate-specific membrane antigen-based PET/CT (PSMA PET/CT) is indicated. In the assessment of M status, the use of skeletal scintigraphy (bone scan), Fluoride PET and PET/CT, Choline PET/CT and MRI of the whole body is indicated (Figure 3).

6. PSA “SCREENING” AND EARLY DETECTION OF PCA: YES OR NO?

Detection of the disease in the presymptomatic stage is called secondary prevention and despite the apparent benefits of PCa screening, its application in clinical practice has been the subject of significant controversy, both in the USA and in Europe. Following PSA screening, which has become widespread since the 1990s, the U.S. has had a 2% increase in PCa incidence per year during 1995, and has been steadily increasing since then, approximately 1% per year, even as the mean age at setting diagnoses of PCa decreased to 66 in 2011 (49-52). Epidemiological data further show a 40% reduction in mortality and 75% fewer patients with locally advanced disease at the time of diagnosis. Currently, of the 1,000 age-adjusted men undergoing PSA screening, 240 will have a positive finding and 100 will have a positive prostate biopsy for PCa (53). However, 20–59% of these tumors carry a low risk of metastasis or shortening of an individual’s lifespan (44). Nevertheless, 80 out of 100 patients will choose surgical treatment or radiotherapy (53). And this is the basic argument against screening, which identifies many indolent PCa that will never result in clinically significant PCa, which is a phenomenon of excessive disease detection and overtreatment (53). These attitudes were basically grounded for the first time in 2009 after the publication of the long-awaited results of two prospective, randomized studies.

One of them, The Prostate Lung Colorectal and Ovarian (PLCO) Cancer screening included 76,693 men aged 55-74 in 10 centers in the United States for annual screening using PSA and DRE (working group) or standard care as a control group. After 7 years of follow-up, the incidence of PCa per 10,000 persons/year was 116 (2820 cancers) in the screening group and 95 (2,322 cancers) in the control group (54). The incidence of death per 10,000 individuals per year was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group. 44% had lower prostate cancer specific mortality in men without or with single comorbidity. The PLCO project team concluded that PCa-induced death was very small and insignificantly different between these two groups of subjects.

The second study, The European Randomized Study of Screening for Prostate Cancer (ERSPC) included 162,243 men from 7 European countries, aged 55-69 years. Men were randomly selected for the PSA screening group on average once every 4 years and for the non-screening group (control group). During the mean follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screening group and 4.8% in the control group. The “Rate ratio for death of PCa” was 0.80 (20% less) in the screening group compared to the control group. The “absolute risk difference” was 0.71 deaths per 1,000 men. This means that 1410 men had to undergo screening to detect 48 additional PCa cases, which needed to be treated to prevent one PCa death. The ERSPC concluded that PSA screening reduces PCa mortality by 20%, as well as 41% reduction in metastatic disease at the time of diagnosis with screening, but is associated with a high risk of “over-diagnosis” (55).

However, after 11 years of follow-up, the ERSPC found that prostate cancer death was 0.79 in favor of screening (56). A subanalysis of patients from one ERSPC study center with a follow-up period of 14 years confirmed a mortality reduction of almost 50%, which could neverthe-
less be a favoring factor for PCa screening (50, 57, 58).

A recent study, with a subanalysis of patients from the ERSCP study in Rotterdam pilot study 1 in a cohort of men randomized in 1991-1992, and for a follow-up period of 19 years provided data on a further reduction in metastatic disease in subjects who were in the screening program than previously reported. The overall relative risk of metastatic (M +) disease and prostate cancer (PCa) death was 0.46 (95% confidence interval (CI):0.19–1.11) and 0.48 (95% CI:0.17–1.36), in favor of screening. This ERCP Rotterdam pilot study 1, presented in a period without significant contamination, shows that PSA-based screening could result in a significant reduction in M + morbidity and mortality, which, if confirmed in larger data sets, should encourage further discussion of advantages and disadvantages of PSA screening (59).

Recent data from The Surveillance, Epidemiology, and End Results (SEER), which provide data on cancer statistics with a view to reducing cancer in the US population, and which challenge PSA screening, suggest that between 2011 and 2013, the overall incidence of PCa declined year in all age groups and races while the rate for age-adjusted men decreased from 147.7/100,000 men in 2010 to 108 in 2013 (56). The National Cancer Database revealed a small increase in the clinical phase of T3 tumors or higher from 2011 to 2013, as well as an increase in the incidence of metastases during the same period (56, 60, 61). Gaylis et al, presented data on the increase in the proportion of Gleason 8 cancers, from 21% in 2011 to 30% in 2014, as well as the increase in Gleason 8-10 cancers (61). Analysis of all Gleason Score 8-10 biopsy specimens increased from 15% in 2010 to 25% in 2015 (61, 62).

7. CONCLUSION

Since 1997, there has been a threefold increase in the incidence of prostate adenocarcinoma, and PSA screening has made a significant contribution to this. Although mortality caused by prostate cancer, especially in the last 1-2 decades, has had a declining trend, more than 92,000 men in Europe still die from PCa each year. Therefore, PCa in some European countries has become the second leading cause of death in the male population from cancer, after mortality caused by lung cancer, and ahead of mortality caused by colorectal cancer. The decades-old view that mass PSA screening is not indicated because of the risk of pre-diagnosis and over-treatment is slowly coming into question. On the other hand, the introduction of prostate MRI and MR guided prostate biopsy reduced the number of unnecessary biopsies and detection of indolent PCa. Subanalyses of the PLCO and ERSPC studies, which are performed after a long follow-up period, however, indicate that PSA screening leads to a reduction in the incidence of metastatic PCa and a reduction in PCa-induced mortality. The latest data, which show that mortality caused by prostate cancer is stagnant and that it is on the rise in some European countries, imposes the need to reconsider attitudes about PSA screening by leading international associations. In this regard, the views are focused on the expectation of changes in the guidelines in terms of the introduction of prostate cancer into routine screening by the European Commission.

Given that COVID-19 has imposed other priorities on all health systems, we hope that the diagnosis of clinically significant prostate cancer and adequate treatment is not questionable at this time (63). However, routine screening of the age-adjusted men, with an inceased risk of prostate cancer, is certainly questionable.

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REFERENCES


