Advances in ureteral stent and ureteroscopy technologies

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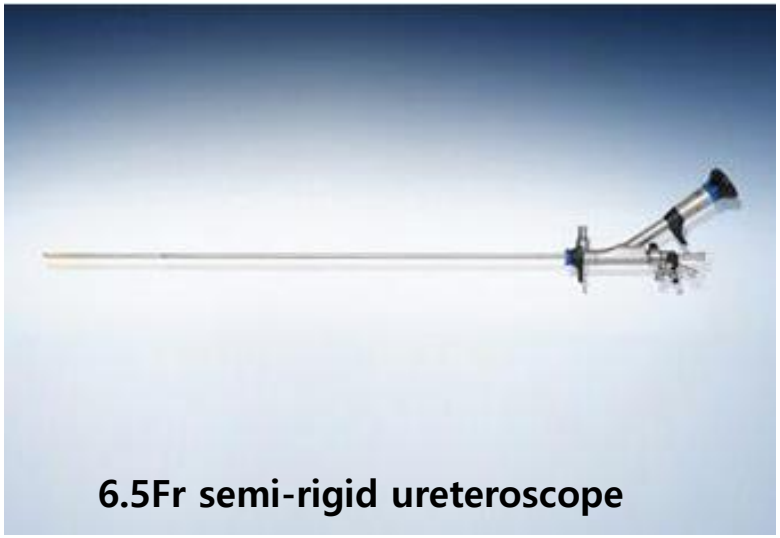
Ureteroscopy

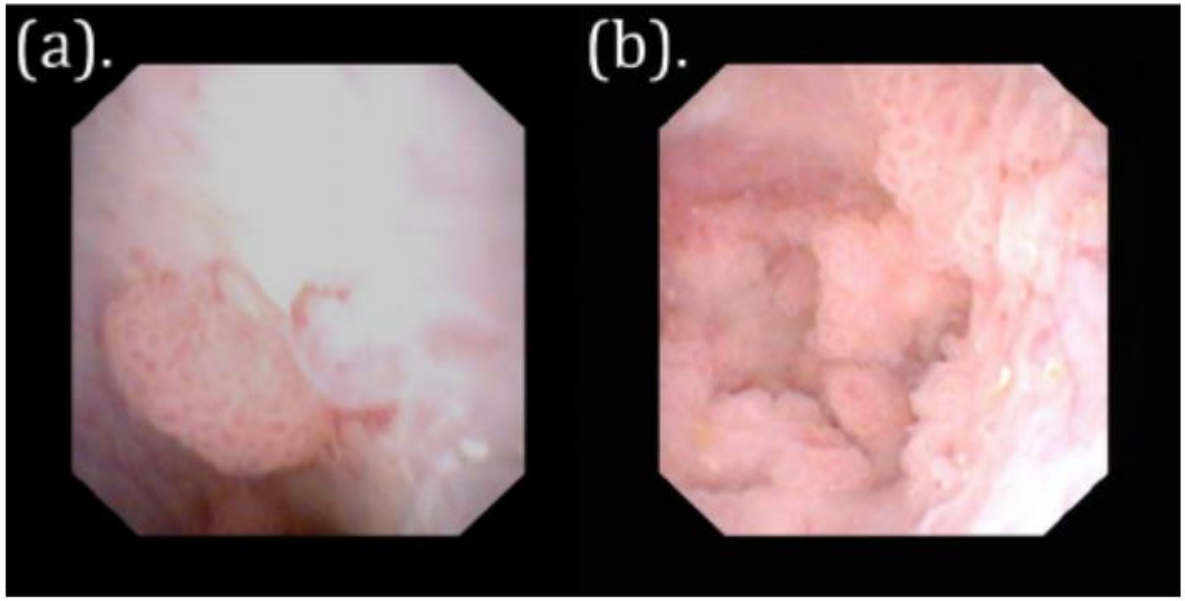
- **Indications**
  - **Urinary stone surgery (kidney and ureter)**
  - **Ureteral stricture management**
  - **Urinary tumor surgery**
  - **Diagnosis of urinary tract tumor**
  - **Diagnosis of urinary tract injury**
  - **Management of urinary tract bleeding**

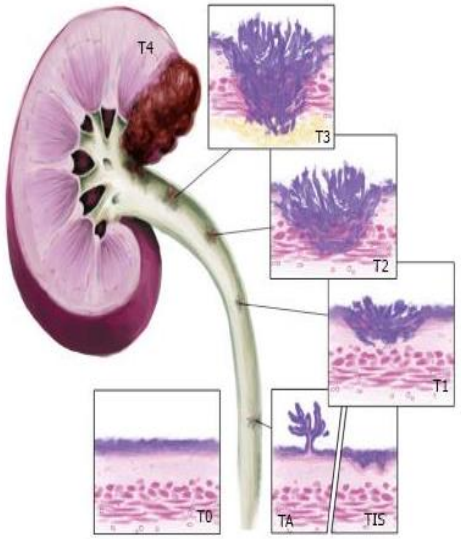


6.5Fr semi-rigid ureteroscope

7.95Fr flexible ureteroscope

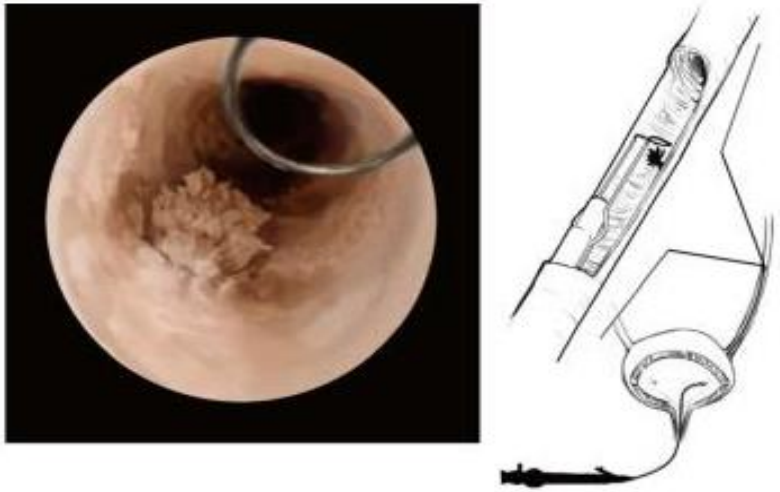
- Upper urinary tract urothelial cancer (UTUC)



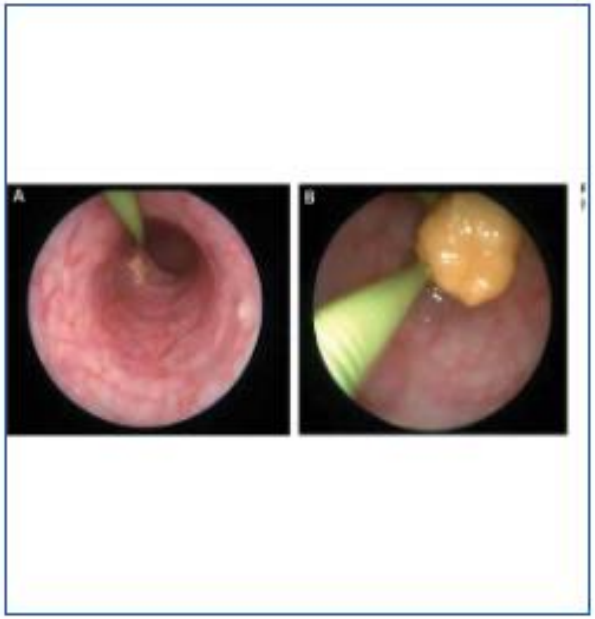


Obtaining tumor specimen for pathologic stage.

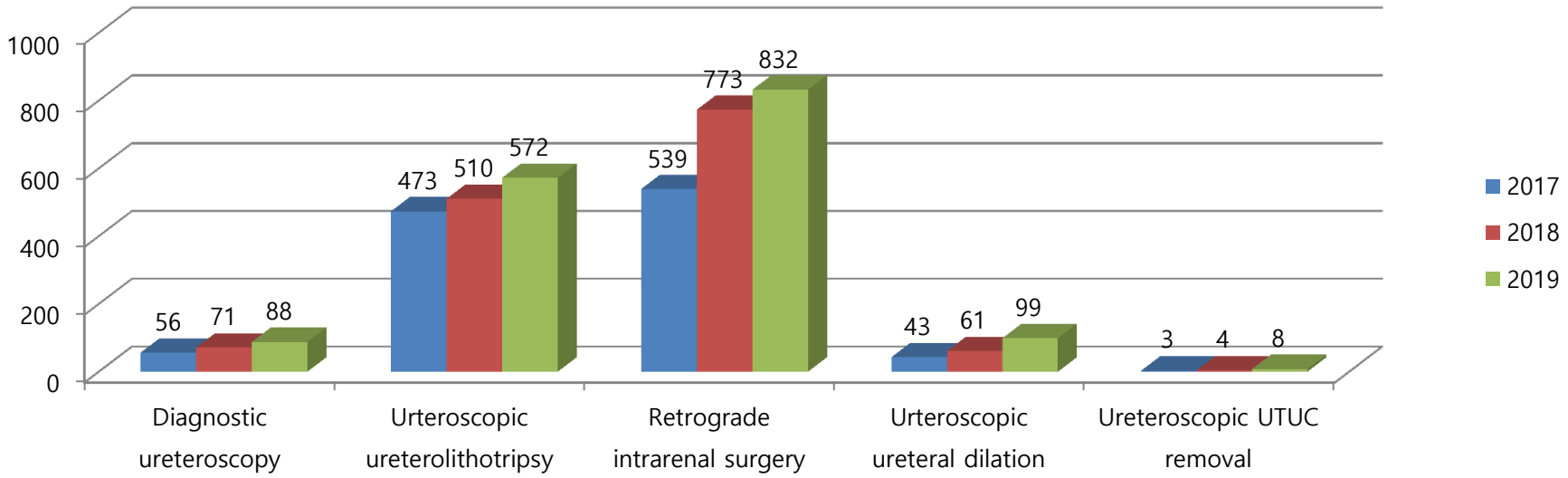
Tumor resection using ureteral resectoscope with loop.



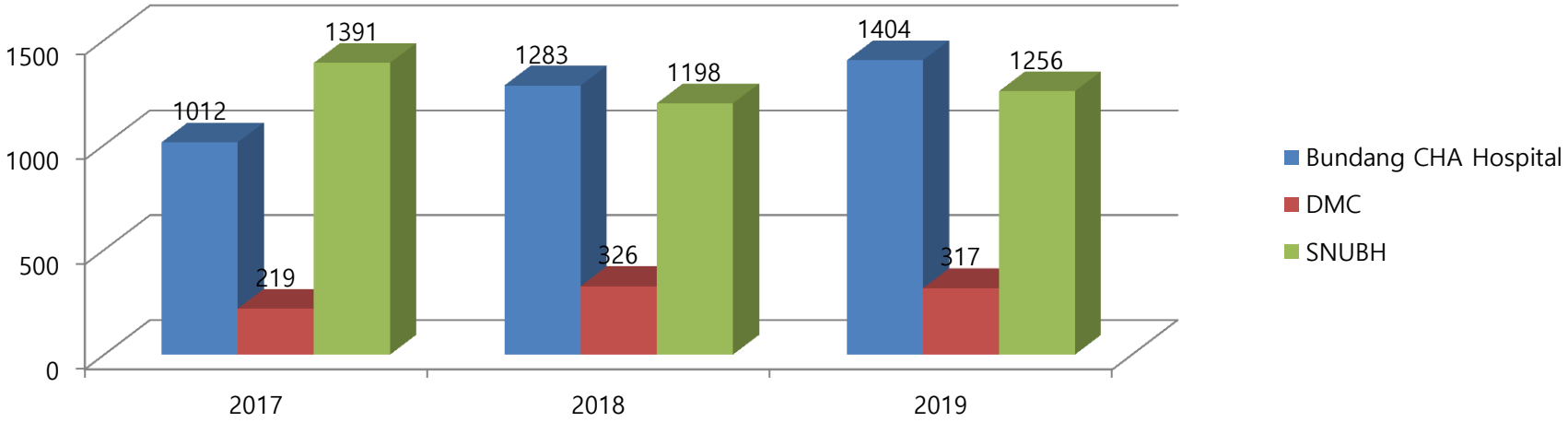
- Ureteroscopic uteterolithotripsy by Holmium-YAG LASER



- Ureteroscopy based surgery performed at Bundang CHA Hospital



- No. of ureteroscopic stone surgeries performed in the local area



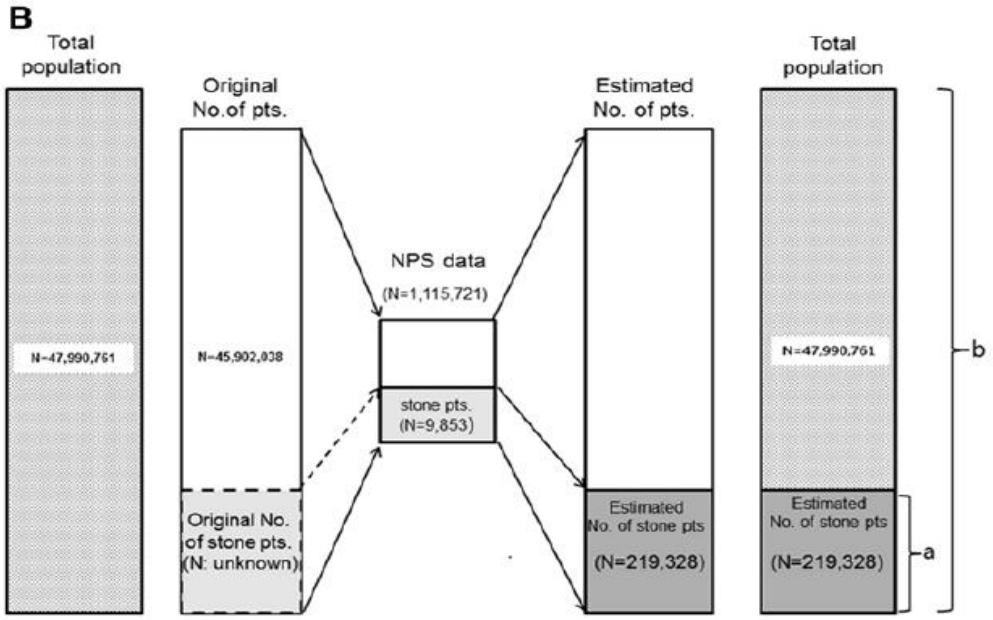
Incidence of reno-ureteral stone

- **Epidemiologic evidence – South Korea**

Urolithiasis (2014) 42:109–114
DOI 10.1007/s00240-014-0643-6

ORIGINAL PAPER

The epidemiology of reno-ureteral stone disease in Koreans: a nationwide population-based study



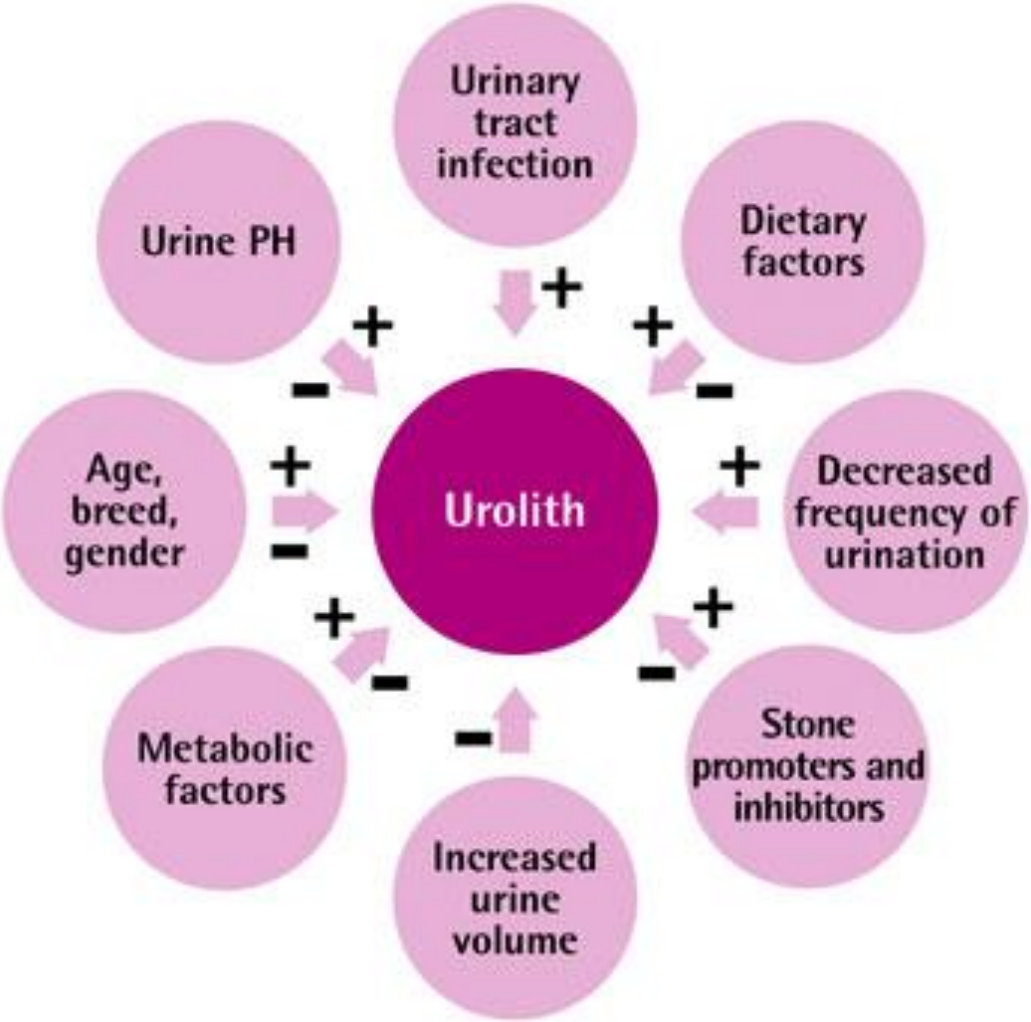
Overall incidence (a/b*100,000)=457 (number per 100,000)

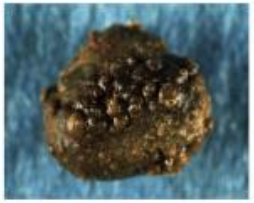
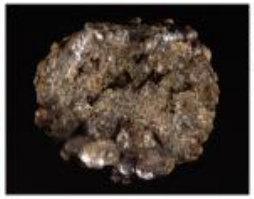
Incidence

- The annual incidence of stone : 457 per 100,000
- Men : Women = 1.8 : 1
- Peaks in incidence : 40-60 years old.

	Total	Inpatients	Outpatients
No. of patients in total population	45,902,038	5,471,423	40,430,615
No. of patients in NPS data	1,115,721	711,285	404,436
No. of stone patients in NPS data	9,853	8,298	1,555
Estimated no. of patients	219,328	63,828	155,500
2010 Concensus number	47,990,761		
Overall incidence (number per 100,000)	457	133	324

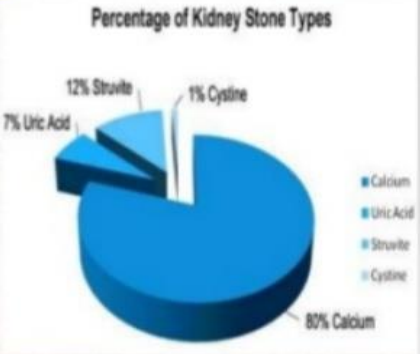
Affecting factors on stone formation

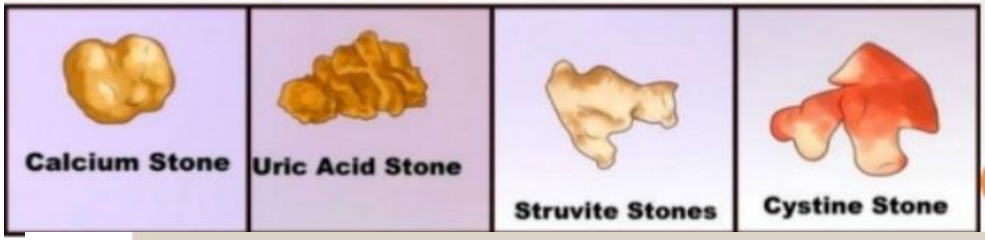


Morphological subtype	Stone morphology		Common etiology
	Main component	Surface	Section	
Type Ia	*Whewellite*			Dietary hyperoxaluria, low diuresis (high oxalate concentration) Randall's plaque
Type Ib	*Whewellite*			Stasis, low diuresis Total crystalline conversion from weddellite to whewellite
Type Ic	*Whewellite*			Primary hyperoxalurias (mainly type 1 by AGXT mutation)
Type Id	*Whewellite*			Malformative uropathy, stasis and confined multiple stones
Type Ie	*Whewellite*			Enteric hyperoxaluria Inflammatory bowel diseases (Crohn disease) Ileal resections Chronic pancreatitis

TYPES OF KIDNEY STONES

- Calcium oxalate
- Calcium phosphate
- Struvite
- Uric acid
- Cystine



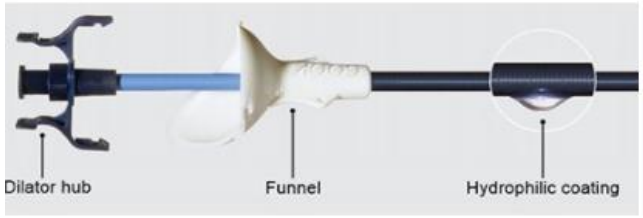


Struvite (Infection) Stones

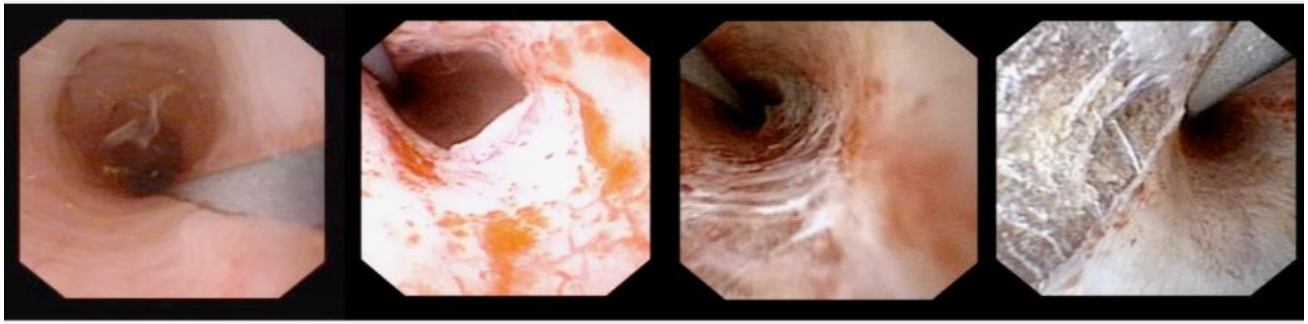
Many of these patients have urinary tract infections, and a urease-producing bacteria causes the stones to form. Since UTIs are more common in females, it is more common to see this stone in females.

5-7%
of all kidney stones

Infection stone accounts for 27.3% of all urinary stone cases surgically treated at Bundang CHA Hospital



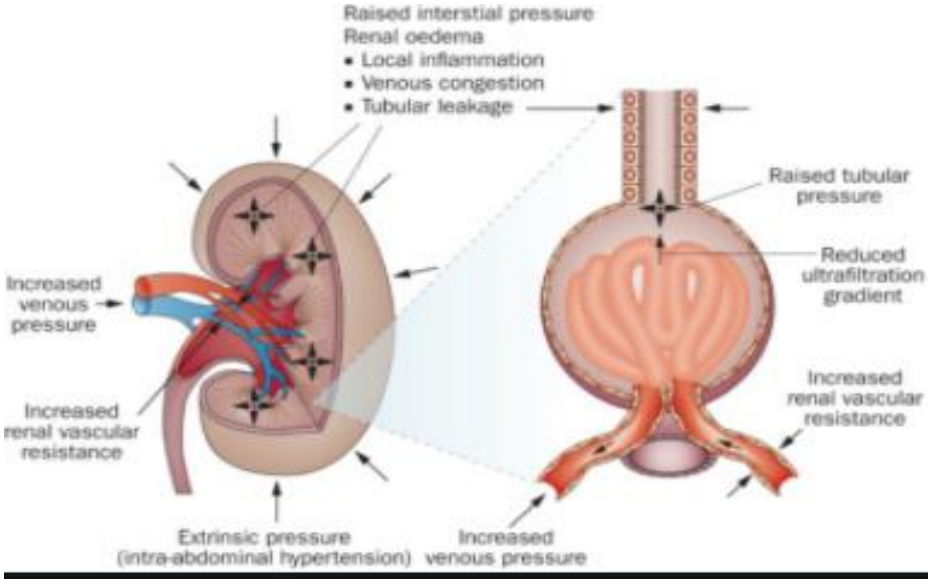
UAS & URETERAL LESION

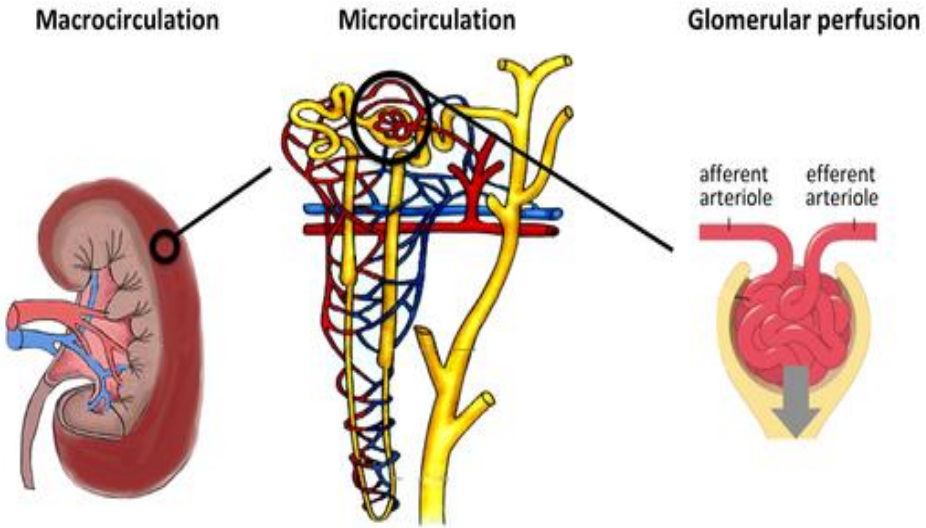


Type 0	Type 1	Type 2	Type 3
53%	33%	10%	4%

Intrarenal pressure and acute kidney injury (AKI)

- **Increased intra-renal pressure during RIRS**
  - Congestion of renal micro-circulation
  - Increased glomerular hydrostatic pressure
  - Increased intra-tubular pressure of glomerulus
  - Tubular reabsorption + tubular obstruction
  - **Acute kidney injury → Rapid loss of kidney function**





World Journal of Urology (2019) 37:125–131
https://doi.org/10.1007/s00345-018-2378-4

INVITED REVIEW

Pressure matters: intrarenal pressures during normal and pathological conditions, and impact of increased values to renal physiology

Theodoros Tokas[1] · Thomas R. W. Herrmann[2] · Andreas Skolarikos[3] · Udo Nagele[1] · Training and Research in Urological Surgery and Technology (T.R.U.S.T.)-Group

Received: 27 April 2018 / Accepted: 12 June 2018 / Published online: 18 June 2018

Infusion pressure set during RIRS: 150-250cmH_20

Table 1 IRPs in different conditions

Condition	Values (cm H_2O)
Pressures during the PPF test	
Normal	12–15 [7]
Intermediate	15–20 [7]
Increased	>20 [7]
Human unobstructed kidney	0–2 [10]
Maximum IRP during diuresis	> 27.2 [11]
Chronic kidney obstruction	68–95.2 [11]
Minimum measured IRPs during obstruction	20 [12]
Mean basal IRP during hydronephrosis	12.1 [13]
IRPs at 50% bladder capacity (intravesical pressure: 8.9 ± 3.1 cm H_2O)	
Non-hydronephrotic kidneys	7.4 ± 1.1 [16]
Hydronephrotic kidneys	20.8 ± 2.1 [16]
Measured IRPs that can cause pyelovenous backflow	40.8–47.6 [11]
Minimum measured IRPs that can cause pyelovenous backflow	13.6–27.2 [17, 18]
Measured IRPs that can cause pyelosinous backflow/forniceal rupture	81.6–95.2 [21, 22] 272 [23]
Measured IRPs that can cause kidney injury and arterial blood flow reduction	20–40 [41]

IRPs intrarenal pressures *PPF* pressure flow test

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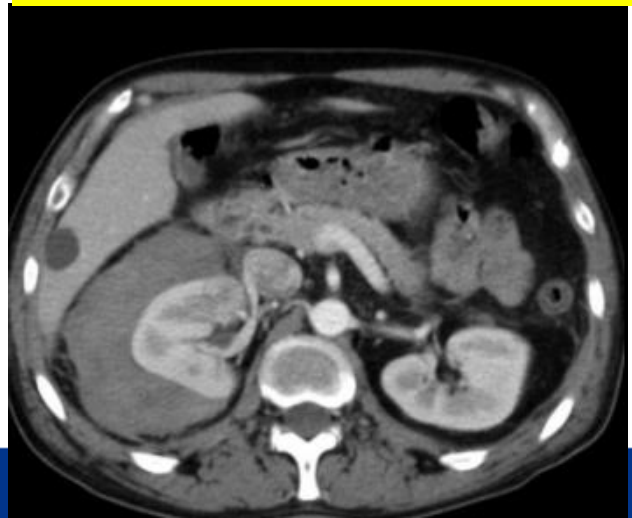
Pressure matters: intrarenal pressures during normal and pathological conditions, and impact of increased values to renal physiology

- Animal studies (porcine model)
  - Kidneys subjected to high pressures can be **irreversibly damaged**
  - IRPs **≥ 204 cmH_2O** have been demonstrated to produce **significant pathological changes** in the kidneys of pigs compared with IRPs < 122.4 cmH_2O
  - Rupture of the collecting system has been noted at 448.8 cmH_2O
  - Forniceal rupture with **pyelosinous backflow** has been associated with perirenal pseudocysts, retroperitoneal edema, fibrolipomatosis, perinephritic abscess, and perirenal hemorrhage

Rt perirenal hematoma post RIRS for renal stone



World Journal of Urology (2019) 37:125–131
https://doi.org/10.1007/s00345-018-2378-4

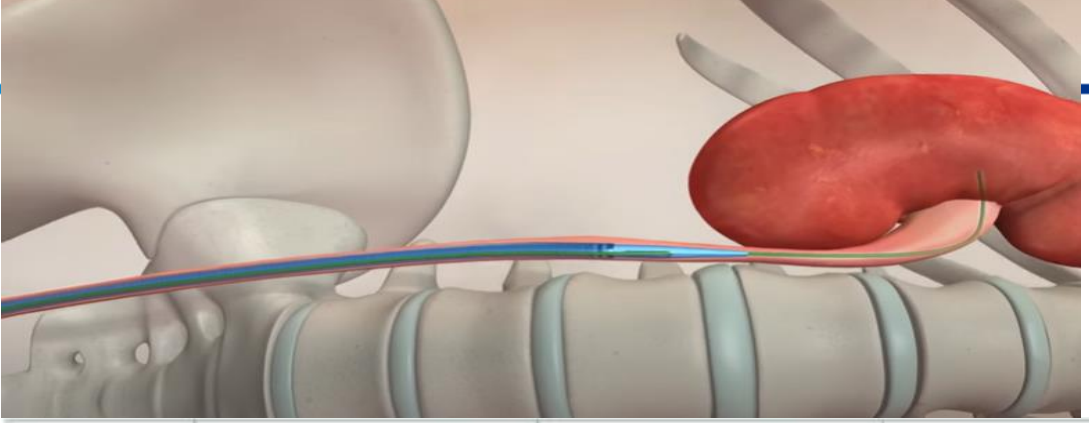
INVITED REVIEW

CrossMark

Pressure matters: intrarenal pressures during normal and pathological conditions, and impact of increased values to renal physiology

- High pressures can result in submucosal edema formation, and congestion
  - These findings **can be present even 4–6 weeks after a procedure**
- High pressures can also induce **renal oxidative damage** and secondary loss of renal function due to insufficient venous flow and compression of microvessels
- **Pyelovenous backflow limits venous outflow to a certain extent, and renal microvessels become compressed by the perfusion pressure**, which decreases the blood supply to the renal parenchyma
  - These factors lead to ischemia/reperfusion damage of the kidney

Company	UAS name	Inner diameter (F)	Outer diameter (F)	Length (cm)
Applied	Forte AxP	10	12–16	20 – 28 – 35 – 45 – 55
	Forte HD	12	14–18	
		14	16–18	20 – 28 – 35
	Forte deflecting	10	14	35 – 55
Bard	Aquaguide	12	14	25 – 35 – 45 – 55
		13	15	
Boston Scientific	Navigator	11	13	28 – 36 – 46
		13	15	
Coloplast	Retrace	12	14	35–45
		10	12	35–45
Cook	Flexor parallel	12	14	13 – 20 – 35 – 45 – 55
	Flexor	9.5	11.5	13 – 20 – 28 – 35 – 45 – 55
		12	14	
		14	16	13 – 20 – 28 – 35 – 45 – 55
	Flexor dual lumen	9.5	14	13 – 20 – 28 – 35 – 45 – 55
		12	17.5	
Olympus–ACMI	Uropass	12	14	24 – 38 – 54
Onset Medical	Pathway	11	14	28 – 36 – 46
		12	15	
Rocamed	RocaUS	10 (10.9)	12	35 – 45
		12	14	



	9,5 / 11,5 Fr Cook Medical	10 / 12 Fr Coloplast ReTrace	10 / 12 Fr Rocamed Bi-Flex	11 / 13 Fr Roston Scientific Navigator HD	12 / 14 Fr Coloplast ReTrace
Olympus URF-P6					
Storz Flex-X2					
Storz Flex-XC					
Wolf Boa					
Olympus URF-V2					
Olympus URF-P5					
Wolf Cobra Vision					
Olympus URF-V					

World Journal of Urology
https://doi.org/10.1007/s00345-018-2379-3

INVITED REVIEW

Pressure matters 2: intrarenal pressure ranges during upper-tract endourological procedures

Theodoros Tokas[1] · Andreas Skolarikos[2] · Thomas R. W. Herrmann[3] · Udo Nagele[1] · Training and Research in Urological Surgery and Technology (T.R.U.S.T.)-Group

Received: 1 May 2018 / Accepted: 12 June 2018

At IP: 60–100 cmH_2O (Roller pump devices)
UAS: **10/12 Fr → IRP: 13.4–57.00 cmH_2O**
UAS: **11/13 Fr → IRP: 4.08–29.00 cmH_2O**
UAS: 12/14 Fr → IRP: 2.72– <20.00 cmH_2O

At IP: 100-272 cmH_2O (Roller pump devices)
UAS: 10/12 Fr -> IRP: 92–149.6 cmH_2O

At IP: 100-272 cmH_2O (50mL syringe manual irrigation)
IRPs reach 156.4 cmH_2O by gentle, and **469.2–557.6 cmH_2O** by powerful irrigation

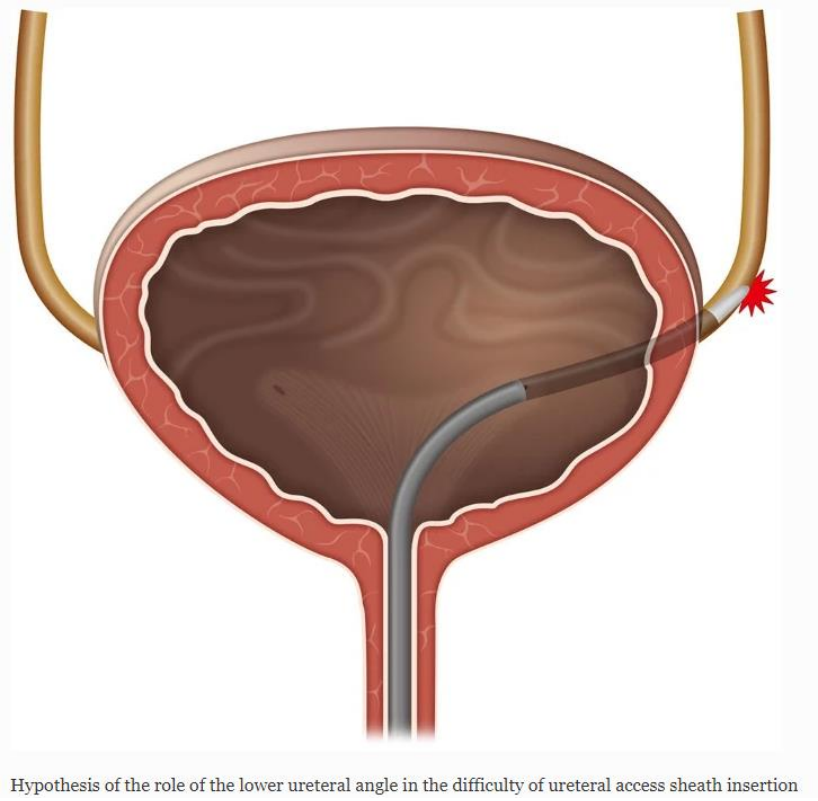
Urology - Original Paper | Published: 29 April 2020

CHA 의과학대학교 CHA 분당차병원

A presumptive role of lower ureteral angles in the difficulty of ureteral access sheath insertion during retrograde intrarenal surgery

Sung Yong Cho, Seung Hoon Ryang & Dong Sup Lee

International Urology and Nephrology **52**, 1657–1663(2020) | Cite this article



Hypothesis of the role of the lower ureteral angle in the difficulty of ureteral access sheath insertion

Alpha angle > 35 degree is recommend for successful UAS insertion

UAS ≥ 12/14 Fr might have a higher ureteral injury rate even with a-angle > 35°

Aim of research

- **Newer design for UAS**
  1) Maintaining good visual during operation
  2) Maintaining lower intrarenal pressure
  3) Flexible enough to overcome small alpha angle
  4) Small outer caliber to minimize ureter injury
  5) Strong hydrophilic outer surface to minimize ureter injury
  6) Large enough inner caliber to remove stone or tissue
  7) Sharp but soft insertion tip to minimize renal injury
- **Designing newer UAS (prototype)**
- **Animal testing of newer UAS**
- **Practical application of newer UAS on human subjects**

Involved researchers:

Olympus Korea
올림푸스한국

Olympus Korea

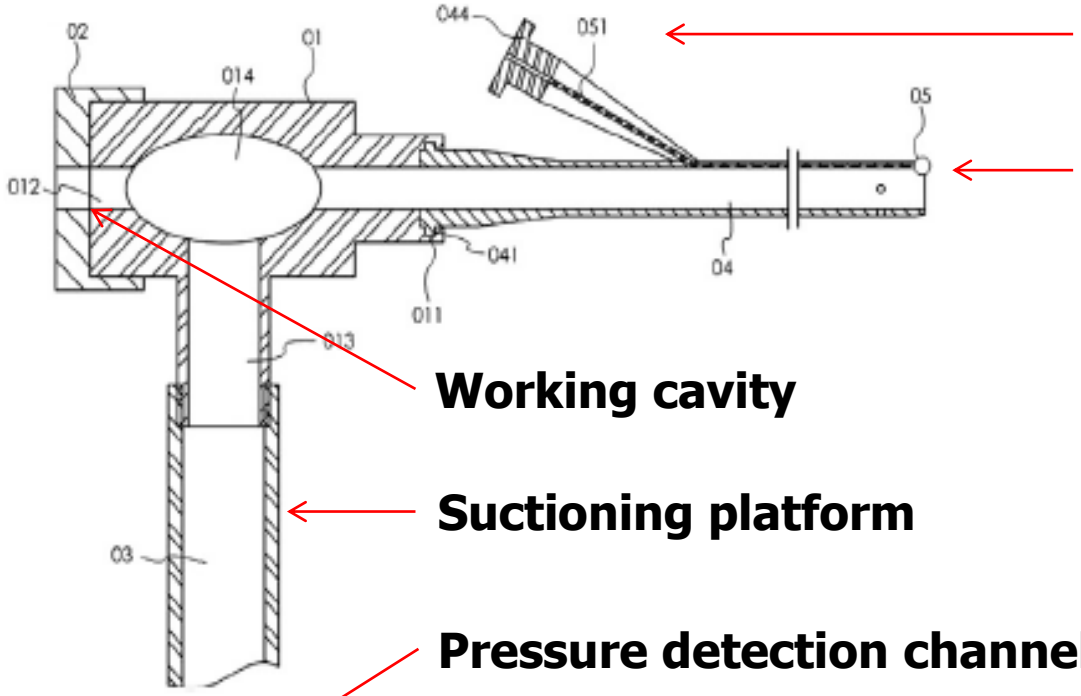
서울대병원
비뇨의학과 조성용교수

중앙대학교병원
비뇨의학과 장인호교수

CURRENT RESEARCH

대한비뇨내시경로봇학회
KOREAN SOCIETY OF ENDOUROLOGY AND ROBOTICS

Automated suctioning platform UAS



Pressure transducer

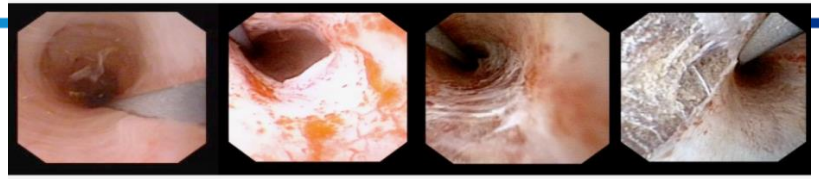
Access pipe

Working cavity

Suctioning platform

Pressure detection channel

UAS & URETERAL LESION



Type 0	Type 1	Type 2	Type 3
53%	33%	10%	4%

Clinical parameters of porcine model measured in RIRS

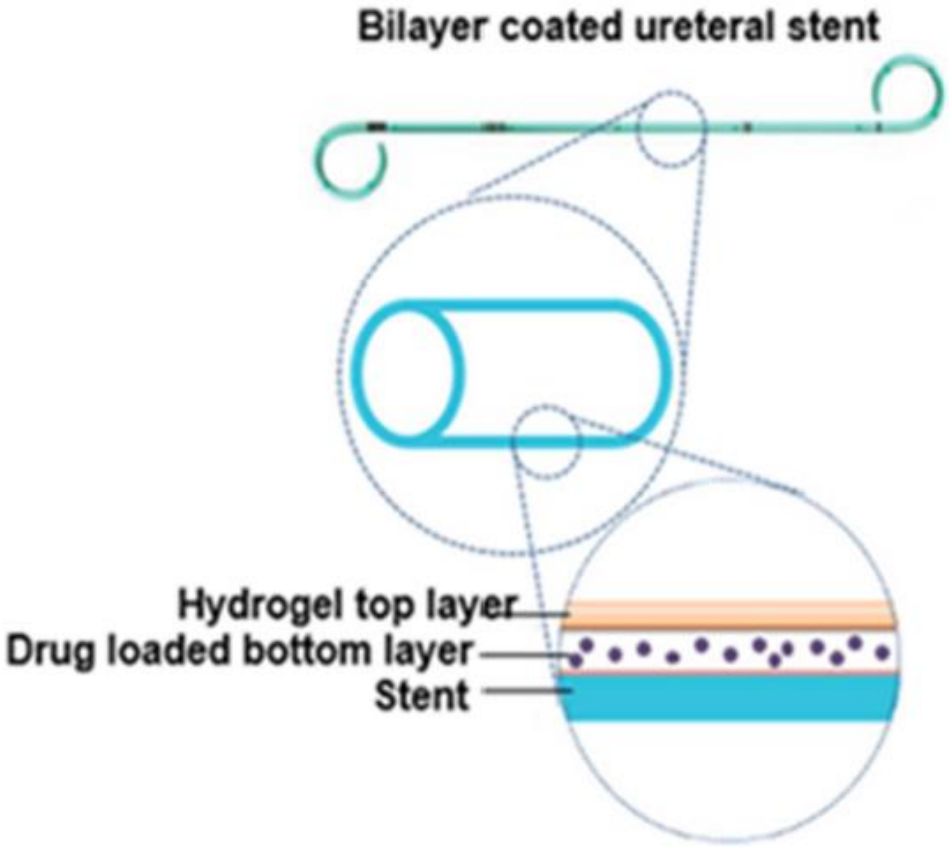
Parameters	Conventional UAS	Suctioning UAS	p-value
No, of subject	35	27	
Caliber	10/12 Fr	10/12 Fr	
Infusion pressure (cmH_20)	200	200	
Mean intrarenal pressure (cmH20)	**142.8**	**23.7**	**<0.001**
UAS induced ureteral lesion, n (%)			0.832
Type 0	**27 (77.1)**	**22 (81.5)**	
Type 1	5 (14.3)	3 (11.1)	
Type 2	3 (8.6)	2 (7.4)	
Type 3	0 (0.0)	0 (0.0)	

Comparison of postoperative parameters (Clinical application)

Clinical data	Conventional UAS	Suctioning UAS	p-value
No. of subjects	56	29	
Gender (male)	56	29	
No. of urethral injury	1	0	
Mean renal stone size (mm)	1.56	1.59	
Mean number of renal stones	1	1	
Mean operation time (min)	64.3	47.1	<0.001
No. of cases with postop fever, n (%)	3 (5.4)	0 (0.0)	0.001
≥Type2 ureteral injury, n (%)	3 (5.4)	2 (6.9)	0.085
Mean IL-6 within 24h after surgery (pg/mL)	9.0	5.3	<0.001
Mean stone clearance rate (%)	94.8	100.0	<0.001
No. of elevated Cr level cases (within postop 48H), n (%)	5	0 (0.0)	0.012
Mean hospital stay (day)	4.14	3.16	0.039

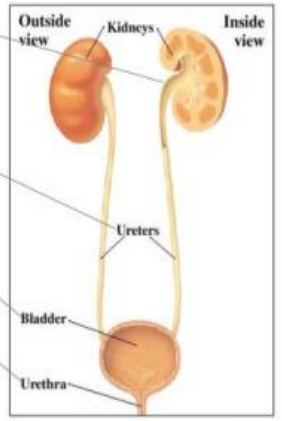
- **Future plan**
  1) Data accumulation (expanding number of study subjects)
  2) Minimizing the device price
  3) Obtaining the patent for the device in overseas
  4) Diversifying caliber size
  5) Increasing flexibility of UAS

Drug delivery via biodegradable ureteral stent for the treatment of upper tract urothelial carcinoma



Upper tract urothelial carcinoma (UTUC; transitional cell carcinoma of the ureter or renal pelvis)

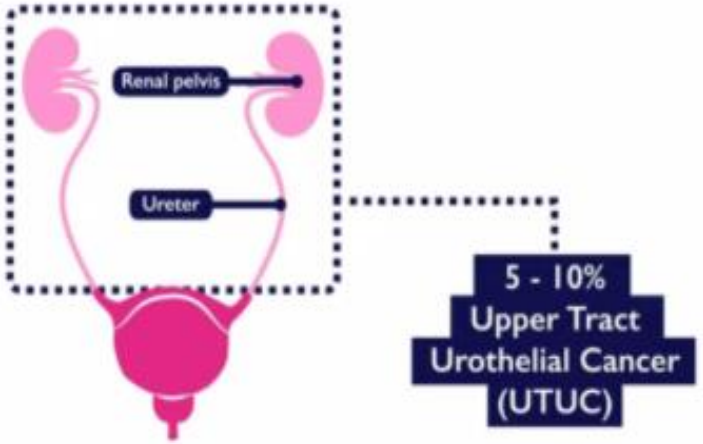
- Definition: Cancer of the lining of the urinary tract
  - Lining of the kidneys (5%)
  - Ureters (2%)
  - Bladder (92%)
  - Urethra (1%)



-Relatively rare, occurring in 2 cases/100,000 population in developed countries

-Scant symptoms and delayed diagnosis mean that tumors are **often muscle-invasive or locally advanced at presentation (56%)**

-Resulting in poorer survival figures than for urothelial carcinoma of the urinary bladder



International Journal of Clinical Oncology (2020) 25:1037–1054
https://doi.org/10.1007/s10147-020-01650-9

REVIEW ARTICLE

Efficacy of neoadjuvant and adjuvant chemotherapy for localized and locally advanced upper tract urothelial carcinoma: a systematic review and meta-analysis

Fahad Quhal[1,2] · Keiichiro Mori[1,3] · Reza Sari Motlagh[1] · Ekaterina Laukhtina[1,4] · Benjamin Pradere[1,5] · Morgan Rouprêt[6] · Andrea Necchi[7] · Marco Moschini[8] · Shahrokh F. Shariat[1,4,9,10,11,12,13,14]

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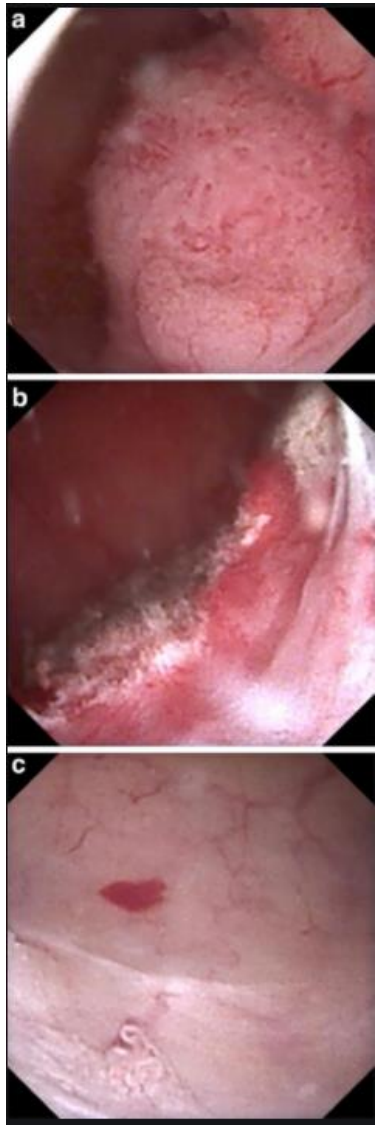
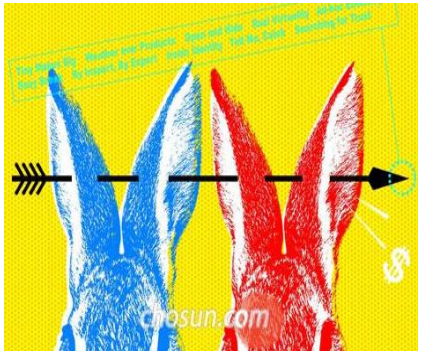


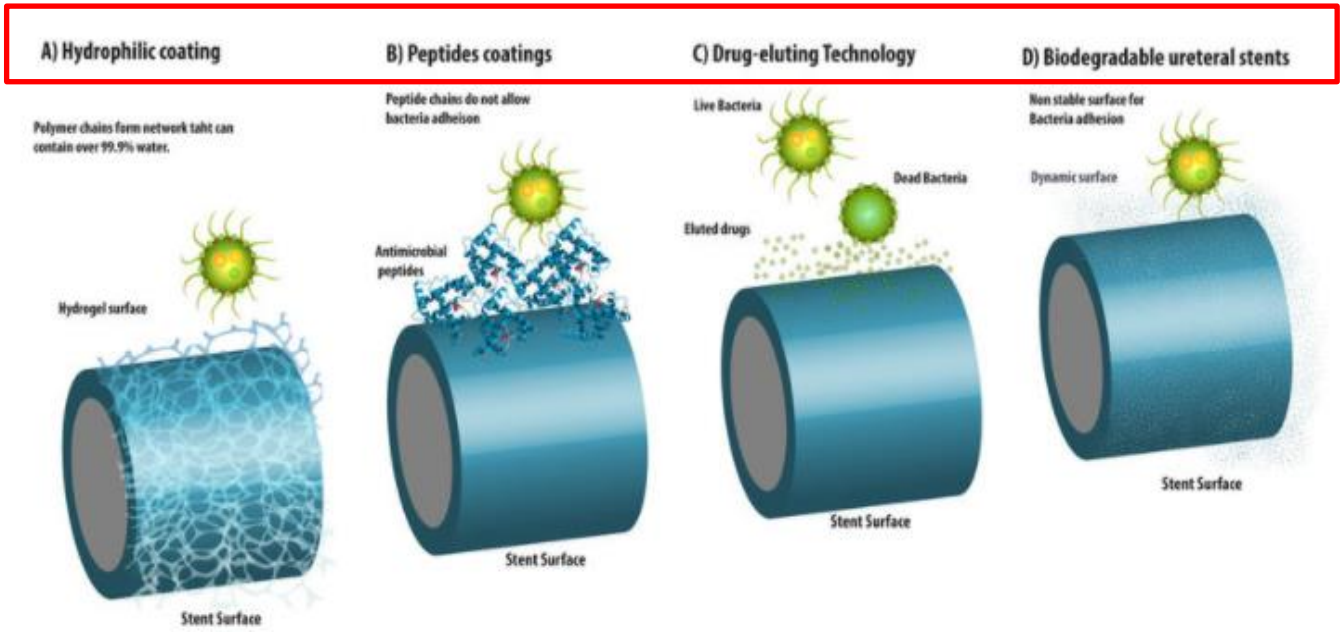
- At this inception, systemic treatment had no proven role for locally advanced UTUC
- Nephroureterectomy followed by surveillance has remained the routine treatment for localized UTUC
- **Low-risk UTUC**: **organ-preservation with endoscopic treatment** is an option
- Local chemotherapy can avoid the recurrence of carcinoma, which has been used as an adjuvant treatment optioin after UTUC
- Due to the characteristics of impermeable urothelium and the continuous washing of urine, the **effectiveness of local chemotherapy was limited**

Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial

Alison Birtle, Mark Johnson, John Chester, Robert Jones, David Dolling, Richard T Bryan, Christopher Harris*, Andrew Winterbottom*, Anthony Blacker, James W F Catto, Prabir Chakraborti, Jenny L Donovan, Paul Anthony Elliott, Ann French, Satinder Jagdev, Benjamin Jenkins, Francis Xavier Keeley Jr, Roger Kockelbergh, Thomas Powles, John Wagstaff, Caroline Wilson, Rachel Todd, Rebecca Lewis, Emma Hall

- **Anti-tumor drug-loaded biodegradable ureteral stent** might be an optional and effective method to solve the clinical problems
- Incorporating coating and eluting as drug loading technologies with multiple advantages in the design of drug-loaded stents is not fully studied





BARD
has joined BD

대한비뇨내시경로봇학회
KOREAN SOCIETY OF ENDOUROLOGY AND ROBOTICS

제1회
대한비뇨내시경로봇학회
로봇수술연구회 심포지움

The 1st Annual Meeting of KORUS
(Korean Robotic Urology Symposium)

일 자 • 2020년 1월 10일(금)~11일(토)
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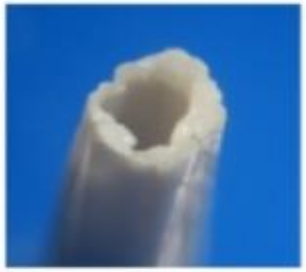
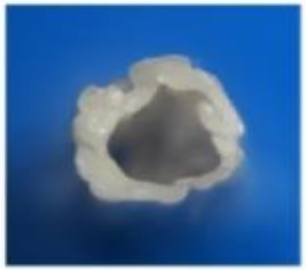
Biodegradable ureteral stent (BUS)

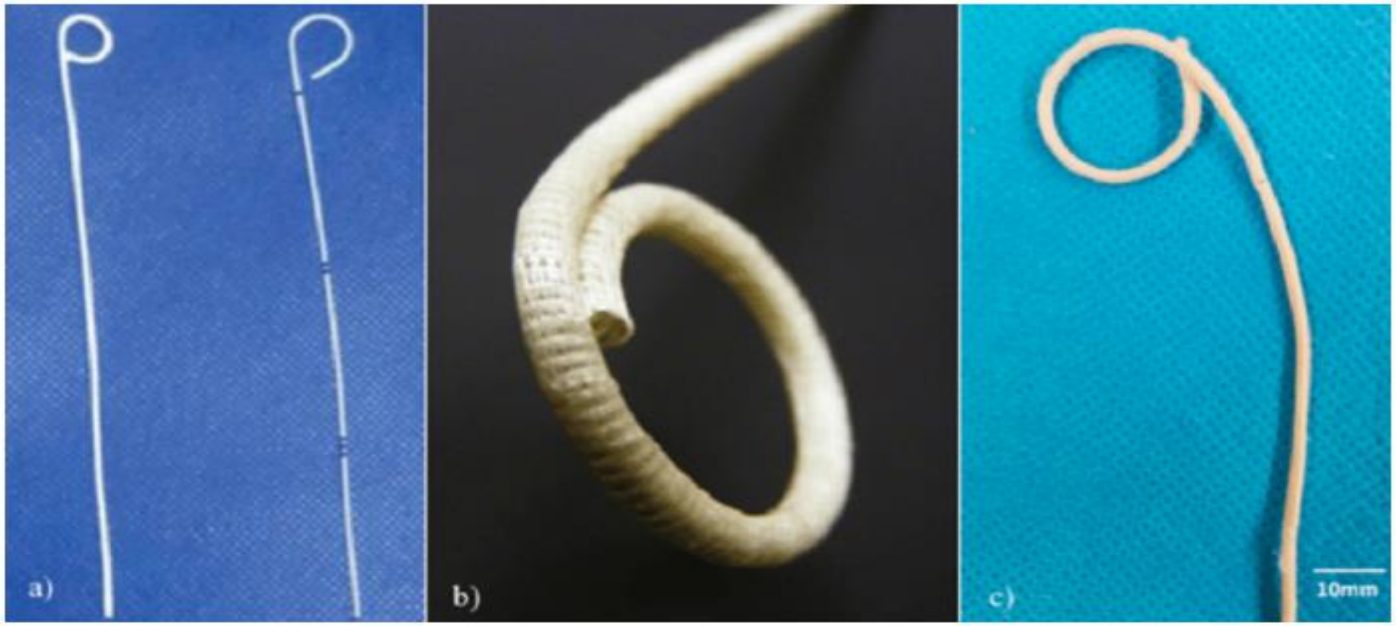
- Need moderate mechanical strength to maintain **intact tubular structure and well-controlled degradation rate**, such as **natural origin polymers, synthetic polymers, and some metals**

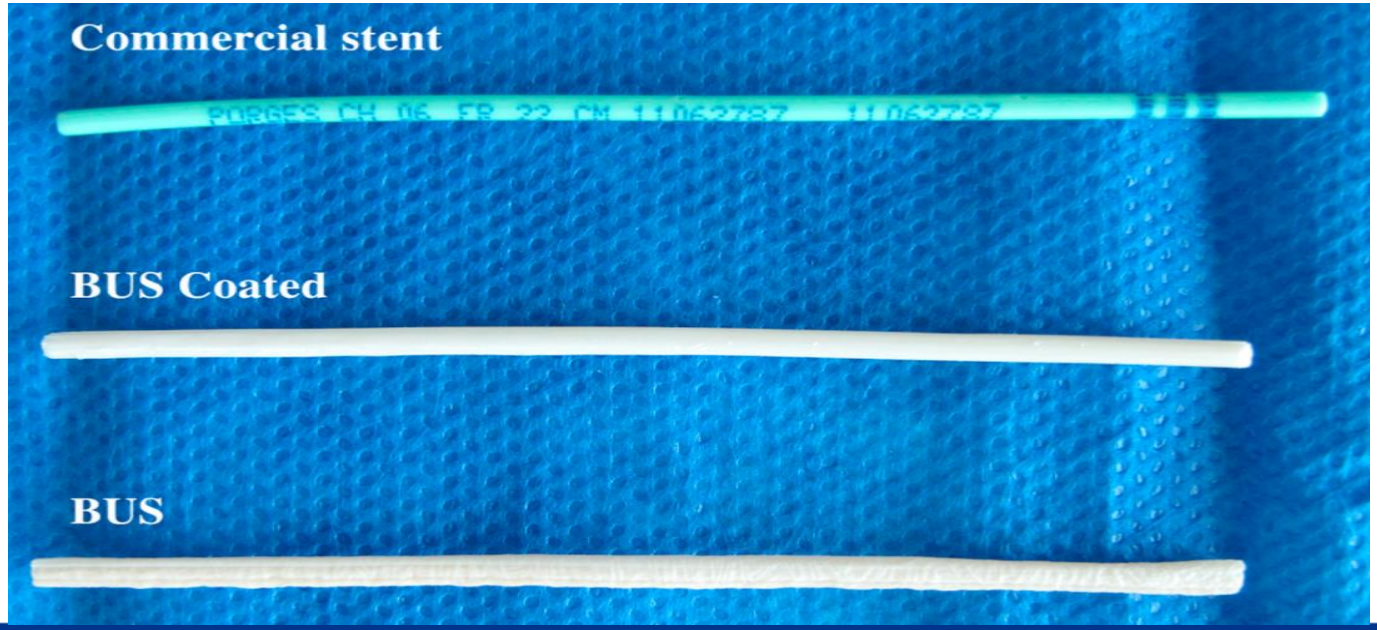
- Most commonly used synthetic polymer
  - **Polylactic acid (PLA)**, polyglycolic acid, poly (lactide-co-glycolide) (PLGA), polycaprolactone (PCL), polyethylene glycol, poly (lactide-cocaprolactone), polydioxanone

- PLA based BUS
  - In porcine model, the conventional BUS exhibited satisfactory drainage characteristics and excellent antireflux effect
  - BUS began to degrade at 3 weeks and were completely degraded by 10 weeks





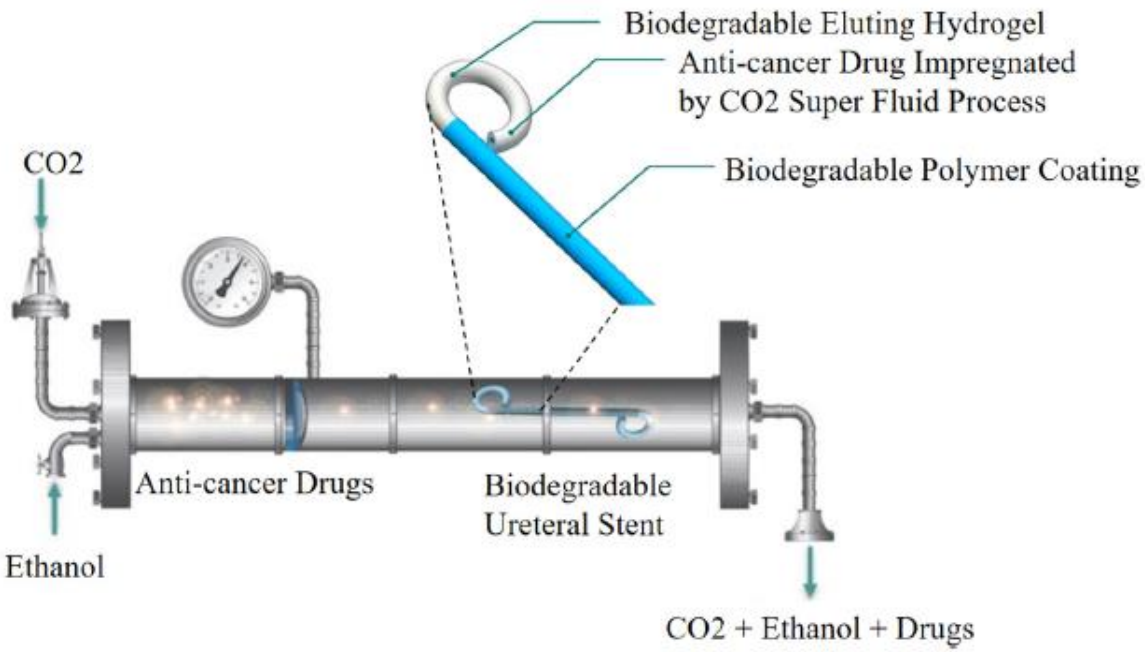

a)
b)
c)
10mm


Commercial stent
BUS Coated
BUS

Drug eluting ureteral stent (DES) production

CO2 Impregnation

- CO_2 in its supercritical state (high pressure, high temperature) can dissolve well into various polymer matrices
- Drug must have **sufficient solubility in CO_2**, low drug loading rate and drug loading efficiency, and the stent shape changes after drug loading

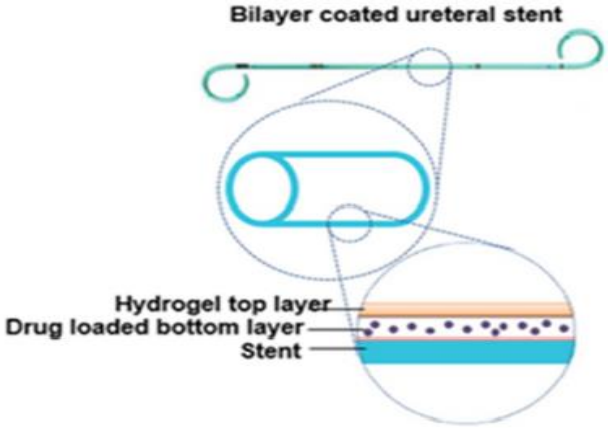


Drug eluting ureteral stent (DES) production – Double drug layer stent

Polyethylene glycol diacrylate (PEGDA) hydrogel coating

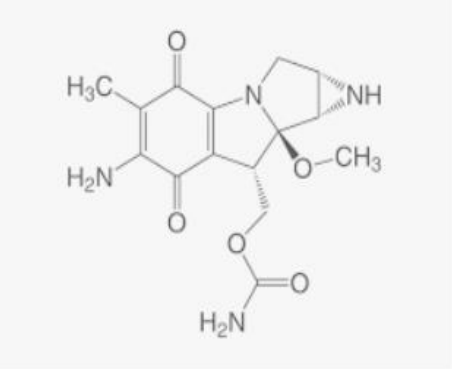
- PEGDA powder dissolved in deionized (DI) water
- Ethanol was added to the PEGDA solution making 0.1% PEGDA solution
- Mixture was exposed to 365nm UV-irradiation for 10 min making hydrogels
- Poly-L-lactide-co-caprolactone (PLC) pellets and mitomycin C (MMC) were dissolved in dichloromethane + PEGDA hydrogel mixture → stirred continuously overnight until homogeneous polymer solutions
- Drug/polymer solution was coated onto the stent section with a spray-coater
- Stent was plasma-treated with oxygen for 5 min at 100W power UV to produce UV-irradiated photo-crosslinking

MediCoat DES | Sono-Tek



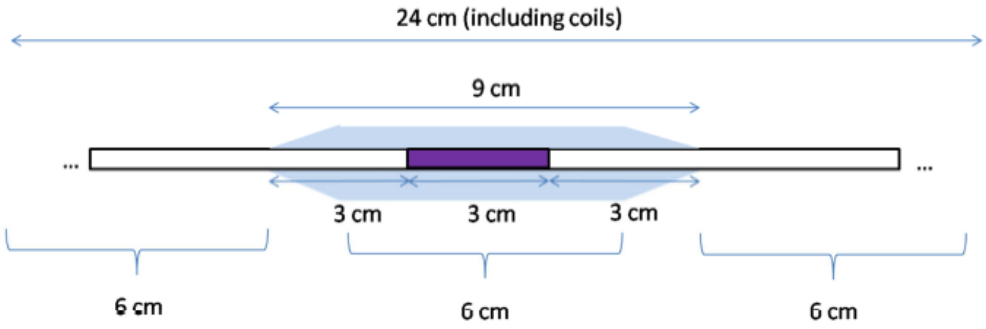
Potential candidates for chemotherapeutic agents

- **Mitomycin C (MMC)** – least damage to normal urothelial cells
- Epirubicin – inferior oncological outcomes in animal models
- Cisplatin
- Gemcitabine



In-Vivo (Porcine) model: preparation

- Cystoscopic retrograde 6Fr-24cm DES (double drug layer) was indwelled to 40kg porcine model: coated stent was inserted into the ureters without significant resistance
- 24H after stent indwelling laparotomy was performed to expose bilateral ureters
- Ureters were harvested and divided into 3 segments, proximal, middle and distal sections, each of 6 cm in length
- Tissue samples were analyzed for presence and quantity of MMC using liquid chromatography mass spectroscopy (LCMS): serum creatinine levels were assessed to measure systemic damage



In-Vivo (Porcine) model: results

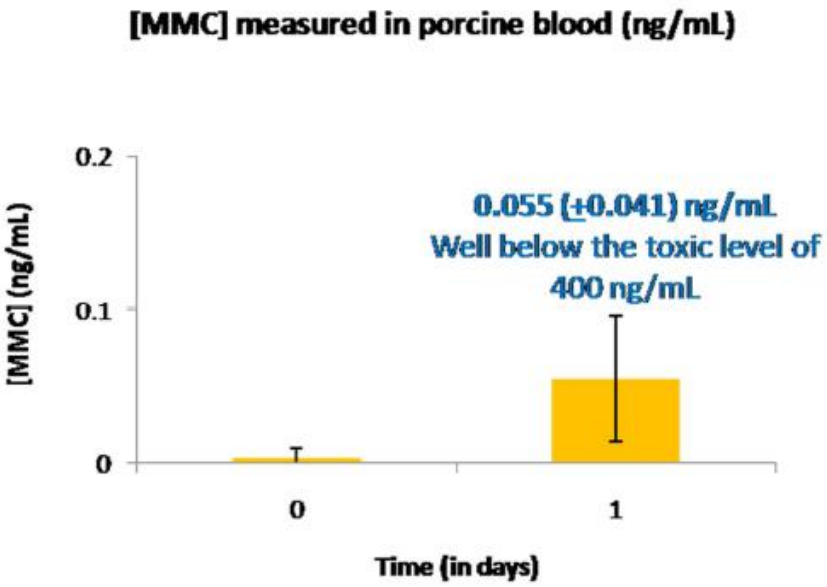
- No stent migration was observed at 24H after indwelling
- Apposition of stent onto ureteral mucosa was believed to be substantial because hydrogel coating section has been designed to swell up to around 7 mm outer diameter
- Harvested ureters showed that the hydrogel layer remained adhered to stent

- Observation of the kidney calyx indicated that there was no distension or swelling

In-Vivo (Porcine) model: results

- A significant amount of MMC was found in the central segment of the stented ureter (close to 400 ng) negligible level of MMC in the peri-ureteric fat segment and in porcine blood

Sections analyzed	Absolute amount of MMC (ng)	Total mass of tissue samples analyzed (g)	Amount of MMC per gram of tissues (ng/g)
Proximal (Test)	4.1	1.6	2.6 ± 1.2
Middle (Test)	384	1.9	202 ± 92
Distal (Test)	4.4	1.8	2.5 ± 1.5
Peri-ureteric fats (Test)	3.6	0.3	15 ± 30



- PEGDA hydrogel stent maintained mechanical stability **without significant mass loss over 4 weeks**
- Marked **decrease in hydrogel swelling after 7 days** from stent indwelling
- When the amount of drug loaded (Co) is greater than the saturated amount of drugs (Cs) in the polymer matrix: **thicker polymer coating released the drug at a slower rate**, due to its longer diffusion path length
  - Optimal parameters need to be evaluated
- Coated stent was successfully implanted and removed in the porcine ureter using the current standard protocol for stent insertion in patients
  - The hydrogel-expandable drug-eluting polymer coating may potentially be applied to other areas

Further requirements

- Longer-term studies with a larger sample size in an in-vivo setting are desired
  - 8 porcine models will be further evaluated within 3 months time

- Presence of any possible iatrogenic injury to the ureters due to device removal need to be evaluated by examining the urothelial lining for signs of damage or inflammation

- Long-term risk evaluation of stent-related symptoms such as encrustation and bacterial infection could also be performed

Thank you for listening