EUROPEAN
CANCER
PATIENT
COALITION

WHITE PAPER
BLADDER CANCER

2016

CONTENTS

FOREWORD

Bladder cancer is the fifth most common cancer in Europe, yet resource provision including funding for research and reimbursement of new medicines does not reflect the high disease burden or societal cost. This lack of investment has resulted in few new treatment options being available to patients, delayed diagnosis and low survival rates. Currently, up to half of all people diagnosed with bladder cancer in Europe, will die within five years.

While some steps have been taken to address the preventable risk factors associated with bladder cancer, there is still much more that can be done at a European level.

European organisations have an important role to play in mandating safer working conditions and improved monitoring & reporting practices for workers interacting with potentially carcinogenic chemicals and materials – the second most common cause of bladder cancer after smoking. They can also support the development of treatment guidelines and counselling best practice, as well as encouraging the formation of multidisciplinary teams and treatment units to improve patient outcomes.

More broadly, ensuring greater resources are provided for research into prevention, diagnosis and treatment at a European level will also go a long way towards improving outcomes for bladder cancer patients.

As an organisation dedicated to ensuring that all European cancer patients have timely and affordable access to the best treatment and care available, we have facilitated the development of this paper to highlight some of the key challenges to improving patient outcomes in bladder cancer. Equally importantly, we have additionally identified areas where there are opportunities to unlock a brighter future for those diagnosed with the disease.

The content has been developed with the support of many well-respected experts in urology across from across Europe, and we hope the recommendations can act as a starting point for the paradigm shift we so desperately need in this neglected, yet deadly disease area.

FRANCESCO DE LORENZO,
PRESIDENT, ECPC

EXECUTIVE SUMMARY

This paper is the result of six months of discussions between members of the ECPC Expert Group on bladder cancer; a working group bringing together recognized experts in the field including urologic oncology (surgery), medical oncology and urologists. Its development was facilitated by the European Cancer Patient Coalition (ECPC).

The working group focused on three key areas they believe will improve patient outcomes in bladder cancer – prevention, diagnosis and treatment.

The following recommendations for the European Commission and member countries were developed in-line with the discussions that took place, and that are set out in this paper:

1. Continue efforts to reduce tobacco consumption in Europe – the main cause of bladder cancer
2. Raise awareness of bladder cancer risk factors and early symptoms amongst clinicians and high risk groups
3. Consider initiatives to reduce and monitor the exposure to carcinogenic chemicals
4. Ensure occupational health and safety legislation encourages continuous health surveillance for those at high risk of developing occupational cancers as well as improved prevention measures and timely access to diagnosis, treatment and care
5. Invest in trials to identify the best approach to early detection in high risk groups
6. Address the lack of resources available for bladder cancer including research funding and reimbursement of medicines
7. Ensure all experts are trained in bladder cancer risk factors to enable them to make connections between exposure and disease
8. Ensure patients have access to multidisciplinary units involving: urologists, medical oncologists, radiation oncologists, pathologists, radiologists, psycho-oncologists, physiotherapists, and palliative care experts

1. INTRODUCTION

INTRODUCTION

More than 175,000 people are diagnosed with bladder cancer in Europe each year; and this number is rising.[1]

In 1985, the European Community launched the first Europe Against Cancer Program. Since then, the European Commission (EC) has developed policies tackling major health determinants and the main risk factors that increase the burden of cancer. The first directives against smoking (1992), marketing and use of certain dangerous residues in and on certain products (1990), and exposure to carcinogens at work (1990) were adopted in the early 1990s.

More than three decades on since these public health measures were enacted to tackle the growing burden of cancer, it is clear that not all cancers have been treated equally.

Bladder cancer, the fifth most common cancer in the Western world and the second most frequent malignancy of the urinary tract after prostate cancer[2], still claims more than 52,000 lives each year in Europe[1]. And while survival rates have improved over the past thirty years, with 50% of people surviving their disease for more than 10 years compared to only a third in the 1970s,[1] – there is still a great deal of work to be done.

The EU has been ambitious in supporting Member States in the development of cancer screening programmes, supplemented with guidelines for breast, cervical and colorectal cancers. Yet despite a prevalence of 13.07 % in the EU27, bladder cancer has been overlooked by both decision-makers and the pharmaceutical industry.

Early diagnosis is key to improving survival rates in bladder cancer. When diagnosed at its earliest stage, more than 8 in 10 people with bladder cancer will survive their disease for five years or more, compared with around 1 in 10 people when the disease is diagnosed at the latest stage.[1] General practitioners (GPs) – the gatekeepers of diagnostic tests and specialist care – are not always aware of the symptoms and as a result opportunities to spot this cancer early are being missed, especially in women who have a consistently lower survival rate than men.

One of the key challenges in improving outcomes for bladder cancer is the heterogeneity of the disease. Current funding levels for research do not reflect the burden, nor the complexity of the disease, and this has been reflected in the limited progress in available treatments over the past 25 years. Public and private funders need to commit more resources to improving diagnostic tools and moving towards a more personalised approach to treatment.

With limited resources to tackle the disease, European coordination will be essential to make real progress in the fight against bladder cancer. Benefits of adopting a coordinated approach have been proven in other disease areas, with much more being able to be achieved.

Examples of such activity could be the European Union, investing in futher research to better understand the connection between potential risk factors and bladder cancer. A European Database for bladder cancer under the European Network of Cancer Registries could also go a long way towards improving our understanding of the disease.

The role of patients and patient associations is also extremely important to sustain awareness campaigns, both at a European level and local level, as well as to help achieve the overarching goals outlined in this paper.

2. PREVENTION

2. PREVENTION

UNDERSTANDING BLADDER CANCER RISK FACTORS

While it is not always possible to prevent bladder cancer, many avoidable risk factors for the condition have been identified.

Unfortunately low levels of awareness of these risk factors, and of the symptoms associated with bladder cancer, could be resulting in elevated prevalence and delayed diagnosis.

Smoking

According to the World Health Organization (WHO), in the Western world, tobacco use is the single most important cause of bladder cancer accounting for an estimated 40-70% of all cases.

Smokers are 2-3 times more likely to develop bladder cancer than non-smokers

Risk increases with the length of time and the quantity an individual has smoked. After giving up on smoking the incidence will reduce, but never back to the level of a non-smoker.

The link between smoking and bladder cancer appears to have grown stronger over time. Current smoking was linked with a threefold increase in risk during 1994-1998, a more than fourfold increase in risk during 1998-2001, and a 5.5-fold increase in risk during 2001-2004.[3]

In the past, experts thought that women were less likely to get bladder cancer from smoking than men. New data however, suggests that female smokers are just as vulnerable to bladder cancer and trends in the disease may change as the number of female smokers rises.[4]

Occupational exposure to carcinogenic substances

A high risk of bladder carcinoma has been observed in workers exposed to some substances such as aromatic amines and polycyclic aromatic hydrocarbons (e.g. in dyes, solvents, paints, combustion products, rubber, and textiles).[5]

It has been estimated that 5-10% of bladder carcinomas in industrialized countries were due to exposures of occupational origin.[6]

According to some studies, 21-27% of all bladder cancers in men and 11% of all bladder cancers in women are a result of work exposure.

A recent study concluded that the profile of contemporary occupations with increased bladder cancer risk is broad and differs for incidence and mortality. Incidence seems to be increasing, and the rate of increase is faster in women than men. Improved detection mechanisms and screening have been identified as possible reasons for this.

Workers exposed to aromatic amine experience the highest incidence, while those exposed to polycyclic aromatic hydrocarbons and heavy metals have the greatest risk of mortality.[7]

2. PREVENTION

Other infections

Urinary infections, kidney and bladder stones, bladder catheters left in place a long time, and other causes of chronic bladder irritation have been linked with bladder cancer.

Certain cancer treatments

People with cancer who have been treated with certain drugs (such as cyclophosphamide) may be at increased risk of bladder cancer. Also, people who have had radiation therapy to the abdomen or pelvis may be at increased risk.

Aging

The risk of developing bladder cancer increases with age.

About 90% of patients are aged >55; the average age at the time of diagnosis is 73 years[8,9]

Genetic factors

The risk of developing bladder cancer increases with some genetic conditions such as Single nucleotide polymorphisms (SNP).

Family history

People with a family history of bladder cancer are at a higher risk of developing the condition themselves.

2. PREVENTION

EU ACTION

Smoking

In recent years, the EU and its Member States have undertaken a number of initiatives to address the burden of tobacco consumption across Europe. The Tobacco Products Directive[10] or the international efforts in the context of the WHO Framework Convention on Tobacco Control (FCTC)[11] are important steps to reduce tobacco consumption, promote smoking cessation and protect all citizens from second-hand smoke. While overall these initiatives have been broadly successful, the rate of smoking is increasing amongst women.

Occupational exposure to carcinogenic substances

An effective policy against occupational cancer cannot only be a Member State competence. This should be reinforced with actions at EU level. In June 2014 the Commission published the EU Strategic Framework on Health and Safety at Work 2014-2020 (COM(2014) 0332), which was adopted in Council in March 2015 and in the Parliament in Nov 2015.

A review of the whole body of occupational health and safety legislation is ongoing as part of the Commission's Regulatory Fitness and Performance programme (REFIT), taking account of findings from national implementation reports. Member States recently submitted their national reports on the implementation of 24 occupational health and safety Directives. The Commission is currently analysing the national implementation reports which will feed into the evaluation. The evaluation will pay particular attention to identifying possible simplifications and/or reductions in administrative burden and will be considered as part of the 2016 review of the Strategic Framework.

There is a risk that a simplification could lead to less enforcement or less effective implementation of the legislation. Ideally, a proposal for the revision of Directive 2004/37/EC should be on the basis of scientific evidence adding more binding occupational exposure limit values where necessary and to develop an assessment system.

Also, more stringent protection of workers should be considered, taking into account not only exposure periods but also the mix of chemical and/or toxic substances to which they are exposed i.e. asbestos exposure, musculoskeletal disorders, a strategy on endocrine disruptors or the rising risks related to handling nanotechnology.

Whilst action has been taken to address the exposure of workers to carcinogens, some occupations are at higher risk of exposure than others. The European Trade Union Institute (ETUI) has advocated for a stronger effort at EU level to protect workers against carcinogens. EU action is encouraged on the grounds of more effectiveness.

Initiatives to reduce the exposure to some chemicals or the creation and further improvement of databases on carcinogen replacement at EU level would be very useful in efforts to prevent bladder cancer.

3. DIAGNOSIS

DIAGNOSIS

EARLY DIAGNOSIS: A CHALLENGE AND A NEED

In current clinical practice, most common tests to diagnose bladder cancer include urinalys, cystoscopy, or ultrasound of the urinary tract. Universal screening for asymptomatic bladder cancer will be difficult to apply in clinical practice due to cost.[12] Early diagnosis programmes however, should be implemented for high risk populations: men between 55 and 75 years of age, smokers of both sexes, workers exposed to carcinogenic products and patients with chronic inflammation of the bladder.

One significant challenge is that available non-invasive tests are not accurate enough to correctly diagnose bladder cancer. More research needs to be undertaken, and more needs to be done to educate physicians and the general population about the risk factors that we already know about.[13]

WOMEN ARE MORE LIKELY TO DIE FROM BLADDER CANCER THAN MEN

While the incidence of bladder cancer is four times higher in men than in women, women are more likely to die from the disease than men.[8,14]

Bladder cancer survival rate is consistently poorer in women than in men, with the exception of Eastern Europe. [14, 15] Some suggest this difference is explained, at least in part, by the fact women tend to be diagnosed at a later stage of disease than men; others suggest it could be attributed to the structure of the male lower urinary tract. In addition, often, women are more likely to present with muscle invasive disease.[16]

Clinicians are also less familiar with female bladder cancer patients. Initial symptoms could be attributed to other common conditions, such as a urinary tract infection or uterine bleeding which could cause a delay in diagnosis and referral to specialist care.

CLASSIFYING TUMOURS: SOME PERSPECTIVES

Classifying malignant tumours relies on pathological criteria from the tissue site of origin (organ) with histological and other clinical characteristics of the tumour determining the target and type of therapeutic intervention.

"My heart fell to the pit of my stomach. I thought they were talking about someone else, and then I said to myself cancer has started this fight, and I am going to finish it."

"Not me. There had to be a mistake. I couldn't imagine living with a bag of urine strapped to the outside of my body. I wondered if I would ever feel normal again."

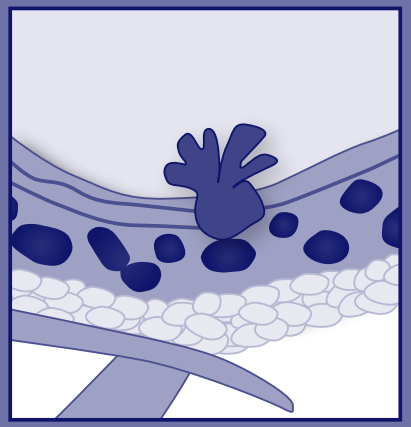
"This was devastating and I felt scared and lonely. Like being hit around the face with a frying pan. I shook from head to toe when I was told."

"In my world time stood still, I heard the words "bladder cancer" from somewhere but it sounded like it would have, had we been walking through a tunnel where the words bounced off the walls and echoed .... I felt cold. It was all too surreal. She wasn't talking about me was she?"

"I felt cold and tears ran down my face without stopping."

DIAGNOSIS

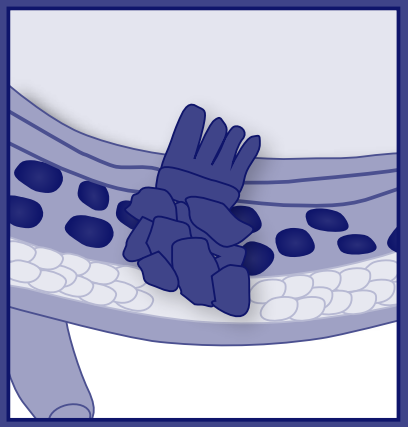
The following classification is used to explain differential pathways of treatment:



NON-INVASIVE DISEASE OR NON-MUSCLE-INVASIVE BLADDER CANCER (NMIBC)

Cancer that has not grown into the muscle wall of the bladder.

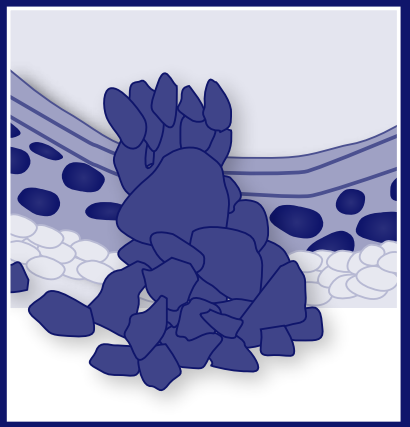
≈51-80% of BC cases are NMIBC at the diagnosis level



LOCALLY INVASIVE DISEASE

Cancer has invaded the muscular wall of the bladder and/or spread to nearby organs and/or lymph nodes.

Invasive bladder cancer is associated with a poor prognosis



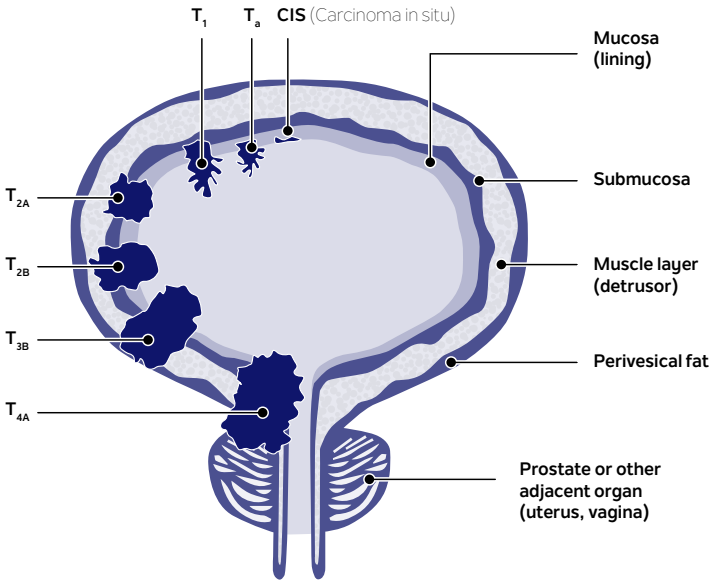
METASTATIC DISEASE OR METASTATIC BLADDER CANCER (MBC)

Cancer that has spread to other parts of the body is called metastatic bladder cancer.

≈4% of patients are diagnosed at this stage

DIAGNOSIS

CIS to T4 - TNM staging system classification of malignant tumours



This approach to classifying cancer, including bladder cancer, is slowly being re-thought as it does not always give an accurate analysis of individual tumours in clinical practice. Consequently, efforts have been taken to complement tumour evaluation with molecular biomarkers and a more precise understanding of the molecular characteristics of tumours is emerging. Such molecular characteristics could help understand the high variability in response to prevention therapies and support in the identification of novel individualised therapies.

Medicine at the molecular level, and the potential treatment applications, could provide a better way to tailor treatment and provide the best outcomes for patients. In bladder cancer this could mean the discovery of novel therapeutic agents leading to better survival rates.

LACK OF MARKERS

A number of markers exist for detection and surveillance of bladder cancers. While these markers may prove to be a better detection method than urinary cytology, the false-positive and false-negative rates need improvement.

The role of bladder cancer tumour markers is an area of significant interest. They could play a significant role in early detection, disease progression evaluation and follow-up of the condition. Further research is needed to potentially improve cancer detection, treatment and prediction of prognosis, as well as the costs and anxiety associated with long-term surveillance.

"Sitting in a waiting room surrounded by men and posters about prostates I never imagined I was about to be told I had bladder cancer at 49. My first thought was that I was going to die because I knew nothing about it. I thought only men got it and that I would lose my bladder and my husband wouldn't find me sexy anymore."

4. TREATMENT

TREATMENT

THE MOST EXPENSIVE CANCER TO TREAT

Due to high recurrence rates, intensive surveillance strategies, and expensive treatment costs, the management of bladder cancer contributes significantly to medical costs.[17] Bladder cancer cost the EU €4.9 billion in 2012, with health care accounting for €2.9 billion (59%) and representing 5% of total health care cancer costs.[18]

A 2012 study estimates that bladder cancer is the most expensive cancer to treat per patient as it requires lifelong monitoring including the repeated use of cystoscopy, blood and urine tests and has a high recurrence rate.[19] The cost of NMIBC is higher than the costs for MIBC due to the high rate of recurrences, which lead to repeated surgical interventions and follow up procedures, including intravesical therapy.[20]

In the UK alone, treatment of bladder cancer costs the NHS €286 millions a year, 5% of the entire cancer health expenditure in 2012.[19] In Italy, a country with an alarming epidemiological pattern of bladder cancer, the annual cost is 7% of total cancer healthcare expenditure.[18]

TREATMENT IN EUROPE

Despite being the fourth leading cause of cancer death in men, and the tenth in women, there has been limited progress in treatment outcomes over the past 25 years.[8] This is not surprising due to the lack of investment in research, innovation and development in this area.

Treatment for muscle invasive bladder cancer has evolved from being purely surgical to multimodal, like in breast, prostate or colon cancers. The biggest challenge today is to improve the ability to predict which patients will respond to which treatments, sparing patients from the unnecessary side effects of therapies that are unlikely to work for them.

Depending on the stage of disease patients will receive different treatments, from endoscopic surgery with or without intravesicale treatment to cystectomy or radio-chemotherapy.[21]

Planning treatment for MIBC involves a team of professionals from different medical disciplines as well as the patient and his/her family. It usually requires a multidisciplinary meeting of different specialists such as urologists, medical oncologists, and radiation oncologists. During the meeting, the treatment plan will be discussed and agreed.

Disease staging and risk assessment are an important part of the treatment process for bladder cancer. Pathological diagnosis should be based on the WHO classification for tumour grading, which stages according to the TNM system.

Prior to and during treatment, it is essential for the patient to be in close contact with his/her treatment team to ensure he/she understands all benefits and risks involved with the treatments available.

It is important to note that since bladder cancer has a high rate of recurrence; patients need to be regularly monitored after treatment is considered complete.

"I actually learned it was stage 4 while I was on chemotherapy. When the doctor told me I froze and then cried seconds later. I was just handed a ***"death sentence"*** *in my mind."*

"Tumour was mentioned and I asked about cancer but was told we would have to wait to see. Then, after 1st TURBT doctor said ***'We think we got all YOUR cancer.'*** *My daughter made him go back and explain properly. He seemed to think we knew all about it."*

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COSTS OF BLADDER CANCER (THOUSANDS OF EUROS) IN THE EUROPEAN UNION, BY COUNTRY, 2012[18]

COUNTRY	HEALTH CARE COSTS						TOTAL CANCER HEALTH EXPENDITURE %	PRODUCTIVITY LOSSES		INFORMAL CARE COSTS	TOTAL COSTS	
	Primary care	Outpatient care	A&E	Inpatient care	Medications	Total health care		Mortality	Morbidity		Total	Total cancer cost %
Austria	1617	2709	1105	34 680	15 784	55 895	4	13 126	9 976	12 153	91 151	3
Belgium	2453	4879	651	33 763	15 922	57 668	5	17 998	18 820	26 503	120 990	3
Bulgaria	416	493	70	2555	2003	5538	4	2776	1905	1567	11 785	3
Croatia	1053	588	2039	2110	3382	9172	4	4537	5382	2881	21 972	3
Cyprus	119	312	123	393	995	1941	6	1130	316	1196	4584	4
Czech Rep.	2793	6836	1320	14 964	9213	35 126	6	7572	7503	6392	56 594	4
Denmark	301	898	264	11 789	9416	22 668	4	21 009	15 804	25 656	85 137	3
Estonia	272	496	237	1485	478	2967	4	1083	598	675	5323	3
Finland	1440	9020	1302	17 395	7202	36 360	4	6817	1 663	7557	52 397	3
France	10 062	15 951	1938	289 682	139 084	456 717	5	97 052	47 475	101 911	703 154	3
Germany	45 531	37 469	989	461 769	64 208	609 965	4	157 594	78 163	170 065	1 015 787	3
Greece	4317	9649	1909	34 199	13 250	63 323	6	10 594	4651	14 035	92 603	4
Hungary	1311	2031	338	7305	10 169	21 155	3	6561	1 606	5671	34 994	3
Ireland	1350	1410	745	10 450	5828	19 782	3	6829	1474	4542	32 627	2
Italy	60 396	67 557	45 120	284 646	76 499	534 216	7	80 530	7671	192 078	814 495	5
Latvia	312	722	63	1029	511	2638	4	1382	494	1155	5669	3
Lithuania	480	470	138	1184	399	2671	4	1875	685	4065	6296	3
Luxembourg	285	516	39	2877	1183	4900	5	1612	884	1425	8821	4
Malta	27	44	16	411	555	1053	5	405	45	511	2012	4
Netherlands	9043	13 858	1206	93 303	16 422	133 832	5	50 550	16 564	28 717	229 663	3
Poland	9042	28 015	1034	30 337	11 977	80 405	6	33 293	20 825	22 216	156 740	4
Portugal	4567	7541	1877	7323	11 342	32 649	5	19 678	4738	13 915	70 980	3
Romania	854	2834	127	6188	8939	18 942	4	11 885	4849	5560	41 237	3
Slovakia	2005	4874	245	3805	5129	16 058	5	1909	2663	2050	22 680	3
Slovenia	217	459	297	4159	2151	7283	4	2709	3508	2514	16 014	3
Spain	43 539	25 406	14 636	131 669	69 662	284 912	5	65 856	19 621	128 151	498 540	4
Sweden	4665	15 309	3618	30 240	12 585	66 416	5	17 313	21 533	18 404	123 666	4
UK	3793	71 664	4192	153 029	53 702	286 380	5	126 204	29 754	101 291	543 630	3
Total EU	**212 258**	**332 009**	**85 637**	**1 672 739**	**567 991**	**2 870 634**	**5**	**769 879**	**329 170**	**899 857**	**4 869 542**	**3**

A&E - accident and emergency;
EU - European Union

TREATMENT

TREATMENT GUIDELINES

Due to the heterogeneity of the disease, it's especially important that each patient is matched with the most appropriate treatment. Because of the challenges in treating bladder cancer, European organisations such as the European Society for Medical Oncology (ESMO) and the European Association of Urology (EAU), developed comprehensive guidelines to align therapeutic options and allow for better characterisation of the disease to personalize treatment and improve outcomes.[22,23,24,25] While clear treatment guidelines for bladder cancer are available, they are not always followed. Below are the abridged guidelines for bladder cancer treatment.

Guidelines for non-muscle-invasive bladder cancer (stages CIS, Ta, T1)

The treatment for this disease stage depends on the probability of the cancer recurring and/or spreading into the muscles of the bladder. In each of the cases, a surgical endoscopic resection of the tumour, a so-called transurethral resection of the bladder tumour (TURBT) is necessary and depending on the risk classification, the following adjuvant treatments may be indicated:

- ✓ Low-risk patients are treated with TURBT, where detected tumours are cut and removed. This is followed by a single dose peri-operative intravesical chemotherapeutic if possible given ideally within 6 hours of the resection;[26]
- ✓ Intermediate-risk patients, on the other hand, may undergo single dose peri-operative intravesical chemotherapy, followed by adjuvant intravesical therapy, either chemotherapy or immunotherapy (BCG);[26]
- ✓ Treatment options for high-risk patients are an intravesical adjuvant therapy with a variant of the Bacillus Calmette-Guérin (BCG) vaccine, and/or in very selected cases radical cystectomy (i.e. removal of the bladder), which leads to urinary diversion.[26] The latter option is mainly reserved for patients who have failed or have been refractory to BCG therapy or who have very few other selected high risk factors.[27]

It is important that TURBT be of very good quality including muscularis propria representation; given that residual tumour rates are reported in up to 50% of the cases. The initial surgical treatment is crucial for correct staging leading to optimized therapy and a decrease in recurrences and unnecessary re-TURBTs.[28] For those patients in whom no muscularis propria is included in the initial resection or in whom resection is incomplete and for all high risk NMIBC a re-section is advised within six weeks.

Guidelines for muscle-invasive bladder cancer (stages II and III)

Treatment of muscle-invasive bladder cancer depends on the degree of cancer spread, and aims to both cure and control the disease locally. The most widely used option is radical cystectomy with bilateral pelvic lymphadenectomy with perioperative chemotherapy. Other options include external radiotherapy (without or with a radio-sensitizer).

In women, radical cystectomy generally involves removal of the bladder and many adjacent organs, including the uterus, fallopian tubes, ovaries, and anterior part of the vaginal wall. Similarly, in males, in addition to the removal of the bladder, the lower parts of the ureter the lymph nodes, prostate, and seminal vesicles

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are removed, which frequently leads to impotence. As discussed, cystectomy may be accompanied with preoperative chemotherapy or adjuvant postoperative chemotherapy depending on the actual pathological stage and patient's renal function.

Cisplatin-based combination chemotherapy should be used before cystectomy or radiotherapy (neoadjuvantly) in cisplatin-eligible patients in order to try to eradicate micro-metastasis, reduce tumour size, and decelerate the spread of tumours (level I evidence). Improvement in overall survival with preoperative chemotherapy is 5% and this has led to its underutilization in clinical practice. Implementation of guidelines in clinical practice can be measured to inform "real-world" conditions and set a benchmark for targeted quality improvement interventions. If preoperative chemotherapy is not given, the use of adjuvant cisplatin-based chemotherapy should be considered/discussed in cisplatin-eligible patients with pathologic T3/T4 or N+ stage who did not receive neoadjuvant chemotherapy, although the evidence for this is less robust than for neoadjuvant chemotherapy. Only cisplatin-based combinations are validated for use in this specific setting. Clinical trials should also be considered.

Organ-preservation therapy (usually with concurrent chemo-radiation) can be used in selected patients to treat the cancer and preserve the bladder where possible. Notably, there has been no published phase III trial with direct comparison between neoadjuvant chemotherapy followed by local therapy vs. chemo-radiation. The SPARE trial, for instance, was shut prematurely due to reluctance of urologists to refer patients for the study, and lack of clinical equipoise.

There are huge disparities in the treatment and care patients receive across the EU. A patient with newly diagnosed muscle-invasive bladder cancer should receive counselling before deciding on their preferred treatment. This counselling should be based on both patient and tumour characteristics and on the side effects (acute and at long-term) of each therapeutic option.

A multidisciplinary outpatient visit that involves urologists, medical oncologists, radiation oncologists, and psycho-oncologists is warranted, as well as a commitment towards a 'bladder cancer unit' in each urologic department.

Guidelines for locally advanced or metastatic bladder cancer (stage IV)

Treatment options to alleviate cancer symptoms (painful urination, blocked kidneys, etc.) depend on the degree of cancer spread. If the cancer is locally advanced, intravenous combination platinum-based chemotherapy can be used, and if good response is noted, radical cystectomy and bilateral pelvic lymphadenectomy, or radical radiotherapy can be considered in well-selected patients. Palliative radiotherapy can also be considered for local control of disease and symptoms.

If however the cancer is too advanced and, as a consequence, patient performance status or organ function is poor or inadequate for active treatment, the patient should be referred for systemic palliative chemotherapy and/or to a palliative care team. Clinical trials should always be considered and encouraged.

Importantly, the access to oncologic treatments may depend on other factors like the provider and facility characteristics (figure 1).[20]

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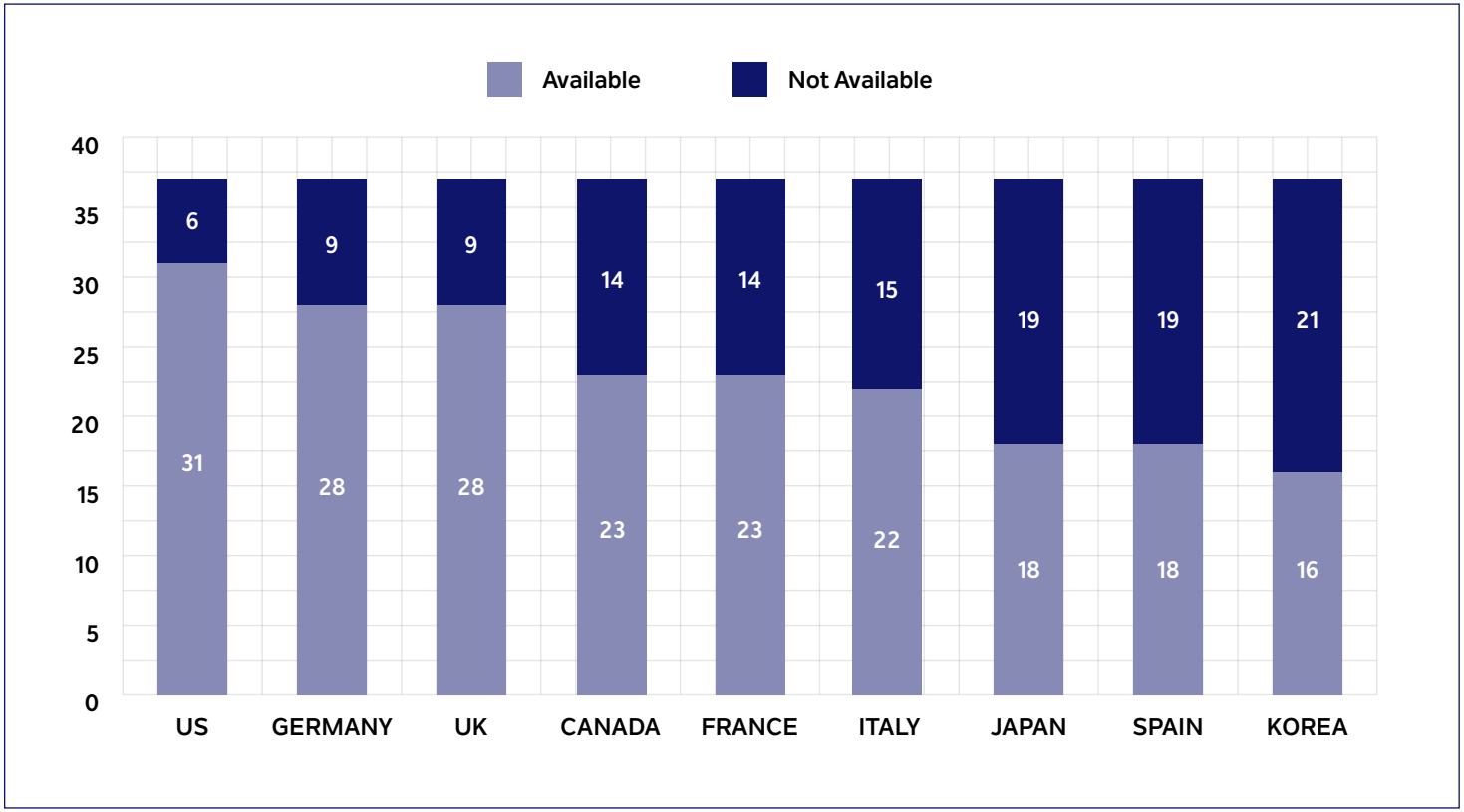

Figure 1. Patient access to novel cancer treatments: *Patient access to new cancer therapies varies according to regulations, local health system priorities, and budgetary constraints. Examining cancer treatments introduced between 2009 and 2013, the US offers the broadest access, while countries such as Spain have less than 50% of these new drugs accessible for patients.*

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REIMBURSEMENT

Health systems in Europe spend the most on cancer, and total expenditure is expected to rise with aging populations and the development of increasingly targeted and increasingly costly therapies. Yet even in these comparatively rich countries, access to new cancer drugs is not guaranteed. Since not all oncology drugs are reimbursed, many novel and effective treatments are out of reach of patients (figure 2).

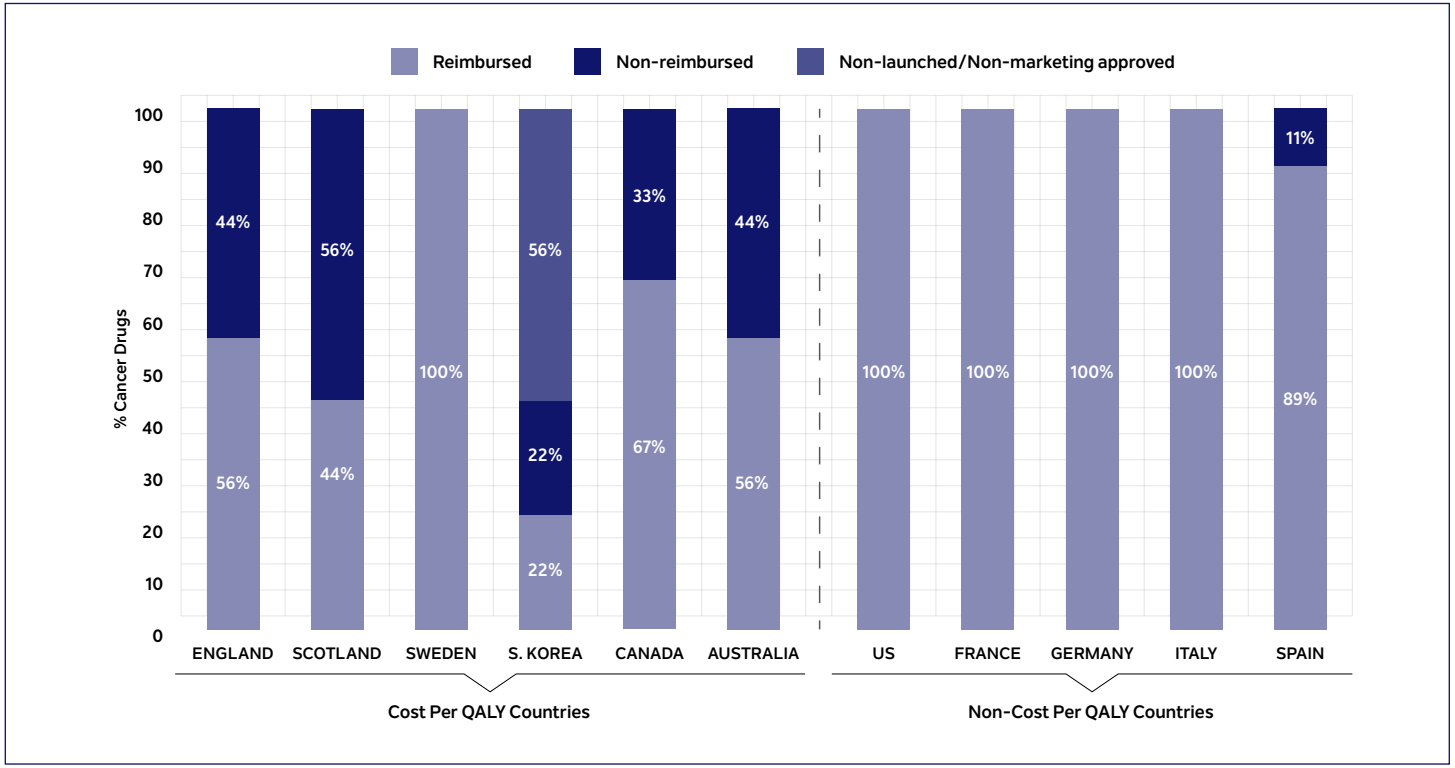

Figure 2. Reimbursement directly impacts access to novel oncological drugs: *Healthcare systems that employ a cost-effectiveness methodology based on cost per quality-adjusted life year (QALY) are less likely to pay for new cancer drugs.*[29]

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Insufficient funding is also problematic. In the UK, for example, the allocated research funding for bladder cancer is not proportional to the disease's economic burden where research funding for bladder cancer (£4.62 M) is five times lower than research funding for prostate cancer (£20.56 M), notwithstanding that both types of cancer incur similar yearly costs per person.[29] Austerity measures, furthermore, hamper the funding and reimbursement of new treatments.

As highlighted above, among all cancers, bladder cancer treatment per patient is the costliest. This is partly due to the risk of recurrence as well as monitoring, rehabilitation and follow-up costs. Inadequate reimbursement can add to the economic burden of bladder cancer. For example, while office-based cystoscopy is normally reimbursed, other indispensable parallel procedures may incur additional costs. Reimbursement may also depend on the location of the procedure (office-based vs. operating theatre), which adds significant cost differentials.

In Europe, different bladder cancer-related procedures for different disease stages (e.g. TURBT, radical cystectomy and cystoscopy) follow different reimbursement paths. For example, reimbursement for cystoscopy in the UK ($620) is approximately 12 times higher than cystoscopy reimbursement in France ($51). Similarly, TURBT reimbursement in Germany ($2,967) is 2.6 times higher than TURBT reimbursement in France ($1,124). The reimbursement of radical cystectomy in the UK ($5,684) is 3.6 times lower than in Germany ($20,507). The absence of a more or less unified reimbursement pathway in the EU adds to the complexity of bladder cancer management in terms of resource allocation and financing. Table 1 gives some insight into reimbursement available for bladder cancer-related procedures (including procedures & hospital stay) in five European countries.[29]

BLADDER CANCER REIMBURSEMENT (INCLUDING PROCEDURES & HOSPITAL STAY) IN FIVE EU COUNTRIES

	UK ($)	GERMANY ($)	FRANCE ($)	ITALY ($)	BELGIUM ($)
CYSTOSCOPY	620	61	51	76	53
TURBT	2,154	2,967	1,124	2,741	2,201
CYSTECTOMY	5,684	20,507	12,897	9,605	14,540

Table 1. *Bladder cancer reimbursement (including procedures & hospital stay) in five EU countries.*[30]

TREATMENT

Bladder cancer costs between $89,287 and $202,203 per patient from diagnosis to death.[31] Interestingly, a wider and systematic use of perioperative intravesical therapy for superficial bladder cancer was reported to substantially lower the economic and humanistic burden of bladder cancer in the U.S.[32]

SECURING CLINICAL TRIAL FUNDING

Bladder cancer clinical trials are critical and should be considered in patient management. One major challenge is that sometimes, the patient is directed to undergo treatments as indicated by the medical doctors, as opposed to being free to choose an appropriate and equally effective treatment of preference. Considering the long-term impact of certain bladder cancer treatments (such as urinary diversion in the case of cystectomy), trial logistics/details, and the need for follow-up for recurrence and survival, many patients may not enrol in clinical trials.

In the organ-confined stages of disease, access to clinical trials primarily depends on the availability of a dedicated multidisciplinary team at the referral institution. This multimodal approach could contribute to improved outcomes for many patients and should be strongly supported at the EU level, ideally through the definition of minimum required criteria for a bladder cancer patient unit.

Patients with metastatic cancer, with more limited treatment options, may be more open to taking part in clinical trials. The challenge in this case is that these patients may rapidly deteriorate and therefore have a relatively short time window to enrol in a trial. This is of utmost importance with the advent of novel immunotherapy agents (e.g. immune checkpoint inhibitors) which are revolutionizing the therapeutic scenario of bladder cancer across the clinical stages, including the non-muscle invasive stages. Novel active compounds are anticipated in the market in the next few years.

A promising regulatory framework: A new EU Clinical Trials Regulation (Regulation (EU) No. 536/2014) was published on 27 May 2014, and it is estimated that the first EU-managed clinical reports will not be accessible before 2019 or 2020.[33]

The European Organization for Research and Treatment of Cancer (EORTC) also contains information on its clinical trials, as well as trials done in collaboration with other organizations.[34]

The European Union's Clinical Trials Register displays approximately 140 search results when *bladder cancer* is entered as a search query.[35] In January 2015, the European Medicines Agency (EMA) introduced a new policy on the publication of clinical trials after the acceptance of market authorization by EU regulatory bodies.[36] This new policy, which was framed through a consultation process with active participation from patient groups, is intended to complement the Clinical Trials Regulation.

The publication of bladder cancer clinical trial data in the context of this regulatory framework will allow the re-evaluation of clinical trials by bladder cancer experts and academics, thus informing further clinical trial designs and treatment decisions.

Furthermore, huge disparities are still recognized in the timing of trial activation and, ultimately, drug approval processes between Europe and United States. Yet these discrepancies are more insightful given the promise of a paradigm change from immunotherapy in the context of available clinical trials. The availability of trials with new more active therapies is still jeopardized and suboptimal in EU.

TREATMENT

Securing appropriate levels of funding for clinical trials is critical to ensure patients and clinicians have access to all the resources they need to complete a trial. Funding also needs to be carefully managed and clinical trials should focus on early diagnosis and the most cost-effective treatment options.

Immunotherapy, personalised molecularly targeted therapies, and non-invasive procedures are promising and need to be advocated for further clinical trial support.

Patients are more and more frequently being asked to provide consent to donate tumour tissue for research purposes. Anticipated new treatments like immune checkpoint inhibitors will likely require patients to provide their tissue outside the trial setting (i.e. standard of care). This would mean patients have to undergo (re)biopsy of their tumour when their available archival tissue is lacking or it is not sufficient for clinical trial purposes. Bladder cancer patients should be informed about the benefits of collaborating in clinical trials to access novel cancer treatments.

Translational correlatives, cost-effectiveness, quality of life, and population discrepancies in outcomes and healthcare access metrics should also be incorporated as endpoints in clinical trials. This approach will contribute to the objective evaluation of value-based care, and will be considered when regulatory agencies and expert panels review the totality of the data to make approval decisions and recommendations.

REHABILITATION AND FOLLOW-UP

Since bladder cancer is a common disease with significant impact on quality of life, clear follow-up guidelines would be a useful tool for clinicians to help patients cope with their condition. Guidelines should include, *inter alia*, the impact of treatment options, palliative care, implications on post-operative sex life, and other insights that affect quality of life in general.

Rehabilitation is very important and must be considered as part of the treatment process. However It can come at significant cost which needs to be factored in. For example, pre-operative and intra-operative bladder cancer management can make up more than 75% of post-diagnosis costs (post-surgical problems, tri-annual and semi-annual diagnostic and lab tests).[37]

ESMO and EAU have follow-up guidelines for bladder cancer patients, however according to ESMO, "*there is no generally accepted follow-up protocol*". Developing European guidelines based on EU and Member State rehabilitation and follow-up frameworks should be considered to ensure bladder cancer patients across Europe have equal access to quality rehabilitation.

INNOVATIVE TOOLS FOR DIAGNOSIS AND TREATMENT

Today, risk stratification is now better achieved with broad-range non-muscle-invasive bladder cancer scoring systems such as those of the European Organisation for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO).[38,39,40] However, there is still a lot of room for improvement.

Similarly, personalized medicine is promising for predicting clinical effectiveness. Biomarkers help in the screening, diagnosis, prognosis and staging of bladder cancer. BTA-Stat, BTA-TRAK, NMP-22, uCyt+ and UroVysion are the five marker tests for the diagnosis of bladder tumours still undergoing clinical research.[41]

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The limitations of the current TURBT procedure (high rate of residual tumours, early recurrence and under-staging of the tumour) has led to the development of new methods of tumour visualisation during cystoscopy and TURBT (e.g. Photodynamic Diagnosis, narrow band imaging (NBI)) to improve the quality of TURBT. Urine tests (BTA, NMP22 and MCMcm5) have also been developed to improve diagnosis of the condition.[42,43]

Interestingly, in the case of urothelial carcinomas, molecular analyses have revealed genomic alterations that can potentially be treated with existing drugs or with drugs currently undergoing clinical trials, thereby paving the way for novel personalized targeted treatment interventions.

After being neglected for years, there are now ever increasing numbers of candidate medicinal products under research for bladder cancer, notably in immunotherapy.[44] These trials will hopefully yield much needed additional treatment options for patients in the near future. Candidates include:

- ✓ MCNA (mycobacterium phlei cell wall-nucleci acid complex), filed to the Food and Drug Administration (FDA) in 2015, and investigated as potential new treatment option for bladder cancer patients who have failed front-line BCG therapy[42,44]
- ✓ Immune checkpoint inhibitors e.g. the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programd cell death protein 1/programd death ligand 1 (PD1/PDL1)[45]
- ✓ Evaluated biomarkers, and there are also immune targets under development
- ✓ Photodynamic therapy is only in experimental stages but looks promising

However, despite high treatment/diagnosis potential in bladder cancer, these therapies are being preferentially tested in most common cancers.

As far as chemotherapy is concerned, a number of drugs are available and several more are currently undergoing clinical and preclinical trials. Biological therapy like interferon in combination with BCG, and other drugs are also under investigation and are considered to be promising. Researchers are also looking into whether adding chemical elements and/or vitamins to the patient's diet can help to halt early bladder cancer recurrence.

Anti-tumour activity can be improved through immunomodulatory chemotherapy/targeted agents, immunogenic cell death agents, vaccines, and radiation therapy, among other agents that may lead to synergistic effects in treating bladder cancer in the future.

Despite some advances in treatment, the survival rates for bladder cancer have not improved in the past decade. Therefore, there is a real need to continue the development and commercialization of novel bladder cancer diagnostics and therapies. The FDA, for instance, has not approved any novel drugs for advanced bladder cancer for the past two decades in the United States.[46]

"I didn't care that much, I was just glad to finally be seen after begging the GP for help for so long, I was actually at the hospital being seen by a urologist telling me there was something very wrong and it wasn't all in my head."

"I was quite relieved I'd been treated for UTI's, and gynaecology problems. The battle is easier when you know what you're fighting. I've always been a very optimistic person, so just thought, ***"well, I've got cancer, what are we going to do about it?""***

5. RECOMMENDATIONS

RECOMMENDATIONS

RECOMMENDATIONS: OPPORTUNITIES AND CHALLENGES

The first EU expert policy roundtable meeting on bladder cancer, which was held in 2013 in the European Parliament, described bladder cancer as the "forgotten cancer". Unfortunately, very little has been done since 2013 to improve patient experience or outcomes. As a very common disease in industrialised EU countries, and with incidence likely to rise in coming years in line with our ageing population, it is time to put steps in place to address the bladder cancer.

Against this background, we recommend the following areas be prioritised to reduce the burden of bladder cancer:

Smoking cessation: The EU and its Member States should continue efforts to reduce tobacco consumption in Europe in the context of the WHO Framework Convention on Tobacco Control (FCTC) and through national legislations.

Occupational cancer: The European Commission should ensure that the planned revision of the existing occupational health and safety legislation on exposure to carcinogens and mutagens at work (Directive 2004/37/EC) encourages continuous health surveillance for those at high risk of developing occupational cancers as well as improved prevention measures and timely access to diagnosis, treatment and care. Initiatives to reduce and monitor the exposure to relevant chemicals and the creation and further improvement of databases on carcinogen replacement at EU level may be very useful in the prevention of bladder cancer.

Early-detection programs for high-risk groups: Different approaches for early detection in very high-risk groups should be tested in clinical trials.

Awareness raising: In the EU, there is considerable lack of awareness of bladder cancer risk factors and early symptoms. Moreover, policymakers lack awareness of the disease's specific healthcare aspects. General practitioners (GPs) need to be vigilant in spotting the symptoms of bladder cancer early and should inform patients who are at risk of bladder cancer (due to exposure to risk factors) of the symptoms.

More research funding: Levels of public and private funding for bladder cancer research should be increased to reflect the disease burden.

Greater resources for bladder cancer: Poor access to medicines for bladder cancer may be leading to high morbidity and mortality rates. Again resources available should reflect the disease burden of bladder cancer – even where austerity measures and budget cuts render this difficult to achieve.

More training of experts: Urologists often lack bladder cancer occupational risk factor training, particularly when there is a lag between exposure and cancer occurrence.

Multidisciplinary 'Bladder Cancer Units': Multidisciplinary units should involve: urologists, medical oncologists, radiation oncologists, pathologists, radiologists, psycho-oncologists, physiotherapists, and palliative care experts. They are needed within the urological

RECOMMENDATIONS

departments of European cancer centres and hospitals to improve training across all the specialities involved in treating bladder cancer. Centralization of care for advanced bladder cancer is also likely to improve outcomes and patient satisfaction.

Investment in research data: More research is required to fully understand the potential risk factors for bladder cancer. Data collected should be comprehensive, clear and conclusive as existing data from EU registers only capture a minor part of the current status of the illness. There is also a need to identify the most appropriate populations for screening and blood/urinary markers for early cancer detection, to characterize tumour heterogeneity at the molecular and pathologic levels in order to apply personalized medicine, and to identify prediction markers for treatment response and prognosis. Centralized as well as Member State-specific data are both needed. Ethical issues regarding personal data protection should be taken into account in a way to protect patient privacy but at the same time not impede medical research.

"I was just happy to get a diagnosis after my GP kept dismissing my concerns and claiming that I either had a bladder stone or a UTI. Once in the system I was treated well and kept informed which I found very positive."

"Bladder cancer is like a bad marriage you can't divorce. You are in for life long treatment and follow up. There needs to be more public awareness, and better compassion for what bladder cancer sufferers go through."

6. CONCLUSIONS

CONCLUSIONS

The improvement of outcomes for patients with bladder cancer will require concerted effort across a range of actions.

We need to increase awareness, improve diagnosis, treatment, and prevention, conduct better clinical and translational research with better methodology and reporting (publishing positive *as well as negative* results), and coordinate work streams to increase funding. Greater attention to the impact of risk factors such as smoking on bladder cancer is needed through campaigns that target children, adolescents, adults, and healthcare professionals in various forums.

With 124,000 people diagnosed and more than 40,000 people dying from the disease each year, European Institutions and Member States need to ensure that appropriate urologic care systems relying on good epidemiologic data collection and investment in cost-effective treatments and pathways are put in place.[1,19]

With this in mind, the EU and its Member States should also ensure access to novel technological tools that enable better treatment, diagnosis and research. The European Commission should work on a European Database for bladder cancer under the European Network of Cancer Registries to guarantee disease and risk factor knowledge as well as comparable/unified data. Biobanks are also important for the development of biomarkers.

Finally, the formal development of bladder cancer patient advocacy groups in European countries and alignment/coordination among them and with similar groups in other countries, e.g. BCAN in United States, will be critical to sustain awareness in local communities as well as help achieve the overarching goals outlined in this paper.

APPENDIX I

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IPSEN Innovation for patient care

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APPENDIX II

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