State of Bladder Cancer policy in Europe

Bringing together viewpoints of healthcare policy makers and stakeholders to reach an EU-wide consensus for improved diagnostic accuracy, effective management and care in bladder cancer
EUROPEAN COMMISSION

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79 Antoni Montserrat Moliner, Senior Expert for Cancer and Rare Diseases, Directorate of Public Health, European Commission
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EUROPEAN PARLIAMENT

78 Daciana Octavia Sarbu MEP

PREVENTION

80 Prof James W.F. Catto, Professor of Urology at the University of Sheffield
92 Prof Morgan Rouprêt, Professor, Université Paris

MANAGEMENT & CARE

82 Dr Anne E. Kiltie, Associate Professor, Department of Oncology, University of Oxford
84 Dr Anne Postulka, Senior Director, Medical and Economic Value, Europe, Cepheid
87 Prof Hein Van Poppel, Adjunct Secretary General - Education, European Association of Urology
88 Dr Laurent Fossion, MD, Head of Urology, Maxima Medisch Centrum
94 Dr Zenichi Ihara, Health Economics Manager, Commercial Excellence, Olympus
100 Dr Gregory Adams, Steve Hurley, Dr Glen MacDonald, Viventia

COST & ECONOMICS

91 Dr J. Alfred Witjes, Department of Urology, Radboud University Nijmegen Medical Centre

POLICY ACTION

83 Louise de Winter, Chief Executive, The Urology Foundation
90 Rik Bryan and Jeannie Rigby, Action on Bladder Cancer
95 Mihaela Militaru, Director, European Cancer Patient Coalition
96 Pablo Perez-Moreno and Elzbieta Zawisla, Roche
98 Arvind Venkataramana, Research Director, ICPS
FOCUSED ON DEVELOPING SPECIALTY TREATMENTS for debilitating diseases that are often difficult to diagnose and treat, providing hope to patients and their families.
The most common cause of work-related deaths in the EU is cancer and bladder cancer was one of the first cancers to be linked to occupation. The European Commission recently proposed changes to the Carcinogens and Mutagens Directive to limit exposure to 13 cancer-causing chemicals in the workplace. **Marianne Thyssen**, European Commissioner for Employment, Social Affairs, Skills and Labour Mobility, explains how workers are currently protected under the EU legislation and elaborates on the latest proposal.

My primary goal is to protect the health and safety of European workers. But this proposal will also benefit employers, member states, and the economy as a whole. As a result, employers will be able to protect their workers better – which I believe is what most of them genuinely want to do.

Employers will now have concrete, measurable yardsticks against which they can ensure compliance. And they will be able to hold on to their healthy, skilled workforce for longer. Member states benefit because the proposal will reduce the healthcare costs related to cancer treatment and rehabilitation. And the economy as a whole will benefit from improved labour productivity and a lower burden on public finances.

Zero-risk does not exist: not in life and not at work. But where we can reduce the risk and save workers’ lives, it is our duty to act. I am doing so with this proposal and I will continue to work, as a matter of priority, on new exposure limits for additional chemicals.

I want Europe to continue to set the world standard on health and safety at work, based on scientific evidence and intense dialogue with our social partners.
As research accumulates, we can be more certain about risk factors for different cancers and develop policies to reduce them. Some are easier to identify than others, and it may take decades before clear links are established between exposure and a particular cancer. However, over time, it has become clear that preventing bladder cancer specifically means tackling at least two key risk factors: occupational exposure to carcinogens and smoking. Legislators can and must play an important role in this process.

Reducing exposure to carcinogens and mutagens in the workplace is critical because in some industries this represents the second biggest risk factor for bladder cancer. EU health and safety rules address some of these workplace risks, but critics argue that the legislation is too weak. Three key problems can be identified. Firstly, exposure limits are defined at European level for only a small number of potentially harmful substances, which means different levels of protection in different member states.

Secondly, the length of time between exposure and onset of disease means that the financial cost of ill-health is mainly paid by healthcare systems later on in a person’s life. This creates little incentive for industry to take preventative action for current employees. Thirdly, the European Commission reports serious problems with implementation of the rules, particularly for small and medium-sized enterprises (SMEs).

The current and long-awaited revision of health and safety legislation may help. Applying exposure limits to a wider range of industrial chemicals in a single directive would increase minimum standards across the EU. Obligatory post-employment monitoring of employees and provision of medical care could improve detection, diagnosis and treatment. Such changes could bring great benefits, especially for those working in large-scale operations with the resources to implement them. But the balance between protecting workers and making legislation realistic for SMEs may prove hard to strike.

Bureaucratic complexity, insufficient guidance from national authorities, and a lack of awareness of responsibilities have already made the laws problematic for small businesses. This is relevant to the discussion about bladder cancer because several higher-risk professions are those in which people are often self-employed or work for SMEs, such as hairdressers, drivers, mechanics, and painters. In these cases, workplace rules may not provide the necessary protection. Closing the gaps in health and safety legislation alone will not be enough.

With smokers being up to four times more likely to contract bladder cancer than non-smokers, tobacco use is still a bigger risk factor than any occupational exposure. The EU and member states have taken important steps on tobacco use in recent years. Most workplaces and many indoor public places are now smoke-free following a 2009 Council recommendation.

More recently, the EU Tobacco Products Directive introduced standardised packaging for cigarettes, including mandatory pictorial and text warnings (the tobacco companies recently failed in their bid to overturn this law in the courts). This is important for governments because it reinforces the health messages around smoking which makes it easier to introduce laws for smoke-free environments. Research now shows high public support for smoking...
bans in places such as bars and restaurants. Those governments which have not yet enacted such bans should take advantage of this popular support to fully implement the 2009 recommendations and reap the health, social and economic benefits that smoke free environments bring. In some member states, the health benefits have been immediately apparent, such as fewer hospital admissions for heart attacks soon after the introduction of smoke-free environments. The effects on other tobacco-related diseases like cancer will be slower to emerge and perhaps harder to quantify, but smoke-free environments are clearly associated with decreasing smoking rates. This can only have a positive impact on health, including a reduced incidence of bladder cancer. EU policy has gone some way in addressing the risks of occupational diseases such as bladder cancer and the wider health risks posed by smoking. Experience has shown that legislation can create healthier environments - whether by introducing smoke free public places or limiting exposure to carcinogens at work. Regular reviews and strengthening of health and safety rules are vital to increasing protection, but this alone is not enough to cover all the professions at risk. A broader strategy including, for example, emissions from road traffic and pesticide limits is equally important if we are to control risk factors for major chronic diseases and enact serious, prevention-based health policies.

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**European Commission’s fight against cancer grows stronger**

**B**ladder cancer is the ninth most common cancer worldwide. Despite significant advances in the treatment of bladder cancer, it remains a growing problem in the European Union. Based on key statistics published in the International Agency for Research on Cancer for 2012, the crude annual incidence of bladder cancer in the European Union is 16.3 per 100,000 of population with 123,000 new cases per year. The mortality in the EU is 4.7 per 100,000, meaning that 40,300 people in the EU die from bladder cancer annually, nearly 30,000 men and 12,000 women respectively. There are some differences in the occurrence of bladder cancer across Europe. Bladder cancer occurs mainly in older people. Roughly 9 out of 10 people with this cancer are over the age of 55. The average age at the time of diagnosis is 73. Men are about 3 to 4 times more likely to get bladder cancer during their lifetime than women. According to the American Cancer Society, the overall chances of men developing bladder cancer during their life is about 1 in 26. For women, the chance is about 1 in 88.

**Action on cancer**

The European Commission aims to reduce the burden of cancer through the Joint Action CANCON (European Guide on Quality Improvement in Comprehensive Cancer Control), European Code Against Cancer and by heavily investing on research. **ANTONI MONTSERRAT MOLINER**, Senior Expert for Cancer and Rare Diseases, Directorate of Public Health, European Commission, elaborates on the EU fight against cancer.

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The European Commission aims to reduce the burden of cancer in the EU in several ways. It aims to increase survival rates and reduce cancer mortality by improving quality of patient care, ensure better quality of life for cancer patients and helps reintegration and palliative care through two main tools, namely the Joint Action CANCON (European Guide on Quality Improvement in Comprehensive Cancer Control) and European Code Against Cancer. The former serves as the official European guide on quality improvement in comprehensive cancer control, and facilitates discussion among member states. It provides an extraordinary...
BEATING BLADDER CANCER

opportunity to address all the topics directly related to bladder cancer, such as quality-based cancer screening programmes, comprehensive cancer network organisations, community-based cancer care and survivorship. The active participation of bladder cancer stakeholders in these discussions will constitute a remarkable input to respond to the needs of patients in a broad and cooperative European context, taking into account that a comprehensive cancer control policy should focus not only on the general aspects of cancer control but also on those that specifically correspond to different cancer sites, as is the case for bladder cancer.

The 4th version of the European Code Against Cancer, produced by the European Commission in close collaboration with the IARC (International Agency for Research on Cancer) in October 2014, provides essential recommendations for preventing cancer to the general public in a friendly, easy-to-read format. The Code is a key communication tool used in the prevention of all cancers, and constitutes the major tool for disseminating preventive measures and contributing to definitively change the perception of cancer around its two very clear messages: one, that certain cancers may be avoided and that health in general can be improved by adopting healthier lifestyles; and two, that cancers may be cured, or the prospects of being cured are high, if detected at an early stage. The messages of the Code are essential to prevent bladder cancer: avoid tobacco smoking and incriminated occupational exposure and regularly eat fresh fruit and vegetables. In addition, prevention and control of urinary tract infections should be recommended for bladder cancer prevention. The active involvement of bladder cancer stakeholders in the promotion and dissemination of the Code will be essential.

In May 2016, the European Commission proposed amending the overarching Occupational Safety and Health (OSH) Framework Directive 89/391/EEC and other Directives specifically dealing with chemical risks. Based on input from scientists, employers, workers, representatives from the different member states and labour inspectors, the Commission has proposed limit values for 13 priority chemical agents identified through the consultation process, including o-Toluidine, which is considered a carcinogen provoking bladder cancer and primarily used in the manufacture of dyes.

Research funding

Research is also essential in better understanding the mechanisms of bladder cancer. A total of 16 projects, with a total investment of 25 million euros, have been supported by EU Research Programmes. The European FP7 project DeCanbio brought together a consortium of clinicians and researchers in genomics, proteomics and bioinformatics to identify and validate biomarkers that hint at a recurring bladder cancer.

The Luxembourgish Centre de Recherche de la Santé (CRP-Santé) joined forces with researchers and clinicians from other member states to develop a simple test to detect this. The European Union Horizon 2020 Programme for research is supporting the project ‘Multimodal, Endoscopic Biophotonic Imaging of Bladder Cancer for Point-of-Care Diagnosis,’ led by the Technical University of Denmark and the Frederiksberg Hospital, which will provide robust, easy-to-use, cost-effective optical methods with superior sensitivity and specificity to enable a step-change in point-of-care diagnostics of bladder cancer.

Large and ambitious initiatives like these can only be implemented through the type of cooperation that the existing European programmes permit. It is a challenge to mobilise common resources and the expertise of European, national and regional authorities as well as scientific partners and patient organisations. It’s a big challenge indeed – but our commitment to organise the efficient and appropriate coordination of these efforts at a European level is even bigger.

Industries at risk within Europe

Several occupations have an elevated risk of bladder cancer. The highest risks occur in workers within tobacco manufacture, dye and rubber production, nurses, hairdressers and radiation workers. Prof James W.F. Catto, Professor of Urology at the University of Sheffield, surveys the occupations at risk of developing bladder cancer and those at risk of death.

Bladder cancer (BC) is the fourth commonest malignancy worldwide and one of the most prevalent in the European Union. (1). The incidence of BC varies greatly around EU member states reflecting patterns of exposure to the main two risk factors: namely tobacco smoke and occupational exposure to cancer forming agents (carcinogens). (1,2) Around half of all BC is caused by tobacco smoke. The impact of smoking upon an individual’s risk of BC varies with the directness of their exposure (self-smoking or inhalation of environmental tobacco smoke), the type of tobacco (black or blonde), gender and the inherited genetic profile (3,4). Legislation to prohibit smoking in public and workplaces is likely to reduce the rate of BC that arise through this route. (2)

The second most common cause of BC is exposure to carcinogens through occupational tasks. This route has been known for many years and has been reduced through workplace health and safety regulations, such as European Union directives (e.g. 90/394/EEC and 98/24/EC) and the 2002 Control of Substances Hazardous to Health Regulations in the UK. The fraction of BCs that arises through

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occupational carcinogens is estimated to be around 5.3% in total and 7.1% for males. (5) This is lower than the 10% estimated by Doll and Petö in 1981 (6) and fits the estimated 20-30 year latency from exposure to cancer. (7, 8)

**Historical occupational bladder cancer**

Bladder Cancer was one of the earliest cancers to be linked to occupation. For example, it was known in the 1920s that workers in the rubber industry had an elevated risk of BC. (9) Subsequent evidence identified the anti-oxidant-naphthylamine (2-naphthylamine) as a bladder carcinogen and lead to its restriction and replacement in rubber manufacture. (8,10) Similar observations were made in the dye, textile and printing industries, and lead to restrictions in the use of Benzidine and 4-Aminobiphenyl.

The rubber, dye, textile and printing industries were characterised by high exposures of workers to aromatic amines, usually through the skin contact or inhalation. (7) Workplace legislation and changing manufacturing processes (e.g. digital publishing rather than printing presses using mineral oils and benzidine pigments, robotic automation within car manufacture) have now reduced aromatic amine exposures and BC risk in these industries. However, current workers still appear to have a higher than expected rate of BC, probably through either unknown agents (11) or continued exposure to known carcinogens (e.g. in recycled tyres). (12)

**Contemporary occupational bladder cancer**

Given changes in manufacturing and workplace health and safety, we recently undertook a systematic review of occupational BC from 1930 to 2010. (13) We reported outcomes in 5 million persons and found significantly elevated BC risks in 42 occupational classes. More worryingly, we also saw an increased risk of mortality from BC in 16 occupational classes. Occupations at risk varied and appeared to differ for BC incidence (new cases) and BC mortality (death from BC).

**Occupations at risk**

Many occupations have an elevated risk of BC. The highest risks occur in workers within tobacco manufacture, dye and rubber production, nurses, hairdressers and radiation workers. The causative chemicals differ between aromatic amines, polycyclic aromatic hydrocarbons (PAHs) and radiation. Tobacco workers are exposed to aromatic amines such as 2-naphthylamine, 4-aminobiphenyl (4-ABP). Dye manufacture, leather and textile workers contact aromatic amines used as dyes and pigments (such as 2-naphthylamine, 4-ABP, nitroso-derivatives of benzidine, direct black 58 and blue 6). (14, 15). BC risk in Hairdressers has declined from 3.2-9.15 fold (14, 16), compared to 1.25 fold [13] following the removal of 4-ABP in hair products. Nursing staff are exposed to PAHs through coal tar dressings and the medical use of radiation.

Plastic manufacture uses a variety of urothelial carcinogens (e.g. 1,1-dichloroethane is a solvent for 1,1,1-trichloroethane production, MBOCA is a curing agent in polyurethane production and 4,4’-methyleneedianiline is used to make polyurethane foams or epoxy resins).

**Occupations at risk of death from bladder cancer**

The risks of BC in the rubber, dye and chemical industries has lead to health education and worker screening programs of ‘at risk’ workers in various countries. (17) These measures appear successful, as elevated BC risks do not necessarily transfer into higher mortality rates. Similar observations occur in medical staff, suggesting rapid BC diagnosis can alter its prognosis. In contrast, there appears to be a number of occupations, e.g. metal, aluminum and glass manufacture, with higher than expected risks of BC death. (13)

Many of these workers are exposed to PAHs through inhalation of atmospheric pollutants or skin contact from lubricants. PAHs are recognised carcinogens graded according to composition (e.g. naphthalene (IARC 2b), benzo[a]pyrene (IARC 1)) and exposure. (18) Metal, machine and automobile workers are exposed to mineral oil metalworking fluids (MWFs), solder/welding fumes, solvents, paints and greases. MWFs are colorless, odorless, light alkane mixtures from a non-vegetable (mineral) source (often a distillate of petroleum), and include paraffinic oils (based on n-alkanes), naphthenic oils (based on cycloalkanes) and aromatic oils (aromatic hydrocarbons).

Mineral oils are known (IARC 1) carcinogens due to their high PAH content. (5, 14) BC risk increases proportionally with the intensity, duration and accumulation of exposure, (19) and the type of mineral oil: straight (high-risk) versus soluble/synthetic fluids (low-risk). (20) PAH exposure during aluminum manufacture arises from coal tar/pitch anode evaporation during electrolysis to produce benzo[a]pyrene vapour (IARC 1) (18). PAH inhalation also occurs in firefighters and bar/entertainment industries staff. Many workers are exposed to diesel fumes, known to contain PAHs and other mutagenic particles [21], including drivers, miners, marine workers and seamen. (22-24) The toxicity of fume inhalation is enhanced by the low volumes of fluid drunk by drivers and the high prevalence of cigarette smoking within these occupations. (25)

**Conclusion**

Many workers are at elevated risks of BC. Geographic patterns will reflect local industries, e.g. Italy, Bulgaria, Greece, Spain and Poland are the main tobacco manufacturers (26), metal workers in the Netherlands, Germany and the UK, and smoking patterns. Health improvement measures should be targeted to workers with higher BC mortality, such as those exposed to PAHs and diesel fumes.

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Managing bladder cancer in the elderly

Bladder cancer is the 4th most common cancer in UK males (14th in females), with 10,341 new cases diagnosed in 2013 and 5,242 deaths in 2012. (1) Three-quarters of patients are men and more than half are over 75 years of age. Around a quarter of patients with the disease suffer from bladder cancer that has invaded the muscle wall. Other patients present initially with the superficial disease confined to the lining of the bladder, but this can progress to muscle-invasive bladder cancer (MIBC) in a proportion of patients. Logically speaking, up to one third of all patients may have muscle-invasive disease at some point.

At the present point, only about half of all MIBC patients are in a position to be fully cured of their cancer 5 years after diagnosis. Dr Anne E Kiltie, Associate Professor, Department of Oncology, University of Oxford, details the management of bladder cancer in the elderly and explains why there is an urgent need to improve current treatment strategies.

Improves the survival rates by 5%.

More recently the use of ‘chemoradiation’ has become a standard of care, where radiotherapy is accompanied by the use of drugs which make the radiation more effective. Chemoradiation is more effective at killing tumour cells than radiation alone, but this may be at the expense of causing increased side effects to the local normal tissues, including the bladder and the adjacent bowel and rectum which inevitably receive some radiation dosage from the treatment fields.

The median age of patients treated with radical radiotherapy, where the treatment intention is to cure the patient rather than just provide symptom relief, in our joint uro-oncology clinic over the past five years was 81 years, which seems quite elderly. However, an 81 year old man in the UK is currently expected to live an additional 7.7 years and an 81 year old woman 9.0 years, so these patients would have been expected to live to nearly 90 years old had they not developed muscle-invasive bladder cancer. (2) A rather shocking statistic is that competing mortality only accounts for one-third of deaths in patients with MIBC over the age of 80 years. (3) This means that two-thirds of these patients are dying of their bladder cancer rather than another cause, reflecting the low numbers receiving radical treatment (12% vs 52% of under 60 year olds).

Patients in their 80s can be treated by cystectomy but in this age group the mortality rate from the operation rises sharply from the 3% expected in younger patients. The median age at cystectomy is 68 years and only a small number of procedures are carried out in the...
What should Europe start, stop and do collectively with bladder cancer?

By Louise de Winter, Chief Executive, The Urology Foundation

In the UK, around 98,000 people are living with bladder cancer and over 10,000 new cases are diagnosed every year with 5,000 deaths. In the EU, there are approximately 123,135 new cases and 40,252 deaths attributed to bladder cancer per year. It is the fifth most common cancer in Western societies but receives a fraction of the research and awareness funding of other cancers. The field is characterised by a lack of scientific advancement. There is therefore an urgent need to overhaul most aspects of bladder cancer management so that improvements in long-term outcomes can rival those seen in other common malignancies.

Bladder cancer is also the costliest lifetime cancer to treat per patient, as patients have to be constantly monitored for potential recurrence, so more efficient and cheaper diagnostic tests need to be developed. In England alone bladder cancer accounts for a total annual cost to the NHS of circa £65 million. Early diagnosis means there is greater chance of survival. Research and clinical trials are vital to unlocking markers for diagnostic tests and drugs for treatment and cures.

Mortality rates for bladder cancer in the UK have not really changed since the NHS was created. Meanwhile, five year survival rates for prostate and kidney cancers have significantly improved in this timeframe. Living in the UK also means that people’s chances of survival are lower than those in other European countries with comparable incidence rates, with overall deaths from the disease higher in England, and the rate appears to be getting worse, not better.

So what could or should we be doing collectively across the EU that will also help to improve survival and outcome rates in the UK?

First, bladder cancer has always been a ‘Cinderella’ cancer in the UK. Even Cancer Research UK has not designated this a priority cancer, despite the lack of new treatments. Charities such as The Urology Foundation are doing what we can to fund research but a more concerted drive is necessary to achieve significant breakthrough in diagnosis and prognosis. We desperately need more research to:

- Develop new tests which will enable earlier detection of bladder cancer in patients.
- Assess new technologies such as Hyperthermia and electromotive drug administration.
- Develop prognostic and predictive biomarkers to identify patients who may benefit from chemotherapy or radiotherapy alone with surgery.
- Investigate surveillance intervals with an aim to improve quality of life for patients.
- Improve the management of the disease that positively impacts on survival.

Collaboration – both pan-EU and, more broadly, international – is fundamental to research. Where EU grants facilitate collaboration, it can help the member states to achieve better results than if they were acting in isolation.

Second, we need to be better at coordinating and using patient data to help innovative treatments to be brought more quickly to patients.

The UK is fortunate in that the cradle-to-grave care provided by the NHS to our socially and ethnically diverse large population provides opportunities for research which are unparalleled internationally. Analysis of patients’ data – such as clinical care data or data from clinical trials and observational studies (among others) - has underpinned our understanding of the disease and enabled development of new treatments and diagnostics, improving outcomes for patients and the wider population.

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Non-muscle invasive bladder cancer and the hope for urinary marker tests

As a result of the persistent risk of recurrence and progression, patients with low, intermediate and high risk of recurrence of bladder tumours need to be followed up regularly at different intervals.

Until now, no urinary marker could replace cystoscopy during follow-up or help to lower cystoscopical frequency in routine fashion.

To date, no non-invasive methods can replace endoscopy. Therefore, follow-up is based on regular cystoscopy. These repeated invasive procedures pose a huge burden on patients and the healthcare systems. Many workgroups and researchers have attempted to identify urinary markers that could detect recurrence before the tumours are large and numerous. The limitation of those urinary markers available is that they still miss a significant portion of tumours found by cystoscopy and therefore cannot be relied upon.

What are the characteristics of a good bladder cancer marker?

- Technically as simple as possible
- Easy to perform, with a short learning curve
- Preferably a point-of-care test, with readily available results
- Reliable and reproducible
- Highly specific to avoid unnecessary workup because of false-positive results
- Highly sensitive to avoid the risk of missing a tumour

Considering the frequency of cystoscopy for follow-up, markers for recurrent urothelial cancer would be especially useful because patients prefer less invasive measures and minimum time spent inside healthcare environments.

According to the discussion at Bladder Cancer Europe 2016 Roundtable organised by the International Centre for Parliamentary Studies in Brussels in June 2016, such biomarkers are impatiently awaited by the urologist and patient community. It seems that promising new markers will be available soon. Respective studies, e.g. UroFollow in Germany, are expected to receive a lot of attention.

By Dr Anne Postulka, Senior Director, Medical and Economic Value, Europe, Cepheid
With a cancer diagnosis, time is the critical factor. Gaining early insight can dramatically impact the efficacy of patient action plans, from quality of life to outcome. Cepheid’s innovative oncology program will bring molecular testing closer to patients to optimize treatment plans from the start. When time matters, early insight means better patient management.

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Epidemiology of bladder cancer in Europe

The European Commission’s Joint Research Centre is spearheading the development of a harmonised cancer information system for Europe in collaboration with the European Network of Cancer Registries. Dr Emanuele Crocetti, MD, Joint Research Centre, Public Health Policy Support Unit, Institute for Health and Consumer Protection, European Commission, explains the role of the ongoing collaboration and presents data relating to epidemiology of bladder cancer.

The most recent data from the EUROCARE-5 project has shown that the 5-year relative survival for bladder cancers, diagnosed between 2000 and 2007, is, on average, around 69% varying from 75% in Northern European countries to 65% in Eastern Europe. Some of these differences are presumably related to the stage at diagnosis. In fact, after one year from diagnosis the probability of surviving an additional 5 years not only improves substantially – it is on average 81%, but the geographical differences decrease from 85% in Southern Europe to 80% in Central Europe.

Finally, unlike many other tumors, bladder cancer survival is higher in men (European age-standardised 5-year relative survival 69%) than in women (66%).

Bladder cancer registration represents a challenge for CR staff due to its complex biology. This includes both non-invasive and invasive tumors and the use of different grade and stage definitions. Moreover, this cancer is typically characterised by multifocal onsets and recurrences. Therefore, comparable and reliable information, collected at EU-28 level, will only be achieved if common classifications and rules are correctly applied in order to ensure that data refer to equivalent lesions. Indeed, the decision to include or exclude non-invasive papillary or flat tumors may affect incidence and survival estimates, making comparisons unreliable. Current ENCR recommendations to European cancer registries recommend full registration (all histological type and stages) of bladder tumors.

To achieve the goal of harmonised European bladder cancer information, ongoing collaboration between the Joint Research Centre and the European Network of Cancer Registries is vital, as well as a strong collaboration with urologists and oncologists, to keep in contact the data collection with all the relevant scientific innovations.

In 2015, estimated new cases were about 131,000 (103,000 men and 28,000 women), and new cases are expected to increase to 141,000 in 2020.

Within the European Union, there is huge variability in incidence rates; among men – from the age-adjusted rate (on the World standard population, ASR) of 31.0, for Belgium, to the lower rate of 9.2 for the UK; and for women, rates range from 7.4, for Hungary, to 2.5 for Cyprus.

The epidemiology of bladder cancer is related to the main risk factor: smoking. Therefore, the temporal trend of age-standardised incidence rates has followed the changes in the prevalence of smokers in the population. Indeed, in many countries, there was a long-standing increasing trend (especially among men) in previous years, followed by a more recent decrease and/or a flattening of trends.

With regards to cancer mortality, in the European Union, bladder cancer represents the ninth most frequent cause of cancer death, with around 40,000 deaths (3% of total cancer deaths,) estimated in 2012, and nearly 43,000 estimated for 2015. Mortality from bladder cancer has decreased over time throughout Europe, among men, while it is relatively stable and/or sometimes decreasing among women.

Approximately 324,000 EU citizens are estimated to have had a bladder cancer diagnosis in the last five years (five-year prevalence). In other words, around 9% (around 3,700,000) of all European citizens who have had a previous (5-year) cancer diagnosis, and are not deceased, had a bladder cancer diagnosis. These patients require clinical follow-up and the assistance of urologists.

As regards survival indicators, the EUROCARE project has compared cancer survival data among European countries for decades, and currently the 6th edition will benefit from fruitful collaboration and coordination with the ENCR-JRC project.
How to improve outcomes in Muscle Invasive Bladder Cancer

Muscle invasive bladder cancer is a complex disease that requires aggressive treatments. Due to the aggressive nature of the disease, timely diagnosis and prompt treatment is required. However, nearly 50% of bladder cancer patients die despite aggressive surgery. Prof Hein Van Poppel, Adjunct Secretary General - Education, European Association of Urology, addresses ways to improve outcomes.

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n the last 30 years, we have not been able to improve the survival rates of our muscle invasive bladder cancer patients. Although we have better surgical and anesthesiological tools, and that there was a dramatic decrease in mortality of cystectomy, bladder cancer continues to kill and about 50% of patients die from the disease despite aggressive surgery. The success of cystectomy in bringing cure depends on the timely indication.

Once invasive bladder cancer cannot be controlled with BCG and once the tumor has invaded the muscular layer, a cystectomy should be proposed and conservative measures are not allowed when the patient is fit for surgery. The cure rates are indeed significantly better in organ confined disease compared to extravesical extension and lymph node invasion. (1) Moreover, unlike in prostate cancer for instance, surgery is relatively urgent since postponing surgery more than 3 months from the diagnosis of muscle invasion has a significantly worse outcome. (2)

Although bladder sparing approaches (transurethral resection, systemic chemotherapy and radiotherapy) can obtain good results in selected patients, a Cochrane database analysis of individual trials shows a benefit of radical surgery over radiation. (3) In the male bladder, extirpation means a radical cystoprostatectomy with eventually simultaneous urethrectomy when the prostatic urethra is invaded. In the female, it equals an anterior exenteration with hysterectomy, ovariectomy, anterior colpectomy and cystourethrectomy.

Obviously, a cystectomy must achieve negative surgical margins since positive surgical margins decrease the 5 year cancer specific survival from 69 to 26.4%. Performance of minimal invasive techniques (laparoscopic and robot assisted cystectomy) are therefore not the optimal approach for advanced bladder cancer. (4) Moreover, it has become clear from multiple studies that an extended lymph node dissection should accompany the cystectomy. Probably the lymph node clearing should encompass the external and internal iliac vessels, the obturator fossa and the common iliac artery up to the ureteral crossing. (5) A super extended lymphadenectomy up to the aorta and vena cava did not provide a benefit versus the extended dissection (6).

Since the publication of the neo-adjuvant chemotherapy studies, it has become clear that this treatment strategy before cystectomy improves the 10 year survival by nearly 6% (7) and therefore it is actually mentioned in the EAU Guidelines on Muscle Invasive Bladder Cancer that neo-adjuvant cisplatin containing combination chemotherapy should be offered in muscle invasive bladder cancer irrespective of further treatment. It is obviously not recommended in patients with a poor performance status or impaired renal function. (8)

Also adjuvant chemotherapy, analysed in a meta-analysis showed a survival advantage (Advanced Bladder Cancer Analysis Collaboration) (9). A recent analysis of an international intergroup randomised phase III trial comparing immediate versus deferred chemotherapy after cystectomy in pT3, pT4 and/or N+ bladder cancer showed a significant improvement in progression free survival, most obvious in node negative patients (10). It is likely that the EAU Guidelines about adjuvant chemotherapy will need to be updated since this recent data.

The last important point is to concentrate the cystectomies in high volume centers. As shown by Barbieri et al, (11) there is a significant reduced mortality in centers that perform more than 60 cystectomies per year. Another study showed that a number of annual procedures favors high volume versus low volume centers. (12)

In conclusion, radical cystectomy with extended pelvic lymph node dissection is the treatment of choice for muscle invasive bladder cancer. Cure implies timely indication for muscle invasive bladder cancer. Cure implies timely indication in performance of cystectomy while bladder sparing and less aggressive approaches must be carefully selected. It is likely that more cisplatin based chemotherapy will ultimately make the difference and this needs a mind change in the urological community and finally surgery is best done in experienced high volume centers.

References:


Why do bladder cancer patients still receive open surgery in 2016?

Laparoscopic, minimal invasive surgery has proved to be a fair alternative for open radical cystectomy, and has reduced preoperative blood loss, intensive care admission, postoperative recovery and hospital stay dramatically. Dr Laurent Fossilin, MD, Head of Urology, Maxima Medisch Centrum discusses the effectiveness of various surgery options available for bladder cancer patients

Bladder cancer is the second most common urologic malignancy after prostate cancer. It is most frequently diagnosed among people aged 75-84 yrs, and has the highest risk to be lethal in this age category. (1) At the time of initial diagnosis, 19% of patients with bladder cancer present with muscle-invasive bladder cancer (MIBC). In the absence of distant metastasis, the treatment of choice for MIBC is radical cystectomy (= removal of the bladder), pelvic lymphadenectomy and urinary diversion. (2,3)

Minimal invasive surgery instead of open surgery

The first laparoscopic radical cystectomy (LRC) for bladder cancer was performed by Sanchez in 1993. (4) Since then several centres have started performing LRC. First published data were single centre/surgeon based and suggested reduced blood loss and faster recovery after laparoscopic surgery in comparison with open radical cystectomy (ORC).

Proved oncologic equivalence

Recently, a large European multicentre study,
coordinated by the European Association of Urology Section of Uro-Technology (ESUT), has confirmed the equivalence in oncologic outcome comparing LRC with the standard of care (i.e. ORC). The ESUT gathered nine bladder cancer centres enrolling 503 patients undergoing LRC for bladder cancer prospectively between 2000 and 2013. This study, the largest to date, showed long-term recurrence free survival, cancer specific survival and overall survival rates after LRC comparable to those reported in current ORC series. (5,6,7)

Advantages of LRC over ORC and RARC

The first randomised control trial (RCT) has now showed the advantages of the LRC-technique over the alternatives: less early complications and faster return to oral intake in comparison with open surgery (ORC) and a significantly shorter operative time and significant reduced cost aspect in comparison with robot assisted surgery (RARC). (8)

The effect of less blood loss in oncologic surgery

There are different studies in the last decades focussing on and the impact of perioperative blood transfusion (PBT) in cancer patients’ survival. Most of them have supported an independent association between PBT and worse survival in those with solid tumor malignancies. Moreover PBT is associated with significantly increased risks of cancer recurrence and mortality following ORC. This supports the choice for minimal invasive surgery in bladder cancer surgery. (9)

LRC safe in elderly

Radical cystectomy in the elderly population (> 75 yrs) is an aggressive surgical treatment with a significant complication rate, hospital readmission and perioperative mortality rate. Accordingly many urologists are reluctant to perform RC in elderly. LRC has showed new perspectives for the elderly. Thanks to the advantages of minimal invasive surgery, the elderly have now become candidates for curation of their malignancy. This is of extreme importance as our life expectancy grows and elderly count for the majority of our bladder cancer patient population. (10)

LRC is the cheapest technique

The total costs of radical cystectomy comprise a significant part of the total costs of bladder cancer treatment. Total costs may be very high for a cystectomy with complications. Peri-operative blood loss seems to be the most important factor associated with high total hospital costs for ORC. If the amount of bleeding can be influenced then substantial reductions in the total costs of cystectomy would seem possible.

Robotic assisted radical cystectomy (RARC) is associated with a significant higher financial cost than the open approach (ORC). LRC has shown equivalent costs as for ORC, even in our learning curve. One can imagine LRC experts have meanwhile obtained reduced financial costs since their experience (i.e. 180 LRC-procedures in our series). (11)

Quality improvement and centralisation of cystectomies in centres of excellence

Several countries have introduced minimal requirements regarding the number of radical cystectomies performed per year and regarding the infrastructure of the hospital (ICU-level, ER-level) to improve the quality of care in bladder cancer surgery. This is based on the principle that high volume centres (e.g. > 20 cystectomies per year) show better outcome and less mortality. The same principle counts specifically for the surgeon/urologist and his bladder cancer team, as the more experience the urologist and his team obtain, the better his knowledge and surgical skills will become. Performing cystectomies in expert centres will allow to improve the outcome results. (12)

Conclusion

Laparoscopic radical cystectomy (LRC) seem to be the best candidate to become the new golden standard for curative treatment for muscle invasive bladder cancer. Equivalence in oncologic outcome, reduced blood loss and faster recovery after laparoscopic surgery has been confirmed in comparison with the standard of care: open radical cystectomy. LRC shows a significantly shorter operative time and significant reduced cost aspect in comparison with robot assisted cystectomy (RARC). Elderly can benefit from this technique.

References:

Path to an upgraded EU policy on bladder cancer

By RIK BRYAN and JEANIE RIGBY, on behalf of Action Bladder Cancer UK

In Western societies, bladder cancer (BC) is the fourth most common cancer in men and ninth most common in women, (1) with a rising number of newly-diagnosed patients globally (2,3). In the UK, the disease accounts for approximately 10,000 new cases and 5,000 deaths per year. (4) Despite high incidence and prevalence, the treatment of BC has changed very little over the past 25 years and outcomes have not improved. (5,6) There is a lack of improvement, even deterioration, in age-standardised mortality rates since the 1980s; and this picture is reflected across Europe. (7) Furthermore, bladder cancer is one of the most expensive malignancies to manage on a per patient basis from diagnosis to death, (8) and does not perform well in the National Cancer Patient Experience Survey. (9) Bladder cancer is thus common, expensive to treat, has experienced little improvement in outcomes, and there is a pattern of poor experiences for patients across the UK – bladder cancer is a forgotten or “Cinderella” cancer.

Patient pathways are complex, prolonged, and practiced in various permutations at every stage. (10) A view shared by many clinicians and academics in the bladder cancer field is that the key contributor to this disappointing scenario is a considerable lack of research funding. (5) We don’t actually have the robust evidence from fundamental research, translational research and clinical trials to support a lot of what we do as clinicians, (10) thus contributing to a lack of progress and a direct negative impact for bladder cancer patients. If we are to address bladder cancer and improve outcomes, as have been achieved for prostate and kidney cancer, then we need to obtain more funding for clinical trials, translational science and health services research.

We also need to tackle the poor awareness of bladder cancer among the general public and the non-urological scientific community (5-7), and there is a necessity for better understanding within primary care. In addition, without a national screening programme (due to lack of accurate and reliable diagnostic tests), bladder cancer is often diagnosed late with a comparatively high percentage of patients diagnosed only upon emergency admission, resulting in a negative effect on longer-term outcomes. (11)

And where are bladder cancer’s new drugs (10,12)? It feels as though the pharmaceutical industry has deserted the disease (10) - no new drugs have emerged into clinical practice for over 20 years. (5,12) More urgently, there is a desperate need to find an alternative to one of the most commonly-used and effective treatments – BCG (TB vaccine, administered into the bladder (13,14)) has been plagued by an unreliable global supply and shortages for 5 years, leaving patients and clinicians in a quandary (15), yet very little appears to be on the horizon as an alternative. (10) This shortage has been compounded by a lack of research in this setting, such that we have poor insight into which patients benefit most from BCG therapy (which is often poorly tolerated), and which patients might be optimally treated by surgery to remove the bladder altogether (cystectomy). (14,16)

Cruelly, cancer research is currently in the midst of a “genomics revolution.” The first sequenced human genome cost almost USD 3 billion and had taken 13 years when completed in 2003. Today, this same achievement costs USD 1000 and takes a few days. (17) This technology is therefore rapidly becoming a reality for the clinic and should enable genuine precision medicine in the cancer setting – identifying which patients will benefit most from which treatments (e.g. BCG, chemotherapy, radiotherapy, etc).

Accompanying this is the potential for early diagnosis and less invasive monitoring by sequencing fragments of abnormal DNA in bodily fluids such as blood or urine. (18) Without funding for the underpinning research in bladder cancer, our patients will miss out on these innovations and we will be impaired in our ability to improve outcomes and reduce the burden of the disease.

Action Bladder Cancer UK is often told by bladder cancer patients that they are angry, feel overlooked, and question why such a serious and common condition is so neglected. By turning the spotlight on bladder cancer, and providing the investment demanded by incidence and prevalence, we strongly feel that improvements in outcomes (and streamlining of treatment pathways and related expenses) could emulate that of other cancers.

References:
How to reduce economic costs of bladder cancer?

Did you know that bladder cancer is the most expensive to treat, owing to the inefficient screening mechanisms?

**Dr. J. Alfred Witjes**, Department of Urology, Radboud University Nijmegen Medical Centre, says there is a lot to be improved in bladder cancer prevention, diagnosis and treatment. Though there are new developments in markers and therapy, he says better awareness of the economic burden would be a great step forward.

One of the first reports dealing with the economics of bladder cancer was published in 2003. (1) Botteman et al. performed a critical systematic review on the health economics of bladder cancer in developed countries. They also tried to identify opportunities or interventions to improve effectiveness of bladder cancer care and thereby reduce burden and costs. Although bladder cancer was identified as the fifth most expensive cancer in total medical care expenditures, per patient costs from diagnosis until death were highest of all cancers, ranging from $96-187 in the US. A similar conclusion for the European situation is difficult to draw. Sievert et al. looked at the European economic aspects and identified 2 interesting aspects. (2). The first was the impact of the fact that bladder cancer has two different entities. Non-muscle-invasive bladder cancer (NMIBC) is treated with local resection (transurethral resection, TUR) of the tumor and subsequent intravesical instillations in the bladder to reduce recurrence rates of the tumor. In spite of this adjuvant treatment, although also depending on the risk category of the tumor, recurrence rates are as high as 61% within one year after TUR in the highest risk group. (3,4). Muscle invasive bladder cancer (MIBC), on the other hand, is treated after diagnosis by TUR with a combination of chemotherapy and surgery (removal of the bladder, radical cystectomy), which is clearly a totally different therapy and with a different outcome and impact on health related quality of life. Sievert et al. reported that two-thirds of bladder cancer costs were related to the TUR procedure for NMIBC. A second interesting point is that costs and benefits in Europe differ significantly per country and health care system. TUR costs, for example, differed between $845 in France as compared to €2,231 in Germany. Radical cystectomy, on the other hand, ranged between €3,867 in the UK and €15,419 in Germany. The overall economic burden of bladder cancer in the European Union (EU) was addressed in 2016 by Leal et al. (5) For the year 2012, €4.9 billion was spent on bladder cancer in the EU. Health care (expenditures on primary, outpatient, emergency, and inpatient care, as well as medications) accounted for €2.9 billion (59%), which represented 5% of total health care cancer costs in the EU. Also taking into account estimation of other costs (23% for productivity losses and 18% for informal care), bladder cancer accounted for 3% of all EU cancer costs, representing an annual healthcare cost of €57 per 10 EU citizens. Again, however, costs varied 10 times between the country with the lowest cost, (Bulgaria, €8 for every 10 citizens), and highest cost (Luxembourg, €93). In summary, bladder cancer is a very costly disease, and costs differ significantly throughout Europe.
Reduction of costs

In 2003, Botteman et al. already identified several points where costs might be reduced. Screening of bladder cancer is not efficient, due to the low incidence rate, not even in high risk patients, and due to the low performance (urinary cytology), costs (cystoscopy) or absence (markers) of diagnostic tests. Especially good urinary markers might improve diagnosis and reduce burden and costs. Currently used therapies, both for NMIBC and MIBC are introduced decades ago, and have not really improved.

For NMIBC current therapies have not proved to be cost effective, since they have not consistently demonstrated survival benefits, nor have been able to prevent radical cystectomies. One small step forward has been the introduction of blue light cystoscopy, which has proven to be clinically effective and cost-effective for diagnosis and treatment of NMIBC, indeed reducing economic burden. (6)

Follow up of bladder cancer patients is not evidence based and predominantly expert opinion. Less frequent and less invasive monitoring will be cost effective, but is difficult to test in the clinical setting. Another potential cost saving strategy is centralization of for example radical surgery. Several reports have shown that the surgical volume is clearly related to morbidity (and costs) and mortality due to the disease and the procedure. Leow et al., for example, found that surgeons performing >7 radical cystectomies had a 45% lower odds ratio of major complications and a cost reduction of $1,690. (7) There was a striking difference in 90-day median hospital costs between patients without complications as compared to those with a major complication ($43 965 vs $24 341; P < 0.001). A clearly defined cut-off for a minimal yearly number of cystectomies, however, remains to be defined. Finally, even though there are guideline recommendations on treatment and follow up, these are not followed well throughout the urological community. (8)

In all there is still a lot to be improved in bladder cancer prevention, diagnosis and treatment, both for NMIBC and MIBC. There are new developments in markers and therapy, but better awareness of the economic burden of bladder cancer for patients, healthcare providers and policy makers would certainly be a step forward. (6)

References:
7. Leow JJ, Reese S, Trinh QD, Bellmunt J, Chung BI, Kibel AS, Chang SL. Impact of surgeon volume on the morbidity and costs of radical cystectomy in the USA: a contemporary population-based analysis. BJUI int 2015;115:713-21

Screening for bladder cancer: rationale and perspectives

Bladder Cancer screening is currently not recommended in routine practice partly because of low overall incidence. However, PROF MORGAN ROPRET, Professor, Université Paris, believes that rational screening policies for smaller groups of people based on the presence of risk factors are most likely to benefit from screening

Screening is a strategy used in a population to identify an unrecognized disease in individuals without signs or symptoms. Screening allows for “early detection” of the disease before it has been revealed by any symptoms. An efficient screening program, thus, impacts the specific mortality of the disease, and the benefit risk/cost must be clearly established.

There is one major disease in the field of
urologic oncology for which the opportunity of a screening programme could and should be considered: bladder carcinomas (BCa).

With the unpleasant clinical outcomes of patients dying from advanced and metastatic BCa, and the recognition that this disease is indeed a public health problem, a logical assumption is that early detection would reduce mortality and morbidity from this disease. (1)

From a general health policy perspective, screening for a specific disease in the general population is useful, contingent upon the fact that five conditions are met.

1. The disease must be a threat to the general population due to its epidemiology (incidence and prevalence) and its specific mortality.
2. There is an effective screening test for the disease.
3. This test is acceptable in terms of its cost and morbidity rate.
4. There is an effective treatment for the disease.
5. This treatment is acceptable in terms of its cost and morbidity rate.

**Does bladder cancer (BCa) meet these five criteria?**

BCa is the sixth most common cancer overall, with an estimated 72,570 new cases and 15,210 deaths in 2013 in the United States [1, 2]. BCa is one of the most diffuse urological malignancies, and it is the most costly in terms of expenditures. BCa screening in the general population has been studied by several investigators [3, 4]; however, partly because of the low overall incidence of BCa (37.5 and 9.3 per 100,000 in men and women, respectively), screening is currently not recommended in routine practice. The United States Preventive Service Task Force (USPSTF) recently concluded that the current evidence is insufficient to assess the risk/benefit ratio of screening for BCa in asymptomatic adults (http://www.uspreventiveservicestaskforce.org/).

“Opportunistic screening” entails the use of diagnostic tests upon the request of an individual. Regarding BCa, the strategy is usually to combine cystoscopy (specific) and a urinary test (sensitive). No study has assessed the diagnostic performance of urinary markers for BCa in the context of screening.

A secondary prevention would be to develop rational screening policies for a smaller group of people based on the presence of risk factors to identify optimal high-risk individuals who are most likely to benefit from screening. Cigarette smoking is the best-established risk factor for BCa, with a relative risk of 1.5 to 3 in past smokers and a RR of 4 to 5 in active smokers [5].

Screening a high-risk group with a history of smoking of ≥ 40 pack-years revealed a significant proportion (3.3%) of individuals with malignancy. In a screening trial in a recent study, the optimal high-risk population most likely to benefit from screening was men older than 60 years, with a smoking history of >30 pack-years; this group had incidence rates of more than 2/1,000 person-years [6]. Thus, a screening strategy for BCa, particularly in smokers, has been previously used, without any convincing data.

It is my personal feeling that the future of screening strategy is hidden in DNA. Cancer is a multifactorial disease that arises from the complex interplay between genetic and environmental factors. Genetic polymorphism is defined as the presence of different allele sequences for a single gene; it is sometimes linked to variations in the expression of constitutive DNA.

Susceptibility means an increased risk conferred by one or more polymorphisms (allele types) of a given gene or genes that expose the individual, family or group of individuals (ethnic/geographic variations) to the genotoxic effects of environmental carcinogens. Differences in the ability to activate carcinogens may contribute to host susceptibility and may be associated with the risk of BCa. The environmental risk factors for developing BCa, such as smoking, are common, although only a fraction of people exposed to these risks will eventually develop these diseases.

Recently, genome-wide association studies (GWAS) have been performed for BCa [7,8]. The GWAS approach allows a search for novel susceptibility loci throughout the genome in a hypothesis-free manner. In recent years, GWAS have emerged as a powerful approach in the discovery of genetics underlying complex traits, such as cancer. Diagnostic tools based on DNA alterations and that can provide high specificity and sensitivity would clearly be of enormous benefit to patients. Screening for BCa in smokers appears to be too broad of a strategy in 2016, and the appropriate method is not to screen only highly exposed patients (tobacco) but to screen only those patients (with DNA susceptibility) who are likely to subsequently develop the disease.

Until these tests are available, in my opinion, smoking avoidance and smoking cessation are the two most important and realistic policies to promote in 2016 (WUOF) has initiated the Global Bladder Cancer Prevention Program, the goal of which is to integrate smoking cessation into urological practices as a primary prevention.

Whether people are healthy or not, is determined by their circumstances and environment. To a large extent, factors such as where we live, the state of our environment, genetics, our income and education level, all have considerable impacts on health. Thus, smoking avoidance and cessation must remain the main strong messages to send to the population if we want to struggle for a good health policy in Europe.

**References:**

Measuring the value of care in the management of bladder cancer

Every action we take delivers an outcome and comes at a cost. What are then the tangible outcomes we would like to see delivered in disease management and the cost it takes to deliver them? It sounds like a trivial question to ask, while in many cases there is no answer, or we have not been looking at it correctly. The outcomes and cost determines the value in health care, although an agreement for a meaningful outcome or the causality with the costs and its breakdown are often missing. (1)

Bladder cancer management, as in most of the progressive chronic diseases starts with a healthy population: to prevent or delay the onset of the disease. In suspected cases, early detection is vital, as well as effective, efficient, and minimally invasive treatment to be implemented. The cycle of detection and treatment may be iterated before reaching a state of recovery, control, or palliative care. In order to monitor the status and determine the actions within each of these steps and across the entire care pathway, an agreed set of measures of success is needed along with the resource requirement associated so the framework be improved, optimized, and made sustainable.

Under the auspices of a European dialogue that brought the stakeholders together – such as policy makers, medical and clinical professionals, academic experts, patients, payers, and industry – the open discussion led to a common ground of recognition around the unmet needs and areas for improvement. Some of my key suggestions are as follows.

Awareness and endorsement

If bladder cancer appreciated less attention in the past compared to the other fields of cancer such as colorectal, lung, or prostate cancer, a systemic approach may be needed to promote the burden of the condition, the current status and future direction. Although the incidence, prevalence, and mortality might be relatively lower than those mentioned above [2], bladder cancer has one of the highest lifetime treatment costs per patient of all cancers, if not the highest [3]. The high recurrence rate and ongoing invasive monitoring requirement are the key contributors.

Set standards of health outcomes and track the success of bladder cancer management

Also in contrast to those “major” cancer areas where a standard set of health outcome measures are defined and agreed, bladder cancer does not seem to have such KPIs as of yet. (4) This should be the priority since any kinds of measurement and monitoring will be dependent on the relevant data determined prospectively.

When an intervention is performed, correct implementation becomes important. Early diagnosis involving flexible cystoscopy or minimally invasive procedures such as plasma resection cannot yield the highest extent of benefit unless the operator is trained and maintains the learning curve. Objective assessment of success and clarification for improvement are possible by tracking the agreed measures of outcome. To that end, working on a screening program and focusing on large-scale registry sounds sensible to collect real-world data in view of connecting the outcomes defined and the costs incurred to deliver them. The use of medical devices and outcomes will also be tracked.

Cost of care and value proposition of interventions

While there is indication of the costs of bladder cancer, most of the evidence is around aggregated macroeconomic figures reported in the health systems that do not relate to the resources used to deliver a particular outcome.
Why is bladder cancer neglected?

The European Cancer Patient Coalition recently launched a White Paper on Bladder Cancer. This paper provides a high level overview of the state of play of bladder cancer in Europe, for prevention, treatment guidelines available and research gaps. The paper will be translated in five languages and will be used at country level to inform policy-makers and the medical community about current shortcomings and the research needs.

By Mihaela Militaru, Director, European Cancer Patient Coalition

In 1985, the European Community launched the first Europe Against Cancer Program. Since then the European Commission has developed policies tackling the main risk factors that increase the burden of cancer. However, to date, not all cancers have been treated equally. The EU has been ambitious in supporting member states in the development of cancer screening programmes accompanied by guidelines for breast, cervical and colorectal cancers.

Despite a prevalence of 13.07% in the EU 27, bladder cancer has been thus far overlooked by both decision makers and the pharmaceutical industry. And it is a pity as bladder cancer still claims more than 52,000 lives each year in Europe and although survival rates have improved over the past 30 years, with 50% of people surviving their disease for more than 10 years compared to only a third in the 1970’s, there is still a lot to be done.

Action at EU level

As bladder cancer is a very common disease in industrialised EU countries and with incidence likely to rise in coming years, there is a need for EU initiatives to reduce the exposure to some chemicals at the workplace as well as more stringent protection of workers, taking into account not only exposure periods but also the mix of chemical and/or toxic substances to which workers are exposed.

In this regard, I greatly welcome the recent campaign launched by the European Trade Union Confederation to address workplace use of carcinogens and work-related cancer.

The European Cancer Patient Coalition recently launched a White Paper on Bladder Cancer in Brussels, which goes in detail on all actions needed in order to improve patient outcomes in bladder cancer.

References:
2. International Agency for Research on Cancer (IARC), GLOBOCAN. 2012, WHO.
Health remains a national competence but European coordination in the fight against cancer has shown that much more can be achieved through coordinated activities. The EU has been effective in supporting EU member states in the development of cancer screening programmes supplemented with guidelines for breast, cervical and colorectal cancer. However, not all cancers have received similar level of attention. Bladder cancer is one of the most common cancers in the western world and the 2nd most frequent malignancy of the urinary tract after prostate cancer, yet it remains outside of health policy priorities.

Raise awareness on bladder cancer in Europe

The awareness of bladder cancer is still low in Europe. Despite its prevalence, specific aspects of the disease are often overlooked. In Roche, we believe that now is the right moment to come out and speak, to ensure that at the European level, bladder cancer discourse is being heard. We are devoted to partner in coordinated efforts to bring bladder cancer higher up the EU agenda in hope of improved treatment outcomes for all bladder cancer patients in Europe.

Act now to improve the situation

Early recognition of symptoms and prevention will play a crucial role in the management of bladder cancer. Healthcare professionals should be taught to identify risk factors and early symptoms so that patients stand a better chance of having access to the right cancer treatment.

Further research is needed to address high mortality among women and work-related risks. With smoking seen as the number one cause of bladder cancer more action is needed to reduce tobacco consumption.

Due to the complexity of the disease, its higher prevalence among an older population and related comorbidities, effective care requires concerted, multidisciplinary approach, integrating the expertise of urologists, oncologists, radiation therapists, imagining experts and nurses.

Until recently, for those people with the advanced disease, prognosis was poor because of the lack of effective treatment options available beyond chemotherapy or radiotherapy. In terminal cases, these treatments are given to relieve symptoms and improve quality of life. Consequently, there is a significant medical need for new treatment options. In Roche, we are committed to exploring treatment solutions to address that need.

In recent years, personalised cancer immunotherapies have been investigated in clinical trials to understand their potential for treating bladder cancer by stimulating a patient’s own immune system to target and kill cancer cells. The aim of personalised cancer immunotherapy (PCI) is to provide individual patients with treatment options that are tailored to their specific needs.

This is an exciting and ever-expanding area of research, which may change how we treat cancer in the future. To date we have been extremely encouraged by the outcomes of our research in this field and believe that cancer immunotherapy may have the potential to drive a paradigm shift in cancer care. Thus far, this class of treatments has shown encouraging results for people diagnosed with bladder cancer.

Recognising the need for consolidated focus on bladder cancer patients’ needs, Roche supports an opportunity for broad collaboration engaging professional societies, nurses, patient organisations and various European institutions. **Pablo Perez-Moreno**, International Medical Director - Oncology and **Elzbieta Zawislak**, International Health Policy Leader from Roche elaborate on the company’s commitment.
Recognising the growing need to act, Roche supports an opportunity for broad collaboration engaging professional societies, nurses, patient organisations and various European institutions.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people’s lives.

Roche is the world’s largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. Twenty-nine medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines.

Urgent policy action needed

More than 175,000 people are diagnosed with Bladder Cancer in Europe each year; and this number is increasing. More people die from BCa than all the UK military deaths in every conflict since 1945. It’s one of the most expensive cancers to treat and affects all genders and age groups.

“We tend to forget that 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”

Francesco de Lorenzo, President of European Cancer Patient Coalition

“Statistics show that up to half of all people diagnosed with bladder cancer in Europe, will die within five years. Nowadays, the advent of new promising drugs like immunotherapeutic compounds is likely to revitalize the field, and new drugs are expected to become available at new standards. For this reason, the access to new drugs for patients with bladder cancer will be a major concern for European regulators in the next few months.”

Dr Andrea Necchi, oncologist and member of ECPC Expert Group on Bladder Cancer

“Whereas many actions need to be implemented at national level, the European Commission should recognise the burden imposed by bladder cancer by promoting the use of guidelines. EAU’s bladder cancer guidelines and its broader use at country level can help to improve clinical outcomes”

Prof Hein Van Poppel, Adjunct Secretary General, European Association of Urology

Where should the EU act?

1. Continue to consider initiatives to reduce and monitor the exposure to carcinogenic chemicals and continue efforts to reduce tobacco consumption in Europe, which is the main cause of bladder cancer.

2. Ensure occupational health and safety legislation; encourage the continuous health surveillance of those at high risk of developing occupational cancers and invest in trials to identify best approaches for early detection.

3. Address lack of resources, increase research funding and ensure all patients have access to multidisciplinary units involving urologists, medical oncologists, radiation oncologists, pathologists, radiologists, psycho-oncologists and palliative care experts.

© Data: European Cancer Patient Coalition
Bladder Cancer – The forgotten killer

By Arvind Venkataramana, Research Director, International Centre for Parliamentary Studies

According to the World Cancer Research Fund International, bladder cancer is the 9th most common cancer. The EU has witnessed more cases than any other part of the world, with Belgium having the highest instances for any country. Although cases of bladder cancer have fallen significantly since the 1970s, it has a prevalence rate of 13.07% and over 52,000 lives are lost each year because of it. Patient groups, medical professionals, leading charities and other key stakeholders have expressed the need for policy makers to take further initiatives to ensure bladder cancer is no longer perceived as the forgotten cancer.

With that in mind, the International Centre for Parliamentary Studies, in partnership with the European Association of Urology, hosted the Bladder Cancer 2016 Roundtable that took place in Brussels on the 21st of June 2016. This Roundtable brought together Members of European Parliament, senior representatives from European Commission, leading urologists, oncologists, patients groups, representatives from non-governmental organisations and representatives from pharmaceutical and technology companies to improve preventative, screening, diagnostics and overall treatment of bladder cancer. Some of their major recommendations have been elaborated below.

Registration and data

Like many other diseases, bladder cancer data capture, storage and the effective use of it across member states needs to improve significantly across the EU. Population-based cancer registers were recommended as the most effective data capture tools, but the quality of data at the time of capture has to be consistent across the board. The EU needs to do more to ensure terms like ‘invasive’ are defined clearly so there is no room for various interpretations.

The true cost

The true cost of tackling bladder cancer needs to be determined not just by the number of deaths as a result of it, but also the number of patients who were successfully treated. The EU should also budget for preventative measures such as education, fast tracking new and cutting edge treatments and drugs, filling the skills gap in urology, implementing strict guidelines on high quality imaging and research and post-market studies. There is scope to reassess current funding models and adopt more result-oriented approaches. Joint action from member states is of utmost importance.

Improving screening

Unlike prostate and breast cancers, bladder cancer does not have an effective screening programme. In addition, screening should...
go beyond just the use of MRIs, as data from radiologists may only provide a one-dimensional view of the existence and severity of the cancer. Again, the EC should work with member states to develop and implement a consistent and effective screening initiative.

**New technologies and treatments**

This year’s meeting also discussed new technologies and drugs in the screening and treatment of bladder cancer. A number of drug companies were in phases two and three of drug development, who have so far had promising results. There is a conscious move from mono to combination therapies, improved minimally invasive and non-invasive treatments and a more complimentary, rather than competitive, approach towards new research between drug companies have been observed. Other developments include the use of biomarkers, improved imaging solutions, the future of robotic surgery and other significant changes in technology.

**Other recommendations for policy makers**

The following recommendations were made for key policy makers to take into account for the future:

- Collection of histology should be an EU – wide policy
- Registration should be harmonised, data collected should adhere to strict EU norms and there should be consensus on the nature of data that is to be collected
- Member states should agree on common terms on invasive and non-invasive measures
- Screening policy needs to be reassessed and should mirror initiatives that have been implemented in Breast and Prostate Cancers
- Policy makers should build consensus on clinical guidelines and a standard for quality cancer care
- Bladder cancer should have a multi-disciplinary approach in the detection and treatment aspects
- The EU needs to have a more ‘open door’ approach towards new treatments and technologies
- Access to existing information should be made simple and consistent
- The availability of grants and funding for research should be clear and access to them should be clearly earmarked by policy makers
- More effort needs to be made on the care and nursing aspects as bladder cancer patients need specialist treatment
- Bladder cancer is not high enough on the list of neglected diseases and more should be done to prioritise it
- Access to multi-disciplinary teams should be available to citizens of all countries
- New research should be funded to explore better diagnostic tools. There is over reliance on retrospective studies – more should be done to encourage new research
- Bladder cancer affects certain people who are exposed to specific environments and working conditions – more should be done to educate both, employers and employees
- Medical innovations should not be perceived as costs but enablers

For more information and for details about the next edition of the Bladder Cancer Roundtable, please visit www.bladdercancerparlicentre.org or email information@parlicentre.org

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**Government Gazette**
Vicinium: A recombinant targeted protein therapeutic for Non-muscle invasive bladder cancer

Vicinium is currently being evaluated in a single arm, registrational phase 3 clinical trial in the USA and Canada in patients with high grade Non Muscle Invasive Bladder Cancer (NMIBC).

Dr Gregory Adams, Chief Development Officer and Steve Hurley, Chief Executive Officer and Dr Glen MacDonald, Viventia Bio, write about why Vicinium is expected to be effective in elderly patients with waning immune systems.

The global prevalence of bladder cancer is estimated at 2.7 million with 430,000 new cases of bladder cancer diagnosed and 165,000 deaths in 2012 (5). The opportunity exists to decrease the morbidity and mortality associated with bladder cancer through the development and implementation of more effective interventions employed before the disease invades the muscle lining the bladder and becomes systemic. Vicinium, a targeted therapeutic agent that is currently in phase 3 clinical trial, directly addresses this need.

Vicinium

Vicinium is a recombinant fusion protein consisting of a single chain antibody fragment (scFv) linked to a truncated form of Pseudomonas exotoxin A (ETA), a potent protein-based toxin that kills cells by inhibiting protein translation. (1) The scFv portion of Vicinium specifically targets epithelial cell adhesion molecule (EpCAM), which is overexpressed in many tumors, including bladder cancer (3), while exhibiting limited expression in normal bladder tissue.

EpCAM overexpression often correlates with more aggressive disease and is considered to be a cancer stem cell marker (2). As Vicinium does not cross the cell membrane without first binding to EpCAM, it is not capable of targeting healthy bladder tissue.

Vicinium is currently being evaluated in a single arm, registrational phase 3 clinical trial in the USA and Canada in patients with high grade Non Muscle Invasive Bladder Cancer (NMIBC). It is administered in the same manner as BCG, by intravesical instillation, and is therefore easily handled by practicing urologists.

Vicinium’s recommended dose of 30 mg per instillation was established in a phase 1 dose escalation clinical trial, which examined doses ranging from 0.1 to 30 mg given weekly for a total of 6 weeks to patients with high grade BCG-refractory or intolerant NMIBC (3). All doses were well tolerated and no dose limiting toxicities or significant systemic exposures were observed. The highest dose, 30 mg, was selected, as it was believed to be associated with the greatest level of tumor exposure to the agent. A total of 64 patients were treated in this study, with a complete response of 41% at three months.

Vicinium was next evaluated in a phase 2 trial conducted in the United States and Canada comparing a standard BCG-like regimen of once a week for 6-week induction phase with a longer once a week for 12-week induction phase (3). Both arms were followed by three maintenance cycles of weekly Vicinium administration for 3 consecutive weeks, every three months (e.g., standard BCG-like schedule). Patients (n=46) with BCG-refractory or intolerant NMIBC (3). All doses were well tolerated and no dose limiting toxicities or significant systemic exposures were observed. The highest dose, 30 mg, was selected, as it was believed to be associated with the greatest level of tumor exposure to the agent. A total of 64 patients were treated in this study, with a complete response of 41% at three months.

Vicinium was found to be safe, well-tolerated and exhibited clinical efficacy with greater efficacy associated with a longer course of induction therapy.

Observation of a longer median time to recurrence in the phase 2 trial in the group that was given more drug in the induction phase (e.g., the 12-week induction phase) suggested that increasing the number of doses of Vicinium would lead to even greater and more prolonged CR rates. Therefore, we modified both the induction and maintenance phase dosing in the phase 3 trial such that the induction phase is now 6 weeks of twice-a-week dosing followed by 6 weeks of once-a-week dosing.

The frequency of the maintenance dosing was also increased to once every other week for the remainder of the two-year study. We believe that increasing the number of doses in the induction phase may increase the CR rate at 3 months and that the increased frequency of the maintenance phase dosing will prevent more patients from recurring.

Vicinium is the only targeted therapeutics in advanced development for the treatment of NMIBC. As it functions by blocking protein production in targeted cells rather than inducing immune stimulation, Vicinium is expected to be effective in elderly patients with waning immune systems – a population that...
can be less responsive to agents like BCG that depend upon a robust immune function

References:


4. Kowalski, M, Guindon, J, Brazas, L, Moore, C, Entwistle, J, Cizeau, J, Jewett, MAS and MacDonald, GC. A Phase II Study of Oportuzumab Monatox: An Immunotoxin Therapy for Patients with Noninvasive Urothelial Carcinoma In Situ Previously Treated with Bacillus Calmette-Guérin