Bladder tumour antigen (BTA stat) test compared to the urine cytology in the diagnosis of bladder cancer: A meta-analysis

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Abstract

Introduction: We evaluate the diagnostic value of bladder tumour antigen (BTA stat) tests compared with urine cytology test in detecting bladder cancer.

Methods: We searched public databases including PubMed, MEDLINE Springer, Elsevier Science Direct, Cochrane Library and Google Scholar before December 2012. To collect relevant data of BTA stat tests and urine cytology tests in patients with bladder cancer, we studied meta-analyses of sensitivity, specificity, positive likelihood ratio (LR), negative LR and diagnostic odds ratios (DOR) of BTA stat tests and cytology tests from published studies. We applied the software of Rev. Man 5.1 and Stata 11.0 to the meta-analysis.

Results: A total of 13 separate studies consisting of 3462 patients with bladder cancer were considered in the meta-analysis. We found that the BTA stat test had a higher sensitivity than the urine cytology test (0.67, 95% confidence interval [CI] 0.64 to 0.69 vs. 0.43, 95% CI 0.40 to 0.46), but the specificity, positive LR, negative LR, DOR, the area under the curve (AUC) and Q index of the BTA stat test were lower compared with the urine cytology test. The results of the Egger's linear regression test showed no publication bias ($p > 0.05$).

Conclusions: Specificity, positive LR, negative LR, DOR, the AUC and the Q index of the urine cytology test may be superior to the BTA stat test, but the BTA stat test has greater sensitivity than the urine cytology test.

Introduction

Bladder cancer is one of the most common urologic malignancies.[1] More than 25% of bladder cancer cases are still muscle-invasive at first diagnosis.[2] Early diagnosis of bladder cancer remains a challenge,[3] because it has low sensitivity and specificity. In recent years, the use of diagnostic categories for extragenital cytology has increasingly been discussed as an approach to improve the quality of reports.[4] However, in corresponding reported urine cytology, the accuracy and sensitivity are highly variable.[5] The bladder tumour antigen (BTA stat) test is a rapid, non-invasive, qualitative urine test that detects bladder tumour associated antigen (human complement factor H related protein) in urine.[6,7] It is an immunochromatographic reaction to detect the bladder tumour antigen in patients with bladder cancer.[8] The limitation of current urinary tumour markers is their low specificity and positive predictive value, which clinically manifests as a high false-positive rate.[9] Despite significant advances in our understanding of the molecular pathology of bladder cancer, it remains a significant health problem. Muscle-invasive bladder cancer is still associated with high morbidity and mortality.[10]

It is debatable whether the diagnostic value of the BTA stat test in detecting bladder cancer is superior to urine cytology.[11-17] To understand the nuances of the BTA test and the urine cytology test in diagnosis, we conducted a systematic review of published findings and used meta-analysis techniques to quantitatively combine results. We made a meta-analysis to assess the sensitivity, specificity, positive likelihood ratio (LR), negative LR, diagnostic odds ratio (DOR) in patients tested by BTA stat or urine cytology.

Methods

Source of material

We retrieved several public databases, mainly PubMed, MEDLINE Springer, Elsevier Science Direct, Cochrane Library and Google Scholar before December 2012. These databases cover all the available English literature. "Bladder

tumor antigen test," "BTA stat," "urine cytology," "cytology," "diagnosis," "bladder cancer," "study" and "trial" were the key words. Moreover, references from retrieved papers were checked for additional studies. We only collected data from published papers, excluding meeting or conference abstracts.

Search methods

Four independent investigators retrieved the electronic databases. An independent PubMed, MEDLINE and Springer retrieve was done by A and B with the same method. An independent Elsevier Science Direct, Cochrane Library and Google Scholar retrieve was done by C and D with the same method. If an investigator's assessment was not consistent with the others, then a discussion ensued regarding the final decision to include the data.

The included papers contained investigations of the patients with bladder cancer (i.e., prospective studies, retrospective studies or cross-sectional studies) and the diagnosis of bladder cancer using the BTA stat test and cytology test. The effect size as odds ratio (OR), sample size, gender or range of age were not limited. We excluded reviews, duplicated studies or reports which only described the BTA stat test data or cytology test data.

Our evaluation included study methods, sample size and recruitment. We selected papers by reading the document title and abstract. We also read the full text of papers for secondary screening to determine whether they were going to be included in the analysis. Two investigators independently completed this task. If there were differences (i.e., extracted data or information was inconsistent with another investigator), we reached an agreement through a discussion.

Extracted data included study details (e.g., the first author's name, research year of study, year of study publication, location of participants, design of studies, follow-up time) and patient characteristics (e.g., age, gender of patients with the BTA test and the cytology test, sample size). Two investigators (A and D) extracted the data independently using the standard protocol, and a third investigator reviewed the results. We contacted authors of incorporated studies to obtain further information for data items that needed clarification. Discrepancies were resolved by discussing with our research team or by contacting the original investigators.

The meta-analysis combined the ORs in the patients with bladder cancer. The point estimates of the ORs and its 95% confidence interval (95% CI) were pooled estimated for each study. We assessed the within- and between-study variation or heterogeneity by testing Cochran's Q-statistic.[18] We also quantified the effect of heterogeneity using $I^2 = 100\% \times (Q-df)/Q$ formula.[19] A significant Q-statistic ($p < 0.10$) or I^2-statistic ($I^2 > 50$) indicated heterogeneity across studies, and then the random effect model was used for meta-analysis and to account for the possibility of heterogeneity between studies; otherwise, the fixed effect model was used.[20] The overall or pooled estimate of ORs was obtained using the Mantel–Haenszel method in the fixed effect model[21] and the DerSimonian and Laid method in the random effect model.[22]

The summary receiver operating characteristic (SROC) curve was used to represent the performance of a diagnostic test,[23] based on data from a meta-analysis. The SROC curve included multiple points, and the cut-off points were determined by the maximal value points, which are the value summations of the sensitivity and specificity.[24] The area under the curve (AUC) and an index Q were discussed as potentially useful summaries of the curve. An upper bound was derived for the AUC based on an exact analytic expression for the homogeneous situation, and a lower bound based on the limit case Q, defined by the point where sensitivity equals specific ity: Q is invariant to heterogeneity.[23]

Analyses were performed using the Meta-DiSc software v.1.4 and the STATA software package v.11.0 (Stata Corporation, College Station, TX). All p values were two-sided. P values less than 0.05 were considered statistically significant.

Results

Characteristics of eligible studies

In total, we had 747 potentially relevant papers (PubMed: 169; MEDLINE: 98; Springer: 154; Elsevier Science Direct: 86; Cochrane Library: 5; Google Scholar: 235) (Fig. 1). After duplicates were removed, we had a total of 204 potentially relevant studies. During the abstract screening, 149 articles were excluded (33 were review articles, 65 did not include urine cytology tests; 51 did not report on bladder cancer). This left us with 55 studies for full publication review. Of these, 42 of these were excluded (23 because they only included urine cytology data and no comparison and 19 because there were no data available).

In the end, we had 13 studies to analyze (Table 1).[7,9,11-17,25-28] These studies were published between 1998 and 2006 and included a total of 3462 patients with bladder cancer. Their sample size ranged from 71 to 739, and mean age from 60 to 70 years.

We summarized the overall meta-analysis of bladder cancer patients with the BTA stat test (Table 2). Of the 13 studies, 3175 patients with bladder cancer were considered in the meta-analysis. We used the random effect model ($Q^2 = 56.23$, $I^2 = 96.4\%$, $p < 0.01$) to combine the data of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) numbers. The overall meta-analysis showed that sensitivity, specificity, positive LR, negative LR and DOR of BTA stat test were 0.67 (95% CI=0.64 to 0.69),

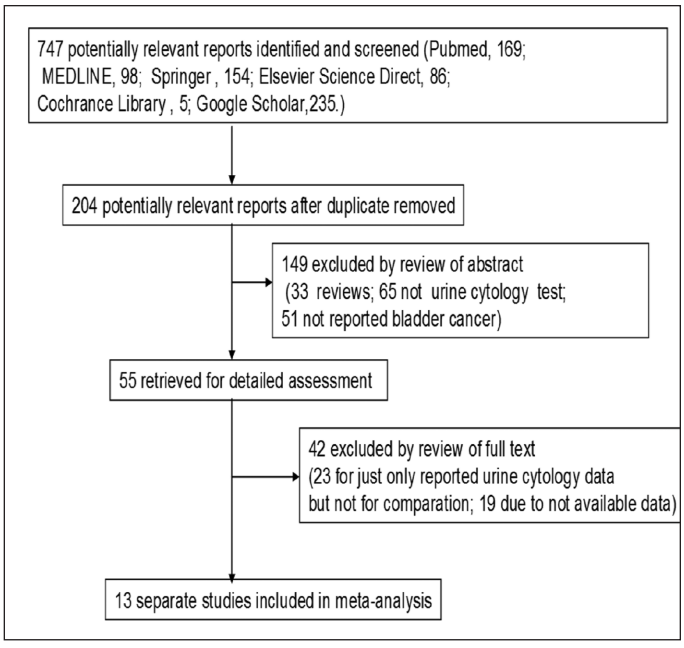

Fig. 1. Flow diagram for selection of studies for the meta-analysis.

0.75 (95% CI=0.73 to 0.77), 2.58 (95% CI=2.07 to 3.20), 0.47 (95% CI=0.39 to 0.55), 5.88 (95% CI=4.06 to 8.63), respectively. The AUC and Q index were 0.75 and 0.69, respectively (Fig. 2, Fig. 3).

We also collected the pooled meta-analysis of bladder cancer patients with the cytology test (Table 2). In the 13 studies, 3122 patients with bladder cancer were considered in this meta-analysis. We used the random effect model ($Q^2 = 68.47$, $I^2 = 97.1\%$, $p < 0.01$) to merge the data of the TP, FP, FN and TN numbers. The overall meta-analysis showed that sensitivity, specificity, positive LR, negative LR and DOR of cytology test were 0.43 (95% CI=0.40 to 0.46), 0.97 (95% CI=0.96 to 0.98), 10.56 (95% CI=6.21 to 17.96), 0.62 (95% CI=0.54 to 0.72), 18.24 (95% CI=10.54 to 31.57), respectively. The AUC and Q index were 0.77 and 0.71, respectively (Fig. 3).

The Egger's test assessed publication bias. For all samples, the Egger's test provided no evidence of publication bias for this meta-analysis (Table 2).

Discussion

Many studies[7,9,13,15,16,25-27] have reported on the diagnostic value of the BTA stat and cytology test in detecting bladder cancer. These studies, however, have demonstrated mixed results due to small sample sizes or low statistical power. In our meta-analysis, we combined 13 separate studies, consisting of 3462 patients to compare the diagnostic value of the BTA stat test with the urine cytology test in detecting bladder cancer. We found that the BTA stat test had higher sensitivity than the urine cytology test, but specificity, positive LR, negative LR, DOR, the AUC and Q index of the BTA stat test were lower compared with the urine cytology test.

The BTA stat test is a "point-of-care" rapid immunochromatographic assay for detecting the bladder tumour antigen (BTA) in the urine.[17] The BTA stat test is one of non-invasive tumour markers in the urine and has become a useful marker in bladder cancer detection.[16] The antigen detected is a human complement factor-H related protein.[17] Similar to the results in other studies,[6,11,13,29] the overall sensitivity of the BTA stat test was superior to urine cytology; the latter, however, had better specificity. Therefore, the study suggested that the BTA stat test would not replace the urine cytology test in detecting bladder cancer. Vriesema and col-

Table 1. Characteristics of studies included in the meta-analysis (n=13)

Study (publication year)	Country	Ethnicity	Sample size	Male (%)	Age, year	BTA stat test				Cytology test			
						TP	FP	FN	TN	TP	FP	FN	TN
Wiener HG, et al.[12] (1998)	Austria	European	291	199 (68)	65	52	64	39	136	54	0	37	200
Leyh H, et al.[11] (1999)	Austria, France, Germany, Italy	European	240	172 (72)	64	70	45	37	79	35	1	72	123
Pode D, et al.[13] (1999)	Israel	Asian	250	207 (83)	NA	106	38	22	84	51	5	77	107
Ramakumar S, et al.[25] (1999)	United States	American	196	152 (78)	66	42	38	15	101	24	3	30	55
Sharma S, et al.[9] (1999)	United States	American	278	NA	NA	23	43	11	201	10	1	24	243
Giannopoulos A, et al.[26] (2000)	Greece	European	168	145 (86)	66	71	30	28	39	38	4	61	65
Poulakis V, et al.[15] (2001)	United States	American	739	485 (66)	67	200	74	85	149	157	13	96	306
Raitanen MP, et al.[7] (2001)	Finland	European	445	NA	NA	63	47	55	280	21	6	97	321
van Rhijn BW, et al.[27] (2001)	Netherlands	European	109	84 (77)	67	13	9	10	35	5	2	18	42
Fukui Y, et al.[14] (2001)	Japan	Asian	71	NA	NA	18	1	13	39	5	0	26	40
Saad A, et al. (2002)	United Kingdom	European	120	100 (83)	70	25	9	27	59	33	12	19	56
Boman H, et al.[28] (2002)	Sweden	European	304	NA	NA	89	54	65	91	60	12	73	131
Sun Y, et al.[16] (2006)	China	Asian	251	177 (71)	60	116	13	35	87	55	0	96	100

BTA: bladder tumour antigen; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

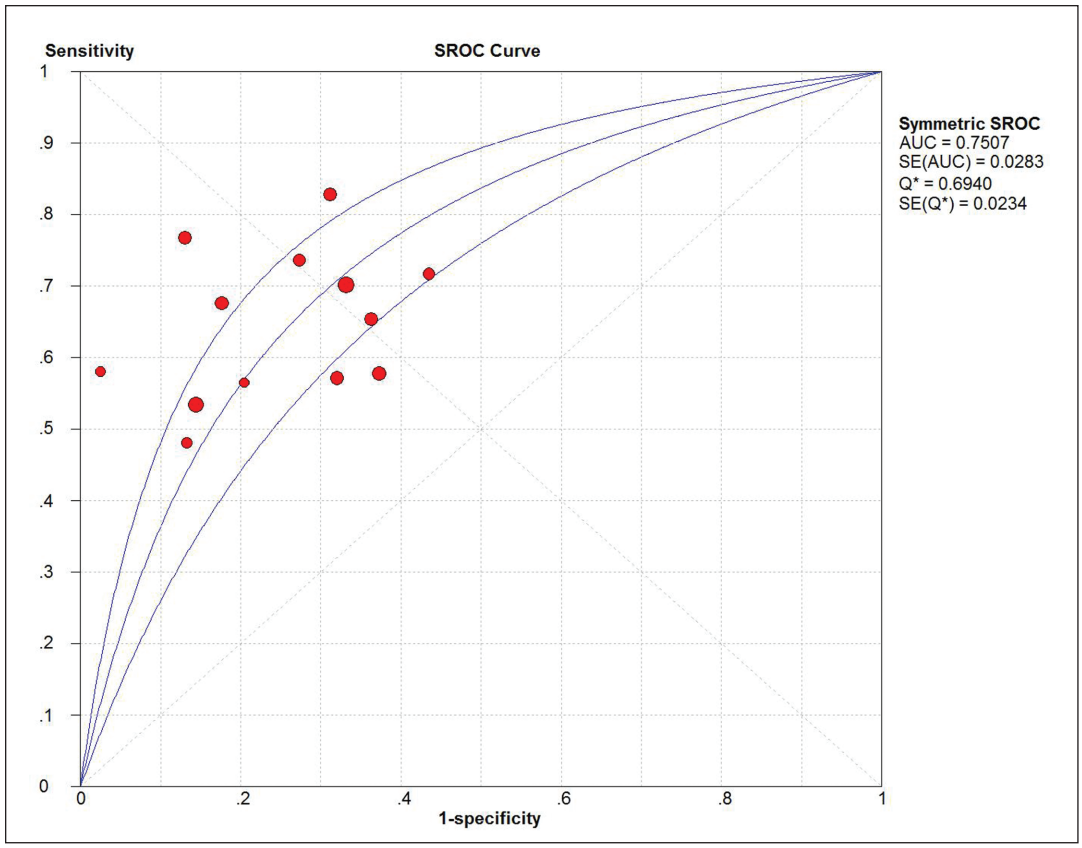

Fig. 2. The summary receiver operating characteristic (SROC) curve of the bladder tumour antigen stat test.

leagues identified that 89% of their patients would prefer cystoscopy as the diagnostic method if a bladder tumour maker's sensitivity was less than 90%.[30]

Diagnostic categories reflect the adequacy of the materials for interpretation and the presence or absence of cancer cells.[4] The potential value of urine cytology has been reduced by the relative inexperience of most pathologists in examining urinary specimens, and by the lack of cellular criteria specifically reflecting the morphology of low-grade papillary and flat lesions of the bladder epithelium.[31] Yet, urine cytology is increasingly accepted as a diagnostic tool to detection and follow patients with bladder cancer.[31] However, its low

Table 2. The indexes of bladder cancer diagnose with by BTA stat test and urine cytology test

Diagnostic methods	Parameter	Test of association		Test of heterogeneity			Model	Egger's test for publication bias	
		Estimates	95% CI	Q	*p* value	I2 (%)		t	*p* value
BTA stat test	Overall	—	—	56.23	<0.01	96.4	Random	1.16	0.27
	Sensitivity	0.67	0.64 to 0.69	55.80	<0.01	78.5	—	—	—
	Specificity	0.75	0.73 to 0.77	105.39	<0.01	88.6	—	—	—
	Positive LR	2.58	2.07 to 3.20	62.08	<0.01	80.7	Random	—	—
	Negative LR	0.47	0.39 to 0.55	46.73	<0.01	74.3	Random	—	—
	DOR	5.88	4.06 to 8.63	53.82	<0.01	77.7	Random	—	—
Cytology test	Overall	—	—	68.47	<0.01	97.1	Random	-0.63	0.54
	Sensitivity	0.43	0.40 to 0.46	116.29	<0.01	89.7	—	—	—
	Specificity	0.97	0.96 to 0.98	72.26	<0.01	83.4	—	—	—
	Positive LR	10.56	6.21 to 17.96	37.69	<0.01	68.2	Random	—	—
	Negative LR	0.62	0.54 to 0.72	131.77	<0.01	90.9	Random	—	—
	DOR	18.24	10.54 to 31.57	30.72	<0.01	60.9	Random	—	—

BTA: Bladder tumour antigen; CI: confidence interval; LR: likelihood ratio; DOR: diagnostic odds ratio.

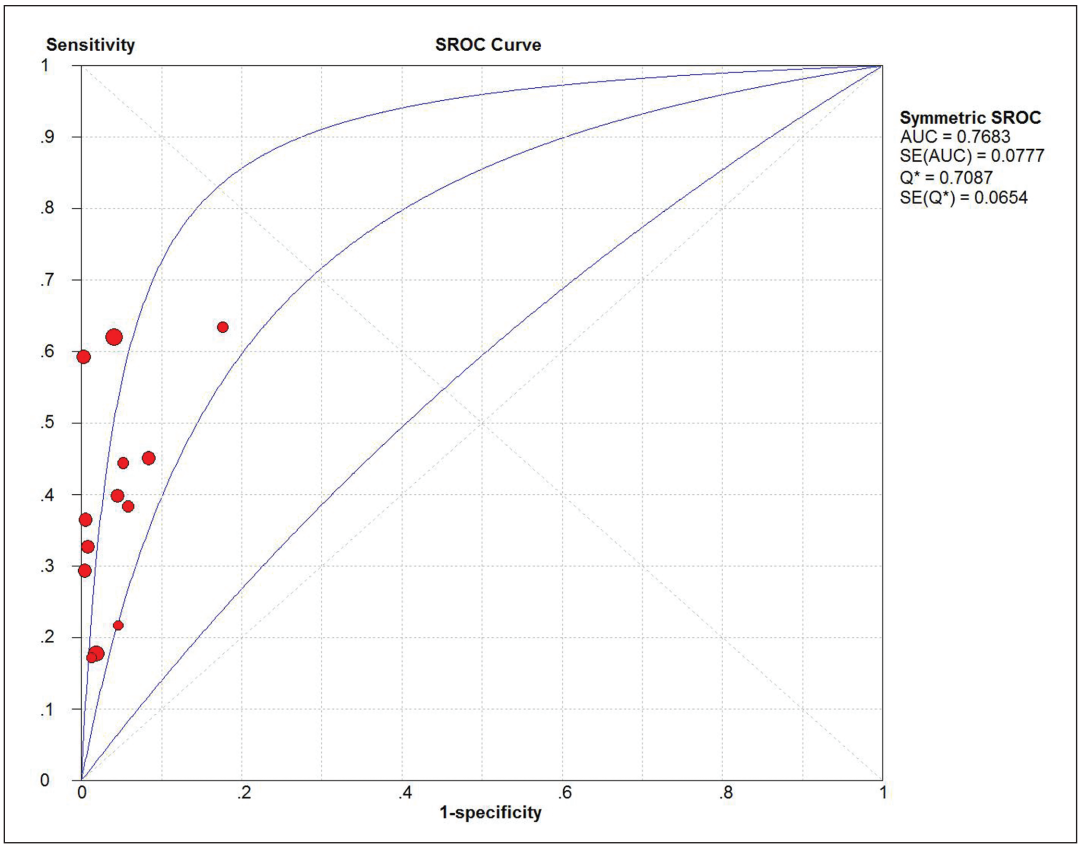

Fig. 3. The summary receiver operating characteristic (SROC) curve of cytology.

sensitivity may limit its use. Interestingly, its sensitivity is highly associated with tumour stage. Millan-Rodriquez and colleagues demonstrated that low-stage tumours had only a 37% recurrence and 0% progression rate, while high-stage tumors had a relative 54% recurrence and 15% progression rates.[32] Hence, for high-stage tumours that are more likely to progress, the sensitivities of common tumour markers are high. The use of diagnostic tools to detect bladder cancer should be based on tumour stage and grade.

Our study has limitations. Only published studies were included; thus, there may be publication bias. In addition, significant between-study heterogeneities were detected in the current meta-analysis, and may have distorted the meta-analysis. The degree of heterogeneity is one of the major concerns in a meta-analysis,[33] as non-homogeneous data are liable to result in misleading results. Different populations may contribute to the heterogeneity among the selected studies. Moreover, the population from each country was not uniform. Hence, the results of this meta-analysis should be interpreted with caution. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search of published studies and by using explicit methods for study selection, data extraction and data analysis.

Conclusion

Sensitivity and specificity of the urine cytology and BTA stat tests are the 2 of the most critical factors in the diagnosis of bladder cancer. In this meta-analysis, we evaluated the pooled data of sensitivity, specificity, positive LR, negative LR, DOR, AUC and Q index from 8 clinical trials. We found that urine cytology test was the most specific and the BTA stat test was the most sensitive in detecting bladder cancer. Due to the limited sample in our meta-analysis, prospective studies with larger samples are warranted.

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Competing interests: Dr. Guo, Dr. Wang, Dr. Gao, Dr. Shi, Dr. Sun and Dr. Wan all declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Sartini D, Muzzonigro G, Milanese G, et al. Upregulation of tissue and urinary nicotinamide N-methyltransferase in bladder cancer: Potential for the development of a urine-based diagnostic test. *Cell Biochem Biophys* 2013;65:473-83. http://dx.doi.org/10.1007/s12013-012-9451-1
2. Zlotta AR, Roumeguere T, Kuk C, et al. Select screening in a specific high-risk population of patients suggests a stage migration toward detection of non-muscle-invasive bladder cancer. *Eur Urol* 2011;59:1026-31. http://dx.doi.org/10.1016/j.eururo.2011.03.027
3. Srivastava AK, Singh PK, Srivastava K, et al. Diagnostic role of survivin in urinary bladder cancer. *Asian Pac J Cancer Prev* 2013;14:81-5. http://dx.doi.org/10.7314/APJCP.2013.14.1.81
4. Takashi M, Schenck U, Kissel K, et al. Use of diagnostic categories in urinary cytology in comparison with the bladder tumour antigen (BTA) test in bladder cancer patients. *Int Urol Nephrol* 1999;31:189-96. http://dx.doi.org/10.1023/A:1007124724817
5. Turco P, Houssami N, Bulgaresi P, et al. Is conventional urinary cytology still reliable for diagnosis of primary bladder carcinoma? Accuracy based on data linkage of a consecutive clinical series and cancer registry. *Acta cytologica* 2011;55:193-6. http://dx.doi.org/10.1159/000320861
6. Raitanen M-P, Marttila T, Kaasinen E, et al. Sensitivity of human complement factor H related protein (BTA stat) test and voided urine cytology in the diagnosis of bladder cancer. *J Urol* 2000;163:1689-92. http://dx.doi.org/10.1016/S0022-5347(05)67521-0
7. Raitanen M-P, Marttila T, Nurmi M, et al. Human complement factor H related protein test for monitoring bladder cancer. *J Urol* 2001;165:374-7. http://dx.doi.org/10.1097/00005392-200102000-00005
8. Gutiérrez Baños JL, Martín García B, Hernández Rodríguez R, et al. Usefulness of BTA Stat test (Bard) in the diagnosis of bladder cancer. Preliminary results and comparison with cytology and cystoscopy [in Spanish]. *Arch Esp Urol* 1998;51:778-82.
9. Sharma S, Zippe CD, Pandrangi L, et al. Exclusion criteria enhance the specificity and positive predictive value of NMP22* and BTA stat [dagger]. *J Urol* 1999;162:53-7. http://dx.doi.org/10.1097/00005392-199907000-00014
10. Morgan R, Bryan RT, Javed S, et al. Expression of Engrailed-2 (EN2) protein in bladder cancer and its potential utility as a urinary diagnostic biomarker. *Eur J Cancer* 2013;49:2214-22. http://dx.doi.org/10.1016/j.ejca.2013.01.019
11. Leyh H, Marberger M, Conort P, et al. Comparison of the BTA statTM test with voided urine cytology and bladder wash cytology in the diagnosis and monitoring of bladder cancer. *Eur Urol* 1999;35:52-6. http://dx.doi.org/10.1159/000019819
12. Wiener H, Mian C, Haitel A, et al. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? *J Urol* 1998;159:1876-80. http://dx.doi.org/10.1016/S0022-5347(01)63184-7
13. Pode D, Shapiro A, Wald M, et al. Noninvasive detection of bladder cancer with the BTA stat test. *J Urol* 1999;161:443-6. http://dx.doi.org/10.1016/S0022-5347(01)61918-9
14. Fukui Y, Samma S, Fujimoto K, et al. Screening methods in the detection of bladder cancer: Comparison of nuclear matrix protein-22, bladder tumor antigen and cytological examinations [in Japanese]. *Hinyokika Kiyo* 2001;47:311-4.
15. Poulakis V, Witzsch U, De Vries R, et al. A comparison of urinary nuclear matrix protein-22 and bladder tumour antigen tests with voided urinary cytology in detecting and following bladder cancer: The prognostic value of false-positive results. *BJU Int* 2001;88:692-701. http://dx.doi.org/10.1046/j.1464-410X.2001.02355.x
16. Sun Y, He D-l, Ma Q, et al. Comparison of seven screening methods in the diagnosis of bladder cancer. *Chin Med J* 2006;119:1763-71.
17. Saad A, Hanbury D, McNicholas T, et al. A study comparing various noninvasive methods of detecting bladder cancer in urine. *BJU Int* 2002;89:369-73. http://dx.doi.org/10.1046/j.1464-4096.2001.01699.x
18. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2001285-312.
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557. http://dx.doi.org/10.1136/bmj.327.7414.557
20. Fan Y, Li LH, Pan HF, et al. Association of ITGAM polymorphism with systemic lupus erythematosus: A meta-analysis. *J Eur Acad Dermatol Venereol* 2011;25:271-5. http://dx.doi.org/10.1111/j.1468-3083.2010.03776.x
21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *The Challenge of Epidemiology: Issues and Selected Readings* 2004;1:533-53.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7:177-88. http://dx.doi.org/10.1016/0197-2456(86)90046-2
23. Walter S. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. *Stat Med* 2002;21:1237-56. http://dx.doi.org/10.1002/sim.1099
24. Altman DG, Bland JM. Diagnostic tests 3: Receiver operating characteristic plots. *BMJ* 1994;309:188. http://dx.doi.org/10.1136/bmj.309.6948.188
25. Ramakumar S, Bhuiyan J, Besse JA, et al. Comparison of screening methods in the detection of bladder cancer. *J Urol* 1999;161:388-94. http://dx.doi.org/10.1016/S0022-5347(01)61899-8
26. Giannopoulos A, Manousakas T, Mitropoulos D, et al. Comparative evaluation of the BTAstat test, NMP22, and voided urine cytology in the detection of primary and recurrent bladder tumors. *Urology* 2000;55:871-5. http://dx.doi.org/10.1016/S0090-4295(00)00489-1
27. van Rhijn BW, Lurkin I, Kirkels WJ, et al. Microsatellite analysis DNA test in urine competes with cystoscopy in follow-up of superficial bladder carcinoma. *Cancer* 2001;92:768-75. http://dx.doi.org/10.1002/1097-0142(20010815)92:4<768::AID-CNCR1381>3.0.CO;2-C
28. Boman H, Hedelin H, Holmang S. Four bladder tumor markers have a disappointingly low sensitivity for small size and low grade recurrence. J Urol 2002;167:80-3. http://dx.doi.org/10.1016/S0022-5347(05)65387-6
29. Sarosdy MF, Hudson MLA, Ellis WJ, et al. Improved detection of recurrent bladder cancer using the bard BTA stat test. *Urology* 1997;50:349-53. http://dx.doi.org/10.1016/S0090-4295(97)00292-6
30. Vriesema J, Poucki M, Kiemeney L, et al. Patient opinion of urinary tests versus flexible urethrocystoscopy in follow-up examination for superficial bladder cancer: A utility analysis. *Urology* 2000;56:793-7. http://dx.doi.org/10.1016/S0090-4295(00)00777-9
31. Murphy WM, Soloway MS, Jukkola AF, et al. Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. *Cancer* 1984;53:1555-65. http://dx.doi.org/10.1002/1097-0142(19840401)53:7<1555::AID-CNCR2820530723>3.0.CO;2-G
32. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, et al. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol* 2000;164:680-4. http://dx.doi.org/10.1016/S0022-5347(05)67280-1
33. Moreno SG, Sutton AJ, Thompson JR, et al. A generalized weighting regression-derived meta-analysis estimator robust to small-study effects and heterogeneity. *Stat Med* 2012;31:1407-17. http://dx.doi.org/10.1002/sim.4488

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