

## Bladder Cancer Test Enables Painless Follow Up

Originally Published in Hebrew by Yedioth Ahronoth on July 8, 2020; Translated to English

*Many bladder cancer patients would prefer to not have a cystoscopy - an invasive and painful test – every few months for doctors monitor them. Now there is a urine test that can detect the recurrence of the disease and reduce the frequency of the painful cystoscopy test.*

**By Prof. Ilan Leibowitz**

Bladder cancer is considered one of the most common cancers in general, particularly in the field of urology. According to the Israel National Cancer Registry, it is the fourth most common cancer in men (after prostate, lung and colorectal cancer) and eighth in women. In addition, the prevalence of the disease increases with age and is most common among those aged 60 and over. In rare cases, it may also appear in young people. The disease mainly affects the bladder, but can also damage the collecting system of the kidneys.

Smoking is the most significant risk factor, and other causes include exposure to substances in various industries (paints, rubber, metal), chronic bladder infections and diabetes. The symptoms of the disease are primarily manifested by blood in the urine (hematuria) which is sometimes not visible and is revealed by microscopic urine examination.

In most cases, the bleeding will occur without any additional symptoms, such as burning, difficulty urinating or pain. Any urinary bleeding event, even a single one, requires consideration or evaluation for bladder cancer, though not all urinary bleeding indicates the presence of cancerous cells and may be caused by other conditions. Bladder cancer can be classified into two main groups:

- "Muscle Invasive Bladder Cancer" (muscle penetrating cancer) - Tumor cells extend beyond the layer of cells that first appeared and infiltrate the bladder muscle (about 30% of the cases). Most often the treatment of these cases will be done through complete bladder removal surgery
- "Non-Muscle Invasive Bladder Cancer" (cancer that does not penetrate the muscle) - the tumor cells are in the first and / or second layer of the bladder and have not infiltrated the bladder (about 70% of the cases). The treatment of these cases will be conservative and the patient will undergo surgery to resect the tumor only through the urethra. Occasionally, in medium and high-risk tumors, additional prophylactic treatment will be given through irrigation of the bladder with chemotherapeutic or biological agents (BCGs)

### **Because of high recurrence rates, it is important to monitor for recurrence of the disease.**

After the treatment of non-muscle invasive bladder cancer, we see very high rates of recurrence – more than 70%. Most of the bladder cancer recurrences occur in the first two years.

As a result, careful and close monitoring is of great importance. As part of the follow-up, every three months the patient undergoes a cystoscopy with an optic fiber inserted into the lower urinary tract through the urethra. This allows the physician to look directly at the walls of the bladder and urethra and check for cancerous tumors. This test is considered to be the "gold standard" in helping the doctor decide whether or not the disease is recurring.

In addition, a urine test called "cytology" can be performed for . This test looks for abnormal cells coming from the bladder wall, which are examined in order to distinguish between benign and cancerous cells. This test is insufficiently sensitive and only

detects 30% - 50% of the cases. Therefore, in cases with a negative result, it is not possible to determine with certainty that there is no recurrence of the tumor.

### **Invasive and painful examination every few months**

The cystoscopy is an invasive test done under local anesthesia and is not pleasant to the patient. Many patients would prefer to skip this test if there was an alternative test with a high sensitivity level. In addition, the test may show false-negative results (not identifying cancerous tumors because they are very small or 'disappearing' on the background of the bladder) or false positives (identifying a suspected tumor as a tumor even though it is a benign inflammatory process).

Monitoring patients for the detection of recurrence is a long process that requires frequent testing. During the first two years from the time of removal of the tumor, two tests are required every three months: cystoscopy and cytology. The tests are then performed every six months for an additional three years, and once a year after five years from the patient's original diagnosis. If the tumor has come back again, the whole process of monitoring starts from the beginning.

For many years, they have tried to develop a non-invasive test that replaces the cystoscopy to detect recurrence. In recent years, Bladder EpiCheck®, a non-invasive urine specimen test that has the ability to detect non-muscle invasive bladder cancer, has been developed and validated. The test is based on the identification and analysis of 15 biomarkers in the patient's urine and examines changes in the methylation pattern on the individual's DNA.

In order to perform the test, the patient provides a urine sample in collection centers around the country. In some cases, the urine sample can be collected from the patient's home.

### **The test that demonstrated high accuracy levels**

The validation study is based on data from 440 non-muscle invasive bladder cancer patients, ages 22 and above, treated at five European and Israeli medical centers. All patients were in the first year of follow-up after surgery for tumor resection and were monitored by conventional tests like cystoscopy and cytology. The results of the standard follow-up tests were compared with the results of the Bladder EpiCheck test performed on those patients. All data were examined twice: once for all patients and all malignancies, and once again for cases with high-grade malignancy tumors.

The results of the study showed that the Bladder EpiCheck test was able to rule out the presence of a high-grade malignancy at 99% certainty, and for all malignancies at 95% certainty. In addition, the test sensitivity in identifying patients with recurrence of high-grade malignancies was 92%, and for all malignancies was 68%. In fact, a significant benefit of the test is its ability to rule out recurrence of bladder cancer at that time. If a negative result is obtained from the test, the likelihood of recurrence is very low.

The incidence of non-muscle invasive bladder cancer is high, and therefore involves a burden on the attending physicians, with invasive follow-up tests at high costs that cause patient's discomfort. For years, various urine tests have been developed to monitor bladder cancer and some have even been approved by the US Food and Drug Administration (FDA), but to date the sensitivity and specificity of the tests have not been high enough for wide use.

Thanks to this urine test, a large proportion of patients may be able to reduce the number of invasive cystoscopies and instead be offered a test with very high degree of certainty (99%) in excluding the presence of high-grade malignancies.