Cost-Effectiveness of Fluorescence In Situ Hybridization in Patients with Atypical Cytology for the Detection of Urothelial Carcinoma

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Purpose: Patients with atypical cytology and equivocal or negative cystoscopy pose a challenge due to uncertainty about the presence of cancer. We determined the cost-effectiveness of using fluorescence in situ hybridization assays to determine the need for biopsy in patients with atypical cytology and equivocal or negative cystoscopy.

Materials and Methods: Data from 2 large prospective studies evaluating the usefulness of fluorescence in situ hybridization in the setting of atypical cytology to detect urothelial carcinoma were combined. The data were used to calculate sensitivity and specificity for the UroVysion® fluorescence in situ hybridization assay in various clinical scenarios. Cost data were obtained from our institution and Medicare reimbursement rates. Evaluations with or without bladder biopsy and with or without upper tract evaluation were considered.

Results: The study included 263 patients with atypical cytology and equivocal (62) or negative (201) cystoscopy. In patients with equivocal cystoscopy (assuming biopsy was performed in the operating room) biopsy based on fluorescence in situ hybridization results saved $1,740 per patient ($3,267 vs $1,527 per patient) and avoided 42 biopsies compared to biopsy in all patients. If office based biopsies were used then cost savings using fluorescence in situ hybridization results were $95 per patient. Among patients with negative cystoscopy biopsy based on fluorescence in situ hybridization resulted in costs savings of $2,241 per patient, avoiding 167 biopsies, compared to biopsy in all patients. Assuming office based biopsy, the cost savings were $216 per patient.

Conclusions: The decision to perform biopsy based on fluorescence in situ hybridization assay in patients with atypical cytology and equivocal or negative cystoscopy was associated with a significant decrease in bladder cancer associated costs.

Key Words: cost-benefit analysis; urinary bladder neoplasms; watchful waiting; tumor markers, biological; in situ hybridization, fluorescence

Abbreviations and Acronyms

CIS = carcinoma in situ

CT = computerized tomography

FISH = fluorescence in situ hybridization

OR = operating room

UC = urothelial cancer

UTUC = upper tract urothelial cancer

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Study received institutional review board approval.

* Nothing to disclose.

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For other articles on related topics see pages 1398 and 1404.

Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1448 and 1449.

Bladder cancer is the fourth most common cancer diagnosed in men in the United States with 73,510 new diagnoses and 14,880 deaths in 2012.[1] In the United States $3.4 billion is spent annually on bladder cancer with $2.9 billion in direct treatment related costs, making it the fifth most expensive cancer.[2,3] Additionally, bladder cancer has the highest cost per patient of all cancers.[3]

Much of the cost associated with bladder cancer is accrued from the lifelong surveillance program.[3–5] Due

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to the risk of recurrence, patients with nonmuscle invasive urothelial cancer undergo frequent and demanding surveillance regimens consisting of multiple cystoscopies, cytologies and transurethral procedures.[3,5,6] However, current surveillance methods are not adequate and have a susceptibility to miss recurrence. Cystoscopy alone can miss up to 10% to 30% of cancer recurrence.[7,8] In addition to cystoscopy, cytology has been shown to have low sensitivity and can often have indeterminate results.[9,10]

An atypical cytology result poses a challenging clinical dilemma, especially with an equivocal or negative cystoscopy. Current options for the management of this predicament include observation with the possibility of missing a diagnosis or biopsy in every patient with the known risks of anesthesia and surgery.[11] Practically, however, performing a biopsy in every patient is neither clinically nor economically sound, let alone feasible. Several methods have been recommended for reducing the economic burden associated with UC surveillance and treatment.[2] One of those methods is the use of urine based markers, and multiple markers are Food and Drug Administration approved for the surveillance of bladder cancer including BladderChek®, UroVysion FISH assay and ImmunoCyt™.

UroVysion is a multitarget FISH assay that detects aneuploidy of chromosomes 3, 7 and 17 and loss of the 9p21 band in exfoliated cells in urine from patients with UC.[3] Previous prospective studies have shown that use of a reflex FISH assay in patients with atypical cytology is beneficial in identifying which patients with equivocal or negative cystoscopy have cancer with 100% sensitivity and reasonable specificity.[11–13] In this study we determined the cost-effectiveness of using FISH assays to determine the need for biopsy in patients with atypical cytology and equivocal or negative cystoscopy.

MATERIALS AND METHODS

After institutional review board approval, data from 2 large prospective studies evaluating the usefulness of FISH after an atypical cytology result to detect urothelial carcinoma were combined (tables 1 and 2).[11,12] The extracted data were used to calculate cancer rates, sensitivity and specificity for the performance of FISH testing in different clinical scenarios for patients with atypical cytology based on cystoscopic findings (equivocal or negative) and FISH findings.

All cytology specimens and FISH analyses were analyzed by cytopathologists specifically trained in genitourinary malignancies. At our center atypical cytology is defined as being neither unequivocally positive or negative. A FISH test is considered positive if 4 or more cells exhibiting apolysomic signal pattern are seen on microscopic examination for chromosomes 3, 7, and 17 or more than 9 cells with loss of both copies of 9p21. An uninformative result occurs when there are insufficient cells to run the assay accurately. Borderline and indeterminate FISH results were considered negative.

Table 1. *FISH outcomes in patients with equivocal cystoscopy from combined studies*

	No. Pts/No. Ca (%)		
	Previous Ca	No Previous Ca	Total (previous + no previous Ca)
Pos	16 / 9 (56.3)	4 / 3 (75)	20 / 12 (60)
Neg	18 / 1 (5.5)	18 / 0 (0)	36 / 1 (2.7)
Borderline	2 / 0 (0)	0 / 0 (0)	2 / 0 (0)
Uninformative	3 / 1 (33.3)	1 / 0 (0)	4 / 1 (25)
Totals	39 / 11 (28.2)	23 / 3 (13)	62 / 14 (22.6)

Cost Data

Cost data are shown in table 3. Hospital cost data for cystoscopy with bladder biopsy were obtained from our institution, and included OR costs, nursing, medication costs, recovery room costs and day surgery costs. Medicare rates were used for cost of FISH, CT urography, surgeon and anesthesia professional fees, and hospital cost. Charge data were not used in our analysis because they do not directly correlate to resources allocated. Therefore, financial analyses were based on cost rather than charges. A complication rate of 5% was used based on prior published studies.[14,15] The cost of complications was based on the difference between patients who had outpatient surgery and those who stayed for 1 night in the hospital. The cumulative cost of a bladder biopsy included the hospital cost, complication cost and professional fees.

Model

TreeAge Pro™ was used to build a decision analysis model to compare the cost-effectiveness of biopsy in all patients with atypical cytology and equivocal or negative cystoscopy vs biopsy based on FISH results in the same cohorts of patients (see figure). In the FISH arm of the model we assumed that biopsy would only occur in patients who were FISH positive. However, every patient would have the cost of the FISH assay.

A separate analysis was done that included the cost of imaging, CT urogram, for upper tract disease. This was included to determine the impact of FISH in patients with vs without imaging. Upper tract imaging was done based on provider preference.

Finally, office based biopsies could theoretically be used and a separate analysis was used assuming office rather than OR biopsies with similar complication rates. Medicare reimburses $751 for office based biopsies.

RESULTS

The combined studies included a total of 263 patients with equivocal (62) or negative (201) cystoscopy, of which 143 had a previous history of UC and 120 were without UC but underwent cystoscopy to evaluate for bladder cancer. All patients included had atypical cytology and FISH was performed as a reflex test. Among the patients with equivocal