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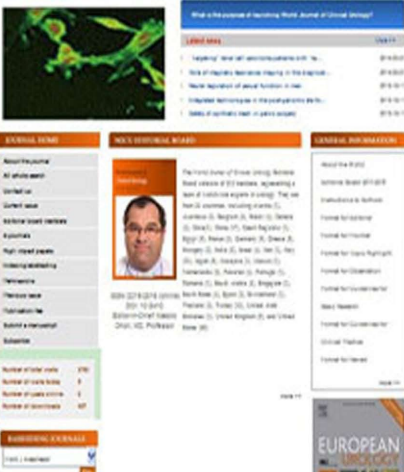


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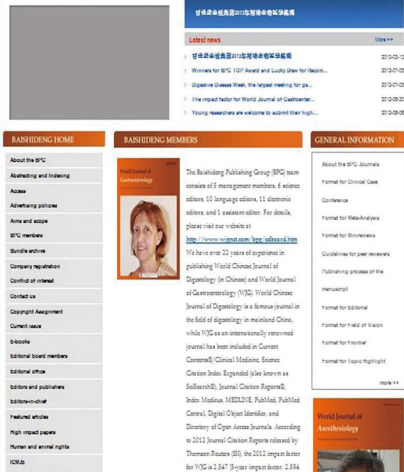


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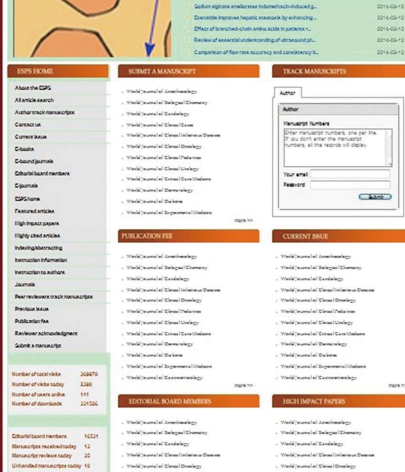
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**THERAPEUTIC
ADVANCES**

1

Is verumontanum resection needed in transurethral resection of the prostate?

Mazaris EM

Contents

World Journal of Clinical Urology
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APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Clinical Urology*, Alexandre de la Taille, MD, PhD, Professor, Head of Research Department Insermu 955eq07, Department of Urology, Chu mondor, 51 av du Mal de Lattre de Tassigny, 94000 Créteil, France

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Is verumontanum resection needed in transurethral resection of the prostate?

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INTRODUCTION

Transurethral resection of the prostate (TURP) remains the "gold standard" for surgical treatment of benign prostatic enlargement although other alternatives have been proposed^[1]. However, this procedure involves several complications with probably incontinence being the most detrimental causing distress and affecting the patients' postoperative quality of life. It is caused by injury to the urinary sphincter during accidental advancement of the resection loop during the operation to the level distal from the verumontanum. Therefore by limiting the resection proximal to the verumontanum hopefully reduces the incidence of this devastating complication and acts as an anatomical boundary for prostate resection. Prostate size and resection time are the two most important factors that affect morbidity after TURP and thus a high level of experience is required to reduce complications such as incontinence^[2].

The authors of this article^[3] address a very interesting issue and their scientific hypothesis that resecting as much prostatic tissue as possible improves outcomes after TURP was partially confirmed. There was a statistically significant improvement at 6 mo in the obstructive International Prostate Symptom score postoperatively for those patients who underwent verumontanum resection. Is that worth the increased risk of injuring the sphincter and causing incontinence? This proved not to be true in the present article since there was not a statistically significant difference in the incidence of incontinence between the groups who underwent or not verumontanum resection.

Abstract

Transurethral resection of the prostate is the mainstay for treatment of bladder outflow obstruction. It is a procedure that involves various complications and has a high success rate. In view of a recent publication presenting the effect of verumontanum resection on functional outcome and possible complications after TURP, the present manuscript presents the available evidence on the subject as well as the possible criticism about the technique suggested by the authors. The results available do not confirm that by resecting the verumontanum there is a clinically significant improvement in the functional outcome, however confirm that continence is not affected. The criticism probably lies in the fact that resecting such a small amount of tissue like the verumontanum (its size probably remains the same with few changes during lifetime) probably does not affect outcome, yet the resection of hyperplastic apical tissue around it may play a role in functional improvement.

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Key words: Transurethral resection; Prostate; Apical tissue; Verumontanum; Sphincter

A point of criticism for this article is probably that resection of the minimal tissue of the verumontanum itself would not probably improve the efficacy of TURP. However, the resection of excessive apical prostatic tissue extending to the level of the verumontanum probably makes a difference in outcomes. The main disadvantage by resecting the verumontanum itself is that you lose an anatomical landmark which undoubtedly guides resection. Therefore the verumontanum should probably either be spared or resected at the final stage of the operation when all other prostatic tissue has been removed.

Another important issue raised is that the operation was performed by experienced surgeons and that is probably one of the key points of this article. Undoubtedly the primary aim of TURP is to remove as much hyperplastic prostatic tissue as possible in order to improve outcomes and decrease re-operation rates, especially in prostates who have excessive apical tissue, however, anatomical boundaries *i.e.*, the external urinary sphincter have to be respected in order to prevent incontinence.

In 1935 Nathaniel Alcock claimed that TURP "...cannot be taught and can be learnt only by hard, tedious expe-

rience"^[4]. Therefore it is our firm belief that resection of the verumontanum and the apical prostatic tissue around it, is not a task for the novice TURP surgeon and therefore should be undertaken with extreme caution by experienced surgeons with careful respect of the prostatic anatomy.

REFERENCES

- 1 **Geavlete P.** Is classical transurethral resection of the prostate, the gold standard endoscopic treatment for benign prostate hyperplasia, in real danger of being replaced? *Eur Urol* 2010; **58**: 356-358; discussion 358-359 [PMID: 20825757 DOI: 10.1016/j.eururo.2010.06.001]
- 2 **Miano R, De Nunzio C, Asimakopoulos AD, Germani S, Tubaro A.** Treatment options for benign prostatic hyperplasia in older men. *Med Sci Monit* 2008; **14**: RA94-R102 [PMID: 18591930]
- 3 **Filiz DN, Yilmaz Y, Koc G, Dirik A, Akgul K.** Effect of verumontanum resection in transurethral resection of the prostate on postoperative voiding function and incontinence. *Surgical Practice* 2011; **15**: 48-53
- 4 **Hawtrey CE, Williams RD.** Historical evolution of transurethral resection at the University of Iowa: Alcock and Flocks. *J Urol* 2008; **180**: 55-61 [PMID: 18485410 DOI: 10.1016/j.juro.2008.03.018]

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hyperten-

sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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- 10 Potential of metastin and metastin receptor as biomarkers for urological
cancers
Shoji S, Sato H, Tomonaga T, Kim H, Soeda S, Nakano M, Uchida T, Terachi T, Takeya K

Contents

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Extraperitoneal robot-assisted radical prostatectomy: Comparison with transperitoneal technique

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Abstract

AIM: To determine peri-operative, oncological, functional and safety profiles of extraperitoneal robot-assisted radical prostatectomy (eRARP) vs transperitoneal robot-assisted radical prostatectomy (tRARP) in a single centre.

METHODS: A total of 120 consecutive patients underwent 50 eRARP and 70 tRARP operations respectively by the same surgical team. Peri-operative and post-operative outcomes including blood loss, hospitalization, complications (Clavien grade), positive surgical margin (PSM) rates, continence and erectile function were compared. The performance of eRARP required several technical modifications. These included development

of Retzius' space by balloon insufflation, laparoscopic dissection of lateral extensions of this area; caudal port positioning; cranial digital stripping of peritoneum for sucker port and lodging the bagged prostate specimen adjacent to the lateral assistant port to permit space for urethro-vesical anastomosis.

RESULTS: Robotic console times were shorter with eRARP vs tRARP (145.1 min vs 198.3 min, $P < 0.0001$). There were no significant differences in blood loss, PSM rates (eRARP 17.7% vs tRARP 22%) or complications (eRARP 8.5% vs tRARP 8%). A drain was used in all patients after tRARP and in 25/70 eRARP cases. Length of hospital stay was shorter after eRARP (mean 1.94 d vs 3.6 d, $P < 0.0002$). There were no differences between techniques in continence or potency at 6 mo. eRARP required several technical modifications: development of Retzius' space by balloon insufflation, laparoscopic dissection of lateral extensions of this area; caudal port positioning; and lodging the bagged prostate specimen adjacent to the lateral assistant port to permit space for urethro-vesical anastomosis.

CONCLUSION: eRARP demonstrated advantages in surgical times, hospital stay and equivalence in PSM rates, complications and functional outcomes. eRARP is a useful alternative to tRARP especially in patients with adhesions, pre-existing inguinal hernias, or those unable to withstand steep Trendelenburg position.

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Key words: Prostatic neoplasms; Robotics; Laparoscopy; Prostatectomy; Complications

Core tip: Extraperitoneal robot-assisted radical prostatectomy (RARP) is a feasible alternative to transperitoneal RARP with equivalent complication rates, and pathological and functional outcomes. This approach replicates the principles of open radical prostatectomy

with minimal requirement for Trendelenburg position or post-operative drain. It is particularly suited for patients with adhesions, pre-existing inguinal herniae and those unable to stand robotic surgery in steep Trendelenburg position.

Anderson C, Ayres B, Issa R, Perry M, Liatsikos E, Stolzenburg JU, Ghani KR. Extraperitoneal robot-assisted radical prostatectomy: Comparison with transperitoneal technique. *World J Clin Urol* 2013; 2(2): 3-9 Available from: URL: <http://www.wjgnet.com/2219-2816/full/v2/i2/3.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v2.i2.3>

INTRODUCTION

Robotic-assisted radical prostatectomy (RARP) using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, United States) has become the predominant method for the surgical treatment of prostate cancer in the United States^[1]. Compared to traditional open and laparoscopic methods, RARP results in similar oncological outcomes with some studies demonstrating improved recovery of continence and potency^[2]. RARP may be performed by either a transperitoneal (tRARP) or extraperitoneal approach (eRARP). However, the overwhelming majority of surgeons use the transperitoneal (TP) approach based on its early description by pioneers of the technique^[3]. Comparative studies of TP *vs* extraperitoneal (EP) approaches to RARP are limited to only four studies^[4-7] and it is not clear whether these theoretical advantages translate into better clinical outcomes. The current study aims to determine the peri-operative, functional, oncological and safety profiles for both techniques in a single centre. We also discuss important technical modifications learnt from our experience of eRARP.

MATERIALS AND METHODS

Patients

Between August 2008 and May 2011, 120 patients underwent RARP by a single surgeon (CA) in a tertiary centre. The first 50 consecutive patients underwent tRARP. The technique was then changed to an EP approach and the next 70 patients (eRARP) analysed. The cases were performed by an experienced pelvic laparoscopic and robotic surgeon but represented the early robotic experience of the personnel at this institution.

Operative technique

For the TP approach, we used the technique described by Menon *et al*^[8]. For the EP approach we used our own modifications of the endoscopic extraperitoneal radical prostatectomy (EERPE) technique described by Stolzenburg *et al*^[9]. A 20 F drain was placed in all patients following tRARP. The steps for access and port placement for eRARP are described below. In both techniques the

assistant was situated on the left side of the patient with two robotic ports placed on the right side of the camera. This configuration was preferred in order to have the ability to use robotic graspers simultaneously on the left and right sides.

Extraperitoneal access and port placement

Equipment: All cases were performed using a 6-port technique with the four-arm da Vinci system^[10]. Three standard 8 mm robotic ports are used along with a threaded 5/150 mm length blunt tipped port for the sucker, a 12/150 mm port with stability cone for the camera and a 12/100 mm assistant port. The camera and suction instrument port have an extra long shaft to overcome the oblique trajectory required to cross the posterior rectus sheath as well as to avoid clashing of the instruments outside the body. A round pre-peritoneal distension balloon is used for creation of the extraperitoneal space (PDB®1000 Balloon, Covidien, Mansfield, MA, United States). As the diameter of the robotic camera is larger than the balloon insufflation port, a laparoscopic camera was used for EP space creation.

Extraperitoneal access: EP access was undertaken with the patient supine. An oblique incision is made 2 cm infero-lateral to the right of the umbilicus. The anterior rectus sheath is incised and the rectus muscle separated to expose the posterior sheath. An index finger is inserted above the posterior sheath in the direction of the pubis to create space for the pre-peritoneal distension balloon. The balloon is manually inflated a small amount to secure it within the retropubic space (Figure 1). Further insufflation is done under direct vision to create the EP space. Once satisfactory the balloon is deflated and removed.

Port placement: An index finger is inserted through the infra-umbilical incision to strip and release left-sided fascial attachments of the peritoneum to anterior abdominal wall. The suction instrument port incision is made 3 cm left of the umbilicus. The port is inserted through the abdominal wall with the tip of the index finger of the other hand, *via* the infra-umbilical incision, protecting its entry. Next, the blunt tipped camera port is inserted *via* the infra-umbilical incision between the rectus muscle fibres and anterior to the posterior rectus muscle sheath with a retractor elevating the anterior sheath to facilitate its insertion. Sutures placed in the anterior sheath tighten the seal around the stability cone of the camera port and secure it in place.

CO₂ insufflation is commenced to a pressure of 12 mmHg. *Via* the suction instrument port, the suction or blunt grasper is used to release any remaining left-sided fascial attachments. At approximately two thirds of the distance from the pubic symphysis to umbilicus and three finger-breadths lateral from the midline, the left robotic port is inserted under direct vision. Using the suction and left robotic ports as working channels, peritoneum on the right side is mobilised off the anterior abdominal wall.

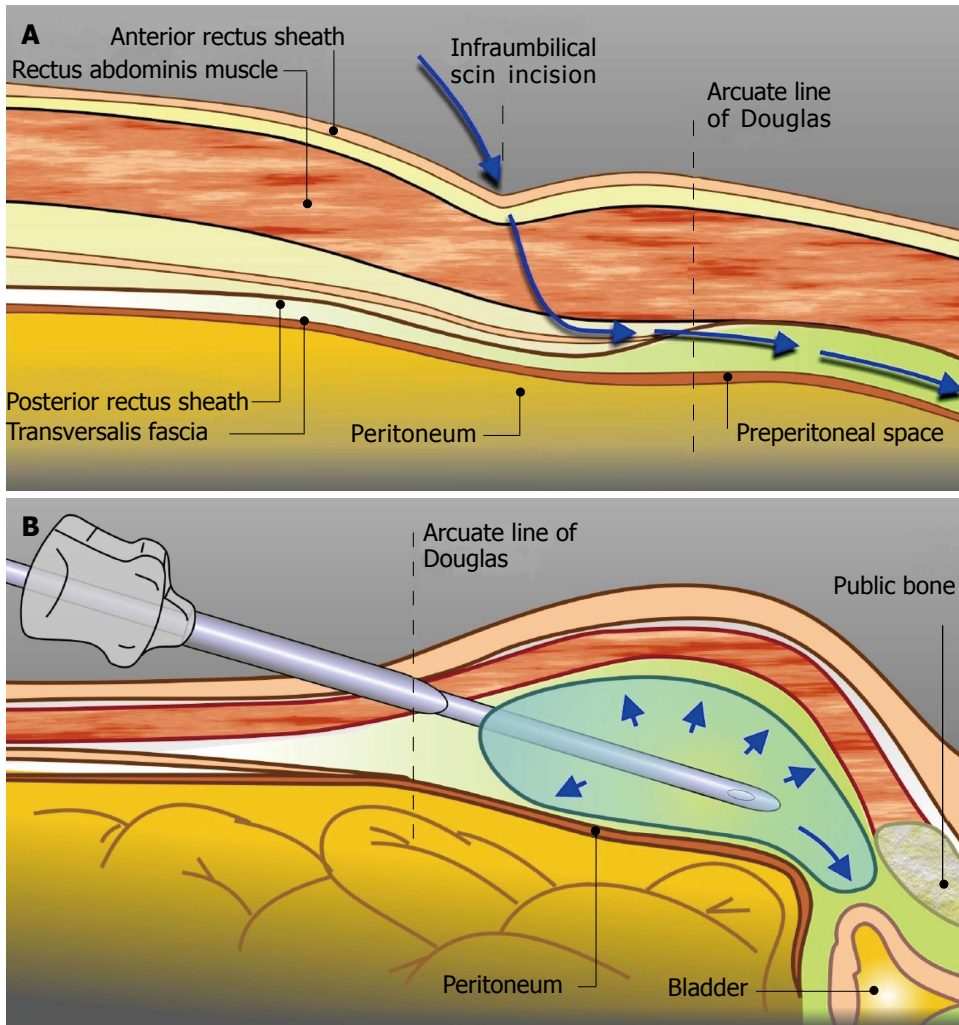


Figure 1 The balloon is manually inflated a small amount to secure it within the retroperitoneal space. A: Extraperitoneal space creation for insertion of the distension balloon; B: Balloon insufflation of the retroperitoneal space. With kind permission from Springer Science + Business Media: Laparoscopic and Robot assisted surgery in urology, Chapter 3.4 extraperitoneal access and trocar placement for pelvic surgery, 2011, Stolzenburg JU, Türk, IA, Liatsikos, EN (Eds.).

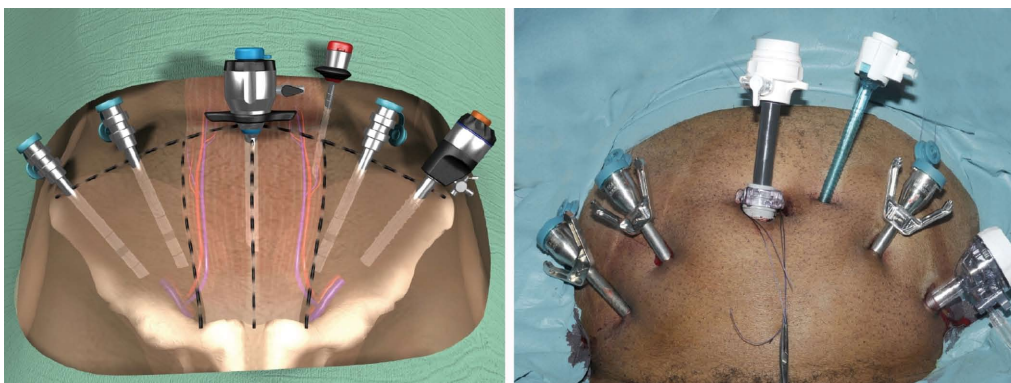


Figure 2 Final six-port configuration for extraperitoneal robot-assisted radical prostatectomy.

Dissection begins lateral to the inferior epigastric vessels and superolateral to the arcuate line.

The first right-sided robotic port (4th arm port) is inserted at point two to three finger-breadths in the line from the right anterior superior iliac spine to umbilicus. The second right-sided robotic port is placed at the same level as the left robotic port, equidistant from the midline. The inferior epigastric vessels must be noted to avoid injury during its insertion. Once all three robotic ports are placed, dissection is continued from the right side

with stripping of peritoneum away from the left anterior abdominal wall. The 12 mm assistant port is placed three finger-breadths in the line between the left anterior superior iliac spine and umbilicus (Figure 2).

Prostatectomy: The patient was placed in a 10°-15° Trendelenburg position and the patient side-cart docked. Standard pelvic lymphadenectomy was done if needed. Prostatectomy was begun with dissection of the endopelvic fascia. The remainder of the procedure was

Table 1 Comparison of peri-operative and safety profiles of transperitoneal and extraperitoneal approaches to robot-assisted radical prostatectomy

Characteristic	tRARP (n = 50)	eRARP (n = 70)
Mean total operative time (min)	255.7 (155-490)	236.8 (170-375)
Prostatectomy console time (min)	198.3 ± 64 (120-420)	145.1 ± 38.7 (96-293)
Mean blood loss (mL)	342 ± 320 (50-2000)	372 ± 368 (100-2500)
Drain use	50/50	25/70
Length of stay (mean)	3.52 ± 2 (2-12)	1.94 ± 1.38 (1-8) (<i>P</i> < 0.0002)
Intra-operative complications (Clavien Grade)	1 Ureteric injury (Grade 2)	1 Rectal injury (Grade 2)
Post-operative complications (Clavien Grade)	1 Arm neuropraxia (Grade 1) 1 Blood transfusion (Grade 2) 1 Anastomotic leak requiring suprapubic catheter insertion on readmission (Grade 3b)	1 Urinary retention (Grade 1) 2 Blood transfusions (Grade 2) 2 Pelvic collection/haematoma requiring percutaneous drainage (Grade 3a)

Data are presented as number or mean ± SD (range). eRARP: Extraperitoneal robot-assisted radical prostatectomy; tRARP: Transperitoneal robot-assisted radical prostatectomy.

Table 2 Clinical characteristics between patients undergoing transperitoneal robot-assisted radical prostatectomy and extraperitoneal robot-assisted radical prostatectomy

Variables	tRARP (n = 50)	eRARP (n = 70)
Age (yr)	60.5 ± 7.5 (42-72)	62.1 ± 6 (47-72)
PSA (ng/mL)	8.67 ± 6.1 (2.8-34.8)	8.66 ± 8.58 (1.3-71.8)
Prostate volume (cc)	39.5 ± 14.66 (15-70)	44.9 ± 17.4 (18-82)
Biopsy Gleason score		
6	26	30
7	20	38
8	3	2
Pathological stage		
T2	37	51
T3a	11	12
T3b	2	7
Specimen Gleason score		
5	1	
6	11	10
7	30	52
8	4	3
9	4	4
Cancer volume (cc)	3.9 ± 3.2 (0.06-14.7)	3.2 ± 3.58 (0.2-23.7)
Positive surgical margin		
T2	13.5% of 37 patients	12.7% of 48 patients
T3	30.5% of 13 patients	22.7% of 22 patients

Data are presented as number or mean ± SD (range). eRARP: Extraperitoneal robot-assisted radical prostatectomy; tRARP: Transperitoneal robot-assisted radical prostatectomy; PSA: Prostate specific antigen.

similar to the TP approach with the only modification being fixation of the bagged prostate specimen adjacent to the assistant's 12 mm port, to enable adequate space for urethro-vesical anastomosis (UVA). A 20 F drain was placed in the retropubic space in selected patients who underwent concomitant lymphadenectomy or the UVA was difficult or blood oozing was present.

Statistical analysis

Data were collected prospectively into a database. Complications were graded using the modified Clavien classification^[11]. Outcomes for erectile function and continence were evaluated using the International Index of Erectile Function 5 (IIEF-5) and ICS male Short Form (SF) questionnaires respectively. These were provided to patients

preoperatively and quarterly postoperatively by a nurse specialist. We defined continence as being either pad free or using one security pad at 6 mo. Initial tests for normality were carried out and appropriate statistical tests chosen (paired *t* test and Kruskal-Wallis test). Commercially available statistics programs were used (GraphPad InStat, version 3.05, GraphPad Software, United States; Medcalc version 7.0, Medcalc Software, Belgium) for statistical comparisons.

RESULTS

Table 1 compares the peri-operative data and complications between the two groups. Patient pathological characteristics are provided in Table 2. There were no significant differences in the prostate specific antigen, prostate TRUS volume, Gleason score, pathological stage or positive surgical margin (PSM) rates between TP and EP groups. Fourteen patients had pelvic lymph node dissection and four had mesh repair for concurrent inguinal hernia in the EP-group. In the TP-group seven patients had lymph node dissection and one had a mesh hernia repair. The hernia repair was done similarly in both groups and the mesh was placed in the EP space at the end of the TP operation in order to avoid its contact with the bowel. Adjusting for these concurrent procedures resulted in mean console times of 145.1 min for eRARP *vs* 198.3 min for tRARP (*P* < 0.0001). The overall operating time was also shorter in the EP-group but this did not reach statistical significance. There were no significant differences in blood loss between eRARP and tRARP techniques (372 mL *vs* 342 mL respectively, *P* < 0.0008). In total there were two blood transfusions in the eRARP group, whilst one transfusion in the TP-group.

The complication rates were similar amongst both techniques (Table 1). Complication rate after tRARP was 8% *vs* 8.5% after eRARP (*P* = 1.0). A drain was used in only 25 patients (36%) in the eRARP *vs* in all patients in the TP group (*P* < 0.0007). The length of stay was shorter with eRARP (mean 1.94 d *vs* 3.52 d, *P* < 0.0001). The proportion of patients discharged on the first post-operative day was significantly higher following an EP

Table 3 Summary of studies determining perioperative, oncological and safety profiles for extraperitoneal robot-assisted radical prostatectomy

Reference	Centre	Level of evidence	No. of patients	Mean operative time (min)	Mean blood loss (mL)	Complication rate (transfusion rate)	PSM rate	Hospital stay (d)	Conversions
Joseph <i>et al</i> ^[12]	Rochester, United States	4	325	180	196	9.8% (1.3%)	13%	96% < 24 h	2 converted to TP
Atug <i>et al</i> ^[4]	New Orleans, United States	4	40	229	221	12.5% (NS)	20%	Mean 1.2	none
Rozet <i>et al</i> ^[13]	Institut Montsouris, France	4	133	166	609	19.4% (9.8%)	19.50%	Mean 5.4	4 converted to LRP
Capello <i>et al</i> ^[6]	Rochester, United States	2b	31	181	199	0% (0%)	3.20%	NS	none
Madi <i>et al</i> ^[5]	Ann Arbor, United States	4	34	214	125	5.9% (0%)	23.50%	Median 1	none
Ploussard <i>et al</i> ^[16]	Henri Mondor, France	4	206	160	504	8.3% (3.4%)	27.70%	Mean 4	1 converted to LRP
Chung <i>et al</i> ^[7]	South Korea	4	155	150	351	7.1% (NS)	22.60%	Mean 5.1	none
This study	St George's, United Kingdom	4	70	145.1	372	8.5% (2.8%)	15.70%	Mean 2	none

NS: Not stated; LRP: Laparoscopic radical prostatectomy; PSM: Positive surgical margin; TP: Transperitoneal.

procedure (49% *vs* 0%, $P < 0.0001$).

Although the EP approach was completed in all patients, small peritoneal breaches and subsequent intraperitoneal insufflation were encountered in 4 (6%) patients. These did not significantly hamper the dissection and by placing a 14 G venous cannula into the abdominal cavity the pneumoperitoneum was kept to a minimum thereby avoiding diminution in the EP space.

At 6 mo the continence rate in the two groups was equivalent with 93% continent in the tRARP group and 94% in the eRARP group. There were no differences in potency outcomes using either technique. At 6 mo, patients undergoing nerve-sparing RARP achieved satisfactory erections (IIEF-5 ≥ 17), with or without oral pharmacotherapy in 67% and 69% for eRARP and tRARP respectively.

DISCUSSION

Table 3 summarises the published data on eRARP^[4-7,12-14] including those studies that directly compare eRARP and tRARP^[4-7]. Studies where the data has been duplicated in larger series are excluded from this analysis^[15,15-18]. Our study is the first report from a United Kingdom centre performing eRARP and demonstrates overall operative times, PSM and complication rates consistent with previously published studies. We found the console time was significantly shorter with the EP approach although there were no significant differences in total operative times between the two techniques. During eRARP console time is saved by avoiding the need to release adhesions if present, and mobilise the bladder to get into the retro-pubic space. However extra time is required to create EP space and access and this is why overall times were not statistically different between groups. It is possible that with increasing experience of EP access for RARP, access times could be shortened. Indeed, two studies have demonstrated reductions in total operative time for eR-

ARP when compared to tRARP^[4,5].

In our study, blood loss was equivalent between patients undergoing eRARP and tRARP. Also, there were no significant differences in transfusion rates between groups. Previous comparisons between tRARP and eRARP have not demonstrated differences in blood loss. Despite using the same discharge criteria for both groups, the length of stay following eRARP in our study was significantly shorter than after tRARP. A drain was used considerably less after eRARP and it is possible that this may have had an influence on the length of stay. However the ability to avoid a drain in the EP approach, as the peritoneal cavity is not breached, is one of the advantages of eRARP.

We found no significant differences in complications between TP and EP approaches to RARP. In a recent comparison by Chung *et al*^[7] of 105 TP-RARP with 155 eRARP's over a two-year period, no significant differences in total operative time or blood loss were demonstrated while console times were significantly shorter with eRARP. Interestingly they found postoperative pain scores were significantly lower in patients undergoing eRARP. Also, TP patients developed more ileus ($\times 7$) as well as a significant increase in the incidence of postoperative hernias. Although TP patients had prolonged ileus in some studies^[4,5], these were smaller studies and we suggest that further large studies might prove the beneficial effect of eRARP in avoiding ileus.

One of the risks of the TP approach to minimally invasive radical prostatectomy (RP), regardless of the use of a robotic system is the possibility of bowel-related complications. In a series of 567 patients undergoing TP-laparoscopic RP by Guillonnet *et al*^[19], 2% of patients had intraperitoneal complications requiring re-intervention. The exact risk of bowel injury during tRARP is difficult to determine and is probably affected by the experience of the robotic surgeon. In a recent study from the Vattikuti Urology Institute, 9 of 3317 patients under-

Table 4 Advantages of transperitoneal and extraperitoneal approaches to robot-assisted radical prostatectomy

Advantages of tRARP	Advantages of eRARP
Larger working space	Reduction in robotic console time
Allows extended pelvic lymphadenectomy	Reduction in bowel related morbidity
Lower incidence of lymphocele	Physiological effects of laparoscopy less marked due to minimal Trendelenburg position
Preferred in patients with mesh hernia repairs	Containment of leak (urine, blood) within retroperic space
	Preferred in patients with pre-existing inguinal hernia (allows mesh repair)
	Preferred in patients with intra-abdominal adhesions (reduces peritoneal viscera interference)

eRARP: Extraperitoneal robot-assisted radical prostatectomy; tRARP: Transperitoneal robot-assisted radical prostatectomy.

going tRARP had a bowel injury requiring enterotomy^[20]. eRARP results in the avoidance of peritoneal entry and bowel contact thereby reducing bowel-related morbidity.

There were no differences in the PSM rates between the different approaches in our study. This finding is corroborated by the existing literature which reveals PSM rates varying from 3.2% to 27.7% after eRARP with no significant differences between eRARP and tRARP. As the working space in eRARP is smaller, there had been concerns that larger prostates may make it more difficult to remove the prostate and therefore contribute to higher PSM rates. So far there is no evidence that larger prostates (> 75 g) result in differences in PSM rates after eRARP^[18].

In our study there was no difference between the two groups for continence at 6 mo with 93% continent in the tRARP group and 94% in the eRARP group. Although, continence rates over a period of 12 mo was available for patients of the TP group, the number of patients of the EP group with 12 mo follow-up data was not adequate for a comparison. In the largest series of eRARP, 96% of 179 patients at 6 mo follow up were continent (without pads)^[12]. In a more recent study by Ploussard *et al.*^[16] of 206 patients, the 12-mo continence rate (no pad use) was 74% whilst it was 98% when patients used a safety pad. In our series, there was no difference in patients who had nerve-sparing technique at 6 mo while 67% and 69% achieved satisfactory erections, with or without oral pharmacotherapy, for eRARP and tRARP respectively. Potency rates after eRARP have been reported between 39% to 70% in previous studies^[12-14].

We confirm the advantage of using the 4th arm in eRARP^[10] and found it particularly helpful during difficult anastomosis in a narrow pelvis by allowing the surgeon to switch to the 4th arm as the working right-sided instrument for suturing instead of the more medial right-sided 3rd arm which can be restrictive in that circumstance. There is also an assumption that the EP approach can sometimes increase the tension on the VUA. This was not borne out in our experience but in cases where there

was perceived difficulty, the VUA was facilitated by applying perineal pressure, and in some cases, freeing the bladder attachments.

In eRARP the peritoneum acts as a natural bowel retractor thereby preventing bowel falling into the operative field. Therefore only 10-15 degrees of Trendelenburg position is necessary. In contrast there are considerable effects of a steep Trendelenburg position on physiology during T-RARP^[21-25]. Patients with cardiovascular or respiratory co-morbidities may not be able to maintain the steep Trendelenburg position and therefore the EP approach which affords a less-steep position may be preferred in such patients. Furthermore, in institutions where long operative times are anticipated, either due to early experience of the surgeon or the requirement for training, the physiological effects of steep Trendelenburg will be more significant and indeed negated with the EP approach. It follows too that the risk of compartment syndrome in the limbs from prolonged operating is also reduced with the EP approach.

Table 4 lists the advantages of both approaches to RARP. One limitation of our study is that some of the improvements in eRARP may have been due to improved performance of robotic surgery as a result of increasing experience. Also, we did not assess functional outcomes at 12 mo although, the primary purpose of this study was a feasibility to determine peri-operative and short-term operative outcomes including PSM rates. In this regard, eRARP performed no worse than tRARP with certain advantages over tRARP as outlined. It is now our standard of care.

In conclusion, our experience and the literature to date demonstrate no differences on the performance of the EP approach for RARP. Console times may be shorter with eRARP. One advantage of eRARP is reduction in bowel-related complications such as ileus. In particular, patients who may benefit from eRARP include those with extensive adhesions, pre-existing inguinal hernias, or unable to withstand a steep Trendelenburg position.

COMMENTS

Background

Robot-assisted radical prostatectomy (RARP) is currently the most common way for removing prostate cancer in the United States. The technique of RARP usually involves an approach which is transperitoneal which predisposes a risk of intraoperative bowel injury or contact of intraperitoneal contents with urine in case of post-operative urine leak. While an extraperitoneal approach is feasible, it is less commonly performed. In this article, the authors study the comparison of an extraperitoneal with transperitoneal approach to RARP.

Research frontiers

This technique of extraperitoneal RARP is feasible and the authors discuss points of technique for its successful adoption.

Innovations and breakthroughs

The authors provide the first analysis of an extraperitoneal approach to RARP from a United Kingdom cancer centre.

Applications

The authors demonstrate equivalent pathological and functional outcomes with the extraperitoneal approach, with added advantages of shorter stay due to less ileus and lower requirement to use a post-operative drain.

Terminology

Extraperitoneal RARP involves entry into the peritoneal cavity, and mobilization of bowel away from the pelvis in order to access the prostate. Transperitoneal RARP replicates principles of open retropubic radical prostatectomy without breaching the peritoneal cavity and no contact with bowels. Not surprisingly, extraperitoneal RARP had lower rates of ileus, lower post-operative stay in hospital and less requirement for post-operative drain.

Peer review

This is a well written paper on a timely topic.

REFERENCES

- 1 **Menon M.** Robot-assisted radical prostatectomy: is the dust settling? *Eur Urol* 2011; **59**: 7-9 [PMID: 21035249 DOI: 10.1016/j.eururo.2010.10.032]
- 2 **Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, Guazzoni G, Guillonnet B, Menon M, Montorsi F, Patel V, Rassweiler J, Van Poppel H.** Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. *Eur Urol* 2009; **55**: 1037-1063 [PMID: 19185977 DOI: 10.1016/j.eururo.2009.01.036]
- 3 **Tewari A, Peabody J, Sarle R, Balakrishnan G, Hemal A, Shrivastava A, Menon M.** Technique of da Vinci robot-assisted anatomic radical prostatectomy. *Urology* 2002; **60**: 569-572 [PMID: 12385908]
- 4 **Atug F, Castle EP, Woods M, Srivastav SK, Thomas R, Davis R.** Transperitoneal versus extraperitoneal robotic-assisted radical prostatectomy: is one better than the other? *Urology* 2006; **68**: 1077-1081 [PMID: 17095060]
- 5 **Madi R, Daignault S, Wood DP.** Extraperitoneal v intraperitoneal robotic prostatectomy: analysis of operative outcomes. *J Endourol* 2007; **21**: 1553-1557 [PMID: 18186697 DOI: 10.1089/end.2007.9872]
- 6 **Capello SA, Boczeko J, Patel HR, Joseph JV.** Randomized comparison of extraperitoneal and transperitoneal access for robot-assisted radical prostatectomy. *J Endourol* 2007; **21**: 1199-1202 [PMID: 17949325]
- 7 **Chung JS, Kim WT, Ham WS, Yu HS, Chae Y, Chung SH, Choi YD.** Comparison of oncological results, functional outcomes, and complications for transperitoneal versus extraperitoneal robot-assisted radical prostatectomy: a single surgeon's experience. *J Endourol* 2011; **25**: 787-792 [PMID: 21114412 DOI: 10.1089/end.2010.0222]
- 8 **Menon M, Tewari A, Peabody J.** Vattikuti Institute prostatectomy: technique. *J Urol* 2003; **169**: 2289-2292 [PMID: 12771773]
- 9 **Stolzenburg JU, Do M, Rabenalt R, Pfeiffer H, Horn L, Truss MC, Jonas U, Dorschner W.** Endoscopic extraperitoneal radical prostatectomy: initial experience after 70 procedures. *J Urol* 2003; **169**: 2066-2071 [PMID: 12771721]
- 10 **Esposito MP, Ilbeigi P, Ahmed M, Lanteri V.** Use of fourth arm in da Vinci robot-assisted extraperitoneal laparoscopic prostatectomy: novel technique. *Urology* 2005; **66**: 649-652 [PMID: 16140096]
- 11 **Dindo D, Demartines N, Clavien PA.** Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542]
- 12 **Joseph JV, Rosenbaum R, Madeb R, Erturk E, Patel HR.** Robotic extraperitoneal radical prostatectomy: an alternative approach. *J Urol* 2006; **175**: 945-950; discussion 951 [PMID: 16469589]
- 13 **Rozet F, Jaffe J, Braud G, Harmon J, Cathelineau X, Barret E, Vallancien G.** A direct comparison of robotic assisted versus pure laparoscopic radical prostatectomy: a single institution experience. *J Urol* 2007; **178**: 478-482 [PMID: 17561160]
- 14 **Ploussard G, Xylinas E, Salomon L, Vordos D, Hoznek A, Abbou CC, De La Taille A.** Robot-assisted extraperitoneal laparoscopic radical prostatectomy: experience in a high-volume laparoscopy reference centre. *BJU Int* 2010; **105**: 1155-1160 [PMID: 19888970 DOI: 10.1111/j.1464-410X.2009.09013.x]
- 15 **Xylinas E, Ploussard G, Salomon L, Paul A, Gillion N, Laet KD, Vordos D, Hoznek A, Abbou CC, de la Taille A.** Intrafascial nerve-sparing radical prostatectomy with a laparoscopic robot-assisted extraperitoneal approach: early oncological and functional results. *J Endourol* 2010; **24**: 577-582 [PMID: 20136397 DOI: 10.1089/end.2009.0069]
- 16 **Ploussard G, Xylinas E, Paul A, Gillion N, Salomon L, Allory Y, Vordos D, Hoznek A, Yiou R, Abbou CC, de la Taille A.** Is robot assistance affecting operating room time compared with pure retroperitoneal laparoscopic radical prostatectomy? *J Endourol* 2009; **23**: 939-943 [PMID: 19473064 DOI: 10.1089/end.2008.0521]
- 17 **Madeb R, Golijanin D, Knopf J, Vicente I, Erturk E, Patel HR, Joseph JV.** Patient-reported validated functional outcome after extraperitoneal robotic-assisted nerve-sparing radical prostatectomy. *JSLs* 2007; **11**: 443-448 [PMID: 18237507]
- 18 **Boczeko J, Erturk E, Golijanin D, Madeb R, Patel H, Joseph JV.** Impact of prostate size in robot-assisted radical prostatectomy. *J Endourol* 2007; **21**: 184-188 [PMID: 17338619]
- 19 **Guillonnet B, Rozet F, Cathelineau X, Lay F, Barret E, Doublet JD, Baumert H, Vallancien G.** Perioperative complications of laparoscopic radical prostatectomy: the Montsouris 3-year experience. *J Urol* 2002; **167**: 51-56 [PMID: 11743274]
- 20 **Agarwal PK, Sammon J, Bhandari A, Dabaja A, Diaz M, Dusik-Fenton S, Satyanarayana R, Simone A, Trinh QD, Baize B, Menon M.** Safety profile of robot-assisted radical prostatectomy: a standardized report of complications in 3317 patients. *Eur Urol* 2011; **59**: 684-698 [PMID: 21324583 DOI: 10.1016/j.eururo.2011.01.045]
- 21 **Kalmar AF, Foubert L, Hendrickx JF, Mottrie A, Absalom A, Mortier EP, Struys MM.** Influence of steep Trendelenburg position and CO(2) pneumoperitoneum on cardiovascular, cerebrovascular, and respiratory homeostasis during robotic prostatectomy. *Br J Anaesth* 2010; **104**: 433-439 [PMID: 20167583 DOI: 10.1093/bja/aeq018]
- 22 **Lestar M, Gunnarsson L, Lagerstrand L, Wiklund P, Odeberg-Wernerman S.** Hemodynamic perturbations during robot-assisted laparoscopic radical prostatectomy in 45° Trendelenburg position. *Anesth Analg* 2011; **113**: 1069-1075 [PMID: 21233502 DOI: 10.1213/ANE.0b013e3182075d1f]
- 23 **Gutt CN, Oniu T, Mehrabi A, Schemmer P, Kashfi A, Kraus T, Büchler MW.** Circulatory and respiratory complications of carbon dioxide insufflation. *Dig Surg* 2004; **21**: 95-105 [PMID: 15010588]
- 24 **Lee JR, Lee PB, Do SH, Jeon YT, Lee JM, Hwang JY, Han SH.** The effect of gynaecological laparoscopic surgery on cerebral oxygenation. *J Int Med Res* 2006; **34**: 531-536 [PMID: 17133783]
- 25 **Stolzenburg JU, Pfeiffer H, Neuhaus J, Sommerfeld M, Dorschner W.** Repair of inguinal hernias using the mesh technique during extraperitoneal pelvic lymph node dissection. *Urol Int* 2001; **67**: 19-23 [PMID: 11464110]

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Potential of metastin and metastin receptor as biomarkers for urological cancers

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Abstract

AIM: To investigate the current state of the research of metastin and metastin receptor in the urological cancer field.

METHODS: For analyzing the value of metastin and metastin receptor as molecular biomarkers for the patients with urological cancer, MEDLINE database searches were performed using these terms: metastin, KISS1, kisspeptin, renal (cell) carcinoma (RCC), kidney cancer or urothelial cancer or bladder cancer or prostate cancer or testicular cancer (tumor). Since the articles were evaluated by the validity of the articles

based on plausibility, credibility, and evidence levels, the articles were graded according to their level of evidence, using the grading system defined by the Oxford Centre for Evidence-based Medicine.

RESULTS: A total of six clinical studies published by individual institutions between 2003 and 2013 were included in this review. The article numbers for each of the evidence levels 2a and 2b were three (50%) and three (50%), respectively. Immunohistochemistry and reverse transcriptase-polymerase chain reaction using tumor tissues were performed to analyze in five articles (83%) and in one article (17%). The value of metastin and/or metastin receptor as molecular biomarkers in clear cell RCC, upper tract urothelial carcinoma, and bladder cancer was evaluated by multivariate analysis. Low expression of metastin receptor in clear cell RCC and low expression of metastin in upper tract urothelial carcinoma were significant risk factors for metastasis, and low metastin expression was an independent prognostic factor in bladder cancer.

CONCLUSION: Metastin and metastin receptor have potential as suitable molecular biomarkers for urological cancers. However, future studies of metastin and metastin receptor should undergo external validation to ensure consistency across different patient series, since individual institutional studies lack generalization.

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Key words: KISS-1; Metastin; Metastin receptor; Metastasis; Renal cell carcinoma; Upper tract urothelial carcinoma; Bladder cancer

Core tip: Metastin and metastin receptor have attracted interest in the field of cancer because of their novelty and potential to inhibit cancer metastasis. Furthermore, they have potential as suitable molecular biomarkers for urological cancers. However, the results of all of

the studies analyzed in this review were retrospectively obtained. Therefore, future studies of metastin and metastin receptor should undergo external validation to ensure consistency across different patient series, since individual institutional studies lack generalization.

Shoji S, Sato H, Tomonaga T, Kim H, Soeda S, Nakano M, Uchida T, Terachi T, Takeya K. Potential of metastin and metastin receptor as biomarkers for urological cancers. *World J Clin Urol* 2013; 2(2): 10-14 Available from: URL: <http://www.wjgnet.com/2219-2816/full/v2/i2/10.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v2.i2.10>

INTRODUCTION

Cancer metastasis is a leading cause of death in cancer patients. Metastasis is a complex, multistage process in which malignant tumor cells spread from the primary tumor to secondary organs. Tumor cells acquire an invasive phenotype to invade the stromal tissue and disrupt the vascular endothelium. Once in the blood, the disseminated tumor cells (DTCs) must survive in the circulating environment and escape physical damage and attack by the immune system. After the tumor cells arrest or adhere to vessel walls, they invade through the capillary wall (extravasation)^[1,2]. Finally, DTCs must adapt to the new microenvironment of the secondary site and start to form micrometastasis or reprogram to a quiescent state, which can last for years^[1,2]. The metastasis suppressor genes are defined by their ability to prevent the development of metastasis by inducing apoptosis or dormancy once the cells have lodged at the secondary site. The proteins encoded by these genes participate in a diverse range of signaling pathways, and in some cases they inhibit not just one but multiple steps in the metastatic cascade^[2]. The *KISS-1* cancer metastasis suppressor gene is located on human chromosome 1q32^[3], and encodes a carboxy-terminal amidated peptide with 54 amino acid residues called metastin (kisspeptin), which was identified as the ligand of a G-protein-coupled receptor, the metastin receptor^[4]. Metastin and metastin receptor inhibit tumor invasion or migration through focal adhesion kinase, paxillin, MAP kinase or RhoA, and have been implicated in melanoma, thyroid cancer, esophageal squamous cell carcinoma, hepatocellular carcinoma, pancreatic carcinoma, breast cancer, ovarian cancer, renal (cell) carcinoma (RCC), upper tract urothelial carcinoma, bladder cancer, and prostate cancer^[5-7]. Furthermore, metastin and metastin receptor were shown to be expressed in the hypothalamus, brain stem, spinal cord, pituitary, ovary, prostate and placenta in normal human tissue, and they play a pivotal role in the control of the hypothalamic pituitary-gonadal axis *via* regulation of gonadotropin-releasing hormone secretion^[8].

The objective of this review article was to investigate the value of metastin and metastin receptor in urological cancers.

MATERIALS AND METHODS

To analyze the clinical study of metastin and/or metastin receptor, MEDLINE database searches were performed using the following terms: metastin, *KISS-1*, kisspeptin, renal (cell) carcinoma or kidney cancer, urothelial carcinoma or bladder cancer or prostate cancer or testicular cancer. Since the articles were evaluated by the validity of the articles based on plausibility, credibility, and evidence levels^[9], the articles were graded according to their level of evidence using the grading system defined by the Oxford Centre for Evidence-based Medicine^[10].

RESULTS

Current state of the literature for metastin and metastin receptor in urological cancer

A total of six articles published between 2003 and 2013 were included in this review. The majority of the data were predominantly obtained *via* nonrandomized, retrospective, but often controlled studies. Immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction analyses of tumor tissues were performed in five articles (83%)^[6,11-14] and in one article (17%)^[15]. Thus, the article numbers for each of the evidence levels^[10] 2a and 2b were three (50%) and three (50%), respectively (Table 1).

Summary of the clinical studies of metastin and metastin receptor in urological cancer

Renal cell carcinoma: Metastin receptor was reported as being more highly expressed in RCCs compared to normal tissue^[11,16]. Chen *et al*^[11] reported that lack of metastin receptor was correlated with rapid progression of clear cell RCC. In an IHC study of 131 patients with clear cell RCC, the absence of metastin receptor was significantly associated with a poor overall or tumor-specific survival in Kaplan-Meier survival analysis ($P < 0.0001$)^[11]. Furthermore, 121 patients with clear cell RCC exhibited positive staining of low to high metastin receptor expression, and the remaining 10 patients with negative immunostaining died because of tumor progression. However, the expression of metastin had no correlation with tumor-specific survival ($P = 0.778$)^[11]. Shoji *et al*^[12] reported that lack of metastin receptor is a predictor of metastasis after radical nephrectomy for pT1 clear cell RCC. IHC analysis of samples from 54 patients with clear cell RCC revealed that the sensitivity, specificity, positive predictive value, and negative predictive value with negative immunostaining of metastin receptor were 85.7%, 97.6%, 46.2%, and 97.6%, respectively^[12]. Metastasis-free survival rates were significantly higher in patients with positive staining (97.6%) than in patients with negative staining (53.8%) ($P < 0.001$)^[12]. In univariate analysis for metastasis-free survival, negative immunostaining of metastin receptor was a significant risk factor for metastasis ($P = 0.001$)^[12]. Furthermore, negative immunostaining of metastin receptor was an independent predictor for metastasis in multivariate analysis ($P = 0.002$)^[12].

Table 1 Summary of metastin and/or metastin receptor literature in the urological cancer field

	Author (yr)	Patients (n)	The methods of the analyses (sample type)	Evidence level ^[14]
Renal cell carcinoma	Chen <i>et al</i> ^[11]	131	IHC (tumor tissue)	2a
	Shoji <i>et al</i> ^[12]	54	IHC (tumor tissue)	2a
Urothelial carcinoma	Takeda <i>et al</i> ^[6]	151	IHC (tumor tissue)	2b
Bladder cancer	Sanchez-Carbayo <i>et al</i> ^[13]	69	IHC (tumor tissue)	2a
	Nicolle <i>et al</i> ^[14]	64	IHC (tumor tissue)	2b
	Cebrian <i>et al</i> ^[15]	205	RT-PCR (tumor tissue)	2b

Level 2a: Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomized controlled trials; Level 2b: Retrospective cohort study or follow-up of untreated control patients in a randomized controlled trial; or derivation of a clinical decision rule or validated on split-sample only. RT-PCR: Reverse transcriptase-polymerase chain reaction; IHC: Immunohistochemical analysis.

Upper urinary tract urothelial carcinoma: Takeda *et al*^[6] reported that 44 patients (29.1%) had distant metastasis during follow-up; 39.1% (27 of 69 patients) with low metastin expression compared with 20.7% (17 of 82 patients) with high metastin expression in an IHC study of 151 patients with upper urinary urothelial carcinoma. Univariate analysis revealed that low metastin expression, pT2 or greater, and positive lymphovascular invasion were significant risk factors for metastasis^[6]. In multivariate analysis, low metastin expression ($P = 0.028$), pT2 or greater ($P = 0.013$), and positive lymphovascular invasion ($P < 0.001$) were independent predictors for metastasis^[6]. The 5-year metastasis-free survival rates were 60.9% for the patients with low expression of metastin and 81.0% for patients with high expression of metastin ($P = 0.012$)^[6].

Bladder cancer: Metastin was reported to be highly expressed in bladder cancers^[13,14]. Sanchez-Carbayo *et al*^[13] reported that metastin expression was significantly associated with stage ($P = 0.031$) and not with tumor grade. In an IHC study of 69 patients with bladder cancer, mean survival time and median survival time of patients with expression lower than 20% was 14.7 and 9.0 mo, respectively^[13]. Furthermore, mean survival time and median survival time of patients with expression higher than 20% was 47.3 and 37.0 mo, respectively^[13]. Nicolle *et al*^[14] reported that metastin receptor was expressed at high levels in bladder cancers compared with normal bladder tissue, and the difference between low- and high-grade groups was significant ($P = 0.03$). However, there was no association between the expression of metastin and grade^[14]. The researchers suggested that the expression of metastin receptor is highly deregulated in invasive and high-grade tumors more often than in superficial and low-grade tumors^[14]. Cebrian *et al*^[15] reported that upregulated metastin expression was found in low-grade and early lesions, compared with high-grade ($P = 0.010$) and invasive bladder tumors ($P = 0.001$). They reported that tumors with metastin methylation had lower transcript expression than unmethylated tumors ($P = 0.037$), and low transcript levels of metastin were significantly associated with increasing stage ($P < 0.0005$) and grade ($P = 0.024$)^[15]. In a series of 205 patients with bladder cancer, high expression of metastin indicated favorable outcomes. Furthermore, multivariate analysis indicated that metastin

expression and tumor stage were independent prognostic factors ($P = 0.001$), with hazard ratios of death of 2.62 (95%CI: 1.49-4.58; $P = 0.001$) and 0.42 (95%CI: 0.20-0.85; $P = 0.017$), respectively^[15].

DISCUSSION

In the current review, the value of metastin and/or metastin receptor as molecular biomarkers in clear cell RCC^[12], upper tract urothelial carcinoma^[6], and bladder cancer^[13] were evaluated in a multivariate analysis of clinical studies. Low expression of metastin receptor in clear cell RCC and low expression of metastin in upper tract urothelial carcinoma were found to be significant risk factors for metastasis^[6,12], and low expression of metastin was an independent prognostic factor in bladder cancer^[15]. However, the results showed that the data in all of the studies were obtained retrospectively. An increasing number of molecular biomarkers have been investigated by numerous teams, with inherent differences regarding population size, demographics, techniques used, and interpretation of results. However, many negative findings have not been published as a result of a lack of enthusiasm by researchers to declare negative findings and because of the reluctance of scientific journals to publish negative reports, thus lending bias to the overall field. Therefore, all studies of molecular biomarker including metastin and metastin receptor should undergo external validation to ensure consistency across different patient series, since individual institutional studies lack generalization^[17].

Metastin receptor was found by Ohtaki *et al*^[4] as a rat orphan receptor (rOT7T175) that was nearly identical to GPR54 during a search for novel G-protein-coupled receptors using a degenerate polymerase chain reaction strategy. To identify the endogenous ligand of a human orphan receptor, these authors established a stable CHO cell line expressing the human counterpart metastin receptor (CHO/h175). Although hOT7T175 has 39.2% amino-acid identity to human galanin receptor GALR2, the cells did not show any response to a panel of known peptides, including galanin and galanin-like peptides. However, human placental extract induced a robust increase in the intracellular calcium ion concentration ($[Ca^{2+}]_i$) in CHO/h175 cells. The amino-terminal sequence obtained for the isolated peptide was identical to

the partial amino-acid sequence (Gly 68 to Ala 88) of the *KISS-1* gene product. This sequence was isolated from human placenta as the endogenous ligand of an orphan G-protein-coupled receptor and was termed “metastin”^[4]. For the function of metastin as a metastasis suppressor protein, excessive formation of focal adhesion and stress fibers by phosphorylation of focal adhesion kinase and paxillin in cells expressing metastin receptor might be one of the mechanisms through which tumor metastasis is inhibited by metastin^[4,18-20]. Takino *et al.*^[21] reported that metastin forms a complex with pro-matrix metalloprotease (MMP) and active MMP-2, while MMP-9, matrix type (MT) 1-MMP, MT3-MMP and MT5-MMP cleave the Gly118-Leu119 peptide bond of both full-length metastin and metastin decapeptide. MMP plays an important role in development and morphogenesis by participating in extracellular matrix re-modeling^[22]. Cancer cells also use MMP for invasion and metastasis. Invading cells are forced to proliferate within an embedded dense three-dimensional matrix composed largely of type I collagen or cross-linked fibrin^[23-26]. Moreover, digestion of the metastin decapeptide by MMP abolished its ligand activity. Takino *et al.*^[21] proposed that: (1) metastin is used as an antimetastatic agent in combination with MMP inhibitor; or (2) MMP-resistant forms of metastin are developed that may also be efficacious.

The mechanisms of metastin and metastin receptor as metastasis suppressor proteins in urological cancers were hypothesized^[6,13,16]. In RCC, metastin induced excessive formation of focal adhesions in RCC cell lines, which are located at the ends of stress fibers in RCC cell lines^[16]. The results of these experiences suggested that metastin regulates focal adhesion and metastasis through the Rho-GTPase route by activating one or several of its members^[16]. In urothelial carcinoma, metastin significantly reduced the invasiveness of a bladder cancer cell line and inhibited the DNA-binding activity of nuclear factor kappa B by blocking its nuclear translocation, leading to a reduction in the expression and activity of MMP-9^[6]. In another study, metastin function was considered as an upstream regulator of E-cadherin^[13]. Furthermore, metastin was aberrantly silenced by CpG island hypermethylation in bladder cancer cell lines^[15]. In bladder cancer, the increased methylation rate together with the loss of transcript expression of *KISS-1* was also found to be associated with increasing tumor stage and poor clinical outcome^[15].

Wang *et al.*^[7] reported the potential of metastin as a molecular biomarker for predicting prognosis in patients with prostate cancer. *In vitro*, metastin inhibited the invasion of a prostate cancer cell line, PC-3M. Furthermore, IHC staining showed weak or lack of metastin expression in prostate cancer tissue^[7]. Although no significant difference in metastin expression was observed between primary and metastatic tissues ($P = 0.3$), loss of metastin expression was positively correlated with clinical stages II / III, IV and metastatic tumors ($P < 0.01$), and metastin expression was significantly lower in metastatic tissues

than in earlier stage primary prostate cancer ($P < 0.01$), indicating that loss of metastin expression correlated with prostate cancer progression^[7]. Moreover, the expression of metastin receptor was weak and only mildly positive in normal prostate tissues, and decreased expression was observed in primary and metastatic tissues^[7].

In conclusion, metastin and metastin receptor have attracted interest in the field of cancer because of their novelty and potential to inhibit cancer metastasis. Furthermore, they have potential as suitable molecular biomarkers for urological cancers. However, the results of all of the studies analyzed in this review were retrospectively obtained. Therefore, future studies of metastin and metastin receptor should undergo external validation to ensure consistency across different patient series, since individual institutional studies lack generalization.

COMMENTS

Background

Cancer metastasis is a leading cause of death in cancer patients. Metastasis is a complex, multistage process in which malignant tumor cells spread from the primary tumor to secondary organs. The *KISS-1* cancer metastasis suppressor gene is located on human chromosome 1q32, and encodes a carboxy-terminal amidated peptide with 54 amino acid residues called metastin (kisspeptin), which was identified as the ligand of a G-protein-coupled receptor, the metastin receptor. Metastin and metastin receptor inhibit tumor invasion or migration through focal adhesion kinase, paxillin, mitogen-activated protein kinase or RhoA, and have been implicated in melanoma, thyroid cancer, esophageal squamous cell carcinoma, hepatocellular carcinoma, pancreatic carcinoma, breast cancer, ovarian cancer, renal (cell) carcinoma (RCC), upper tract urothelial carcinoma, bladder cancer, and prostate cancer.

Research frontiers

In the current review, the value of metastin and/or metastin receptor as molecular biomarkers in clear cell RCC, upper tract urothelial carcinoma, and bladder cancer were evaluated in a multivariate analysis of clinical studies.

Innovations and breakthroughs

Low expression of metastin receptor in clear cell RCC and low expression of metastin in upper tract urothelial carcinoma were found to be significant risk factors for metastasis, and low expression of metastin was an independent prognostic factor in bladder cancer.

Applications

Metastin and metastin receptor have attracted interest in the field of cancer because of their novelty and potential to inhibit cancer metastasis. Furthermore, they have potential as suitable molecular biomarkers for urological cancers.

Peer review

This paper is meaningful because a description of metastin and metastin receptor was clarified as suitable molecular biomarkers for urological cancers.

REFERENCES

- 1 Páez D, Labonte MJ, Bohanes P, Zhang W, Benhanim L, Ning Y, Wakatsuki T, Loupakis F, Lenz HJ. Cancer dormancy: a model of early dissemination and late cancer recurrence. *Clin Cancer Res* 2012; **18**: 645-653 [PMID: 22156560 DOI: 10.1158/1078-0432.CCR-11-2186]
- 2 Horak CE, Lee JH, Marshall JC, Shreeve SM, Steeg PS. The role of metastasis suppressor genes in metastatic dormancy. *APMIS* 2008; **116**: 586-601 [PMID: 18834404 DOI: 10.1111/j.1600-0463.2008.01213.x]
- 3 West A, Vojta PJ, Welch DR, Weissman BE. Chromosome localization and genomic structure of the *KISS-1* metastasis suppressor gene (*KISS1*). *Genomics* 1998; **54**: 145-148 [PMID: 9806840 DOI: 10.1006/geno.1998.5566]
- 4 Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A,

- Kanehashi K, Terao Y, Kumano S, Takatsu Y, Masuda Y, Ishibashi Y, Watanabe T, Asada M, Yamada T, Suenaga M, Kitada C, Usuki S, Kurokawa T, Onda H, Nishimura O, Fujino M. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. *Nature* 2001; **411**: 613-617 [PMID: 11385580 DOI: 10.1038/35079135]
- 5 **Shoji S**, Tang XY, Sato H, Usui Y, Uchida T, Terachi T. Metastin has potential as a suitable biomarker and novel effective therapy for cancer metastasis (Review). *Oncol Lett* 2010; **1**: 783-788 [PMID: 22966379 DOI: 10.3892/ol.00000136]
- 6 **Takeda T**, Kikuchi E, Mikami S, Suzuki E, Matsumoto K, Miyajima A, Okada Y, Oya M. Prognostic role of KiSS-1 and possibility of therapeutic modality of metastin, the final peptide of the KiSS-1 gene, in urothelial carcinoma. *Mol Cancer Ther* 2012; **11**: 853-863 [PMID: 22367780 DOI: 10.1158/1535-7163.MCT-11-0521]
- 7 **Wang H**, Jones J, Turner T, He QP, Hardy S, Grizzle WE, Welch DR, Yates C. Clinical and biological significance of KiSS1 expression in prostate cancer. *Am J Pathol* 2012; **180**: 1170-1178 [PMID: 22226740 DOI: 10.1016/j.ajpath.2011.11.020]
- 8 **Roseweir AK**, Millar RP. The role of kisspeptin in the control of gonadotrophin secretion. *Hum Reprod Update* 2009; **15**: 203-212 [PMID: 19109311 DOI: 10.1093/humupd/dmn058]
- 9 **Hammersley M**. Reading ethnographic research: a critical guide. 2nd ed. New York: Longman, 1998
- 10 **Centre for Evidenced-Based Medicine**. Secondary Centre for Evidenced-Based Medicine, 2009. Available from: URL: <http://www.cebm.net/?o=1025>
- 11 **Chen Y**, Yusenko MV, Kovacs G. Lack of KiSS1R expression is associated with rapid progression of conventional renal cell carcinomas. *J Pathol* 2011; **223**: 46-53 [PMID: 20922711 DOI: 10.1002/path.2764]
- 12 **Shoji S**, Nakano M, Tomonaga T, Kim H, Hanai K, Usui Y, Nagata Y, Miyazawa M, Sato H, Tang XY, Osamura YR, Uchida T, Terachi T, Takeya K. Value of metastin receptor immunohistochemistry in predicting metastasis after radical nephrectomy for pT1 clear cell renal cell carcinoma. *Clin Exp Metastasis* 2013; **30**: 607-614 [PMID: 23277422 DOI: 10.1007/s10585-012-9564-3]
- 13 **Sanchez-Carbayo M**, Capodiceci P, Cordon-Cardo C. Tumor suppressor role of KiSS-1 in bladder cancer: loss of KiSS-1 expression is associated with bladder cancer progression and clinical outcome. *Am J Pathol* 2003; **162**: 609-617 [PMID: 12547718 DOI: 10.1016/S0002-9440(10)63854-0]
- 14 **Nicolle G**, Comperat E, Nicolaiew N, Cancel-Tassin G, Cussenot O. Metastin (KiSS-1) and metastin-coupled receptor (GPR54) expression in transitional cell carcinoma of the bladder. *Ann Oncol* 2007; **18**: 605-607 [PMID: 17164231 DOI: 10.1093/annonc/mdl421]
- 15 **Cebrian V**, Fierro M, Orenes-Piñero E, Grau L, Moya P, Ecke T, Alvarez M, Gil M, Algaba F, Bellmunt J, Cordon-Cardo C, Catto J, López-Beltrán A, Sánchez-Carbayo M. KiSS1 methylation and expression as tumor stratification biomarkers and clinical outcome prognosticators for bladder cancer patients. *Am J Pathol* 2011; **179**: 540-546 [PMID: 21683672 DOI: 10.1016/j.ajpath.2011.05.009]
- 16 **Shoji S**, Tang XY, Umemura S, Itoh J, Takekoshi S, Shima M, Usui Y, Nagata Y, Uchida T, Osamura RY, Terachi T. Metastin inhibits migration and invasion of renal cell carcinoma with overexpression of metastin receptor. *Eur Urol* 2009; **55**: 441-449 [PMID: 18395325 DOI: 10.1016/j.eururo.2008.02.048]
- 17 **Bleeker SE**, Moll HA, Steyerberg EW, Donders AR, Derksen-Lubsen G, Grobbee DE, Moons KG. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol* 2003; **56**: 826-832 [PMID: 14505766]
- 18 **Kotani M**, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, Brézillon S, Tyldesley R, Suarez-Huerta N, Vandeput F, Blanpain C, Schiffmann SN, Vassart G, Parmentier M. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *J Biol Chem* 2001; **276**: 34631-34636 [PMID: 11457843 DOI: 10.1074/jbc.M104847200]
- 19 **Hori A**, Honda S, Asada M, Ohtaki T, Oda K, Watanabe T, Shintani Y, Yamada T, Suenaga M, Kitada C, Onda H, Kurokawa T, Nishimura O, Fujino M. Metastin suppresses the motility and growth of CHO cells transfected with its receptor. *Biochem Biophys Res Commun* 2001; **286**: 958-963 [PMID: 11527393 DOI: 10.1006/bbrc.2001.5470]
- 20 **Yan C**, Wang H, Boyd DD. KiSS-1 represses 92-kDa type IV collagenase expression by down-regulating NF-kappa B binding to the promoter as a consequence of Ikappa Balpha-induced block of p65/p50 nuclear translocation. *J Biol Chem* 2001; **276**: 1164-1172 [PMID: 11060311 DOI: 10.1074/jbc.M008681200]
- 21 **Takino T**, Koshikawa N, Miyamori H, Tanaka M, Sasaki T, Okada Y, Seiki M, Sato H. Cleavage of metastasis suppressor gene product KiSS-1 protein/metastin by matrix metalloproteinases. *Oncogene* 2003; **22**: 4617-4626 [PMID: 12879005 DOI: 10.1038/sj.onc.1206542]
- 22 **Liotta LA**, Thorgeirsson UP, Garbisa S. Role of collagenases in tumor cell invasion. *Cancer Metastasis Rev* 1982; **1**: 277-288 [PMID: 6309368]
- 23 **Fisher KE**, Sacharidou A, Stratman AN, Mayo AM, Fisher SB, Mahan RD, Davis MJ, Davis GE. MT1-MMP- and Cdc42-dependent signaling co-regulate cell invasion and tunnel formation in 3D collagen matrices. *J Cell Sci* 2009; **122**: 4558-4569 [PMID: 19934222 DOI: 10.1242/jcs.050724]
- 24 **Makareeva E**, Han S, Vera JC, Sackett DL, Holmbeck K, Phillips CL, Visse R, Nagase H, Leikin S. Carcinomas contain a matrix metalloproteinase-resistant isoform of type I collagen exerting selective support to invasion. *Cancer Res* 2010; **70**: 4366-4374 [PMID: 20460529 DOI: 10.1158/0008-5472]
- 25 **Maquoi E**, Assent D, Detilleux J, Pequeux C, Foidart JM, Noël A. MT1-MMP protects breast carcinoma cells against type I collagen-induced apoptosis. *Oncogene* 2012; **31**: 480-493 [PMID: 21706048 DOI: 10.1038/ncr.2011.249]
- 26 **Sarkar SK**, Marmer B, Goldberg G, Neuman KC. Single-molecule tracking of collagenase on native type I collagen fibrils reveals degradation mechanism. *Curr Biol* 2012; **22**: 1047-1056 [PMID: 22578418 DOI: 10.1016/j.cub.2012.04.012]

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Volume End





Contents

Four-monthly Volume 2 Number 3 November 24, 2013

- | | | |
|----------------------|----|--|
| EDITORIAL | 15 | Safety of synthetic mesh in pelvic surgery
<i>Osborn DJ, Dmochowski R</i> |
| REVIEW | 20 | Integrated technologies in the post-genomic era for discovery of bladder cancer urinary markers
<i>Eissa S, Matboli M</i> |
| MINIREVIEWS | 32 | Neural regulation of sexual function in men
<i>Azadzo KM, Yang J, Siroky MB</i> |
| | 42 | Professionalism and patient education in urologic surgery
<i>Stimson CJ, Dmochowski RR</i> |
| BRIEF ARTICLE | 46 | How to improve a urology outpatient service? A survey of patient satisfaction
<i>Lukacs S, Tschobotko B, Mukerji G, Vale J, Mazaris E</i> |

Contents

World Journal of Clinical Urology
Volume 2 Number 3 November 24, 2013

APPENDIX I-V Instructions to authors

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Safety of synthetic mesh in pelvic surgery

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Abstract

Mesh in the form of a midurethral sling is an acceptable and generally safe treatment option for stress urinary incontinence in patients who have failed conservative treatment options such as weight loss and pelvic floor muscle training. In patients with pelvic organ prolapse, when outcomes are measured in terms of improvement in postoperative physical exam (anatomic success), many studies have demonstrated that mesh augmented repairs are superior to prolapse repairs not using mesh (native tissue). However, from a symptomatic standpoint, the outcomes of mesh and native tissue repairs are equivalent. This means that even though the physician may see more prolapse on physical exam after native tissue repair, most patients do not perceive this as a problem because their sensation of a vaginal bulge is gone. The vaginal bulge is one of the most common complaints of a patient prior to pelvic organ prolapse repair. Based on interpretation of the available literature, it does not appear that mesh is superior to native tissue repair for anterior (cystocele) and posterior (rectocele) compartment pelvic organ prolapse repair. However, for apical repairs the native tissue repairs are more technically challenging and it appears that suspension of the apex of the vagina with mesh to the sacrum (sacrocolpopexy) may yield better outcomes. Unfortunately, like all mesh surgeries there is a significant risk of mesh complications with sacrocolpopexy. Surgeons should thoroughly counsel their patients about the permanent nature of synthetic mesh and the

potential serious complications related to its use. Mesh augmented pelvic organ prolapse repairs carry unique complications that are not present with native tissue repairs and may not provide better outcomes.

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Key words: Complication; Prolapse; Incontinence; Sling; Prosthesis; Graft

Core tip: Mesh does not provide superior results to native tissue repair and has higher rates of dyspareunia and unique potential serious complications. In general, native tissue repairs are more technically challenging than mesh augmented repair and require the surgeon to have a greater understanding of the anatomy of pelvic organ support.

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In the field of pelvic reconstruction, synthetic mesh is commonly used for the treatment of pelvic organ prolapse and stress urinary incontinence (SUI). The use of mesh during pelvic organ prolapse surgery is not more effective for symptomatic relief than native tissue repair and has unique potentially serious complications. Though mesh for stress incontinence also has unique complications, these surgeries appear to be less morbid and equally efficacious to traditional surgeries for stress urinary incontinence.

The most common complications of mesh surgery are mesh exposure and dyspareunia, and the most serious complications are perforation of organs such as the bladder, urethra and bowel. In 2010 the International Continence Society and International Urogynecological Association released a report intended to clarify and standardize the terminology related to complications from insertion of synthetic and biological materials in female

pelvic floor surgery^[1]. According to this report, synthetic mesh is termed a prosthesis and a biological implant is termed a graft. Mesh located in the bladder or urethra is termed a perforation and extrusion of mesh through the vagina or skin is termed exposure.

Research has shown that pelvic organ prolapse affects 2.9% of women over the age of 20 and though only 2% of women are symptomatic, women have an approximately 30%-50% lifetime risk of developing pelvic organ prolapse^[2,3]. The current prevalence of urinary incontinence in adult women in the United States is much higher than pelvic organ prolapse and is estimated to be between 47% and 51% and increasing^[4,5]. Not surprisingly, the rates of surgery for urinary incontinence and pelvic organ prolapse are also increasing^[6,7].

Prior to 1998, the most common surgeries for stress urinary incontinence were needle suspensions, autologous pubovaginal slings and collagen injections^[8]. In 1998, the Food and Drug Administration (FDA) approved the first midurethral sling for stress urinary incontinence. Then, over the next 10 years the utilization of the midurethral sling increased almost 30 fold and multiple studies have shown its benefit over traditional surgeries for stress urinary incontinence not utilizing mesh^[8,9]. However, as the utilization of synthetic mesh increased, problems with mesh exposure and perforation started to become apparent^[10].

With interventions such as pelvic floor muscle training, weight loss and pessaries, the initial treatment of symptomatic pelvic organ prolapse should be conservative. When conservative measures fail, the ideal pelvic organ prolapse procedure would restore the body's normal support structure while returning the prolapsed organ to its normal anatomic position with minimal side effects^[11]. Prior to 2001, the majority of pelvic surgeons sought to achieve this ideal using native tissue repairs. However, following successful outcomes for mesh for SUI, researchers started looking at mesh to help with pelvic organ prolapse. Starting in 2001, multiple studies were published showing the benefits of mesh augmented repairs for pelvic organ prolapse^[12,13]. From 2001 to 2008 mesh augmented pelvic organ prolapse repairs were commonly performed with little discussion regarding the safety of mesh. However, in October 2008, the United States FDA released a public health notification (PHN) alerting the public about potential "rare" complications and problems related to transvaginal mesh for pelvic organ prolapse^[14]. In 2011, the FDA modified this alert by removing the term "rare" and stating that surgical mesh does not conclusively improve outcomes over traditional non-mesh or native tissue repair^[15]. Paradoxically, after the initial PHN the rate of vaginal mesh implantation increased^[16].

The FDA became aware of problems related to synthetic mesh because of information contained in the manufacturer and user facility device experience (MAUDE) database. MAUDE is a database that houses medical device reports (MDRs) of adverse events submitted to the FDA by manufacturers and healthcare professionals. According to MAUDE data, in regards to

midurethral slings, from 2008 to 2010 there were 1371 voluntary and involuntary self reported medical device reports of complications^[17]. Bladder and urethra perforation were some of the most common reported MDR's. Similarly high, over the same time period, there were 1503 MDRs for synthetic mesh used during pelvic organ prolapse surgery. In July 2011, the FDA released a statement that summarizes their opinion entitled "Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse"^[17].

Today, polypropylene is the most commonly used type of synthetic mesh for pelvic surgery. However, surgeons have been using mesh during pelvic surgery for over 50 years. In 1955, Moore and colleagues reported their experience with a screen made from the metallic element tantalum^[18]. They found a 100% anatomic cure rate with an unfortunate 40% graft exposure rate. More contemporary studies have shown a 75% to 91% cure rate and a 0% to 5.6% mesh exposure rate^[12,19,20].

Polypropylene has become the most commonly implanted material because it is a monofilament with minimal tissue reactivity that can be formatted into mesh with large sized pores. The standard system for classifying mesh was proposed by Amid^[21] in 1997 and emphasizes pore size and filament type. Amid classified mesh into four different categories. The ideal mesh type according to Amid is type 1 mesh. Type 1 mesh is made of a monofilament mesh loosely woven with large pores. Mesh is considered to have large pores if the open space between the fibers is greater than 75 μm . This large pore size promotes flexibility, angiogenesis and macrophage penetration^[22,23]. Multifilament material can theoretically harbor and promote the growth of bacteria and result in more infection and inflammation. This problem was seen in a 2001 study by Falconer *et al*^[24] that showed significantly more histological evidence of inflammation in patients with mersilene suburethral slings compared to patients with polypropylene. In addition, it seems that mesh with smaller pore sizes such as Gore-tex do not become incorporated into tissue and have a high rate of perforation or exposure^[25,26].

The management of mesh exposure is within the scope of practice of most pelvic surgeons, however, mesh perforation may require tertiary referral. There are several studies that propose observing any exposure of mesh less than 1 cm because the area may heal spontaneously with mixed results^[27-30]. Depending on the preference of the surgeon and the size of the exposure, the next step for intervention may be operative management. Operative management involves excision of the exposed mesh, thorough irrigation with antibiotic solution and closure of vaginal flaps. The addition of topical antibiotics and estrogen may theoretically improve tissue quality prior to surgical intervention. In a series of 48 patients who underwent partial mesh excision, only 6 had persistent exposure^[29].

Perforation of mesh slings into the urethra or bladder should be managed with more extensive mesh excision

to the level of the pubic bone or ischiopubic rami. This type of excision leaves behind the arms of the mesh that tunnel into the retropubic space or obturator fossa. It is typically not necessary to enter these spaces because the mesh at this location is no longer under tension and is far from the urethra or bladder. The authors prefer an inverted-U incision because this allows for a vaginal epithelial flap that avoids overlapping suture lines and should decrease the risk of a fistula. In general, reconstruction should involve non-overlapping suture lines and interposition of tissue such as a labial fat pad, greater omentum or autologous fascial sling. In rare cases of mesh complications from slings, when non-operative therapy has failed, such as extreme pain or infection it may be necessary to attempt a complete mesh excision from both sides of the bone. In the case of retropubic slings this involves an abdominal and vaginal incision and in the case of the trans-obturator slings this involves a medial thigh and vaginal incision.

If mesh placed to augment pelvic organ prolapse repair perforates into the bladder or urethra, this is usually best managed with a midline incision and raising flaps of vaginal epithelium. Similar to mesh perforation from slings, prolapse mesh perforation should also be managed with non-overlapping suture lines and interposition of another tissue. Unlike slings, it is often difficult to remove all of the prolapse repair mesh to the level of the pubic bone and ischiopubic rami. The authors attempt to remove the mesh as far away from the bladder or urethra closure as possible and try to avoid tension on any suture lines.

Ranging from 2.7% to 5.7% in the literature, vaginal exposure rates are relatively high with midurethral slings^[31,32]. The rate of bladder or urethral perforation with a trocar at the time of surgery is as high as 5.3% and 5.4%^[32,33]. Though widely reported, the rate of mesh perforation into the bladder or urethra during midurethral sling surgery is unclear and ranges from 0.6% to 0.75% in the literature^[34,35]. Ranging from 3% to 20%, dyspareunia and worsened sexual function are common after midurethral sling surgery^[36,37]. The traditional non-mesh repairs for stress urinary incontinence are autologous pubovaginal slings and burch colposuspension. These two procedures are similarly efficacious to midurethral slings, but, have complication rates requiring surgical intervention as high as 13% and 20% in randomized clinical trials^[38]. The rates of dyspareunia and sexual dysfunction after a pubovaginal sling and bladder neck suspension in the literature are lower than midurethral slings^[39,40]. In another multicenter randomized clinical trial comparing bladder neck suspension to midurethral slings, the former was found to have more postoperative complications and longer recovery with equal efficacy^[9].

Mesh exposure rates of synthetic mesh for pelvic organ prolapse range from 0% to 16.9%^[12,19,41,42]. Dyspareunia rates after prolapse repair with mesh are as high as 20% with anterior mesh and 63% with posterior mesh^[43]. However, a thorough Cochrane review of surgical management of pelvic organ prolapse from 2011 found that

mesh repair and native tissue repair had similar rates of dyspareunia^[44]. Mesh perforation rates are as high as 0.7%^[45]. *De novo* SUI may be more common after mesh POP repair than native tissue repair^[46]. Due to concerns about dyspareunia and efficacy, some surgeons advise against the use of synthetic mesh in the posterior compartment and mesh augmentation does not improve outcomes^[47]. The lack of benefit from graft use in the posterior compartment might be due to the durable nature of the fascia in the posterior compartment. Abdominal sacral colpopexy with mesh has a lower complication rate than transvaginal apical support surgeries utilizing mesh^[48].

When comparing the outcomes of native tissue repair and mesh-augmented repairs using anatomical results only, mesh surgeries have better outcomes^[12,49]. However, when focusing on patient reported symptomatic outcomes, the difference between native tissue repair and the use of mesh is minimal^[13,28,42]. An analysis of the data from the CARE trial in 2009 found that the absence of vaginal bulge symptoms had the strongest correlation with patient perception of treatment success^[50].

It does not appear that transvaginal mesh for pelvic organ prolapse provides more symptomatic benefit than native tissue repair and has common, unique potentially serious complications that are not present with native tissue repair. Unlike mesh for pelvic organ prolapse, mesh with midurethral slings has similar efficacy with less overall morbidity than needle suspensions and pubovaginal slings for SUI. The current perception of many patients is that mesh for vaginal prolapse is a safety concern. Even if future literature demonstrates the safety of transvaginal mesh, some patients may still be reluctant to have foreign material placed in their bodies. Therefore, physicians may need to return to a time when native tissue repairs were more common. Lastly, a reevaluation of how we define a successful outcome may be necessary as many surgeons move away from the use of mesh for pelvic organ prolapse.

REFERENCES

- 1 **Haylen BT**, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, Dwyer PL, Faton B, Kocjancic E, Lee J, Maher C, Petri E, Rizk DE, Sand PK, Schaer GN, Webb R; International Urogynecological Association; International Continence Society; Joint IUGA/ICS Working Group on Complications Terminology. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. *Neurourol Urodyn* 2011; **30**: 2-12 [PMID: 21181958 DOI: 10.1002/nau.21036]
- 2 **Samuelsson EC**, Victor FT, Tibblin G, Svärdsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. *Am J Obstet Gynecol* 1999; **180**: 299-305 [PMID: 9988790 DOI: 10.1016/S0002-9378(99)70203-6]
- 3 **Nygaard I**, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, Spino C, Whitehead WE, Wu J, Brody DJ. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA* 2008; **300**: 1311-1316 [PMID: 18799443 DOI: 10.1001/jama.300.11.1311]

- 4 **Markland AD**, Richter HE, Fwu CW, Eggers P, Kusek JW. Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. *J Urol* 2011; **186**: 589-593 [PMID: 21684555 DOI: 10.1016/j.juro.2011.03.114]
- 5 **Waetjen LE**, Liao S, Johnson WO, Sampsel CM, Sternfield B, Harlow SD, Gold EB. Factors associated with prevalent and incident urinary incontinence in a cohort of midlife women: a longitudinal analysis of data: study of women's health across the nation. *Am J Epidemiol* 2007; **165**: 309-318 [PMID: 17132698]
- 6 **Rogo-Gupta L**, Litwin MS, Saigal CS, Anger JT. Trends in the surgical management of stress urinary incontinence among female Medicare beneficiaries, 2002-2007. *Urology* 2013; **82**: 38-41 [PMID: 23706251 DOI: 10.1016/j.urology.2012.10.087]
- 7 **Wu JM**, Kawasaki A, Hundley AF, Dieter AA, Myers ER, Sung VW. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. *Am J Obstet Gynecol* 2011; **205**: 230.e1-230.e5 [PMID: 21600549 DOI: 10.1016/j.ajog.2011.03.046]
- 8 **Jonsson Funk M**, Levin PJ, Wu JM. Trends in the surgical management of stress urinary incontinence. *Obstet Gynecol* 2012; **119**: 845-851 [PMID: 22433349 DOI: 10.1097/AOG.0b013e31824b2e3e]
- 9 **Ward K**, Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ* 2002; **325**: 67 [PMID: 12114234 DOI: 10.1136/bmj.325.7355.67]
- 10 **Novara G**, Galfano A, Boscolo-Berto R, Secco S, Cavalleri S, Ficarra V, Artibani W. Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. *Eur Urol* 2008; **53**: 288-308 [PMID: 18031923 DOI: 10.1016/j.eururo.2007.10.073]
- 11 **Subak LL**, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. *J Urol* 2009; **182**: S2-S7 [PMID: 19846133 DOI: 10.1016/j.juro.2009.08.071]
- 12 **Sand PK**, Koduri S, Lobel RW, Winkler HA, Tomezsko J, Culligan PJ, Goldberg R. Prospective randomized trial of polyglactin 910 mesh to prevent recurrence of cystoceles and rectoceles. *Am J Obstet Gynecol* 2001; **184**: 1357-1362; discussion 1362-1364 [PMID: 11408853 DOI: 10.1067/mob.2001.115118]
- 13 **Weber AM**, Walters MD, Piedmonte MR, Ballard LA. Anterior colporrhaphy: a randomized trial of three surgical techniques. *Am J Obstet Gynecol* 2001; **185**: 1299-1304; discussion 1304-1306 [PMID: 11744900 DOI: 10.1067/mob.2001.119081]
- 14 **FDA Public Health Notification**. Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence. Food and Drug Administration. Available from: URL: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm>, accessed June 21, 2013
- 15 **FDA Safety Communication**. UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse. Food and Drug Administration. Available from: URL: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>, accessed June 21, 2013
- 16 **Reynolds WS**, Gold KP, Ni S, Kaufman MR, Dmochowski RR, Penson DF. Immediate effects of the initial FDA notification on the use of surgical mesh for pelvic organ prolapse surgery in medicare beneficiaries. *Neurourol Urodyn* 2013; **32**: 330-335 [PMID: 23001605 DOI: 10.1002/nau.22318]
- 17 **US Food and Drug Administration : Center for Devices and Radiological Health**. Urogynecologic surgical mesh: update on the safety and effectiveness of transvaginal placement for pelvic organ prolapse. July 2011. Available from: URL: <http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf>
- 18 **Moore J**, Armstrong JT, Willis SH. The use of tantalum mesh in cystocele with critical report of ten cases. *Am J Obstet Gynecol* 1955; **69**: 1127-1135 [PMID: 14361539]
- 19 **Carey M**, Higgs P, Goh J, Lim J, Leong A, Krause H, Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. *BJOG* 2009; **116**: 1380-1386 [PMID: 19583714 DOI: 10.1111/j.1471-0528.2009.02254.x]
- 20 **Groutz A**, Chaikin DC, Theusen E, Blaivas JG. Use of cadaveric solvent-dehydrated fascia lata for cystocele repair--preliminary results. *Urology* 2001; **58**: 179-183 [PMID: 11489693 DOI: 10.1016/S0090-4295(01)01177-3]
- 21 **Amid PK**. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997. Available from: URL: <http://link.springer.com/article/10.1007/BF02426382>
- 22 **Dwyer PL**. Evolution of biological and synthetic grafts in reconstructive pelvic surgery. *Int Urogynecol J Pelvic Floor Dysfunct* 2006; **17** Suppl 1: S10-S15 [PMID: 16738742 DOI: 10.1007/s00192-006-0103-0]
- 23 **Deprest J**, Zheng F, Konstantinovic M, Spelzini F, Claerhout F, Steensma A, Ozog Y, De Ridder D. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. *Int Urogynecol J Pelvic Floor Dysfunct* 2006; **17** Suppl 1: S16-S25 [PMID: 16738743 DOI: 10.1007/s00192-006-0101-2]
- 24 **Falconer C**, Söderberg M, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. *Int Urogynecol J Pelvic Floor Dysfunct* 2001; **12** Suppl 2: S19-S23 [PMID: 11450975 DOI: 10.1007/s001920170007]
- 25 **Thompson PK**, Pugmire JE and Sangi-Hagheykar H. Abdominal Sacrocolpopexy Utilizing Gore-Tex in Genital Prolapse. Unresolved Issues. *Female Pelvic Med Reconstr Surg* 2004; **10**
- 26 **Cundiff GW**, Varner E, Visco AG, Zyczynski HM, Nager CW, Norton PA, Schaffer J, Brown MB, Brubaker L. Risk factors for mesh/suture erosion following sacral colpopexy. *Am J Obstet Gynecol* 2008; **199**: 688.e1-688.e5 [PMID: 18976976 DOI: 10.1016/j.ajog.2008.07.029]
- 27 **Huang KH**, Kung FT, Liang HM, Chang SY. Management of polypropylene mesh erosion after intravaginal midurethral sling operation for female stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 2005; **16**: 437-440 [PMID: 15654499 DOI: 10.1007/s00192-004-1275-0]
- 28 **Nieminen K**, Hiltunen R, Takala T, Heiskanen E, Merikari M, Niemi K, Heinonen PK. Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up. *Am J Obstet Gynecol* 2010; **203**: 235.e1-235.e8 [PMID: 20494332 DOI: 10.1007/s00192-013-2092-0]
- 29 **Tijdink MM**, Vierhout ME, Heesakkers JP, Withagen MI. Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh. *Int Urogynecol J* 2011; **22**: 1395-1404 [PMID: 21681595 DOI: 10.1007/s00192-011-1476-2]
- 30 **Kobashi KC**, Govier FE. Management of vaginal erosion of polypropylene mesh slings. *J Urol* 2003; **169**: 2242-2243 [PMID: 12771759 DOI: 10.1097/01.ju.0000060119.43064.f6]
- 31 **Paraiso MF**, Walters MD, Karra MM, Barber MD. Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial. *Obstet Gynecol* 2004; **104**: 1249-1258 [PMID: 15572485 DOI: 10.1097/01.AOG.0000146290.10472.b3]
- 32 **Richter HE**, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, Kraus SR, Chai TC, Lemack GE, Dandreo KJ, Varner RE, Menefee S, Ghetti C, Brubaker L, Nygaard I, Khandwala S, Rozanski TA, Johnson H, Schaffer J, Stoddard AM, Holley RL, Nager CW, Moalli P, Mueller E, Arisco AM, Corton M, Tennstedt S, Chang TD, Gormley EA, Litman HJ. Retropubic

- versus transobturator midurethral slings for stress incontinence. *N Engl J Med* 2010; **362**: 2066-2076 [PMID: 20479459 DOI: 10.1056/NEJMoa0912658]
- 33 **Pushkar DY**, Godunov BN, Gvozdev M, Kasyan GR. Complications of mid-urethral slings for treatment of stress urinary incontinence. *Int J Gynaecol Obstet* 2011; **113**: 54-57 [PMID: 21315346 DOI: 10.1016/j.ijgo.2010.10.024]
 - 34 **Kuuvva N**, Nilsson CG. A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure. *Acta Obstet Gynecol Scand* 2002; **81**: 72-77 [PMID: 11942891 DOI: 10.1034/j.1600-0412.2002.810113.x]
 - 35 **Hammad FT**, Kennedy-Smith A, Robinson RG. Erosions and urinary retention following polypropylene synthetic sling: Australasian survey. *Eur Urol* 2005; **47**: 641-646; discussion 646-647 [PMID: 15826756 DOI: 10.1016/j.eururo.2004.11.019]
 - 36 **Stav K**, Dwyer PL, Rosamilia A, Schierlitz L, Lim YN, Lee J. Risk factors of treatment failure of midurethral sling procedures for women with urinary stress incontinence. *Int Urogynecol J* 2010; **21**: 149-155 [PMID: 19855914 DOI: 10.1007/s00192-009-1020-9]
 - 37 **Mazouni C**, Karsenty G, Bretelle F, Bladou F, Gamerre M, Serment G. Urinary complications and sexual function after the tension-free vaginal tape procedure. *Acta Obstet Gynecol Scand* 2004; **83**: 955-961 [PMID: 15453893 DOI: 10.1111/j.0001-6349.2004.00524.x]
 - 38 **Albo ME**, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med* 2007; **356**: 2143-2155 [PMID: 17517855]
 - 39 **Wright EJ**, Iselin CE, Carr LK, Webster GD. Pubovaginal sling using cadaveric allograft fascia for the treatment of intrinsic sphincter deficiency. *J Urol* 1998; **160**: 759-762 [PMID: 9720541 DOI: 10.1016/S0022-5347(01)62779-4]
 - 40 **Demirci F**, Yucel O. Comparison of pubovaginal sling and burch colposuspension procedures in type I/II genuine stress incontinence. *Arch Gynecol Obstet* 2001; **265**: 190-194 [PMID: 11789743 DOI: 10.1007/s004040000159]
 - 41 **Fatton B**, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift technique)-a case series multicentric study. *Int Urogynecol J Pelvic Floor Dysfunct* 2007; **18**: 743-752 [PMID: 17131170 DOI: 10.1007/s00192-006-0234-3]
 - 42 **Withagen MI**, Milani AL, den Boon J, Vervest HA, Vierhout ME. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. *Obstet Gynecol* 2011; **117**: 242-250 [PMID: 21252735 DOI: 10.1097/AOG.0b013e318203e6a5]
 - 43 **Milani R**, Salvatore S, Soligo M, Pifarotti P, Meschia M, Cortese M. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. *BJOG* 2005; **112**: 107-111 [PMID: 15663408 DOI: 10.1111/j.1471-0528.2004.00332.x]
 - 44 **Maher CM**, Feiner B, Baessler K, Glazener CM. Surgical management of pelvic organ prolapse in women: the updated summary version Cochrane review. *Int Urogynecol J* 2011; **22**: 1445-1457 [PMID: 21927941 DOI: 10.1007/s00192-011-1542-9]
 - 45 **Caquant F**, Collinet P, Debodinance P, Berrocal J, Garbin O, Rosenthal C, Clave H, Villet R, Jacquetin B, Cosson M. Safety of Trans Vaginal Mesh procedure: retrospective study of 684 patients. *J Obstet Gynaecol Res* 2008; **34**: 449-456 [PMID: 18937698 DOI: 10.1111/j.1447-0756.2008.00820.x]
 - 46 **Altman D**, Väyrynen T, Engh ME, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic organ prolapse. *N Engl J Med* 2011; **364**: 1826-1836 [PMID: 21561348 DOI: 10.1056/NEJMoa1009521]
 - 47 **Grimes CL**, Tan-Kim J, Whitcomb EL, Lukacz ES, Menefee SA. Long-term outcomes after native tissue vs. biological graft-augmented repair in the posterior compartment. *Int Urogynecol J* 2012; **23**: 597-604 [PMID: 22113260 DOI: 10.1007/s00192-011-1607-9]
 - 48 **Maher C**, Baessler K, Glazener CM, Adams EJ, Hagen S. Surgical management of pelvic organ prolapse in women: a short version Cochrane review. *Neurourol Urodyn* 2008; **27**: 3-12 [PMID: 18092333 DOI: 10.1002/nau.20542]
 - 49 **Nguyen JN**, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. *Obstet Gynecol* 2008; **111**: 891-898 [PMID: 18378748 DOI: 10.1097/AOG.0b013e31816a2489]
 - 50 **Barber MD**, Brubaker L, Nygaard I, Wheeler TL, Schaffer J, Chen Z, Spino C. Defining success after surgery for pelvic organ prolapse. *Obstet Gynecol* 2009; **114**: 600-609 [PMID: 19701041 DOI: 10.1097/AOG.0b013e3181b2b1ae]

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Integrated technologies in the post-genomic era for discovery of bladder cancer urinary markers

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Abstract

The incidence of bladder cancer (BC) continues to rise with high recurrence and mortality rate, especially in the past three decades. The development of accurate and successful BC treatment relies mainly on early diagnosis. BC is a heterogeneous disease reflected by the presence of many potential biomarkers associated with different disease phenotypes. Nowadays, cystoscopy and urinary cytology are considered the gold standard diagnostic tools for BC. There are many limitations to cystoscopy including being invasive, labor-intensive and carcinoma *in situ* of the bladder may easily be missed. Urinary cytology is still a noninvasive technique with high accuracy in high-grade BC with a median sensitivity of 35%. Furthermore, the need for a sensitive, specific, non invasive, easily accessible BC biomarker is a major clinical need. The field of urinary BC biomarkers discovery is still a rapidly evolving discipline in which more recent technologies are evaluated and often optimized if they are not clinically significant to the urologists. Most of the current strategies for BC urinary biomarker detection depend on integration of information gleaned from the fields of genomics, transcriptomics, proteomics, epigenetics, metabolomics and bionano-

technology. Effort is currently being made to identify the most potentially beneficial urinary biomarkers. The purpose of this review is to summarize and explore the efficacy of gathering the information revealed from the cooperation of different omic strategies that paves the way towards various urinary markers discovery for screening, diagnosis and prognosis of human BC.

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Key words: Bladder cancer; Urinary biomarkers; Genomics; Proteomics; Bionanotechnology; Metabolomics; Transcriptomics; Epigenetics

Core tip: Capturing information from in silico data, proteomic data, gene expression data and bionanotechnology data outlines a promising approach to discover significant urinary biomarkers whose activity patterns are discriminative of bladder cancer *vs* control.

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INTRODUCTION

It is estimated that urinary bladder cancer (BC) is the sixth most common cancer worldwide, with approximately 382660 new cases of BC each year^[1,2].

Although the main symptom of BC is hematuria, no symptoms are found in an early stage. About 70% to 80% of patients with newly diagnosed BC present with early stage BC (*i.e.*, stage Ta, Tis, or T1) and low-grade neoplasms that are associated with an excellent prognosis. However, these tumors have a 30% to 70% recur-

rence rate and a strong tendency to progress to invasive cancers in 10% to 30% of patients, with increased risk of metastasis and subsequent mortality. So, early detection of BC is urgently needed to improve prognosis and long-term survival^[3].

Nowadays, the standard of care for BC diagnosis and follow-up is through the combination of cystoscopic examination, cytology and histology^[4]. However, these methods have a significant financial cost and poor sensitivity for low-grade, well-differentiated lesions. They are also highly subjective investigations and provide little about the molecular characteristics of cancers^[5]. Recently, numerous urinary markers have been under study in order to reduce the cost and the frequency of cystoscopies or replace them by non-invasive tests. An ideal test for the detection of bladder tumors should have high sensitivity and specificity; moreover, it is necessary to be objective, accurate, rapid and easy to administer^[6].

Urine is an ideal biological fluid representing a gold mine suitable for clinical analysis due to simple, economic and non-invasive collection with large quantities of samples available. Therefore, it has been proposed as a substitute to blood collection as a diagnostic tool or at least as a screening test^[7]. Nevertheless, the very low abundance of many candidate targets in urine and the presence of different interfering substances have impeded the development of novel urinary biomarkers that may be clinically useful for BC diagnosis^[8].

Integration of different biomolecular signature data set through capturing information from *in silico* data with multiple omic technologies for genomics, gene expression (transcriptomics) and proteomics is increasingly important to maximize value in biomarker discovery, validation and utilization for early diagnosis or prognosis of cancer^[9]. Each one of these technologies provides a snapshot of cell function. However, dynamic understanding of disease processes really needs the integration of all these modalities to the greatest possible extent^[10].

LITERATURE SELECTION

The published studies that discussed BC biomarkers were identified by searching PubMed for studies that were published between January 2000 and September 2013. The search terms that were used were “bladder”, “carcinoma” or “cancer” and “biomarkers” or “bioinformatics” and “genomic”, “proteomic” or “epigenetic”, or “nanoparticles” without restrictions. In addition, the reference lists of retrieved papers and recent reviews were also examined.

STUDY SELECTION

Any study that matched the following criteria was included: (1) a case-control study design; (2) an association between BC and biomarkers in humans; and (3) BC confirmed by the accepted diagnostic criteria. To evaluate the eligibility of all the studies retrieved from the

databases on the basis of the predetermined selection criteria, two independent investigators were used. Disagreements were resolved by discussion.

BIOINFORMATICS AND BC URINARY BIOMARKERS

BC subtypes and biomarkers have been identified using technologies that combine clustering algorithms and visualization tools into web-based bioinformatic databases and those that analyze high-throughput gene expression data^[11]. Common analytical tools include the following: Atlas of Genetics and Cytogenetics in Oncology and Hematology (<http://atlasgeneticsoncology.org/>) is a database that deals with chromosome abnormalities in cancer and genes involved in cancer. This database is provided by experts in cytogenetics, molecular biology with clinicians in oncology and in hematology, and pathologists^[12]; Catalogue of Somatic Mutations in Cancer COSMIC database (<http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>) stores and supplies information about somatic mutations in cancer. This database collects information about publications, mutations and samples; Human protein atlas database (<http://www.proteinatlas.org/>) displays protein expression profiles based on immunohistochemistry for a large number of human tissues, cancers and cell lines, subcellular localization in three cell lines and transcript expression levels in three cell lines; OmniBiomarker (<http://omnibiomarker.bme.gatech.edu/>) is a web-based bioinformatics tool for developing biomarkers in oncology to anticipate the clinical outcome of promising biomolecules as a biomarker; The NCI's Cancer Biomedical Informatics Grid® (caBIG®) initiative is the most widely used tool at every stage of cancer that facilitates biomarker discovery beginning from selection of target groups until clinical validation step. At the same time, caBIG® also provides information related to basic research free of charge; Gene Expression Profile Analysis Suite or GEPAS (<http://www.gepas.org>) for microarray analysis; Array Express (<http://www.ebi.ac.uk/microarray-as/ac/ca>) and the Cancer Biomedical Informatics Grid (caBIG) (<https://cabig.nci.nih.gov>) are used for storage and management of expression data; Biomedical knowledge discovery server, BioGraph (<http://www.biograph.be/about/welcome>), is a data integration platform for the purpose and discovery of biomedical information^[13]. The database offers prioritizations of supposed disease genes, supported by functional hypotheses. BioGraph can retrospectively validate recently discovered disease genes and identify susceptible genes, surpassing recent technologies, without requiring previous domain knowledge. Briefly, such computational methods integrating multi-omics data will be very precious to select molecular targets, biomarker candidates and to translate them into biologically meaningful hypotheses.

GENOMICS IN BC URINARY BIOMARKERS

Genomics is a discipline that applies recombinant DNA,

DNA sequencing methods and bioinformatics to analyze the function and structure of the whole set of DNA within the cell of an organism, allowing increase of the width of the field with the number of newer markers identification^[14,15]. Applying technologies such as gene microarray that can analyze huge number of DNA sequences from many patients very quickly, the field of genomics has identified thousands of genetic duplications and aberrations that may take part in bladder carcinogenesis^[16]. BC, with tumor cells being bathed in urine, perhaps provides the best potential use of DNA markers. However, such markers will not become clinically significant until easier detection methods are found, marker standardization occurs and more clear and specific applications for primary diagnosis compared to recurrent disease are performed^[17]. Some of the common genetic markers including *FGFR-3* mutations, *p53* and retinoblastoma genes have elucidated several molecular pathways in BC development^[18,19].

Larré *et al.*^[20] designed a comparative genome hybridization (CGH) chip, including loci proposed to be associated with BC for the assessment of bladder tissues. The CGH data were used to develop a diagnostic test that could be performed on urothelial cell pellets. This test had an overall diagnostic accuracy of 91% in 44 samples. The detection of specific urothelial gene mutations is also applicable to disease evaluation^[20].

Kucukgergin *et al.*^[21] assessed stromal cell derived factor 1 (*SDF-1*) 3'A, monocyte chemoattractant protein-1 (*MCP-1*) A2518G, and chemokine receptors *CCR2A*, *CCR5* Δ32 and *CXCR4* gene polymorphisms by PCR and PCR-restriction fragment length polymorphism (RFLP) methods in 142 histologically confirmed BC patients and 197 controls in a Turkish population. Their results suggest that the genetic variants of *SDF-1* 3'A, *CCR2A* V64I and *CCR5* Δ32 gene may contribute to muscle invasive BC in a Turkish population^[21].

Al-Kashwan *et al.*^[22] analyzed TP53 alterations by PCR-single strand conformational polymorphism analysis and DNA sequencing in twenty-nine bladder carcinomas. They found infrequent TP53 mutations, especially insertion A and 196 hotspot codons in 37.9% of the cases, while TP53 overexpression occurred in 58.6% among the Iraqi patients who were exposed to war environmental hazards^[22]. Eissa *et al.*^[23] also evaluated diagnostic efficacy of mutant p53 patients by PCR-SSCP followed by DNA sequencing in urine of 100 patients diagnosed with BC, 93 patients with benign urological disorders and 47 healthy volunteers. The sensitivity and specificity were 59% and 91.4% for cytology, and 37% and 100% for mutant p53, with a significant association observed between disease recurrence and mutant p53, stage and lymph node involvement^[23].

Wang *et al.*^[24] adopted co-amplification at lower denaturation temperature-polymerase chain reaction (COLD-PCR) as a straightforward method with no additional reagents requirements or instruments as a highly sensitive, specific and expedient clinical assay for mutation detection in the *H-ras* gene, including exons 1 and 2,

in Chinese patients diagnosed with BC, yielding a 36% improvement in mutation detection compared with conventional PCR. They concluded that silent mutations might be important genomic alterations in BC pathogenesis and recurrence^[24].

EPIGENETICS IN BC URINARY BIOMARKERS

DNA methylation

Epigenetics is a field that refers to reversible changes in gene expression caused by mechanisms other than any change in genetic sequence^[22]. DNA methylation is the most common epigenetic changes addressed in BC biomarkers. DNA methyltransferase catalyzes the transfer of the methyl group to the cytosine ring of the CpG dinucleotides. When these CpGs present in promoter regions of genes at high density, CpG islands and gene silencing may be caused by their methylation^[25]. Hypermethylation of tumor suppressor genes is a common event during tumorigenesis^[26,27]. A large number of genes and their methylation state were assessed in their relationship to urothelial cancer. DNA methylation analysis is usually carried out by methylation specific PCR, bisulfate sequencing, methylation sensitive restriction enzymes and methylated DNA immunoprecipitation (MeDIP)^[21].

An Egyptian study was conducted on 210 BC patients, 61 patients with benign urological conditions and 49 healthy volunteers. Eissa *et al.*^[28] evaluated promoter methylation of *RARβ(2)* and *APC* in DNA extracted from exfoliated cells by methylation specific PCR. Methylated *RARβ(2)* and *APC* were significantly higher in BC patients (62.8%, 59.5%) than benign (16.4%, 5%) but not detected in healthy volunteers (0%) at ($P < 0.0001$). Both sensitivities and specificities of the methylated genes for BC detection were superior to urine cytology^[28].

DNA methylation status of specific gene promoter regions in bladder tumor cells has been proposed as a marker for primary diagnosis and for detection of recurrence. García-Baquero *et al.*^[29] conducted evaluation of the methylation of 18 tumor suppressor genes using methylation specific multiplex ligation-dependent probe amplification in 2 prospective, training urine sample sets of 120 preparations and validation set of 128 from patients with BC (170) and controls (78). *HLTF*, *DLC1*, *PRDM2*, *BNIP3*, *ID4*, *H2AFX*, *CACNA1G*, *TGIF* and *CACNA1A* were methylated in BC. The methylation status of 5 genes (*CCND2*, *SCGB3A1*, *BNIP3*, *ID4* and *RUNX3*) was identified as an epigenetic biomarker for BC and achieved very high accuracy when used as a panel in analysis of urine sediments. ROC analysis revealed significant diagnostic accuracy for *RUNX3* and *CACNA1A* in the training set and for *RUNX3* and *ID4* in the validation set. *CACNA1A* methylation correlated with recurrence in the training set, while in the validation set, *PRDM2* and *BNIP3* were significantly associated

with recurrence respectively^[29].

Kandimalla *et al.*^[30] reported a panel of epigenetic target genes. Genome-wide methylation analysis was performed on 44 bladder tumors using human CpG island microarray, then validation was performed using a next generation sequencer in a retrospective group of 77 independent tumors and urine DNA from four healthy males > 50 years of age was used as reference. They found 4 genes, Zic family member 4 (*ZIC4*), T-box 2 (*TBX2*), T-box 3 (*TBX3*) and GATA binding protein 2 (*GATA2*), that were significantly hypermethylated in tumor samples methylation and associated with progression to muscle-invasive disease in pTa tumors. Individually, methylation of *TBX2* alone showed a sensitivity of 100%, a specificity of 80%, a positive predictive value of 78%, and a negative predictive value of 100%. This panel of methylated gene increased the sensitivity to 91.7% and the specificity to 87.6%. They also declared that the multivariate analysis showed that methylation of *TBX3* and *GATA2* are independent predictors of progression when compared to clinicopathological variables. They further identified and validated 110 CpG islands with differential methylation between tumor cells and control urine. This study was limited by the small number of patients analyzed for testing and validation.

Scher group has reported that the methylation of 3 genes (*BCL2*, *CDKN2A* and *NID2*) detected by nested methylation specific polymerase chain is associated with BC. They were able to differentiate BC from other urogenital malignancies and nonmalignant conditions with a sensitivity of 80.9% and a specificity of 86.4%.

The epigenetic markers provide a new paradigm in urinary biomarker development for BC^[31]. However, the above mentioned markers have been tested in single institutions and with relatively small case control or pilot studies. At the present time, there is no standard method to assess these markers.

microRNA

Hence, it seems to be a good strategy to find cancer-related genes by categorizing methylated genes and microRNA discovery is another major epigenetic event. MicroRNA as a key post-transcriptional regulator of gene expression is small non-coding RNA of 20-22 nucleotides and involved in crucial biological processes, including development, apoptosis and cell division, through improper pairing with target messenger RNA (mRNA)^[32]. Array-based profiling, deep-sequencing technologies and qPCR for miRNA analysis are becoming routine technically. They are suitable for the classification of tumors because of aberrant expression of miRNAs in human cancer^[33].

Yamada *et al.*^[34] found the expression level of miR-96 and miR-183 in urine samples was significantly higher in 100 BC than in healthy controls by qPCR. Their results demonstrated that each microRNA has good sensitivity and specificity (miR-96, 71.0% and 89.2%; and miR-183, 74.0% and 77.3%).

Hanke *et al.*^[35] monitored a number of 157 microRNA species by quantitative reverse transcriptase-polymerase chain reaction in exfoliated urothelial cells in 36 samples. Subsequently, those microRNAs with a higher abundance in urine samples from BC patients were validated in an independent set of urine samples. The study reported that the ratio of miR-126 to miR-182 achieved 72% sensitivity and 82% specificity in 47 samples.

Differential expression of miRNAs was identified by Wszolek *et al.*^[36] by microarray analysis between noninvasive and invasive BC cell lines and confirmed using (qRT-PCR) within these cell lines. They reported reduced expression of miR-21, miR-30b, miR-31, miR-141, miR-200 and miR-205 in invasive lesions and overexpressed miR-99a in noninvasive BC lesions. Such a diagnostic test, depending on the three most discriminatory miRNAs in this panel (miR-200c, miR-141 and miR-30b), showed a sensitivity of 100% and a specificity of 96.2%.

Tölle *et al.*^[37] explored the expression of 754 human miRNAs from the Sanger database v14 in the blood and urine samples from 4 controls and from patients suffering from superficial and invasive BC using miRNA microarray. Using the RT-qPCR technique, 6 of the differentially expressed miRNAs were validated in the controls and patients with superficial or invasive tumors. Three blood miRNAs (miR-26b-5p, miR-144-5p, miR-374-5p) were found to be significantly upregulated in invasive bladder tumor patients when compared to the control group. The expression of 2 urinary miRNAs (miR-618, miR-1255b-5p) in patients with invasive tumors was significantly increased in comparison to the control group. The urine miR-1255b-5p had 68% specificity and 85% sensitivity in the diagnosis of invasive bladder tumors.

Pignot *et al.*^[38] evaluated expression level of miRNAs by quantitative real-time RT-PCR in 11 human normal bladder and 166 bladder tumor samples. The expression level of 804 miRNAs was initially measured and then the differential miRNAs in tumor samples compared to normal bladder tissue were selected for RT-PCR validation in a series of 152 bladder tumors and in six BC cell lines. They reported a panel of 3-miRNA signature (miR-9, miR-182 and miR-200b) was found to be related to bladder tumor aggressiveness and was associated with both recurrence-free and overall survival.

Aberrations in miRNA expression identified between non-muscle invasive BC and muscle-invasive BC provide valuable insight into the molecular mechanisms known to distinguish the unique pathways of bladder carcinogenesis. The limited reproducibility of changes in miRNA expression profiles between studies utilizing in silico miR target-prediction models is due to the heterogeneity of tumor specimens and research methods^[39].

TRANSCRIPTOME IN BC URINARY BIOMARKERS

Another component available to be detected in urine is

soluble RNA, including both mRNA and microRNA (miRNA) targets. Quantitative reverse transcription PCR (Q-PCR) and conventional RT-PCR for RNA isolated from exfoliated urothelial cells in urine are the most widely used techniques in novel biomarkers in BC identification and validation^[40].

Diverse markers have been discovered but nowadays a very promising mRNA ratio has been assessed^[40]. Hanke *et al.*^[40] isolated RNA from urinary cell pellet and quantified it by reverse transcription quantitative-PCR in 61 patients with BC and 37 healthy donors. The RNA ratio of v-ets erythroblastosis virus E26 oncogene homolog 2 (avian; ETS2) to urokinase plasminogen activator (uPA) enabled the most specific (100%) and sensitive (75.4%) detection of BC from normal urine.

Eissa *et al.*^[41] evaluated hyaluronidase (HYAL1) and survivin RNA expression by qualitative and semiquantitative reverse transcriptase-polymerase chain reaction in urothelial cells from voided urine in 166 patients with BC, 112 with benign bladder lesions and 100 healthy volunteers. They reported that positivity rates of HYAL1 RNA and survivin RNA on qualitative reverse transcriptase-polymerase chain reaction were significantly different among the study groups. Mean rank using semiquantitative RT-PCR was higher in the malignant compared to the control groups. Using the best cutoffs HYAL1 and survivin RNA sensitivity was 91% and 75%, respectively, with 100% specificity. HYAL1 RNA detected all patients with early stage BC and is more sensitive and specific than urine cytology which is validated in many publications^[41-44].

Another study published by this group assessed urinary fibronectin (FN), relative telomerase activity (RTA) and cytokeratin 20 (CK20) mRNA in comparison with voided urine cytology (VUC) in 132 patients with BC, 60 patients with benign bladder diseases, and 48 apparently healthy individuals^[45]. Detection of CK20 was carried out by conventional RT-PCR in urothelial cells from voided urine, estimation of fibronectin by ELISA and relative telomerase activity by telomeric repeat amplification protocol (TRAP). The overall sensitivity (89.3%) and specificity (98.4%) were the highest for CK20 mRNA compared to all investigated markers. The efficacy of urinary CK20 mRNA in BC diagnosis was validated in many publications^[46-50].

C-X-C chemokine receptor 4 (CXCR4) and CXCR7 were estimated by Yates *et al.*^[51] in BC cell lines, tissues (normal = 25; BC = 44) and urine specimens ($n = 186$) by qPCR and/or immunohistochemistry. CXCR7 messenger RNA levels were 5 to 37-fold higher than those for CXCR4. CXCR7 messenger RNA levels and CXCR7 staining scores were significantly higher in BC than in normal tissues. CXCR7 level was elevated in exfoliated urothelial cells from high-grade BC patients (90% sensitivity; 75% specificity) while CXCR4 level was unaltered.

Bongiovanni *et al.*^[52] performed real-time reverse transcriptase-polymerase chain reaction to evaluate Bradeion/SEPT4 transcript levels in urine samples from 17

healthy controls and 41 patients with BC. Relative quantification analysis of Bradeion transcript showed 92.68% sensitivity and 64.71% specificity. This preliminary study supports the possible usefulness of Bradeion as a urinary marker of BC.

Brems-Eskildsen *et al.*^[53] measured urinary mRNA levels of PPP1CA, hTERT, MCM5 and SENP1 by q-RT-PCR from 123 prospectively cross-sectional collected urine samples from patients with BC (54 patients with recurrent BC at sampling, 59 patients with previous BC and no tumor at sampling, 10 patients with a primary BC at sampling). The sensitivity and specificity of these mRNA markers were: for hTERT: 86%; SENP1: 71.7%; MCM5: 95.45%; and PPP1CA: 91.3%. Follow-up data resulted in sensitivity and specificity values: for hTERT: 62/84; SENP1: 63%; MCM5: 83.6%; and PPP1CA: 98.5%. The best combination was hTERT and cytology with a sensitivity of 71% and a specificity of 86%, but the combination of hTERT and MCM5 also increased the detection rate.

Rosser *et al.*^[54] applied cDNA microarray to explore the molecular signatures of BC in urine pellet from 46 individuals. They reported 14 overexpressed and 10 decreased genes in exfoliated tumor cells. Finally, they built a panel of 14 genes as a potential molecular pattern for diagnosing BC with 90% sensitivity and 65% specificity. This study is limited by the small sample size and low specificity but is still significant as it used the exfoliated cells as a source to perform cDNA microarray analysis. This molecular signature motivated another group to validate them in a larger study applying Q-PCR. Holyake *et al.*^[55] investigated the expression of 14 different genes by Q-PCR using voided urine from 75 transitional cell carcinoma (TCC) patients and 77 control patients. In their analyses they developed a panel of 4-marker involving CDC-2, HOX-A13, MDK and IGBP-5 mRNAs detected 48%, 90% and 100% of stage Ta, T1, and > T1 TCCs, respectively, at a specificity of 85%.

PROTEOMICS IN BC URINARY BIOMARKERS

Proteomics refers to the large-scale experimental analysis of proteins, mainly their structures and functions using diverse technologies such as 2-dimensional gel electrophoresis (2-DE) and mass spectrometry (MS)^[56]. After initial screening, more traditional tests (*e.g.*, ELISA, zymography, western blot) can be carried out to evaluate the clinical efficacy of promising biomarkers^[57].

SELDI (surface enhanced laser desorption/ionization) is the best MS-technique used to characterize biomarkers from biological fluids such as urine and blood^[58]. Such high throughput technology can analyze only small molecular mass proteins and miss relatively higher molecular mass biomarkers. Several markers have been gleaned from such technology, including TATI (tumor associated trypsin inhibitor), MMPs (matrix metalloproteinase) and CXCL-1^[59].

Chen *et al.*^[60] used 17 biomarkers for BC diagnosis which were already discovered using isobaric tagging absolute and relative quantitation (iTRAQ), then validated by multiple reaction monitoring-based mass spectrometry in urine samples from 57 patients with hernia, 76 BC and 23 urinary tract infection. Prothrombin had the highest sensitivity, 71.1% and 75.0% specificity for discriminating BC from non-cancerous patients. They generated six-peptide panel (apolipoprotein A-II precursor, ceruloplasmin, adiponectin, afamin, complement C4 gamma chain and prothrombin) to differentiate BC subjects from non-cancerous subjects, with a 76.3% positive predictive value and a 77.5% negative predictive value.

Rosse *et al.*^[61] evaluated the urinary concentration of eight biomarkers (CA9, APOE, MMP-9, PAI-1, VEGF, IL-8, ANG and MMP-10) by ELISA assay in 102 BC subjects and 206 subjects with different urological disorders. They reported that this 7-biomarker model has a sensitivity of 74% and specificity of 90%. This study was limited by being performed on banked urines and the lack of VUC and UroVysion data on controls.

In another study published by Goodison *et al.*^[62], the urinary concentration of 14 biomarkers (OPN, MMP-9, MMP-10, APOE, CCL18, A1AT, ANG, VEGF, CD44, CA9, PAI-1, IL-8, PTX3 and SDC1) was measured by ELISA in voided urines from 127 patients (64 tumor bearing subjects). They reported a panel of 8-biomarker achieving the most accurate BC diagnosis (sensitivity 92%, specificity 97%) and highly accurate combination of 3 of the 8 biomarkers (IL-8, VEGF and APOE) (sensitivity 90%, specificity 97%) in comparison with the commercial BTA-Trak ELISA test (sensitivity of 79% and a specificity of 83%) and voided urine cytology (33% sensitivity) in the same subjects.

Li *et al.*^[63] identified 16 urinary proteins including Gc-globulin (GC) from BC patients and normal controls by two-dimensional fluorescent differential gel electrophoresis (2D-DIGE) and matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF/TOF MS). The urinary GC protein from cases and controls were further assessed by western blotting and ELISA showing 82.61% sensitivity and 88.24% specificity. Another Chinese group used 2-dimensional electrophoresis combined with MALDI-TOF/TOF MS and SWISS-PROT database to explore urinary proteins in patients with BC and in normal controls^[64]. They identified 14 proteins, including 2 putative proteins [fatty acid-binding protein adipocyte, myoglobin, beta-2-microglobulin isoform 2 of fibrinogen alpha chain, apoA-I, gelsolin, isoform 1 of gelsolin, prostaglandin D(2) synthase 21 kDa (brain), keratin type II cytoskeletal 1, type II cytoskeletal 8, protein AMBP, transthyretin, putative uncharacterized protein ALB, putative uncharacterized protein MASP2 (fragment)]. apoA-I was confirmed by western blot analysis, concluding that proteomic analysis of urine may be a noninvasive and highly efficient strategy for searching for new bladder tumor biomarkers.

Zoidakis *et al.*^[65] applied immobilized metal affinity

chromatography in urine samples from patients with non invasive and invasive BC and the eluted proteins were analyzed by 1D-SDS-PAGE followed by band excision and liquid chromatography tandem MS. They found that MMP9, fibrinogen forms, clusterin, aminopeptidase N, profilin 1 and myeloblastin were differentially expressed in urine from patients with aggressive compared with non aggressive BC and benign controls, then further validated by western blot or ELISA analysis. This study reported that profilin 1 is strongly associated with BC paving the way for its further assessment in BC diagnostics.

Lindén *et al.*^[66] screened the urine samples from BC patients by mass spectrometry (MS) and western blot (WB)/dot blot (DB). 29 proteins had a significantly higher abundance in BC samples compared with control urine samples. Then four selected proteins were confirmed with western blot: apolipoprotein E, fibrinogen β chain precursor, leucine-rich α -2-glycoprotein 1 and α -1-antitrypsin. Dot blot analysis of a separate urine sample set pointed out fibrinogen β chain and α -1-antitrypsin as the most significant biomarkers with sensitivity and specificity values in the range of 66%-85%. When the Human Protein Atlas (HPA) was explored, it also revealed that BC tumors are the proposed source of these proteins.

Bryan *et al.*^[67] explored urine samples from 751 patients with BC and 127 controls using MALDI-TOF-MS. They declared that albumin, total protein and hematuria were elevated in T2+ patients. Hematuria was found in 39% of patients with Ta/T1 disease and in 77% of patients with T2+ disease. Taken together, great consideration should be given when applying omic in searching for urinary biomarkers because blood proteins may give false-positive results.

METABOLOMICS IN BC URINARY BIOMARKERS

Metabolomics is defined as “quantitative measurement of the unique chemical fingerprints that elucidate metabolic response of living systems to pathophysiological stimuli or genetic modification”^[68]. It provides information that cannot be obtained directly from the gene expression profiles or even the proteomic fingerprint of an individual. Application of urine-based metabolic profiling is achieved using high pressure liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) which may identify specific biomarker patterns that can aid diagnosis of BC^[69].

In a study published by the Pasikanti group, gas chromatography mass spectrometry (GC-MS) was used for urinary metabolic profiling of BC patients and non-BC controls and concluded that urinary metabolomics is highly compliant to the noninvasive diagnosis of BC^[70].

Huang *et al.*^[71] enrolled twenty-seven BC patients and 32 healthy volunteers to perform metabolomic profiling to identify a potential unique biomarker pattern in urine

as a noninvasive strategy for BC detection. They utilized a liquid chromatography-mass spectrometry based method. Carnitine C9:1 and component I were identified as a biomarker panel, with 92.6% sensitivity and 96.9% specificity for all patients and 90.5% and 96.9%, respectively, for low-grade BC patients.

Pasikanti *et al.*^[72] conducted a urinary metabotyping in another study in 38 BC patients and 61 non-BC controls using two-dimensional gas chromatography time-of-flight mass spectrometry (GC×GC-TOFMS). Urinary metabotyping characterized 46 metabolites which are human specific to BC with 100% specificity and 71% sensitivity in detecting BC *vs* 100% specificity and 46% sensitivity for cytology. They suggested potential roles of kynurenine in the malignancy and therapy of BC. In addition, altered metabolic pathways extracted from urinary metabotyping shed new insights on the mechanism of BC.

BIONANOTECHNOLOGY IN BC URINARY BIOMARKERS

However, the above mentioned BC diagnostic methods are not very powerful methods in detection of very early stages of cancer^[73]. Also, some of them are quite costly and not available for many people. Therefore, the development of novel, specific, reliable and easily accessible technology for detecting BC early is of great importance^[74-82].

Nanotechnology has been progressing very rapidly during the last few years and with this, properties of nanoparticles that provide an enriched medium for the selective capture and uptake of urine biomarkers due to their unique optical, chemical and physical magnetic properties^[74,83]. Many classes of nanoparticles (such as gold nanoparticles, quantum dots, magnetic nanoparticles) have been proposed to be applicable in diagnosis, monitoring and treatment of disease^[75,84-86].

The Wang *et al.*^[87] has reported that human telomerase activity can be visualized by using primer-modified Au nanoparticles. Our research group developed a gold nanoparticle (AuNP) assay for direct detection of unamplified hepatoma upregulated protein (HURP RNA) in urine samples from 50 bladder carcinoma patients, 25 benign bladder lesions and 25 controls^[88]. They purified HURP RNA using magnetic nanoparticles functionalized with HURP RNA-specific oligonucleotides and detected by RT-PCR and gold nanoparticles. The developed HURP RNA AuNP assay has sensitivity and a specificity of 88.5% and 94%, respectively, and a detection limit of 2.4 nmol/L. Nossier *et al.*^[89] developed a simple colorimetric gold nanoparticle (AuNP) assay for rapid and sensitive detection of urinary HAase activity. The assay depends on charge interaction between polyanionic hyaluronic acid (HA) and cationic AuNPs stabilized with cetyltrimethylammonium bromide (CTAB) led to formation of gold aggregates and a red to blue color shift. HAase digests HA into small fragments preventing

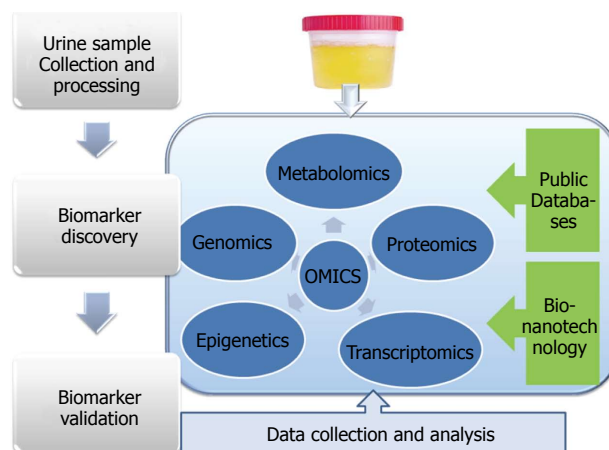


Figure 1 Integration of OMICS strategies for urinary bladder cancer biomarker discovery and validation.

the aggregation of cationic AuNPs. The AuNP HAse assay has a sensitivity of 82.5% and a specificity of 96.1% and a short turnaround time of 2 h^[89].

IDENTIFICATION OF WHOLE TUMOR CELLS BY RAMAN SPECTROSCOPY

Raman spectroscopy is a technique based on excitation of vibrational models in the chemical bonds that hold molecules together^[90]. Thus, it provides a measure of biologically active molecular groups^[91,92]. Many authors applied Raman spectroscopy successfully in discriminating tumor cells from normal cells. Beside accuracy and non invasiveness, Raman spectroscopy is a fast and promising tool for BC screening in high risk populations^[93,94]. Shapiro *et al.*^[95] used a Falcon Raman microscope to diagnose BC from epithelial cells found in urine of 344 patients (116 patients without urothelial cancer, 92 patients with low grade tumors and 132 patients with high grade tumors). They concluded that Raman molecular imaging is a powerful technique for BC diagnosis, with 92% sensitivity and 91% specificity in agreement with many recent studies^[96].

Finally, although many policies and guidelines have been developed to evaluate potential BC biomarkers, no proper validation has been achieved until now, except for a few biomarkers^[97]. For clinical application, any biomarker should be validated in a large number of samples with different ethnic origin and in different institutes, followed by approval from the FDA^[98]. Public and private resources should offer financial support. Collaboration among researchers in universities, clinicians and industrial participants should be encouraged to bring biomarkers from the bench to the clinic^[99,100].

CONCLUSION

BC remains an expensive cancer due to life-long surveillance involving upper tract imaging, urinary cytology and cystoscopy. However, as combined cystoscopy

Table 1 Urinary bladder cancer biomarkers

Biomarker/signature	Technology used	Ref.
MCP-1 A2518G, SDF-1 3'A and chemokine receptors CCR2A V64I, CCR5 Δ32, CCR5 59029 and CXCR4 TP53	PCR-restriction fragment length polymorphism	[21]
	PCR-single strand conformational polymorphism analysis, DNA sequencing and immunohistochemical analysis	[22]
<i>H-ras</i> gene mutations	COLD-PCR	[23]
<i>RARβ</i> (2) and <i>APC</i> promoter methylation	Methylation specific PCR	[27]
<i>SCGB3A1</i> , <i>BNIP3</i> , <i>ID4</i> and <i>RUNX3</i>	Multiplex ligation-dependent probe amplification	[28]
<i>TBX2</i> , <i>TBX3</i> , <i>GATA2</i> and <i>ZIC4</i>	Genome-wide methylation analysis	[29]
<i>BCL2</i> , <i>CDKN2A</i> and <i>NID2</i> genes methylation	Nested methylation specific polymerase chain	[30]
miR-96 and miR-183	Q-PCR	[33]
miR-618, miR-1255b-5p	RT-qPCR	[36]
RNA ratio of v-ets erythroblastosis virus E26 oncogene homolog 2 (avian; ETS2) to urokinase plasminogen activator (uPA)	Reverse transcription quantitative-PCR	[41]
HYAL1 and survivin RNA	Qualitative and semiquantitative reverse transcriptase-polymerase chain reaction	[42]
FN, RTA, and CK20	Detection of CK20 by conventional RT-PCR, estimation of fibronectin by ELISA and relative telomerase activity by TRAP	[46]
CXCR4 and CXCR7	qPCR and/or immunohistochemistry	[52]
Bradeion/SEPT4 transcript	Real-time reverse transcriptase-polymerase chain reaction	[53]
hTERT, SENP1, PPP1CA, and MCM5 mRNA	q-RT-PCR	[54]
HOX-A13, IGBP-5, MDK, and CDC-2	cDNA microarray, Q-PCR	[55,56]
Afamin, adiponectin, complement C4 gamma chain, apolipoprotein A-II precursor, ceruloplasmin and prothrombin	iTRAQ	[61]
IL-8, MMP-9, MMP-10, PAI-1, VEGF, ANG, CA9 and APOE	ELISA assay	[62]
IL-8, MMP-9, MMP-10, SDC1, CCL18, PAI-1, CD44, VEGF, ANG, CA9, A1AT, OPN, PTX3 and APOE	ELISA assay	[63]
GC	Two-dimensional fluorescent differential gel electrophoresis and MALDI-TOF/TOF MS	[64]
beta-2-microglobulin, fatty acid-binding protein adipocyte, gelsolin, isoform 1 of gelsolin, myoglobin, isoform 2 of fibrinogen alpha chain, apoA-I, prostaglandin D(2) synthase 21 kDa, protein AMBP, transthyretin, keratin type II cytoskeletal 1, type II cytoskeletal 8, putative uncharacterized protein ALB, putative uncharacterized protein MASP2 (fragment)	2-dimensional electrophoresis combined with MALDI-TOF/TOF MS and SWISS-PROT database	[65]
MMP9, fibrinogen forms, and clusterin, aminopeptidase N, profilin 1 and myeloblastin	1D-SDS-PAGE followed by band excision and liquid chromatography tandem MS	[66]
Fibrinogen α chain precursor, apolipoprotein E, α-1-antitrypsin, and leucine-rich α-2-glycoprotein 1	MS and western blot/dot blot	[67]
Carnitine C9:1 and component I	Liquid chromatography-mass spectrometry based method	[72]
Kynurenine	Two-dimensional gas chromatography time-of-flight mass spectrometry (GC×GC-TOFMS)	[73]
HURP RNA	Conventional RT-PCR and AuNP nanoassay	[89]

MCP-1: Monocyte chemoattractant protein-1; SDF-1: Stromal cell derived factor 1; COLD-PCR: Co-amplification at lower denaturation temperature-polymerase chain reaction; ZIC4: Zic family member 4; Q-PCR: Quantitative real time PCR; FN: Fibronectin; TBX2: T-box 2; CXCR4: C-X-C chemokine receptor 4; RTA: Relative telomerase activity; CK20: Cytokeratin 20; GATA2: GATA binding protein 2; HYAL1: Hyaluronidase; TRAP: Telomeric repeat amplification protocol; iTRAQ: Isobaric tagging absolute and relative quantitation; CXCR4: C-X-C chemokine receptor 4; GC: Gc-globulin; MALDI-TOF/TOF MS: Matrix-assisted laser desorption time-of-flight mass spectrometry; MS: Mass spectrometry.

with cytology is considered the corner stone for BC diagnosis, it is necessary to search for an economical and efficient method to replace these deficient traditional methods. Many of the urinary markers currently available appear to be alternatives to cytology with a lower price and higher sensitivity, especially in detecting low-grade, non-muscle invasive cancers. Modern technologies, including mass spectroscopy, liquid chromatography, next generation sequencing, gene-expression profiling, metabolic profiling, nanoassays and epigenetic markers, are promoting more and more biomarker discoveries each month (Table 1, Figure 1). Finally, these versatile and newer strategies should be

integrated to trace which markers may be clinically efficient and refinement of these markers which will help the urologist in critical evaluation of BC. Consequently, further and in-depth studies are required to determine the accuracy and widespread applicability of these modalities in guiding urinary markers discovery in BC.

REFERENCES

- 1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA-Cancer J Clin* 2013; **63**: 11-30 [DOI: 10.3322/caac.21166]
- 2 Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA

- (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Available from: URL: http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013
- 3 **Millán-Rodríguez F**, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodríguez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol* 2000; **164**: 680-684 [PMID: 10954628 DOI: 10.1016/S0022-5347(05)67280-1]
 - 4 **Proctor I**, Stoeber K, Williams GH. Biomarkers in bladder cancer. *Histopathology* 2010; **57**: 1-13 [PMID: 20579130 DOI: 10.1111/j.1365-2559.2010.03592.x]
 - 5 **Lotan Y**, Svatek RS, Sagalowsky AI. Should we screen for bladder cancer in a high-risk population?: A cost per life-year saved analysis. *Cancer* 2006; **107**: 982-990 [PMID: 16862567 DOI: 10.1002/cncr.22084]
 - 6 **Avritscher EB**, Cooksley CD, Grossman HB, Sabichi AL, Hamblin L, Dinney CP, Elting LS. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology* 2006; **68**: 549-553 [PMID: 16979735 DOI: 10.1016/j.urology.2006.03.062]
 - 7 **Yossepowitch O**, Herr HW, Donat SM. Use of urinary biomarkers for bladder cancer surveillance: patient perspectives. *J Urol* 2007; **177**: 1277-1282; discussion 1282 [PMID: 17382711 DOI: 10.1016/j.juro.2006.11.066]
 - 8 **Vrooman OP**, Witjes JA. Urinary markers in bladder cancer. *Eur Urol* 2008; **53**: 909-916 [PMID: 18162285 DOI: 10.1016/j.eururo.2007.12.006]
 - 9 **Thomas RS**, Clewell HJ, Allen BC, Wesselkamper SC, Wang NC, Lambert JC, Hess-Wilson JK, Zhao QJ, Andersen ME. Application of transcriptional benchmark dose values in quantitative cancer and noncancer risk assessment. *Toxicol Sci* 2011; **120**: 194-205 [PMID: 21097997 DOI: 10.1093/toxsci/kfq355]
 - 10 **Ideker T**, Dutkowski J, Hood L. Boosting signal-to-noise in complex biology: prior knowledge is power. *Cell* 2011; **144**: 860-863 [PMID: 21414478 DOI: 10.1016/j.cell.2011.03.007]
 - 11 **Andrechek ER**, Cardiff RD, Chang JT, Gatzda ML, Acharya CR, Potti A, Nevins JR. Genetic heterogeneity of Myc-induced mammary tumors reflecting diverse phenotypes including metastatic potential. *Proc Natl Acad Sci U S A* 2009; **106**: 16387-16392 [PMID: 19805309 DOI: 10.1073/pnas.0901250106]
 - 12 **Huret JL**, Minor SL, Dorkeld F, Dessen P, Bernheim A. Atlas of genetics and cytogenetics in oncology and haematology, an interactive database. *Nucleic Acids Res* 2000; **28**: 349-351 [PMID: 10592271]
 - 13 **Liekens AM**, De Knijf J, Daelemans W, Goethals B, De Rijk P, Del-Favero J. BioGraph: unsupervised biomedical knowledge discovery via automated hypothesis generation. *Genome Biol* 2011; **12**: R57 [PMID: 21696594 DOI: 10.1186/gm2]
 - 14 **Auffray C**, Chen Z, Hood L. Systems medicine: the future of medical genomics and healthcare. *Genome Med* 2009; **1**: 2 [PMID: 19348689]
 - 15 **National Human Genome Research Institute**. A Brief Guide to Genomics. Available from: URL: <http://www.genome.gov/18016863>
 - 16 **Lam T**, Nabi G. Potential of urinary biomarkers in early bladder cancer diagnosis. *Expert Rev Anticancer Ther* 2007; **7**: 1105-1115 [PMID: 18028019 DOI: 10.1586/14737140.7.8.1105]
 - 17 **Kim WJ**, Bae SC. Molecular biomarkers in urothelial bladder cancer. *Cancer Sci* 2008; **99**: 646-652 [PMID: 18377416 DOI: 10.1111/j.1349-7006.2008.00735.x]
 - 18 **Mitra AP**, Birkhahn M, Cote RJ. p53 and retinoblastoma pathways in bladder cancer. *World J Urol* 2007; **25**: 563-571 [PMID: 17710407 DOI: 10.1007/s00345-007-0197-0]
 - 19 **Billerey C**, Chopin D, Aubriot-Lorton MH, Ricol D, Gil Diez de Medina S, Van Rhijn B, Bralet MP, Lefrere-Belda MA, Lahaye JB, Abbou CC, Bonaventure J, Zafrani ES, van der Kwast T, Thiery JP, Radvanyi F. Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors. *Am J Pathol* 2001; **158**: 1955-1959 [PMID: 11395371 DOI: 10.1016/S0002-9440(10)64665-2]
 - 20 **Larré S**, Camparo P, Comperat E, Gil Diez De Medina S, Traxer O, Roupert M, Sebe P, Cancel-Tassin G, Sighar K, Lozach F, Cussenot O. Diagnostic, staging, and grading of urothelial carcinomas from urine: performance of BCA-1, a mini-array comparative genomic hybridisation-based test. *Eur Urol* 2011; **59**: 250-257 [PMID: 21056532 DOI: 10.1016/j.eururo.2010.10.007]
 - 21 **Kucukgergin C**, Isman FK, Dasdemir S, Cakmakoglu B, Sanli O, Gokkusu C, Seckin S. The role of chemokine and chemokine receptor gene variants on the susceptibility and clinicopathological characteristics of bladder cancer. *Gene* 2012; **511**: 7-11 [PMID: 22982413 DOI: 10.1016/j.gene.2012.09.011]
 - 22 **Al-Kashwan TA**, Houshmand M, Al-Janabi A, Melconian AK, Al-Abbasi D, Al-Musawi MN, Rostami M, Yasseen AA. Specific-mutational patterns of p53 gene in bladder transitional cell carcinoma among a group of Iraqi patients exposed to war environmental hazards. *BMC Res Notes* 2012; **5**: 466 [PMID: 22929185 DOI: 10.1186/1756-0500-5-466]
 - 23 **Eissa S**, Zohny SF, Zekri AR, El-Zayat TM, Maher AM. Diagnostic value of fibronectin and mutant p53 in the urine of patients with bladder cancer: impact on clinicopathological features and disease recurrence. *Med Oncol* 2010; **27**: 1286-1294 [PMID: 20012564 DOI: 10.1007/s12032-009-9375-9]
 - 24 **Wang AX**, Chang JW, Li CY, Liu K, Lin YL. H-ras mutation detection in bladder cancer by COLD-PCR analysis and direct sequencing. *Urol Int* 2012; **88**: 350-357 [PMID: 22433386 DOI: 10.1159/000336132]
 - 25 **Kim YK**, Kim WJ. Epigenetic markers as promising prognosticators for bladder cancer. *Int J Urol* 2009; **16**: 17-22 [PMID: 18721202 DOI: 10.1111/j.1442-2042.2008.02143.x]
 - 26 **Esteller M**. Epigenetics in cancer. *N Engl J Med* 2008; **358**: 1148-1159 [PMID: 18337604 DOI: 10.1056/NEJMra072067]
 - 27 **Baylin SB**, Herman JG. DNA hypermethylation in tumorigenesis: epigenetics joins genetics. *Trends Genet* 2000; **16**: 168-174 [PMID: 10729832 DOI: 10.1016/S0168-9525(99)01971-X]
 - 28 **Eissa S**, Swellam M, El-Khouly IM, Kassim SK, Shehata H, Mansour A, Esmat M, Nossier AI, Hamdy MA, Awad NM, El-Ahmady O. Aberrant methylation of RARBeta2 and APC genes in voided urine as molecular markers for early detection of bilharzial and nonbilharzial bladder cancer. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 1657-1664 [PMID: 21680534 DOI: 10.1158/1055-9965.EPI-11-0237]
 - 29 **García-Baquero R**, Puerta P, Beltran M, Alvarez M, Sacristan R, Alvarez-Ossorio JL, Sánchez-Carbayo M. Methylation of a novel panel of tumor suppressor genes in urine moves forward noninvasive diagnosis and prognosis of bladder cancer: a 2-center prospective study. *J Urol* 2013; **190**: 723-730 [PMID: 23485510 DOI: 10.1016/j.juro.2013.01.105]
 - 30 **Kandimalla R**, van Tilborg AA, Kompier LC, Stumpel DJ, Stam RW, Bangma CH, Zwarthoff EC. Genome-wide analysis of CpG island methylation in bladder cancer identified TBX2, TBX3, GATA2, and ZIC4 as pTa-specific prognostic markers. *Eur Urol* 2012; **61**: 1245-1256 [PMID: 22284968 DOI: 10.1016/j.eururo.2012.01.011]
 - 31 **Scher MB**, Elbaum MB, Mogilevkin Y, Hilbert DW, Mydlow JH, Sidi AA, Adelson ME, Mordechay E, Trama JP. Detecting DNA methylation of the BCL2, CDKN2A and NID2 genes in urine using a nested methylation specific polymerase chain reaction assay to predict bladder cancer. *J Urol* 2012; **188**: 2101-2107 [PMID: 23083854 DOI: 10.1016/j.juro.2012.08.015]
 - 32 **Ichimi T**, Enokida H, Okuno Y, Kunimoto R, Chiyomaru T, Kawamoto K, Kawahara K, Toki K, Kawakami K, Nishiyama K, Tsujimoto G, Nakagawa M, Seki N. Identification of novel microRNA targets based on microRNA signatures in bladder cancer. *Int J Cancer* 2009; **125**: 345-352 [PMID:

- 19378336]
- 33 **Wang G**, Chan ES, Kwan BC, Li PK, Yip SK, Szeto CC, Ng CF. Expression of microRNAs in the urine of patients with bladder cancer. *Clin Genitourin Cancer* 2012; **10**: 106-113 [PMID: 22386240 DOI: 10.1016/j.clgc.2012.01.001]
 - 34 **Yamada Y**, Enokida H, Kojima S, Kawakami K, Chiyomaru T, Tatarano S, Yoshino H, Kawahara K, Nishiyama K, Seki N, Nakagawa M. MiR-96 and miR-183 detection in urine serve as potential tumor markers of urothelial carcinoma: correlation with stage and grade, and comparison with urinary cytology. *Cancer Sci* 2011; **102**: 522-529 [PMID: 21166959 DOI: 10.1111/j.1349-7006.2010.01816.x]
 - 35 **Hanke M**, Hoefig K, Merz H, Feller AC, Kausch I, Jocham D, Warnecke JM, Sczakiel G. A robust methodology to study urine microRNA as tumor marker: microRNA-126 and microRNA-182 are related to urinary bladder cancer. *Urol Oncol* 2010; **28**: 655-661 [PMID: 19375957 DOI: 10.1016/j.urolonc.2009.01.027]
 - 36 **Wszolek MF**, Rieger-Christ KM, Kenney PA, Gould JJ, Silva Neto B, Lavoie AK, Logvinenko T, Libertino JA, Summerhayes IC. A MicroRNA expression profile defining the invasive bladder tumor phenotype. *Urol Oncol* 2011; **29**: 794-801. e1 [PMID: 19945312 DOI: 10.1016/j.urolonc.2009.08.024]
 - 37 **Tölle A**, Jung M, Rabenhorst S, Kilic E, Jung K, Weikert S. Identification of microRNAs in blood and urine as tumour markers for the detection of urinary bladder cancer. *Oncol Rep* 2013; **30**: 1949-1956 [PMID: 23877086 DOI: 10.3892/or.2013.2621]
 - 38 **Pignot G**, Cizeron-Clairac G, Vacher S, Susini A, Tozlu S, Vieillefond A, Zerbib M, Lidereau R, Debre B, Amsellem-Ouazana D, Bieche I. microRNA expression profile in a large series of bladder tumors: identification of a 3-miRNA signature associated with aggressiveness of muscle-invasive bladder cancer. *Int J Cancer* 2013; **132**: 2479-2491 [PMID: 23169479 DOI: 10.1002/ijc.27949]
 - 39 **Guancial EA**, Bellmunt J, Yeh S, Rosenberg JE, Berman DM. The evolving understanding of microRNA in bladder cancer. *Urol Oncol* 2013 Aug 1; [Epub ahead of print] [PMID: 23911686 DOI: 10.1016/j.urolonc.2013.04.014]
 - 40 **Hanke M**, Kausch I, Dahmen G, Jocham D, Warnecke JM. Detailed technical analysis of urine RNA-based tumor diagnostics reveals ETS2/urokinase plasminogen activator to be a novel marker for bladder cancer. *Clin Chem* 2007; **53**: 2070-2077 [PMID: 17921261 DOI: 10.1373/clinchem.2007.091363]
 - 41 **Eissa S**, Swellam M, Shehata H, El-Khouly IM, El-Zayat T, El-Ahmady O. Expression of HYAL1 and survivin RNA as diagnostic molecular markers for bladder cancer. *J Urol* 2010; **183**: 493-498 [PMID: 20006858 DOI: 10.1016/j.juro.2009.10.024]
 - 42 **Shimwell NJ**, Bryan RT, Wei W, James ND, Cheng KK, Zeegers MP, Johnson PJ, Martin A, Ward DG. Combined proteome and transcriptome analyses for the discovery of urinary biomarkers for urothelial carcinoma. *Br J Cancer* 2013; **108**: 1854-1861 [PMID: 23591195 DOI: 10.1038/bjc.2013.157]
 - 43 **Eissa S**, Shehata H, Mansour A, Esmat M, El-Ahmady O. Detection of hyaluronidase RNA and activity in urine of schistosomal and non-schistosomal bladder cancer. *Med Oncol* 2012; **29**: 3345-3351 [PMID: 22760792 DOI: 10.1007/s12032-012-0295-8]
 - 44 **Kramer MW**, Escudero DO, Lokeshwar SD, Golshani R, Ekwenna OO, Acosta K, Merseburger AS, Soloway M, Lokeshwar VB. Association of hyaluronic acid family members (HAS1, HAS2, and HYAL-1) with bladder cancer diagnosis and prognosis. *Cancer* 2011; **117**: 1197-1209 [PMID: 20960509 DOI: 10.1002/cncr.25565]
 - 45 **Eissa S**, Swellam M, Amin A, Balbaa ME, Yacout GA, El-Zayat TM. The clinical relevance of urine-based markers for diagnosis of bladder cancer. *Med Oncol* 2011; **28**: 513-518 [PMID: 21437743 DOI: 10.1007/s12032-010-9422-6]
 - 46 **Eissa S**, Zohny SF, Swellam M, Mahmoud MH, El-Zayat TM, Salem AM. Comparison of CD44 and cytokeratin 20 mRNA in voided urine samples as diagnostic tools for bladder cancer. *Clin Biochem* 2008; **41**: 1335-1341 [PMID: 18804101 DOI: 10.1016/j.clinbiochem.2008.08.085]
 - 47 **Guo B**, Luo C, Xun C, Xie J, Wu X, Pu J. Quantitative detection of cytokeratin 20 mRNA in urine samples as diagnostic tools for bladder cancer by real-time PCR. *Exp Oncol* 2009; **31**: 43-47 [PMID: 19300416]
 - 48 **Inoue T**, Nakanishi H, Inada K, Hioki T, Tatematsu M, Sugimura Y. Real time reverse transcriptase polymerase chain reaction of urinary cytokeratin 20 detects transitional cell carcinoma cells. *J Urol* 2001; **166**: 2134-2141 [PMID: 11696722 DOI: 10.1016/S0022-5347(05)65521-8]
 - 49 **Christoph F**, Müller M, Schostak M, Soong R, Tabiti K, Miller K. Quantitative detection of cytokeratin 20 mRNA expression in bladder carcinoma by real-time reverse transcriptase-polymerase chain reaction. *Urology* 2004; **64**: 157-161 [PMID: 15245962 DOI: 10.1016/j.urol.2004.02.020]
 - 50 **Retz M**, Lehmann J, Amann E, Wullich B, Röder C, Stöckle M. Mucin 7 and cytokeratin 20 as new diagnostic urinary markers for bladder tumor. *J Urol* 2003; **169**: 86-89 [PMID: 12478110 DOI: 10.1016/S0022-5347(05)64042-6]
 - 51 **Yates TJ**, Knapp J, Gosalbez M, Lokeshwar SD, Gomez CS, Benitez A, Ekwenna OO, Young EE, Manoharan M, Lokeshwar VB. C-X-C chemokine receptor 7: a functionally associated molecular marker for bladder cancer. *Cancer* 2013; **119**: 61-71 [PMID: 22736438 DOI: 10.1002/cncr.27661]
 - 52 **Bongiovanni L**, Pirozzi F, Guidi F, Orsini M, Chiurazzi P, Bassi PF, Racioppi M, Bradeion (SEPT4) as a urinary marker of transitional cell bladder cancer: a real-time polymerase chain reaction study of gene expression. *J Urol* 2012; **187**: 2223-2227 [PMID: 22503047 DOI: 10.1016/j.juro.2012.01.031]
 - 53 **Brems-Eskildsen AS**, Zieger K, Tolddod H, Holcomb C, Higuchi R, Mansilla F, Munksgaard PP, Borre M, Ørntoft TF, Dyrskjøl L. Prediction and diagnosis of bladder cancer recurrence based on urinary content of hTERT, SENP1, PPP1CA, and MCM5 transcripts. *BMC Cancer* 2010; **10**: 646 [PMID: 21106093 DOI: 10.1186/1471-2407-10-646]
 - 54 **Rosser CJ**, Liu L, Sun Y, Villicana P, McCullers M, Porvasnik S, Young PR, Parker AS, Goodison S. Bladder cancer-associated gene expression signatures identified by profiling of exfoliated urothelia. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 444-453 [PMID: 19190164 DOI: 10.1158/1055-9965.EPI-08-1002]
 - 55 **Holyoake A**, O'Sullivan P, Pollock R, Best T, Watanabe J, Kajita Y, Matsui Y, Ito M, Nishiyama H, Kerr N, da Silva Tatley F, Cambridge L, Toro T, Ogawa O, Guilford P. Development of a multiplex RNA urine test for the detection and stratification of transitional cell carcinoma of the bladder. *Clin Cancer Res* 2008; **14**: 742-749 [PMID: 18245534 DOI: 10.1158/1078-0432.CCR-07-1672]
 - 56 **Anderson NL**, Anderson NG. Proteome and proteomics: new technologies, new concepts, and new words. *Electrophoresis* 1998; **19**: 1853-1861 [PMID: 9740045]
 - 57 **Petricoin EF**, Zoon KC, Kohn EC, Barrett JC, Liotta LA. Clinical proteomics: translating benchside promise into bedside reality. *Nat Rev Drug Discov* 2002; **1**: 683-695 [PMID: 12209149 DOI: 10.1038/nrd891]
 - 58 **Schiffer E**, Mischak H, Theodorescu D, Vlahou A. Challenges of using mass spectrometry as a bladder cancer biomarker discovery platform. *World J Urol* 2008; **26**: 67-74 [PMID: 18175124 DOI: 10.1007/s00345-007-0234-z]
 - 59 **Diamandis EP**. How are we going to discover new cancer biomarkers? A proteomic approach for bladder cancer. *Clin Chem* 2004; **50**: 793-795 [PMID: 15105344 DOI: 10.1373/clinchem.2004.032177]
 - 60 **Chen YT**, Chen HW, Domanski D, Smith DS, Liang KH, Wu CC, Chen CL, Chung T, Chen MC, Chang YS, Parker

- CE, Borchers CH, Yu JS. Multiplexed quantification of 63 proteins in human urine by multiple reaction monitoring-based mass spectrometry for discovery of potential bladder cancer biomarkers. *J Proteomics* 2012; **75**: 3529-3545 [PMID: 22236518 DOI: 10.1016/j.jprot.2011.12.031]
- 61 Rosser CJ, Ross S, Chang M, Dai Y, Mengual L, Zhang G, Kim J, Urquidi V, Alcaraz A, Goodison S. Multiplex protein signature for the detection of bladder cancer in voided urine samples. *J Urol* 2013; **190**: 2257-2262 [PMID: 23764080 DOI: 10.1016/j.juro.2013.06.011]
 - 62 Goodison S, Chang M, Dai Y, Urquidi V, Rosser CJ. A multi-analyte assay for the non-invasive detection of bladder cancer. *PLoS One* 2012; **7**: e47469 [PMID: 23094052 DOI: 10.1371/journal.pone.0047469]
 - 63 Li F, Chen DN, He CW, Zhou Y, Olkkonen VM, He N, Chen W, Wan P, Chen SS, Zhu YT, Lan KJ, Tan WL. Identification of urinary Gc-globulin as a novel biomarker for bladder cancer by two-dimensional fluorescent differential gel electrophoresis (2D-DIGE). *J Proteomics* 2012; **77**: 225-236 [PMID: 22986152 DOI: 10.1016/j.jprot.2012.09.002]
 - 64 Lei T, Zhao X, Jin S, Meng Q, Zhou H, Zhang M. Discovery of potential bladder cancer biomarkers by comparative urine proteomics and analysis. *Clin Genitourin Cancer* 2013; **11**: 56-62 [PMID: 22982111 DOI: 10.1016/j.clgc.2012.06.003]
 - 65 Zoidakis J, Makridakis M, Zerefos PG, Bitsika V, Esteban S, Frantzi M, Stravodimos K, Anagnou NP, Roubelakis MG, Sanchez-Carbajo M, Vlahou A. Profilin 1 is a potential biomarker for bladder cancer aggressiveness. *Mol Cell Proteomics* 2012; **11**: M111.009449 [PMID: 22159600 DOI: 10.1074/mcp.M111.009449]
 - 66 Lindén M, Lind SB, Mayrhofer C, Segersten U, Wester K, Lyutvinskiy Y, Zubarev R, Malmström PU, Pettersson U. Proteomic analysis of urinary biomarker candidates for non-muscle invasive bladder cancer. *Proteomics* 2012; **12**: 135-144 [PMID: 22065568 DOI: 10.1002/pmic.201000810]
 - 67 Bryan RT, Wei W, Shimwell NJ, Collins SI, Hussain SA, Billingham LJ, Murray PG, Deshmukh N, James ND, Wallace DM, Johnson PJ, Zeegers MP, Cheng KK, Martin A, Ward DG. Assessment of high-throughput high-resolution MALDI-TOF-MS of urinary peptides for the detection of muscle-invasive bladder cancer. *Proteomics Clin Appl* 2011; **5**: 493-503 [PMID: 21805675 DOI: 10.1002/prca.201100011]
 - 68 Daviss B. Growing pains for metabolomics. *The Scientist* 2005; **19**: 25-28
 - 69 Jordan KW, Nordenstam J, Lauwers GY, Rothenberger DA, Alavi K, Garwood M, Cheng LL. Metabolomic characterization of human rectal adenocarcinoma with intact tissue magnetic resonance spectroscopy. *Dis Colon Rectum* 2009; **52**: 520-525 [PMID: 19333056 DOI: 10.1007/DCR.0b013e31819c9a2c]
 - 70 Pasikanti KK, Esuvaranathan K, Ho PC, Mahendran R, Kamaraj R, Wu QH, Chiong E, Chan EC. Noninvasive urinary metabolomic diagnosis of human bladder cancer. *J Proteome Res* 2010; **9**: 2988-2995 [PMID: 20337499 DOI: 10.1021/pr901173v]
 - 71 Huang Z, Lin L, Gao Y, Chen Y, Yan X, Xing J, Hang W. Bladder cancer determination via two urinary metabolites: a biomarker pattern approach. *Mol Cell Proteomics* 2011; **10**: M111.007922 [PMID: 21799048 DOI: 10.1074/mcp.M111.007922]
 - 72 Pasikanti KK, Esuvaranathan K, Hong Y, Ho PC, Mahendran R, Raman Nee Mani L, Chiong E, Chan EC. Urinary metabolotyping of bladder cancer using two-dimensional gas chromatography time-of-flight mass spectrometry. *J Proteome Res* 2013; **12**: 3865-3873 [PMID: 23885889 DOI: 10.1021/pr4000448]
 - 73 Choi Y, Kwak J and Park JW. Nanotechnology for Early Cancer Detection. *Sensors* 2010; **10**: 428-455 [DOI: 10.3390/s100100428]
 - 74 Zhang X, Guo Q, Cui D. Recent advances in nanotechnology applied to biosensors. *Sensors* (Basel) 2009; **9**: 1033-1053 [PMID: 22399954 DOI: 10.3390/s90201033]
 - 75 Azzazy HM, Mansour MM, Kazmierczak SC. Nanodiagnosics: a new frontier for clinical laboratory medicine. *Clin Chem* 2006; **52**: 1238-1246 [PMID: 16709623 DOI: 10.1373/clinchem.2006.066654]
 - 76 Radwan SH, Azzazy HM. Gold nanoparticles for molecular diagnostics. *Expert Rev Mol Diagn* 2009; **9**: 511-524 [PMID: 19580434 DOI: 10.1586/erm.09.33]
 - 77 Joshi VG, Chindera K, Singh AK, Sahoo AP, Dighe VD, Thakuria D, Tiwari AK, Kumar S. Rapid label-free visual assay for the detection and quantification of viral RNA using peptide nucleic acid (PNA) and gold nanoparticles (AuNPs). *Anal Chim Acta* 2013; **795**: 1-7 [PMID: 23998531 DOI: 10.1016/j.aca.2013.06.037]
 - 78 Kouassi GK, Irudayaraj J, McCarty G. Activity of glucose oxidase functionalized onto magnetic nanoparticles. *Bio-magn Res Technol* 2005; **3**: 1 [PMID: 15762994 DOI: 10.1186/1477-044X-3-1]
 - 79 Kouassi GK, Irudayaraj J. Magnetic and gold-coated magnetic nanoparticles as a DNA sensor. *Anal Chem* 2006; **78**: 3234-3241 [PMID: 16689521 DOI: 10.1021/ac051621j]
 - 80 Hill HD, Mirkin CA. The bio-barcode assay for the detection of protein and nucleic acid targets using DTT-induced ligand exchange. *Nat Protoc* 2006; **1**: 324-336 [PMID: 17406253 DOI: 10.1038/nprot.2006.51]
 - 81 Storhoff JJ, Elghanian R, Mucic RC, Mirkin CA, Letsinger RL. One-pot colorimetric differentiation of polynucleotides with single base imperfections using gold nanoparticle probes. *J Am Chem Soc* 1998; **120**: 1959-1964 [DOI: 10.1021/ja972332i]
 - 82 Liu X, Atwater M, Wang J, Huo Q. Extinction coefficient of gold nanoparticles with different sizes and different capping ligands. *Colloids Surf B Biointerfaces* 2007; **58**: 3-7 [PMID: 16997536 DOI: 10.1016/j.colsurfb.2006.08.005]
 - 83 Shawky SM, Bald D, Azzazy HM. Direct detection of unamplified hepatitis C virus RNA using unmodified gold nanoparticles. *Clin Biochem* 2010; **43**: 1163-1168 [PMID: 20627095 DOI: 10.1016/j.clinbiochem.2010.07.001]
 - 84 Li H, Rothberg LJ. Label-free colorimetric detection of specific sequences in genomic DNA amplified by the polymerase chain reaction. *J Am Chem Soc* 2004; **126**: 10958-10961 [PMID: 15339181 DOI: 10.1021/ja048749n]
 - 85 Li H, Rothberg L. Detection of specific sequences in RNA using differential adsorption of single-stranded oligonucleotides on gold nanoparticles. *Anal Chem* 2005; **77**: 6229-6233 [PMID: 16194083 DOI: 10.1021/ac050921y]
 - 86 Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer* 2005; **5**: 161-171 [PMID: 15738981 DOI: 10.1038/nrc1566]
 - 87 Wang J, Wu L, Ren J, Qu X. Visualizing Human Telomerase Activity with Primer-Modified Au Nanoparticles. *Small* 2011 Nov 15; Epub ahead of print [PMID: 22083963 DOI: 10.1002/sml.201101938]
 - 88 Eissa S, Shawky SM, Matboli M, Mohamed S, Azzazy HM. Direct detection of unamplified hepatoma upregulated protein RNA in urine using gold nanoparticles for bladder cancer diagnosis. *Clin Biochem* 2013 Oct 29; Epub ahead of print [PMID: 24183881 DOI: 10.1016/j.clinbiochem.2013.10.022]
 - 89 Nossier AI, Eissa S, Ismail MF, Hamdy MA, Azzazy HM. Direct Detection of hyaluronidase in urine using cationic gold nanoparticles: A potential diagnostic test for bladder cancer. *Biosens Bioelectron* 2013 Oct 31; Epub ahead of print [PMID: 24240162 DOI: 10.1016/j.bios.2013.10.024]
 - 90 de Jong BW, Bakker Schut TC, Wolffenbuttel KP, Nijman JM, Kok DJ, Puppels GJ. Identification of bladder wall layers by Raman spectroscopy. *J Urol* 2002; **168**: 1771-1778 [PMID: 12352357 DOI: 10.1016/S0022-5347(05)64411-4]
 - 91 Kidder LH, Kalasinsky VF, Luke JL, Levin IW, Lewis EN. Visualization of silicone gel in human breast tissue us-

- ing new infrared imaging spectroscopy. *Nat Med* 1997; **3**: 235-237 [PMID: 9018246 DOI: 10.1038/nm0297-235]
- 92 **Morris H**, Hoyt CC, Miller P, Treado PJ. Liquid crystal tunable filter Raman chemical imaging. *Appl Spect* 1996; **50**: 805-811 [DOI: 10.1366/0003702963905655]
- 93 **Stone N**, Hart Prieto MC, Crow P, Uff J, Ritchie AW. The use of Raman spectroscopy to provide an estimation of the gross biochemistry associated with urological pathologies. *Anal Bioanal Chem* 2007; **387**: 1657-1668 [PMID: 17123068 DOI: 10.1007/s00216-006-0937-9]
- 94 **Crow P**, Barrass B, Kendall C, Hart-Prieto M, Wright M, Persad R, Stone N. The use of Raman spectroscopy to differentiate between different prostatic adenocarcinoma cell lines. *Br J Cancer* 2005; **92**: 2166-2170 [PMID: 15928665]
- 95 **Shapiro A**, Gofrit ON, Pizov G, Cohen JK, Maier J. Raman molecular imaging: a novel spectroscopic technique for diagnosis of bladder cancer in urine specimens. *Eur Urol* 2011; **59**: 106-112 [PMID: 21035247 DOI: 10.1016/j.eururo.2010.10.027]
- 96 **Sommerauer M**, Jocham D, Laturnus JM. [Non-muscle invasive transitional cell carcinoma of the bladder. New developments in diagnostics and therapy]. *Urologe A* 2012; **51**: 791-797 [PMID: 22618669 DOI: 10.1007/s00120-012-2897-3]
- 97 **Srivastava S**, Gray JW, Reid BJ, Grad O, Greenwood A, Hawk ET. Translational Research Working Group developmental pathway for biospecimen-based assessment modalities. *Clin Cancer Res* 2008; **14**: 5672-5677 [PMID: 18794074 DOI: 10.1158/1078-0432.CCR-08-1267]
- 98 **Pepe MS**, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, Winget M, Yasui Y. Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 2001; **93**: 1054-1061 [PMID: 11459866 DOI: 10.1093/jnci/93.14.1054]
- 99 **Bosman FT**, Yan P, Tejpar S, Fiocca R, Van Cutsem E, Kennedy RD, Dietrich D, Roth A. Tissue biomarker development in a multicentre trial context: a feasibility study on the PETACC3 stage II and III colon cancer adjuvant treatment trial. *Clin Cancer Res* 2009; **15**: 5528-5533 [PMID: 19690194 DOI: 10.1158/1078-0432.CCR-09-0741]
- 100 **Xylinas E**, Kluth LA, Rieken M, Karakiewicz PI, Lotan Y, Shariat SF. Urine markers for detection and surveillance of bladder cancer. *Urol Oncol* 2013 Sep 17; Epub ahead of print [PMID: 24054865]

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Neural regulation of sexual function in men

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Abstract

Male sexual response is controlled by a series of neurally mediated phenomena regulating libido, motivation, arousal and genital responses such as penile erection and ejaculation. These neural events that occur in a hormonally defined milieu involve different neurophysiological, neurochemical, and neuropsychological parameters controlled by central mechanisms, spinal reflexes and peripheral nervous system. Epidemiologic studies have suggested the high prevalence of male sexual dysfunction worldwide with significant impact on the quality of life of patients suffering from this problem. The incidence of sexual dysfunction is particularly high among men with neurologic disorders. Sexual dysfunction in men, such as loss of sexual desire, erectile dysfunction (ED), changes in arousal, and disturbances in orgasm and ejaculation may involve organic causes, psychological problems, or both. Organic male sexual disorders include a wide variety of neurologic, vasculogenic, neurovascular or hormonal factors that interfere with libido,

erection, ejaculation and orgasm. Neurogenic sexual dysfunction may result from a specific neurologic problem or it could be the presenting symptom of a developing neurologic disease. Neurologic ED could result from complications of chronic neurologic disorders, trauma, surgical injury or iatrogenic causes. These etiologic factors and the underlying pathophysiologic conditions could overlap, which should be considered when making a diagnosis and selecting a treatment. A detailed history of physical examination, neurologic disorders, as well as any past history of psychological and psychiatric disturbances, and a thorough neurological examination will provide better understanding of the underlying causes of neurogenic sexual dysfunction. In patients with spinal cord injury, the location of the lesion and the time of onset of injury should be determined. Therapeutic strategies against erectile dysfunction are initiated with the least invasive options using the phosphodiesterase inhibitors. When oral medication options are exhausted, intraurethral and intracavernosal therapies and ultimately vacuum constriction devices and penile implants are considered. Recent basic research has suggested the potential role of stem cell-based therapeutic strategies to protect penile neural integrity and reverse cavernosal neurodegeneration in experimental models. Further insight into the central, spinal and peripheral neural mechanisms of male sexual response may help precise diagnosis and better management of neurogenic sexual dysfunction in men.

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Key words: Sexual function; Nerve; Erection; Penis; Neurotransmission

Core tip: Despite considerable advances in our understanding of male sexual function over the past two decades, crucial central mechanisms and peripheral pathways of male sexual response are still largely unknown. Neural responses to sexual stimulation precede vascular, smooth muscle, and endothelial cell reactions and play leading role in initiating fundamental pathways of

male sexual arousal, erection, orgasm and ejaculation. These pathways involve a dedicated subset of central mechanisms, spinal reflexes, peripheral nerves, and neurotransmission systems that operate at different levels individually and in conjugation. Further research into the neurophysiology of sexual function may help better management of neurogenic sexual dysfunction in men.

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INTRODUCTION

The nervous system is intricately involved in the regulation of male sexual response. Our knowledge into the central and peripheral neural regulation of male sexual function has gained ground with remarkable scientific advances over the past two decades. However, the precise central neural events and the intercommunication between central, spinal, and peripheral nervous system during male sexual response are still largely unknown. Male sexual arousal involves a dedicated subset of neural mechanisms in central nervous system that depend on fundamental neuronal responses, generalized brain activity, initiation of spinal reflexes, and peripheral neural mechanisms that operate at different levels individually and in conjugation.

Neural aspects of male sexual function are essential to most critical phases of sexual response in men including sexual desire, penile erection, and the development of arousal, orgasm and ejaculation. Penile erection is a complex physiological process involving central and peripheral neural mechanisms, blood vessels, and penile smooth muscle and endothelial cells^[1]. Male orgasm is a subjective, perceptual-cognitive event of peak sexual pleasure that coincides with ejaculation. The autonomic nerves mediate one of the most important aspects of the male sexual response as their impulses travel through the cavernous nerves to regulate penile smooth muscle and vascular tone during penile erection and detumescence.

Sexual dysfunction in men involves psychological factors and organic problems. Most cases, however, correlate with organic causes that influence the mechanistic pathways of male sexual response or alter the structure of male sexual organs. Organic sexual dysfunction in men could result from changes in central and peripheral nervous system, hormones, penile vasculature and alterations of erectile tissue endothelium and smooth muscle cells. Loss of sexual drive in men correlates with increase in age^[2]. However, the degree of this decline varies, and most men seem to maintain some amount of libido well into their 60s and 70s^[2]. Other underlying conditions for loss of sex drive in men include depression, stress, decrease in male sex hormones and changes resulting from medications side effects.

Neurologic disorders compromise penile neural integrity and may lead to neural structural damage, functional deficit, or both^[2-5]. Therefore, neurogenic erectile dysfunction (ED) could be an early symptom of progressive neurologic problems. Neurogenic ED may also relate to neural risk factors including alcoholism and other forms of substance abuse, depression, anxiety, stress, surgical treatment of prostate cancer, removal of enlarged prostate, surgical injuries to the pelvic area, and side effects of certain medications^[3]. In most cases, however, neurogenic ED relates to impairment of the cavernous nerve pathways by surgical procedures or traumatic injury. An accurate diagnosis and successful treatment of nerve injury associated ED would depend on functional assessment of the prospective nerves and evaluation of the extent of nerve damage using diagnostic methods to accurately confirm cavernous nerve impairment. In this review, we focus attention on the neuroanatomy and neurophysiology of male sexual response.

NEURAL INTEGRITY AND MALE SEXUAL FUNCTION

An impeccable sexual response in men depends on central and peripheral neural integrity for achieving adequate arousal, erection and orgasm. Neural regulation of male sexual function could be disrupted by changes in central control of sexual response, alterations in spinal and peripheral neural pathways, changes in neurotransmission, or loss of neural function due to traumatic injury^[5,6]. Neurogenic sexual dysfunction is the inability to initiate and maintain sexual activities due to a neurologic disorder. Underlying causes of neurogenic sexual dysfunction in men includes brain and spinal cord injuries, radical pelvic surgeries, diabetes mellitus, multiple sclerosis, stroke and Parkinson disease^[7,8]. The peripheral mechanisms involved in penile erection and ejaculation have been extensively elucidated in the past three decades. However, the contribution of the central mechanisms into sexual response is still less well defined.

Basic research on the central regulation of sexual response using experimental models is currently underway in several institutions. Therapeutic strategies using growth factors and gene therapy have also been used to delay neurodegeneration and stimulate new nerve fiber outgrowth in penile erectile tissue^[9,10]. In clinical studies, positron emission tomography scanners and functional magnetic resonance imaging have been used to explore regional brain activities during sexual stimulation, sexual excitement, and penile erection^[11-13]. Further insight into the central pathways and peripheral neural mechanisms of male sexual response may lead to more precise diagnosis and treatment of specific neural deficits in neurogenic ED, anorgasmia and ejaculation disorders.

NEUROANATOMY

The neuroanatomy of male sexual response encompasses

a wide variety of anatomical structures in the brain, spinal cord, and peripheral nervous system including autonomic, somatic, sensory and motor neuronal structures^[14]. At the spinal cord at the T9 to L4 levels, the intermediolateral column of gray matter gives rise to the sympathetic preganglionic nerve bundles. At the level of S2 to S4, the intermediolateral column gives rise to the parasympathetic nerves^[15,16]. Continuation of these nerves assembles the framework of the pelvic and hypogastric plexuses. The penis is innervated by both autonomic and somatic nervous system^[15]. At the spinal and peripheral levels, the autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) nerves extend to innervate the penis^[17].

Parasympathetic nerves

The neurons in the intermediolateral cell columns of the second, third and fourth sacral spinal cord segments (pelvic nerves) provide parasympathetic nerve fibers to the penis. At the level of the pelvic plexus, the preganglionic nerves are joined by sympathetic nerves originating from the hypogastric plexus. This plexus gives rise to branches that innervate the rectum, bladder, prostate and sphincters. The pelvic plexus give rise to a neural framework called cavernosal nerves that innervate the penile corpora cavernosa including terminal arterioles and erectile tissue^[18]. The cavernosal nerves pass the prostate posterolaterally and then extend lateral to the membranous urethra and anterior to the bulbous urethra where they enter the hilum of the penis. The cavernosal nerve may be easily injured during radical pelvic surgery as well as transurethral prostatectomy, external sphincterotomy or any procedure using electrocautery in that region because it is closely applied to the apex of the prostate and membranous urethra.

Studies of penile tissue samples from human and experimental models have suggested that nitrergic nerves contributing to erection originate from the ganglia close to the corpus cavernosum^[19,20]. The preganglionic cavernosal nerves are believed to synapse with nitrergic nerves within or near the tunica albuginea^[19,20]. Penile erection following stimulation of the pelvic or the cavernosal nerves has been documented in both humans^[21] and in animal models^[22,23]. However, the precise nature of the cavernous nerve and whether or not it is a purely parasympathetic nerve remains controversial. Retrograde labeling and high resolution autoradiographic studies have suggested that some sympathetic fibers emanating from the lumbosacral sympathetic chain exist in the pelvic nerve of the male rat^[24].

Sympathetic nerves

The sympathetic nerves to the male genital organs, which contribute to the regulation of penile detumescence and ejaculation, originate from the preganglionic neurons of the tenth to twelfth thoracic and first and second lumbar segments of the spinal cord. These preganglionic fibers pass *via* rami to the paravertebral sympathetic chain gan-

glia and descend to make synaptic connections with the postganglionic neurons then travel *via* the pelvic splanchnic nerves to the inferior mesenteric plexus, the hypogastric plexus and the perivesical plexus. Some fibers travel *via* the hypogastric nerve to the pelvic plexus. The hypogastric nerve is a discrete branch from these plexuses that enters the perivesical plexus where it may communicate with parasympathetic nerve fibers. The pelvic plexus is a crucial site in the integration of the autonomic input to the male genitalia.

Studies of experimental models have shown that stimulation of the hypogastric nerve or the sympathetic trunk has no significant effect on intracavernosal pressure in the flaccid state of penis but its stimulation during an erection causes penile detumescence^[25]. These observations suggest that some sympathetic fibers may travel *via* the cavernous nerves to the penile corpora cavernosa. In the erect state of the penis, stimulation of the cut distal end of the pudendal nerve results in detumescence^[25]. It is thought that some sympathetic fibers, especially the sensory branch, may travel *via* the pudendal nerve. Intracavernosal pressure rise and penile tumescence after stimulation of the sympathetic nerves has been documented in the rat model^[26]. The precise mechanism of proerectile activity following sympathetic nerve stimulation remains unclear. One possibility may be the intercommunication between sympathetic fibers and nitrergic nerves within the penile erectile tissue to release nitric oxide. Another possibility is sympathetic-mediated pelvic vasoconstriction and shunting of blood flow toward the penile erectile tissue.

Sensory nerves

The sensory nerves of the penis are primarily in the penile skin and glans as free and specialized nerve endings and receptors. The most numerous nerve terminals in the glans penis are free nerve endings (FNEs). Genital end bulbs are denser in the corona and near the frenulum and are present throughout the glans. The ratio of FNE to corpuscular receptors is approximately 10:1^[27]. Axon terminals that resemble a tangled web of FNEs are present at the genital end bulbs unique to the glans penis^[27]. Sensory nerves relaying pain and pressure sensation are also present in the urethra and corpora cavernosa^[27]. Pain mediating signals and temperature sensation travel from free nerve endings *via* small diameter, thinly myelinated or unmyelinated nerve fibers. Large diameter myelinated fibers mediate the sense of vibration, touch and pressure^[28]. These nerve fibers merge to assemble the dorsal nerve of the penis^[27,28]. The dorsal nerve converges with other perineal nerves to become the internal pudendal nerve, which ascends to the dorsal roots of the second to fourth sacral nerves. The ascending pathways in the spinal cord travel *via* the spinothalamic tract to the thalamus and to the sensory cortex^[27,28].

Somatic nerves

The ventral roots of sacral segments two through four along with coalesce form the paired pudendal nerves

provide somatic motor nerves to the penis. These nerves descend together with the internal pudendal vessels as they travel *via* Alcock's canal then provide somatic fibers to the striated muscle of the pelvis. These nerves extend as perineal nerve into the perineum and innervate the bulbocavernosus and ischiocavernosus muscles. These muscles are believed to provide temporary increases in intracavernosal pressure and contribute to penile rigidity during erection^[29]. This is thought to aid in allowing successful vaginal penetration.

Co-existence and co-release of neurotransmitters

Immunohistochemical staining have revealed the co-existence of vesicular acetylcholine transporter, neural nitric oxide synthase (nNOS), vasoactive intestinal polypeptide (VIP), tyrosine hydroxylase, and heme oxygenase in tissue samples from human corpus cavernosum and spongiosum^[30]. Immunoreactivity for endothelial nitric oxide synthase (eNOS) and heme oxygenase has been detected in the endothelial lining of corpus cavernosum and penile arteries^[30]. Calcitonin gene related peptide has been localized within cavernosal nerves, cavernosal smooth muscle and cavernous arterial wall^[31]. Co-release of neuropeptide Y and noradrenaline in autonomic nerves and release of calcitonin gene related peptide in the sensory nerves have been documented in the rat corpus cavernosum^[32]. A rich sympathetic adrenergic innervation has been demonstrated in the human penile cavernosal tissue, penile microvasculature and helicine arteries^[33,34]. Co-release of norepinephrine and neuropeptide Y from the penile adrenergic nerves has been documented in rats^[34]. Downregulation of cavernosal nNOS and eNOS after bilateral cavernosal nerve injury was found simultaneous with upregulation of Rho-associated protein kinase in rat erectile tissue^[35]. Inhibition of Rho-kinase was associated with increased nitric oxide (NO) signaling in the rat erectile tissue^[35].

NEUROPHYSIOLOGY OF MALE SEXUAL RESPONSE

Male sexual response is a complex multidisciplinary biologic process involving central pathways and peripheral neural mechanisms controlling libido, arousability, penile erection and rigidity, orgasm and ejaculation. Neurologic disorders that can compromise central pathways and peripheral neuronal mechanisms would disrupt physiological sexual response during sexual stimulation. The central, spinal, and peripheral neural mechanisms that regulate male sexual response are summarized below.

Central control of male sexual function

Central regulation of male sexual function is less explored in comparison with the peripheral neural pathways. Multi-regional central neural mechanisms and inter-regional brain communications appear to be involved in male sexual response. It is known that cerebrocortical function is crucial to the initiation of sexual response

in men^[36,37]. However, the precise areas of the cerebral cortex involved in regulating libido, sexual fantasy and arousal are not well characterized. Studies of patients with traumatic brain injury suggest that the temporal and frontal lobes may play a crucial role in regulating sexual interest and behavior^[37]. The septal portion of the hippocampus, the anterior cingulate gyrus, the anterior thalamic nuclei, the mammillothalamic tract and the mammillary bodies control penile erectile activities^[36,37]. The medial dorsal nucleus of the thalamus and the medial pre-optic area appear to play crucial roles in the control of penile erection and sexual drive^[38,39].

Central neurotransmitters

Central control of male sexual response involves multiple neurotransmitters including serotonin (5-hydroxytryptamine), dopamine, norepinephrine, nitric oxide and many others. Serotonin tends to block the penile erectile pathway at both spinal^[40] and supraspinal sites^[41]. Gamma amino butyric acid^[42], prolactin^[43] and endogenous opioid peptides^[44] are also known as the central inhibitors of sexual activity in men. Dopamine is thought to regulate erection by acting on oxytocin containing neurons in the paraventricular nucleus of the hypothalamus^[45,46].

In experimental animal models, systemic administration of dopamine and dopamine agonists such as apomorphine induce erectile activity *via* central mechanisms^[45,46]. Norepinephrine plays various roles in central regulation of male sexual function^[47]. Inhibition of central alpha-2 adrenoceptors facilitates sexual function while stimulation of these receptors produces the opposite effect^[47]. Increased sexual motivation has been documented after administration of yohimbine, a central alpha-2 receptor blocker^[48]. Oxytocin that has been localized in descending pathways from hypothalamus to brain stem is thought to mediate the effects of dopamine on penile erection *via* the oxytocin containing neurons^[49,50]. Ascending sensory stimuli from the dorsal penile nerve stimulates oxytocin-containing cells in the supraoptic nucleus^[49,50]. Dense nitric oxide synthase is localized in the paraventricular nucleus of the hypothalamus^[51]. Administration of nitric oxide synthase blockers to the lateral ventricles or to the hypothalamus prevents erectogenic effects of dopamine agonists and oxytocin in experimental models^[52]. The role of adrenocorticotropin and related peptides (melanocortin) in penile erection and ejaculation has been documented in patients with psychogenic erectile dysfunction^[53]. A synthetic analogue of alpha-melanocyte stimulating hormone was shown to reverse erectile dysfunction in these patients^[53].

Role of spinal reflexes

Spinal reflexes are crucial determinant of both the initiation and the maintenance of male sexual response. The spinal cord, paraspinal sympathetic ganglia, and parasympathetic nerves play a direct role in regulating functional changes of the male genitals. Sympathetic nerve fibers involved in sexual response originate from the interme-

diolateral column of gray matter at the level of T9-L4 in the spinal cord. The intermediolateral column at the levels of S2-S4 gives rise to the parasympathetic nerve fibers that innervate male genitalia. These nerve fibers descend to form the most important plexuses involved in sexual physiology, the pelvic and hypogastric plexus. The cavernosal nerve originates from the pelvic plexus and travels through the pelvic fascia and posterolateral aspect of the prostate. The parasympathetic nerves exit the spinal cord through the ventral roots and constitute the pelvic nerves. Upon sexual stimulation by visual, olfactory, and imaginary stimuli, penile erection takes place as a spinal reflex that is initiated by recruitment of penile stimulation traveling *via* the dorsal penile nerve^[36,37]. The reflex that involves both autonomic and somatic efferent is heavily modulated by supraspinal influences. Local segmental reflexes in the lumbosacral cord subserve penile erection^[36,37]. These reflexes are generally under the net tonic inhibitory control by higher centers^[37].

Peripheral mechanisms

The peripheral neural pathways of sexual response particularly penile erection have received greater research and clinical attention than the central and spinal mechanisms. Basic research on the hemodynamic of penile erection and regulation of penile smooth muscle contractility resulted in the development of oral medications for erectile dysfunction. It was shown that a dedicated subset of neuronal mechanisms involving the adrenergic, cholinergic, and non-adrenergic non-cholinergic neurotransmission regulate cavernosal smooth muscle tone which determines penile tumescence and detumescence^[23,54,55].

Basic research with experimental models have shown that electrical stimulation of the pelvic plexus and the cavernous nerve leads to erection, while stimulation of the hypogastric nerve or the sympathetic trunk induces detumescence^[23,54,55]. It was shown that the sacral parasympathetic regulates penile tumescence and that the thoracolumbar sympathetic input mediates detumescence^[25-27]. Follow up studies demonstrated that sensory stimuli relating to initiation and maintenance of erection originate primarily from the glans and travel *via* the dorsal nerve of the penis^[27,28]. The most crucial step in the peripheral motor control of penile erection depend on smooth muscle tone in the erectile tissue and penile arterioles in the corpora cavernosa^[56,57]. Alterations of smooth muscle tone in the tumescence and detumescence states of the penis are regulated by sympathetic and parasympathetic nervous systems and endothelial-mediated mechanisms^[54,55]. It was shown that coordinated changes in smooth muscle tone of the penile erectile tissue and arterioles control the amount of blood entering to the cavernosal sinusoids and the amount of blood exiting the corpora^[54,55].

Role of the adrenergic nerves

The primary adrenergic transmitter in the penis that controls smooth muscle contraction and induces penile

detumescence is norepinephrine^[56-59]. The regulation of adrenergic nerve activity and neurotransmission discharge in the penis is complex and appears to involve intercommunication with the cholinergic and the non-adrenergic non-cholinergic systems. As example, norepinephrine release from adrenergic nerves is pre-junctionally regulated by the cholinergic nerves^[56]. The alpha and beta adrenergic receptors are localized in both penile blood vessels^[57] and cavernous smooth muscle cells^[34]. Alpha-1 adrenoceptors are more abundant in the erectile tissue smooth muscle while both alpha-1 and alpha-2 receptors have been localized in the penile arterioles^[58,59]. Alpha-2 receptors have been localized both on pre-junctional sites of the adrenergic nerves and on erectile tissue smooth muscle^[58].

Alpha-2 adrenoceptors on prejunctional sites mediate the feedback inhibition of norepinephrine discharge from the adrenergic nerves^[56]. Upon release from the adrenergic nerves, norepinephrine binds to the pre-junctional alpha-2 adrenoceptor on the adrenergic nerves and inhibits norepinephrine release. This observation suggests that inhibition of alpha-2 receptor with selective antagonists such as yohimbine would inhibit erection by increasing norepinephrine release. It is also suggested that after release from adrenergic nerves, norepinephrine binds to the pre-junctional alpha-2 adrenoceptor on the non-adrenergic, non-cholinergic nerves and inhibits nitric oxide production and bioavailability^[56,59,60]. It is thought that inhibition of this reaction by selective alpha-2 receptor antagonists will increase nitric oxide synthesis and promote erection. The smooth muscle alpha-2 adrenoceptors appear to play a role in the mediation of penile smooth muscle cell contraction^[60]. Erectile tissue exposure to alpha-2 adrenoceptor agonists results in smooth muscle contraction^[58,59]. In contrast, inhibition of smooth muscle alpha-2 adrenoceptors induces penile smooth muscle relaxation and promotes erection^[56,59,60].

Role of the cholinergic nerves

Dense cholinergic innervation has been immunostained in penile corpus cavernosum and corpus spongiosum^[30]. Immunohistochemical staining has also revealed that penile cholinergic nerves contain NO synthase and VIP. These observations led to the notion that vasodilators such as NO and VIP may be co-released along with acetylcholine from the cholinergic nerves^[30,61]. These studies suggested that acetylcholine, whether released from the cholinergic nerves or applied directly to corpus cavernosum, initiates a variety of reactions in the erectile tissue.

Functional assessments of experimental models revealed erectile response to acetylcholine administered systemically or directly into the cavernosal tissue^[62-64]. While having no effect on relaxed erectile tissues, acetylcholine produced concentration-dependent relaxation of erectile tissues that has been precontracted with norepinephrine^[65,66]. Subsequent mechanistic studies with isolated erectile tissues from human and animals showed that the relaxing effects acetylcholine is partially blocked

by atropine but it could be abolished by removal of the endothelium^[65,66]. The relaxing effect of acetylcholine that was markedly attenuated by removal of the endothelium introduced the theory of endothelial derived relaxing factor released from the endothelium under the influence of acetylcholine in the erectile tissue^[67]. These findings indicated that acetylcholine may act on adrenergic nerve terminals to suppress the release of norepinephrine^[65,66,68]. These observations collectively suggested that acetylcholine may induce cavernosal smooth muscle relaxation by co-release of nitric oxide and perhaps VIP from cholinergic nerve terminals, release of nitric oxide from the vascular endothelium, and suppression of norepinephrine release. The involvement of endothelium was an astonishing finding that led researchers to search for a non-adrenergic non-cholinergic mechanism of penile smooth muscle relaxation.

Role of non-adrenergic non-cholinergic neurotransmission

NO is well established as an important non-adrenergic non-cholinergic (NANC) neurotransmitter in the physiology of penile erection^[67-71]. The NO/cyclic guanosine monophosphate signaling pathway has been widely recognized as the primary mediator of cavernosal smooth muscle relaxation and penile erection^[67,69]. Mechanistic studies showed relaxation of human and rabbit penile smooth muscle in response to a solution saturated with NO gas^[67]. Subsequent studies characterized nitric oxide synthase (NOS) as the enzyme that catalyzes the interaction of L-arginine and molecular oxygen in a process that consumes NADPH to produce NO and L-citrulline^[67,69]. NOS exists in constitutive neuronal (nNOS) and endothelial (eNOS) forms, and inducible (iNOS) form. The constitutive forms of the enzyme are coupled to Ca^{2+} and calmodulin and are crucial to penile smooth muscle relaxation and erection.

Basal production of NO is regulated by constitutive NOS that is known to be involved in a variety of physiologic conditions such as cardiac and pulmonary perfusion, heart rate, myocardial contractility, vasodilation and penile erection^[70]. iNOS is independent of Ca^{2+} and calmodulin and is believed to be upregulated in cellular stress and pathologic conditions^[71]. In experimental models, long-term exposure of penile erectile tissue to ischemia has resulted in progressive downregulation of nNOS and eNOS and a significant increase in iNOS expression^[72].

The relaxing role of NO in penile smooth muscle cells involves production and accumulation of the cyclic guanosine-3',5'-monophosphate (cGMP) in erectile tissue. Upon release from cavernous nerves and endothelium, NO diffuses locally into adjacent smooth muscle cells then activates guanylate cyclase to catalyze the formation of cGMP from guanosine-5'-triphosphate^[67,69]. The increased levels of cGMP initiate a cascade of intracellular changes leading to activation of protein kinase G, also known as cGMP-dependent protein kinase I. These

events result in the reduction of cytosolic free calcium by various mechanisms leading to smooth muscle relaxation^[67,69].

Relaxation of the trabecular smooth muscle and arterioles results in increased intracavernosal blood flow and activation of corporal veno-occlusive mechanism leading to penile erection. Another cellular mechanism that is thought to maintain penile erection is regulated by phosphatidylinositol 3-kinase (PI3-kinase) pathway that activates the serine/threonine protein kinase Akt, also known as protein kinase B^[73]. This induces eNOS phosphorylation, reduces the enzyme's calcium requirement, and enhances NO production^[73]. It is believed that after the initiation of erectile process, PI3-kinase/Akt mediated phosphorylation of eNOS result in sustained NO production and penile erection.

Other NANC factors in penile erection

Vasoactive neuropeptides including VIP, substance P, neuropeptide Y, somatostatin, peptide histidine-isoleucine, enkephalins and calcitonin gene-related peptide have been localized along the nerves supplying the penis^[74-76]. The precise role of these neuropeptides is not well understood. VIP is believed to be co-released with NO from the cholinergic nerves^[74,75]. Vasoconstrictive paracrine factors such as endothelin^[77], angiotensin^[78], prostaglandin F₂-alpha^[79], thromboxane^[80] and histamine^[81] have also been localized in penile erectile tissue but whether they synergize with other neurotransmitters or are modulators of smooth muscle tone is unclear.

Endothelins localized in the penile erectile tissue are potent constrictors of smooth muscle cells^[77]. Three isoforms of endothelin called ET-1, ET-2 and ET-3 and two different receptors named ET_A and ET_B have been reported in penile erectile tissue^[77]. The ET_A and ET_B receptors are located on vascular smooth muscle and endothelial cells, respectively. ET_A receptor mediates contraction and proliferation while the ET_B receptor contributes to vasodilation^[77]. Angiotensin I and II and two subtypes of angiotensin II receptor (AT₁ and AT₂) have been characterized^[82-84]. It was shown that AT₁ receptor is expressed in the erectile tissue^[83] and that angiotensin II causes a dose-dependent contraction of cavernosal smooth muscle^[84].

Some of the prostaglandins (PGs) in the penis appear to act as modulators of cavernosal smooth muscle reactivity^[85,86]. PGF_{2α}, PGI₂ and thromboxane A₂ cause cavernosal smooth muscle contraction while PGE₁ and PGE₂ induce relaxation^[87]. In addition to direct vascular smooth muscle relaxation, PGE₁ may also act to inhibit the release of neuronal norepinephrine^[88]. A variety of pathologic conditions interfere with the production and action of prostaglandins in erectile tissue. For example, hypoxia was shown to inhibit production of prostanoids in the cavernosal tissue^[89,90]. Castration in experimental models was shown to diminish cavernosal smooth muscle relaxation in response to PGE₁, suggesting that androgens may be a prerequisite for their action^[91].

Bradykinin relaxes corpus cavernosum tissue and its effects appear to be mediated through cyclic adenosine monophosphate and cGMP^[78]. It is thought that bradykinin acts on cavernosal BK2 receptors and stimulates the release of endothelial nitric oxide^[92]. Histamine appears to induce endothelium-independent relaxation of erectile tissue and penile microvasculature^[81,93]. The relaxatory effects of histamine seem to be mediated by histamine H2 receptors located on vascular smooth muscle. Histamine appears to act on smooth muscle cells without the intervention of nitric oxide or relaxant prostanoids^[93].

SUMMARY

Neurophysiology of male sexual response involves multi-regional central neural mechanisms, inter-regional brain communications, and intricate spinal and peripheral neural mechanisms. Our knowledge into the central and peripheral neural regulation of male sexual function continues to gain ground with remarkable scientific advances over the past two decades. Peripheral neural events in male sexual response and the mechanism of penile smooth muscle relaxation have been extensively studied and newer components in these pathways are emerging. A variety of neurologic disorders contribute to the development of male sexual dysfunction and, in some cases, neurologic sexual dysfunction may be a presenting symptom of the impending neurologic disease. Mechanistic knowledge into downstream pathways of NO/cGMP signaling introduced newer concepts in the molecular mechanism of erection and led to the investigation of innovative therapeutic strategies against erectile dysfunction, including the possibility of gene therapy and use of stem cells. However, despite such advances, the precise diagnosis of central problems and peripheral neural factors in neurogenic sexual dysfunction still remain as a major clinical challenge. Nonspecific therapies have been somewhat effective in early-state neurogenic erectile dysfunction but have failed to restore erection in most patients with advanced neurologic problems. Further research into the central, spinal and peripheral neural regulation of sexual function may help the development of more precise diagnostic tools, newer therapeutic strategies, and better management of neurogenic sexual dysfunction in men.

REFERENCES

- 1 **Lizza EF**, Rosen RC. Definition and classification of erectile dysfunction: report of the Nomenclature Committee of the International Society of Impotence Research. *Int J Impot Res* 1999; **11**: 141-143 [PMID: 10404282 DOI: 10.1038/sj.ijir.3900396]
- 2 **Ginsberg TB**. Aging and sexuality. *Med Clin North Am* 2006; **90**: 1025-1036 [PMID: 16962855 DOI: 10.1016/j.mcna.2006.06.003]
- 3 **Nusbaum MR**. Erectile dysfunction: prevalence, etiology, and major risk factors. *J Am Osteopath Assoc* 2002; **102**: S1-S6 [PMID: 12572634]
- 4 **Shafik A**, El-Sibai O. Mechanism of ejection during ejaculation: identification of a urethrocavernosus reflex. *Arch Androl* 2000; **44**: 77-83 [PMID: 10690768 DOI: 10.1038/sc.2009.172]
- 5 **Everaert K**, de Waard WL, Van Hoof T, Kiekens C, Mulliez T, D'herde C. Neuroanatomy and neurophysiology related to sexual dysfunction in male neurogenic patients with lesions to the spinal cord or peripheral nerves. *Spinal Cord* 2010; **48**: 182-191 [PMID: 20048757]
- 6 **Yang CC**, Jiang X. Clinical autonomic neurophysiology and the male sexual response: an overview. *J Sex Med* 2009; **6** Suppl 3: 221-228 [PMID: 19267845 DOI: 10.1111/j.1743-6109.2008.01180.x]
- 7 **Sáenz de Tejada I**, Angulo J, Celtek S, González-Cadavid N, Heaton J, Pickard R, Simonsen U. Pathophysiology of erectile dysfunction. *J Sex Med* 2005; **2**: 26-39 [PMID: 16422902 DOI: 10.1111/j.1743-6109.2005.20103.x]
- 8 **Lewis RW**, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, Martin-Morales A. Epidemiology/risk factors of sexual dysfunction. *J Sex Med* 2004; **1**: 35-39 [PMID: 16422981 DOI: 10.1111/j.1743-6109.2004.10106.x]
- 9 **Mills JN**, Dall'Era JE, Carlsen SN, Koul H, Meacham RB. Gene therapy for erectile dysfunction. *Pharmacogenomics* 2007; **8**: 979-984 [PMID: 17716231 DOI: 10.2217/14622416.8.8.979]
- 10 **Lin G**, Albersen M, Harraz AM, Fandel TM, Garcia M, McGrath MH, Konety BR, Lue TF, Lin CS. Cavernous nerve repair with allogenic adipose matrix and autologous adipose-derived stem cells. *Urology* 2011; **77**: 1509.e1-1509.e8 [PMID: 21492917 DOI: 10.1016/j.urology.2010.12.076]
- 11 **Stoléru S**, Grégoire MC, Gérard D, Decety J, Lafarge E, Cinotti L, Lavenne F, Le Bars D, Vernet-Maury E, Rada H, Collet C, Mazoyer B, Forest MG, Magnin F, Spira A, Comar D. Neuroanatomical correlates of visually evoked sexual arousal in human males. *Arch Sex Behav* 1999; **28**: 1-21 [PMID: 10097801]
- 12 **Redouté J**, Stoléru S, Grégoire MC, Costes N, Cinotti L, Lavenne F, Le Bars D, Forest MG, Pujol JF. Brain processing of visual sexual stimuli in human males. *Hum Brain Mapp* 2000; **11**: 162-177 [PMID: 11098795 DOI: 10.1002/1097-0193(200011)11]
- 13 **Maravilla KR**, Deliganis AV, Heiman J. BOLD fMRI evaluation of normal female sexual arousal response: sites of cerebral activation correlated with subjective and objective measures of arousal. *Proc Intl Soc Mag Reson Med* 2000; **8**: 918 Available from: URL: <http://cds.ismrm.org/ismrm-2000/PDF4/0918.pdf>
- 14 **Giuliano F**, Rampin O. Neural control of erection. *Physiol Behav* 2004; **83**: 189-201 [PMID: 15488539]
- 15 **Breza J**, Aboseif SR, Orvis BR, Lue TF, Tanagho EA. Detailed anatomy of penile neurovascular structures: surgical significance. *J Urol* 1989; **141**: 437-443 [PMID: 2913372]
- 16 **Giuliano FA**, Rampin O, Benoit G, Jardin A. Neural control of penile erection. *Urol Clin North Am* 1995; **22**: 747-766 [PMID: 7483126]
- 17 **Rampin O**, Bernabé J, Giuliano F. Spinal control of penile erection. *World J Urol* 1997; **15**: 2-13 [PMID: 9066088 DOI: 10.1007/BF01275150]
- 18 **Paick JS**, Donatucci CF, Lue TF. Anatomy of cavernous nerves distal to prostate: microdissection study in adult male cadavers. *Urology* 1993; **42**: 145-149 [PMID: 8367921 DOI: 10.1016/0090-4295(93)90637-P]
- 19 **Alsaid B**, Moszkowicz D, Peschaud F, Bessede T, Zaitouna M, Karam I, Droupy S, Benoit G. Autonomic-somatic communications in the human pelvis: computer-assisted anatomic dissection in male and female fetuses. *J Anat* 2011; **219**: 565-573 [PMID: 21781094 DOI: 10.1111/j.1469-7580.2011.01416.x]
- 20 **Ayajiki K**, Hayashida H, Tawa M, Okamura T, Toda N. Characterization of nitrergic function in monkey penile erection in vivo and in vitro. *Hypertens Res* 2009; **32**: 685-689 [PMID: 19498439 DOI: 10.1038/hr.2009.84]
- 21 **Brindley GS**, Polkey CE, Rushton DN, Cardozo L. Sacral anterior root stimulators for bladder control in paraplegia:

- the first 50 cases. *J Neurol Neurosurg Psychiatry* 1986; **49**: 1104-1114 [PMID: 3491180 DOI: 10.1136/jnnp.49.10.1104]
- 22 **Lue TF**, Takamura T, Schmidt RA, Palubinskas AJ, Tanagho EA. Hemodynamics of erection in the monkey. *J Urol* 1983; **130**: 1237-1241 [PMID: 6417346]
 - 23 **Azadzoï KM**, Vlachiotis J, Pontari M, Siroky MB. Hemodynamics of penile erection: III. Measurement of deep intracavernosal and subtunical blood flow and oxygen tension. *J Urol* 1995; **153**: 521-526 [PMID: 7815637 DOI: 10.1097/00005392-199502000-00075]
 - 24 **Giuliano F**, Facchinetti P, Bernabé J, Benoit G, Calas A, Rampin O. Evidence of sympathetic fibers in the male rat pelvic nerve by gross anatomy, retrograde labeling and high resolution autoradiographic study. *Int J Impot Res* 1997; **9**: 179-185 [PMID: 9442414 DOI: 10.1038/sj.ijir.3900292]
 - 25 **Argiolas A**, Melis MR. The neurophysiology of the sexual cycle. *J Endocrinol Invest* 2003; **26**: 20-22 [PMID: 12834016]
 - 26 **Giuliano F**, Bernabé J, Brown K, Droupy S, Benoit G, Rampin O. Erectile response to hypothalamic stimulation in rats: role of peripheral nerves. *Am J Physiol* 1997; **273**: R1990-R1997 [PMID: 9435653]
 - 27 **Halata Z**, Munger BL. The neuroanatomical basis for the protopathic sensibility of the human glans penis. *Brain Res* 1986; **371**: 205-230 [PMID: 3697758 DOI: 10.1016/0006-8993(86)90357-4]
 - 28 **Yang CC**, Bradley WE. Peripheral distribution of the human dorsal nerve of the penis. *J Urol* 1998; **159**: 1912-1916; discussion 1916-1917 [PMID: 9598486 DOI: 10.1016/S0022-5347(01)63194-X]
 - 29 **Wespes E**, Nogueira MC, Herbaut AG, Caufriez M, Schulman CC. Role of the bulbocavernosus muscles on the mechanism of human erection. *Eur Urol* 1990; **18**: 45-48 [PMID: 2401306]
 - 30 **Hedlund P**, Ny L, Alm P, Andersson KE. Cholinergic nerves in human corpus cavernosum and spongiosum contain nitric oxide synthase and heme oxygenase. *J Urol* 2000; **164**: 868-875 [PMID: 10953170 DOI: 10.1016/S0022-5347(05)67329-6]
 - 31 **Stief CG**, Benard F, Bosch R, Aboseif S, Wetterauer U, Lue TF, Tanagho EA. Calcitonin gene-related peptide: possibly neurotransmitter contributes to penile erection in monkeys. *Urology* 1993; **41**: 397-401 [PMID: 8470332 DOI: 10.1016/0090-4295(93)90608-D]
 - 32 **Morrison JF**, Dhanasekaran S, Howarth FC. Neuropeptides in the rat corpus cavernosum and seminal vesicle: effects of age and two types of diabetes. *Auton Neurosci* 2009; **146**: 76-80 [PMID: 19152794 DOI: 10.1016/j.autneu.2008.11.016]
 - 33 **Hauser-Kronberger C**, Hacker GW, Graf AH, Mack D, Sundler F, Dietze O, Frick J. Neuropeptides in the human penis: an immunohistochemical study. *J Androl* 1994; **15**: 510-520 [PMID: 7536724]
 - 34 **Andersson KE**, Hedlund P, Alm P. Sympathetic pathways and adrenergic innervation of the penis. *Int J Impot Res* 2000; **12**: S5-S12 [PMID: 10849560 DOI: 10.1038/sj.ijir.3900513]
 - 35 **Hannan JL**, Albersen M, Kutlu O, Gratzke C, Stief CG, Burnett AL, Lysiak JJ, Hedlund P, Bivalacqua TJ. Inhibition of Rho-kinase improves erectile function, increases nitric oxide signaling and decreases penile apoptosis in a rat model of cavernous nerve injury. *J Urol* 2013; **189**: 1155-1161 [PMID: 23021998 DOI: 10.1016/j.juro.2012.09.104]
 - 36 **Giuliano F**, Rampin O, Bernabé J, Rousseau JP. Neural control of penile erection in the rat. *J Auton Nerv Syst* 1995; **55**: 36-44 [PMID: 8690849 DOI: 10.1016/0165-1838(95)00025-S]
 - 37 **Steers WD**. Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications. *Neurosci Biobehav Rev* 2000; **24**: 507-516 [PMID: 10880817 DOI: 10.1016/S0149-7634(00)00019-1]
 - 38 **MacLean PD**, Ploog DW. Cerebral representation of penile erection. *J Neurophysiol* 1962; **25**: 29-55. Available from: URL: <http://jn.physiology.org/content/25/1/29.full.pdf+html>
 - 39 **Slimp JC**, Hart BL, Goy RW. Heterosexual, autosexual and social behavior of adult male rhesus monkeys with medial preoptic-anterior hypothalamic lesions. *Brain Res* 1978; **142**: 105-122 [PMID: 414825 DOI: 10.1016/0006-8993(78)90180-4]
 - 40 **Marson L**, McKenna KE. A role for 5-hydroxytryptamine in descending inhibition of spinal sexual reflexes. *Exp Brain Res* 1992; **88**: 313-320 [PMID: 1577105 DOI: 10.1007/BF02259106]
 - 41 **McIntosh TK**, Barfield RJ. Brain monoaminergic control of male reproductive behavior. I. Serotonin and the post-ejaculatory refractory period. *Behav Brain Res* 1984; **12**: 255-265 [PMID: 6235821 DOI: 10.1016/0166-4328(84)90151-7]
 - 42 **Fernández-Guasti A**, Larsson K, Beyer C. GABAergic control of masculine sexual behavior. *Pharmacol Biochem Behav* 1986; **24**: 1065-1070 [PMID: 3012591 DOI: 10.1016/0091-3057(86)90456-9]
 - 43 **Rehman J**, Christ G, Alyskewycz M, Kerr E, Melman A. Experimental hyperprolactinemia in a rat model: alteration in centrally mediated neuroerectile mechanisms. *Int J Impot Res* 2000; **12**: 23-32 [PMID: 10982309 DOI: 10.1038/sj.ijir.3900473]
 - 44 **Pfaus JG**, Gorzalka BB. Opioids and sexual behavior. *Neurosci Biobehav Rev* 1987; **11**: 1-34 [PMID: 3554038 DOI: 10.1016/S0149-7634(87)80002-7]
 - 45 **Pehek EA**, Thompson JT, Eaton RC, Bazzett TJ, Hull EM. Apomorphine and haloperidol, but not domperidone, affect penile reflexes in rats. *Pharmacol Biochem Behav* 1988; **31**: 201-208 [PMID: 3252251 DOI: 10.1016/0091-3057(88)90334-6]
 - 46 **Giuliano F**, Allard J. Dopamine and sexual function. *Int J Impot Res* 2001; **13** Suppl 3: S18-S28 [PMID: 11477488 DOI: 10.1038/sj.ijir.3900719]
 - 47 **Giuliano F**, Rampin O. Central noradrenergic control of penile erection. *Int J Impot Res* 2000; **12** Suppl 1: S13-S19 [PMID: 10845760 DOI: 10.1038/sj.ijir.3900509]
 - 48 **Morales A**. Yohimbine in erectile dysfunction: the facts. *Int J Impot Res* 2000; **12** Suppl 1: S70-S74 [PMID: 10845767]
 - 49 **Honda K**, Yanagimoto M, Negoro H, Narita K, Murata T, Higuchi T. Excitation of oxytocin cells in the hypothalamic supraoptic nucleus by electrical stimulation of the dorsal penile nerve and tactile stimulation of the penis in the rat. *Brain Res Bull* 1999; **48**: 309-313 [PMID: 10229339 DOI: 10.1016/S0361-9230(98)00180-4]
 - 50 **Argiolas A**, Melis MR, Stancampiano R. Role of central oxytocinergic pathways in the expression of penile erection. *Regul Pept* 1993; **45**: 139-142 [PMID: 8511336 DOI: 10.1016/0167-0115(93)90196-F]
 - 51 **Argiolas A**. Nitric oxide is a central mediator of penile erection. *Neuropharmacology* 1994; **33**: 1339-1344 [PMID: 7870289 DOI: 10.1016/0028-3908(94)90034-5]
 - 52 **Melis MR**, Argiolas A. Role of central nitric oxide in the control of penile erection and yawning. *Prog Neuropsychopharmacol Biol Psychiatry* 1997; **21**: 899-922 [PMID: 9380788 DOI: 10.1016/S0278-5846(97)00088-2]
 - 53 **Argiolas A**, Melis MR, Murgia S, Schiöth HB. ACTH- and alpha-MSH-induced grooming, stretching, yawning and penile erection in male rats: site of action in the brain and role of melanocortin receptors. *Brain Res Bull* 2000; **51**: 425-431 [PMID: 10715564 DOI: 10.1016/S0361-9230(99)00270-1]
 - 54 **Bosch RJ**, Benard F, Aboseif SR, Stief CG, Lue TF, Tanagho EA. Penile detumescence: characterization of three phases. *J Urol* 1991; **146**: 867-871 [PMID: 1875515]
 - 55 **Lue TF**, Takamura T, Umraiya M, Schmidt RA, Tanagho EA. Hemodynamics of canine corpora cavernosa during erection. *Urology* 1984; **24**: 347-352 [PMID: 6485194 DOI: 10.1016/0090-4295(84)90208-5]
 - 56 **Saenz de Tejada I**, Kim NN, Goldstein I, Traish AM. Regulation of pre-synaptic alpha adrenergic activity in the corpus cavernosum. *Int J Impot Res* 2000; **12** Suppl 1: S20-S25 [PMID: 10845761 DOI: 10.1038/sj.ijir.3900500]
 - 57 **McConnell J**, Benson GS. Innervation of human penile blood vessels. *Neurorol Urodyn* 1982; **1**: 199-210 [DOI: 10.1002/nau.1930010213]
 - 58 **Levin RM**, Wein AJ. Adrenergic alpha receptors outnumber

- beta receptors in human penile corpus cavernosum. *Invest Urol* 1980; **18**: 225-226 [PMID: 6253412]
- 59 **Hedlund H**, Andersson KE. Comparison of the responses to drugs acting on adrenoreceptors and muscarinic receptors in human isolated corpus cavernosum and cavernous artery. *J Auton Pharmacol* 1985; **5**: 81-88 [PMID: 3157689 DOI: 10.1111/j.1474-8673.1985.tb00568.x]
- 60 **Costa P**, Soulie-Vassal ML, Sarrazin B, Rebillard X, Navratil H, Bali JP. Adrenergic receptors on smooth muscle cells isolated from human penile corpus cavernosum. *J Urol* 1993; **150**: 859-863 [PMID: 8393943]
- 61 **Hedlund P**, Alm P, Andersson KE. NO synthase in cholinergic nerves and NO-induced relaxation in the rat isolated corpus cavernosum. *Br J Pharmacol* 1999; **127**: 349-360 [PMID: 10385233 DOI: 10.1038/sj.bjp.0702556]
- 62 **Dorr LD**, Brody MJ. Hemodynamic mechanisms of erection in the canine penis. *Am J Physiol* 1967; **213**: 1526-1531 [PMID: 4383805]
- 63 **Carati CJ**, Creed KE, Keogh EJ. Vascular changes during penile erection in the dog. *J Physiol* 1988; **400**: 75-88 [PMID: 3418543]
- 64 **Stief C**, Benard F, Bosch R, Aboseif S, Nunes L, Lue TF, Tanagho EA. Acetylcholine as a possible neurotransmitter in penile erection. *J Urol* 1989; **141**: 1444-1448 [PMID: 2566691]
- 65 **Hedlund H**, Andersson KE, Mattiasson A. Pre- and post-junctional adreno- and muscarinic receptor functions in the isolated human corpus spongiosum urethrae. *J Auton Pharmacol* 1984; **4**: 241-249 [PMID: 6152266 DOI: 10.1111/j.1474-8673.1984.tb00101.x]
- 66 **Saenz de Tejada I**, Blanco R, Goldstein I, Azadzoï K, de las Morenas A, Krane RJ, Cohen RA. Cholinergic neurotransmission in human corpus cavernosum. I. Responses of isolated tissue. *Am J Physiol* 1988; **254**: H459-H467 [PMID: 2894778]
- 67 **Kim N**, Azadzoï KM, Goldstein I, Saenz de Tejada I. A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. *J Clin Invest* 1991; **88**: 112-118 [PMID: 1647413 DOI: 10.1172/JCI115266]
- 68 **Aydin S**, Ozbek H, Yilmaz Y, Atilla MK, Bayrakli H, Cetin H. Effects of sildenafil citrate, acetylcholine, and sodium nitroprusside on the relaxation of rabbit cavernosal tissue in vitro. *Urology* 2001; **58**: 119-124 [PMID: 11445502 DOI: 10.1016/S0090-4295(01)01006-8]
- 69 **Ignarro LJ**, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem Biophys Res Commun* 1990; **170**: 843-850 [PMID: 2166511 DOI: 10.1016/0006-291X(90)92168-Y]
- 70 **Bredt DS**, Snyder SH. Nitric oxide: a physiologic messenger molecule. *Annu Rev Biochem* 1994; **63**: 175-195 [PMID: 7526779 DOI: 10.1146/annurev.bi.63.070194.001135]
- 71 **Gonzalez-Cadavid NF**, Rajfer J. The pleiotropic effects of inducible nitric oxide synthase (iNOS) on the physiology and pathology of penile erection. *Curr Pharm Des* 2005; **11**: 4041-4046 [PMID: 16378509 DOI: 10.2174/138161205774913372]
- 72 **Azadzoï KM**, Master TA, Siroky MB. Effect of chronic ischemia on constitutive and inducible nitric oxide synthase expression in erectile tissue. *J Androl* 2004; **25**: 382-388 [PMID: 15064316]
- 73 **Hurt KJ**, Musicki B, Palese MA, Crone JK, Becker RE, Moriarity JL, Snyder SH, Burnett AL. Akt-dependent phosphorylation of endothelial nitric-oxide synthase mediates penile erection. *Proc Natl Acad Sci USA* 2002; **99**: 4061-4066 [PMID: 11904450 DOI: 10.1073/pnas.052712499]
- 74 **Lincoln J**, Crowe R, Blacklay PF, Pryor JP, Lumley JS, Burnstock G. Changes in the VIPergic, cholinergic and adrenergic innervation of human penile tissue in diabetic and non-diabetic impotent males. *J Urol* 1987; **137**: 1053-1059 [PMID: 2437329]
- 75 **Helm G**, Ottesen B, Fahrenkrug J, Larsen JJ, Owman C, Sjöberg NO, Stølberg B, Sundler F, Wallés B. Vasoactive intestinal polypeptide (VIP) in the human female reproductive tract: distribution and motor effects. *Biol Reprod* 1981; **25**: 227-234 [PMID: 7025928 DOI: 10.1095/biolreprod25.1.227]
- 76 **Kirkeby HJ**, Jørgensen JC, Ottesen B. Neuropeptide Y (NPY) in human penile corpus cavernosum tissue and circumflex veins--occurrence and in vitro effects. *J Urol* 1991; **145**: 605-609 [PMID: 1997717]
- 77 **Saenz de Tejada I**, Carson MP, de las Morenas A, Goldstein I, Traish AM. Endothelin: localization, synthesis, activity, and receptor types in human penile corpus cavernosum. *Am J Physiol* 1991; **261**: H1078-H1085 [PMID: 1656784]
- 78 **Becker AJ**, Uckert S, Stief CG, Truss MC, Machtens S, Scheller F, Knapp WH, Hartmann U, Jonas U. Possible role of bradykinin and angiotensin II in the regulation of penile erection and detumescence. *Urology* 2001; **57**: 193-198 [PMID: 11164180 DOI: 10.1016/S0090-4295(00)00881-5]
- 79 **Hedlund H**, Andersson KE, Fovaeus M, Holmquist F, Uski T. Characterization of contraction-mediating prostanoïd receptors in human penile erectile tissues. *J Urol* 1989; **141**: 182-186 [PMID: 2521189]
- 80 **Azadzoï KM**, Krane RJ, Saenz de Tejada I, Goldstein I, Siroky MB. Relative roles of cyclooxygenase and nitric oxide synthase pathways in ischemia-induced increased contraction of cavernosal smooth muscle. *J Urol* 1999; **161**: 1324-1328 [PMID: 10081902 DOI: 10.1016/S0022-5347(01)61678-1]
- 81 **Kim YC**, Davies MG, Lee TH, Hagen PO, Carson CC. Characterization and function of histamine receptors in corpus cavernosum. *J Urol* 1995; **153**: 506-510 [PMID: 7815635 DOI: 10.1097/00005392-199502000-00072]
- 82 **Kifor I**, Williams GH, Vickers MA, Sullivan MP, Jodbert P, Dluhy RG. Tissue angiotensin II as a modulator of erectile function. I. Angiotensin peptide content, secretion and effects in the corpus cavernosum. *J Urol* 1997; **157**: 1920-1925 [PMID: 9112563 DOI: 10.1016/S0022-5347(01)64901-2]
- 83 **Park JK**, Kim SZ, Kim SH, Park YK, Cho KW. Renin angiotensin system in rabbit corpus cavernosum: functional characterization of angiotensin II receptors. *J Urol* 1997; **158**: 653-658 [PMID: 9224386 DOI: 10.1016/S0022-5347(01)64577-4]
- 84 **Comiter CV**, Sullivan MP, Yalla SV, Kifor I. Effect of angiotensin II on corpus cavernosum smooth muscle in relation to nitric oxide environment: in vitro studies in canines. *Int J Impot Res* 1997; **9**: 135-140 [PMID: 9315490 DOI: 10.1038/sj.jir.3900261]
- 85 **Trigo-Rocha F**, Hsu GL, Donatucci CF, Martinez-Piñeiro L, Lue TF, Tanagho EA. Intracellular mechanism of penile erection in monkeys. *Neurourol Urodyn* 1994; **13**: 71-80 [PMID: 8156077 DOI: 10.1002/nau.1930130110]
- 86 **Minhas S**, Cartledge J, Eardley I. The role of prostaglandins in penile erection. *Prostaglandins Leukot Essent Fatty Acids* 2000; **62**: 137-146 [PMID: 10841035 DOI: 10.1054/plf.2000.0133]
- 87 **Kirkeby HJ**, Andersson KE, Forman A. Comparison of the effects of prostanoïds on human penile circumflex veins and corpus cavernosum tissue. *Br J Urol* 1993; **72**: 220-225 [PMID: 8402026]
- 88 **Italiano G**, Calabrò A, Aragona F, Pagano F. Effects of prostaglandin E1, and papaverine on non-neurogenic and neurogenic contraction of the isolated rabbit erectile tissue. *Pharmacol Res* 1995; **31**: 313-317 [PMID: 7479529 DOI: 10.1016/1043-6618(95)80037-9]
- 89 **Daley JT**, Brown ML, Watkins T, Traish AM, Huang YH, Moreland RB, De Tejada IS. Prostanoid production in rabbit corpus cavernosum: I. regulation by oxygen tension. *J Urol* 1996; **155**: 1482-1487 [PMID: 8632615 DOI: 10.1016/S0022-5347(01)66311-0]
- 90 **Meghdadi S**, Porst H, Stackl W, Friehe H, Rodrigues M,

- Sinzinger H. Presence of PGE1 binding determines the erectile response to PGE1. *Prostaglandins Leukot Essent Fatty Acids* 1999; **60**: 111-113 [PMID: 10328331 DOI: 10.1054/plef.1998.0016]
- 91 **Bivalacqua TJ**, Rajasekaran M, Champion HC, Wang R, Sikka SC, Kadowitz PJ, Hellstrom WJ. The influence of castration on pharmacologically induced penile erection in the cat. *J Androl* 1998; **19**: 551-557 [PMID: 9796614]
- 92 **Teixeira CE**, Moreno RA, Ferreira U, Rodrigues Netto N, Fregonesi A, Antunes E, De Nucci G. Pharmacological characterization of kinin-induced relaxation of human corpus cavernosum. *Br J Urol* 1998; **81**: 432-436 [PMID: 9523665 DOI: 10.1046/j.1464-410x.1998.00533.x]
- 93 **Martínez AC**, Prieto D, Raposo R, Delgado JA, Resel L, García-Sacristán A, Benedito S. Endothelium-independent relaxation induced by histamine in human dorsal penile artery. *Clin Exp Pharmacol Physiol* 2000; **27**: 500-507 [PMID: 10874506 DOI: 10.1046/j.1440-1681.2000.03280.x]

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Professionalism and patient education in urologic surgery

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Abstract

Medical professionalism provides the guidelines that govern the patient-physician relationship. This implicit contract requires that patients be informed before making decisions regarding their medical care. Educating patients about diagnostic and treatment decisions is critical to an informed decision-making process. Shared decision-making is a recent paradigm shift in patient education that allows patients to make decisions based both on the counsel of their physicians and according to their own preferences and values. This approach moves away from previous models that focused on physicians or third-party payers as the arbiters of diagnostic and treatment choices. Urologic surgeons have been at the forefront of shared decision-making research and continue to promote this concept in the most recent American Urological Association Guideline on Detection of Prostate Cancer. Unfortunately, the fee-for-service financial structure that predominates in the United States' health care system provides a disincentive for shared decision-making. By promoting patient volume rather than time spent with patients, this system rewards physicians who spend less time educating patients about diagnostic and treatment options. Therefore, to promote adherence to the educational responsibility inherent in medical professionalism, we

recommend physician payment reform that rewards physicians for time spent with patients rather than the volume of patients seen.

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Key words: Urology; Health care reform; Professionalism; Patient education; Decision making; Informed consent

Core tip: Medical professionalism provides the guidelines that govern the patient-physician relationship. This implicit contract requires that patients be educated regarding their diagnostic and treatment decisions. Shared decision-making is a recent paradigm shift in patient education that allows patients to make decisions based both on the counsel of their physicians and according to their own preferences and values. To promote adherence to the educational responsibility inherent in medical professionalism, we recommend physician payment reform that rewards physicians for time spent with patients rather than the volume of patients seen.

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Health care is a dynamic environment. Beyond advances in diagnostic tests and treatments, there is a perpetual shift in the both the landscape of pathology and in the landscape of the health system itself^[1-4]. This is particularly true in the United States where the Patient Care and Affordable Care Act will bring significant change to the health care system^[5-14]. In the midst of this dynamic space, however, there is a constant and immutable center: medical professionalism. What this term means and its role in the physician-patient relationship will be explored in this piece, as will the interplay between professionalism

and the growing movement behind patient education. Finally, we will explore the potential role for public policy in promoting professionalism and patient education in urologic surgery.

Although medical professionalism is difficult to define, the literature is certainly not bereft of efforts to do so^[15-28]. The most notable and durable effort was the publication of *Medical Professionalism in the New Millennium: A Physician Charter*. A collaborative work by the American Board of Internal Medicine Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine, the Charter was published simultaneously in the *Annals of Internal Medicine* and *The Lancet* in 2002^[29,30]. The Charter defines professionalism as “the basis of medicine’s contract with society”, asserting that an implicit contract exists between patients and their physicians. Understood in these terms, it is the implied contract of medical professionalism that legitimizes the intimate and often invasive role of physicians in the lives of their patients. In other words, medical professionalism defines the set of standards that physicians must adhere to in exchange for the privilege of diagnosing and treating patients.

The Charter identifies three fundamental principles that define medical professional standards and expounds on these principles with ten specific professional responsibilities. The fundamental principles include the primacy of patient welfare, patient autonomy, and social justice. These principles require physicians to place patient interests above their own, empower patients to make informed decisions, and promote the equitable distribution of health care resources across society. The professional responsibilities most apropos to the current discussion of patient education in urologic surgery include commitments to professional competence, honesty with patients, and maintenance of trust by managing conflicts of interest. Together these responsibilities demand that urologic surgeons commit themselves and their peers to maintaining the knowledge and skills necessary to deliver high quality care and ensure that patients are making medical decisions based on complete information without consideration of physician gain or personal advantage.

The professional obligation to ensure patient autonomy and informed decision-making has led to a new emphasis on patient-centered care^[31-42]. Unlike previous eras when decision-making was driven first by physicians and then later by payers, contemporary health reforms now focus on putting patients at the center of care decisions. Nowhere is this more evident than in the sections of the Patient Care and Affordable Care Act that provide grants to promote patient-centered care^[43]. Specifically, the Act promotes “shared decision-making” and “patient decision aids” as a means of promoting patient-centered care in those clinical settings where the literature supports multiple diagnostic and/or treatment options. Shared decision-making is defined as a decision-making process that allows patients to consider medical care choices based on clinical evidence and personal preferences, and patient decision aids are the educational tools provided

to patients to support this shared decision-making process^[44-47]. To illustrate this concept consider a patient diagnosed with clinically localized, intermediate risk prostate cancer. Current evidence supports radiation and surgery as equivalent treatment options for cancer control and survival, although each has a distinct risk profile, while active surveillance is appropriate in certain populations^[48]. In the shared decision-making paradigm the patient and his urologic surgeon would discuss the risks and benefits for each option and account for the patient’s values and preferences when considering the different approaches. In this example, a patient with bothersome lower urinary tract symptoms might choose surgery over radiation because of a desire to avoid potential radiation injury to the bladder, while a patient with similar disease may choose radiation to avoid the risks of anesthesia. In both instances the urologic surgeon uses shared decision-making to educate patients and ensure that treatment decisions reflect the patients’ values and preferences.

Notably, there is a longstanding history between urologic surgery, patient education and shared decision-making. The early research on shared decision-making centered on urologic surgery patients choosing between surgical and non-surgical management of benign prostatic hypertrophy^[49,50]. These studies demonstrated that patient preferences had a significant impact on treatment decisions, and that patient preferences flowed from the education that patients were receiving about the treatment options. More recently, the revised 2013 AUA guideline for the early detection of prostate cancer prominently features shared decision-making. For men ages 55 to 69 who are considering prostate cancer screening with a serum prostate specific antigen, the guideline explicitly recommends “shared decision-making” and consideration of each patient’s “values and preferences”^[51].

To advance physicians’ professional obligation to engage patients in shared decision-making will require innovative health care reform. Specifically, physicians should no longer be incentivized to maximize clinical throughput, but should instead be rewarded for spending time with patients to counsel them about their diagnoses and treatment options. One potential mechanism would be to compensate physicians based on the amount of time spent with patients rather than according to fee schedules for particular diagnoses or types of visits. A payment system based on the time spent rather than patients seen would discourage physicians from rushing through clinic visits and elevate the value of the patient-physician relationship. Furthermore, patients could exercise more control over health care spending by comparing the costs and benefits associated with lengthy versus abbreviated clinic visits.

Medical professionalism defines the obligations that urologic surgeons owe to their patients, including ensuring patient autonomy by allowing patients to serve as the primary arbiters of their medical decisions. Towards this end, there has been renewed interest in delivering patient-centered care through patient education. Serving as the nexus between medical professionalism and patient

education, shared decision-making defines the formal process of patients arriving at medical decisions based on the counsel of their urologic surgeon and an evaluation of their own preferences and values. This approach is in sharp contrast to the historically paternalistic medical decision-making process and provides an opportunity to minimize the health care system's disincentives to deliver on medical professionalism's promise of patient autonomy.

REFERENCES

- Borgese F**, Garcia-Romeu F, Motais R. Catecholamine-induced transport systems in trout erythrocyte. Na⁺/H⁺ countertransport or NaCl cotransport? *J Gen Physiol* 1986; **87**: 551-566 [PMID: 3701298 DOI: 10.1056/NEJMsa1212321]
- Naylor CD**, Naylor KT. Seven provocative principles for health care reform. *JAMA* 2012; **307**: 919-920 [PMID: 22396512 DOI: 10.1001/jama.2012.252]
- Horton R**. The Darzi vision: quality, engagement, and professionalism. *Lancet* 2008; **372**: 3-4 [PMID: 18603140 DOI: 10.1016/S0140-6736(08)60963-0]
- Rosenbaum L**, Shrank WH. Taking our medicine--improving adherence in the accountability era. *N Engl J Med* 2013; **369**: 694-695 [PMID: 23964931 DOI: 10.1056/NEJMp1307084]
- Rosenbaum S**, Sommers BD. Using Medicaid to buy private health insurance--the great new experiment? *N Engl J Med* 2013; **369**: 7-9 [PMID: 23822776 DOI: 10.1056/NEJMp1304170]
- Wilensky GR**. The shortfalls of "Obamacare". *N Engl J Med* 2012; **367**: 1479-1481 [PMID: 23050511 DOI: 10.1056/NEJMp1210763]
- Oberlander J**. Beyond repeal--the future of health care reform. *N Engl J Med* 2010; **363**: 2277-2279 [PMID: 21083378 DOI: 10.1056/NEJMp1012779]
- McDonough JE**. The road ahead for the Affordable Care Act. *N Engl J Med* 2012; **367**: 199-201 [PMID: 22747178 DOI: 10.1056/NEJMp1206845]
- Fineberg HV**. Shattuck Lecture. A successful and sustainable health system--how to get there from here. *N Engl J Med* 2012; **366**: 1020-1027 [PMID: 22417255 DOI: 10.1056/NEJMsa1114777]
- Oberlander J**, Morrison M. Failure to launch? The Independent Payment Advisory Board's uncertain prospects. *N Engl J Med* 2013; **369**: 105-107 [PMID: 23718154]
- Eibner C**, Hussey PS, Girosi F. The effects of the Affordable Care Act on workers' health insurance coverage. *N Engl J Med* 2010; **363**: 1393-1395 [PMID: 20925541 DOI: 10.1056/NEJMp1008047]
- Orszag PR**, Emanuel EJ. Health care reform and cost control. *N Engl J Med* 2010; **363**: 601-603 [PMID: 20554975 DOI: 10.1056/NEJMp1006571]
- Sommers BD**, Bindman AB. New physicians, the Affordable Care Act, and the changing practice of medicine. *JAMA* 2012; **307**: 1697-1698 [PMID: 22535852 DOI: 10.1001/jama.2012.523]
- Landon BE**, Roberts DH. Reenvisioning specialty care and payment under global payment systems. *JAMA* 2013; **310**: 371-372 [PMID: 23917283 DOI: 10.1001/jama.2013.75247]
- Arora VM**, Farnan JM, Humphrey HJ. Professionalism in the era of duty hours: time for a shift change? *JAMA* 2012; **308**: 2195-2196 [PMID: 23212495 DOI: 10.1001/jama.2012.14584]
- The "top 5" lists in primary care: meeting the responsibility of professionalism. *Arch Intern Med* 2011; **171**: 1385-1390 [PMID: 21606090 DOI: 10.1001/archinternmed.2011.231]
- Lesser CS**, Lucey CR, Egner B, Braddock CH, Linas SL, Levinson W. A behavioral and systems view of professionalism. *JAMA* 2010; **304**: 2732-2737 [PMID: 21177508 DOI: 10.1001/jama.2010.1864]
- Black C**. Advancing 21st-century medical professionalism: a multistakeholder approach. *JAMA* 2009; **301**: 2156-2158 [PMID: 19470992 DOI: 10.1001/jama.2009.735]
- Reed DA**, West CP, Mueller PS, Ficalora RD, Engstler GJ, Beckman TJ. Behaviors of highly professional resident physicians. *JAMA* 2008; **300**: 1326-1333 [PMID: 18799445 DOI: 10.1001/jama.300.11.1326]
- Gordon G**, Chu V. Medical professionalism in Laos. *Lancet* 2006; **367**: 1302-1304 [PMID: 16631897 DOI: 10.1016/S0140-6736(06)68557-7]
- Helms E**. A lesson from the third year. *Ann Intern Med* 2004; **141**: 736 [PMID: 15520436]
- Farnan JM**, Snyder Sulmasy L, Worster BK, Chaudhry HJ, Rhyne JA, Arora VM. Online medical professionalism: patient and public relationships: policy statement from the American College of Physicians and the Federation of State Medical Boards. *Ann Intern Med* 2013; **158**: 620-627 [PMID: 23579867 DOI: 10.7326/0003-4819-158-8-201304160-00100]
- Sox HC**. The ethical foundations of professionalism: a sociologic history. *Chest* 2007; **131**: 1532-1540 [PMID: 17494802 DOI: 10.1378/chest.07-0464]
- Hafferty FW**. Definitions of professionalism: a search for meaning and identity. *Clin Orthop Relat Res* 2006; **449**: 193-204 [PMID: 16770288 DOI: 10.1097/01.blo.0000229273.20829.d0]
- van Mook WN**, de Grave WS, Wass V, O'Sullivan H, Zwaveling JH, Schuwirth LW, van der Vleuten CP. Professionalism: evolution of the concept. *Eur J Intern Med* 2009; **20**: e81-e84 [PMID: 19524164 DOI: 10.1016/j.ejim.2008.10.005]
- van Mook WN**, van Luijk SJ, O'Sullivan H, Wass V, Harm Zwaveling J, Schuwirth LW, van der Vleuten CP. The concepts of professionalism and professional behaviour: conflicts in both definition and learning outcomes. *Eur J Intern Med* 2009; **20**: e85-e89 [PMID: 19524165 DOI: 10.1016/j.ejim.2008.10.006]
- Hodges BD**, Ginsburg S, Cruess R, Cruess S, Delpont R, Hafferty F, Ho MJ, Holmboe E, Holtman M, Ohbu S, Rees C, Ten Cate O, Tsugawa Y, Van Mook W, Wass V, Wilkinson T, Wade W. Assessment of professionalism: recommendations from the Ottawa 2010 Conference. *Med Teach* 2011; **33**: 354-363 [PMID: 21517683 DOI: 10.3109/0142159X.2011.577300]
- Borgstrom E**, Cohn S, Barclay S. Medical professionalism: conflicting values for tomorrow's doctors. *J Gen Intern Med* 2010; **25**: 1330-1336 [PMID: 20740324 DOI: 10.1007/s11606-010-1485-8]
- Medical professionalism in the new millennium: a physician charter. *Ann Intern Med* 2002; **136**: 243-246 [PMID: 11827500]
- Medical Professionalism Project**. Medical professionalism in the new millennium: a physicians' charter. *Lancet* 2002; **359**: 520-522 [PMID: 11853819 DOI: 10.1016/S0140-6736(02)07684-5]
- Gillick MR**. The critical role of caregivers in achieving patient-centered care. *JAMA* 2013; **310**: 575-576 [PMID: 23867885 DOI: 10.1001/jama.2013.7310]
- Daschle T**, Domenici P, Frist W, Rivlin A. Prescription for patient-centered care and cost containment. *N Engl J Med* 2013; **369**: 471-474 [PMID: 23803133 DOI: 10.1056/NEJMs1306639]
- White A**, Danis M. Enhancing patient-centered communication and collaboration by using the electronic health record in the examination room. *JAMA* 2013; **309**: 2327-2328 [PMID: 23757080 DOI: 10.1001/jama.2013.6030]
- Weiner SJ**, Schwartz A, Sharma G, Binns-Calvey A, Ashley N, Kelly B, Dayal A, Patel S, Weaver FM, Harris I. Patient-centered decision making and health care outcomes: an observational study. *Ann Intern Med* 2013; **158**: 573-579 [PMID: 23588745 DOI: 10.7326/0003-4819-158-8-201304160-00001]
- Bergman J**, Brook RH, Litwin MS. A call to action: improving value by emphasizing patient-centered care at the end of life. *JAMA Surg* 2013; **148**: 215-216 [PMID: 23552885 DOI: 10.1001/jamasurg.2013.1568]
- Hauptman PJ**, Chibnall JT, Guild C, Armbrecht ES. Pa-

- tient perceptions, physician communication, and the implantable cardioverter-defibrillator. *JAMA Intern Med* 2013; **173**: 571-577 [PMID: 23420455 DOI: 10.1001/jamainternmed.2013.3171]
- 37 **Lin GA**, Matlock DD. Less patient-centered care: an unintended consequence of guidelines? *JAMA Intern Med* 2013; **173**: 578-579 [PMID: 23420530 DOI: 10.1001/jamainternmed.2013.4187]
 - 38 **Horwitz LI**, Moriarty JP, Chen C, Fogerty RL, Brewster UC, Kanade S, Ziaiean B, Jenq GY, Krumholz HM. Quality of Discharge Practices and Patient Understanding at an Academic Medical Center. *JAMA Intern Med* 2013 Aug 19; Epub ahead of print [PMID: 23958851 DOI: 10.1001/jamainternmed.2013.9318]
 - 39 **Rhodes KV**. Completing the Play or Dropping the Ball?: The Case for Comprehensive Patient-Centered Discharge Planning. *JAMA Intern Med* 2013 Aug 19; Epub ahead of print [PMID: 23959515 DOI: 10.1001/jamainternmed.2013.7854]
 - 40 **Hibbard JH**, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. *Health Aff (Millwood)* 2013; **32**: 207-214 [PMID: 23381511 DOI: 10.1377/hlthaff.2012.1061]
 - 41 **Roseman D**, Osborne-Stafsnes J, Amy CH, Boslaugh S, Slate-Miller K. Early lessons from four 'aligning forces for quality' communities bolster the case for patient-centered care. *Health Aff (Millwood)* 2013; **32**: 232-241 [PMID: 23381515 DOI: 10.1377/hlthaff.2012.1085]
 - 42 **Bernabeo E**, Holmboe ES. Patients, providers, and systems need to acquire a specific set of competencies to achieve truly patient-centered care. *Health Aff (Millwood)* 2013; **32**: 250-258 [PMID: 23381517 DOI: 10.1377/hlthaff.2012.1120]
 - 43 **Oshima Lee E**, Emanuel EJ. Shared decision making to improve care and reduce costs. *N Engl J Med* 2013; **368**: 6-8 [PMID: 23281971 DOI: 10.1056/NEJMp1209500]
 - 44 **McAneny BL**. Report of the Council on Medical Service. American Medical Association. CMS Rep 7-A-10: 1-6
 - 45 **Friedberg MW**, Van Busum K, Wexler R, Bowen M, Schneider EC. A demonstration of shared decision making in primary care highlights barriers to adoption and potential remedies. *Health Aff (Millwood)* 2013; **32**: 268-275 [PMID: 23381519 DOI: 10.1377/hlthaff.2012.1084]
 - 46 **Légaré F**, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. *Health Aff (Millwood)* 2013; **32**: 276-284 [PMID: 23381520 DOI: 10.1377/hlthaff.2012.1078]
 - 47 **Blumenthal-Barby JS**, Cantor SB, Russell HV, Naik AD, Volk RJ. Decision aids: when 'nudging' patients to make a particular choice is more ethical than balanced, nondirective content. *Health Aff (Millwood)* 2013; **32**: 303-310 [PMID: 23381523 DOI: 10.1377/hlthaff.2012.0761]
 - 48 **Mohan R**, Schellhammer PF. Treatment options for localized prostate cancer. *Am Fam Physician* 2011; **84**: 413-420 [PMID: 21842788]
 - 49 **Barry MJ**, Fowler FJ, Mulley AG, Henderson JV, Wennberg JE. Patient reactions to a program designed to facilitate patient participation in treatment decisions for benign prostatic hyperplasia. *Med Care* 1995; **33**: 771-782 [PMID: 7543639]
 - 50 **Krumins PE**, Fihn SD, Kent DL. Symptom severity and patients' values in the decision to perform a transurethral resection of the prostate. *Med Decis Making* 1988; **8**: 1-8 [PMID: 2448577]
 - 51 **Carter HB**, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH, Penson DF, Zietman AL. Early detection of prostate cancer: AUA Guideline. *J Urol* 2013; **190**: 419-426 [PMID: 23659877 DOI: 10.1016/j.juro.2013.04.119]

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How to improve a urology outpatient service? A survey of patient satisfaction

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Abstract

AIM: To investigate and improve our out-patients department patient satisfaction, provide minimum consultation delay and appropriate consultation duration to meet with targets.

METHODS: We distributed the modified satisfaction with outpatient service (SWOPS) questionnaires developed for use in Irish hospitals by the Health Services Research between August and December 2012. The patient disclosed their age and sex and completed the modified SWOPS questionnaire anonymously. Every patient was eligible to participate in the study who attended any of the Urology Outpatient Clinics. Patients lacking capacity to consent were excluded. Additionally, each patient was only permitted to complete one questionnaire regardless of repeat attendances within the 4 mo study period. The answers to every question were presented as percentages. One-way ANOVA was used to establish whether there was a significant difference in appointment delay and "Overall Satisfaction"

on the different clinic days. The unpaired *t*-test was applied to establish whether "Overall Satisfaction" was affected by diagnosis (benign or malignant). Paired *t*-test was used to establish whether "Overall Satisfaction" was affected by appointment delay and appointment length.

RESULTS: Three hundred and forty-eight questionnaires were completed with an overall > 65% participation rate. Eighty-one point six percent were male and 18.4% female with a mean age of 65 ± 21 years. Mean delay time was 32 min, which 30.6% stated should be an improvement priority. The delay times for Wednesday (mean 13 min) were significantly ($P < 0.05$) lower than for other days (mean 36 min). Generally 12-15 min outpatient appointment length is acceptable and adequate for patients as 97.70% suggested, however 31.60% of patients would favour longer duration. Eleven point four nine percent do not want to see different doctors each time, and 31.60% of the patient feel that no change is required. Average satisfaction was 84.65%. There was no significant relationship between satisfaction and clinic day, diagnosis and consultation length, whether the patient was reviewed by a registrar or consultant. Satisfaction was universally high and independent of consultation delay/length and diagnosis. Dissatisfaction in delay times with a significant improvement on Wednesday suggests necessary and achievable improvements. Notably, the Wednesday clinic has less patients per doctor per hour and enforces a 1 patient per 15 min slot with a no over-booking policy.

CONCLUSION: Surveying our patient dissatisfaction would require more frequent audits by clinicians to improve patient satisfaction and to achieve better quality of care.

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Key words: Satisfaction with outpatient service ques-

tionnaire; Patient satisfaction; Outpatient department; Survey; Service delivery

Core tip: With our survey we would like to emphasize the need of regular audit activity at the outpatient clinic to improve patient satisfaction and to identify potential pitfalls of the outpatient pathway. Ideally every outpatient clinic or medical practice should conduct a survey yearly for quality improvement purposes to improve patient care and outcomes through systematic review of care against explicit criteria and implement changes if necessary.

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INTRODUCTION

The National Health Service (NHS) in the United Kingdom and the health system in the United States of America seek to develop so called “patient centred care”^[1,2], as patient perception of their healthcare experience has gained increasing attention over the past 20 years^[3]. Researching patients’ healthcare experience is an important method of creating effective action plans for quality improvement in health care organisations^[4].

Currently, there is a drive for reducing patient waiting times for the benefit of patients, healthcare providers, managers, and Department of Health. Consequently, Out-patient clinics have also been subject to new targets. The Department of Health’s Operating Framework for 2012/13^[5] confirmed the NHS Constitution guarantees that patients should expect to receive treatment for non-urgent conditions at an inpatient or outpatient basis within 18 wk. In addition all GP referrals with suspected malignancy should receive specialist review within 2 wk.

As we are searching for ways to make our Outpatient’s Department service more responsive to the general public and in order to improve the patient experience at our Urology Out-Patient’s Department, we conducted a prospective study of patient satisfaction among patients attending between August 2012 and December 2012. Our modified satisfaction with outpatient service (SWOPS) questionnaires (Figure 1) were used. St Mary’s Urology out-patients department targets maximum patient satisfaction as it is one of the key criteria by which the quality of health care service is evaluated^[6,7]. This survey aimed to develop a framework for identifying factors affecting patient satisfaction, and to identify potential, and correctable causes in order to improve overall satisfaction and healthcare quality improvement. Therefore we focused on patient dissatisfaction in order to identify reasons which make patients disappointed with the service provided.

MATERIALS AND METHODS

The survey was performed in four Outpatient Urology Clinics held weekly (Monday, Wednesday, Thursday and Friday) at St Mary’s Hospital, Imperial Healthcare NHS Trust, London. These are led by the same 2 consultants and 2 registrars. Patients were seen, reviewed and consulted randomly; the next patient was seen by the next available doctor. It is of note, that Wednesday clinic has less patients per doctor per hour and enforces a 1 patient per 15 min slot with a no over-booking policy, which results into a smooth continuously flowing clinic without significant delays.

Data was collected prospectively between August 2012 and December 2012 using our modified SWOPS questionnaires (Figure 1). The SWOPS questionnaire is multi-dimensional outpatient instrument, which was developed for use in Irish hospitals by the Health Services Research Centre at the Department of Psychology, Royal College of Surgeons in Ireland (RCSI). The generic items of the questionnaire make up an overall dimension with an α co-efficient of 0.84. The high reliability co-efficient of each of these dimensions allows users to “select” questions whilst maintaining validity. Therefore the modified SWOPS questionnaire is valid^[8]. Every patient who attended our four Urology clinics was asked to complete the modified SWOPS questionnaires, the doctor completed sections including consultation length and delay, diagnosis (benign or proven malignant), whether the consultation was Registrar or Consultant led and whether the patient was new or follow-up. The patients disclosed their age and sex and completed 12 of the questions of the modified SWOPS questionnaire anonymously. At the end of the questionnaire 2 open questions were provided for the patients to express their personal view, impression and recommendations. Every patient was eligible to participate in the survey who attended the Urology Outpatient Clinic. Patients with diagnosed mental health disorder and patients lacking capacity to consent to completing the questionnaire were excluded. Additionally, each patient was only permitted to complete one questionnaire regardless of repeat attendances within the 4 mo study period. Doctors were unaware of the collected data and feedback until the end of the survey. The Questionnaire was completed at the end of the consultation by the patient in the waiting area and were collected at the Outpatient Department Reception in a sealed container.

The responses to each question by each patient were recorded onto Microsoft Excel spreadsheet 2010. The number of answers were recorded as percentages. The responses to the “scalable” questions (Questions 1-6 and Questions 8-11) were recorded as a percentage of the maximum score for that question. In order to ensure that these questions were consistently “scalable” for the calculation of “Overall Satisfaction” the following rules were applied: (1) For Question 2, response options 4 and 5 were not taken into account (for the calculation of overall satisfaction); (2) For Question 4, response op-

Urology SWOPS Questionnaire

Please take a few minutes to fill out this survey. The Urology department welcomes your feedback and your answers will be kept confidential. Thank you for your participation.

Age: _____ years Gender: Male Female

1. Did you have enough time to discuss your health or medical problem with the doctor?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
2. Did the doctor explain the reasons for any treatment or action in a way that you could understand?
☐ Yes, definitely ☐ Yes, to some extent ☐ No ☐ I did not need an explanation ☐ No treatment or action was needed
3. Did the doctor listen to what you had to say?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
4. If you had an important question to ask the doctor, did you get answers that you could understand?
☐ Yes, definitely ☐ Yes, to some extent ☐ No ☐ I did not need to ask ☐ I did not have an opportunity to ask
5. Did you have confidence and trust in the doctor examining and treating you?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
6. Did the doctor seem aware of your medical history?
☐ He/She knew enough ☐ He/She knew something but not enough ☐ He/She knew little or nothing ☐ Don't know/Can't say
7. Do you have concerns about seeing different doctors each time?
☐ I see the same doctor ☐ No, I don't mind ☐ Yes, I have concerns
8. Were you involved as much as you wanted to be in the decisions made about your care and treatment?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
9. Overall, how would you rate the care that you received in the Outpatients Department?
☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor ☐ Very poor
10. Would you recommend this Outpatients Department to your family and friends?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
11. When I left the clinic I knew what was going to happen next and when?
☐ Yes, definitely ☐ Yes, to some extent ☐ No
12. What would you most like to improve in this Outpatients Department?
☐ Waiting time in clinic ☐ Time spent with doctor ☐ Seeing different doctors each time ☐ Quality of care ☐ No changes needed
13. Are there any areas where you feel we could make improvements?
14. Comments

For office use only
 Diagnosis: B / M Type: New / F/u / BBN
 Seen by: Cons / Reg
 Date of OPD: Scheduled Time:
 Start Time: Finish Time:

Thank you for taking the time to fill out our survey. We rely on your feedback to help us improve our services. Your input is greatly appreciated.

Figure 1 Satisfaction with outpatient service (SWOPS) questionnaire.

tions 4 and 5 were not taken into account; (3) For Question 6, response option “Don’t Know” was excluded.

The average percentage score, *i.e.*, “Overall Satisfaction” was then calculated.

Statistical analysis

The unpaired *t*-test was applied to establish whether “Overall Satisfaction” was affected by diagnosis (benign or malignant).

The paired *t*-test was used to establish whether “Overall Satisfaction” was affected by appointment delay and appointment length.

Furthermore one-way ANOVA was used to establish whether there was a significant difference in appointment delay and “Overall Satisfaction” on the different clinic days.

RESULTS

The survey had an overall > 65% participation rate. A

total of 348 patients completed and returned the questionnaire. The demographic characteristics of the survey consisted of 284 males (81.6%) and 64 females (18.4%) with an average age of 61 years and a mean age 65 ± 21 years. 29.88% of patients ($n = 104$) were new referrals to the clinic with no previous experience with the Department and 244 (70.12%) were at least seen once previously so called follow up patient. All clinics were a mixture of patients diagnosed with benign and malignant urological diseases. Overall 214 (61.49%) patients attended clinic for benign urological problems and 134 (38.51%) for a histologically proven malignancy either as a new diagnosis or follow up. One hundred and fifty-six (44.82%) patients were seen by the Consultant and 192 (55.17%) patients by the registrars. Groups seen by Consultant and registrar were identical demographically (age, sex), in terms of medical condition (new or follow up) and histological diagnosis (benign or malignant) as a result of random outpatient consultation. Overall statis-

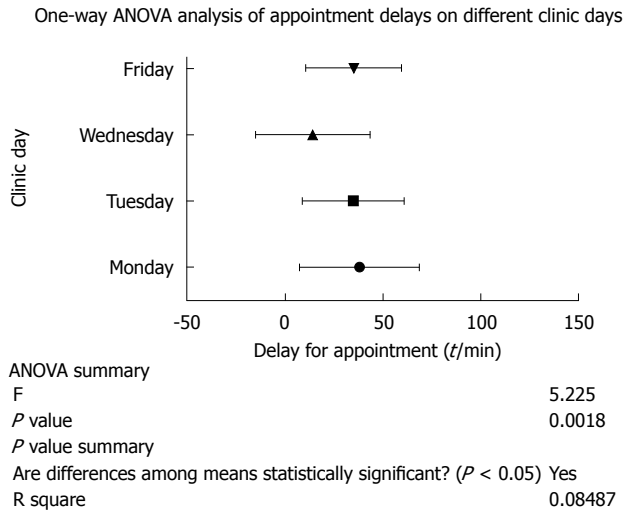


Figure 2 One-way ANOVA analysis of appointment delays for appointment on different clinic days.

Table 1 Analysis of consultant *vs* registrar led consultation duration time, delay of consultation, and patient satisfaction

	Consultant led clinic		Registrar led clinic	
	Mean	SD	Mean	SD
Consultation time (min)	13.61	10.58	13.81	10.19
Delay of consultation (min)	33.71	18.84	36.48	20.22
Patient satisfaction	0.90	0.14	0.89	0.12

tical analysis did not reveal any significant difference between consultant and registrar led consultation in duration time, delay of consultation, and patient satisfaction (Table 1).

The number of patients who completed the questionnaire for every clinic were respectively for the Monday clinic 98 (28.16%), Wednesday clinic 52 (14.94%), Thursday clinic 74 (21.26%), Friday clinic 124 (35.63%).

Analysis of the Appointment Length and Appointment Delay Times (Table 2), clearly showed similarities in appointment or consultation length by average of 13 min per consultation. On Question 12, only 16.66% ($n = 58$) of the patients found this consultation length inadequate. Further analysis of Appointment Delay time to patient schedule showed that notably Wednesday appointment delay length was only 14 min far less compared with other clinics, where patients have nearly 35-min delay to see the doctor. One-way ANOVA Analysis of Appointment Delays on Different Clinic Days (Figure 2) is statistically significantly different with a P value of less than 0.0018. On Question 12, 31.60% ($n = 110$) of patients stated the waiting time in clinic needs to improve.

Analysis of the individual Clinic days (Table 3), showed no statistically significant difference between the clinic days or whether the visit was a result of a benign or malignant diagnosis. However, the Wednesday clinic had the highest overall satisfaction rate with 87.7% of the attending patients with the lowest standard deviation

compared with any other clinic days.

The individual answers to the questions of the questionnaire are presented in percentages in Table 4.

DISCUSSION

A prospectively administered exit survey questionnaire is a reasonably effective way of eliciting the view of members of the public but it is important to be aware of the limitation of this method. Firstly response rate can be often quite low and depends on the quality of the questionnaire, the clinical set up, the selling point of the questionnaire and also the willingness of those approached in this way to respond truly. Patients who are extremely satisfied or dissatisfied will more commonly be willing to express their feelings, and fill the questionnaire which can result in a significant bias for the study. Our survey participation rate after excluding the ineligible patients was 65%.

For better understanding of the large amount of data collected, we divided the questionnaires into 3 major areas. First was the sufficient appointment length surveyed by the first question. Generally a 12-15 min outpatient appointment length is acceptable and adequate for patients as 97.70% were not dissatisfied, however, when patients answered the last question 16.66% of them would like to spend more time with their doctor. We concluded that an average of 20 min consultation time (3 patients/h) would be satisfactory for both doctors and patients. This would result at an average of 12 patients over a half day clinical session. The second part is focus on doctor-patient interaction and communication (Q 2, 3, 4, 5, 6, 7, 8, 11). Good communication between patients and healthcare professionals has long been seen as the bedrock of quality from the patient's perspective^[9]. Generally doctors and healthcare professionals are appreciated more when they are genuinely interested in what patients have to say or ask, when they provide clear explanation and examples about the possible treatment options, as well as offer sufficient time for patient interaction. Direct patient involvement by having the opportunity to choose treatment options or decision how to manage their condition is becoming more common^[10]. A shared decision approach may be the preferred way, however the extent of patient involvement in their decision making process is dependent upon the background knowledge and education. Our survey results showed that generally patients were happy, however, in some cases the lack of notes resulted in lack of confidence and dissatisfaction for the doctor and the Department. Therefore this group of questions focused on the received care, expectations and area of improvement (Q9, 10, 12).

Furthermore we concluded the following from the patient answers (Table 3): Question two highlights the importance of good patient/doctor interaction and involvement in the decision making process to improve patient understanding of their disease and medical management plan, resulting in improvement of patient

Table 2 Mean \pm SD appointment delay time and appointment length times on various days of the week in our Urology Outpatient Clinics

Clinic day	Appointment delayed length mean (min)	Appointment delayed \pm SD (min)	Appointment length mean (min)	Appointment length \pm SD
Monday	38	30	13	7
Wednesday	14	28	12	9
Thursday	35	25	14	12
Friday	35	23	14	11

Table 3 Patient satisfaction outcomes and their standard deviation by clinic days and according to patient histological diagnosis

Factor	Satisfaction (%)	SD
Monday clinic	83.4	16
Wednesday clinic	87.7	15.7
Thursday clinic	83.2	17.7
Friday clinic	84.3	18.9
Benign diagnosis	83	18.6
Malignant diagnosis	86	15.3

compliance to treatment. Question three indicates the importance of doctor/patient interaction, especially underlining the importance of active listening to the patient. Question four demonstrated that answering patient questions about their problem is extremely important, however, that should be explained in a way that the patient understands. In question five 1.72% of the patients have no confidence in their doctor, a fact probably difficult to correct, however 74.71% answered “Yes, definitely” and 23.56% answered “Yes, to some extent” being confident in their doctor. Patient perception of the delivered quality of care is commonly measured by the doctors’ knowledge of patient’s disease and past medical history. Question six supported that most patients were generally satisfied (92.52%) with our service, however, improvement was required to satisfy the remaining 7.5%. Question seven surprisingly revealed, that patients not necessarily wanted to see the same doctor, providing that their medical records were updated and the presently treating medical doctor were made aware of their condition. Question eight suggested that 97.70% of patients feel that the consultation was adequately managed, and they were involved in the decision making process fully in 58.62%. Question nine revealed that an overall 86.20% had excellent or good opinion about the care that they received, 8.62% found it fair, however 6.32% of the patients were dissatisfied (18 patients in total). Both the 14 questionnaires which found our service poor and the remaining 4 that found it very poor were analysed independently. Overall from the group of these 18 patients, 17 would probably have been satisfied with the department, however their average delay to be seen was more than 65 min, which resulted to major disappointment. The remaining patient was dissatisfied as he was delayed by 45 min, his notes were missing and the doctor was unaware of his history. Question ten confirmed however, when it is about recommending the de-

partment to family members only 3.44% of the patients would not make such a recommendation, which might suggest individual or personal issues, and was independent from the quality of care which they received. Question eleven underlines the importance of sharing future management plan with patients to improve patient compliance. At last but not least question twelve highlights the expectation of the patient and suggestion for further improvement. Thirty-one point six percent of patients seemed happy with the present status quo, however that does not necessarily mean a happy customer. Moreover there is plenty of room for improvement as 76.43% would favour changes to improve service delivery. By far more than 31.6% of patients would like to reduce the waiting time in the clinic (time spent in the department waiting for consultation), which turned out one of the independent factors influencing patient satisfaction.

Some outpatient urology clinics are performing minimal invasive procedures as well during their outpatient consultation, such as flexible cystoscopies, prostatic biopsies or even ureteric stenting^[11]. In these circumstances a sufficient pain management is mandatory and could result in further improvement in patient satisfaction^[12] and outpatient service.

Alternatively for the measurement of patient satisfaction the Patient Satisfaction Questionnaire Short Form (PSQ-18) can also be used, which is an adaptable, reliable, and validated tool that may be applied to various settings, as well as comparing interventions^[13,14].

It seems that in the era of financial constraints, hospital managers focus more on the number of patients seen in clinic in order to reduce waiting times, satisfy targets and earn more financially for their hospitals. However, quantity is not only what matters, quality in the delivery of care has to be a priority for every physician. Therefore it is very important to evaluate patient satisfaction and implement new strategies to provide quality care to our patients.

COMMENTS

Background

Patient satisfaction gained increasing attention over the past 20 years as one of the primary factors to measure quality of care. The findings of this study are important because, to our knowledge, such specific outpatient survey and feedback is rarely undertaken in the hospital setting. Satisfaction surveys are mainly used by hospital managers who evaluate their staff in their working environment.

Research frontiers

In an era when reductions in patient waiting times (and to meet the increasing

Table 4 Individual question results of the satisfaction with outpatient service questionnaire *n* (%)

Question	Total responses	Response	Responses
Question 1 Did you have enough time to discuss your health or medical problem with the doctor?	348	Yes, definitely	242 (69.54)
		Yes, to some extent	98 (28.16)
		No	8 (2.29)
		Yes, definitely	252 (72.41)
Question 2 Did the doctor explain the reasons for any treatment or action in a way that you could understand?	348	Yes, to some extent	72 (20.68)
		No	8 (2.29)
		I did not need an explanation	6 (1.72)
		No treatment or action was needed	10 (2.87)
Question 3 Did the doctor listen to what you had to say?	348	Yes, definitely	268 (77.01)
		Yes, to some extent	80 (22.98)
		No	0 (0)
		Yes, definitely	202 (58.04)
Question 4 If you had an important question to ask the doctor, did you get the answers that you could understand?	348	Yes, to some extent	94 (27.01)
		No	14 (4.02)
		I did not need to ask	30 (8.62)
		I did not have an opportunity to ask	8 (2.29)
Question 5 Did you have the confidence and trust in the doctor examining treating you?	348	Yes, definitely	260 (74.71)
		Yes, to some extent	82 (23.56)
		No	6 (1.72)
		He/she new enough	234 (67.24)
Question 6 Did the doctor seem aware of yor medical history?	348	He/she knew something but not enough	88 (25.28)
		He/she knew little or nothing	16 (4.59)
		Don't know/Can't say	10 (2.87)
		I see the same doctor	74 (21.26)
Question 7 Do you have concerns about seeing different doctors each time?	348	No, I don't mind	214 (61.49)
		Yes, I have concerns	60 (17.24)
		Yes, definitely	204 (58.62)
		Yes, to some extent	136 (39.08)
Question 8 Were you involved as much as you wanted to be in the decisions made about your care and treatment?	348	No	8 (2.29)
		Excellent	120 (34.48)
		Very good	100 (28.73)
		Good	80 (22.98)
Question 9 Overall, how would you rate the care that you received in the Outpatients Department?	348	Fair	30 (8.62)
		Poor	14 (4.02)
		Very poor	4 (1.11)
		Yes, definitely	212 (60.91)
Question 10 Would you recommend this Outpatients Department to your family and friends?	348	Yes, to some extent	124 (35.63)
		No	12 (3.44)
		Yes, definitely	246 (70.68)
		Yes, to some extent	94 (27.01)
Question 11 When I left the clinic I knew what was going to happen next and when?	348	No	8 (2.29)
		Waiting time in clinic	110 (30.60)
		Time spent with doctor	58 (16.66)
		Seeing different doctors each time	40 (11.49)
Question 12 What would you most like to improve in this Outpatients Department?	348	Quality of care	30 (8.62)
		No changes needed	110 (31.60)

demand) is the main priority of all parties (patient, healthcare provider, managers, and ministry), organizing and running an effective outpatient clinic could face a major challenge. On this ground more and more clinicians are trying to come up with a solution to improve patient satisfaction by not compromising managerial and financial targets at the same time.

Innovations and breakthroughs

Satisfaction with outpatient service (SWOPS) questionnaire is multi-dimensional outpatient instrument, was developed by the Health Services Research Centre at the Department of Psychology, Royal College of Surgeons in Ireland for use in Irish hospitals. The generic items of the questionnaire make up an overall dimension with an α co-efficient of 0.84. The high reliability co-efficient of each of these dimensions allows users to "select" questions whilst maintaining validity, providing a valid questionnaire for researchers and clinicians to audit their patient satisfaction and outcomes.

Applications

SWOPS questionnaire can be used in any clinical setting from outpatient to inpatient and ward setting. Also it is a useful tool in the primary care to monitor quality of care.

Terminology

Patient satisfaction is the perception of the patient of one or more aspects of the received care, thus a tool for measuring quality of care.

Peer review

This is an interesting topic as outpatient department service is very important in the diagnostic, therapeutic and follow-up process of many urological pathologies.

REFERENCES

- 1 **Department of Health.** The NHS plan. London: Department of Health, 2000: 88-95. Available from: URL: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_118522.pdf
- 2 **Institute of Medicine.** Crossing the quality chasm: a new health system for the 21st century. Washington D.C.: National Academy Press, 2001

- 3 **Coulter A.** The Autonomous Patient: Ending Paternalism in Medical Care. London: Stationery Office (for the Nuffield Trust), 2002: 128
- 4 **Levine AS,** Plume SK, Nelson EC. Transforming patient feedback into strategic action plans. *Qual Manag Health Care* 1997; **5**: 28-40 [PMID: 10168370]
- 5 The operating framework for the NHS in England 2012-13. Available from: URL: <https://www.gov.uk/government/publications/the-operating-framework-for-the-nhs-in-england-2012-13>
- 6 **Young GJ,** Meterko M, Desai KR. Patient satisfaction with hospital care: effects of demographic and institutional characteristics. *Med Care* 2000; **38**: 325-334 [PMID: 10718357 DOI: 10.1097/00005650-200003000-00009]
- 7 **Goldwag R,** Berg A, Yuval D, Benbassat J. Predictors of patient dissatisfaction with emergency care. *Isr Med Assoc J* 2002; **4**: 603-606 [PMID: 12183864]
- 8 **Keegan O,** McGee H. A guide to hospital outpatient satisfaction survey: practical recommendations and the Satisfaction with Outpatient' (SWOP) Questionnaire. Dublin: Royal College of Surgeons in Ireland, 2003
- 9 **Grol R,** Wensing M, Mainz J, Jung HP, Ferreira P, Hearnshaw H, Hjortdahl P, Olesen F, Reis S, Ribacke M, Szecsenyi J. Patients in Europe evaluate general practice care: an international comparison. *Br J Gen Pract* 2000; **50**: 882-887 [PMID: 11141874]
- 10 **Sitzia J,** Wood N. Patient satisfaction: a review of issues and concepts. *Soc Sci Med* 1997; **45**: 1829-1843 [PMID: 9447632 DOI: 10.1016/S0277-9536(97)00128-7]
- 11 **Masood J,** Ismail M, El-Husseiny T, Moraitis K, Albanis S, Papatsoris A, Buchholz N. 'An interventional urology list' - a novel concept for UK urological services. *Ann R Coll Surg Engl* 2011; **93**: 27-30 [PMID: 20977835 DOI: 10.1308/003588411X12851639107115]
- 12 **Young A,** Ismail M, Papatsoris AG, Barua JM, Callear JG, Masood J. Entonox® inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. *Ann R Coll Surg Engl* 2012; **94**: 8-11 [PMID: 22524905 DOI: 10.1308/003588412X13171221499702]
- 13 **Dawn AG,** Lee PP, Hall-Stone T, Gable W. Development of a patient satisfaction survey for outpatient care: a brief report. *J Med Pract Manage* 2003; **19**: 166-169 [PMID: 14730826]
- 14 **Marshall GN,** Hays RD, Santa Monica. The patient satisfaction questionnaire short form (PSQ-18). CA: RAND Corporation, 1994: 7865

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