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The diagnostic value of abdominal ultrasound, urine cytology and PSA testing in the LUTS clinic

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2 Title: The diagnostic value of abdominal ultrasound, urine cytology and PSA testing
3 in the LUTS clinic.
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3 Abstract:

4 Introduction – Lower urinary tract symptoms (LUTS) affect 18-26% of men aged 40-
5 79, many of whom present with a fear of having cancer. Current guidelines for the
6 assessment of LUTS focus mainly upon benign prostatic hypertrophy. It has been our
7 practice to perform an abdominal ultrasound scan, a prostate specific antigen (PSA)
8 blood test and urine cytology during the assessment of males presenting with LUTS in
9 order to investigate the alternative potentially life threatening causes for LUTS. We
10 report on the added value of these tests during the assessment of men with LUTS.
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20 Results - A total of 263/3976 (6.6%) patients investigated for LUTS were found to
21 have incidental urological malignancies, urinary tract calculi or abdominal aortic
22 aneurysms (AAA). Abdominal ultrasound scans resulted in the incidental diagnosis of
23 4 renal carcinomas (0.1%), 45 AAAs (incidence = 1.1%) and 44 urinary tract calculi
24 (1.1%). Urine cytology testing and bladder ultrasound scans helped diagnose 17 new
25 bladder cancers (0.4%), 5 of which did not present with haematuria. Patients found to
26 have an elevated age specific PSA had a 23.6% chance of being diagnosed with
27 prostate cancer (3.8%).
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39 Conclusion - The addition of abdominal ultrasound scanning, urine cytology and PSA
40 testing as part of a LUTS assessment protocol can help to diagnose significant,
41 potentially life threatening conditions in up to 6.6% of patients. Whilst the pick up
42 rate of each individual condition is no higher in the LUTS patient than in the general
43 population, the combined pick up rate may justify these additional investigations.
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2 Key Words:

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5 LUTS, Screening, Cancer, Stones, AAA, Cytology
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10 Q 'What is already known about this topic?'

11 A Whilst BPH is the commonest cause of LUTS in the aging male other significant
12 causes include bladder cancer, prostate cancer and ureteric calculi. Guidelines on the
13 assessment of male LUTS patients have focused on the evaluation of BPH and have
14 not recommended the use of USS, cytology and PSA. This is a potential concern as
15 the commonest reason for patient presentation is the fear of underlying malignancy.
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23 Q 'What does this article add?'

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27 A This article presents a large series patients in whom USS, cytology and PSA were
28 routinely performed as part of their LUTS assessment with the specific aim of
29 investigating patients for other significant/potentially life threatening causes for
30 LUTS. We present for the first time the added value of routinely performing these
31 additional diagnostics tests in the setting of a LUTS assessment clinic.
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40 Author Contributions:

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42 Nilay S Patel – Drafting Article & Data Analysis

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44 Christopher Blick- Data Collection

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46 PVS Kumar – Critical Revision of Article

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48 Peter Malone – Concept/design
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3 Introduction:

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6 Bothersome lower urinary tract symptoms (LUTS) are amongst the most common
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8 complaints of the aging male. Numerous population based studies have demonstrated
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10 that bothersome LUTS affect between 18- 26% of men aged 40-79[1]. LUTS can
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12 impair an individual's quality of life to a greater degree than the physical impact of
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14 cancer and diabetes[1].
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18 Benign prostatic hyperplasia (BPH) is the most common cause for LUTS in the aging
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20 male. The current guidelines for the assessment of BPH from the European
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22 Association of Urology (EAU) do not focus on investigating the alternative
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24 potentially life threatening causes for LUTS [2]. This is particularly important as one
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26 of the main drivers for presentation in aging males is the fear of having an underlying
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28 cancer [3].
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32 In this study we reviewed 3976 patients who underwent investigation for bothersome
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34 LUTS at our hospital. As part of their routine investigations these patients received an
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36 abdominal ultrasound scan, urine cytology and PSA blood test.
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38 This paper discusses the additional value of these investigations in assessing LUTS in
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40 the aging male.
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2 Methods and Materials:
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5 Between April 1994 and February 2007 male patients presenting with lower urinary
6 tract symptoms to our department were evaluated in accordance with the EAU
7 guidelines with the following investigations; urine microscopy and culture, urinary
8 flow rate and measurement of post-micturition residual volume (PMRV),
9 International Prostate Symptom Score (IPSS) and serum creatinine. Uniquely our
10 nurse led clinic is run with a radiographer who performs an abdominal ultrasound
11 scan in addition to measuring the PMRV. All patients also had a urine cytology and
12 PSA blood test.
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23 Patient data was prospectively collected and entered into a FileMaker Pro database.
24 The database was searched in April 2007 and any incomplete data was obtained
25 retrospectively from the patient notes. Consent for this study was obtained from the
26 Royal Berkshire Hospital NHS Trust Audit department.
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Results:

Over a 13 year period a total of 3976 patients were investigated for bothersome LUTS. The mean patient age was 65 (range 15-91). The results of the urinary flow rates, IPSS, serum creatinine, routine urine microscopy and culture were not the focus of this study.

Abdominal Ultrasound Scan (USS)

The presence of a dedicated uro-radiographer within our department permitted the incorporation of an abdominal ultrasound within our LUTS assessment protocol with minimal additional cost. An abdominal USS in the LUTS patient was performed in order to identify any pathology which may alter future management; namely hydronephrosis and bladder calculi.

Ultrasound evaluation of the upper tracts demonstrated hydronephrosis in 59/3976 (1.5%) patients of which 23 had bilateral hydronephrosis secondary to bladder outlet obstruction. The remaining 36 patients had incidental unilateral hydronephrosis requiring further investigation. With regards to bladder calculi, a total of 4/3976 (0.1%) patients were noted to have bladder stones on USS all of whom were subsequently managed with a Transurethral Resection of the Prostate (TURP).

Upper urinary tract calculi can present with bothersome LUTS particularly when stones become impacted at the vesico-ureteric junction. A total of 40 (1%) patients had upper urinary tract calculi identified using USS; 36 had renal stones and 4 had ureteric stones. None of these patients experienced macroscopic haematuria. A total of 20/36 (55%) patients diagnosed with renal stones and 3/4 (75%) patients with

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ureteric stones had microscopic haematuria. Only one of these patients was a known stone former. A total of 14 patients required further treatment as a result of screen detected urinary tract calculi (0.4%). Interestingly only 2/4 (50%) of the patients with impacted ureteric stones reported the classical symptoms of renal colic.

Routine abdominal ultrasonography led to the detection of a number of incidental pathologies. A total of 18/3976 patients had abnormal ultrasounds with features suggestive of a renal malignancy. Fifteen patients had suspicious solid or cystic lesions which were investigated with CT scans, 3 patients with abnormalities of the pelvi-calyceal system were investigated with intravenous urograms. In total 4/3976 patients were found to have incidental renal/adrenal malignancies following routine renal ultrasound scanning. These comprised; 3 renal cell carcinomas one of which was bilateral and one metastatic lymphomatous adrenal lesion. One again none of these 5 patients reported a history of macroscopic haematuria, with only 3/5 (60%) presenting with microscopic haematuria at the time of their LUTS assessment. The remaining 14 patients were noted to have benign cysts upon further investigation.

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The routine use of renal tract USS also served as a screening tool for the detection of abdominal aortic aneurysms (AAA). In this study we regarded an aorta to be aneurysmal if the maximal diameter was greater than 3cm [4]. A total of 45 incidental AAAs were picked during the course of our routine LUTS investigation of which 10 were greater than 5.5cm in diameter.

Urine Cytology

Transitional cell carcinoma of the bladder and in particular carcinoma in situ can present with bothersome LUTS. All patients presenting to our LUTS assessment clinic were routinely investigated with urine cytology in addition to an ultrasound scan of the bladder.

70 patients were noted to have atypical urine cytology, in this study all abnormal urine cytology reports were regarded with suspicion. Further investigations included repeat urine cytology which was normal in 7 patients. The remaining 63 patients proceeded to cystoscopy with 17 new bladder cancers cases being diagnosed. Of these 17 patients, 5 did not have any evidence of haematuria, 3/5 of these men were smokers. No other risk factors were present in this sub-group of patients. Histological assessment of the bladder tumours diagnosed 3 low risk superficial tumours, 10 high risk superficial tumours and 4 high grade muscle invasive tumours.

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PSA Blood Test

As part of their evaluation all patients over the age of 40 had a routine PSA blood test. The results were compared with the age specific normal range at our institution (0 - 49 yrs < 2.5; 50 - 59 yrs < 3.5; 60 - 69 yrs < 4.0; 70 - 79 yrs < 6.5). Any patients with elevated PSA levels were considered for trans-rectal ultrasound guided prostate biopsies.

Of the 3976 patients, 647 had a PSA above their expected age specific value (16.3%). Of these patients 548 (85%) went on to have prostate biopsies. 99 (15%) patients did

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2 not have prostate biopsies for the following reasons: 74 patients had a borderline PSA
3 rise which on repeat sampling had reduced and was attributed to UTI or prostatitis; 6
4 patients were over 85 years of age and it was deemed inappropriate, 1 patient was
5 considered unfit for the procedure and in 18 patients there was no documented reason
6 found.
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14 Of the patients who underwent prostate biopsies, 153 patients were diagnosed with
15 prostate cancer, 364 patients with benign prostatic hyperplasia and 31 patients with
16 prostatitis. The overall incidence of prostate cancer was 3.8%, however, patients
17 presenting with LUTS found to have an elevated age specific PSA had a 23.6%
18 chance of being diagnosed with prostate cancer.
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Discussion

A one stop LUTS/Prostate Assessment Clinic aims to streamline and optimize the investigation and management of men suffering from bothersome LUTS. The investigations performed during the evaluation of these patients have conventionally focused on the assessment of BPH. In our LUTS assessment clinic we have additionally incorporated abdominal ultrasonography, urine cytology and PSA testing in order to detect alternative significant causes of LUTS.

Abdominal USS were initially performed to look for secondary features of bladder outlet obstruction such as hydronephrosis and bladder stones. Only 27/3976 patients were noted to have either bilateral hydronephrosis or bladder calculi. This low yield has led to the current EAU guideline that renal tract ultrasound scanning is only indicated in the presence of renal impairment [2].

The true added value of routine ultrasonography is in the detection of incidental intra-abdominal pathology. In our series renal tract ultrasound diagnosed 40 upper tract urinary tract stones (1.1%), of which 4 (10%) went on to require urgent surgical intervention. Screening for asymptomatic stones is not warranted as most renal stones do not require treatment; however some patients with impacted stones at the vesico-ureteric junction present not with haematuria and classical renal colic but with LUTS. In these patients an USS can help to promptly make a diagnosis and prevent obstructive renal injury.

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Routine renal tract ultrasound scanning was able to detect 4 incidental renal tumours. The use of ultrasound to screen for renal malignancies has recently been advocated as renal cell carcinoma (RCC) fulfils many of the screening criteria defined by the WHO [5]. Interest in screening for RCC is driven by the fact that the incidence of renal cell carcinomas is increasing and that small early tumours are potentially curable with considerably better prognosis than more advanced disease [6]. In our study the pick up rate of incidental renal/adrenal malignancies (0.1%), was similar to previously reported series (0.1-0.3%) [7]. Screening for RCC in isolation is unlikely to be cost effective as a national screening program; however opportunistic screening at the time of LUTS assessment may be justified.

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AAAs are relatively common in the aging male with an incidence of between 5 and 10% in men 65-79 years of age. Numerous trials have studied the potential survival benefits of ultrasound screening for AAA, the biggest of which is the multi-centre aneurysm screening study (MASS trial), which showed a 50% AAA specific survival advantage in the screened population [8, 9]. In our study the overall incidence of AAA in target age group of 65-75 was relatively low at 1.4%, with 4 patients (0.1%) in this age group having AAA > 5.5cms that were suitable for elective repair. In the UK, the NHS AAA screening programme will be introduced in 2009-10. In this programme, all men aged 65 will be offered an abdominal USS looking for an AAA. Aneurysms sized between 3 and 5.5cm will be managed conservatively with regular follow up, whilst men with AAAs larger than 5.5cm will be offered surgery. In the absence of similar national screening programmes, opportunistic detection of AAAs at the time of LUTS assessment clinics may help to reduce AAA specific mortality in the aging male.

Most patients diagnosed with bladder cancer present with haematuria, however a few present with irritative lower urinary tract symptoms (LUTS) in the absence of haematuria. With increasing medical management of presumed benign prostatic hyperplasia there is a potential risk that in some patients, the diagnosis of bladder cancer/CIS may be delayed.

In 1999 we reported our initial experience of using urine cytology in the setting of a LUTS assessment clinic [10]. Silent bladder tumours were detected as a result of urine cytology in 2/336 men with LUTS and no evidence of haematuria. Over the past 14 years we have used a combination of urine cytology and ultrasound to detect 17 new bladder cancers, of which 5 did not present with haematuria. Fourteen of the seventeen cases were either aggressive high risk superficial cancers or muscle invasive tumours. The routine use of urine cytology led to the early diagnosis and treatment of at least 5 “silent” bladder tumours and could potentially have led to a significant survival benefit.

Of the 17 bladder tumours identified only one was picked up on the basis of an USS only, the rest being picked up either on the basis of cytology only (12/17) or both (4/17). As a diagnostic modality USS is of limited value in looking for bladder tumours. When tumours are detected however USS can give an indication of tumour size, location and number. When tumours are detected with confidence a flexible cystoscopy can be avoided and the patient scheduled directly for a transurethral resection (TURBT).

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PSA testing is of some value in the assessment of men with symptomatic BPH, it's main role however in this setting is in screening for prostate cancer. The aging male is increasingly aware of the risks of prostate cancer and the role of PSA screening in diagnosing this disease. Although most prostate cancers start in the peripheral zone away from the urethra, 20% of prostate cancers do develop in the peri-urethral transition zone and it is possible that these or more advanced peripheral zone cancers can cause obstruction and LUTS. When a patient presents with LUTS, therefore, it is important to consider prostatic malignancy as a cause. To make such a diagnosis, in this era, requires both a digital rectal examination and a PSA in order to reassure patients that their symptoms are unlikely to be caused by cancer. In so doing, many cancers that were not the cause of the patient's symptoms will also be picked up.

In our study, 16.3% of patients had an elevated age specific PSA resulting in an overall incidence of prostate cancer in the study group of 3.8%. Patients noted to have an elevated age specific PSA had a 23.6 % chance of being diagnosed with prostate cancer. This is comparable with the incidence of prostate cancer in patients with a raised PSA and or abnormal digital rectal examinations in the control arm of the Prostate Cancer Prevention Trial (29.5%) [11].

The screen detected incidence of prostate cancer in our study is in keeping with the European Randomized Study of Screening for Prostate Cancer (ERSPC) a multi-centre randomized control trial designed to determine the value of screening for prostate cancer [12]. The data from the ERSPC trial showed that PSA-based screening reduced the rate of death from prostate cancer by 20% over a follow-up period of 9 years. However the trial also showed that PSA screening may lead to over

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diagnosis of prostate cancer as highlighted by the fact that 1410 men would need to be screened and 48 cases of prostate cancer would need to be treated to prevent one death from prostate cancer [13]. A similar screening trial conducted in the USA (PLCO) concluded that the rate of death from prostate cancer was very low and did not differ significantly between the screened and unscreened group [14]. The control group in this study was unfortunately contaminated with a high proportion of patients having had a PSA test.

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Conclusion

Male patients presenting with LUTS are often concerned about the underlying cause for their symptoms and in particular are worried about the risk of an underlying cancer. Current guidelines for the assessment of BPH do not recommend the routine use of PSA testing, urine cytology and abdominal ultrasound scanning at the time of LUTS assessment clinic. The incorporation of these tests can help to diagnose potentially life threatening non BPH causes for LUTS that may otherwise be missed. The use of abdominal ultrasound scanning can also serve as an opportunistic screening tool for the detection of incidental AAA and renal malignancies. Whilst the pick up rate of each individual condition is no higher in the LUTS patient than in the general population; the combined pick up rate may justify the use of these additional investigations.

Deleted: To date there is limited data on the absolute benefits of screening for prostate cancer. The ERSPC and PLCO trials are expected to report their findings in the near future and in doing so help to determine the value of national screening programmes for prostate cancer [12, 13]. ¶

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Tables

Age	N	Number of abnormal Renal USS	Urinary Tract Calculi	Renal/adrenal Cancers	Bladder Cancers	AAA	AAA > 5.5cm
< 40	141	1	1	0	0	0	0
40-49	287	4	4	0	0	0	0
50-59	724	16	10	2	1	2	0
60-69	1218	20	11	2	0	7	1
70-79	1175	37	12	0	2	22	4
> 80	431	20	2	0	2	14	5
TOTAL	3976	94	40	4	5	45	10

Table 1. Incidental diagnosis detected with abdominal ultrasound

Age Group	Normal Age Specific PSA	Number of patients	Number of patients with high age specific PSA (%)	Number of Patients with Prostate Cancer (%)	% of patients with high PSA and prostate cancer
< 40	<2.5	141	0 (0)	0 (0)	0
40-49	<2.6	287	7 (2.4)	0 (0)	0
50-59	<3.5	724	89 (12.3)	13 (1.8)	14.6
60-69	<4.0	1218	248 (20.4)	41 (3.4)	16.5
70-79	<6.5	1175	208 (17.7)	69 (5.9)	33.2
>80		431	95 (22.0)	30 (7.0)	31.6
TOTAL		3976	647 (16.3)	153	23.6

Table 2. The value of PSA testing in screening for Prostate Cancer.

Diagnosis	Investigation	Positive pick up rate	% of positive cases
Urinary Tract Calculi	USS	40/3976	1.0
Bladder Cancer	Cytology	16/3976	0.4
Bladder Cancer	USS	5/3976	0.1
Kidney Cancer	USS	5/3976	0.1
AAA	USS	45/3976	1.1
Prostate Cancer	PSA	153/3976	3.8

Table 3. Overall detection rates for incidental pathology resulting from the routine use of abdominal ultrasound scans, urine cytology and PSA blood tests at the time of LUTS assessment.

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