

PROSTATE CANCER

*Recommendations to lower the risk
and mortality rate of the most
frequent cancer in men*



eau
European
Association
of Urology

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FOREWORD

Prostate cancer (PCa) is on the rise, and is the most frequent cancer and the third most common cause of death in men in Europe with important consequences for healthcare systems. Saving lives and ensuring a high quality of life requires immediate European action.

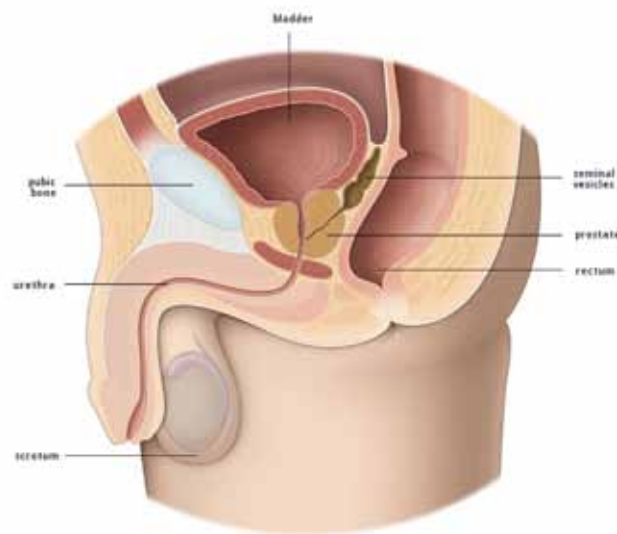


Figure 1: A healthy prostate in the lower urinary tract.

The incidence of PCa has increased significantly over the last two decades and continues to rise with the increasing lifespan of the population in developed countries. It is a chronic disease that causes many emotional and social problems for patients and their families.

Although the average age for the diagnosis of PCa is 69 years, it is a common misconception that it is a non-life-threatening older man's disease. Today, over 10% of new diagnoses in the

United States occur in young men aged ≤ 55 years¹. The continuing increase in the incidence of early onset PCa in particular² underscores the importance of early detection and effective treatment to ensure an increased quality of life for men.

The principal requirement is a wider recognition of PCa as a European healthcare problem to engage closer collaboration between Member States within the healthcare sector, including patient representatives, and an agreed approach to tackling it. At present, effective treatments exist, but consistency in getting them to patients is complicated by European and national rules on screening programmes, treatment guidelines authorisation, pricing, reimbursement and prescription.

Today's research is suboptimal because of inadequate funding, too stringent data protection rules, lack of coordination, and outdated clinical trial requirements. To overcome this it is necessary to ease access to innovative treatments through better funding, greater recognition of PCa as a European health burden, and elimination of inequalities in care.

It is also critical to boost research with a more supportive regulatory environment, more aligned cross-border collaboration, and more facilities and incentives to invest. Patients and health professionals must be involved in policy development.

Efficient and effective action for PCa patients depends on a coherent European strategy, and a common approach to mobilising and integrating scarce and scattered resources. This white paper provides general information on PCa, highlights the key challenges in improving patient outcomes, and identifies what can be done at European level.

1. INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men with more than 417,000 new cases and 92,000 deaths in Europe recorded each year³.

Currently, 1 in 7 men in Europe will develop detectable PCa before the age of 85. More than two million men in Europe are living with this disease.

PCa is a malignant tumour in the prostate. Most of the tumours develop slowly and do not cause any symptoms. The risk of getting PCa increases with age. PCa is in early stage generally asymptomatic, which means that there are no clear symptoms to indicate its presence. In most cases, symptoms such as trouble urinating are caused by an infection or by benign prostatic enlargement (BPE), a non-cancerous growth of the prostate. If PCa does cause symptoms it is usually a sign that the disease is at an advanced stage. The symptoms of advanced PCa include: rapid onset of local symptoms or pain in the hips, back, chest, or legs from cancer that has spread to the bones and blood in the semen.

Incidence rates of PCa in European countries vary by more than 7-fold, 25–193 per 100,000 men (Fig 1). The rates increase and remain most elevated in the highest-income regions including Northern and Western Europe.

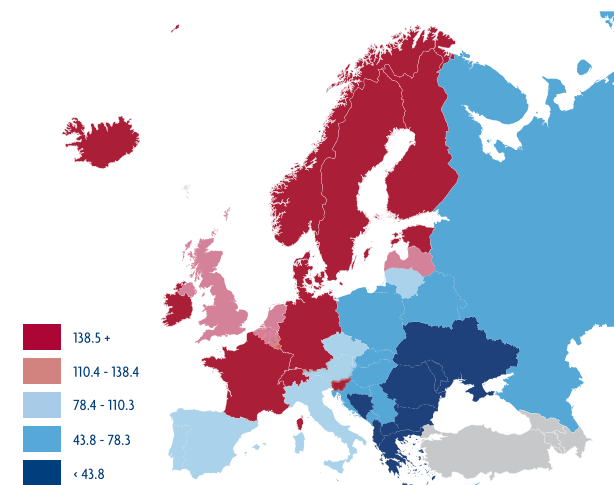


Figure 1: Estimated incidence prostate cancer in men, 2012

The disparities in incidence between countries are likely to be due to differences in the prevalence of risk factors (ageing

population, ethnic origin and genetic factors), the availability of detection tools primarily the prostate specific antigen (PSA) test in population screening programmes, the precision of disease coding/recording and differences in nutritional behaviour and lifestyle. The incidence of advanced PCa in some countries is likely a reflection of the late detection because of the lack of awareness of the necessity of early detection or the lack of proper diagnostic tools⁴.

Unacceptable inequalities persist in PCa survival, which varies from 88% in Central European countries to 72% in Eastern European countries⁵ (Fig 2). The variation in mortality between countries may be due to differences in the quality of care or an unequally implemented early detection programme⁴.

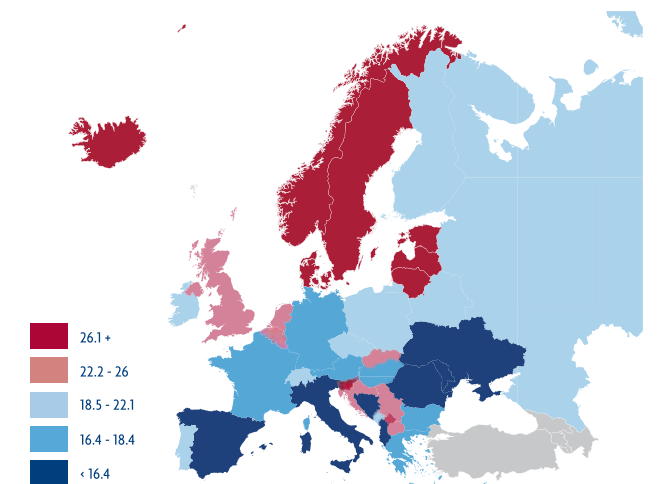


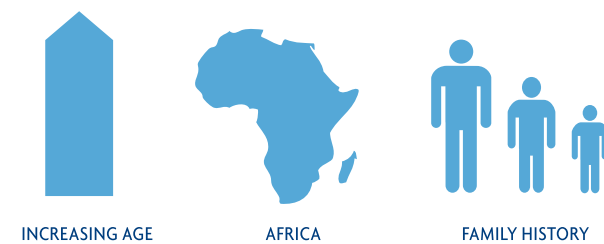
Figure 2: Estimated mortality from prostate cancer in men, 2012

The health care burden of PCa is expected to increase dramatically throughout Europe over the coming years. The EU must raise greater awareness of PCa, highlighting the risk factors, symptoms, treatment options, quality of life issues and social consequences. This report also aims to raise awareness of early detection strategies and the necessary implementation which is monitored at the EU level and national level. Additional investments in clinical research and new technologies are necessary for improving diagnostic and therapeutic accuracy which will contribute to the development of new treatments, which could result in better stratified management of PCa in Europe.

2. RISK FACTORS AND PREVENTION

ESTABLISHED RISK FACTORS

The three well-established risk factors for PCa are increasing age, ethnic origin and family history.



INCREASING AGE

The risk of developing PCa increases with age. The average age at the time of diagnosis of PCa is 69 years.

ETHNIC ORIGIN

PCa is most commonly diagnosed in men of African descent and least in Asian men. It is still unknown what causes these differences.

FAMILY HISTORY

Men with a family history of PCa are at higher risk of developing the condition themselves. Family history is an often lacking or insufficiently explored risk factor.

RISK FACTORS WITH CONFLICTING OR LIMITED EVIDENCE

A meta-analysis evaluated the association between metabolic syndrome, its components and the risk of PCa. Among the individual components of the syndrome (body mass index,

dysglycemia or dyslipidemia, high triglycerides, low HDL-cholesterol) only hypertension and waist circumference (>102 cm) are associated with a trend towards higher risk of PCa, increasing it by 15% (p=0.035) and 56% (p=0.07) respectively.

Although associations vary with geography, metabolic syndrome is weakly associated with PCa risk⁶. A recent systematic review and meta-analysis demonstrated that hypertension may be associated with an increased risk of PCa. Well-designed studies are needed to confirm these preliminary findings⁷. There is still conflicting evidence regarding the association of obesity (body mass index ≥ 30) and the risk of developing PCa. However, obese men with PCa are more likely to have aggressive disease⁸. Exogenous factors such as obesity may have an important impact on the progression of PCa.

"OBESE MEN WITH PCa ARE MORE LIKELY TO HAVE AGGRESSIVE DISEASE"

NO HIGH-LEVEL EVIDENCE-BASED PREVENTIVE MEASURES FOR PROSTATE CANCER

It has been estimated that up to half of the cancer burden can be prevented. The European Code against Cancer is a set of recommendations providing advice on cancer prevention to European citizens (www.cancer-code-europe.iarc.fr). Its 4th edition published in 2015⁹, based on the current best available scientific evidence, is an update of the 3rd edition of 2003. The Code including 12 recommendations aims to reduce the cancer risk by informing people how to avoid or reduce carcinogenic

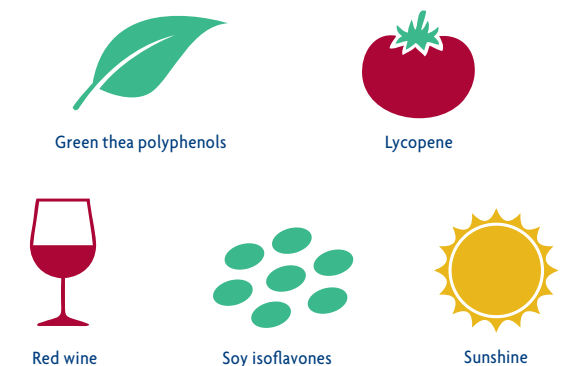
exposures, adopt a healthy life style, or participate in vaccination programmes or organized screening programmes for bowel cancer, breast cancer and cervical cancer. The set of recommendations is approved by a Scientific Committee of leading European cancer experts^{9,10}. Beside these 12 ways to reduce the cancer risk overall, there is currently no high-level evidence that more specific preventive measures may reduce the risk of PCa, in particular.

Given the epidemiological differences between Asia, North America, Northern and Southern Europe it seems that dietary differences (a diet low in animal fat and rich in fruits, cereals and vegetables, specifically non-fermented soy containing isoflavones, a group of phenolic compounds that are considered to be bioactive), may contribute to a lower risk of PCa. A balanced diet and regular exercise are recommended because they are beneficial for overall health. It is advisable for all PCa patients to exercise and maintain a healthy weight.

Currently, there are no data to suggest that pharmacological intervention would reduce the progression of PCa. Although it seems that 5-alpha-reductase inhibitors (5-ARIs) have potential benefits in preventing or delaying the development of PCa (least aggressive disease; Gleason score 6 or Grade 1 disease)¹¹, it must be weighed against the harm of treatment as well as the potential for an increased risk of detecting high-grade PCa¹². None of these agents are EMA approved for PCa prevention. There are conflicting data on the association between the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and PCa risk¹³. A meta-analysis and the results of the REDUCE study did not confirm a preventive effect of statins on PCa risk^{6,14}. Results of a recent Danish study using

nationwide high-quality registry data indicate that statins may lower the mortality rate of PCa¹⁵. Further studies are required.

Currently, there is no high-level evidence that preventive measures may reduce the risk of PCa¹². However, it is suggested that green tea polyphenols, soy isoflavones, phytoestrogens, lycopene, red wine¹⁶ and sunshine may have a favourable effect on PCa prevention.



Large prospective randomised studies are required to define the benefits of potential chemoprevention agents for PCa. Based on the findings from a recent meta-analysis, red meat or processed meat intake do not appear to be associated with increased risk of PCa¹⁷.

Researchers continue to look for foods and dietary supplements that can help lower PCa risk. The options of PCa chemoprevention should be further explored and future research should focus on determining the target population¹⁶. The link between obesity and PCa risk and whether weight loss might reduce the PCa risk should also be investigated in well-designed studies⁸.

3. DIAGNOSIS

DIAGNOSTIC TOOLS

PSA TESTING

PSA testing is a test that measures the amount of prostate-specific antigen (PSA) in the blood. PSA values may be used to estimate the risk of PCa in men. A raised PSA level may be an indication of PCa but it is not specific to cancer. PSA levels may be raised by a benign enlargement of the prostate, a urinary infection or prostatitis (infection of the prostate) or following ejaculation. Conversely, men with PCa may have low or normal levels of PSA. Making the decision to conduct a PSA test depends on many factors, including the policy of the doctor or hospital, or the national health policies of the country. Age and family history are always crucial. The main advantage of PSA testing is that men at higher risk for PCa are more likely to get an early diagnosis and may need less aggressive treatment - thus reducing the risk of side effects such as erectile dysfunction and incontinence. The main setback of PSA testing is detection of indolent tumours that do not need treatment. In other words, many PSA detected tumours might not have caused problems or shortened life of affected men. To prevent over-treatment, some urologists and healthcare funders are against routine PCa screening with regular PSA testing. However, early diagnosis should not necessarily result in over-treatment but enable a risk-adapted therapeutic approach. Stratification of risks at the level of diagnosis is vital to moderate the spiralling rise of incidence and unnecessary treatment.

DIGITAL RECTAL EXAMINATION

Another diagnostic tool is digital rectal examination (DRE) in which the doctor puts a gloved, lubricated finger into the rectum to feel the prostate gland. DRE is less effective for tumours at an early stage, but will successfully diagnose later stage cancers.

IMAGING

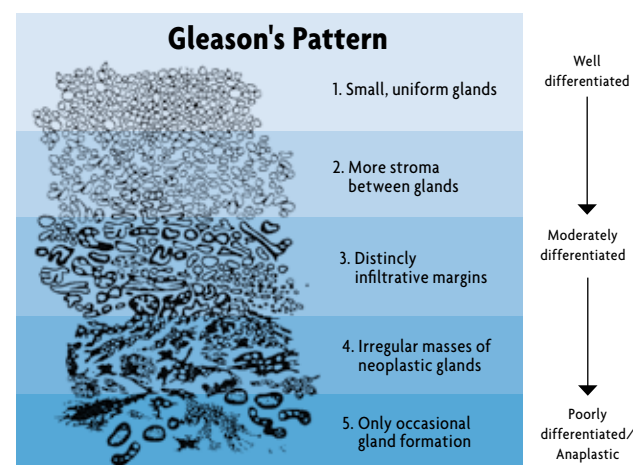
There is a limited role for imaging in primary diagnostics of PCa. The most used tool is transrectal ultrasound. The most promising tool is multiparametric MRI.

BIOPSY

A prostate biopsy is indicated if the PSA is too high, if there is a suspicious result of digital rectal examination or a rapid PSA increase. Prostate biopsy is the only test that can confirm a PCa diagnosis.

HOW ARE PROSTATE CANCER TUMOURS CLASSIFIED?

By analysing tumour tissue, the pathologist determines the characteristics of the tumour. PCa tumours are classified according to the stage of the tumour and the grade of the tumour cells. The tumour stage is based on the TNM classification. It describes how large, invasive and advanced the tumour is (T stage) and whether or not the cancer has spread to the lymph nodes (N stage) or other parts of the body (M; metastases). The Gleason (G) score provides a rating that helps predict the aggressiveness of the cancer cells and how fast the tumour will grow. The Gleason score ranges from 6 to 10 or grade 1 to 5 according to the new grading system. A higher Gleason score or grade indicates a more aggressive tumour with a worse prognosis.



The following terms are used to indicate how advanced the PCa is:

LOCALIZED PCA

The cancer is limited to the prostate gland and has not spread. It may be a stage T1 or T2 tumour, depending on the size and where it is located in the prostate. T1 tumours in a normal prostate on digital rectal examination are diagnosed by microscopy. T2 tumours can be either palpated or seen on imaging.

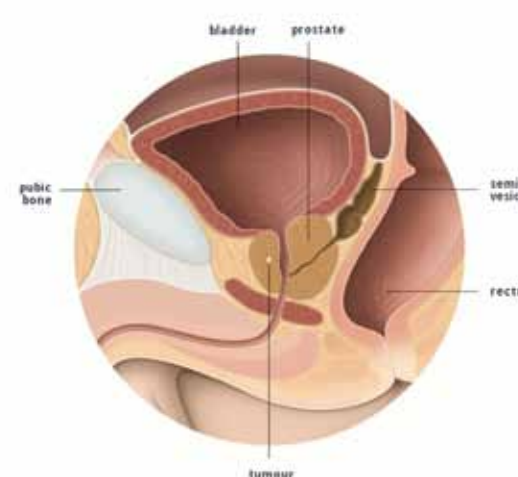


Fig. 1: A T1 prostate tumour is too small to be felt during examination or seen on a scan.

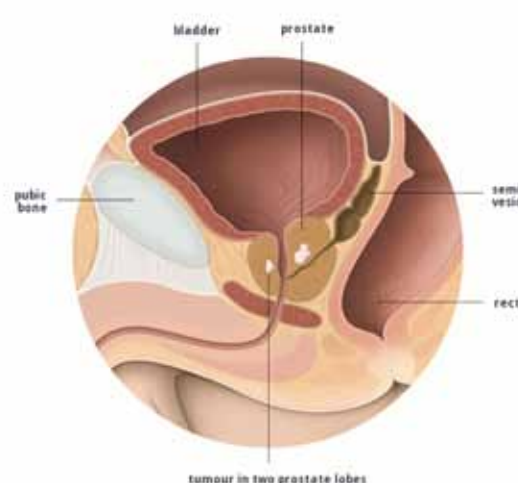


Fig. 2: A T2 prostate tumour is limited to the prostate.

LOCALLY-ADVANCED PCA

The cancer has broken through the capsule surrounding the prostate gland. It may be a T3 or T4 tumour depending on where and how far outside the prostate it has grown.

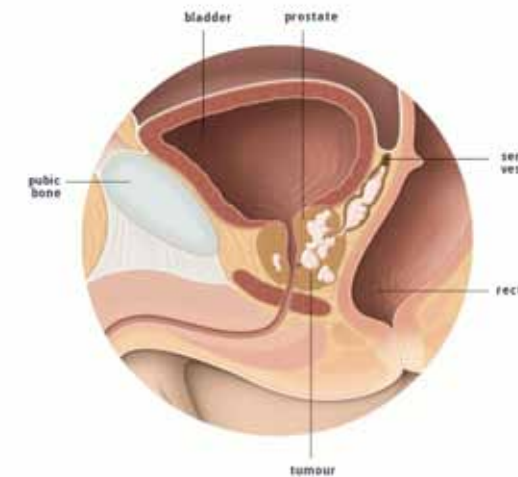


Fig. 3: A T3 prostate tumour which has spread through the capsule or to the seminal vesicles.

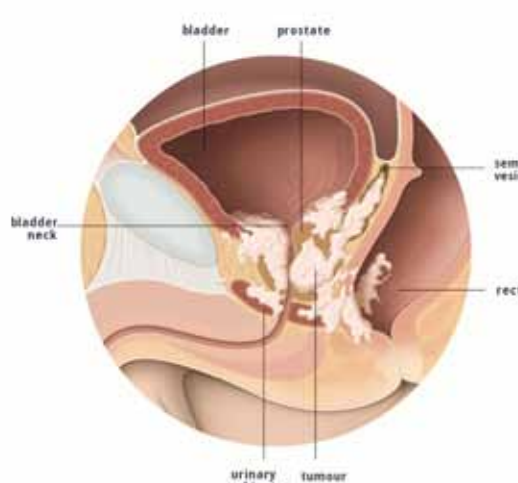


Fig. 4: A T4 prostate tumour which has spread to the bladder neck, urinary sphincter or rectum.

LYMPH NODE POSITIVE PCA

The cancer has spread to the lymph pelvic nodes. The N in the TNM staging stands for lymph node and is split into NX (lymph nodes cannot be checked), N0 (no cancer cells in the lymph nodes) and N1 (cancer cells detectable in the lymph nodes near the prostate).

METASTATIC PCA

The cancer has spread to other parts of the body such as the bones or the spine and at a later stage to the lungs, the liver, distant lymph nodes, and the brain. Metastatic PCa cannot be cured. Instead, the treatment will try to slow the growth of the tumour and the metastases.

CASTRATION-RESISTANT PCA

Usually develops during treatment for metastatic disease. The tumour and metastases continue to grow because the PCa cells no longer respond to hormonal castration treatment. This generally happens 2-3 years after hormonal therapy started. In a recent study, the median time to metastatic castration-resistant PCa after hormonal castration treatment was 11 months¹⁸. Castration-resistant PCa can be treated by many new emerging treatments and drugs that can prolong cancer specific survival.

ASSESSING THE RISK OF DEVELOPING PROSTATE CANCER

Three well-established risk factors for PCa have been identified: increasing age, ethnic origin and family history. The classification of the tumour combined with age, family history and general state of health is used to form the risk stratification of PCa.

THE MULTIDISCIPLINARY MEDICAL TEAM

- **Urologist:** a urologist specializes in health and diseases of the urinary tract, he or she is usually a surgeon
- **Medical oncologist:** a medical oncologist specializes in all types of cancer and uses drugs to treat them
- **Onco-urologist:** an onco-urologist specializes in urological cancers of, for instance, the bladder, kidney, prostate, or testicles
- **Radiation oncologist:** a radiation oncologist uses radiation therapy to treat cancer
- **Pathologist:** a pathologist studies tissue, blood, or urine to understand the specific characteristics of diseases. In cancer treatment, the pathologist helps with the classification of tumours
- **Radiologist:** a radiologist specializes in imaging techniques and analyses ultrasound, CT, MRI, or other scans done to diagnose or monitor a tumour

This allows clinicians to develop a treatment plan and to determine a patient's prognosis.

Screening methods based on the commonly-used biomarker PSA have low specificity and can result in over-diagnosis and over-treatment of localized tumours that might never progress to symptomatic cancer. Screening should therefore target high-risk men who will benefit from early detection. The development and application of multivariable risk-prediction tools and novel biomarkers will help men to find out their risk category and improve the accuracy of PSA screening. Currently available risk-prediction tools include the PCa Prevention Trial (PCPT) risk calculator, the European Randomised Screening Study on PCa (ERSPC) risk calculator, and the Sunnybrook risk calculator. Specific genetic mutations linked to PCa have been identified and have resulted in the development of new biomarkers. PCa antigen 3 (PCA3) and TMPRSS2-ERG are promising PCa-specific biomarkers that can be measured in urine but which are not often used in clinical practice. It is suggested that the integration of genomic tests may advance the diagnosis of PCa through early identification of high-risk patients who might benefit from screening or from chemoprevention trials. Some of these tests may also be useful in distinguishing aggressive from non-aggressive forms of PCa¹⁹.

RESEARCH

There is a need to develop research on lifestyles and their actual contribution to the forming of the risks factors and the resulting stratification of populations according to these risks. Additionally, there is an urgent need for the research into the differences based on the delivery of PCa care and on the outcomes and to provide experience-based data that could improve and optimise services (including qualitative and systems' research).

Risk based assessment and targeted screening will be necessary to improve PCa outcomes. Risk-prediction calculators need to be further improved¹⁹ to better identify clinically significant tumours. Research into diagnostic PCa biomarkers continues²⁰. Image-guided fusion biopsies²¹ and the colour Doppler ultrasound²² (which measures blood flow within the prostate) may make biopsies more accurate (tumours often have more blood vessels around them than normal tissue).

Newer imaging methods, based on Magnetic Resonance Imaging (MRI) are becoming invaluable to PCa management. These include multiparametric MRI²³, enhanced MRI, multiparametric ultrasound, and novel positron-emission tomography (PET) tracers such as choline and prostate-specific membrane antigen (PSMA)²⁴.

4. TREATMENT

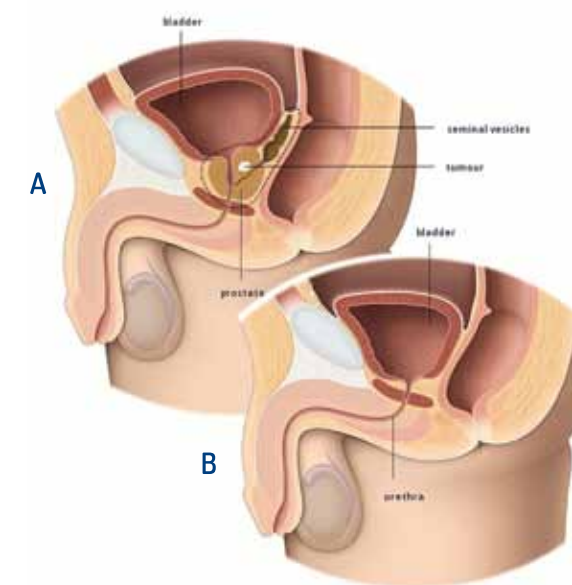
HOW IS PROSTATE CANCER TREATED?

The most important factors for selecting treatment are the stage and the aggressiveness of the disease. Other factors are individual life expectancy, general state of health and the preference of the individual patient who may give more weight to aspects of quality of life. It should also be borne in mind that individual recommendations may depend on the country and health care system.

LOCALIZED AND LOCALLY ADVANCED PCA

RADICAL PROSTATECTOMY

A surgical treatment in which the entire prostate and the seminal vesicles are removed.



Situation before (A) and after (B) radical prostatectomy.

RADIATION THERAPY

To control and destroy cancer cells [external beam radiation therapy or internal radiation therapy (brachytherapy)]. Radiotherapy can be given either alone or combined with androgen deprivation therapy.

ANDROGEN DEPRIVATION THERAPY

Hormonal therapy to stop the production or block the action of male sex hormones (androgens) that help the tumour grow.

In the past, men were sometimes offered orchiectomy (the surgical removal of the testicles) to stop the production of testosterone. Today, androgen deprivation therapy with drugs has replaced this approach as it is less invasive and the effects are reversible. A wide variety of drugs are now available and treatment most often consists of:

- Continuous gonadotropin releasing hormone (GnRH) agonist or antagonist therapy (depot injections)
- Maximal androgen blockade (MAB): combination of GnRH with anti-androgens (oral)
- Intermittent androgen deprivation therapy

These drugs can also be given in combination with surgery or radiotherapy.

ACTIVE SURVEILLANCE

A way of not immediately treating a recently detected localized PCa, but monitoring the disease using serum PSA levels and repeat biopsies to delay or avoid active treatment and possible side effects. Active treatment options will be proposed when signs of progression occur. Active surveillance (AS) is an alternative to radical treatment for highly selected low-risk patients with the lowest risk for progression. It is a non-curative management modality. Because of the connotations in the public mind concerning any form of cancer the option of postponing radical treatment by AS may be seen by some men as counter-intuitive. Where men with a low-risk diagnosis are being offered such treatment options they may need significant additional advice on the pros and cons and a clear understanding of the likely post-treatment effects of radical treatments in terms of the patient's quality of life.

WATCHFUL WAITING

Away of monitoring as a less intensive type of follow-up, relying more on changes in a man's symptoms to decide if treatment is needed. Other treatment options will be selected only when symptoms appear. It is a treatment modality for patients not eligible for local curative treatment and those with a shorter life expectancy.

EXPERIMENTAL LOCAL TREATMENTS

Cryosurgical ablation: a minimally invasive surgical treatment in which controlled freezing kills the cancer cells.

High-intensity focused ultrasound (HIFU): uses the energy of high-frequency sound waves to heat and destroy the cancer cells. Photodynamic therapy: A non-invasive technique to destroy only small tumours in the prostate. Tumour cells are targeted directly while sparing the surrounding normal tissue.

METASTATIC PCA

Androgen deprivation therapy: surgical or medical castration and anti-androgen drugs. For patients with newly diagnosed metastatic PCA, the addition of chemotherapy with docetaxel has shown to improve survival dramatically.

METASTATICCASTRATION-RESISTANT PCA (MCRPC)

Research on mCRPC is ongoing and treatment options change quickly.

NEW HORMONAL AGENTS

Used when standard hormonal treatment is no longer effective e.g. abiraterone acetate and enzalutamide.

CHEMOTHERAPY

Uses chemicals to kill or stop the growth of metastatic cancer cells (e.g. docetaxel and cabazitaxel).

PERSONALIZED IMMUNOTHERAPY

Restores or enhances the ability of the immune system to fight the cancer cells, e.g. Sipuleucel-T. The patient's own blood cells (dendritic cells) are prepared and upregulated in vitro and then given back to the patient. This leads to better recognition and destruction of the cancer in the individual patient.

BONE-SEEKING RADIONUCLIDES

Ra-223 is an intravenously administered bone seeking radionuclide that has been associated with improved survival in patients with mCRPC. Zoledronic acid and denosumab are bone targeted agents that can be used to decrease the risk of skeletal-related complications, that result from metastases in the bones.

RESEARCH

New radiation techniques [intensity modulated radiation therapy (IMRT), proton beam radiation, image-guided radiotherapy (IGRT) and high-dose-rate (HDR) brachytherapy] aim to increase the

effectiveness of therapy while reducing the side effects²⁵.

New surgical techniques such as robotic assisted laparoscopy are now used more and more frequently. Several newer forms of hormone therapy are now being studied. 5-alpha reductase inhibitors are being tested, either in addition to active surveillance or if the PSA level rises after surgery. New chemotherapy drugs and combinations of drugs are being studied as well.

Cancer vaccines to treat PCA are being tested in clinical trials. A new promising approach in PCA research is the use of immune checkpoint inhibitors that help the body to restore the immune system and recognize and attack cancer cells. These agents are, for example, nivolumab, pembrolizumab and atezolizumab which target the immune checkpoint protein PD-1/PDL1 and ipilimumab which targets the checkpoint protein CTLA-4.

Future goals are to investigate the effect of immune therapy combinations and immunotherapy combined with conventional cancer therapies. The strategy of checkpoint blockade represents one of the recent main oncological breakthroughs with good results in several cancer types, but so far rather disappointing results in PCA^{26,27}.

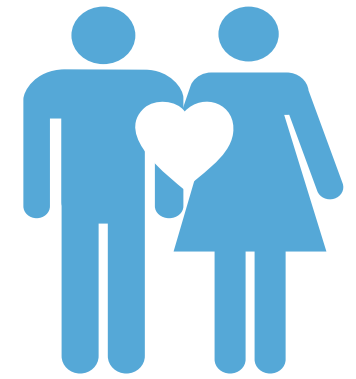
Several new targeted drugs such as angiogenesis inhibitors which target the growth of the new blood vessels that tumours need to grow, are under development and some are currently under investigation in clinical trials e.g. cabozantinib²⁸.

New research on gene mutations linked to PCA may lead to the development of new drugs which target those genetic changes (personalized medicine)²⁹.

In light of these interesting developments, it is crucial to ensure equal and fair access to innovative treatments for all European PCA patients who would benefit from them. Equitable access to innovation is fundamental to decrease the already high degree of inequalities in PCA care and survival.

It is essential to take into account both the quality as well as the quantity of life. Individual's preferences may be different from the health professionals' perspective. These aspects have to be explored and researched, especially in view of the incoming therapies, which sometimes extend life expectancy at very modest or no added value in terms of the quality of life.

5. LIVING WITH PROSTATE CANCER



As the number of PCA survivors is increasing, patients, general practitioners and the broader public should be better informed about the needs of cancer survivors in order to improve their quality of life. PCA and its treatment can affect men physically and emotionally. It may have a significant impact on their everyday life, work, social life and sexuality.

Patients need to obtain balanced and fair information on the advantages as well as the adverse side-effects of their treatment plans. They need to be able to decide on their own choices and preferences (adapted to their level of acceptance, culture and societal expectations).

If PCA patients have no symptoms of PCA they can usually continue with their daily activities. However, just as importantly, they may be anxious about their prognosis. This may make them feel nervous and depressed. If PCA progresses, survivors may need help from family, friends, or professional home carers to do their daily activities. After surgery or other treatment, such as radiotherapy or chemotherapy, they will probably feel tired or sick and may have to stop working at least for a period of time.

Treatment of PCA can have several side effects which may interfere with daily life requirements. Common side effects of radiation therapy are a burning sensation when urinating, urinary frequency and anal irritation. Radical prostatectomy may cause stress urinary incontinence. Another common risk of radical prostatectomy is erectile dysfunction (impotence), which also exists with radiotherapy but often to a lesser extent. Younger PCA patients should be informed about existing fertility preservation techniques. Androgen deprivation therapy has serious side-effects including osteoporosis, anemia, hot flashes, erectile dysfunction, loss of muscle mass, breast tenderness and growth of breast tissue, decline in cognitive function, depression, weight gain, metabolic changes, and an increased risk of cardiovascular events. Intermittent androgen deprivation therapy has been widely tested to reduce side-effects and costs and to delay the development of castration resistant PCA³⁰. The side effects of

treatment or the fact that patients feel too sick or tired can make it difficult for them to take part in social activities. This can make them feel lonely or isolated from others.

The role of patient organisations is pivotal to provide support and more detailed information about coping with PCA in relation to the socio-economic difficulties and their cancer survivorship way of life. In particular, the European Association of Urology (EAU) plays a role in providing more and better information to patient organisations for them to raise awareness on the specific needs of PCA patients on:

- Physical, psychological, sexual, and nutritional rehabilitation
- Late effects related to the treatment, with particular regard to the metabolic syndrome
- The issue of returning to work after the acute treatment phase

Many middle-aged men in Europe and North America are notorious for not maintaining a healthy lifestyle. If they are obese on diagnosis, the importance of adopting lifestyle changes, during and after treatment, should be emphasized - including a healthy diet and regular physical activity. Evidence is building that exercise can help men with PCA to reduce their symptoms and improve their quality of life³¹. Therefore, it is likely that exercise and lifestyle adaptations may be important for men with PCA as early as possible after diagnosis. Secondary and tertiary prevention are essential for all patients.

After treatment for PCA a PSA test and eventually a digital rectal examination, will be performed during regular follow-up visits. Follow-up is important to check general health, to manage any side effects from treatment, to watch for a return of the PCA (known as recurrent PCA), and to watch for other types of cancers.

All the steps of proper follow-up should be included into a personalized PCA survivorship cancer plan, to empower individual patients and make sure that each patient would have all the information and would retain full control over his life after the acute treatment.

6. THE ROLE OF THE EUROPEAN ASSOCIATION OF UROLOGY

The EAU is the leading authority within Europe on urological practice, research and education. Overall 16,000 medical professionals are members and contribute to our mission: to raise the level of urological care throughout Europe and beyond. The EAU has carried out a range of activities specifically focused on PCa which have contributed to improve medical practice and patient care in different ways.

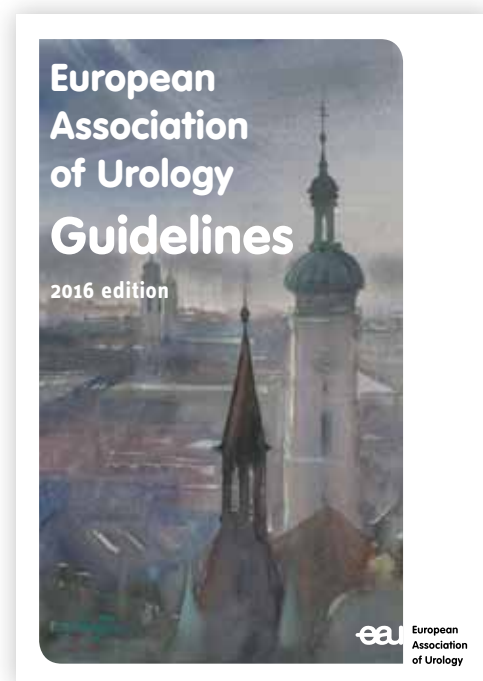
EDUCATION

The EAU provides the latest scientific evidence, expert recommendations and high quality information on PCa for medical professionals and patients (e.g. patient information leaflets) in 16 European languages. The European School of Urology (ESU) meets the educational needs of urologists on behalf of the EAU Education Office. Medical professionals benefit from online education, webinars, teaching courses and surgical training. The up-to-date information provided is in line with the EAU Prostate Cancer guidelines to guarantee consistency in content and quality.

EAU GUIDELINES

The PCa guidelines are officially endorsed by the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Society of Geriatric Oncology (SIOG). The PCa panel has prepared guidelines (www.uroweb.org) to assist practicing clinicians in making evidence-based treatment decisions and improve patients' care. They are implemented and updated annually based on a structured literature search and systematic reviews. The PCa panel consists of an international multidisciplinary group of urologists, radiation oncologist (official representative of ESTRO), medical oncologists, a radiologist (official representative of ESUR), a pathologist, and a patient stakeholder organisation representative.

The EAU guidelines were recently updated with the treatment guidelines for senior adults (i.e., aged 70 years or older) with PCa, developed by SIOG. These patients should be treated according to their individual health status and not according to their numerical age.



Currently, screening for PCa is one of the most controversial topics in urological literature³². The EAU performed a systematic review of the published literature from 1990 to 2013 and updated its recommendations for PCa screening³³. The updated EAU guidelines recommend on early detection of PCa, as published in European Urology, the world highest impact journal in the field of urology¹⁹:

- *Early detection reduces PCa-related mortality [in combination with guideline-based treatment].*
- *Early detection reduces the risk of being diagnosed with and developing advanced and metastatic PCa.*
- *A baseline serum PSA screening should be offered to all men 40-45 years of age to initiate a risk-adapted follow-up approach with the purpose of reducing PCa-related mortality and development of advanced or metastatic disease.*
- *The screening interval should be every 2 to 4 years if the patient's baseline PSA is greater than 1 ng/ml at 45-59 years of age and every 8 years if their baseline PSA is less than or equal to 1 ng/ml.*
- *PSA screening should be offered to men with a life expectancy of 10 or more years, independent of their chronological age.*
- *The use of multivariable risk-prediction tools need to be integrated into the decision-making process to improve the accuracy of PSA screening and to prevent over-diagnosis and over-treatment.*

The findings of an updated publication³⁴ were almost identical to those of the 2013 Cochrane review.

Since 2013, the European Randomised Study of Screening for Prostate Cancer (ERSPC) data have been updated with 13 years of follow-up³⁵. These data show that mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However, the number needed to screen and to treat is decreasing and is now below the number needed to screen observed in breast cancer trials. The recommendations for screening and early detection are further updated in the 2016 EAU guidelines¹².

Population-based screening without criteria is not recommended, while individual early detection in a well-informed patient based on DRE and PSA testing should be endorsed. Individual screening requires the informed consent of the patient following discussion with their physician on the pros and cons of the procedure, taking into account the patient's risk factors, age and life expectancy. The interval for follow-up screening depends on the patient's age and baseline PSA level.

The 2016 EAU guidelines¹² recommend:

- Not subjecting men to PSA testing without counselling them on the potential risks and benefits
- Offering an individualized risk-adapted strategy for early detection to a well-informed man with good performance status and a life expectancy of at least 10-15 years
- Offering early PSA testing in men with an elevated risk of having PCa:
 - over 50 years of age
 - over 45 years of age with a family history of PCa
 - African-Americans over 45 years of age
 - PSA greater than 1 ng/mL at 40 years of age
 - PSA greater than 2 ng/mL at 60 years of age
- Offering a risk-adapted strategy (based on initial PSA level) with follow-up intervals of 2 years for those initially at risk
 - PSA greater than 1 ng/ml at 40 years of age
 - PSA greater than 2 ng/ml at 60 years of age
- Postponing follow-up to up to 8 years in those not at risk.
- Deciding on the age at which early diagnosis should be stopped based on life expectancy and performance status; men who have a life-expectancy of less than 15 years are unlikely to benefit based on data from the PIVOT and the ERSPC trials^{35,36}.

Future updates of the EAU guidelines should take into consideration the recommendations made by the European Commission's Joint Action on Cancer Control (CANCON) in relation to the creation of survivorship cancer plans, to be provided by the urologist to the patients as a guide to facilitate the return of the patient to a normal life.

The EAU guidelines on PCa have been endorsed by the national societies of all 28 EU Member States and in 27 countries outside Europe including China, Australia, India.

The EAU's Patient Information Initiative has produced patient information leaflets on PCa with the help of medical experts, patient groups, specialized nurses, PCa patients, a medical writer and medical illustrator. All participated in the writing and critical review of the information ensuring it is understandable for the general public. The medical facts in

these patient information leaflets are consistent with EAU guidelines ensuring the information is unbiased and reliable.

EAU patient information offers detailed information on diagnosis and treatment of localized, advanced and metastatic PCa as well as on palliative care and a frequently asked questions section for patients and their relatives. To better understand the treatment path, EAU patient information on PCa is supported by educational images that illustrate diagnostic and surgical procedures. Information leaflets on PCa have been translated into seven languages, including English, German, Spanish, Bulgarian, Czech, Polish and Turkish. Translation into Chinese and Portuguese are underway.

The EAU patient information on PCa is part of the *EAU Patient Information Project* (patients.uroweb.org), which started in 2012. It covers 9 urological conditions and has been translated into 15 languages. More urological topics are under development and are expected to be launched in 2017.

THE ROLE OF PERSONALIZED MEDICINE

The idea behind personalized medicine is tailoring health care to a patient's individual genetic make-up. Personalized medicine is characterized by the identification of 'new' biomarkers for selecting the best targets for an individually personalized therapy.

New research on gene mutations linked to PCa (inherited genetics and acquired genomic events) may lead to the development of diagnostic and prognostic markers, risk-stratification and more effective drugs that target those genetic changes (targeted therapy). These new personalized treatments may further improve clinical effectiveness and may have fewer side effects.

Genomic tests will help to find out a patient's risk category and to tailor treatment for PCa patients. The Oncotype DX Prostate Cancer Test might help to select candidates for active surveillance. The Prolaris test might impact the follow-up of patients at risk. The Decipher test might detect candidates for early adjuvant treatment in high-risk groups. The combination of clinical criteria and genomic tests might improve the personalisation of treatment in PCa patients^{37,38}.

The EAU organized a roundtable meeting on the subject in 2015 and recognized the need for personalized medicine in the treatment of urological cancers. It was also one of the topics discussed at the European PCa Awareness Day (EPAD) in 2015 and at the EU-level expert policy roundtable in 2016. The EAU is collaborating with the European Alliance for Personalized

Medicine (EAPM) which this year organized the first Summer School on personalized medicine specifically designed for clinicians and healthcare professionals.

There is still a need to increase awareness on the potential of personalized medicine to both European and national decision makers. To achieve this goal, the EAU will partner with the large European Cancer Patient Coalition (ECPC) and the European Prostate Cancer Coalition (Europa Uomo) to ensure that patients and policymakers are aware of the need to facilitate research into personalized medicines for PCa.

FACILITATING ACCESS TO DIAGNOSIS AND TREATMENT - PATIENT-CENTRED MULTIDISCIPLINARY APPROACH

A close collaboration of multiple specialists in addition to urologists, such as pathologists, radiation oncologists, medical oncologists, nuclear medicine physicians, imaging specialists, psychologists, sexual therapists, physiotherapists, geriatricians and experts in palliative and supportive care is important to improve the outcome of PCa, to improve patients' care and to lower the costs. The close involvement of well-informed patient representatives should be part of this approach.

EXAMPLES OF EAU INITIATIVES

- In partnership with Europa Uomo, the EAU organized a European PCa Awareness Day (EPAD) in 2015. Key policy makers, scientific experts, European urological associations and representatives of patient groups gathered at the European Parliament in Brussels to discuss the impact of PCa in Europe.
- The PCa Unit Initiative in Europe: a position paper of the European School of Oncology' describes the minimum criteria for setting up Prostate Cancer Units (PCU) which facilitate access to PCa care in European countries³⁹.
- The European Multidisciplinary Meeting on Urological Cancers (EMUC) focusses during an annual three-day congress on controversial diagnostic issues and treatment strategies with the collaboration of the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the EAU.
- Participation in the International Centre for Parliamentary Studies (ICPS) initiatives on Prostate Cancer and publications in the Government Gazette.

To ensure a true patient-centred approach, PCa patients should be provided with thorough information on multidisciplinary treatment strategies, in order to allow them to make an informed choice on the various possible treatment options for each patient, based on their individual risk-benefit assessment.

7. WHAT CAN THE EU DO?

THE EU ACTIVITIES ON CANCER

Although significant advances are being made in the fight against the disease, cancer remains a key public health concern and a tremendous burden on European societies. It is for this reason that a range of activities on cancer have taken place at EU level to help Member States in the fight against cancer.

In 2003, the EU Health Ministers unanimously adopted a Council Recommendation on cancer screening, setting out principles of best practice in the early detection of cancer. The Recommendation invited all Member States to take common action to implement national population-based screening programmes for breast, cervical and colorectal cancer, with appropriate quality assurance at all levels.

From 2009 to 2013, the Commission ran the European Partnership for Action Against Cancer to help Member States and other stakeholders tackle cancer more efficiently.

In 2014, the European Commission established the Expert Group on Cancer Control. In the same year, an EU Joint Action on Cancer Control (CANCON) was launched to develop an EU Guide on Quality Improvement in Comprehensive Cancer Control. This will provide, among others, also guidance and recommendations concerning prostate cancer screening, its options and feasibility.

More recently, the European Commission initiated a ground-breaking project to develop a European quality assurance scheme for breast cancer services underpinned by accreditation and referring to high quality, evidence-based guidelines. Alongside this, the European Commission, through its consecutive Research Programmes has supported a number of EU collaborative research projects in cancer, including projects specifically focused on PCa.

RECOMMENDATIONS FOR EU ACTION ON PROSTATE CANCER

With this in mind, we believe that there would be value in more action to be taken at EU level to assist Member States to tackle PCa more efficiently.

SUPPORT FOR AN EU-WIDE AWARENESS RAISING CAMPAIGN

Given the EU competence in public health and prevention, the

EU could certainly do more to help raise awareness of medical practitioners and citizens on PCa.

Programmes such as the EU Health Programme could provide support to a pan-European awareness raising campaign on PCa, either through a specific call for proposals for projects on this topic, or through making cancer a priority for framework partnership agreements with European non-governmental organisations.

- The campaign should target, amongst others:
 - Patients and patient organisations, which remain a key source of information for both patients and their carers and could greatly benefit from the dissemination of scientifically validated information on PCa, in particular in the field of survivorship and rehabilitation.
 - General Practitioners (GPs) across Europe, who play a key role in informing patients who are at risk of PCa and raise awareness of the importance of early detection.
- Although there are currently no high-level preventive measures, healthy lifestyles and maintaining a healthy weight should be promoted, targeted in particular at the population at risk of PCa.

'ALTHOUGH THERE ARE CURRENTLY NO HIGH-LEVEL PREVENTIVE MEASURES, HEALTHY LIFESTYLES AND MAINTAINING A HEALTHY WEIGHT SHOULD BE PROMOTED, TARGETED IN PARTICULAR AT THE POPULATION AT RISK OF PCA.'

DEVELOP EU GUIDELINES ON PROSTATE CANCER

The 2003 Council Recommendation recommends population-based screening for breast, cervical and colorectal cancers. To assist the Member States with these screening activities, the Commission has produced European guidelines for quality assurance screening and diagnosis for these cancers. With the quick progress in medical science and the Council Recommendation being 14 years old, it is now time to take a fresh look at it and to consider how the Recommendation could be expanded to cover PCa.

Early detection of PCa is crucial to reduce the risk of developing advanced and metastatic PCa and thus PCa-related mortality. The EAU Guidelines are the most comprehensive and most respected clinical practice guidelines globally. Today, 53 national

urological associations endorse them internationally. The EU should promote early diagnosis of PCa in patients at risk, based on the EAU guidelines (2016) for screening and early detection of PCa (see section EAU Guidelines).

CANCON has specifically considered the step-wise decision-making concerning potential new cancer screening programmes. In light of currently available evidence, some prostate cancer screening policies may be cost-effective but questions remain on the optimal balance of benefit and harm. Based on the assessment utilizing the ERSPC results, a screening programme with three screens at age 55-59 with a two-year interval may be cost-effective (given the threshold value in many European countries), at a reasonable harm-benefit ratio.

MAINTAINING A CONDUCTIVE EU RESEARCH ENVIRONMENT FOR PROSTATE CANCER

The current EU Joint Action on cancer control 'CANCON' has the mission of improving the quality of cancer care across the EU and ameliorating the lives of people living with cancer. The aim of the collaboration is to create a European Guide on Quality Improvement in Comprehensive Cancer Control, which is intended for governments, parliamentarians, health care providers and funders and cancer care professionals at every level.

As the EU considers its plans for the next European Joint Action on cancer, it could prioritise the area of PCa as a work package, and use this as a platform to develop the EU guidelines on PCa, which are referred to in the previous section of this publication. The EU research and innovation programme, Horizon 2020, and its successor can support an environment conducive to translational research in key areas for PCa, such as personalized medicine, in vitro diagnostics (IVDs) and the socio-economic impact of cancer, in order to support three main areas where research gaps are still wide:

1. Prevention

The possibilities of preventive measures for PCa should be further examined and research should focus on determining the target population. The link between obesity and PCa should be highlighted and further investigated.

2. Innovative tools for diagnosis and treatment

- Multivariable risk-prediction tools and biomarkers to differentiate between low-risk and high-risk PCa patients will be necessary to improve the accuracy of PSA screening and to prevent over-diagnosis and over-treatment. Several commercial genomic tests are currently available, but further understanding of the benefits and limitations of these tests is needed. The most studied tests, Prolaris,

Oncotype DX Prostate Cancer, and Decipher may be used in addition to clinical parameters or clinical nomograms to guide clinical management of diseases (e.g. surgery vs. active surveillance), but to date, there are no established predictive biomarkers to choose one particular treatment for the individual patient.

- Personalized medicine is characterized by the identification of 'new' biomarkers for selecting the best targets for an individually personalized therapy. This is a promising direction since clinical effectiveness and quality of life may further improve. However, the problem with PCa is that it often presents as multifocal/multiclonal lesions with different metastatic potential. Once a personalized treatment is started, other PCa cell clones may take over the lead with new metastatic potential. The multiplicity of potential 'new' biomarkers may lead to individualized risk assessment guiding biopsy and treatment decisions. Research projects for personalized management of PCa should be supported.
- Newer techniques that make biopsies and imaging more accurate should be encouraged.

3. Novel therapies

- There is a need to support new developments in immunotherapy for PCa. Candidates for new drugs are immune checkpoint inhibitors e.g. T-lymphocyte-associated protein 4 (CTLA-4) and the programmed death protein 1/ programmed death ligand (PD-1/PD-L1). Use of these promising drugs in combination with other cancer drugs is under investigation. The research on tumour vaccines continues.
- Several newer forms of hormone therapy are being tested.
- New chemotherapy drugs and combinations of drugs and optimal drug timing are being studied as well. Several new targeted drugs such as angiogenesis inhibitors are currently under investigation in clinical trials.
- Research on newer radiation techniques that aim to increase the effectiveness of therapy while reducing the side effects should be continued.

The EU can also use the Innovative Medicines Initiative (IMI2) – the world's largest public private partnership between the European Commission and the European Pharmaceutical Industrial association, EFPIA to fill some of the gaps in the research pipeline for PCa. The 2016 IMI call for proposals on how big data could support better diagnosis and treatment outcomes for PCa is a welcome initiative and could lead to further collaboration between industry and other non-profit stakeholders to speed up the development of better and safer medicines for patients with PCa.

8. CONCLUSIONS

The European Union needs to raise men's awareness of PCa as well as consistent EU actions in this area. PCa is a considerable healthcare problem that would benefit from a uniform EU-wide risk adapted early detection programme for PCa.

The EU needs to increase funding to improve both the diagnosis and treatment of men with PCa. It needs to fund work to better understand the association between potential risk factors and lethal PCa.

1. With more than 417,000 men diagnosed and more than 92,000 men recorded dying from PCa, European institutions and Member States need to ensure that PCa patients receive high quality, standardized, and integrated care with a focus on a patient-centred multidisciplinary approach.

2. The EU and its Member States should also ensure equitable access to novel technological tools that enable better diagnosis, treatment and research. The future is likely to encompass risk adapted treatment programmes that require contemporary imaging and diagnostic tools.

3. Access to innovative treatments and personalized medicines should be made fast and equitable for all PCa patients who can benefit from them. This aligns with Health Ministers EU Council Conclusions that were issued by Luxembourg and Dutch EU Presidencies of 2015 & 2016.

4. Prompt and consistent Health Technology Assessment (HTA) should be performed on all new screening, diagnostic, therapeutic and rehabilitation technologies in order to provide the base for effective and efficient, targeted and optimised allocation of resources in urology and specific prostate cancer services.

5. It is essential to sustain awareness campaigns, both at European and national level and to help achieve the main goals set out in this paper.

6. Finally, the EU and its Member States should promote the implementation of survivorship cancer plans, including specific plans for PCa patients, to facilitate the return to a normal life for all European PCa patients.

The EAU has a wealth of expertise, scientific resources and tools targeting both clinicians and patients on which the EU work on PCa could build and expand. In collaboration with PCa patient advocacy groups, the EAU will actively engage with all EU institutions to create a better future for all Europe's PCa patients.

The role of PCa patient advocacy groups is also extremely important to sustain awareness campaigns, both at European and national level and to help achieve the main goals set out in this paper.

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