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BRIEF ARTICLE

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BRIEF ARTICLE

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 eRARP 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.

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 Trendelenberg 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.

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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.

CO_2 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.

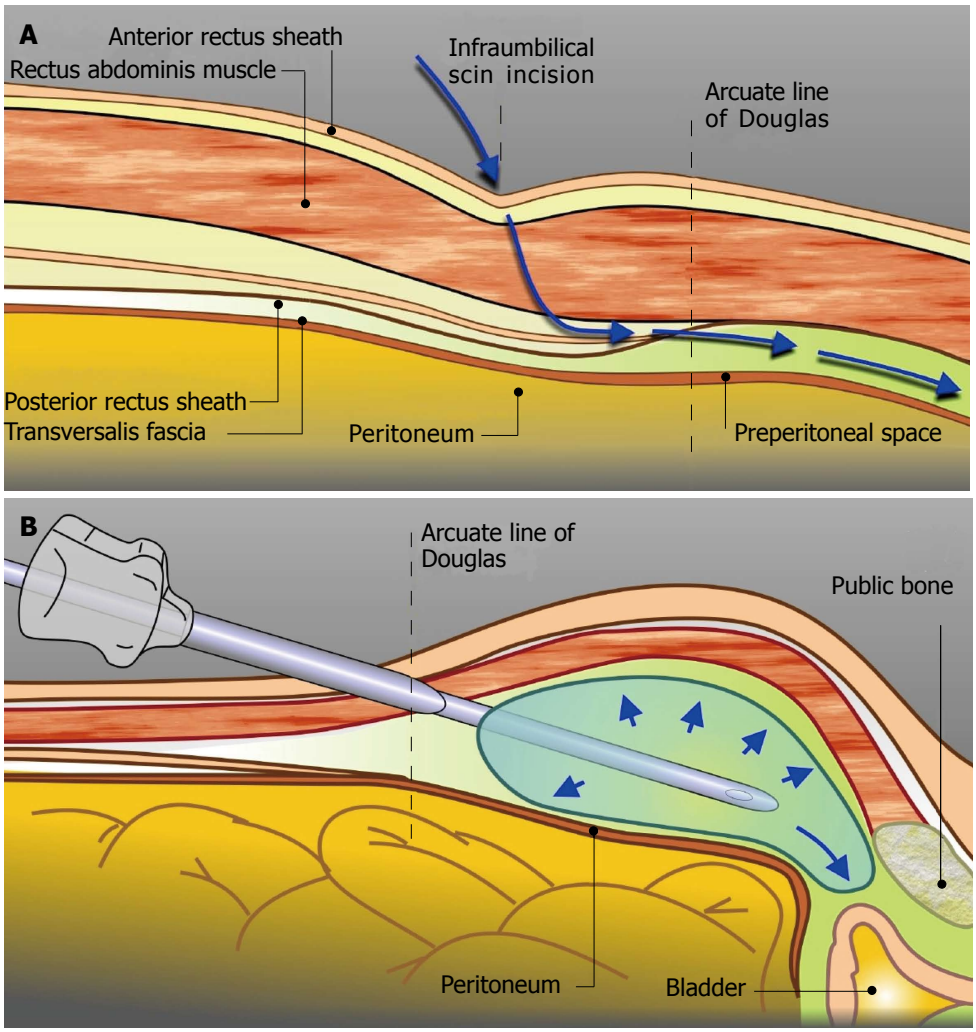

Figure 1 The balloon is manually inflated a small amount to secure it within the retropubic space. A: Extraperitoneal space creation for insertion of the distension balloon; B: Balloon insufflation of the retropubic space. With kind permission from Springer Science + Business Media: Laparoscopic and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

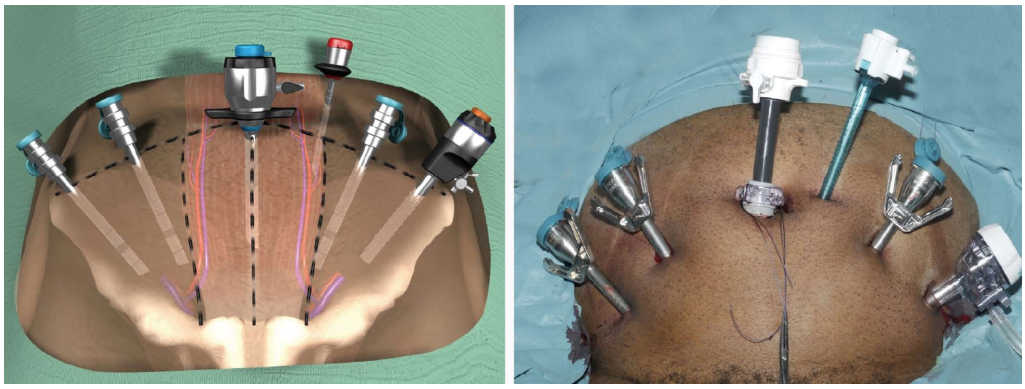

Figure 2 Final six-port configuration for extraperitoneal robot-assisted radical prostatectomy.

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 Comparision 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) (P < 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 Urinary retention (Grade 1)
	1 Blood transfusion (Grade 2)	2 Blood transfusions (Grade 2)
	1 Anastomotic leak requiring suprapubic catheter insertion on readmission (Grade 3b)	2 Pelvic collection/haematoma requiring percuataneous 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-vescial 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 postoperative 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 *et al*[12]	Rochester, United States	4	325	180	196	9.8% (1.3%)	13%	96% < 24 h	2 converted to TP
Atug *et al*[4]	New Orleans, United States	4	40	229	221	12.5% (NS)	20%	Mean 1.2	none
Rozet *et al*[13]	Institut Montsouris, France	4	133	166	609	19.4% (9.8%)	19.50%	Mean 5.4	4 converted to LRP
Capello *et al*[6]	Rochester, United States	2b	31	181	199	0% (0%)	3.20%	NS	none
Madi *et al*[5]	Ann Arbor, United States	4	34	214	125	5.9% (0%)	23.50%	Median 1	none
Ploussard *et al*[16]	Henri Mondor, France	4	206	160	504	8.3% (3.4%)	27.70%	Mean 4	1 converted to LRP
Chung *et al*[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 $\geqslant$ 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[13,15-18]. 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 retropubic 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 eRARP 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 (× 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 Guillonneau *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 retropubic 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.

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BRIEF ARTICLE

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.

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 *et al*[11]	131	IHC (tumor tissue)	2a
	Shoji *et al*[12]	54	IHC (tumor tissue)	2a
Urothelial carcinoma	Takeda *et al*[6]	151	IHC (tumor tissue)	2b
Bladder cancer	Sanchez-Carbayo *et al*[13]	69	IHC (tumor tissue)	2a
	Nicolle *et al*[14]	64	IHC (tumor tissue)	2b
	Cebrian *et al*[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[15] 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 clearfied as suitable molecular biomarkers for urological cancers.

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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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Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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