

2019

요로생식기손상재건연구회 비뇨기계기초의학연구회 공동심포지엄

| 주최 | 대한비뇨기과학회, 대한비뇨기과학재단

| 주관 | 요로생식기손상재건연구회, 비뇨기계기초의학연구회

| 일시 | 2019년 2월 16일 토요일 08:20-13:00

| 장소 | 고려대학교 의과대학 315호, 316호

| 평점 | 대한의사협회 4점



INVITATION

존경하는 비뇨의학과 회원 여러분 안녕하십니까?

2019년 대한비뇨기과학회의 요로생식기손상재건연구회와 비뇨기계기초의학연구회 공동심포지엄이 2019년 2월 16일 개최됨을 알려드립니다.

이번 심포지엄의 공동 세션 중 요로생식기 손상재건 분야에서는 최근 연구 결과들을 바탕으로 urethroplasty의 controversy에 대한 토의 시간을 가질 예정이며, 기초 의학연구회 분야에서는 비뇨기계암에서 최근 각광을 받고 있는 personalized medicine과 immuno-oncology에 대한 최신 지견을 나누고자 합니다. 이 외에도 최근 해외연수를 다녀오신 교수님들의 최근 연구 동향에 대해 새로운 지식을 공유하고 토론하는 자리를 마련하였습니다.


대한비뇨기과학회의 요로생식기손상재건연구회와 비뇨기계기초의학연구회의 발전에 힘써 주신 회원분들께 깊은 감사의 말씀을 드리며, 바쁘신 가운데도 꼭 참석해 주셔서 많은 관심과 성원 부탁드립니다.

감사합니다.

2019년 2월

요로생식기손상재건연구회장 **박 홍 석**

비뇨기계기초의학연구회장 **이 상 돈**



요로생식기손상재건연구회

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편집이사	류 지 간	인 하 의 대
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2019

요로생식기손상재건연구회

비뇨기계기초의학연구회

공동심포지엄

| 일시 | 2019년 2월 16일 토요일 08:20-13:00

| 장소 | 고려대학교 의과대학 315호, 316호

사회: 강석호 (비뇨기계기초의학연구회 학술이사)

08:20-08:50	Registration	
08:50-08:55	Welcome & Introduction	이상돈 (비뇨기계기초의학연구회장) 박홍석 (요로생식기손상재건연구회장)
08:55-09:00	KUA President's Welcome	이규성 (대한비뇨기과학회장)
	Session I. Controversies in Urethroplasty	좌장: 박홍석 (고려의대)
09:00-09:30	Management of pelvic fracture urethral injuries: primary realignment or suprapubic cystostomy with delayed repair?	조 석 (인제의대)
09:30-10:00	The use of dorsal vs ventral placement of the graft in bulbar urethroplasty	이정우 (동국의대)
	Session II. Special Lecture	좌장: 이상돈 (부산의대)
10:00-10:30	Personalized medicine in urologic cancers	박경화 (고려의대 종양내과)
10:30-11:00	Immuno-oncology in urologic cancers	서호경 (국립암센터)
11:00-11:20	Break	
	Session III. 해외연수를 통한 최신 연구경험	좌장: 강석호 (고려의대)
11:20-11:40	Evidence based medicine: what is evidence?	정재홍 (연세의대)
11:40-12:00	Endoluminal ultrasound imaging technique to determine urethral stricture	유호송 (전남의대)
	Session IV. (기초) Current Status of Urological Research in Korea 좌장: 한웅규 (연세의대)	Session IV. (손상) Urologic Emergency and Reconstruction 좌장: 문홍상 (한양의대) (장소이동: 316호)
12:00-12:20	홍합에서 추출한 생체용 수중 접착단백물질의 요누공 치료효과에 대한 연구: 방광-질 누공 돼지모델에 적용한 전임상 실험 편종현 (성균관의대)	Blunt testicular trauma - is surgical exploration necessary? 태범식 (고려의대)
12:20-12:40	The immunotherapeutic Effects of recombinant Bacillus Calmette-Guérin to resistant Antimicrobial Peptide on Bladder Cancer Cells 장인호 (중앙의대)	Surgical Reconstructive Techniques in the Management of Penile cancer 육형동 (인제의대)
12:40-13:00	투명신세포암에서 mitochondria의 분자생물학적 양상이 암 진행 및 악성도의 예측 마커로서의 가능성 제시 나준채 (연세의대)	Case Discussion

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요로생식기손상재건연구회

비뇨기계기초의학연구회

공동심포지엄

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비뇨기계기초의학연구회

공동심포지엄

Session I. Controversies in Urethroplasty

좌장: 박홍석 (고려의대)

Management of pelvic fracture urethral injuries:
primary realignment or suprapubic cystostomy with delayed repair?

조 석 (인제의대)

The use of dorsal vs ventral placement of the graft in bulbar urethroplasty

이정우 (동국의대)

Management of pelvis fracture urethral injuries: Primary realignment or suprapubic cystostomy with delayed repair

조 석

인제대학교

골반 골절은 그 자체로도 출혈과 골반 내 장기의 손상 등으로 환자에게 심한 후유증을 남길 수 있는 의학적 응급상황이다. 이러한 골반 골절에서 요도 손상이 발생하는 경우는 1.6%-25% 정도로 보고되고 있다.(1-3) 골반 골절과 관련된 요도의 손상은 전부 요도에서 발생할 수도 있지만, 방광 경부와 전립선을 포함하는 후부 요도의 손상을 일으킬 수 있으며, 이러한 손상은 흔히 요도 협착을 일으키며, 발기 부전이나, 실금 증상을 유발하여 손상 이후 환자의 삶의 질을 떨어뜨리는 결과를 가져오게 된다.

하지만, 골반 골절과 관련된 요도의 손상의 가장 적합한 치료에 대해서는 아직 정립된 바가 없이 논란의 여지가 있다. 조기 요도 정렬술(primary urethral realignment)은 근위부 요도를 당겨 원위부 요도와 연결함으로써, 협착의 발생과 정도를 감소시키도록 치유과정을 촉진하는 데 목표가 있다.(4) 최근에는 내시경 장비의 발달로 내시경을 통하여 조기에 요도 정렬을 시도하는 연구가 있으며, 좋은 결과를 보고하고 있다.(5, 6) 하지만, 환자의 생체징후가 안정적인 상황에서만 시행되어야 하며, 출혈이나 혈종 등의 합병증 가능성이 있고, 골반 골절이 있는 환자에서는 움직임이 제한되기 때문에, 우선 치골 상부 도뇨관을 유치한 후에 수 개월 뒤에 환자의 전반적인 컨디션이 회복 된 이후 손상부위를 제거, 복구하는 방법(suprapubic cystostomy with delayed repair)을 선호하는 그룹도 있다.(7, 8)

이에 골반 골절로 인한 요도 손상이 확인된 환자에서 두 방법을 사용하였을 때, 치료 이후의 요도 협착 발생율이나, 장기간 관찰하였을 때의 발기부전, 요실금 가능성 등의 합병증 가능성에 대해 그간 발표된 연구를 확인하고, 각각의 장단점을 비교하고자 한다.

References

1. Koraitim MM. Pelvic fracture urethral injuries: evaluation of various methods of management. The Journal of urology. 1996;156(4):1288-91.
2. Basta AM, Blackmore CC, Wessells H. Predicting urethral injury from pelvic fracture patterns in male patients with blunt trauma. The Journal of urology. 2007;177(2):571-5.
3. Bjurlin MA, Fantus RJ, Mellett MM, Goble SM. Genitourinary injuries in pelvic fracture morbidity and mortality using the

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4. Herschorn S, Thijssen A, Radomski SB. The value of immediate or early catheterization of the traumatized posterior urethra. *The Journal of urology*. 1992;148(5):1428-31.
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The use of dorsal vs ventral placement of the graft in bulbar urethroplasty

Jeong Woo Lee

Dongguk University Medical Center

Indications

Traditional algorithm

- Bulbar strictures <2 cm in length
→ Excision and primary anastomosis
- Bulbar strictures >2 cm in length
→ Augmented anastomotic urethroplasty



Buccal mucosa graft (BMG)

- The use of BMG in urethroplasty is arguably the gold standard for treatment of medium- and long-length strictures.

Bhargava S et al. BJU Int 2004;93:1191-3

- Various techniques of BMG augmentation urethroplasty



Figure 40.22 Various techniques of graft inlay. A, Ventral onlay with aponeuroticity. B, Lateral onlay with splitting to the bulbocavernosus muscle. C, Dorsal onlay with spread fixation of the graft.

Buccal mucosa graft (BMG)

- In comparison to skin
 - hairless
 - accustomed to a moist environment
 - thicker epithelial layer
 - thinner lamina propria
 - a greater density of capillaries with an abundance of Type IV collagen

→ All these qualities are thought to improve graft inosculation and survival after transplantation.

Vinikatesan R et al. Ar Urol 2015;2015:397936

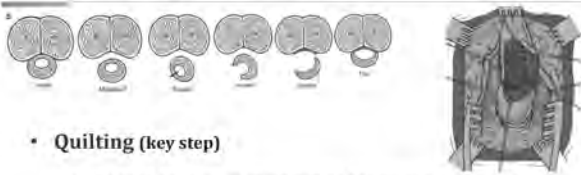
Dorsal Onlay



- Be first described by Barbagli *et al.* in 1998
- Circumferential bulbar urethral dissection, dorsal stricturotomy followed by augmentation of the stricturotomy by BMG.

Barbagli G et al. J Urol 1998;160:1307-9

Dorsal Onlay



- **Quilting (key step)**
 - Spread fixation of the graft on the tunica albuginea
 - Microfenetration of the graft (↓ hematoma)

→ sufficient graft apposition to the well-vascularized tissue of the corpora cavernosa

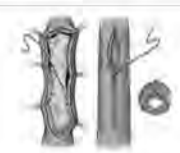
→ minimizing the risks of graft contracture and pseudodiverticular formation.

Dorsal Onlay

- **Advantage**
 - relatively bloodless
 - versatility and applicability for strictures of any length and location
- **Disadvantage**
 - the need to circumferentially mobilize the urethra

Venkatesan R et al. *Av Urol* 2015;20(15):397936

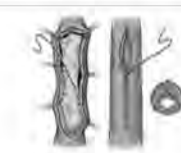
Ventral Onlay



Morey AJ et al. *Urol* 1996;40:194-6

- Ventral "patch" onlay urethroplasty for complex pediatric hypospadias repair by Morey and McAninch in 1996
- Direct sagittal ventral urethrotomy through the diseased bulbar urethra, followed by sewing of the graft to each edge of the native urethral mucosa. Subsequently, the corpus spongiosum is closed over the graft in a second layer and the bulbospongiosus muscle over this.

Ventral Onlay



Morey AJ et al. *Urol* 1996;40:194-6

- While there is no separate tissue to which the graft can be "quilted", the spongiosal closure typically incorporates a small "bite" of the graft, to increase proper apposition to the spongiosum that will provide its bloody supply.

• **Dorsal vs Ventral** : the subject of intense debate ever since

Ventral Onlay

- **Proponents**
 - not requiring extensive circumferential mobilization
→ feel comfortable
 - thicker, ventrally placed corpus spongiosum
→ more robust vascular bed for buccal mucosa engraftment

Venkatesan R et al. *Av Urol* 2015;20(15):397936

- clear advantage in exposure for very prox. bulbar stricture

Patterson JM et al. *Eur Urol* 2008;53:1162-71

- no significant impact on sexual QoL and improved most measures of sexual life, aside from postejaculatory dribbling

Palmeri E et al. *Urology* 2013;81:891-8

Ventral Onlay

- **Proponents**
 - Ventral approach is amenable to use in complex situations.
 - ✓ Recurrent stricture Heinkel T et al. *Urology* 2003;61:1004-7
 - ✓ After radiation Ahyai SA et al. *J Urol* 2015;194:441-6
 - ✓ With adjunct maneuvers such as gracilis muscle flap coverage
 - ✓ High risk, long segment strictures Palmer DA et al. *J Urol* 2014;193:902-5
 - Preservation of bilateral vascular supports to the urethra

Phanpuh YJNM et al. *Eur Urol* 2009;56:201-6

Ventral Onlay

- **Opponents**
 - Need to make incision through the thicker ventral corpus spongiosum → bloodier operation
 - There is a concern about increased risk of sacculation, diverticulum, or pouch formation, as well as more frequent irritative voiding symptoms and urine infection.

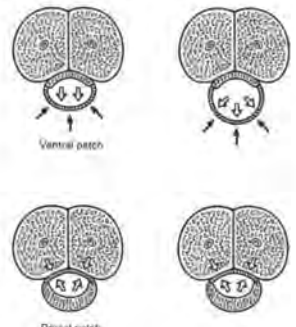
Andrich DE et al. BJU Int 2001;88:385-9

- Incidence of urethrocutaneous fistulae

Dolley D et al. BJU Int 2005;95:625-9
Fichtner J et al. Urology 2004;64:648-50

Ventral Onlay

- **Opponents**



- The principle of the Barbagli technique, showing how the intraurethral pressure on voiding, coupled with the lack of external support, causes stretching and out-pouching of a ventral patch.
- However, a dorsal patch is well supported and out-pouching does not occur.

Andrich DE et al. BJU Int 2001;88:385-9

Ventral Onlay

- **Opponents**
 - In review of 11 series in ventral onlay
Higher incidence of sacculation or diverticulum formation
→ worse postvoid dribbling

Andrich DE et al. BJU Int 2001;88:385-9

- An equal number of series found no significant anatomic or clinical difference in these findings in comparing ventral or dorsal onlay.

Isaacsom JM and Chapple CR. Eur Urol 2008;54:1162-71

Ventral Onlay

- **Opponents**
 - The issue of sacculation seems dramatically higher in older series based on the use of skin, versus the more modern use of BMG.

Margarita S and Chapple CR et al. BJU Int 2004;93:1191-3

- What is ultimately evident is that, in experienced hands and with meticulous technique, these issues can be minimized.

Isaacsom JM and Chapple CR. Eur Urol 2008;54:1162-71

Dorsal vs Ventral

- **Retrospective comparison for success rate**
 - Dorsal onlay BMGU : 85-97%
 - Ventral onlay BMGU : 83-94%

➤ There is no significant difference in success rates.

Barbagli G et al. J Urol 2005;174:955-7; discussion 957-8
Wessells H. Urol Clin North Am 2002;29:381-7
Iselin CE and Webster GD. J Urol 1999;161:815-8
Margarita S and Chapple CR. BJU Int 2004;93:1191-3
Andrich DE et al. BJU Int 2001;88:385-9
Lundhnik ML and Webster GD. J Urol 2001;165:1496-503
Kane CJ et al. J Urol 2002;167:1334-7
Rahner DS et al. J Urol 2004;171:726-9
Gillmt SP et al. J Urol 2003;169:1754-7

Dorsal vs Ventral

Christopher C et al. Urology 2014;83:S31-S47

SIU/ICUD Consultation on Urethral Strictures: The Management of Anterior Urethral Stricture Disease Using Substitution Urethroplasty

Christopher Chapple, Doreto Andrich, Anthony Akala, Gavin Barbagli, Zeno Cosentino, Sergio Nuland, Alif Mangera, and Tuncer Polatoglu

- Systematic review of 66 articles for BMG bulbar urethroplasty
- Doral onlay urethroplasty
 - ✓ 934 patients, average follow up of 42 months
 - ✓ Mean success rates : 88.3%
- Ventral onlay urethroplasty
 - ✓ 563 patients, average follow up of 34.4 months
 - ✓ Mean success rates : 88.8%

Dorsal vs Ventral

INTERNATIONAL JOURNAL OF UROLOGY
Recommended Journal of Urology (2013) 12, 461-471

Original Article: Clinical Investigation

Dorsal vs Ventral onlay buccal mucosal graft urethroplasty for long-segment bulbar urethral stricture: A prospective randomized study

Christopher Chapple, Dean de Almeida, Anthony Atala, Susan Barbagli, David Cosentino, Sergey Kulkarni, Atul Mangrui, and Youssef Fakhri

- **Recommendations**
 - Oral mucosa is the most versatile augmentation (substitution) material (level 3; A).
 - There is no significant difference in outcome between a ventral, lateral, dorsal, or combined approach to augmentation (substitution) urethral reconstruction (level 2; A).

Dorsal vs Ventral

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- **Complication**
 - Complications can include wound and/or urine infection, urethrocutaneous fistula, perineal hematoma, blood loss requiring transfusion, or nerve injuries related to positioning.
 - The overall incidence is low, and, in their series comparing dorsal, ventral, and lateral approaches, Barbagli et al. noted no such complications amongst 50 patients.

Venkatesan K et al. *Am Urol* 2015;2015:397936
Barbagli G et al. *J Urol* 2005;174:955-7; discussion 957-8

Dorsal vs Ventral

INTERNATIONAL JOURNAL OF UROLOGY
Recommended Journal of Urology (2013) 12, 461-471

Original Article: Clinical Investigation

Dorsal versus ventral onlay buccal mucosal graft urethroplasty for long-segment bulbar urethral stricture: A prospective randomized study

Pawan Vasudeva, Binwaji Nanda, Anup Kumar, Ninj Kumar, Harbinder Singh and Rohit Kumar
Department of Urology, V. M. Medical College and Sethi Hospital, New Delhi, India

- A single center, prospective randomized trial
- Patients with long-segment (>2 cm) incomplete bulbar urethral stricture
- August 2011 – August 2014
- Group A (dorsal onlay buccal mucosa graft urethroplasty, n=40)
- Group B (ventral onlay buccal mucosa graft urethroplasty, n=40)

Dorsal vs Ventral

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Original Article: Clinical Investigation

Dorsal versus ventral onlay buccal mucosal graft urethroplasty for long-segment bulbar urethral stricture: A prospective randomized study

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	Group A (n=40)	Group B (n=40)	P-value
Age (years)	48.5 ± 11.5	49.2 ± 12.4	0.93
Duration of stricture (years)	4.5 ± 3.8	4.1 ± 3.5	0.81
Preoperative Qmax (ml/s)	9.8 ± 3.5	10.1 ± 3.2	0.85
Preoperative Q10 (ml/s)	10.1 ± 3.2	10.3 ± 3.1	0.88
Preoperative Q15 (ml/s)	10.2 ± 3.3	10.4 ± 3.2	0.89
Preoperative Q30 (ml/s)	10.3 ± 3.4	10.5 ± 3.3	0.90
Preoperative Q60 (ml/s)	10.4 ± 3.5	10.6 ± 3.4	0.91
Preoperative Qmax (ml/s)	10.5 ± 3.6	10.7 ± 3.5	0.92
Preoperative Q10 (ml/s)	10.6 ± 3.7	10.8 ± 3.6	0.93
Preoperative Q15 (ml/s)	10.7 ± 3.8	10.9 ± 3.7	0.94
Preoperative Q30 (ml/s)	10.8 ± 3.9	11.0 ± 3.8	0.95
Preoperative Q60 (ml/s)	10.9 ± 4.0	11.1 ± 3.9	0.96
Preoperative Qmax (ml/s)	11.0 ± 4.1	11.2 ± 4.0	0.97
Preoperative Q10 (ml/s)	11.1 ± 4.2	11.3 ± 4.1	0.98
Preoperative Q15 (ml/s)	11.2 ± 4.3	11.4 ± 4.2	0.99
Preoperative Q30 (ml/s)	11.3 ± 4.4	11.5 ± 4.3	1.00
Preoperative Q60 (ml/s)	11.4 ± 4.5	11.6 ± 4.4	1.00
Preoperative Qmax (ml/s)	11.5 ± 4.6	11.7 ± 4.5	1.00
Preoperative Q10 (ml/s)	11.6 ± 4.7	11.8 ± 4.6	1.00
Preoperative Q15 (ml/s)	11.7 ± 4.8	11.9 ± 4.7	1.00
Preoperative Q30 (ml/s)	11.8 ± 4.9	12.0 ± 4.8	1.00
Preoperative Q60 (ml/s)	11.9 ± 5.0	12.1 ± 4.9	1.00
Preoperative Qmax (ml/s)	12.0 ± 5.1	12.2 ± 5.0	1.00
Preoperative Q10 (ml/s)	12.1 ± 5.2	12.3 ± 5.1	1.00
Preoperative Q15 (ml/s)	12.2 ± 5.3	12.4 ± 5.2	1.00
Preoperative Q30 (ml/s)	12.3 ± 5.4	12.5 ± 5.3	1.00
Preoperative Q60 (ml/s)	12.4 ± 5.5	12.6 ± 5.4	1.00
Preoperative Qmax (ml/s)	12.5 ± 5.6	12.7 ± 5.5	1.00
Preoperative Q10 (ml/s)	12.6 ± 5.7	12.8 ± 5.6	1.00
Preoperative Q15 (ml/s)	12.7 ± 5.8	12.9 ± 5.7	1.00
Preoperative Q30 (ml/s)	12.8 ± 5.9	13.0 ± 5.8	1.00
Preoperative Q60 (ml/s)	12.9 ± 6.0	13.1 ± 5.9	1.00
Preoperative Qmax (ml/s)	13.0 ± 6.1	13.2 ± 6.0	1.00
Preoperative Q10 (ml/s)	13.1 ± 6.2	13.3 ± 6.1	1.00
Preoperative Q15 (ml/s)	13.2 ± 6.3	13.4 ± 6.2	1.00
Preoperative Q30 (ml/s)	13.3 ± 6.4	13.5 ± 6.3	1.00
Preoperative Q60 (ml/s)	13.4 ± 6.5	13.6 ± 6.4	1.00
Preoperative Qmax (ml/s)	13.5 ± 6.6	13.7 ± 6.5	1.00
Preoperative Q10 (ml/s)	13.6 ± 6.7	13.8 ± 6.6	1.00
Preoperative Q15 (ml/s)	13.7 ± 6.8	13.9 ± 6.7	1.00
Preoperative Q30 (ml/s)	13.8 ± 6.9	14.0 ± 6.8	1.00
Preoperative Q60 (ml/s)	13.9 ± 7.0	14.1 ± 6.9	1.00
Preoperative Qmax (ml/s)	14.0 ± 7.1	14.2 ± 7.0	1.00
Preoperative Q10 (ml/s)	14.1 ± 7.2	14.3 ± 7.1	1.00
Preoperative Q15 (ml/s)	14.2 ± 7.3	14.4 ± 7.2	1.00
Preoperative Q30 (ml/s)	14.3 ± 7.4	14.5 ± 7.3	1.00
Preoperative Q60 (ml/s)	14.4 ± 7.5	14.6 ± 7.4	1.00
Preoperative Qmax (ml/s)	14.5 ± 7.6	14.7 ± 7.5	1.00
Preoperative Q10 (ml/s)	14.6 ± 7.7	14.8 ± 7.6	1.00
Preoperative Q15 (ml/s)	14.7 ± 7.8	14.9 ± 7.7	1.00
Preoperative Q30 (ml/s)	14.8 ± 7.9	15.0 ± 7.8	1.00
Preoperative Q60 (ml/s)	14.9 ± 8.0	15.1 ± 7.9	1.00
Preoperative Qmax (ml/s)	15.0 ± 8.1	15.2 ± 8.0	1.00
Preoperative Q10 (ml/s)	15.1 ± 8.2	15.3 ± 8.1	1.00
Preoperative Q15 (ml/s)	15.2 ± 8.3	15.4 ± 8.2	1.00
Preoperative Q30 (ml/s)	15.3 ± 8.4	15.5 ± 8.3	1.00
Preoperative Q60 (ml/s)	15.4 ± 8.5	15.6 ± 8.4	1.00
Preoperative Qmax (ml/s)	15.5 ± 8.6	15.7 ± 8.5	1.00
Preoperative Q10 (ml/s)	15.6 ± 8.7	15.8 ± 8.6	1.00
Preoperative Q15 (ml/s)	15.7 ± 8.8	15.9 ± 8.7	1.00
Preoperative Q30 (ml/s)	15.8 ± 8.9	16.0 ± 8.8	1.00
Preoperative Q60 (ml/s)	15.9 ± 9.0	16.1 ± 8.9	1.00
Preoperative Qmax (ml/s)	16.0 ± 9.1	16.2 ± 9.0	1.00
Preoperative Q10 (ml/s)	16.1 ± 9.2	16.3 ± 9.1	1.00
Preoperative Q15 (ml/s)	16.2 ± 9.3	16.4 ± 9.2	1.00
Preoperative Q30 (ml/s)	16.3 ± 9.4	16.5 ± 9.3	1.00
Preoperative Q60 (ml/s)	16.4 ± 9.5	16.6 ± 9.4	1.00
Preoperative Qmax (ml/s)	16.5 ± 9.6	16.7 ± 9.5	1.00
Preoperative Q10 (ml/s)	16.6 ± 9.7	16.8 ± 9.6	1.00
Preoperative Q15 (ml/s)	16.7 ± 9.8	16.9 ± 9.7	1.00
Preoperative Q30 (ml/s)	16.8 ± 9.9	17.0 ± 9.8	1.00
Preoperative Q60 (ml/s)	16.9 ± 10.0	17.1 ± 9.9	1.00
Preoperative Qmax (ml/s)	17.0 ± 10.1	17.2 ± 10.0	1.00
Preoperative Q10 (ml/s)	17.1 ± 10.2	17.3 ± 10.1	1.00
Preoperative Q15 (ml/s)	17.2 ± 10.3	17.4 ± 10.2	1.00
Preoperative Q30 (ml/s)	17.3 ± 10.4	17.5 ± 10.3	1.00
Preoperative Q60 (ml/s)	17.4 ± 10.5	17.6 ± 10.4	1.00
Preoperative Qmax (ml/s)	17.5 ± 10.6	17.7 ± 10.5	1.00
Preoperative Q10 (ml/s)	17.6 ± 10.7	17.8 ± 10.6	1.00
Preoperative Q15 (ml/s)	17.7 ± 10.8	17.9 ± 10.7	1.00
Preoperative Q30 (ml/s)	17.8 ± 10.9	18.0 ± 10.8	1.00
Preoperative Q60 (ml/s)	17.9 ± 11.0	18.1 ± 10.9	1.00
Preoperative Qmax (ml/s)	18.0 ± 11.1	18.2 ± 11.0	1.00
Preoperative Q10 (ml/s)	18.1 ± 11.2	18.3 ± 11.1	1.00
Preoperative Q15 (ml/s)	18.2 ± 11.3	18.4 ± 11.2	1.00
Preoperative Q30 (ml/s)	18.3 ± 11.4	18.5 ± 11.3	1.00
Preoperative Q60 (ml/s)	18.4 ± 11.5	18.6 ± 11.4	1.00
Preoperative Qmax (ml/s)	18.5 ± 11.6	18.7 ± 11.5	1.00
Preoperative Q10 (ml/s)	18.6 ± 11.7	18.8 ± 11.6	1.00
Preoperative Q15 (ml/s)	18.7 ± 11.8	18.9 ± 11.7	1.00
Preoperative Q30 (ml/s)	18.8 ± 11.9	19.0 ± 11.8	1.00
Preoperative Q60 (ml/s)	18.9 ± 12.0	19.1 ± 11.9	1.00
Preoperative Qmax (ml/s)	19.0 ± 12.1	19.2 ± 12.0	1.00
Preoperative Q10 (ml/s)	19.1 ± 12.2	19.3 ± 12.1	1.00
Preoperative Q15 (ml/s)	19.2 ± 12.3	19.4 ± 12.2	1.00
Preoperative Q30 (ml/s)	19.3 ± 12.4	19.5 ± 12.3	1.00
Preoperative Q60 (ml/s)	19.4 ± 12.5	19.6 ± 12.4	1.00
Preoperative Qmax (ml/s)	19.5 ± 12.6	19.7 ± 12.5	1.00
Preoperative Q10 (ml/s)	19.6 ± 12.7	19.8 ± 12.6	1.00
Preoperative Q15 (ml/s)	19.7 ± 12.8	19.9 ± 12.7	1.00
Preoperative Q30 (ml/s)	19.8 ± 12.9	20.0 ± 12.8	1.00
Preoperative Q60 (ml/s)	19.9 ± 13.0	20.1 ± 12.9	1.00
Preoperative Qmax (ml/s)	20.0 ± 13.1	20.2 ± 13.0	1.00
Preoperative Q10 (ml/s)	20.1 ± 13.2	20.3 ± 13.1	1.00
Preoperative Q15 (ml/s)	20.2 ± 13.3	20.4 ± 13.2	1.00
Preoperative Q30 (ml/s)	20.3 ± 13.4	20.5 ± 13.3	1.00
Preoperative Q60 (ml/s)	20.4 ± 13.5	20.6 ± 13.4	1.00
Preoperative Qmax (ml/s)	20.5 ± 13.6	20.7 ± 13.5	1.00
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Preoperative Q15 (ml/s)	20.7 ± 13.8	20.9 ± 13.7	1.00
Preoperative Q30 (ml/s)	20.8 ± 13.9	21.0 ± 13.8	1.00
Preoperative Q60 (ml/s)	20.9 ± 14.0	21.1 ± 13.9	1.00
Preoperative Qmax (ml/s)	21.0 ± 14.1	21.2 ± 14.0	1.00
Preoperative Q10 (ml/s)	21.1 ± 14.2	21.3 ± 14.1	1.00
Preoperative Q15 (ml/s)	21.2 ± 14.3	21.4 ± 14.2	1.00
Preoperative Q30 (ml/s)	21.3 ± 14.4	21.5 ± 14.3	1.00
Preoperative Q60 (ml/s)	21.4 ± 14.5	21.6 ± 14.4	1.00
Preoperative Qmax (ml/s)	21.5 ± 14.6	21.7 ± 14.5	1.00
Preoperative Q10 (ml/s)	21.6 ± 14.7	21.8 ± 14.6	1.00
Preoperative Q15 (ml/s)	21.7 ± 14.8	21.9 ± 14.7	1.00
Preoperative Q30 (ml/s)	21.8 ± 14.9	22.0 ± 14.8	1.00
Preoperative Q60 (ml/s)	21.9 ± 15.0	22.1 ± 14.9	1.00
Preoperative Qmax (ml/s)	22.0 ± 15.1	22.2 ± 15.0	1.00
Preoperative Q10 (ml/s)	22.1 ± 15.2	22.3 ± 15.1	1.00
Preoperative Q15 (ml/s)	22.2 ± 15.3	22.4 ± 15.2	1.00
Preoperative Q30 (ml/s)	22.3 ± 15.4	22.5 ± 15.3	1.00
Preoperative Q60 (ml/s)	22.4 ± 15.5	22.6 ± 15.4	1.00
Preoperative Qmax (ml/s)	22.5 ± 15.6	22.7 ± 15.5	1.00
Preoperative Q10 (ml/s)	22.6 ± 15.7	22.8 ± 15.6	1.00
Preoperative Q15 (ml/s)	22.7 ± 15.8	22.9 ± 15.7	1.00
Preoperative Q30 (ml/s)	22.8 ± 15.9	23.0 ± 15.8	1.00
Preoperative Q60 (ml/s)	22.9 ± 16.0	23.1 ± 15.9	1.00
Preoperative Qmax (ml/s)	23.0 ± 16.1	23.2 ± 16.0	1.00
Preoperative Q10 (ml/s)	23.1 ± 16.2	23.3 ± 16.1	1.00
Preoperative Q15 (ml/s)	23.2 ± 16.3	23.4 ± 16.2	1.00
Preoperative Q30 (ml/s)	23.3 ± 16.4	23.5 ± 16.3	1.00
Preoperative Q60 (ml/s)	23.4 ± 16.5	23.6 ± 16.4	1.00
Preoperative Qmax (ml/s)	23.5 ± 16.6	23.7 ± 16.5	1.00
Preoperative Q10 (ml/s)	23.6 ± 16.7	23.8 ± 16.6	1.00
Preoperative Q15 (ml/s)	23.7 ± 16.8	23.9 ± 16.7	1.00
Preoperative Q30 (ml/s)	23.8 ± 16.9	24.0 ± 16.8	1.00
Preoperative Q60 (ml/s)	23.9 ± 17.0	24.1 ± 16.9	1.00
Preoperative Qmax (ml/s)	24.0 ± 17.1	24.2 ± 17.0	1.00
Preoperative Q10 (ml/s)	24.1 ± 17.2	24.3 ± 17.1	1.00
Preoperative Q15 (ml/s)	24.2 ± 17.3	24.4 ± 17.2	1.00
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Preoperative Qmax (ml/s)	24.5 ± 17.6	24.7 ± 17.5	1.00
Preoperative Q10 (ml/s)	24.6 ± 17.7	24.8 ± 17.6	1.00
Preoperative Q15 (ml/s)	24.7 ± 17.8	24.9 ± 17.7	1.00
Preoperative Q30 (ml/s)	24.8 ± 17.9	25.0 ± 17.8	1.00
Preoperative Q60 (ml/s)	24.9 ± 18.0	25.1 ± 17.9	1.00
Preoperative Qmax (ml/s)	25.0 ± 18.1	25.2 ± 18.0	1.00
Preoperative Q10 (ml/s)	25.1 ± 18.2	25.3 ± 18.1	1.00
Preoperative Q15 (ml/s)	25.2 ± 18.3	25.4 ± 18.2	1.00
Preoperative Q30 (ml/s)	25.3 ± 18.4	25.5 ± 18.3	1.00
Preoperative Q60 (ml/s)	25.4 ± 18.5	25.6 ± 18.4	1.00
Preoperative Qmax (ml/s)	25.5 ± 18.6	25.7 ± 18.5	1.00
Preoperative Q10 (ml/s)	25.6 ± 18.7	25.8 ± 18.6	1.00
Preoperative Q15 (ml/s)	25.7 ± 18.8	25.9 ± 18.7	1.00
Preoperative Q30 (ml/s)	25.8 ± 18.9	26.0 ± 18.8	1.00
Preoperative Q60 (ml/s)	25.9 ± 19.0	26.1 ± 18.9	1.00
Preoperative Qmax (ml/s)	26.0 ± 19.1	26.2 ± 19.0	1.00
Preoperative Q10 (ml/s)	26.1 ± 19.2	26.3 ± 19.1	1.00
Preoperative Q15 (ml/s)	26.2 ± 19.3	26.4 ± 19.2	1.00
Preoperative Q30 (ml/s)	26.3 ± 19.4	26.5 ± 19.3	1.00
Preoperative Q60 (ml/s)	26.4 ± 19.5	26.6 ± 19.4	1.00
Preoperative Qmax (ml/s)	26.5 ± 19.6	26.7 ± 19.5	1.00
Preoperative Q10 (ml/s)	26.6 ± 19.7	26.8 ± 19.6	1.00
Preoperative Q15 (ml/s)	26.7 ± 19.8	26.9 ± 19.7	1.00
Preoperative Q30 (ml/s)	26.8 ± 19.9	27.0 ± 19.8	1.00
Preoperative Q60 (ml/s)	26.9 ± 20.0	27.1 ± 19.9	1.00
Preoperative Qmax (ml/s)	27.0 ± 20.1	27.2 ± 20.0	1.00
Preoperative Q10 (ml/s)	27.1 ± 20.2	27.3 ± 20.1	1.00
Preoperative Q15 (ml/s)	27.2 ± 20.3	27.4 ± 20.2	1.00
Preoperative Q30 (ml/s)	27.3 ± 20.4	27.5 ± 20.3	1.00
Preoperative Q60 (ml/s)	27.4 ± 20.5	27.6 ± 20.4	

Conclusions

- Because the dorsal or ventral placement of BMG is typically determined based on location and length of stricture and surgeon preference, comparative studies are limited.
- Patency outcomes are similar for each technique, appropriate patient selection is paramount to utilize the strengths of a given technique and avoid its shortcoming.

경청해 주셔서 대단히 감사합니다.



Jeong Woo Lee



2019

요로생식기손상재건연구회

비뇨기계기초의학연구회

공동심포지엄

Session II, Special Lecture

좌장: 이상돈 (부산의대)

Personalized medicine in urologic cancers

박경화 (고려의대 중양내과)

Immuno-oncology in urologic cancers

서호경 (국립암센터)

Precision medicine in advanced prostate cancer

Kyong Hwa Park

Medical Oncology, Department of Internal Medicine, Korea University College of Medicine

Recent advances in genomic profiling with NGS technology enabled us to profile most of the cancers including urologic cancers. Data and information from new genetic analysis is changing treatment strategies across cancer types. In addition, genomic alterations in cell-free DNA (cfDNA) from patient blood samples can complement biopsies as tumor cells can undergo evolution as treatments progress. Thus, molecular mechanisms for drug resistance and identification of new targets could be a unique area for liquid biopsy.

Unlike primary prostate cancers, metastatic CRPCs are known to harbor highly recurrent targetable genomic alterations. The genomic profiles implicated that castration-resistant cancers have evolutionary genetic alterations; AR splice variants or mutants, pathogenic somatic and germline mutations in BRCA1/2, ATM, BRCA1, CDK12, FANCA, RAD51B, and RAD51C. Of note, recurrent mutations in the phosphoinositide 3-kinase (PI3K) pathway; through loss of PTEN, amplification of PIK3CA/B, and activating mutation of PIK3CA/B and AKT1. Recent development of PI3K isoforms inhibitors and clinical trials in solid cancers may bring new hope for CRPC patients. Immunotherapy is one of the major interest in CRPC as in other solid cancers. Although the most mature efforts have been made in CRPC in the form of cell therapy; sipuleucel-T, now immune checkpoint inhibitors more likely to represent tumor immunotherapy. And, a subset of CRPC patients with high mutational burden from genetic alterations in mismatch repair genes (MLH1, MSH2) may be the first candidates for immune checkpoint inhibitors.

Other genetic alterations in important cellular pathways have been identified in CRPC; WNT and Cell cycle pathways. More refined approach with newer technologies and effective targeted agents might bring CRPC patients qualified life extension.

Implementation of precision medicine in clinical practice is still challenging as most of the Korean general hospitals are at the initial stage of infrastructure building. Multidisciplinary approach is essential from tissue biopsy, genomic alterations sequencing, genomic analysis, and reporting results. As there are small proportion of patient who can get chance to have new therapeutics, parallel clinical trials to test innovative drugs are essential.

In conclusion, concept of precision medicine in advanced prostate cancer is an appealing approach due to lethality of the disease. Characterization of the genomic landscapes of Korean prostate cancers might guide future research and clinical practice.

Immuno-Oncology in urologic cancers

Ho Kyung Seo

Center for Urological Cancer, Hospital
Division of Tumor Immunology, Research Institute, National Cancer Center

Disclosure

- Nothing

Agenda

- What is Immuno-Oncology
- Role of checkpoint inhibitors in Urothelial Cancer
- Role of checkpoint inhibitors in Renal Cell Carcinoma
- Role of checkpoint inhibitors in Prostate Cancer
- Take home message

War on Cancer

- We have been fighting the War on Cancer since 1971, when President Richard M. Nixon declared that the "time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease.
- Four decades later, 1,665,540 Americans per year hear the dreaded diagnosis, and about 585,720 die annually from some variety of the disease, according to the American Cancer Society.
- We have come to the uneasy conclusion that cancer is smarter than we are

Therapeutic Targeting of the Hallmarks of Cancer



The Hallmarks of Cancer Cell, Vol. 144, Mar 2011

What is Immuno-Oncology(IO)?

- A type of immunotherapy that is specifically targeted to fight cancer

The immune system has the greatest potential

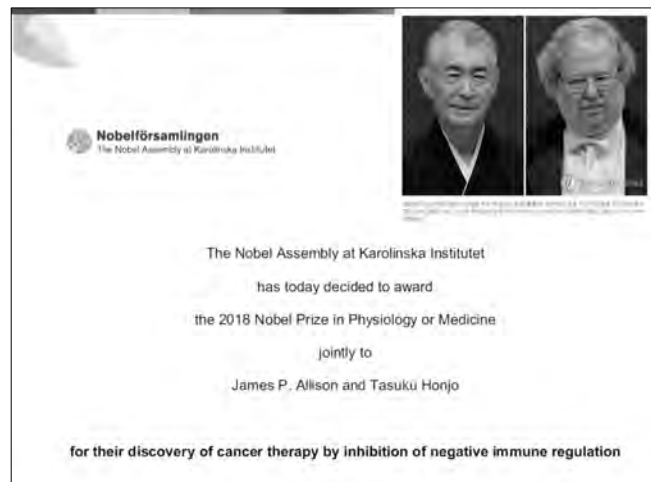
- Specific destruction of tumor (self vs non-self)
- No toxicity to normal tissue
- Long-term memory that can prevent cancer recurrence

Therapeutic approaches of IO

- Cytokines
- Checkpoint inhibitors
- Adoptive T cell therapy (CAR-T)
- Oncolytic viruses
- Therapies directed at other cell types
 - NK cell, dendritic cell (Sipuleucel-T)
- Vaccines

What is Immune checkpoint?

- One of regulators of the immune system.
- Preventing **destruction of normal tissues and autoimmunity**
- Multiple type of cancers sometimes use these checkpoints to avoid being attacked by the immune system → considered as new targets for cancer immunotherapy
- **Restoring active T-cell response**
- Currently available and approved checkpoint inhibitors block **CTLA4 and PD-1/L1**



Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

The Nobel Assembly at Karolinska Institutet
has today decided to award
the 2018 Nobel Prize in Physiology or Medicine
jointly to
James P. Allison and Tasaku Honjo
for their discovery of cancer therapy by inhibition of negative immune regulation

Agenda

- What is Immuno-Oncology
- **Role of checkpoint inhibitors in Urothelial Cancer**
- Role of checkpoint inhibitors in Renal Cell Carcinoma
- Role of checkpoint inhibitors in Prostate Cancer
- Take home message

Bladder Cancer Classification and treatments

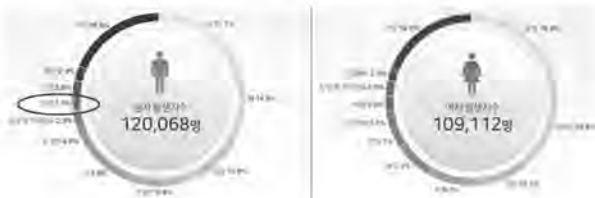
- Bladder cancer is clinically classified as non-muscle-invasive (NMIBC), muscle-invasive (MIBC), or metastatic (MBC)

Classification	TNM Staging	Brief Description	Treatment Goals	Standard of care	Prognosis
Stage 0/I	NMIBC	Ta, T1, Tis, Tis, Tis, Tis	Local tumor confined to the subepithelial connective tissue	TURBT, intravesical CT or BCG + PD-1/PDL-1 inhibitor	85%-95% 5-year survival
Stage II-IV	MIBC	T2-T4, N0-N1, M0	Tumor extends into or through the muscularis propria	Radical cystectomy (+ resective CT) or multimodal therapy + PD-1/PDL-1 inhibitor	46%-55% 5-year survival
Stage IV	MBC	Any T, N2-N3, M1	Cancer has spread to lymph nodes or distant organs	Platinum-based, CDOP based + PD-1/PDL-1 inhibitor + CTLA4 inhibitor + EGFR inhibitor + Antigen-Drug Conjugator	15%

Currently available treatments unchanged over the past 10 years

Incidence of Bladder Cancer

- Bladder cancer is the fifth most prevalent cancer worldwide
- About 386,300 new cases and 150,200 deaths from bladder cancer were reported in 2008 *CA Cancer J Clin* 61:69-90
- 4,361 new cases were diagnosed in 2016 in Korea



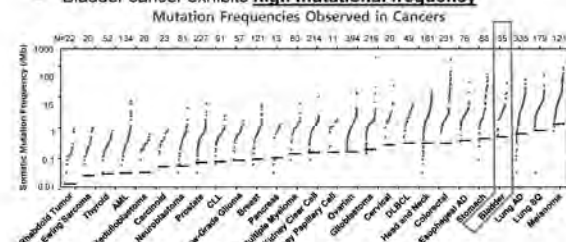
Bladder Cancer Classification

Stage at presentation	Patients Percent per year
Ta, Tis	
T1	(70%) non-muscle invasive bladder cancer (NMIBC)
T2a	
T2b	(25%) muscle invasive bladder cancer (MIBC)
T3a	(5%) metastatic bladder cancer(MBC)
T3b	

NMIBC: at diagnosis 70%~ 3,052명
 MIBC: at diagnosis 25%~ 1,090명 + progress from NMIBC 15%~ 458명=1,548명
 MBC: at diagnosis 5%: 228명 + recur after Tx of MIBC 50% ~ 774 = 1002
 2nd line treatment of MBC: 851

Rationale for Immunotherapy in Bladder Cancer

- Bladder cancer is classified as a **highly immunogenic tumor**
 - Responsiveness to **intravesical immunotherapy with BCG**
 - Bladder cancer exhibits **high mutational frequency**



Lawrence MS et al. *Nature* 2013;499:214-18. Rizvi NA et al. *Science* 2015;345:124-8

Immune checkpoint inhibitors in patients with bladder cancer.

Currently studied ICI in Bladder cancer (Phase II and III trials)

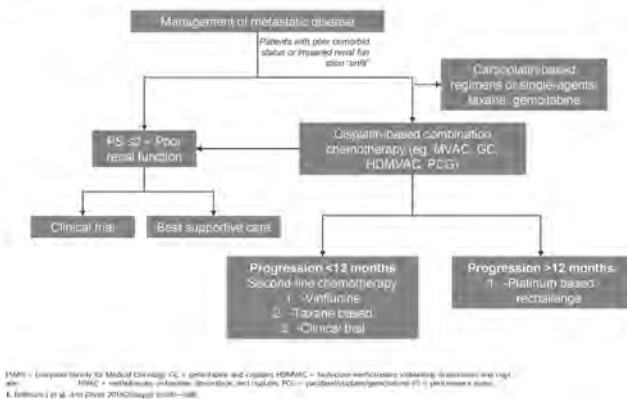
Agent	Mechanism	Dosage	FDA	KFDA	Reimbursement
Atezolizumab	PD-L1	1200mg, 3wks	0	0	0
Pembrolizumab	PD-1	200mg, 3wks	0	0	
Nivolumab	PD-1	3mg/kg, 2wks	0	0	
Durvalumab	PD-L1	10mg/kg, 2wks	0		
Avelumab	PD-L1	10mg/kg, 2wks	0		
Ipilimumab	CTLA-4				
Tremelimumab	CTLA-4				

Immune checkpoint inhibitors in MBC after platinum failure (2nd Line)

Unmet needs in Metastatic Bladder Cancer(MBC)

- Cisplatin-based systemic chemotherapy is the SoC of MBC
 - GC: **ORR: 50%-60%**, Median OS 15mons, **5-yr Survival Rate ≤15%**
 - GCarbo: ORR 36%, mOS 9mons
- Recurrent or progressive disease:** no standard therapy
 - No therapies have demonstrated OS benefit over BSC
 - Commonly used agents include taxanes, pemetrexed, and vinflunine
 - Clinical benefit is limited: ORR 12%, median OS of 5-7 months
 - Significant toxicity profile**

Management of Metastatic Disease for Bladder Cancer: ESMO Guidelines¹



Subsequent systemic therapy for locally advanced or metastatic disease

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum) ¹	
Participation in clinical trials of new agents is recommended	
Preferred regimen	Other recommended regimens
• Pembrolizumab (category 1) ¹⁶	• Nab-paclitaxel ¹⁵
	• Paclitaxel or docetaxel ¹⁴
	• Gemcitabine ¹⁴
	• Pemetrexed ²³
Alternative preferred regimens	Useful in certain circumstances based on prior medical therapy
• Atezolizumab ¹⁸	• Irinotecan ²⁷
• Nivolumab ²⁸	• Methotrexate
• Duvulizumab ²¹	• Ifosfamide, doxorubicin, and gemcitabine ¹⁵
• Avelumab ^{22,33}	• Gemcitabine and paclitaxel ¹⁵
	• Gemcitabine and cisplatin ⁵
	• DDMVAC with growth factor support ²

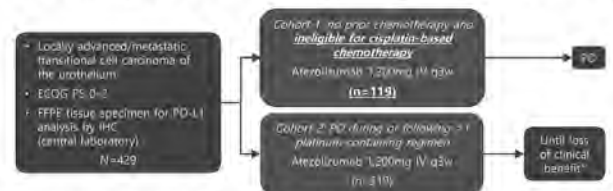
Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor)	
Participation in clinical trials of new agents is recommended	
Preferred regimen for cisplatin ineligible chemotherapy naïve	Other recommended regimens
• Gemcitabine/carboplatin	• Nab-paclitaxel ¹⁸
	• Paclitaxel or docetaxel ¹⁴
	• Gemcitabine ¹⁴
	• Pemetrexed ²
Preferred regimen for cisplatin eligible chemotherapy naïve	Useful in certain circumstances based on prior medical therapy
• Gemcitabine and cisplatin ⁴	• Ifosfamide ²⁷
• DDMVAC with growth factor support ²	• Methotrexate
	• Ifosfamide, doxorubicin, and gemcitabine ¹⁸
	• Gemcitabine and paclitaxel ¹⁵

1. NCCN Guidelines Version 5.2018

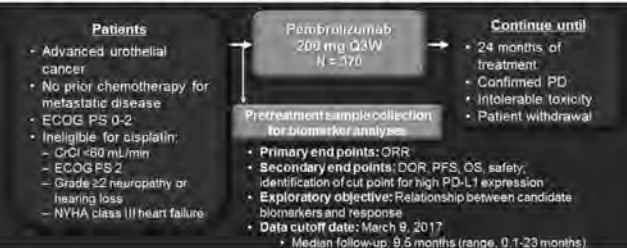
2. Bladder Cancer

Immune checkpoint inhibitors in platinum unfit metastatic urothelial cancer (1st Line)

Atezolizumab: Phase 2 1st line, CDDP unfit (IMvigor 210 Cohort 1)



Pembrolizumab: Phase2 1st line, CDDP unfit (Keynote-052)



- The first 100 patients are included in this planned interim analysis to evaluate ORR and determine the PD-L1-high (CPS-high) expression cut point as examined by expression in tumor and immune cells.

O'Donnell PH et al. ASCO 2017

KEYNOTE-052 vs IMvigor210 cohort 1 vs EORTC 30986 (Gem/carbo) Baseline Characteristics

1. KEYNOTE-052: NCT01280030; IMvigor210: NCT01280030; EORTC 30986: NCT01280030

Randomized phase III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinorelbine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986.

2. Bellmunt J, et al. Ann Oncol. 2010;21(10):2039-2046.

Baseline Characteristic	KEYNOTE-052 ¹	IMvigor 210 ² (cohort 1)	Gem/carbo ³ (EORTC 30986)
ECOG PS 2	42% ¹ (156/370)	27% ² (32/119)	44.5% ³
Renal impairment ⁴	58% ¹ (217/370)	77% ² (91/119)	82.4%
Other reason for cis ineligibility	9% ¹ (33/370)	20% ² (24/119)	
Visceral Mets	85% ¹ (315/370)	56% ² (78/119)	46.2%
Liver Mets	21% ¹ (77/370)	21% ² (25/119)	16.8%
Upper Tract	19% ¹ (69/370)	28% ² (33/119)	20.2%
Age median (range)	74 (34-94)	73 (51-92)	70 (36-87)

제시된 임상시험은 동일한 조건에서 진행된 것이 아니므로 객관적 비교가 어려움

1. Vally J, et al. ASCO 2016 Poster Presentation 4524. 2. Balar A, et al. Lancet. 2017; 389: 67-76. 3. De Santis M, et al. J Clin Oncol. 2012; 30:191-199.

Efficacy results compare with prior phase II

	Historical G/Carbo	Atezolizumab Imvigor 210 cohort1	Pembrolizumab KEYNOTE 052
n	119	119 (median f/u 17mos)	370 (median f/u 8mos)
ORR	41.2% (36.1% confirmed response)	24% (28/119)	29% (107/370)
CR		3% (9/119)	8.1% (30/370)
ORR in PD-L1+ (CPS ≥10, IC2/3)		28% (9/32)	47.3% (52/110)
ORR in PD-L1- (CPS <10, IC0/1)		21% (18/84)	20.7% (52/251)
CR in PD-L1+ (CPS ≥10, IC2/3)		12.5% (4/32)	19.1% (21/110)
OS	9.3 mos	16.3 (10.4, 24.5)	11.5 (10.0, 13.3)
1yr OS Rate	37%	58%	47.5%
2yr OS Rate	18%	41%	
adverse event (all/G3-4)		66%/15%	67%/16%

Metastatic Bladder Cancer 1st line Ongoing study

- NCT02807636: IMvigor130 (Phase 3)
 - Atezolizumab+Gemcitabine+Cisplatin/Carboplatin
 - Placebo+Gemcitabine+Cisplatin/Carboplatin
- NCT02853305: Keynote-361 (Phase 3)
 - Pembrolizumab

Early data from two clinical trials (Keynote-361 and IMvigor130) show **reduced survival with pembrolizumab and atezolizumab** when used **as first-line treatments** for urothelial cancer in patients with **low expressions of PD-L1**.

Keytruda and Tecentriq should be used for first-line treatment of urothelial cancer in patients with **high levels of PD-L1**

Principles of First-line chemotherapy for locally advanced or metastatic disease

	Standard regimens	Alternate regimens for select patients
Cisplatin eligible	Gemcitabine and cisplatin (category 1) DDMVAC with growth factor support (category 1)	
Cisplatin ineligible	Gemcitabine and carboplatin Atezolizumab Pembrolizumab (only for pts whose tumors express PD-L1 or who are not eligible for any platinum-containing CTx regardless of PD-L1 expression)	Gemcitabine Gemcitabine and paclitaxel Ifosfamide, doxorubicin, and gemcitabine (for patients with good kidney function and good PS)

- The presence of both **visceral metastases** and **ECOG performance score ≥2** strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy.

NCCN Guidelines Version 5.2015
Bladder Cancer

Immune checkpoint inhibitors in Non- Muscle Invasive and Muscle Invasive Bladder

MIBC Guidelines

Neoadjuvant chemotherapy

Neoadjuvant cisplatin-containing combination chemotherapy (NAC) improves overall survival (5-8% at five years), irrespective of the type of definitive treatment. Currently, no tools are available to select patients who have a higher probability of benefitting from NAC. However, NAC has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.

Recommendations for neoadjuvant chemotherapy	Strength rating
Offer NAC for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

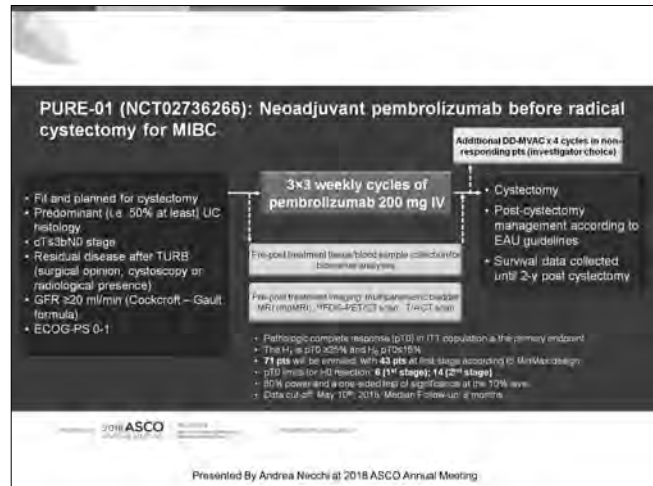
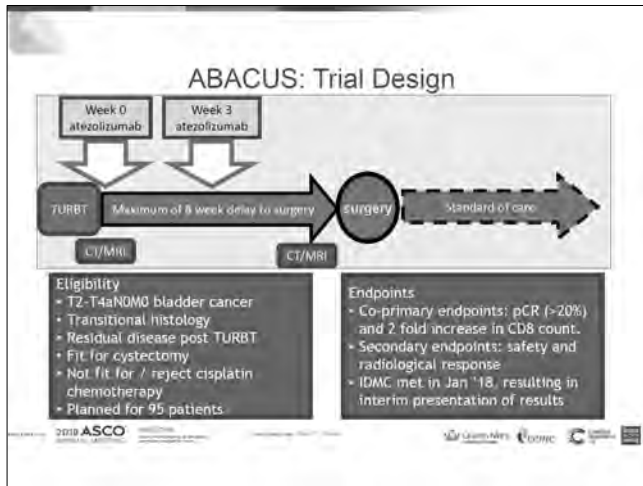
Cisplatin-based neoadjuvant chemotherapy

Pros

- pCR rates: about 30%
- Median 5-year OS benefit: 5-8%
- Mortality risk reduction: 16%
- neoadjuvant chemotherapy is not associated with higher perioperative morbidity or mortality

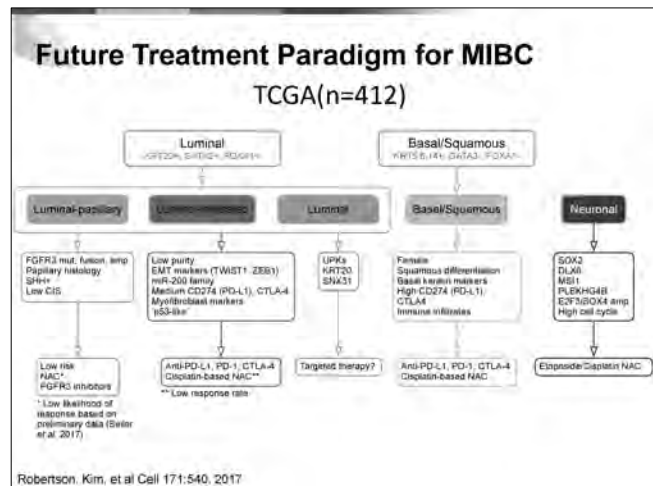
Cons

- chemotherapy-associated toxicities
- delayed cystectomy
- no available biomarkers
- more than 50% of patients are not eligible for cisplatin



Results of the phase II ABACUS and PURE-01 trial testing atezolizumab and pembrolizumab in the neoadjuvant setting prior to radical cystectomy

	ABACUS	PURE-01
Phase	II	II
Study population (n)	68	43
Checkpoint inhibitor	Atezolizumab	Pembrolizumab
Number of cycles	2	3
Cisplatin-fit?	Cisplatin-unfit	Cisplatin-fit
Residual tumor after TURB	Yes	Yes
TNM for inclusion	cT2-T4aNM0-N1	cT3bN0
pCR	Overall: 29% PD-L1+: 40% (25% IC) PD-L1-: 16%	Overall: 39.5% 50% (CPS score ≥ 20%) PD-L1+ and DDR/RB1-GA: 90% DDR and/or RB1-GA: 60%
Discontinuation/progression during CPI (n)	1 (1.5%)	1 (2.3%)
Most common AEs	21% fatigue	11% hyperthyroidism
Biomarkers	PD-L1 CD8	CPS Score, TMB 22-gene T-cell



Definition of BCG-unresponsive

- Adopted by the GU ASCO Group and the International Bladder Cancer Group (IBCG)
- to identify patients in whom further BCG is not indicated
- refractory to BCG or relapse within 12 months of the last adequate BCG
- Adequate BCG therapy
 - At least 5 of 6 instillations of induction BCG (adequate induction) + at least 2 of 3 doses of maintenance therapy or 2 of 6 doses of a second induction course

1. Simeoni et al. J Clin Oncol. 2015;33:1957-1964. 2. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 3. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 4. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 5. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 6. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 7. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 8. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 9. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 10. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 11. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 12. Pohl-Regnier et al. Eur Urol. 2015;67:100-106. 13. Pohl-Regnier et al. Eur Urol. 2015;67:100-106.

What can You Do in BCG Unresponsive

Treatment	Medication
Standard of care for BCG Unresponsive: radical cystectomy	
Radical cystectomy is associated with morbidity/mortality and a negative impact on quality of life	
Many patients refuse or are ineligible for cystectomy	
↓	
Urgent need for novel therapies to reduce risk for recurrence and preserve bladder in BCG unresponsive high risk NMIBC	
Device-assisted therapies	Electromotive administration of mitomycin Microwave hyperthermia and mitomycin
ICORTx	
Immuno-Oncology	PD1/L1 inhibitor

Phase 2 Study of Pembrolizumab Monotherapy for High-Risk, Non-Muscle Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin: Interim Results from KEYNOTE-057

Arjun V. Balar,¹ Girish Kulkarni,² Edward Uchio,³ Joost Boormans,⁴ Loic Mourey,⁵ Laurence Krieger,⁶ Eric A. Singer,⁷ Dean Bajorin,⁸ Ashish Kamat,⁹ Petros Grivas,¹⁰ Ho Kyung Seo,¹¹ Hiroaki Nishiyama,¹² Kijoeng Nam,¹³ Ekta Kapadia,¹³ Tara Frenkl,¹³ Ronald De Wit¹

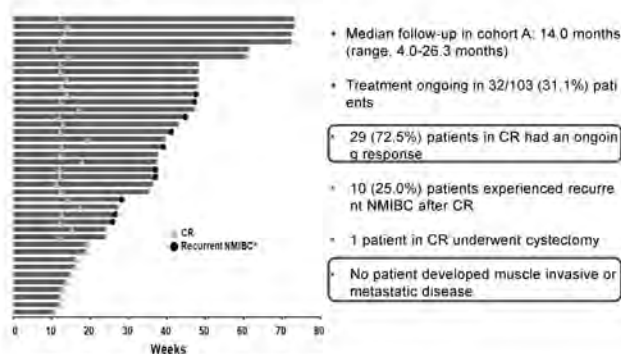


Overall Response Rate at Month 3^a

Response	N	%	95% CI
CR	40	38.8	29.4-48.9
Non-CR	57	55.3	45.2-65.1
Persistent ^b	47	45.6	35.8-55.7
NMIBC stage progression ^c	9	8.7	4.1-15.9
Non-bladder malignancy ^d	1	1.0	0.0-5.3
Progression to T2	0	0	—
Nonevaluable^e	6	5.8	2.2-12.2

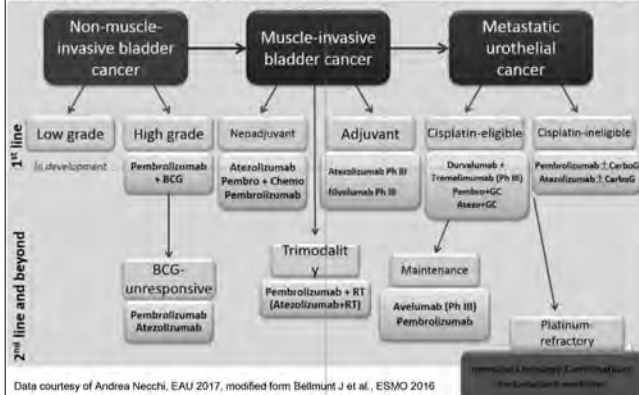
^aSummary of overall response of high-risk NMIBC per central assessment at month 3 in all patients who received ≥1 dose of study treatment, had baseline evaluations, and also had ≥1 postbaseline disease assessment. ^bCR was defined as patients with CIS at baseline who at month 3 also had CIS a papillary tumor, increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. ^cCR was defined as patients with invasive urothelial carcinoma or transitional cell carcinoma in imaging. ^dPatients developed new liver lesions on imaging and were later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scans showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. ^ePatients whose postbaseline efficacy assessments were missing or were discontinued from the trial for reasons other than PD are considered not evaluable for efficacy.

Time to CR and Development of Recurrent HR NMIBC



*Recurrent NMIBC in high-risk NMIBC (CIS and/or high-grade Ta and/or T1 disease) after ≥1 disease-free interval (at least month 3 after CR).

Immune checkpoint inhibitor in bladder cancer Tx



Immune checkpoint inhibitors approved for mUC

	Pembrolizumab	Atezolizumab	Nivolumab
허용사준	1L cis-ineligible 2L	1L cis-ineligible 2L	2L 가, 백금기반 화학요법 후에 중 또는 후에 질병 진행 나, 백금기반의 수술 전 보조요 법(neoadjuvant) 또는 수술 후 보 조요법(adjuvant) 치료 12개월 이내에 질병 진행
급여	Under review	2L PD-L1 (IC2/3)	Under review
투여량	3주 1회 30분 200 mg	3주 1회 30분 1200 mg (초회 투여시 60분)	2주 1회 60분 3 mg/kg
주요 임상시험	1L: Keynote 052 (Phase 2) 2L: Keynote 045 (Phase 3)	1/2L: IMvigor 210 (Phase 2) 2L: IMvigor 213 (Phase 3)	2L: Checkmate 275 (Phase 2)
Primary endpoint	1L ORR in allcomer/CPS≥10 2L OS/PFS in allcomer/CPS≥10	IMvigor 210 ORR in allcomer ORR in IC 1/2/3 ORR in IC 2/3 OS in allcomer OS in IC 1/2/3 OS in IC 2/3	ORR in allcomer ORR in PD-L1 ≥ 1% ORR in PD-L1 ≥ 5%

Overall summary

- PD-1/L1 inhibitors associated with long-term durable remission who cisplatin refractory as well as cisplatin ineligible metastatic urothelial carcinoma.
- PD-1/L1 inhibitors were generally well tolerated in both 1L and platinum refractory metastatic urothelial carcinoma

But...

- 70~80% of patients do not respond
- Combination or sequencing therapy
- Additional clinical trials and longer follow-up will be required to define their role in the first-line setting, neoadjuvant, adjuvant and NMIBC.

Thank YOU



2019

요로생식기손상재건연구회

비뇨기계기초의학연구회

공동심포지엄

Session III. 해외연수를 통한 최신 연구경험

좌장: 강석호 (고려의대)

Evidence based medicine: what is evidence?

정재홍 (연세의대)

Endoluminal ultrasound imaging technique to determine urethral stricture

유호송 (전남의대)

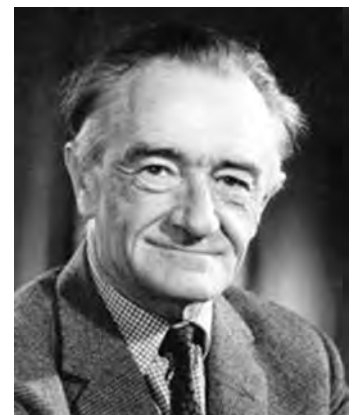
Cochrane Collaboration (<https://www.cochrane.org/>)

정 재 흥
연세의대

Cochrane is a non-profit organization established in 1993 to facilitate evidence-based choices about health interventions for clinicians, patients, and policy makers. Cochrane's 13,000 members and over 50,000 supporters come from more than 130 countries, worldwide. Global independent network with volunteers and contributors in Cochrane Collaboration gathers and summarizes the best evidence from research to help physician, patients, and policy maker make informed choices about treatment.

Cochrane was developed in response to Archie Cochrane's call for up-to-date, systematic reviews of all relevant randomized controlled trials of health care. Many physicians are familiar with Cochrane Reviews and the Cochrane Library, but few know much about Archibald Cochrane himself, the father of Evidence-Based Medicine. Archibald Leman Cochrane (12 January 1909 - 18 June 1988) was a Scottish doctor noted for his book *Effectiveness and Efficiency: Random Reflections on Health Services*. This book advocated the use of randomized control trials to make medicine more effective and efficient. His advocacy of randomized controlled trials eventually led to the development of the Cochrane Library database of systematic reviews and the establishment of the international Cochrane Collaboration. He is known as one of the fathers of modern clinical epidemiology and evidence-based medicine and is considered to be the originator of the idea of evidence-based medicine.

Cochrane's logo illustrates the summary results from an iconic systematic review: 'Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth'. Two Cs form a circle which represent that it is a global collaboration. In the center, a Forest plot is shown, which illustrates the summary



of a meta-analysis. This review suggests that corticosteroids given to women who are about to give birth prematurely can save the life of the newborn child. Before publication of this review, most obstetricians had not realized that the treatment was so effective and therefore many premature babies probably suffered or died unnecessarily.

To produce high-quality, relevant, up-to-date systematic reviews and other synthesized research evidence to inform health decision making. There are now over 7,500 Cochrane Systematic Reviews which Cochrane Review Groups publish in the Cochrane Library (<http://www.cochranelibrary.com/>). As one of Cochrane Review Groups, Cochrane Urology which is based in the Minneapolis VA Health Care System and the University of Minnesota, Minnesota, USA conduct and disseminate systematic reviews of health care interventions and diagnostic accuracy for prostatic diseases, male sexual dysfunction, urology-related renal topics and urologic cancers.

Clinicians interested in participating in Cochrane Reviews can either submit a proposal for a new review or assist with updating a previous review. After registering a protocol, a team of researchers is assembled. It is important that team members undergo training as to how to perform a systematic review through a series of online modules, as well as face-to-face workshops such as the Grading of Recommendations Assessment, Development and Evaluation (short GRADE) approach for rating the evidence (a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations: <http://www.gradeworkinggroup.org/>). The process of conducting a systematic review is supported by the editorial team for each Cochrane Group. Ultimately, it is the editorial team that decides whether a systematic review meets methodological expectations and merits publication. The Cochrane Handbook provides detailed instructions on how to perform a Systematic Review and Meta-Analysis.

Cochrane Collaboration also plays a key role in developing new methods in evidence synthesis.

Cochrane do not accept commercial or conflicted funding. This is vital to generate authoritative and reliable information, working freely, unconstrained by commercial and financial interests.

Endoluminal ultrasound imaging technique to determine urethral stricture

유 호 송

전남의대

Urethral strictures are a disease of fibrosis and collagen deposition that narrows the urethral lumen. The result is a poor urinary flow, lower urinary tract symptoms (LUTS), and possible bladder and upper tract decompensation. It is important to identify the stricture location, length, and luminal cross-sectional area (CSA) and depth of the fibrotic lesion for appropriate surgical management. Traditionally, this has been accomplished with a combination of cystourethroscopy, voiding cystourethrogram (VCUG), and retrograde urethrogram (RUG). Less commonly and more recently trans-perineal ultrasonography has been employed for diagnosis.

The current modalities of stricture work-up have multiple limitations. Urethroscopy facilitates visualization of the distal extent of stricture location, but cannot comment on stricture length. RUG by itself cannot comment on the length of stricture but when used in tandem with VCUG the element of urethral stricture length is estimated. At minimum, VCUG necessitates urethral catheterization through a stricture and may require placement of a suprapubic tube with tight or dense strictures. Both RUG and VCUG require ionizing radiation to the patient, technologist and urologist. Additionally, both RUG and VCUG show two-dimensional images which could lead to underestimation of stricture length and severity based on patient positioning.

Urethral ultrasonography by trans-scrotal or trans-perineal approach has been explored as an adjuvant to RUG to characterize penile as well as bulbar urethral strictures. These approaches are not intraluminal and cannot comment on the distended urethral diameter as would occur in voiding. Development of a minimally invasive and reproducible endoluminal technique to evaluate and monitor stricture disease would be valuable in both the diagnostic and post-surgical follow up phases. In the present study, we developed and validated a novel, quantitative, reproducible endoluminal ultrasound (ELUS) imaging technique in a rabbit model.

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Cross-Sectional Area. J Endourol 2018;32(12):1082-92

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3. Gupta N, Dubey D, Mandhani A, et al. Urethral stricture assessment: a prospective study evaluating urethral ultrasonography and conventional radiological studies. BJU Int 2006;98:149-53.
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2019
요로생식기손상재건연구회
비뇨기계기초의학연구회
공동심포지엄

Session IV. (기초) Current Status of Urological Research in Korea

좌장: 한웅규 (연세의대)

홍합에서 추출한 생체용 수중 겹착단백물질의 요누공 치료효과에 대한 연구:
방광-질 누공 돼지모델에 적용한 전임상 실험

편종현 (성균관대의대)

The immunotherapeutic Effects of recombinant Bacillus Calmette-Guérin
to resistant Antimicrobial Peptide on Bladder Cancer Cells

장인호 (중앙의대)

투명신세포암에서 mitochondria의 분자생물학적 양상이 암 진행 및 악성도의
예측 마커로서의 가능성 제시

나준채 (연세의대)

Application of Mussel Protein-based Underwater Tissue Adhesive Sealant for Urinary Fistula Treatment: Pre-clinical Study in Porcine Vesico-Vaginal Fistula Model

홍합에서 추출한 생체용 수중 접착단백물질의 요 누공 치료효과에 대한 연구:
방광-질 누공 돼지 모델에 적용한 전임상 실험


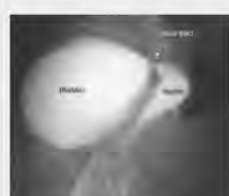
Jong Hyun Pyun

Department of Urology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine

Background

Urinary Tract Fistula (요 누공)
↳ Abnormal openings of a urinary tract organ

Vesico-vaginal Fistula (VVF)
(방광) (질) (누공)

► Continuous involuntary discharge of urine into the vaginal vault (요실금)

Background

Vesico-Vaginal Fistula (VVF)
Etiology & Clinical features

“more than 2 million young women live with untreated fistula and around 50,000 to 100,000 women are newly affected each year throughout the world”
-World Health Organization (WHO) 2006-


In high income countries : Iatrogenic cause

- ✓ **Surgical intervention** (수술적 치료)
- ✓ **Radiation therapy** (방사선 치료)

In low income countries

- ✓ **Prolonged or obstructed labour** (난산)

VVF have devastating consequences!!!






- Incontinence
- Low self-esteem
- Depression
- Loss of libido
- Divorce
- Isolation

Background



Vesico-Vaginal Fistula (VVF)
Surgical management

Trans-Abdominal approach **Trans-Vaginal approach**

- High success rate (80-100%)
- Extensive dissection for exposure is required (**Tension-free, watertight closure**)
- Surgical approach is difficult
- The procedure is highly dependent on an individual surgeon's experience
- Surgical repair fail repeatedly (40%~)
- Re-hospitalization and longer recovery periods → high cost


M. Stamatakis et al. Indian J surg. 2014

Background

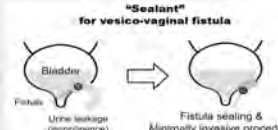
Requirement of Medical Adhesives

[Injectable Tissue Adhesive]



- Facile application
- Injectable
- Less-invasive


“Sealant” for vesico-vaginal fistula



Bladder Uterus Vagina

Urine leakage (incontinence) → Fistula sealing & Minimally invasive procedure

Cyanoacrylate glue **Fibrin sealants** **Protein-aldehyde systems**



- Exothermal polymerization
- High self-polymerized product
- Adverse toxicity of degradation products (limited to topical uses)
- Poor biocompatibility
- Risk of transferring blood-borne disease, allergic reaction, & infection transmission
- Poor adhesion strength
- Severe inflammation or edema
- Risk of sensitization due to free glutaraldehyde
- Poor adhesion in the presence of water

Background

Effective Underwater Bonding Requires..

	Internal body	Solutions
Dynamic environments	Bodily fluids	Water immiscible property
Contaminants	Cells Lipids Cellular debris Polelectrolytes (proteins, carbohydrates)	Strong interfacial adhesion
Continuous shear stresses	Blood stream Contraction & Expansion	Controlled solidification

Ideal for "Effective Underwater Adhesion"

"The entire range of natural glue properties"



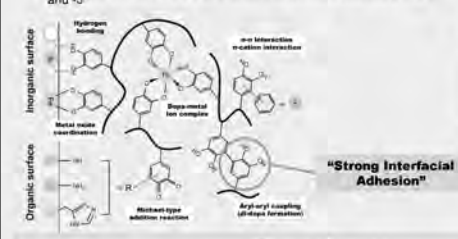
"The entire range of natural glue properties" ➔ **Aquatic organisms**

Background

Strong Interfacial Adhesion

Mussel Adhesive Proteins (MAPs)

- To endure continuous mechanical stresses (tides, buoyancy, and drag)
- Six major types of foot proteins (fp-1 to fp-6)
- High Dopa (3,4-dihydroxy-L-phenylalanine) contents, especially in fp-3 and -5



"Strong Interfacial Adhesion"

Tissue Adhesive : DOPA-modified recombinant MAP (mrMAP) / hyaluronic acid coacervate

POSTECH

Background

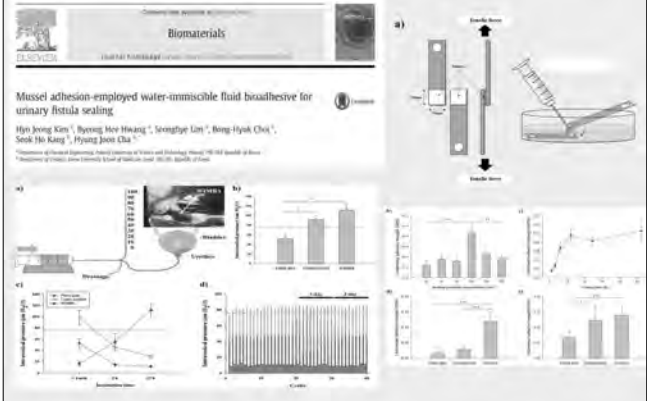
In vitro Experiment

Biomaterials

Mussel adhesion-employed water-immiscible fluid bioadhesive for urinary fistula sealing

Hyeon Jeong Kim¹, Byoung Hyeon Hwang¹, Seungyeon Lim¹, Hyeon Hyeon Choi¹, Seok Ho Kang¹, Hyung Joon Cha¹

¹Department of Chemical Engineering, Seoul National University, Seoul 151-747, Korea



In vivo Animal Experiment

Pilot experiment

New Zealand white rabbit

1 week: VVF formation

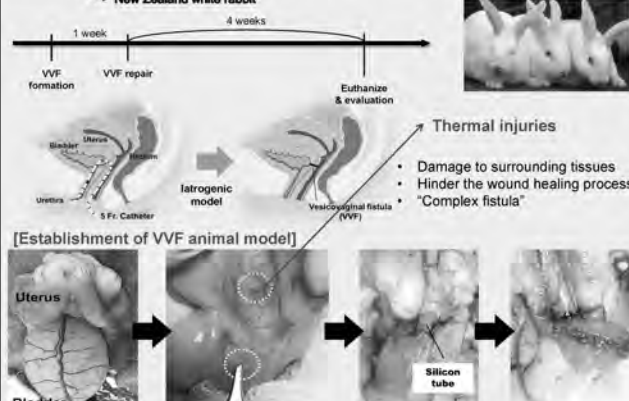
4 weeks: VVF repair

Euthanize & evaluation

Thermal injuries

- Damage to surrounding tissues
- Hinder the wound healing process
- "Complex fistula"

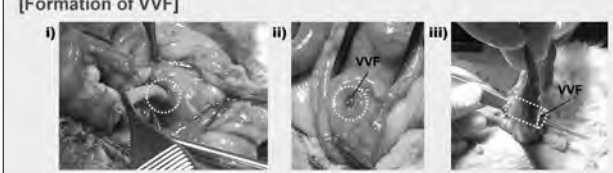
[Establishment of VVF animal model]




In vivo Animal Experiment

Pilot experiment

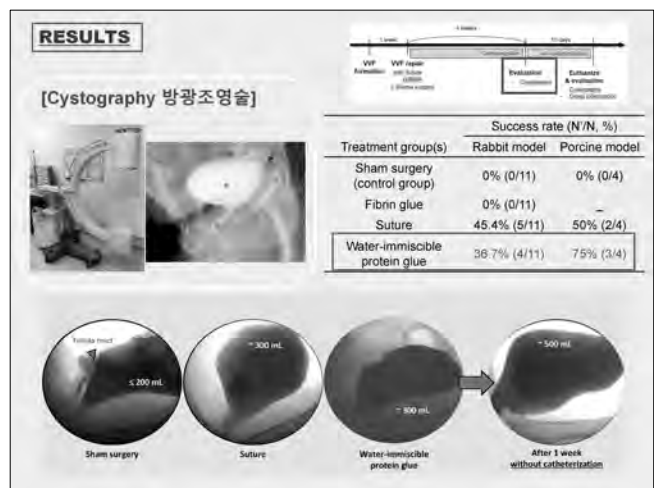
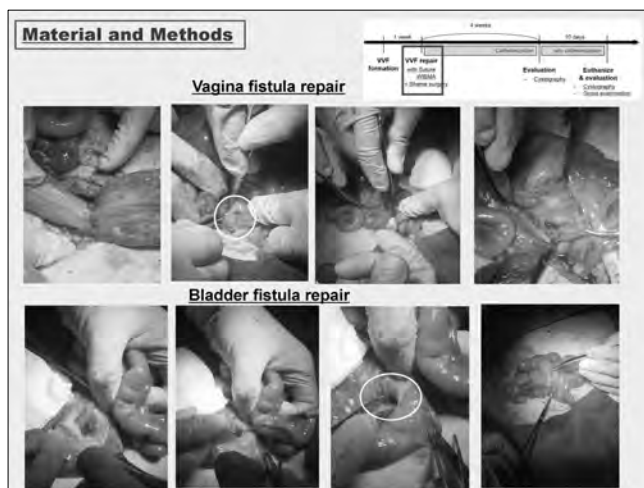
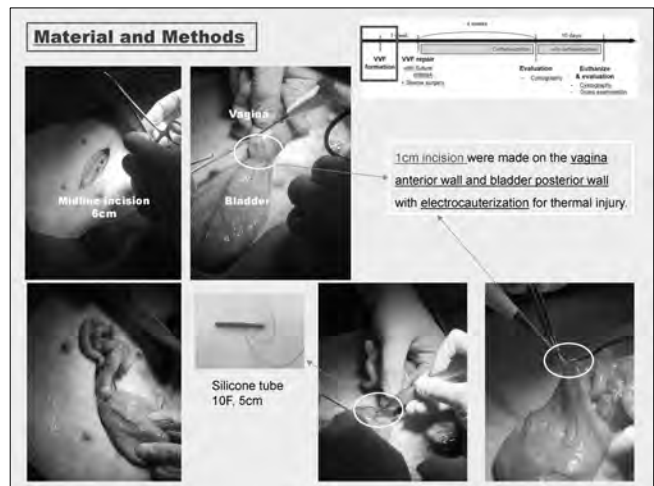
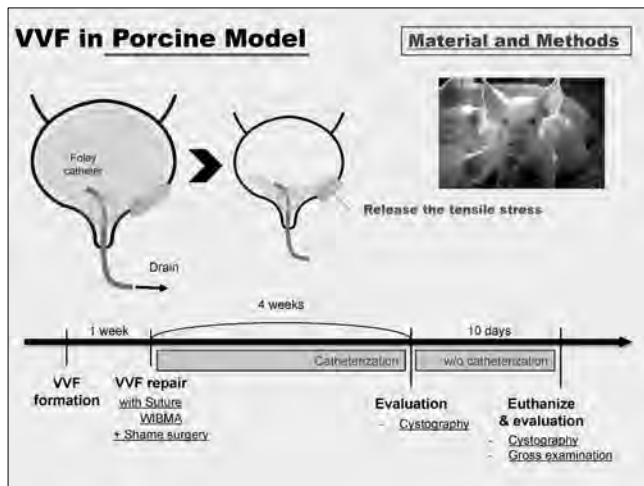
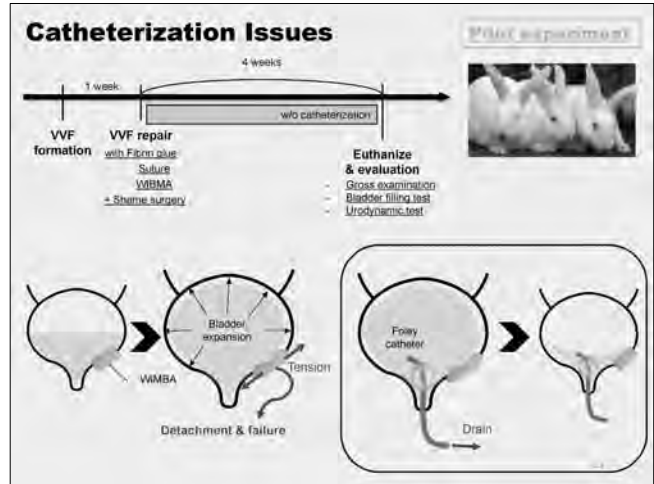
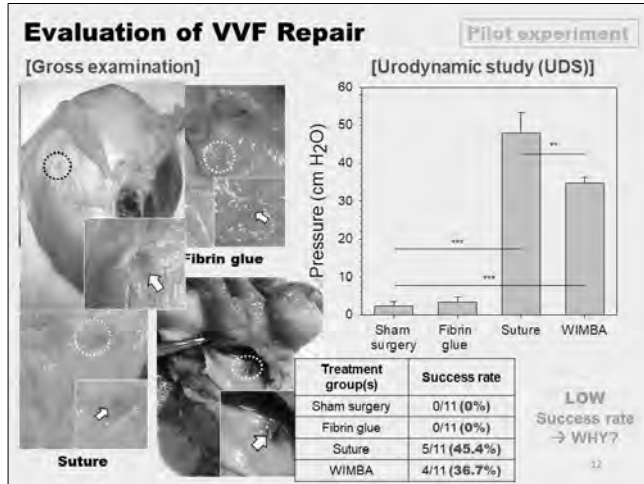
[Formation of VVF]

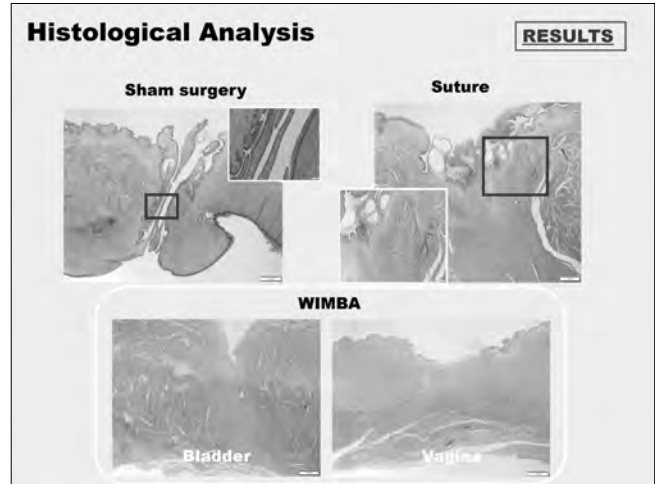
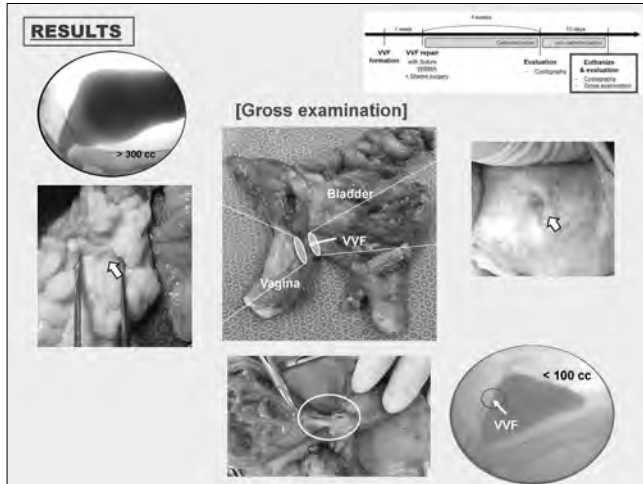


[VVF Repair]



Sham surgery Fibrin glue Suture WIMBA





Conclusion

- WIMBA has **good water immiscible property and strong interfacial adhesion**
- **Feasibility of WIMBA in VVF repair**
 - Good performance *ex vivo* and *in vivo*
 - Performance of WIMBA in VVF repair is **comparable to that of surgical closure**
- **No histotoxicity**

감사합니다

The immunotherapeutic effects of recombinant *Bacillus Calmette-Guerin* resistant to antimicrobial peptides on bladder cancer cells

장 인 호

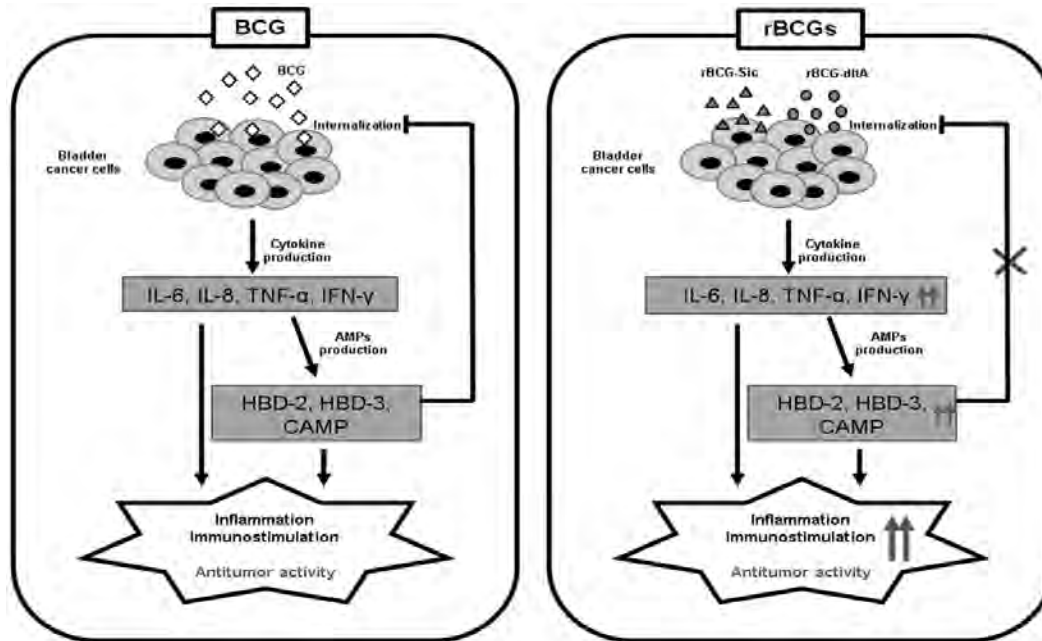
중앙의대

Purpose: Although *Mycobacterium bovis* *Bacillus Calmette-Guérin* (BCG) is the most widely used bladder cancer immunotherapy, innate immune responses involving antimicrobial peptides (AMPs) cause BCG failure and unwanted side effects. Here, we generated genetically modified BCG strains with improved immunotherapeutic effects by adding genes that confer evasion of AMPs.

Materials and methods: We constructed recombinant BCG (rBCG) strains expressing Streptococcal inhibitor of complement (Sic), which confers resistance to human α -defensin-1 and cathelicidin, and dalanyl carrier protein ligase (dltA), which confers resistance to cationic AMPs. Sic and dltA were separately cloned into the pMV306 plasmid and introduced into BCG via electroporation. Then, the efficacy of the rBCGs was tested in a growth inhibition assay using two bladder cancer cell lines (5637, T24).

Results: We confirmed the presence of cDNA segments corresponding to the Sic and dltA genes in total mRNA of the rBCG strains containing Sic (rBCG-Sic) and dltA (rBCG-dltA), and these rBCGs showed higher survival against AMPs. The growth inhibitory effects of rBCGs on bladder cancer cells were significantly enhanced compared to those of the parent BCG, and THP-1 migration also increased. After 8 h of infection, the levels of internalization were higher in rBCG-infected bladder cancer cells than in BCG-infected cells, and cells infected with rBCGs showed increased release of antitumor cytokines, such as IL-6/12, TNF- α , and INF- γ , resulting in inhibition of bacterial killing and immune modulation via antimicrobial peptides.

Conclusions: rBCG-Sic and rBCG-dltA can effectively evade BCG-stimulated AMPs, and may be significantly improved immunotherapeutic tools to treat bladder cancer.



Hypothetical schema of BCG and rBCG internalization in bladder cancer cell lines. rBCGs enhance the antitumor effect of BCG on bladder cancer cells by avoiding the innate immune system and promoting the internalization of bladder cancer cells and by increasing the cytokines IL-6, IL-8, TNF-α and IFN-γ.

The biological features of Mitochondria in clear cell renal cell carcinoma indicates the potential as a prediction marker for cancer progression and integrity

Joon Chae Na¹, Sook Young Kim¹, Hyung Ho Lee³, Young Eun Yoon⁴,
Sung Joon Hong^{1,2}, Woong Kyu Han^{1,2}

¹Department of Urology, Urological Science Institute, Yonsei University College of Medicine

²Brain Korea 21 PLUS Project for Medical Science

³Department of Urology, National Health Insurance Service Ilsan Hospital, Goyang, Korea

⁴Department of Urology, Hanyang University College of Medicine, Seoul, Korea

Introduction

- 투명신세포암의 형태상 가장 큰 특징은 지질이 축적된 clear cytoplasm 이다.
- 세포내 축적된 물질들은 대부분 대사에 관여하며 이의 중심에는 Mitochondria가 관여한다.
- 본 연구자의 기존 연구에서도 투명신세포암에서 Mitochondria의 변화는 dynamic하게 있다는 것을 알 수 있었다.
- 이에 투명신세포암에서의 Mitochondria의 분자생물학적 변화를 관찰하고 주요한 역할에 대해 알아보고자 한다.

Fig. 1 Clear cell RCC와 Chromophobe의 TEM 관찰

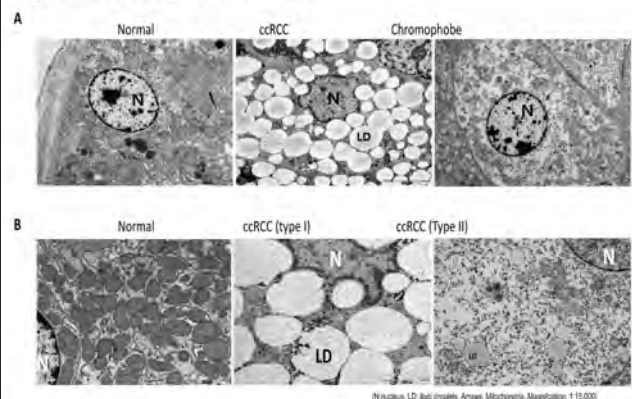


Fig. 2 기존 다양한 ccRCC stage 와 mitochondrial protein 변화의 상관 관계 관찰

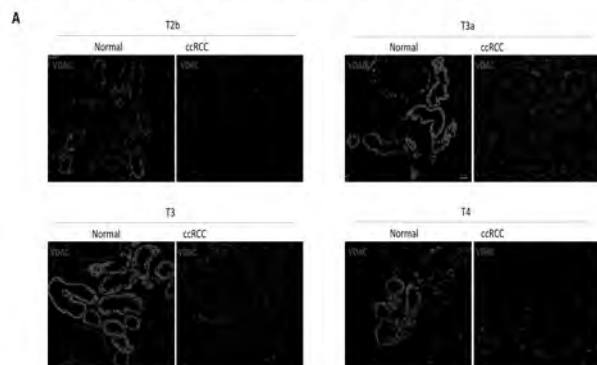
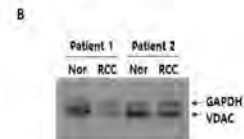
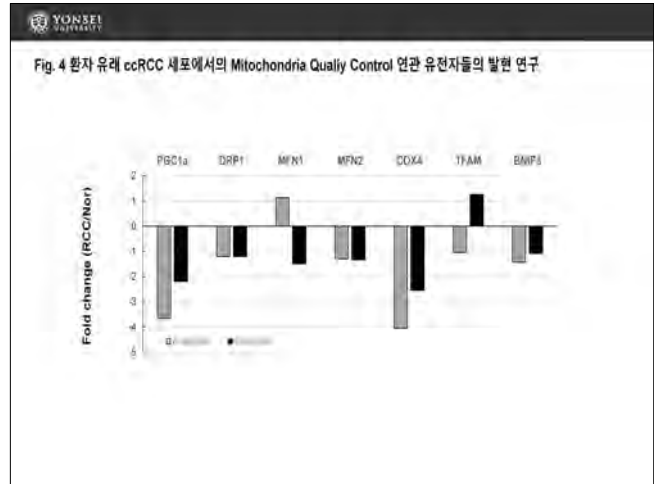
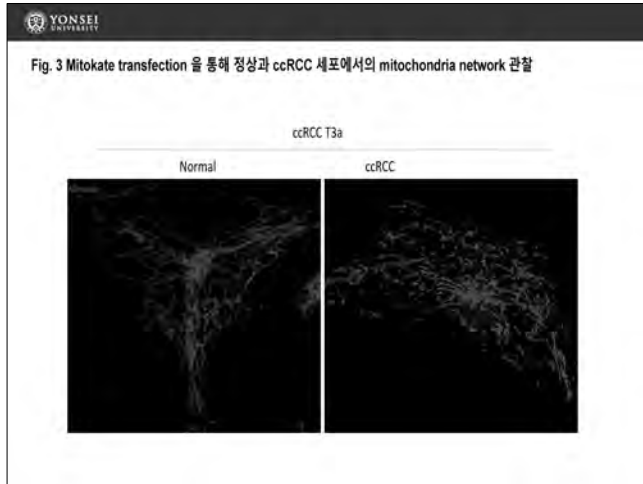


Fig. 2 기존 다양한 ccRCC stage 와 mitochondrial protein 변화의 상관 관계 관찰

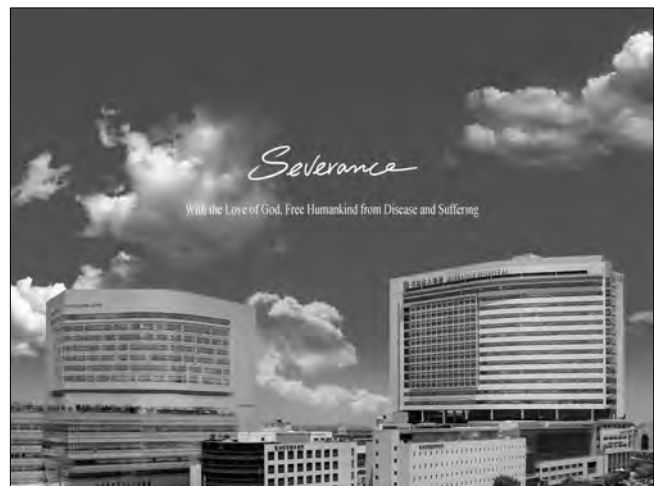




YONSEI UNIVERSITY

Conclusion

- 투명 신세포암의 진행에 따라 세포내 대사적인 변화를 갖기 위해, Mitochondria가 주요한 역할을 할 것이라 여겨진다.
- 또한, 단지 크기의 기준으로 나누던 기존 신세포암의 stage 결정 방법으로는 투명신세포암의 세포내 환경을 대변하지 못했다.
- 본 연구는 Mitochondria의 분자 생물적 다양한 양상이 있음을 관찰하였고, 이러한 정보들이 암의 진행 정도 뿐 아니라 암의 악성 및 전이까지도 표현해줄 새로운 기준을 제시해 줄 것이라 판단된다.



2019

요로생식기손상재건연구회

비뇨기계기초의학연구회

공동심포지엄

(장소이동: 316호)

Session IV. (손상) Urologic Emergency and Reconstruction

좌장: 문홍상 (한양의대)

Blunt testicular trauma - is surgical exploration necessary?

태범식 (고려의대)

Surgical Reconstructive Techniques in the Management of Penile cancer

육형동 (인제의대)

Blunt testicular trauma - is surgical exploration necessary?

Bum Sik Tae

Korea University Ansan Hospital

Testicular Rupture in Textbook

Although ultrasonography may assist in detection of testicular fracture or hematoma, a normal or equivocal ultrasound study should not delay surgical exploration when physical examination findings suggest testicular damage; definitive diagnosis is often made in the operating room.



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Campbell urology 11th edition

Diagnosis Accuracy

Accuracy of Ultrasonography in Diagnosis of Testicular Rupture After Blunt Scrotal Trauma

Table 2. Accuracy of ultrasonography for testis injuries

	Hematocoele	Tunica albuginea breach	Testis Rupture	Testicular Hematoma	Scrotal Hematoma	Epididymis injuries	Testis avulsion	None
Sensitivity	87%	50%	100%	71%	86%	57%	100%	87%
Specificity	89%	76%	85%	77%	58%	85%	97%	100%
PPV	95%	67%	73%	45%	60%	50%	50%	100%
NPV	72%	62%	100%	91%	85%	92%	100%	97%

PPV = positive predictive value; NPV = negative predictive value.

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Guillaume et al. J Urol 2008.

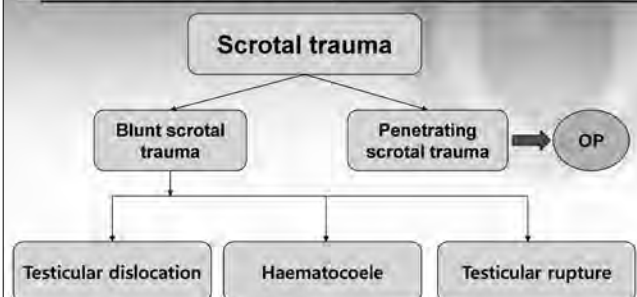
Testicular rupture Grade

- ✓ Grade I as contusion or hematoma,
- ✓ Grade II as subclinical laceration of tunica albuginea,
- ✓ Grade III as laceration of tunica albuginea with < 50% parenchymal loss,
- ✓ Grade IV as major laceration of tunica albuginea with ≥ 50% parenchymal loss
- ✓ Grade V as total testicular destruction or avulsion.

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Moore EE et al. J Trauma. 1996

Testicular Trauma



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EAU Guideline. 2017

AUA Guideline

Guideline Statement 30.

Surgeons should perform scrotal exploration and debridement with tunical closure (when possible) or orchiectomy (when non-salvageable) in patients with suspected testicular rupture. (Standard; Evidence Strength: Grade B)

Testicular rupture after blunt or penetrating scrotal injuries may be suggested by scrotal ecchymosis and swelling or difficulty in identifying the contours of the testicle on physical exam. The most specific findings on ultrasonography are loss of testicular contour and heterogeneous echotexture of parenchyma, which should prompt testicular repair.¹⁵⁵ Early exploration and repair may prevent complications, such as ischemic atrophy of the testis and infection.¹⁴⁵ Repair of the ruptured testis by debriding non-viable tissue and closing the tunica albuginea is preferred when possible.^{145,164} Scrotal injury may raise the suspicion of concomitant urethral injury. Expert opinion is that tunica vaginalis grafts may be used to provide closure when the tunica albuginea cannot be closed primarily. For penetrating scrotal injuries, immediate exploration with debridement and repair is encouraged to prevent complications.

Surgical Exploration Recommend

KORU
Korea Urological Research Unit

AUA Guideline, 2017

Trend

ORIGINAL ARTICLE JKMS

Trends in Testicular Injury in Korea, 1986-2015

Table 1. Etiology of testicular injury stratified by decade

Period	Assault	Spont.	Fall	Traffic accident	Other
First decade	17 (54.8)	3 (9.7)	4 (12.9)	6 (19.4)	1 (3.2)
Second decade	14 (41.8)	12 (37.5)	1 (3.1)	4 (12.5)	1 (3.1)

모든 Blunt Testicular injury 가 Exploration을 필요로 할까?

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Lee SH, et al. JKMS, 2017

Q1 : 보존적 치료 위험하지 않는가?

Q2 : 어떠한 경우에 보존적 치료?

Q3 : 그럼에도 불구하고 반드시 수술 필요?

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Conservative

Q1 : 보존적 치료 위험하지 않는가?

Fertility

Atrophy

Pain

Hypogonadal state

social confidence

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Korea Urological Research Unit

Conservative

ORIGINAL ARTICLE JKMS

Trends in Testicular Injury in Korea, 1986-2015

Table 2. Ultrasonographic and surgical findings of patients

Ultrasonographic findings	No. of patients (%) by surgical findings	Conservative management	P-value	P
Echogenicity of testicular parenchyma			0.682	<0.001
Homogeneous	6 (15.4)	1 (2.3)	1 (15.4)	
Heterogeneous	12 (27.3)	15 (34.1)	16 (39.4)	
Contour of testicular parenchyma			0.758	<0.001
Intact contour	10 (24.4)	3 (4.9)	2 (4.8)	
Loss of contour	8 (19.0)	14 (33.3)	20 (47.6)	
Pattern of hematoma			0.584	<0.001
Extra-testicular	2 (5.0)	0 (0)	0 (0)	
Intra-testicular	8 (29.6)	5 (11.5)	6 (22.2)	
Intra- and extra-testicular	4 (14.8)	9 (23.2)	14 (31.9)	

Q1 : 보존적 치료 위험하지 않는가?

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Korea Urological Research Unit

Lee SH, et al. JKMS, 2017

Conservative

ORIGINAL ARTICLE JKMS

Blunt testicular trauma - is surgical exploration necessary?

Median age at presentation was 20 years (8-84).

24/37pts
13 testicular rupture,
11 large haematocoele >3x size of contralateral testis

All Conservative Treatment

Orchiectomy 0/37
Testicular atrophy 4/37
Asymptomatic hydrocele 4/37

KOREA
Korea Urological Research Unit

Redmond et al. Irish JMSc 2018

Conservative

Irish Journal of Medical Science (1975) 112(118): 111-112
https://doi.org/10.1007/BF01582112

ORIGINAL ARTICLE

Blunt testicular trauma – is surgical exploration necessary?

E. J. Redmond¹ · E. T. Mac Neasa^{1,2} · S. R. Din³ · H. D. Flood⁴

Table 3 Comparison of outcomes following conservative and operative management of blunt scrotal trauma

	n	Management	Partial orchiectomy	Orchiectomy	Testis size
*Our Study	37	Conservative	0/37 (0%)	0/37 (0%)	4.37 (10%)
Cubillos et al. [5]	7	Conservative	0/7 (0%)	0/7 (0%)	0.7

Semen analysis가 시행되지 않음

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Redmond et al. Irish JMSC 2018

Anti-spermatic Antibody

Q1 : 보존적 치료 위험하지 않는가?

Testes contain a natural barrier (blood-testes barrier)

Acts as a protective layer that prevents immune cells from being able to access sperm within the male reproductive tract.

Injury

Allowing the immune cells to come into contact with the sperm

Once the barrier is broken, immune cells are able to detect the presence of sperm due to their unique antigen surface

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Check et al. Clin Exp Obstet Gynecol 2010.

Conservative

Q2 : 어떠한 경우에 보존적 치료?

Trauma Grade

Age

Dislocation

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Testicular rupture Grade

- ✓ Grade I as contusion or hematoma.
- ✓ Grade II as subclinical laceration of tunica albuginea.
- ✓ Grade III as laceration of tunica albuginea with < 50% parenchymal loss.
- ✓ Grade IV as major laceration of tunica albuginea with ≥ 50% parenchymal loss
- ✓ Grade V as total testicular destruction or avulsion.

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Moore EE et al. J Trauma. 1996

British Association of Urological Surgeons (BAUS) consensus document for the management of male genital emergencies - testicular trauma

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BJU International © 2018 BJU International | doi:10.1111/bju.14163
Published by John Wiley & Sons Ltd, www.bju.org

Intra-testicular Haematoma Without Tunical Breach

- 1 Small intra-testicular haematomas with only mild-to-moderate pain require conservative treatment only.
- 2 Repeat US should be performed within 48 h to assess progression.
- 3 Exploration should be considered in large intra-testicular haematomas with severe pain or those that continue to expand.

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Conservative

Aetiology, epidemiology and management strategies for blunt scrotal trauma

D.M. Dalton¹, N.F. Davis, D.C. O'Neill, C.M. Bready, E.A. Kelly, M.F. O'Brien

Department of Urology, Cork University Hospital, Cork, Ireland

Table 2 – Diagnosis after ultrasonography for scrotal trauma.

Diagnosis with ultrasonography	Number (n)
*Testicular rupture	6
Intra-testicular haematoma	8
Hemato-scrotum	4
Scrotal wall haematoma	3
Testis not identified	1
*Normal testis	4
Total	26

SONO Rupture (+) : 11 -> OP

SONO Rupture (-) : 15 -> Conservative

No patients managed conservatively developed a complication.

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Dalton et al. Surgeon. 2016 Feb;14(1):18-21.

A Conservative Approach to Testicular Rupture in Adolescent Boys

Jimena Cubillos, Edward F. Reda, Jordan Gitlin, Paul Zelkovic and Lane S. Palmer*

From the Divisions of Pediatric Urology, Children's Division & Medical Center of New York-Lang Island Jewish Health System, New Hyde Park and Westchester Medical Center (EFR, JG) Valhalla, New York

Ultrasound Finding	No. Pts (%)
Heterogeneity	7 (100)
Herniaticula	7 (100)
Irregular contour	3 (43)
Intratesticular hematoma	3 (43)
Tunica tear	3 (43)
Scrotal wall edema	3 (43)
Seminiferous tubule extrusion	1 (14)

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Cubillos et al. J urol. 2010

A Conservative Approach to Testicular Rupture in Adolescent Boys

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From the Divisions of Pediatric Urology, Children's Division & Medical Center of New York-Lang Island Jewish Health System, New Hyde Park and Westchester Medical Center (EFR, JG) Valhalla, New York

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Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery

Sung Hoon Lee, Chong Won Bak, Min Ho Choi, Han Sae Lee, Min Sung Lee and Sang Jin Yoon

Department of Urology, Gil Medical Center, Gachon University of Medicine and Science, Incheon, South Korea

Rupture) 2/10 patients who conservative treatment -> Atrophy -> Orchiectomy

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Lee et al. BJU. 2008

Operation

Q3 : 그럼에도 불구하고 반드시 수술 필요?

Trauma Grade

Age

Dislocation

Pain

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Grade

Management of Intratesticular Hematoma

```

    BLUNT SCROTAL TRAUMA → POSITIVE EXAM
    |
    | INCONCLUSIVE EXAM (Ultrasound)
    |
    | INTRATESTICULAR HEMATOMA With Intact Tunica Albuginea
    |
    | Moderate Pain No Expansion → OBSERVATION Serial Scrotal Ultrasonids
    |
    | Severe Pain Expanding → SURGICAL EXPLORATION
  
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Diana et al. Central European Journal of Urology. 2014

Management of testicular rupture after blunt trauma in children

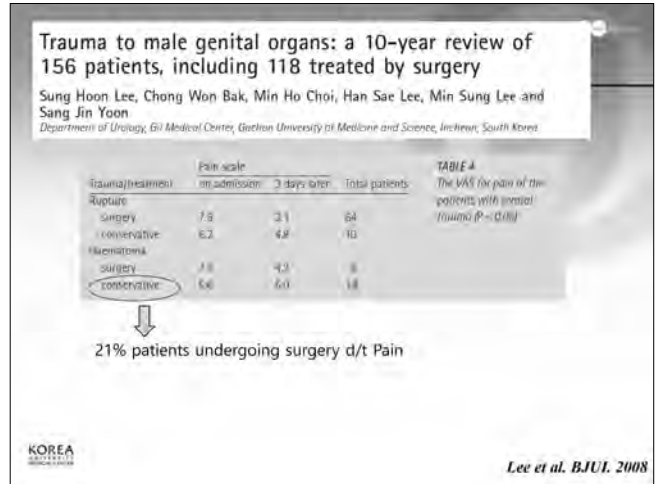
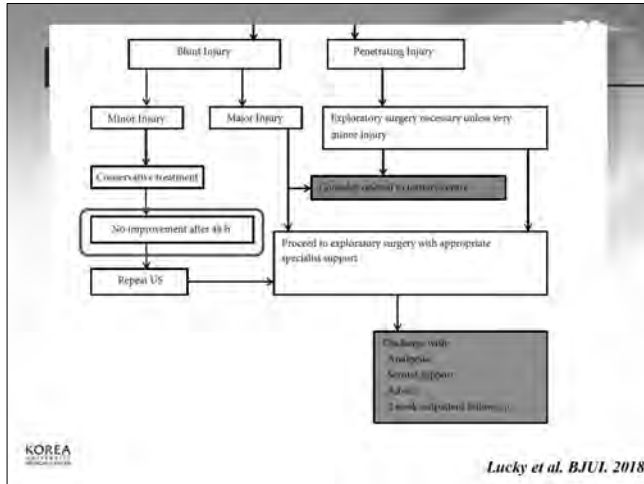
Zoran Popović, Ivo Jurk, Milivoj Bošić, Dubravko Furlan, Dražen Budimir, Juhon Tudorčić, Kladimir Pijer Milosavljević

Table 2 Semen analysis

Patient	Time after surgery	Motility (%)	Morphology		Volume (ml)	pH	Lipofraction	Concentration of spermatozoa (x 10 ⁶ ml)	Conclusion
			Normal (%)	Abnormal (%)					
001	14 days	57	46	54	0.6	7.5	After 20 min	14.50	Hypogonadotropism
	6 months	84	82	18	1.8	7.7	After 20 min	35.00	Normospermia
	1 year	89	82	18	2.1	7.5	After 20 min	37.70	Normospermia
002	14 days	75	74	26	3.3	7.8	After 20 min	31.25	Normospermia
	6 months	91	85	15	4.1	7.6	After 20 min	42.90	Normospermia
	1 year	93	82	18	3.8	7.4	After 20 min	44.50	Normospermia
004	14 days	-	-	-	-	-	-	-	-
	6 months	78	80	20	1.8	8.0	After 20 min	28.00	Normospermia
	1 year	86	80	20	2.5	7.6	After 20 min	31.25	Normospermia
005	14 days	55	51	49	2.0	7.3	After 20 min	9.90	Oligospermia
	6 months	84	80	20	2.8	7.3	After 20 min	25.75	Normospermia
	1 year	83	80	20	2.9	7.8	After 20 min	32.50	Normospermia
007	14 days	61	52	48	1.6	8.3	After 20 min	11.70	Oligospermia
	6 months	81	80	20	3.2	8.5	After 20 min	29.75	Normospermia
	1 year	91	80	20	2.9	8.0	After 20 min	39.00	Normospermia

Semen analysis was not performed in patients 003 and 006, because they were 11 and 14-year old

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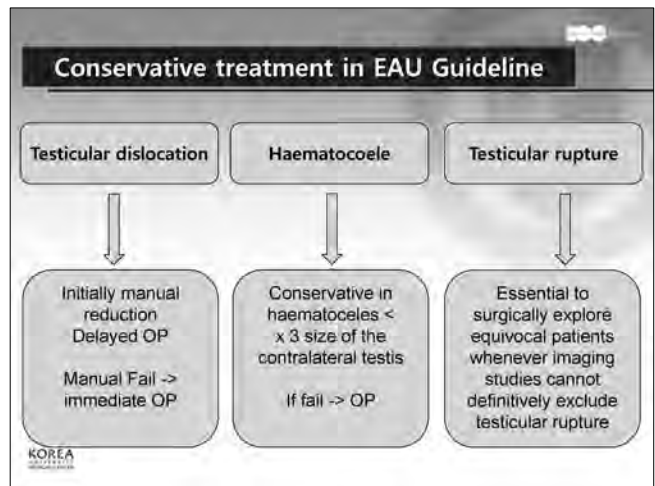
Dislocation

Bilateral dislocation of the testes has been reported in up to 25%
Nagarajan et al. Urology, 1983

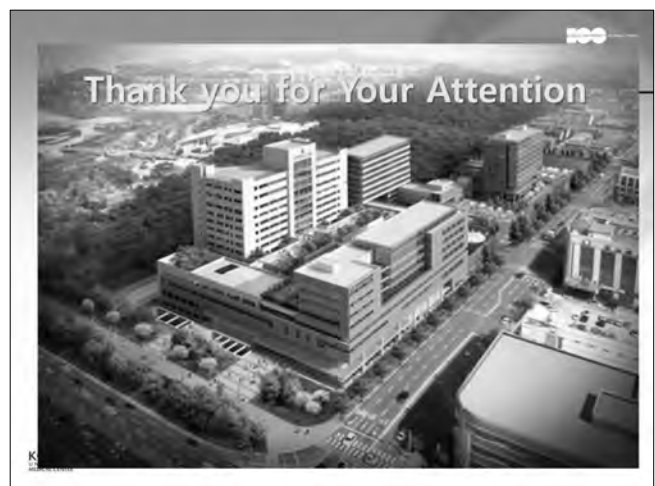
Testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity.

To preserve testicular function and to avoid the risk of malignant transformation.
Bromberg et al. J Trauma. 2003

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- ### Summary
- Rupture가 없다면 보존적 치료를 고려 할 수 있다.
 - Rupture가 있으면 수술적 치료가 원칙이나 일부 selected pts에서는 보존적 치료 고려할 수 있다.
 - Blunt trauma 양상, 나이, 통증 등을 고려하여 수술적 치료를 미루어서도 안된다.
- KOREA UNIVERSITY*



Surgical Reconstructive Techniques in the Management of Penile cancer

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EAU & NCCN guideline

[illegible]

Surgical consideration

- Oncologic control
- Sexual function
- Cosmesis
- Psychosocial impact
- Ability to void

Penile organ sparing approaches

- Wide local excision
- Glans resurfacing
- Glansectomy
- Mohs micrographic surgery (MMS)

Partial and total penectomy

- Partial penectomy with reconstruction
- Total penectomy with perineal urethrostomy
- Total penectomy with free flap phalloplasty

Reconstruction

- Flap or grafting techniques
- Local flaps: rotational flaps from preputial skin, scrotal skin, urethral tissue
- Free grafts: buccal mucosa, STSG, FTSG

Free and local pedicled flaps for phalloplasty

Type of Flap	Flap Size	Innervation	Blood Supply	Phallus Length
Gross flap	Site 1 to 10	Not known	Superficial circumflex iliac artery	7-10cm
Ramus flap	Site 1 to 10	Genitofemoral nerve	Deep inferior epigastric artery and vein	1-10cm
Superficial inferior epigastric flap	Site 1 to 10	Not known	Superficial inferior epigastric artery and vein	1-10cm
Anterolateral thigh flap	Site 1 to 10	Lateral femoral circumflex artery	Descending branch of the lateral femoral circumflex artery	10-12cm
Tensor fascia lata flap	Site 1 to 10	Lateral femoral circumflex artery	Ascending branch of the lateral femoral circumflex artery	10-12cm
Radiolateral forearm flap	Site 1 to 10	Lateral antebrachial cutaneous nerve	Radiolateral artery	Free flap
Lateral arm flap	Site 1 to 10	Proximal radial nerve of forearm	Proximal radial collateral artery	Free flap
Flap flap	Site 1 to 10	Not known	Proximal artery	Free flap
Latissimus flap	Site 1 to 10	Thoracoacromial artery	Thoracoacromial artery	10-12cm
Inferior flap	Site 1 to 10	Not known	Superior branch of circumflex iliac artery	1-10cm

Glans Resurfacing

- Confined glans, prepuce
- Noninvasive penile cancer (Tis, Ta, T1a)
- Sensation of the tip of the penis
- STSG, FTSG

Glans Resurfacing



Oncological outcomes after glans resurfacing

Study	Tumor Stage	No. of Patients	Recurrence (No Study Found Progression)	Cancer-Specific Survival, %
Ayres et al., ¹⁸ 2012	T1a	36	Recurrence: 2	NR
Hadway et al., ¹⁹ 2008	CIS	10	Recurrence: 0	100
Hakansson et al., ¹⁷ 2015	CIS	12	Recurrence: 0	100
Palimintier, ¹⁶ 2007	T1-T2	5	Recurrence: 0	NR
Shabbir et al., ¹⁰ 2011	CIS	25	Recurrence: 1	NR
Shabbir et al., ¹⁰ 2011	T1a	7	Recurrence: 1	NR

Wide excision of penile shaft skin



- Tis, Ta, T1, low-grade
- Cosmetic appearance
- Optimal extensibility for penile erection
- Penile shaft coverage : FTSG > STFG

Glansectomy



Oncological outcomes after glansectomy

Study	Tumor Stage	No. of Patients	Local Recurrence	Cancer-Specific Survival, %
Gulino et al., ²¹ 2013	Ta-T3	42	NR	100
Hakansson et al., ¹⁷ 2015	T0-T3	15	Recurrence: 0	100
Morelli et al., ²⁸ 2009	Ta-T3	15	Recurrence: 0 Metastases (nodal): 1	93.3
O'Kane et al., ²² 2011	T1-T3	25	Recurrence: 1 Metastases (nodal): 2	92
Palantieri, ¹⁸ 2007	T1-T2	15	Recurrence: 0	NR
Smith et al., ²³ 2007	T1-T2	22	Recurrence: 3	NR

Mohs micrographic surgery (MMS)

- Carcinoma In Situ, Ta, and T1
- Maximal tissue preservation by using tissue resection
- High rate of recurrence

Oncological efficacy of organ-sparing surgery

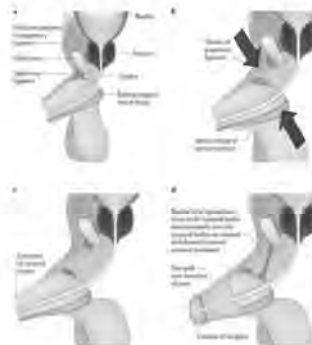
- Organ sparing surgery vs partial penectomy
 - local recurrence : 26% vs 4%
 - mortality: 17% vs 10%
- Intraoperative frozen section: local recurrences < 5%

Functional efficacy of organ-sparing surgery

Glansectomy vs limited partial penectomy

- Rigid erections 73%
- Normal orgasm and ejaculation 76%
- Libido and 71%

Penile lengthening and enhancement



- Maximize outward penile protrusion and length
- Enable upright voiding and sexual intercourse
- Division of the suspensory ligament dorsally
- Penoscrotal skin ventrally releases

Total phallic reconstruction

- Competent genitoperineal: standing voiding
- Restoration of erogenous and tactile sensation
- Insertion of a prosthetic device
- Sexual function
- More than 20 different types of flaps available
- Radial artery free flap : the most common technique

Radial artery free flap phalloplasty



- A full thickness flap is raised on the radial artery with cutaneous nerves
- Flap is formed in two parts to create the urethra and phallus
- The neophallus is detached from the donor site and put into position
- Anastomosing the blood vessels and connecting the cutaneous nerves

Tissue Engineering in Phallic Regeneration

- Several trials have shown the potential of tissue-engineered corpus cavernosum as an alternative for surgical total phallic reconstruction
- Corporal bodies have been created using acellular corporal matrices seeded with autologous smooth muscle and endothelial cells in animals
- Bioengineered corpora allowing male rabbits to successfully mate with female rabbits.

Penile transplant



- First : in 2006 in Guangzhou, China
- Second : in South Africa in 2014
- The first in US, Massachusetts General Hospital in May 2016



2019
요로생식기손상재건연구회
비뇨기계기초의학연구회
공동심포지엄

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