

## HEALTH

# Signs, symptoms and treatment of bladder cancer – your questions answered by experts

Knowing what signs to look out for is crucial in the fight to prevent cases of this disease becoming life-limiting

By David Cox

In the last couple of years, Professor Syed Hussain has become increasingly concerned by the growing number of patients presenting with bladder cancer at an advanced stage.

“Since Covid, there has been an issue with patients not managing to get their GP appointments,” says Prof Hussain, a professor of medical oncology at the University of Sheffield and an honorary consultant at Sheffield Teaching Hospitals. “And as a result, we are seeing more cases coming in later, once their cancer has become a life-limiting illness.”

A recent breakthrough in diagnostics could make it easier to detect patients early. Various NHS trusts are currently evaluating a test developed by Professor Richard Bryan, the director of the Bladder Cancer Research Centre at the University of Birmingham, and his team called Galeas Bladder which detects signs of cancerous DNA in the urine and can diagnose the disease with 90 per cent accuracy.

So how does bladder cancer develop and what are the most common causes?

### What is bladder cancer?

Bladder cancer is defined as abnormal cancerous growths which arise from cells in the bladder. More than 90 per cent of all bladder cancers are known as transitional cell carcinomas, which arise from the layers of urothelial cells which line the bladder and the rest of the urinary tract. Urothelial cells are particularly specialised because, unlike many of the other cells which line our internal organs, they help to store fluid – in this case urine which has been excreted from the kidneys – rather than absorbing it back into the body.

“The bladder is designed to be able to expand and contract without damage,” says Prof Bryan. “So the bladder lining is quite specialised and slowly regenerates because it doesn’t have to deal with the same amount of local trauma as the gut, for example. But it’s from this lining where bladder cancers arise.”

However, there are also some other rare forms. Around 5 per cent of patients have metaplastic cancers, which tend to be caused by chronic inflammation, either from a chronic urinary tract infection, long-term catheter implantation for severely disabled patients or water-borne parasites. This causes normal cells to morph into different types of cells which can become cancerous.



### How does bladder cancer develop and what are the most common causes?

#### How common is bladder cancer?

Approximately 21,185 people in the UK are diagnosed with the disease every year according to statistics from the charity Fight Bladder Cancer. “This puts it right up there as quite a common cancer, and probably the fourth or fifth most common cancer in men,” says Prof Bryan.

#### The different categories of bladder cancer

The vast majority of bladder cancer research has focused on transitional cell carcinomas. Most patients have non-muscle invasive cancer, in which the tumours are either still confined to the bladder lining or the layer immediately beneath. Prof Bryan explains that they are then categorised as either low risk, intermediate risk, high risk or very high risk, depending on how aggressive the cancer appears to be.

“This is determined by the number of tumours a patient has, because bladder cancers frequently involve multiple tumours, and also the size of the tumours,” says Prof Bryan.

However, there is also an even more serious form of the disease in which the tumours have progressed beyond the bladder lining and into the muscle.

#### What causes bladder cancer?

Around half of all bladder cancers are directly linked to the ingestion of toxic chemicals known as aromatic amines and polycyclic aromatic hydrocarbons, which are abundant in industrial and manufacturing plants and diesel exhaust. “If we go back to the history of bladder cancer, it was often linked to people who had worked for decades in synthetic dye manufacturing plants as well as tyre manufacturing and rubber manufacturing,” says Prof Bryan.

However the biggest contributor of all to bladder cancer is smoking, which is associated with 40 per cent of transitional cell carcinomas. Cigarette smoke is rich in aromatic amines and polycyclic aromatic hydrocarbons, which are absorbed through the lungs and into the bloodstream. The liver metabolises these chemicals which

are then excreted into the bladder via the kidneys.

“They react with other constituents of the urine and are almost reactivated as carcinogens,” says Prof Bryan. “So you have your urine sitting in your bladder for hours on end, containing potential carcinogens which can damage the DNA in those urothelial cells lining the bladder, starting the process of transformation to malignancy. If you’re a 20-a-day smoker and have been for 10 years, you have four times the risk of developing bladder cancer than somebody who’s never smoked.”

The other major risk factor for bladder cancer is simply being male. Three times more men develop the disease compared to women, and Prof Bryan’s research group is trying to understand why this is the case, and whether it could point towards future therapeutic options.

“This is mere speculation, but perhaps females have some sort of inherent protection from bladder cancer,” says Prof Bryan. “It could be hormonally related. In all likelihood it will ultimately be related to how the immune system works, and immune surveillance of bladder cells that have gone rogue is better in females than it is in males. But these are just hypotheses.”

### What are the symptoms?

Oncologists estimate that between 60 per cent and 80 per cent of patients diagnosed with bladder cancer have visited their doctor after seeing blood in their urine, a symptom known as hematuria.

“That’s quite an important sign not to miss,” says Prof Hussain. “Not every hematuria will be bladder cancer, it can also be related to urinary infections, but it could be an early manifestation of cancer. People seeing this should present to their GP and then be referred to urology services where hospitals have a one-stop clinic doing imaging scans for anyone who presents with hematuria.”

### How is bladder cancer diagnosed?

For many years, bladder cancer has been diagnosed through flexible cystoscopy, a test in which a thin, fibre-optic tube is passed through the urethra and enables the doctor to look directly at the lining of the bladder.

However, this has a number of limitations, from discomfort for patients, to the number of trained specialists required to perform the examination. If NHS evaluations confirm that the Galeas Bladder urine test is comparable to flexible cystoscopy, it could be rolled out on a national scale.

Simon Crabb, a professor of experimental cancer

therapeutics at the University of Southampton, says that if urine-based tests are proven to be sufficiently accurate, they could be utilised as part of screening programmes in future.

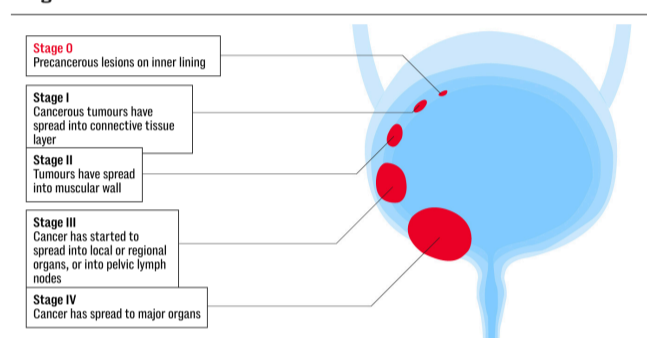
“We don’t have a screening test for bladder cancer at the moment,” says Prof Crabb. “A lot of advice around early detection is about people recognising blood in the urine. Many patients will have something perfectly benign, but it’s the best way at the moment to detect it at an early stage. Bladder cancer and urine-based tests make sense, and that may be the way to go.”

Any patient diagnosed with bladder cancer, even at an early stage, will have to get used to regular ongoing surveillance. “For patients who’ve been treated for early bladder cancer, their management will rely on monitoring by a camera (cystoscopy) inspection,” says Prof Bryan. “Some patients will be having that every three or six months, for many years.”

### How is it treated?

There are four different stages.

#### Stages of bladder cancer



Like many cancers, the severity depends largely on how swiftly it is caught. Prof Bryan estimates that up to 80 per cent of patients are diagnosed at a stage where the cancer can still be sent into remission. However, once the disease has penetrated the bladder muscle layer, the prognosis deteriorates rapidly, with five-year survival rates of just 50 per cent.

Patients with early-stage bladder cancer can usually be managed effectively with a form of immunotherapy known as Bacillus Calmette Guérin (BCG) which is administered directly into the organ via a catheter. Prof Hussain says that in many cases, this can effectively manage the cancer and send it into remission, and surgery is only considered in instances where the cancer has penetrated into the muscle.

In the 20 to 25 per cent of patients who have muscle-

invasive bladder, there are two main options, either chemotherapy followed by surgery or chemoradiotherapy. The latter case is an alternative to removing the bladder in an operation and involves having chemotherapy and radiotherapy treatment together in order to sensitise the cancer cells to radiotherapy.

However, just under one in 10 patients are found to have advanced or metastatic bladder cancer, which has not just penetrated the bladder muscle but spread beyond the bladder into other organs.

“Here, treatments will unfortunately be not curable but only palliative,” says Prof Hussain. “But in metastatic cancer, the treatment landscape has significantly changed and there’s a lot more hope. There are a number of new drug options, patients are living longer and they’re staying well.”

Prof Hussain says that while the average survival rate for a patient with metastatic bladder cancer used to be between 12 and 18 months, this has now increased to between 24 and 30 months in the last few years, particularly with the advent of a new class of drugs called immune checkpoint inhibitors which are administered into the bloodstream through a drip. These drugs are now available on the NHS as a standard of care.

More recently, clinical trials of immune checkpoint inhibitors in combination with another class of drugs called antibody-drug conjugates have shown promising results in improving survival outcomes for patients with metastatic bladder cancer.

“You can only really give six cycles of chemotherapy, for around three to four months, because then the patient’s bone marrow starts to crack,” says Prof Hussain. “But immune checkpoint inhibitors are very clever drugs, using your own immune cells to find camouflaged cancer cells and attack them.”

A new clinical trial is testing whether it is safe to administer immune checkpoint inhibitors directly into the bladder in patients with early-stage cancer, to see whether this can treat their cancer more effectively. Prof Hussain is currently involved in a trial which is looking at a particular immune checkpoint inhibitor called atezolizumab in patients with non-muscle invasive cancer, for whom BCG has not worked, or people who have muscle-invasive cancer but are not well enough to undergo chemotherapy.

“I think it’s important to highlight the hope that we are seeing,” says Prof Hussain. “Patients are living longer, and with good quality of life which is all down to these new drugs.”