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A Cost Comparison of the Diagnostic Modalities Used in the Detection of Urothelial Carcinoma in Patients Undergoing Evaluation for Hematuria

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ABSTRACT

BACKGROUND: The incidence of bladder cancer was estimated at 61,420 in the United States in 2006, and the rate is increasing with the aging population. Studies have shown that 6% to 12% of hematuria evaluations yield diagnoses of urothelial carcinoma (UC) and upper tract tumors. This correlation translates into 500,000 to 1,000,000 hematuria evaluations per year in the United States, with a corresponding cost of $500 million to $1 billion annually. Because no studies have looked at the economic cost of hematuria evaluation, we reviewed our experience with the current recommended diagnostic approach and report the related medical costs associated with hematuria evaluation at our institution.

METHODS: A retrospective review was performed on 744 consecutive patients who underwent evaluation for gross or microscopic hematuria. Of these patients, 373 patients underwent cystoscopy and CT urogram and had urine collected for nuclear matrix protein-22 (**NMP-22) testing and cytology. The Medicare reimbursement rates as of January 1, 2006 were obtained for each of the above modalities. The McNemar test was used for pair-wise comparison of sensitivity and specificity.**

RESULTS: Through dividing the direct medical cost of each modality by the observed sensitivity, we determined the cost per diagnosis of NMP-22 ($39.82), cytology ($54.96), cystoscopy ($430.14), and CT urogram ($989.06). Cystoscopy was found to be more sensitive than CT scan, cytology, and NMP-22 in the diagnosis of UC ($p < 0.05$), and combining cystoscopy with other tests yielded no statistically significant improvements in sensitivity.

CONCLUSION: We showed that the workup of hematuria in terms of financial cost is not insignificant. In our specific patient series, cystoscopy proved to be the most effective modality at diagnosing UC, with 96% sensitivity and 97% specificity. Although imaging is an important part of the upper tract evaluation, the development and usage of better urinary markers may complement less expensive imaging modalities with less radiation exposure.

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KEYWORDS: Urothelial carcinoma, NMP-22, CT urogram, Cost comparison

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INTRODUCTION

Bladder cancer is one of the most common urologic cancers, with an estimated incidence of 61,420 in the United States in 2006. It is the fourth most common cancer in men and the ninth most common in women [1]. It is a disease of the elderly, with approximately 80% of cases being diagnosed in patients over the age of 60. The most common presenting symptom is hematuria, which is typically intermittent, macroscopic (gross) or microscopic, and painless. Studies have shown that 6% to 12% of hematuria evaluations yield diagnoses of urothelial carcinoma (UC) [2-5].

The importance of the hematuria evaluation has been well established due to its indication of significant urologic diseases [6]. The American Urological Association Best Practice Guidelines for evaluation of microscopic hematuria recommends the use of upper tract imaging, cystoscopy, and urine cytology in patients with risk factors for UC [7]. Urinary markers, such as nuclear matrix protein-22 (NMP-22), have shown utility in the evaluation of hematuria as well [8]. Despite all of this, an extensive review of the literature with regard to hematuria evaluation performed by Rodgers *et al.* [8] indicates that no single study to date has addressed the complete diagnostic process for hematuria, nor has a study evaluated the effectiveness of these diagnostic algorithms, and finally, no financial costs have been investigated.

The first presentation of gross hematuria or multiple episodes of microscopic hematuria warrants a full urologic evaluation (upper tract imaging, cystoscopy, and urine cytology) due to its indication of potentially significant urologic diseases [9]. CT scans are often used as the upper tract imaging modality of choice. Urinary biomarker assays, including tests for NMP-22, have proven useful in the diagnosis of UC as well [10]. An estimated 500,000 to 1,000,000 hematuria evaluations are performed per year because of the percentages that yield a diagnosis of UC. Assuming that CT scans, cystoscopies, and urine cytologies are performed and obtained from all patients, we estimate the direct medical costs of the evaluation of hematuria to be between $518 million to $1.04 billion per year in the United States. In this study, we evaluate our experience with the current diagnostic approach and direct medical costs associated with the evaluation of hematuria in an urban population, evaluating sensitivity, specificity, and cost-effectiveness.

METHODS

We performed a retrospective review of 744 consecutive patients who underwent initial evaluation for gross or microscopic hematuria at our institution from October 1999 to April 2005. Microscopic hematuria is defined by the American Urological Association Best Practice Guidelines as 3 or more red blood cells per high-power field on microscopic evaluation from 2 of 3 urinalysis specimens [11]. Clinical data on these patients was obtained through a review of charts and queries of our hematuria database approved by an institutional review board. Of the 744 individuals, 373 consecutive patients who underwent cystoscopy, CT urogram, and had urine specimens sent for cytology and NMP-22 were included for analysis. Other studies (renal ultrasound, intravenous pyelogram (IVP), MRI, etc.) were performed as needed. Medicare reimbursement rates as of January 1, 2006 were used as a basis for the direct medical costs for each of these modalities. Cytology was collected from either voided or barbotaged specimens, whereas NMP-22 was collected from voided specimens only.

Cytology results were reported by staff pathologists at our institution. Only cytology results reported as "positive" were defined as positive for UC. All other results, including the lack of tumor cells and atypical, suspicious, moderate, or severe dysplasia, were defined as negative results. A positive value for NMP-22 was set at greater than or equal to 10 U/ml [12]. CT urograms were interpreted by staff radiologists at our institution.

Number of Patients	373
Median age (range)	52 years (18-87)
Number male (%)	209 (56%)
Number with gross hematuria (%)	157 (42%)
Number with microhematuria (%)	216 (58%)
Number of smokers (%)	131 (35%)
Mean serum creatinine (range)	1.0 mg/dl (0.2 – 8.6)

Table 1. Demographic data

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RESULTS

Our analysis included 373 patients (Table 1). The median age of the population was 52, with a range from 18 to 87 years, and 209 patients were male and 164 were female. Of the 373, 157 patients had gross hematuria, while 216 patients had microhematuria. 131 patients had a history of tobacco use, 19 had a history of prostate cancer (13 patients with radiation therapy, 2 with prostatectomy, and 1 with brachytherapy) and 21 patients had a prior stone history.

UC was the final diagnosis in 26 patients (7%; 20 male, 6 female). There were 25 cases of bladder UC, and 1 case of UC in the renal pelvis. These results were also stratified according to grade and stage (Tables 2 and 3). Of these patients, 24 presented with gross hematuria and 2 with microscopic hematuria. There were 9 smokers with a 20 pack per year or greater history, while the remainder were nonsmokers. 19 patients were over the age of 60.

The remaining diagnoses included stones (68 patients), benign prostatic hypertrophy (34), cystitis (18), urinary tract infection (16), prostate cancer (3), nephrogenic adenoma (1), schistosomiasis of the bladder (1), urachal adenocarcinoma (1), and idiopathic hematuria (231). The patient presenting with schistosomiasis had a negative cytology and NMP-22, whereas the patient with urachal adenocarcinoma had an atypical cytology and a negative NMP-22 result.

In the diagnosis of UC, the sensitivity and specificity of cystoscopy were 96% and 97% respectively (Table 4). This was better than the sensitivity of cytology (27%), NMP-22 (73%), and CT urogram (62%). The differences in sensitivity for CT urogram ($p = 0.003$), NMP-22 ($p = 0.0339$), and cytology ($p = <0.0001$) were statistically significant when compared to cystoscopy. However, there was no statistically significant difference in specificity among each of the single tests. Cystoscopy alone missed no cases of bladder UC in our sample. The single UC of the upper tract was missed by all modalitites except for NMP-22. Urine cytology was the most specific diagnostic modality, with a positive result indicating UC 100% of the time in our sample. Similarly, its positive predictive value was also 100%, indicating its possible utility in verifying cases of UC. NMP-22 and CT urogram had specificities of 76% and 98%, respectively. CT urogram also yielded diagnoses for other pathologies, as listed in Table 5.

	Tis	Ta	T1	T2	T3	T4
Male	2	8	3	4	3	0
Female	0	3	0	3	0	0

Table 2. UC grade
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	CIS	Grade 1	Grade 2	Grade 3
Male	2	2	8	8
Female	0	1	4	1

Table 3. UC stage
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Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Cytology	27% (12-48%)	100% (99-100%)	100%	95%
NMP-22	73% (52-88%)	76% (71-80%)	19%	97%
Cystoscopy	96% (79-97%)	97% (95-99%)	74%	99%
CT Urogram	62% (41-80%)	98% (96-99%)	67%	97%
All Four Tests	100% (87-100%)	74% (69-78%)	22%	100%

Table 4. Effectiveness of diagnostic modalities in the evaluation of hematuria
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The combination of cystoscopy with other tests yielded no statistically significant improvements in sensitivity when compared to that of cystoscopy alone. The specificity of any combination of tests was lower than that of cystoscopy alone (with the exception of cystoscopy and/or cytology), indicating an increase in false positives with additional tests.

With regard to costs, urine cytology had a direct medical cost based on Medicare's 2006 reimbursement schedule of $14.84. NMP-22 had a direct medical cost of $29.07, cystoscopy cost $412.93, and CT urogram (charged as CT abdomen and pelvis) was $607.64 (Table 6). Through dividing the direct medical cost of each modality by the observed sensitivity, the cost per diagnosis of NMP-22 was determined as $39.82, cytology was $54.96, cystoscopy was $430.14, and CT urogram was $989.06.

CT Findings	Number of Patients
Renal Cysts	107
Nephrolithiasis	55
Ureterolithiasis	10
Hepatic Cysts	9
Uterine Fibroids	8
Adrenal Mass Consistent with Adenoma	7
Cholelithiasis	6
Hepatic Hemangioma	5
Bladder Calculi	3
Ovarian Cysts	3
Diverticulitis	2
Diverticulosis	1
Paget's Disease	1
Hiatal Hernia	1

Table 5. CT findings of alternate diagnoses in the entire study population
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DISCUSSION

As shown in our results, cystoscopy is the single most accurate modality for the evaluation of hematuria at our institution. However, the visualization of lesions with cystoscopy in patients with significant hematuria or with flat neoplasia is difficult and cannot be used to evaluate the upper urinary tracts. Due to these limitations, urinary tests play an integral role in the hematuria work-up. Urinary markers, including NMP-22, bladder tumor antigen (BTA), and telomerase, have all been shown to have a higher sensitivity and a lower specificity than cytology for the detection of UC in a meta-analysis of 42 studies [13]. Previous researchers have shown that both cytology and NMP-22 are sensitive for detecting high-grade UC [14-16]. Additionally, it has been shown that upper tract UC is often a higher stage and higher grade disease than bladder UC [17]. Cases of upper tract UC, therefore, may be detected earlier in their course with the use of a combination of urinary marker(s) and cytology.

In our patient population, all cases of UC were diagnosed using a combination of cystoscopy and NMP-22, with NMP-22 being the only modality that indicated the presence of the 1 upper tract UC (Grade 2, Stage Ta). It should be noted that this case demonstrated atypia on urine cytology, and in combination with the NMP-22 findings, triggered further workup of the upper tracts in this patient. Currently, bladder markers are not commonly used by urologists because of the increased cost without significant improvement in specificity when compared to cytology. However, its utility is clear in cases such as the upper tract tumor. These markers can give the practitioner further evidence to support of the use of more extensive diagnostic modalities in patients with otherwise normal workups.

A number of institutions have chosen the CT scan as the upper tract imaging modality of choice because it is the choice of radiological clinical practices and because of its potential for diagnosing other conditions, including urolithiasis, renal and perirenal infection, and associated complications. Additionally, recent evidence indicates the superiority of CT urography to excretory urography in the initial evaluation of hematuria for all possible causes including UC [18]. With respect to upper tract UC, Albani *et al.* [18] reported that among 259 patients evaluated with CT urogram, 6 cases of renal pelvic masses were accurately diagnosed, superior to the results seen with intravenous pyelography (IVP), whereas the sole renal pelvic mass went undetected. While indicating its efficacy, this implies a 2.3% incidence of upper tract UC among all patients evaluated for hematuria. This is well above studied estimates and indicates that 0.5% of all urothelial tumors are found in the upper tract [19]. This is likely due to the high-risk population of patients seen at the Cleveland Clinic and may account for the difference in results when compared with our study. The authors conclude that CT urogram may be best used in patients at high risk for disease, as the expected sensitivity and specificity of imaging would be expected to be quite low

Diagnostic Test	CPT Code	2006 Medicare Reimbursement
Urine Cytology	88104	$14.84
NMP-22	86316	$29.07
Cystoscopy	52000	$412.93
CT Scan	74170 & 72194	$607.64
Renal Ultrasound	76775	$94.52

Table 6. Reimbursement schedule for tests used in hematuria evaluation
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with its low yield in patients without any UC risk factors.

CT urogram proved useful in the detection of urolithiasis and other conditions as seen in Table 5. Interestingly, no cases of renal masses were diagnosed with the use of CT scan among the 373 patients analyzed in this study. Patients with renal masses were likely excluded from our study based on our inclusion parameters requiring the use of all 4 diagnostic modalities. Out of the larger pool of 744 patients, 2 were found to have renal masses. Our results indicate that CT scan may be an expensive part of the hematuria evaluation for patients and could be used more selectively in a higher risk population for UC.

The significant costs associated with the evaluation of hematuria have been previously described but generally included older imaging modalities [2]. The cost of a full evaluation including all 4 tests in these patients is $1064.48 (fig. 1). Applying current reimbursement rates to our sample indicates that these 4 tests led to direct medical costs of $397,051 ($1064.48 x 373 patients), of which $226,650 was accounted for by the CT scan, which did not yield unique information in the diagnosis of UC.

In our patient population, the utilization of ultrasonography, namely renal ultrasound (direct medical costs = $94.52), may prove to be more cost-effective than CT scan when used in conjunction with cystoscopy and urinary markers in the evaluation of the upper and lower urinary tracts in selected patients presenting with hematuria. This has also been shown in the Rodgers study [8], with a dramatically improved cost effectiveness using renal ultrasound over CT scan in patients at low risk for significant urological diseases. The analysis has also shown that the use of ultrasound followed by CT scan is less expensive than the use of CT scan alone in diagnosing significant disease in high risk patients (patients with a likelihood of disease ≥ 30%). It should be noted, however, that no research has been performed regarding outcomes due to a delay in imaging using CT scan. Using renal ultrasound in place of CT scan would bring the direct medical costs of a hematuria evaluation down to $551.36, 48% less expensive than the current standard.

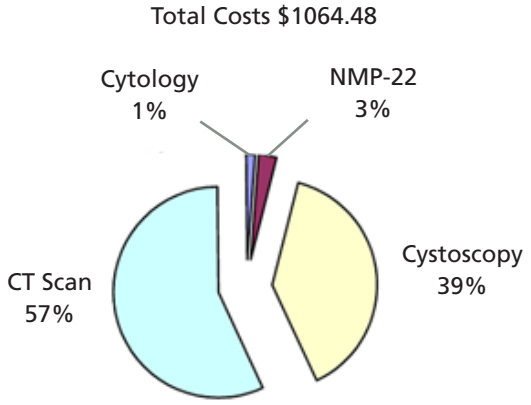

Figure 1. Contribution of current standard diagnostic modalities to direct medical costs of hematuria evaluation

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Given these findings, we believe that patients at low-risk for UC based on presentation (microscopic hematuria with an absence of risk factors for UC) should be evaluated with the use of cystoscopy, urinary markers, cytology and renal sonography as opposed to CT urogram. However, given the current data regarding sensitivity and specificity of NMP-22, we do not believe that the use of urinary markers with sonography can replace the use of CT urogram in high risk patients. Further improvements in urinary markers with regard to sensitivity and specificity, as well as decreases in costs of these tests, are necessary before implementing their routine use and substituting the use of expensive yet powerful radiographic imaging such as CT. Randomized, prospective studies must be performed to investigate other modalities in the hematuria workup in order to drive down the costs of this common yet potentially serious indicator of significant disease.

There are clear limitations inherent to this study, including its retrospective design, small sample size, and its representation of a single institution's experience. It is difficult to draw firm conclusions based on a small subset of patients. However, it is important to note the questions raised regarding the cost effectiveness of commonly used modalities in the evaluation of hematuria. These questions could lead to further prospective studies to investigate the efficacy and cost-effectiveness of the hematuria diagnostic algorithm in the anticipation of the rising costs of clinical diagnostics in hematuria of the aging population.

CONCLUSIONS

We show that the workup of hematuria in terms of financial cost is not insignificant. In our patient population, cystoscopy was the most sensitive and specific modality. CT urogram contributed to the diagnosis of many urologic disease states but most were of benign origin. It did, however, add the most to the cost of the diagnostic workup without contributing significantly to the identification of UC in our patients, since only one patient had upper tract TCC. NMP-22 was the only modality that diagnosed the upper tract tumor, but had lower specificity than any of the other 3 tests.

REFERENCES

[1] American Cancer Society. Cancer Facts and Figures 2006. Atlanta: American Cancer Society; 2006.

[2] Mariani AJ, Mariani MC, Macchioni C, Stams KU, Hariharan A, Moriera A. The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. J Urol. 1989 Feb;141(2):350-5.

[3] Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000 Feb;163(2):524-7.

[4] Messing EM, Young TB, Hunt VB, Roecker EB, Vaillancourt AM, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Home screening for hematuria: Results of a multi-clinic study. J Urol. 1992 Aug;148(2 Pt 1):289-92.

[5] Cohen RA, Brown RS. Clinical practice. Microscopic hematuria. N Engl J Med. 2003 Jun 5;348(23):2330-8.

[6] Buntinx F, Wauters H. The diagnostic value of macroscopic haematuria in diagnosing urological cancers: A meta-analysis. Fam Pract. 1997 Feb;14(1):63-8.

[7] Grossfeld GD, Litwin MS, Wolf JS, Hricak J, Shuler CL, Agerter DC, Carroll PR. Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association Best Practice Policy – Part II: Patient Evaluation, Cytology, Voided Markers, Imaging, Cystoscopy, Nephrology Evaluation, and Follow-Up. Urology. 2001 Apr;57(4):604-10.

[8] Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, Duffy S, Ritchie G, Kleijnen J, Westwood M. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. Health Technol Assess. 2006 Jun;10(18):iii-iv, xi-259.

[9] Messing EM, Young TB, Hunt VB, Wehbie JM, Rust P. Urinary tract cancers found by homescreening with hematuria dipsticks in healthy men over 50 years of age. Cancer. 1989 Dec 1;64(11):2361-7.

[10] Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, Shen Y. Detection of bladder cancer using a point-of-care proteomic assay. JAMA. 2005 Feb 16;293(7):810-6.

[11] Grossfeld GD, Litwin MS, Wolf JS, Hricak J, Shuler CL, Agerter DC, Carroll PR. Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association Best Practice Policy – Part I: Definition, Detection, Prevalence, and Etiology. Urology. 2001 Apr;57(4):599-603.

[12] Zippe C, Pandrangi L, Agarwal A. NMP22 is a sensitive, cost-effective test in patients at risk for bladder cancer. J Urol. 1999 Jan;161(1):62-5.

[13] Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PM, Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol. 2003 Jun;169(6):1975-82.

[14] Ponsky LE, Sharma S, Pandrangi L, Kedia S, Nelson D, Agarwal A, Zippe CD. Screening and monitoring for bladder cancer: Refining the use of NMP-22. J Urol. 2001 Jul;166(1):75-8.

[15] Hofland CA, Mariani, AJ. Is cytology required for a hematuria evaluation? J Urol. 2004 Jan;171(1):324-6.

[16] Schroeder GL, Lorenzo-Gomez MF, Hautmann SH, Friedrich MG, Ekici S, Huland H, Lokeshwar V. A side by side comparison of cytology and biomarkers for bladder cancer detection. J Urol. 2004 Sep;172(3):1123-6.

[17] Stewart GD, Bariol SV, Grigor KM, Tolley DA, McNeill SA. A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract. BJU Int. 2005 Apr;95(6):791-3.

[18] Albani JM, Ciaschini MW, Streem SB, Herts BR, Angermeier KW. The role of computerized tomographic urography in the initial evaluation of hematuria. J Urol. 2007 Feb;177(2):644-8.

[19] Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: Incidence and survival over the last 2 decades. J Urol. 2000 Nov;164(5):1523-5.

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