Applicability of the FISH Test For Bladder Cancer

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In the U.S., bladder cancer is estimated to be diagnosed in 70,530 individuals in 2010, with 14,680 deaths attributed to this disease [National Cancer Institute (NCI), 2010]. Risks for bladder cancer include being over 40 years of age, smoking, occupations with known carcinogens in the workplace, parasite infections, and previous treatment or exposure to cyclophosphamide or arsenic. Ethnically, bladder cancer occurs twice as frequently among Caucasians when compared to African Americans, and it occurs least frequently among Asians. Men are two to three times more likely to be diagnosed with bladder cancer than women, and family members are more likely to get this disease. The identification of a gene linked to bladder cancer has yet to be identified.

Bladder Physiology

The bladder is a flexible, muscular organ that receives and stores urine excreted from the kidneys (Hall & Chang, 2007). The primary function of the bladder is to store urine; normally, a bladder is capable of retaining between 50 and 500 ml of urine. Once the parasympathetic nervous system is stimulated, the smooth muscle layer of the bladder wall (the detrusor muscle) contracts, and urine is released. Anatomically, the walls of the bladder consist of several layers of cells. The urothelium consists of transitional cells that form the surface of the bladder and comes into direct contact with urine, the lamina propria (submucosa) is a thin layer of highly vascular connective tissue, the muscular propria is a thicker layer of smooth muscle tissue, and the detrusor muscle is the smooth muscle layer of the bladder wall that initiates voiding. The outermost layer of the bladder is called the adventitia and consists of fatty tissue that protects and cushions the bladder. Most of the bladder is covered by a serosal mesothelial surface within the abdominal cavity and pelvis (Messing & Catalona, 2007).

Blood supply to the bladder is provided by the internal iliac artery and the superior, middle, and inferior vesicle arteries (Legg, 2008). Blood is also supplied by the obturator and inferior gluteal arteries. In women, the smaller arteries arising from the uterus and vagina also provide blood to the bladder. Lymphatic drainage is supplied by interstitial vesical lymphatics (Legg, 2008).

Symptoms of Bladder Cancer

Symptoms associated with bladder cancer include hematuria and painful and/or frequent urination. The American Urologic Association’s (AUA) best practice guidelines for the evaluation of microscopic hematuria recommend a full urologic work up for all high-risk patients or those with

Notes: Objectives and CNE Evaluation Form appear on page 222.

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two or more documented positive urinalyses (Hall & Chang, 2007). The diagnostic work up may include a physical examination, urine tests, intravenous pyelogram, and cystoscopy. Tissue samples can be obtained during a cystoscopy and are sent to the pathologist for microscopic review. Pathologically, most malignant bladder cancers begin in the cells that line the bladder wall. These cancers are named for the type of cell present (transitional, squamous, or adenocarcinoma) (Messing & Catalona, 2007). If the initial review determines that the tissue obtained is cancerous, further diagnostic testing may be warranted. This may include computerized tomography (CT) or magnetic resonance imaging (MRI) scans, sonograms, intravenous pyelogram, bone scan, and a chest X-ray. These tests determine if the bladder cancer is present locally or elsewhere in the body and are necessary to stage the disease (Pashos, Botteman, Laskin, & Redaelli, 2002). There are five stages for bladder cancer (0 to IV) associated with the extent of the disease within the bladder, surrounding tissues, or other organs. Treatments for bladder cancer consist of surgery, radiation therapy, chemotherapy, and biological therapy (NCI, 2010).

Cost and Clinical Treatment Of Bladder Cancer

Estimated costs associated with the diagnosis and subsequent treatments of bladder cancer have been determined by Arritscher and associates (2006). These researchers performed a retrospective medical record chart review of 208 patients diagnosed and treated for bladder cancer between 1991 to 1999, and inflated costs to 2006 U.S. dollars. Future costs were estimated based on best-case and worst-case scenarios, where the bladder cancer recurs and if the patient dies of disease. The results of this study indicate that the average lifetime cost to treat bladder cancer is $65,158.00. Sixty percent of these costs ($39,393.00) were associated with surveillance and treatment of recurrences, with 30% ($19,811.00) of these costs contributed to treatment/prevention of complications.

According to the AUA Best Practice Guidelines (Hall & Chang, 2007), the potential for disease recurrence and progression typically necessitates follow-up strategies. According to The Committee for Establishment of the Clinical Practice Guidelines for the Management of Bladder Cancer and the Japanese Urological Association (2010), recurrence rates for bladder cancer at low risk for recurrence and progression have a 45% reported recurrence rate. Follow up is recommended every month for the first two years, every six months for the next two years, and then annually thereafter (Liou, 2006). Cytology and urine cytology provide the present standard of care, yet each of these tests has limitations. Better surveillance strategies would identify recurrence/progression, and thus, include cost effectiveness with appropriate treatment.

Presently, six U.S. Food and Drug Administration (FDA)-approved, urine-based markers can be used to assist in the diagnosis and surveillance of invasive urothelial cancer. These markers tests include 1) the bladder tumor antigen STAT test (Bard Diagnostics, Redmond, WA, U.S.), 2) the BTA TRAK test (Poly Med Co, Cortlandt Manor, NY, U.S.), 3) the nuclear matrix protein (NMP) 22, 4) NMP22 BladderChek assays (Matritech, Newton, MA, U.S.), 5) ImmunoCyt test (Dignocure Inc, Quebec City, Quebec, Canada), and 6) fluorescence in situ hybridization (FISH) analysis (Urovysion Systems Vysis, Abbott Laboratories, Abbott Park, IL, U.S.) (Gaston & Pruthi, 2004). Other recently investigated tests and identified markers include Quanticyt (Gentian Scientific, Niawer, The Netherlands), BLCA-4, hyaluronic acid, telomerase, LewisX blood group antigens, microsatellite polymorphism analysis, cytokeratins, and survivin (Konety, 2006). The potential for these urine-based markers to support or replace cytology or cystoscopy has yet to be determined. Using a case study, this article presents the challenges associated with using FISH analysis of voided urine in diagnostic activities and the role of the nurse when this diagnostic tool is used.

The FISH Test

The FDA approved FISH analysis in 2001 for use in conjunction with cystoscopy to monitor for recurrence among those with previously diagnosed bladder cancer. Since then, a multitude of studies have confirmed the usefulness of including FISH analysis when monitoring for recurrence (Skacel et al., 2003). A systematic review of the use of urine markers for bladder cancer surveillance was performed by van Rhijn, van der Poel, and van der Kwast (2005). Comparing the results of 64 articles that used 18 different marker analyses, six different assays (including FISH) were identified as the most promising in identifying recurrence. While many of these tests are promising, it was not suggested by these authors that urine assay testing be substituted for cystoscopic follow up.

FISH analysis uses a computer algorithm model to evaluate and compare cells for abnormality. If abnormal, these cells may be considered suspicious or diagnostic for cancer. The presence of four or more abnormal cells is considered diagnostic for bladder cancer. Thus, a grey area may exist when there are one to three abnormal cells present. Clinical judgment skills, experience with FISH analysis, knowledge of the patient’s medical history, and/or consultation with other patholo-
gists may be necessary for appropriate diagnosing. Low-grade bladder cancers rarely demonstrate changes that can be detected by FISH analysis. Thus, a clinical benefit of FISH is its ability to identify the more aggressive bladder cancers earlier. Identifying the tumor type that may eventually become life-limiting allows the patient and health care providers to initiate a treatment plan that includes scheduled surveillance and pro-active or appropriate treatment.

Clinical Application of the FISH Test

Gofrit and associates (2008) followed patients diagnosed with non-muscle invasive bladder cancer treated by transurethral resection for a median of 13.5 months. An abnormal FISH result preceded the diagnosis of tumor recurrence in 18 of 21 cases (86%), including all high-grade recurrences. These data suggest that FISH assay may be a particularly useful tool for predicting tumor recurrence. However, the implementation of FISH analysis or any other assay as a substitution for cystoscopy is not recommended at this time. Gofrit et al. (2008) suggest that cystoscopy may be spared and surveillance intervals widened in patients with a history of low-grade tumors and normal FISH test(s).

The initial clinical testing using FISH as a diagnostic tool included 497 patients receiving care at 23 health care sites (Sarosdy et al., 2006). Participation in this study was limited to individuals who presented with hematuria and had no previous history of bladder cancer. After excluding very low-grade tumors, FISH was able to detect cancer in 25 of 30 (84%) cases; cytology was detected 15 (50%) cases. The capability of FISH to detect bladder cancer is somewhat less if the patient has a smoking history or presently smokes. In patients with a greater than 40-pack-per-year history of smoking, FISH was able to detect cancer 65% of the time. For those with less than 20 or 20-to-40-pack-per-year smoking history, this ability decreased to 13.6% to 24.2%. Overall, the results of this study indicate that FISH demonstrates a 68.6% clinical sensitivity and a 77.7% clinical specificity in detecting bladder cancer. Based on these results, the FDA approved Abbott’s UroVysion™ DNA probe (FISH) as a diagnostic tool for bladder cancer in 2005. Presently, FISH is used as an aid in the initial diagnosis of bladder cancer in patients with hematuria. In 2005, Sarosdy stated; “This... should allow physicians to make an earlier diagnosis, with earlier treatment” (p. 1).

Hajdinjak (2008) identified and reviewed 14 research articles that included the FISH assay as a tool used in diagnosing bladder cancer. Synthesizing the results of these studies reveals that the sensitivity of FISH ranges from 69% to 75% (mean 72%), and the specificity ranges from 82% to 85% (mean 83%). The overall performance for FISH was higher than that obtained using cystoscopy, yet these differences almost disappear after superficial cancer cases are excluded. This author states that a positive FISH result moderately increases the probability of the presence of any stage of bladder cancer, and a negative result reduces this probability by a small but significant amount. Thus, while the FISH test results cannot provide conclusive evidence for the presence or absence of cancer, both positive and negative results should influence the probability of the disease.

Ferra and associates (2009) evaluated the effectiveness of FISH among 161 patients with suspicious cytology results. The aim of this study was to identify those for whom an aggressive work up was indicated. These results indicate that a negative FISH test did not rule out the presence of a low- or high-grade cancer when the urine specimen was suspicious. Thus, these authors conclude that an aggressive work up is not indicated when patients display a suspicious cytology, positive FISH result, and a negative cystoscopic evaluation.

Research has demonstrated the clinical value and diagnostic significance of FISH, but these findings are not universal nor considered confirmative as yet. Wild and colleagues (2009) state that the FISH test is capable of detecting symptoms of malignancy on the molecular level. This may lead to earlier diagnosis and therapy, and it may potentially extend survival. FISH makes it possible to make decisions in cases of atypical or unclear cytological findings. According to Reid-Nicholson and colleagues (2009), FISH results cannot be used to definitely diagnose squamous carcinoma or adenocarcinoma, nor can it be used to differentiate the two from urothelial carcinoma. However, it may be useful as a surveillance tool in established primary and secondary bladder adenocarcinoma. When urine specimens are suspicious, the role of FISH is questionable, especially in light of the high cost associated with this test. According to the AUA (Hall & Chang, 2007), cystoscopy remains the gold standard in the diagnosis and surveillance of bladder cancer.

Case Study

Bob is a 54-year-old Caucasian factory worker with complaints of hematuria and frequent/painful urination for the previous month. The results of his FISH test are positive, but his cystoscopy and histology are negative for cancer. His physician recommends no further treatment but admits the inability to explain the symptoms; other causes (infection, prostate, and abdominal reasons) have been ruled out. Bob and his family are confused and have accessed the Internet for health care informa-
tion. According to the information they have read, the possibility or probability of cancer in the future has not been sufficiently ruled out.

Application of the evidence needs to include demographic and employment history data. Knowing Bob's ethnicity, the fact that he has been a cigarette smoker for the past 25 years and works in the automobile industry increase his chances for bladder cancer. His recent test results may indicate either a false or anticipatory positive FISH result. This is especially important for Bob, since his lifestyle choices may influence FISH results. Research has reported eventual tumor recurrence rates between 39% (Zellweger et al., 2006) and 50% (Grossman et al., 2006) when follow up is performed between three and 46 months later. While Bob's test results may at present be negative for a diagnosis of cancer, he is at risk, and routine follow up should be encouraged. In addition to follow up, Bob should be instructed to contact his physician if any changes in his health are noted, particularly if hematuria is noted or urinary function becomes impaired.

Nursing Implications

While cystoscopy and urine tests provide the gold standard for diagnosing bladder cancer, other procedures that demonstrate the ability to identify some types of bladder cancer are available. Despite the inconsistency of the results, urine-based markers can provide important information that assists in the diagnosis and surveillance of invasive urothelial cancer. Nurses need to be aware of the emerging presence of these other diagnostic procedures, as well as their reliability and sensitivity. The potential or actual diagnosis of bladder cancer results in an unfamiliar world for most patients, and interpreting modern diagnostic test results is challenging. Thus, providing evidence-based care requires that nurses are aware of not only the availability of diagnostic and follow-up tests, but how these tests apply to each individual patient. Laboratory tests cannot discriminate or know the specific demographic and lifestyle variables that accompany every patient. All of these impact the use and results of urine-based markers, such as FISH analysis.

Conclusion

While the research evidence supports the use of FISH in bladder cancer surveillance activities, it has been FDA-approved as a diagnostic test. FISH results provide the ability to diagnose some bladder cancers while at the molecular level. This represents new information that may be confusing and must be coordinated with other medical information and specific patient demographic information. In comparison to cystoscopy, the results of FISH at the time of initial diagnosis may blur the situation. While the potential exists for under or over-diagnosing bladder cancer, the potential also exists for diagnosing this life-threatening disease while it is at an early stage, treatable, and controllable.

References


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