A Comparison of BTA stat and NMP 22 as Non-Invasive Screening Methods for Bladder Cancer. A Systematic Review.

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Abstract

Background

The purpose of this study was to systematically review the effects of bladder tumor antigen (BTA) stat and nuclear matrix protein (NMP) 22 as a screening method in an asymptomatic population.

Methods

We evaluated 381 international studies by selecting randomized controlled trials (RCTs). We descriptively evaluated and summarized all of the 381 studies to identify their strengths and weaknesses in terms of the use of BTA stat and NMP 22.

Results

We did not identify any RCTs that used BTA stat or NMP 22 as a pure screening tools. We also did not identify any studies that used an asymptomatic population. Different cut-off values and individualized methods were discussed for NMP 22 based on age, sex, risk factors, and history of bladder cancer, introducing significant heterogeneity and bias. Interestingly, the use of NMP 22 demonstrated only in men younger than 65 years positive results.

Conclusions

RCTs are needed to show a reliable sensitivity and specificity of using BTA stat or NMP 22 as a screening test. It may be worth investigating in future studies whether it would be useful to offer NMP 22 to only a certain profile of patients. Based on our findings and in consent with national and international guidelines, a screening recommendation using NMP 22 and/or BTA stat can not be given for bladder cancer in an asymptomatic population.

Backround

Bladder cancer (BC), including non-invasive carcinoma, is a disease of worldwide importance because of its high incidence. Symptoms that are typically associated with bladder cancer include microscopic and macroscopic hematuria, dysuria, and pollakisuria, which are also known symptoms found in inflammatory diseases and urinary tract infections (UTIs).

The most important risk factor for BC development is the consumption of tobacco; however, age, gender, and family risk and occupational exposure to aluminum, for example, are also general risk factors. Other known risk factors are radiation exposure to the lower pelvis, chemotherapy with cyclophosphamide, chronic bladder inflammation, bilharzia, and exposure to arsenic and chrome in drinking water [2].

In Germany, BC is the fourth most common cancer in men, and the fourteenth most common in women. Stage T4 is equally diagnosed at 7% in both genders. According to the Robert Koch Institute, men with stage T1 tend to have a higher five-year survival rate (47%) compared to women [1]. Currently, urinary cystoscopy is the gold standard for the detection of BC. The practice of using monoclonal antibodies against tumor-associated antigens might improve the diagnosis of BC in the future when sensitivity is increased, but at present, they are mostly used as follow-up in patients with a history of BC [3].

The present systematic review provides a descriptive overview of recent studies. It also analyzes the strengths and weaknesses of screening methods and associated results using two non-invasive screening methods for bladder cancer—bladder tumor antigen (BTA) stat and nuclear matrix protein 22 (NMP 22)—in an asymptomatic population and in patients with suspicion of or a history of BC. Our preference was to identify and review randomized controlled trials (RCTs) that focused on screening in patients with a history of BC, but no such studies were found.

Methods

Based on their widespread use, we concentrated our efforts on two tests—NMP 22 and BTA stat. Both of these tests are able to detect specific cell components of urothelial cancer.

Bladder tumor antigen stat

BTA works by using antibodies to identify concentrations of complement factor H-related proteins in urine that were raised as a result of BC. At the point of the present systematic review, there were two accessible BTA tests: the BTA stat, which is a qualitative point-of-care test, and the BTA Trak, which is a qualitative enzyme-linked immunosorbent assay. For the purposes of this study, we concentrated our efforts on BTA stat.

Nuclear matrix protein 22

Nuclear matrix protein (NMP) 22 is an unspecific test that is used for the identification of BC. The NMP 22 protein is found in concentrations 25-fold higher in malignant urothelial cells compared to healthy cells [19]. Therefore, patients with BC produce more NMP 22, which can be identified by apoptotic cells in urine. Cut-off levels vary in studies because of grades and stages of cancer and because of questions about mass screenings, but a general recommended cut-off by the manufacturer of the NMP 22 test is 10 U/ml [15, 20, 21].

Search strategy

We searched the following databases systematically for RCTs: PubMed MEDLINE using the Ovid platform (1948–2017), and EMBASE (1980–2017). The following keyword searches were used: “NMP AND 22 OR nuclear matrix protein 22” and “BTA AND stat OR human complement factor H”. The final search was performed on November 18, 2017.

Selection process

The original intention of this systematic review was to find RCTs in an asymptomatic population; however, no RCTs were found. A total of 381 studies were identified from the databases—306 BTA stat studies and 75 NMP 22 studies. For an in-depth review, we only selected original work studies from published papers, well-designed studies with at least 100 subjects, only studies published in English were selected, and only publications with ethical approval were incorporated. We excluded meeting or conference abstracts, studies with animal models, inaccurate description of the methodology and results.

Data extraction

All of the studies included in our review were analyzed by two independent reviewers who used data-collection sheets. The following information was collected: characteristics of the trial participants, type of intervention, type of outcome measures, and results.

Results

11 studies were selected for BTA stat and 11 studies for the test NMP 22 were chosen. Tables 1 and 2 give an overview of number of patients, BC history/ no BC history, sensitivity, specificity and country of performance.

Table 1
Studies performed with the BTA stat

Study & Publication year	n=	No BC history	Sensitivity	Specificity	PPV	NPV	Country
Toma *et al.* 2004[3]	126	78	66.6%	78.2%	71.4%	75.4%	Germany
Miyake *et al.* 2012 [4]	126	62	72%	53%	NA	NA	USA
Raitanen *et al.* 2008 [8]	490	0	56.6%	76.4%	NA	NA	Finland
Poulakis *et al.* 2001 [9]	739	353	70%	92%	13%	88%	USA
García-Velandria *et al.* 2014 [10]	237	31	63.2%	82.9%	NA	92.2%	Spain
Raitanen *et al.* 1999[13]	100	100	100%	98%	2%	98%	USA
Nasuti *et al.* 1998 [14]	100	100	100%	84%	16%	84%	USA
Wiener *et al.* 1998 [15]	291	190	57%	68%	45%	78%	Austria
Giannopoulos *et al.* 2000 [16]	147	101	71.7%	56.5%	70.3%	58.2%	Greece
Boman *et al.* 2002 [17]	289	66	75%	52%	62%	58%	Sweden
Sun *et al.* 2006 [18]	251	100	76.8%	87.0%	89.9%	71.3%	China

Table 2
Studies performed with the NMP 22

Study & Publication year	n=	No BC history	Sensitivity	Specificity	PPV	NPV	Country	Recommend U/mL
Toma *et al.* 2004[3]	126	78	68.5%	65.2%	53.6%	77.9%	Germany	
Poulakis *et al.* 2001 [9]	739	353	85%	94%	18%	91%	USA	8.25
Wiener *et al.* 1998 [15]	291	190	48%	69%	41%	74%	Austria	10
Giannopoulos *et al.* 2000 [16]	147	101	62.6%	73.9%	72.9%	61.4%	Greece	8
Boman *et al.*2002 [17]	299	66	65%	75%	NA	NA	Sweden	4
Sun *et al.*2006 [18]	251	100	77.5%	81.0%	86.0%	64.8%	China	10
Stampfer *et al.* 1996 [20]	231	0	31%	NA	NA	NA	USA	6.4
Mian *et al.* 2000 [21]	240	81	55.5%	79%	45%	86%	Austria	10
Todenhöfer *et al.* 2012 [22]	1386	1386	79.2%	34.5%	86.5%	76.1%	Germany	10
Lee *et al.* 2000 [23]	137	101	69%	72%	NA	97%	Taiwan	3.75–18.95
Bangma *et al.* 201 [30]	1747	1747	25%	96.6%	7.1%	99.2%	The Netherlands	10

NA: not answered

What are some problems associated with the use of BTA stat?

Most studies criticized the correlation between hematuria, the leading symptom of BC, and BTA stat. In a cohort of 126 patients, including 64 patients with BC, the BTA showed a sensitivity of 72% and a specificity of 53%. The association between hemoglobin and BTA was 0.73 [4]. Oge et al. demonstrated that in a healthy group of 25 volunteers, an increased number of false-positive rates were observed according to dilution. A specificity of 24% and a false-positive rate of 76% in a dilution of 1/200 was observed [5].

What can we summarize for BTA stat from a cohort with a history of or suspicion of BC?

The latest review by Budman et al. compared the largest studies and gave a clear disapproval for the use of BTA stat or NMP 22 in either the detection or surveillance of BC. Instead, they recommended keeping cytology and cystoscopy as the gold standard [6]. However, a meta-analysis of 3,462 patients published by Guo et al. found that the sensitivity and specificity of BTA stat in comparison to urine cytology in patients with BC history showed a higher sensitivity (0.67 [95% confidence interval (CI): 0.64–0.69] vs 0.43 [95% CI: 0.40–0.46], respectively) [7]. In

addition, a study by Raitanen et al. showed that the percentage of patients (n = 445) with an apparent false-positive BTA stat showed a recurrence of BC in cystoscopy [8]. The study with the highest number of patients suspected of BC (n = 739) was published by Poulakis et al., and a follow-up at 27 months showed 406 patients with BC. Looking closely at the results, the BTA stat resulted in a sensitivity of 90% for histological grade 3, but only a sensitivity of 68% for histological grade 2 and 38% for histological grade 1. The specificity of BTA stat was 67%. The specificity varied according to patients with and without an UTI. A specificity of 92% with no UTI was found versus a specificity of 52% with UTI diagnosis. False-positive results did not correlate with future recurrences at follow-up [9]. A study by García-Velandria et al. compared 237 patients (87% of which were surveillance cases) using cytology and BTA stat. Interestingly, cytology and BTA stat achieved almost the same results: a sensitivity of 57.9% and 63.2%, respectively and a specificity of 84.4% and 82.9%, respectively. Therefore, this study showed a higher sensitivity of 5,3 % in BTA stat than cytology. Also the negative predicted value (NPV) in the surveillance patients with low-grade tumors was equal: cytology had an NPV of 95.7% and BTA stat of 95.0%. Their recommendation was to use BTA stat instead of cystoscopy in surveillance cases with previous low-grade tumors for cost reasons [10].

The study by Raitanen et al. and the study by van der Poel et al., gave no recommendation for BTA stat use in place of cystoscopy for diagnostic purposes. However, those studies did suggest replacing cytology with BTA stat in low-grade diseases for patients with no UTI and BC history [11, 12].

The sensitivity of BTA stat ranged from 57–100%, and the specificity ranged from 52–98% (Table 1).

What are the results for a general screening in a healthy population?

A study by Raitanen et al. investigated 100 healthy subjects, 87% of which were female. The results showed a specificity of 98% in a general screening assessment; no other study was identified with healthy subjects, a comparable number of patients, and a similarly high specificity. However, no follow-up was undertaken and the study did not use an RCT design, which would have strengthened the high-specificity finding [13]. In comparison, the study by Nasuti et al. has to be taken in consideration. One hundred healthy subjects with no BC history, but who showed symptoms of dysuria, incontinence, and gross hematuria or microhematuria, were tested using BTA stat. The sensitivity, specificity, and positive predicted value (PPV) were 100%, 84%, and 16%, respectively. The authors did not give a recommendation for the use of BTA stat [14].

What problems are associated with the use of NMP 22?

Most of the studies that we reviewed criticized the correlation between hematuria and inflammation, the leading symptoms of BC, and NMP 22 tests. Todenhöfer et al. described a false-positive rate for NMP 22 of 85.3% in patients with inflammation compared to a rate of 61.4% when cytology, immunocytology, and Fluorescent in situ hybridization (FISH) were used [22]. Lee et al. established different cut-off values in NMP 22 for patients with hematuria. Patients with hematuria received a cut-off value of 6.39 U/ml, while patients with no hematuria got a cut-off value of 18.95 U/ml. Patients with confirmed urothelial carcinoma and a cut-off level > 6 U/ml showed a sensitivity of 81% and the specificity of 50%. Comparing the sensitivity and the specificity now to the same urothelial carcinoma patients with a cut-off level > 10 U/ml the sensitivity and the specificity changed to 69% and 72% [23].

What can we summarize for NMP22 from a cohort with a history of BC or suspicion of BC?

As already discussed in the BTA stat section, the review by Budman et al. and Toma et al. gave no recommendation for NMP 22 testing in terms of BC detection or surveillance, and instead recommended the continued use of cytology and cystoscopy as the gold standard [3, 6]. Looking closely at histological grades of transitional cell carcinoma Poulakis et al. showed a sensitivity of 82%, 89%, and 94% for the use of NMP22 for grades 1–3, respectively, with an optimal value of 8.25 U/ml, compared to a sensitivity of 53%, 76%, and 90% for the use of BTA stat for grades 1–3, respectively. NMP 22 achieved even higher results than voided urine cytology (VUC; the examination of cells under a microscope), which showed a sensitivity of 38%, 68%, and 90% for grades 1–3, respectively. However, VUC presented a specificity of 96%, compared to 68% for NMP22 and 67% for BTA stat. Nevertheless, the study showed a significant change in specificity from 94% (NMP22) and 92% (BTA stat) in patients with no apparent genitourinary disease to a specificity of 52% (in both tests) for patients with chronic UTI. To summarize, NMP 22 presented better results than VUC for the detection of superficial and low-grade BC after the exclusion of risk factors such as chronic UTIs, and the overall specificity also increased [9].

In a German study by Todenhöfer et al., NMP 22 was used on a population of 1,386 patients with possible BC. The specificity of NMP 22 was only 34.5%, with a cut-off value of 10 U/ml, so no recommendation was given for NMP 22 [22]. Lotan et al. developed an NMP22-based algorithm for BC in an asymptomatic but high-risk population. Risk was defined by smoking history, age, presence of hematuria, occupation, race, and gender. The general PPV was 20.3% and the NPV was 96.9%, but the PPV raised to 24% when only the male group was considered compared to 13% in the female group. Also a change in the PPV of more than 5% was observed when the group was divided into males under 65 (16.8%) and over 65 (23.5%). However, it was reduced to 77% in the male-only group when gross hematuria and smoking history were included. The NPV in the over 65-year old female group was 100% [25–27].

What are the results for mass screening in a healthy population?

The largest general screening study was performed by Bangma et al. in the Netherlands. In that study, 1,747 male patients were screened at home with NMP 22, in addition to other molecular-marker tests. In the study population, 23.4% were positive for hematuria (mainly smokers), 17% were current smokers, 58% were past smokers, and 36% had been exposed to occupational risk factors. Seventy-one of 75 men with positive molecular markers underwent cystoscopy. Four BCs and one kidney tumor was found, but in total one BC as well as one kidney tumor were missed. However, it reduced in total number of unneeded cystoscopies. The authors mentioned the possibility of a healthy-subject bias, and they did not give a recommendation for NMP 22 to be used for general screening [28].

Our systematic review of the literature found that the sensitivity of NMP 22 ranged from 25–85% and the specificity ranged from 34.5–96.6% (Table 2).

Discussion

We found it remarkable that there are currently no RCTs that exist that investigate either BTA stat or NMP 22 in an asymptomatic or a symptomatic study cohort. The studies that described molecular markers had study questions that primarily dealt with risk factors, they used varying methods and algorithms, they did not include an intervention group, and they often had short follow-up periods. None of the studies described medical or surgical treatments or the mortality rate during the follow-up periods. Most of the studies recommended NMP 22 or BTA stat before other diagnostics to reduce the number of VUCs and cystoscopies, but this was recommended primarily in low-grade BCs [8–10, 23]. Looking closely at BTA stat, it often showed the highest sensitivity and specificity in

patients with BC history in comparison with other molecular markers, but it was not as useful for general screening [7]. The BTA stat had a sensitivity of 90% in grade-3 tumors, whereas Raitanen et al. showed a high false-positive rate in patients with a history of BC [8, 9]. García-Velandria *et al.* recommended BTA stat instead of cystoscopy in surveillance cases with previous low-grade tumors for reasons of cost-effectiveness [10]. However, it is a questionable recommendation because of the high false-positive rate and the low sensitivity for grade 1 and 2 tumors and is therefore until today, not recommended in the German guidelines. In Table 1, we compared the results of the studies with the largest samples sizes in terms of the use of BTA stat with or without BC history. Based on the studies we reviewed, no recommendation could be made for the use of BTA stat for either mass screening or surveillance. RCTs, studies that provide a clear profile of patients with and without risk factors, and with longer follow-up periods are needed to determine the sensitivity and specificity of mass screening programs [13].

All of the NMP 22 studies are difficult to compare. For example, the PPV changed depending on sex, age, and risk factors. Consideration should be given to the observation that the PPV showed the best results in male groups under 65 years of age [25–27]. Also, different recommendations for NMP 22 cut-off levels were found; the cut-off for a diagnosis of primary cancer was 7.7 U/ml, the cut-off for patients showing hematuria was greater than 6 U/ml, and the median cut-off in healthy cohorts was 3.75 U/ml [24]. Reviewing the current state of art, the European Association of Urology (EAU) as well as the German guideline do not recommend using any tests for diagnosis [2].

However, with regards to the German health care system which is not covering the use of this test, still some clinics and private practices recommend patients to pay privately for the tests even though no recommendation is given. After reviewing the complete body of evidence, we also are unable to give a recommendation for the use of either NMP 22 and/or BTA stat usage, which is in line with as the German guidelines and the EAU guidelines. Patients need to be informed about current guideline recommendations and the uncertain debatable benefit of both tests, prior to the use of this direct payer service.

Conclusion

RCTs must be performed to show a reliable sensitivity and specificity and to give a recommendation for the use of BTA stat and NMP 22. Today, only a few studies recommend NMP 22 or BTA stat for primary diagnosis or surveillance cases, but these recommendations are not based on RCTs in a general population. Future studies may explore if it is useful to offer NMP 22 to only a certain profile of patients based on age and risk factors. According to our findings, general application of NMP22 and BTA stat is not recommended due to heterogeneous results in regard to sex, age, risk factors.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

All authors declare consent for the publication

Availability of data and materials:

The data that support the findings of this study are available at https://pubmed.ncbi.nlm.nih.gov/

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SL: project development, Data collection or management, Data analysis, Manuscript writing/editing

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