



Connecting Patients to Clinical Trials With Artificial Intelligence

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Patient Summary (synthetic)

This is a 78 year-old male with h/o BPH s/p multiple urological procedures, including s/p Suprapubic prostatectomy. He was noted to have low urine output and bladder scan showed 360cc residual. It was impossible for staff to pass a foley. Urology was consulted, performed a flexible cystoscopy in the ICU and found severe 2cm bulbar urethral stricture. They were able to pass small catheter through and left in place. The patient leaked around the catheter, the catheter eventually came out but he continued to have good urine output and post-void bladder scans

Candidate Clinical Trial & TrialGPT Predictions

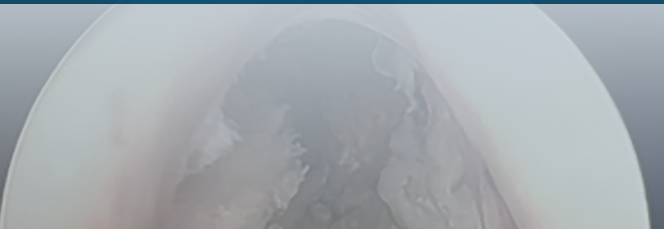
Efficiency of Cold vs. Laser Internal Urethrotomy Treatment of Urethral Strictures (IU)
The purpose of this study is to determine whether laser internal urethrotomy (IU) is as efficient as cold knife internal urethrotomy for treatment of anterior urethral strictures regarding post operative urination outflow, stricture recurrence rate and possible post- operative complications

Inclusion Criteria
Men over 18 years old with urethral stricture **[TrialGPT: included]**
TrialGPT explanation: The patient is a 78 year-old male, which meets the age and gender requirement. The patient note also mentions that he has a urethral stricture, which is the target disease for the clinical trial. Therefore, the patient meets this criterion.

Exclusion Criteria
S/P urethral reconstruction **[TrialGPT: not excluded]**

Management of Outlet Obstruction Before and After Radiation Therapy for Prostate Cancer

Joshua A. Cohn, MD
Eric M. Ghiraldi, DO
Justin I. Friedlander, MD



Safeguarding Telehealth's Future Beyond 2024

Chad Ellimoottil, MD, MS



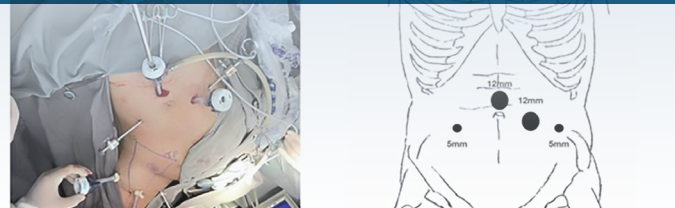
Emerging Trends That Herald the Future of Robotic Surgical Simulation

Ahmed Ghazi, MD, FEBU, MHPE

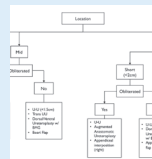
Advanced Skills (A)	Procedural Models* (P)
A.1 Access to narrow spaces (Extraperitoneal, retroperitoneal, trans-vesicle) A.2 Repositioning to avoid collision with fascia A.3 Working in narrow spaces A.4 Complex retraction to expose difficult areas A.5 Autonomous control of dissection A.6 Limited assistance from bedside assistant A.7 Balancing the traction/countertraction	P.1 Extraperitoneal Radical Prostatectomy P.2 Retroperitoneal Partial Nephrectomy P.3 Trans-vesical Simple Prostatectomy P.4 Trans/Retroperitoneal Pyeloplasty <small>*All 40 procedural models listed in the accompanying table.</small>

Video Endoscopic Inguinal and Simultaneous Pelvic Lymph Node Dissection in Penile Cancer

Marcos Tobias-Machado, MD
Marcel Aranha, MD
Alexandre Kyoshi Hidaka, MD, MBBS
Rene Sotelo, MD



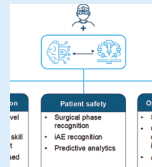
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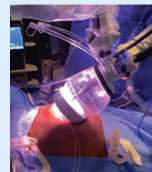
Robotic-Assisted Upper Urinary Tract Reconstruction: Tips and Tricks



Missing Voices: Thematic Analysis and How It Can Inform Surgeons in Reconstructive Urology



Robotic Surgery and Artificial Intelligence: A Synergistic Nexus



Developing an Algorithm on Multiport and Single Port Use for Robotic Prostate and Kidney Surgery

COMING SOON in March AUA**News**Extra

Global State of Urology Focus Issue

Urology in Canada: Navigating Challenges, Embracing Opportunities
State of Urology in Saudi Arabia
What Urology Looks Like in Colombia: The Perspective of a Resident
Urology Training in the UK: My Experience With the Global Residents Leadership Retreat
Urology Down Under: The State of Urology in Australia
Challenges of Urology in Colombia
Urology in Peru
Exchanging Experiences Makes the Recommendation Level Much More Than an Expert Opinion



NOW APPROVED IN nmCSPC WITH HIGH-RISK BCR¹

NOW APPROVED IN nmCSPC WITH HIGH-RISK BCR¹

Harness the power of XTANDI + GnRH therapy*[†] for your appropriate patients with nmCSPC with high-risk BCR for **proven efficacy benefits** vs placebo + GnRH therapy*[‡]

BICR, blinded independent central review; **CI**, confidence interval; **ECOG**, Eastern Cooperative Oncology Group; **GnRH**, gonadotropin-releasing hormone; **HR**, hazard ratio; **NR**, not reached; **PSA**, prostate-specific antigen; **RP**, radical prostatectomy; **RT**, radiotherapy. Metastasis-free survival was defined as the time from randomization to whichever of the following occurred first: 1) radiographic progression per BICR or 2) death.¹

***Leuprolide**.¹

[†]Patients with nmCSPC with high-risk BCR receiving XTANDI may be treated with or without GnRH therapy.¹

[‡]Includes multiple terms.¹

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in eight randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients

on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on XTANDI versus 1.1% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo.

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

Adverse Reactions (ARs)

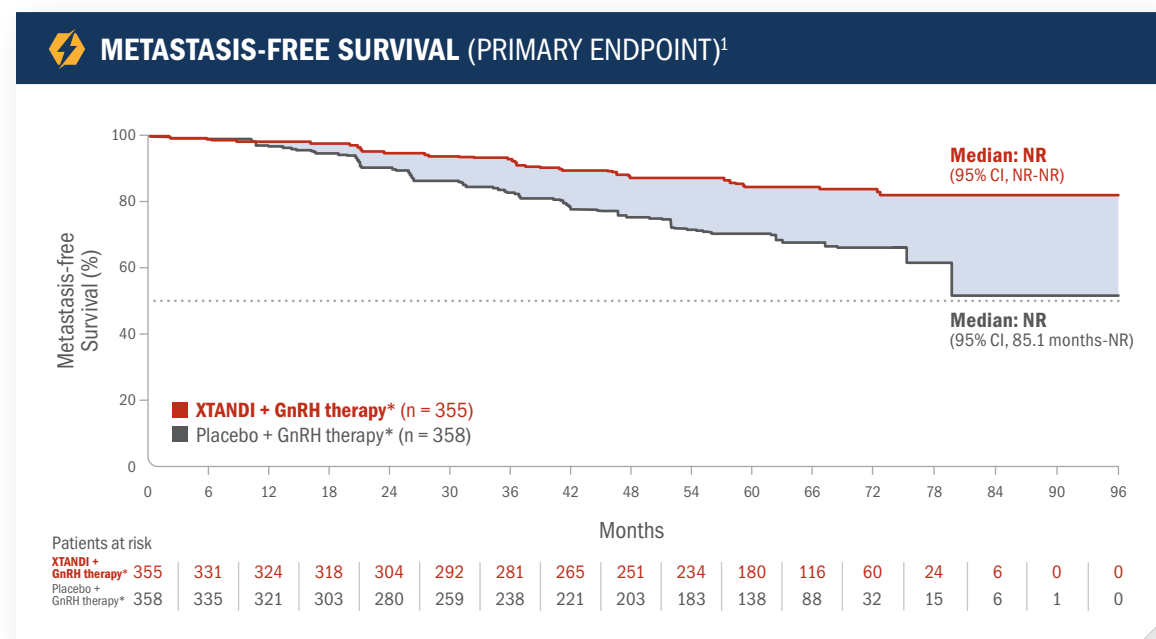
In the data from the five randomized placebo-controlled trials, the most common ARs ($\geq 10\%$) that occurred more frequently ($\geq 2\%$ over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. In the bicalutamide-controlled study, the most common ARs ($\geq 10\%$) reported in XTANDI-treated patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated patients. Discontinuations due to ARs were reported for 16% of XTANDI-treated patients. In PREVAIL, the

XTANDI is indicated for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR), metastatic castration-sensitive prostate cancer (mCSPC), or castration-resistant prostate cancer (CRPC).¹

EMBARK was a randomized phase 3 trial that assessed the efficacy and safety of XTANDI + GnRH therapy* vs placebo + GnRH therapy* in 1068 patients with nmCSPC with high-risk BCR^{1,2}

XTANDI + GnRH THERAPY* SIGNIFICANTLY IMPROVED METASTASIS-FREE SURVIVAL VS PLACEBO + GnRH THERAPY*¹



IN nmCSPC WITH HIGH-RISK BCR¹

METASTASIS-FREE SURVIVAL

58% reduction in the risk of metastasis or death

with XTANDI + GnRH therapy* vs placebo + GnRH therapy* (HR = 0.42 [95% CI, 0.30-0.61]; $P < 0.0001$)

- Number of events: 45 (12.7%) with XTANDI + GnRH therapy* vs 92 (25.7%) with placebo + GnRH therapy*¹
- Median metastasis-free survival was not reached in either the XTANDI + GnRH therapy* arm or the placebo + GnRH therapy* arm¹

Overall survival data were not mature at the time of metastasis-free survival analysis (12.2% deaths across the overall population of 1068 patients had been reported)¹

In the EMBARK trial, the adverse reactions that occurred at $\geq 5\%$ (Grade 1-4) or $\geq 2\%$ (Grade 3-4) higher frequency in the XTANDI + GnRH therapy* arm than in the placebo + GnRH therapy* arm were hot flush (Grade 1-4: 69% vs 57%; Grade 3-4: 0.6% vs 0.8%), fatigue[†] (Grade 1-4: 50% vs 38%; Grade 3-4: 4% vs 1.7%), musculoskeletal pain[†] (Grade 1-4: 50% vs 43%; Grade 3-4: 4.8% vs 2.3%), fall (Grade 1-4: 21% vs 14%; Grade 3-4: 1.1% vs 1.1%), hemorrhage[†] (Grade 1-4: 20% vs 15%; Grade 3-4: 3.4% vs 1.7%), fracture[†] (Grade 1-4: 18% vs 13%; Grade 3-4: 4% vs 2.5%), diarrhea[†] (Grade 1-4: 15% vs 9%; Grade 3-4: 0.6% vs 0.8%), cognitive disorder[†] (Grade 1-4: 10% vs 4.8%; Grade 3-4: 0.3% vs 0.6%), osteoarthritis (Grade 1-4: 6% vs 4.2%; Grade 3-4: 2.8% vs 0.6%), and syncope (Grade 1-4: 4.8% vs 2.3%; Grade 3-4: 4.2% vs 1.7%).¹

Patient population: All patients had prior definitive therapy with RP or RT (including brachytherapy) with curative intent, or both; confirmation of nonmetastatic disease by BICR; screening PSA ≥ 1 ng/mL after RP (with or without RT) as the primary treatment for prostate cancer or at least 2 ng/mL above the nadir after prior RT only; PSA doubling time ≤ 9 months; testosterone ≥ 150 ng/dL; ECOG Performance Status 0-1 at screening.^{1,2}

Exclusion criteria (select): prior/current distant metastasis; prior hormonal therapy generally not allowed except for short courses ≤ 36 months in duration and ≥ 9 months before randomization; suitable candidate for salvage RT if prior prostatectomy; prior cytotoxic chemotherapy/systemic biologic therapy, including immunotherapy, for prostate cancer; history of seizure or any seizure-predisposing condition; and clinically significant cardiovascular disease.³

Patients were offered a treatment suspension once at Week 37 if PSA was < 0.2 ng/mL at Week 36; treatment was reinitiated when PSA values increased to ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for patients without prior prostatectomy. In the XTANDI + GnRH therapy* and placebo + GnRH therapy* arms, GnRH therapy* was also suspended.¹

placebo-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to ARs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 ARs were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AR as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of nonmetastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AR as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients.

In ARCHES, the placebo-controlled study of metastatic CSPC (mCSPC) patients, Grade 3 or higher ARs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to ARs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

In EMBARK, the placebo-controlled study of nonmetastatic CSPC (nmCSPC) with high-risk biochemical recurrence (BCR) patients, Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide.

Lab Abnormalities: Lab abnormalities that occurred in $\geq 5\%$ of patients, and more frequently ($> 2\%$) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies are hemoglobin decrease, neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, hyperphosphatemia, and hypercalcemia.

Hypertension: In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14.2% of XTANDI patients and 7.4% of placebo patients. Hypertension led to study discontinuation in $< 1\%$ of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid coadministration with strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI.

Avoid coadministration with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs Avoid coadministration with certain CYP3A4, CYP2C9, and CYP2C19 substrates for which minimal decrease in concentration may lead to therapeutic failure of the substrate. If coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. 2. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. *N Engl J Med* 2023;389(16):1453-65. 3. Freedland SJ, De Giorgi U, Gleave M, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design. *BMJ Open* (Epub) 08-12-2021.

START WITH XTANDI NOW



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XTANDI® (enzalutamide) capsules, for oral use
XTANDI® (enzalutamide) tablets, for oral use

Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:

- castration-resistant prostate cancer
- metastatic castration-sensitive prostate cancer
- nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high-risk for metastasis

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Seizure

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 2250 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in eight randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease

In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on the XTANDI arm compared to 1.1% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture

and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo. Grade 3-4 fractures occurred in 3.4% of patients treated with XTANDI and in 1.9% of patients treated with placebo. The median time to onset of fracture was 420 days (range: 1 to 2348 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS and PRECAUTIONS reflect eight randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, EMBARK, Asian PREVAIL (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N = 3651), mCSPC (N = 752), or nmCSPC with high-risk BCR (N = 707) treated with XTANDI. Patients received XTANDI 160 mg (N = 5110) or placebo orally once daily (N = 2829) or bicalutamide 50 mg orally once daily (N = 387). In these eight trials, the median duration of treatment was 22.1 months (range: < 0.1 to 95.0) in patients that received XTANDI.

In five placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, ARCHES, and EMBARK), the median duration of treatment was 19.4 months (range: < 0.1 to 90.4) in the XTANDI group. In these five trials, the most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache.

AFFIRM: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse reactions were reported for 16% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4 ¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions ²	51	9	44	9
Peripheral Edema	15	1	13	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26	5	24	4
Arthralgia	21	2.5	17	1.8
Musculoskeletal Pain	15	1.3	12	0.3
Muscular Weakness	10	1.5	7	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0
Gastrointestinal Disorders				
Diarrhea	22	1.1	18	0.3
Vascular Disorders				
Hot Flush	20	0	10	0
Hypertension	6	2.1	2.8	1.3
Nervous System Disorders				
Headache	12	0.9	5	0
Dizziness ³	9	0.5	7	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7	7	4.5	3.8
Paresthesia	7	0	4.5	0
Mental Impairment Disorders ⁴	4.3	0.3	1.8	0
Hypoesthesia	4	0.3	1.8	0

Table 1. Adverse Reactions in AFFIRM (cont'd)

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Infections and Infestations				
Upper Respiratory Tract Infection⁵	11	0	6	0.3
Lower Respiratory Tract And Lung Infection⁶	8	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	9	0	6	0.5
Anxiety	6	0.3	4	0
Renal and Urinary Disorders				
Hematuria	7	1.8	4.5	1
Pollakiuria	4.8	0	2.5	0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0
Non-pathologic Fractures	4	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0	1.3	0
Dry Skin	3.5	0	1.3	0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3
1. CTCAE v 4. 2. Includes asthenia and fatigue. 3. Includes dizziness and vertigo. 4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. 5. Includes dyspnea, exertional dyspnea, and dyspnea at rest. 6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis. 6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.				

PREVAIL: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse reactions were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions²	47	3.4	33	2.8
Peripheral Edema	12	0.2	8	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	29	2	22	3
Arthralgia	21	1.6	16	1.1
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.4
Diarrhea	17	0.3	14	0.4
Vascular Disorders				
Hot Flush	18	0.1	8	0
Hypertension	14	7	4.1	2.3
Nervous System Disorders				
Dizziness³	11	0.3	7	0
Headache	11	0.2	7	0.4
Dysgeusia	8	0.1	3.7	0
Mental Impairment Disorders⁴	6	0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0
Respiratory Disorders				
Dyspnea⁵	11	0.6	8	0.6
Infections and Infestations				
Upper Respiratory Tract Infection⁶	16	0	11	0
Lower Respiratory Tract And Lung Infection⁷	8	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8	0.1	6	0
Renal and Urinary Disorders				
Hematuria	9	1.3	6	1.3
Injury, Poisoning and Procedural Complications				
Fall	13	1.6	5	0.7
Non-Pathological Fracture	9	2.1	3	1.1

Table 2. Adverse Reactions in PREVAIL (cont'd)

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	19	0.3	16	0.7
Investigations				
Weight Decreased	12	0.8	8	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0	1.4	0
1. CTCAE v 4. 2. Includes asthenia and fatigue. 3. Includes dizziness and vertigo. 4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. 5. Includes dyspnea, exertional dyspnea, and dyspnea at rest. 6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis. 7. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.				

TERRAIN: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse reaction as the primary reason were reported for 8% of XTANDI-treated patients and 6% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

	XTANDI (N = 183)		Bicalutamide (N = 189)	
	Grade 1-4¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Overall	94	39	94	38
General Disorders				
Asthenic Conditions²	32	1.6	23	1.1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	19	2.7	18	1.6
Musculoskeletal Pain³	16	1.1	14	0.5
Vascular Disorders				
Hot Flush	15	0	11	0
Hypertension	14	7	7	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhea	12	0	9	1.1
Infections and Infestations				
Upper Respiratory Tract Infection⁴	12	0	6	0.5
Investigational				
Weight Loss	11	0.5	8	0.5
1. CTCAE v 4. 2. Includes asthenia and fatigue. 3. Includes musculoskeletal pain and pain in extremity. 4. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.				

PROSPER: XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse reactions. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse reactions of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse reaction as the primary reason were reported for 9% of XTANDI-treated patients and 6% of placebo-treated patients. Of these, the most common adverse reaction leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 4. Adverse Reactions in PROSPER

	XTANDI (N = 930)		Placebo (N = 465)	
	Grade 1-4 ¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	10	0.2	3.9	0.2
Nervous System Disorders				
Dizziness ²	12	0.5	5	0
Headache	9	0.2	4.5	0
Cognitive And Attention Disorders ³	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	8	0
Hypertension	12	4.6	5	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	9	0
Constipation	9	0.2	7	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions ⁴	40	4	20	0.9
Investigations				
Weight Decreased	6	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fall	11	1.3	4.1	0.6
Fractures ⁵	10	2	4.9	1.7
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0
1. CTCAE v 4. 2. Includes dizziness and vertigo. 3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. 4. Includes asthenia and fatigue. 5. Includes all osseous fractures from all sites.				

ARCHES: XTANDI versus Placebo in Metastatic CSPC Patients

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analog concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). The median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo. Overall, 10 patients (1.7%) receiving XTANDI died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 3), sepsis (n = 2) and pulmonary embolism (n = 2). Eight patients (1.4%) receiving placebo died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 2) and sudden death (n = 2). Grade 3 or higher adverse reactions were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse reactions as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse reactions resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common adverse reactions leading to permanent discontinuation in placebo-treated patients were arthralgia, and fatigue, each in 0.3%. Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients. Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4 ¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	4.9	0.2	2.6	0
Nervous System Disorders				
Cognitive and Memory Impairment ²	4.5	0.7	2.1	0
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27	0.3	22	0
Hypertension	8	3.3	6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions ³	24	1.7	20	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6	0.2	4	0.2

Table 5. Adverse Reactions in ARCHES (cont'd)

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4 ¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Injury, Poisoning and Procedural Complications				
Fractures ⁴	6	1	4.2	1
1. CTCAE v 4.03. 2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia alzheimer's type, mental impairment, senile dementia and vascular dementia. 3. Includes asthenia and fatigue. 4. Includes Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.				

EMBARC: XTANDI versus Placebo in Nonmetastatic CSPC Patients with High-risk BCR

EMBARC enrolled 1068 patients with high-risk BCR, of whom 1061 patients received at least one dose of study drug. Patients received XTANDI at a dose of 160 mg once daily concurrently with leuprolide (N = 353), XTANDI at a dose of 160 mg once daily as open-label monotherapy (N = 354), or placebo concurrently with leuprolide (N = 354). At week 37, treatment was suspended for patients whose PSA values were undetectable (< 0.2 ng/mL) at week 36. Treatment was reinitiated when PSA values increased to ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for patients without prior prostatectomy. For patients whose PSA values were detectable (≥ 0.2 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met. Table 6 shows the total duration of treatment for the three treatment arms.

Table 6. Drug Treatment and Suspension in EMBARK

	XTANDI + Leuprolide (N = 353)	Placebo + Leuprolide (N = 354)	XTANDI (N = 354)
Total Duration of Treatment¹			
Median, months	60.6	55.6	60.4
Range, months	0.1 – 90.4	0.7 – 94.1	0.4 – 95.0
Duration Receiving Drug Treatment			
Median, months	32.4	35.4	45.9
Range, months	0.1 – 83.4	0.7 – 85.7	0.4 – 88.9
Duration of Suspension from Drug Treatment			
Median, months	20.2	16.8	11.1
Range, months	5.7 – 87.9	3.4 – 83.0	2.3 – 84.9
Patients who had Drug Treatment Suspended at Week 37			
Number of Patients (%)	321 (90.9)	240 (67.8)	304 (85.9)
1. Inclusive of time receiving drug treatment plus any time during which drug treatment was suspended because of undetectable PSA levels.			

Overall, deaths from adverse reactions during the total duration of treatment occurred in 6 patients (1.7%) receiving XTANDI plus leuprolide, 8 patients (2.3%) receiving XTANDI as a single agent, and 3 patients (0.8%) receiving placebo plus leuprolide. The reason for death in ≥ 2 patients receiving XTANDI plus leuprolide was infection (n = 2), and the reason for death in ≥ 2 patients receiving XTANDI as a single agent was arterial thromboembolism (n = 2). Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide. The most common adverse reactions resulting in permanent discontinuation included fatigue (3.4% of patients treated with XTANDI plus leuprolide, 3.7% of patients receiving XTANDI as a single agent, and 1.4% of patients receiving placebo plus leuprolide), hot flush (2% of patients treated with XTANDI plus leuprolide, 0% of patients receiving XTANDI as a single agent, and 1.1% of patients receiving placebo plus leuprolide), nausea (1.1% of patients treated with XTANDI plus leuprolide, 0.6% of patients receiving XTANDI as a single agent, and 0.3% of patients receiving placebo plus leuprolide), and cognitive disorder (1.1% of patients treated with XTANDI plus leuprolide, 1.4% of patients receiving XTANDI as a single agent, and 0.8% of patients receiving placebo plus leuprolide).

Dose reductions due to an adverse reaction occurred in 7% of patients who received XTANDI plus leuprolide, 16% of patients who received XTANDI as a single agent, and 4.5% of patients who received placebo plus leuprolide. Fatigue was the most frequent adverse reaction requiring dose reduction in 3.1% of patients treated with XTANDI plus leuprolide, 10% of patients receiving XTANDI as a single agent, and 1.7% of patients receiving placebo plus leuprolide.

Table 7 shows adverse reactions reported in EMBARK that occurred at a ≥ 5% (Grade 1-4) or ≥ 2% (Grade 3-4) higher frequency in either of the XTANDI arms than in the placebo arm.

Table 7. Adverse Reactions in EMBARK

	XTANDI + Leuprolide (N = 353)		Placebo + Leuprolide (N = 354)		XTANDI (N = 354)	
	Grade 1-4 ¹ (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Nervous System Disorders						
Cognitive Disorder ²	10	0.3	4.8	0.6	10	0.3
Syncope	4.8	4.2	2.3	1.7	2.5	2
Vascular Disorders						
Hot Flush	69	0.6	57	0.8	22	0.3
Hemorrhage ²	20	3.4	15	1.7	21	3.7
Gastrointestinal Disorders						
Diarrhea ²	15	0.6	9	0.8	14	0.3
Nausea	12	0.3	8	0.3	15	0.6
Investigations						
Weight Decreased	7	0.3	3.4	0	11	0.3
General Disorders and Administration Site Conditions						
Fatigue ²	50	4	38	1.7	54	4.8
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain ²	50	4.8	43	2.3	48	3.1
Osteoarthritis	6	2.8	4.2	0.6	5	0.6
Injury, Poisoning and Procedural Complications						
Fall	21	1.1	14	1.1	16	2
Fracture ²	18	4	13	2.5	11	2
Reproductive System and Breast Disorders						
Gynecomastia ²	9	0	10	0	49	0.8
Breast Tenderness ²	5	0	2.8	0	35	0
Cardiac Disorders						
Ischemic Heart Disease ²	5	4	6	3.1	9	6
1. CTCAE v 4.03. 2. Includes multiple terms.						

Laboratory Abnormalities

Table 8 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 8. Laboratory Abnormalities

	XTANDI (N = 3526)		Placebo (N = 2636)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hematology				
Hemoglobin decreased	50	1.8	47	1.5
Neutrophil count decreased	20	1	17	0.5
White blood cell decreased	18	0.5	11	0.2
Chemistry				
Hyperglycemia	86	3.7	78	4.3
Hypermagnesemia	17	0.1	14	0.3
Hyponatremia	14	1.6	9	1.4
Hypophosphatemia	10	1.4	7	0.8
Hypercalcemia	8	0.1	5	0.1

Hypertension

In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14% of patients receiving XTANDI and 7% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting
Immune System Disorders: hypersensitivity (edema of the face, tongue, lip, or pharynx)
Neurological Disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia
Skin and Subcutaneous Tissue Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

DRUG INTERACTIONS

Effect of Other Drugs on XTANDI

Strong CYP2C8 Inhibitors
The coadministration of XTANDI with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of XTANDI. Avoid the coadministration of XTANDI with strong CYP2C8 inhibitors. If the coadministration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of XTANDI.

Strong CYP3A4 Inducers

The coadministration of XTANDI with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of XTANDI. Avoid the coadministration of XTANDI with a strong CYP3A4 inducer with strong CYP3A4 inducers. If the coadministration of XTANDI cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs

Certain CYP3A4, CYP2C9, or CYP2C19 Substrates

XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of XTANDI decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates, which may reduce the efficacy of these substrates. Avoid the coadministration of XTANDI with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose (*see Data*).

Data

Animal Data
In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

Lactation

Risk Summary

The safety and efficacy of XTANDI have not been established in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats (*see Data*).

Data

Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

Females and Males of Reproductive Potential

Contraception

Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use

Of 5110 patients who received XTANDI in eight randomized, controlled clinical trials, 78% were 65 and over, while 33% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] \geq 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease.

Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment.

OVERDOSAGE

In the event of an overdosage, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at \leq 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdosage.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (\geq 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at \geq 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at \geq 4 mg/kg/day (0.3 times the human exposure based on AUC).

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ARTIFICIAL INTELLIGENCE

Connecting Patients to Clinical Trials With Artificial Intelligence

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In the evolving landscape of health care research, the efficient recruitment of patients for clinical trials stands as an important yet challenging task. Clinical trials play a vital role in drug development and evidence-based medicine. Traditionally, patient recruitment for clinical trials involves a painstaking review of patient histories and trial criteria. This task demands not only a deep understanding of the medical nuances but also a meticulous cross-referencing of patient data against trial requirements. The complexity and variability of medical records, coupled with the diverse and often ambiguous criteria of clinical trials, further complicate this process. As a result, the entire process of matching patients

Patient Summary (synthetic)

This is a 78 year-old male with h/o BPH s/p multiple urological procedures, including s/p Suprapubic prostatectomy. He was noted to have low urine output and bladder scan showed 360cc residual. It was impossible for staff to pass a foley. Urology was consulted, performed a flexible cystoscopy in the ICU and found severe 2cm bulbar urethral stricture. They were able to pass small catheter through and left in place. The patient leaked around the catheter, the catheter eventually came out but he continued to have good urine output and post-void bladder scans were performed q4h to ensure he did not have high residual volume. Urology suggested that when patient is stable he will have to be taken to the OR to have the stricture surgically fixed.

Figure 1. An example patient summary from the Text Retrieval Conference Clinical Trials Track in 2021. BPH indicates benign prostatic hyperplasia; OR, operating room.

with the right trials is often a bottleneck, leading to delays in treatment initiation and potential missed opportunities for both patients and researchers.¹

Recent large language models (LLMs) such as GPT-4² have demonstrated remarkable capabilities in understanding conversational contexts and generating human-like

texts. They have achieved new state-of-the-art performance in a wide range of domains, including biomedicine and health care.³ For example, they can improve scientific literature search,⁴ summarize clinical evidence,⁵ and answer various biomedical questions.^{6,7} Therefore, we introduced TrialGPT, which utilizes LLMs to streamline matching patients with clinical trials by analyzing and understanding texts such as patient medical records and trial eligibility requirements.⁸

The functionality of TrialGPT is twofold. Firstly, it analyzes a patient's medical history and evaluates each criterion of a potential trial for eligibility. This is enabled through a sophisticated understanding of natural language by LLMs, allowing TrialGPT to parse and interpret medical notes with remarkable accuracy. Secondly, TrialGPT aggregates these criterion-level assessments to generate a trial-level score, effectively ranking trials based on their suitability for the patient. In both steps, TrialGPT also generates the explanation in natural language for its predictions, providing further interpretability to potential users.

For example, Figure 1 shows a synthetic patient note used in a machine learning competition⁹ and Figure 2 shows a clinical trial for which the patient is annotated as eligible by the competition organizers. The predictions generated by TrialGPT are also shown in Figure 2, which include the criterion-level eligibility predictions and the natural language explanation for them. TrialGPT successfully predicts that the patient meets the inclusion criterion, with the evidence of both the age and the condition correctly explained. For the first exclusion criterion, TrialGPT infers from the patient summary that the patient does not meet this criterion. Regarding the second exclusion criterion, TrialGPT successfully uses its medical knowledge to classify the

Candidate Clinical Trial & TrialGPT Predictions

Efficiency of Cold vs. Laser Internal Urethrotomy Treatment of Urethral Strictures (IU)

The purpose of this study is to determine whether laser internal urethrotomy (IU) is as efficient as cold knife internal urethrotomy for treatment of anterior urethral strictures regarding post operative urination outflow, stricture recurrence rate and possible post-operative complications

Inclusion Criteria

Men over 18 years old with urethral stricture **[TrialGPT: included]**

TrialGPT explanation: The patient is a 78 year-old male, which meets the age and gender requirement. The patient note also mentions that he has a urethral stricture, which is the target disease for the clinical trial. Therefore, the patient meets this criterion.

Exclusion Criteria

S/P urethral reconstruction **[TrialGPT: not excluded]**

TrialGPT explanation: The patient has a history of multiple urological procedures, including Suprapubic prostatectomy. However, there is no direct evidence of urethral reconstruction. Given the patient's urological history, it is unlikely that such a significant procedure would be omitted from the note.

Posterior urethral strictures **[TrialGPT: not excluded]**

TrialGPT explanation: The patient note mentions a "2cm bulbar urethral stricture", which is an anterior, not posterior, stricture.

Figure 2. A candidate clinical trial (NCT01196572) with TrialGPT predictions for the patient summary shown in Figure 1.



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AUNews

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CONNECTING PATIENTS TO CLINICAL TRIALS WITH ARTIFICIAL INTELLIGENCE

→ Continued from page 9

patient's bulbar urethral stricture as an anterior urethral stricture, and thus should not be excluded by the criterion. Providing such transparent and explainable predictions to clinical trial recruiters can greatly reduce the manual reviewing efforts and facilitate the matching process.

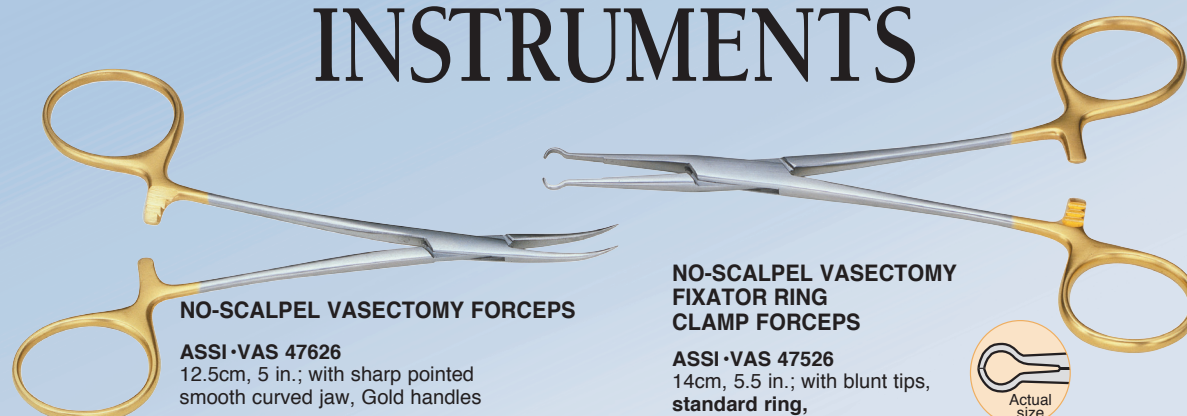
We showed a case study of how TrialGPT can assist patient-to-trial matching above. More details on the systematic evaluations of TrialGPT can be found in our preprint.⁸ To summarize, we conducted extensive tests across 3 patient cohorts, comprising 184 individuals and over 18,000 trial eligibility annotations. TrialGPT demonstrated an expert-level accuracy in criterion-level predictions. In addition, at the trial level, TrialGPT's scoring system was highly correlated with human eligibility judgments, outperforming existing models by significant margins. To further evaluate TrialGPT's efficacy in real-world settings, we also conducted a pilot user study at a cancer center, and the results show that TrialGPT significantly reduces the time taken for patient trial matching by 42.6%. This substantial decrease in screening time not only signifies a leap in efficiency but also hints at a future where more patients can access potentially life-saving trials quicker than ever before. While our preliminary results with TrialGPT are promising, future investigations with larger sample sizes and a prospective study design are needed to validate its effectiveness.

To summarize, TrialGPT shows significant potential to efficiently and effectively match patients to clinical trials, standing at the forefront of a new era in clinical trial matching. Because TrialGPT can facilitate the trial matching process by nonexperts, it has the potential to decrease the disparities in clinical trial enrollment. As we continue to refine and enhance TrialGPT, its integration into clinical settings holds the promise of improving patient recruitment and ultimately accelerating clinical care. ■

Support: This research was supported by the NIH Intramural Research Program, National Library of Medicine.

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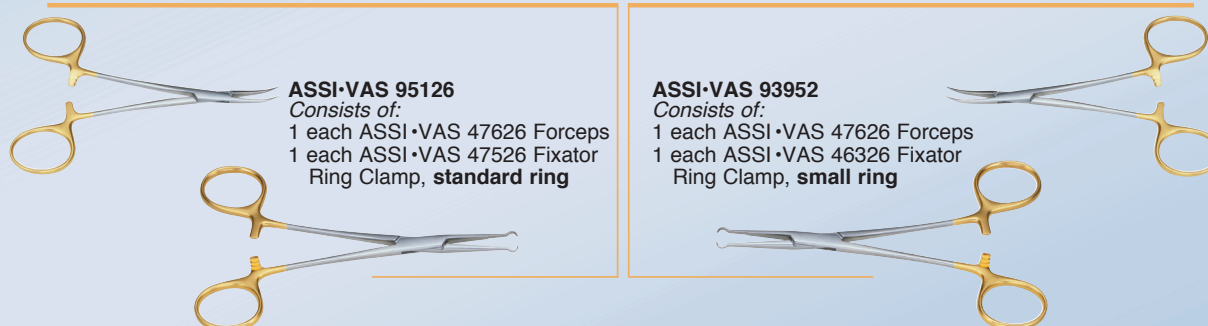
ASSI-VAS 47726
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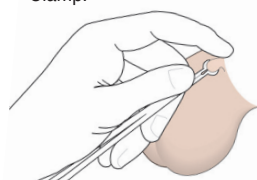
ASSI-VAS 47526
14cm, 5.5 in.; with blunt tips, **standard ring**, Gold handles

ASSI-VAS 46326
14cm, 5.5 in.; with blunt tips, **small ring**, Gold handles

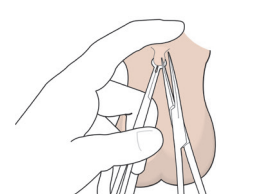
NO-SCALPEL VASECTOMY INSTRUMENT SETS



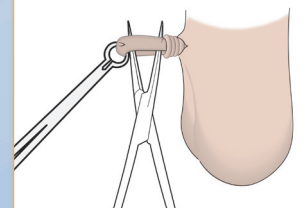
1 Fixation of the vas under the scrotal skin using the extracutaneous vas fixation clamp, ASSI® No-Scalpel Vasectomy Fixator Ring Clamp.



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Management of Outlet Obstruction Before and After Radiation Therapy for Prostate Cancer

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The incidence of prostate cancer in the United States in 2023 was estimated to be 288,300.¹ Most patients will choose to undergo radiation therapy (RT).² Given the frequency with which symptomatic prostatic obstruction impacts men in the same age demographic, overlap is inevitably common.³ However, data informing optimal treatment and modality for men with symptomatic prostatic obstruction before or after RT are lacking.

The AUA guidelines on management of benign prostatic hyperplasia (BPH) outline optional use index cases for minimally invasive, endoscopic, and enucleative therapies primarily based upon prostate size and the presence or absence of a significant median lobe component.^{4,5} RT, however, presents unique challenges, including a greater incidence of coexistent bladder pathology such as detrusor overactivity (DO) or altered compliance, prostatic urethral stenosis, or compromised external sphincter function as well as radiation cystitis and radiation necrosis.^{6,7} Each of these potential factors can render traditional BPH therapies suboptimal at best and potentially devastating at worst.

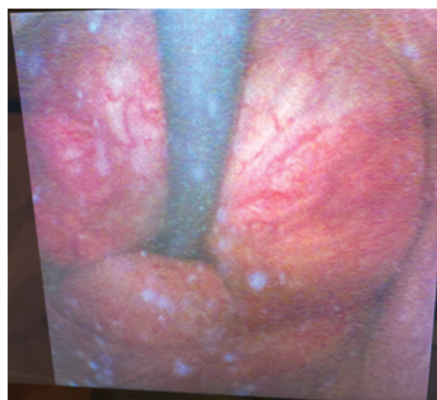


Figure 1. Classically enlarged median lobe. This patient underwent selective enucleation.

One aspect of care that must be determined is whether the best defense is a good offense. That is to say, should we identify men with bothersome lower urinary tract symptoms secondary to prostatic obstruction for treatment prior to RT so that outlet reduction surgery—and healing—take place in a non-radiated field. In our institution, we have developed a protocol for preradiation referral and when indicated pressure-flow testing and cystoscopy. Men who are symptomatic and obstructed are treated prior to RT based upon prostate size, anatomy, and surgeon and patient preference balancing side effects/risks of treatment and durability. However, some men may undergo unnecessary surgery as outlet obstruction may have been adequately relieved or not meaningfully worsened by prostate-directed cancer therapy. We are also inevitably missing men who are minimally symptomatic but nevertheless obstructed and may ultimately present with rather complex lower urinary tract symptoms subsequent to RT.

The motivation, however, for attempting to treat symptomatic obstruction prior to radiation are the challenges patients experience when obstruction presents after RT. Limited available data suggest we should expect high rates of incontinence (8%-70%) regardless of BPH treatment modality.⁸⁻¹¹ However, these studies tend to (1) be outdated, not considering modern treatment options for RT or bladder outlet surgery, (2) not include potentially valuable inputs such as urodynamic and cystoscopic findings, or both. In nonradiated patients, terminal DO, earlier and high-amplitude DO, and peak flow rate have all been associated with persistent storage symptoms after relief of outlet obstruction^{12,13}; however, it is not known if these same factors are predictive in the post-radiation patient population.

While acknowledging the absence of robust data, we incorporate cystometric and cystoscopic data in our patient counseling and clinical decision-making in the



Figure 2. Apical (A) and intravesical (B) radionecrosis at 3 months. C and D, When radionecrosis is visualized in the first 3 months following completion of radiation, repeat cystoscopy to evaluate for healing is performed at 6 months. The patient underwent selective enucleation of the median lobe.

postradiation patient with suspected outlet obstruction from prostatic enlargement.

Cystometric Findings

Bladder contractility

Our understanding of the impact of extensive prostatic resection (eg, enucleation) vs more limited therapy (eg, channel transurethral resection of the prostate, prostatic urethral lift) is limited. However, flow is linked to bladder contractility and diameter of the urethra.¹⁴ It follows, then, that patients with preserved bladder contractility may better “afford” to consider balancing side effects from more extensive prostatic resection, whereas those with poor contractility cannot. The cutoff for meaningfully poor contractility is not established, and studies defining it by bladder contractility index < 100 fail to capture the difference between patients with marked detrusor underactivity with urinary retention and

those with weakened but adequate contractility.¹⁵ Nonradiated data suggest that when detrusor contractility is markedly diminished or absent, enucleation performs better than standard resection—and in some cases quite well.¹⁶⁻¹⁸ Our preference, therefore, is typically for enucleation in prostates of suitable size when contractility is markedly diminished, frequently in patients with urinary retention.

DO and altered compliance

The combination of long-standing prostatic obstruction and radiation may result in marked storage abnormalities, including DO and altered compliance. Routine changes in cystometric capacity may be experienced as early as 3 months after RT,¹⁹ but the development of DO and altered compliance is not universal even at 18 months.²⁰ However, logic dictates that storage changes are likely to be more

MANAGEMENT OF OUTLET OBSTRUCTION BEFORE AND AFTER RADIATION THERAPY

→ Continued from page 12

frequent among those with refractory symptoms. In nonradiated patients, altered bladder compliance has been associated with worse outcomes after outlet reduction surgery²¹ and poorer response to overactive bladder therapy,²² and the presence of high-amplitude DO predicts its persistence.^{12,13} Therefore, we counsel patients with altered compliance that a satisfactory outcome may not be possible, and those with DO that the likelihood of need for subsequent overactive bladder therapy is high and its efficacy uncertain.

Cystoscopic Findings

Enlarged and/or “ball valving” median lobe

Some patients may be found to have marked enlargement and intravesical protrusion of the median lobe (Figure 1). In the nonradiated patient, selective treatment of the median lobe has been associated with durable relief of voiding symptoms.^{23,24} We have found this experience to extend to our radiated patients, with the important caveat that formal study is ongoing. Selective enucleation is our treatment of choice in patients with classically enlarged median lobes with preserved bladder contractility and relatively limited lateral lobe coaptation. The rationale is a theoretically reduced surface area for potential radionecrosis-associated calcification, reduced risk of incontinence, and potentially preserved ejaculatory function if present. However, we do also counsel patients that a failure to improve and pressure-flow studies indicative of persistent obstruction may warrant repeat surgery. Most are interested in this “staged” approach when their evaluation suggests it should be considered.

Radiation cystitis and radionecrosis

In historical cohorts, as many as 20% of patients who had received RT required hospital admission for genitourinary toxicity, of which approximately 60% was hematuria.⁶ Two percent required major operative interventions, including

urinary diversion in 0.2%. One of the challenges in managing prostatic obstruction after RT is trying to avoid pushing a patient who is otherwise managing reasonably well onto a path of repeated hospitalizations, life-threatening complications, and/or severely debilitating symptoms necessitating cystectomy. One such sign of potential for a disastrous outcome intervention may be radiation cystitis and radionecrosis. If marked radiation changes are encountered in the prostatic urethra within the acute phase of toxicity after RT (within the first 2-3 months),⁷ we favor delayed intervention with repeat cystoscopy at the 4- to 6-month time frame to evaluate for continued healing (Figure 2). When significant calcifications or tissue loss is encountered, particularly remote from RT, we discourage significant endoscopic intervention if symptoms are manageable and encourage patients to consider urinary diversion if symptoms are severe and debilitating (Figure 3). When heroic endoscopic interventions are to be attempted, patients ideally understand the potential for their disease to progress to needing urinary diversion even in the absence of intervention and for our interventions to result in complications that mandate it.

Conclusions

Management of prostatic obstruction after prostate RT is one of the most challenging and uncharted clinical dilemmas in urology. Given improvements in RT, with reduced associated toxicity, some patients may have fairly

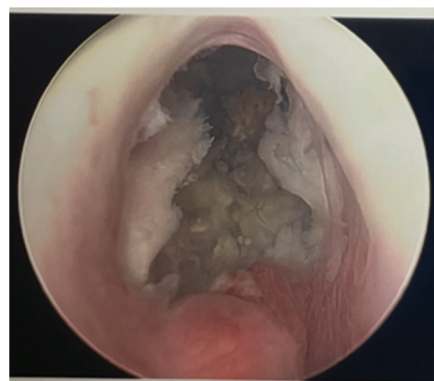


Figure 3. Severe radionecrosis in a patient who underwent transurethral resection of the prostate prior to subsequent radiation therapy. Further endoscopic interventions are performed with extreme caution.

“One of the challenges in managing prostatic obstruction after RT is trying to avoid pushing a patient who is otherwise managing reasonably well onto a path of repeated hospitalizations, life-threatening complications, and/or severely debilitating symptoms necessitating cystectomy.”

normal physiology and potential for healing and be treated similarly to their nonradiated counterparts. However, the heterogeneous group of post-RT patients will inevitably include those with marked detrusor dysfunction, severe radiation changes, and every gradation in between. Finding the right balance between undertreatment and disaster requires incorporating symptoms, patient priorities, cystometric and cystoscopic findings, and humility into clinical decision-making. ■

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AUA ADVOCACY

Safeguarding Telehealth's Future Beyond 2024

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University of Michigan, Ann Arbor

As a proud member of the AUA Telehealth Task Force, a telehealth policy researcher, and the Medical Director of Virtual Care at the University of Michigan, I had the distinct honor of representing both my insights and the broader perspective of the urology community during my testimony to the US Senate Committee on Finance, Subcommittee on Health Care, on November 14, 2023 (Figure). The hearing, entitled “Ensuring Medicare Beneficiary Access: A Path to Telehealth Permanency,” was not only a career milestone for me but also a pivotal moment in the ongoing advocacy for telehealth services.¹

The pandemic-era flexibilities, such as the removal of geographic restrictions and the inclusion of audio-only coverage, played a crucial role in telehealth's expansion. Currently, telehealth is well integrated into most urology practices, and numerous studies in our field have underscored its effectiveness and widespread acceptance.

However, this positive trend in telehealth faces potential disruption after December 31, 2024. Many of the pandemic-era flexibilities that have facilitated the widespread use of telehealth are set to expire on this date, absent proactive measures from Congress and the Medicare program. During my testimony on November 14, I emphasized

“Currently, telehealth is well integrated into most urology practices, and numerous studies in our field have underscored its effectiveness and widespread acceptance.”

various strategies Congress could adopt to prevent the “Fast and Slow Death” of telehealth. Specifically, I highlighted that a rapid decline, or “fast death,” of telehealth could occur if pre-pandemic geographic and site restrictions are reinstated on December 31, 2024. These restrictions would predominantly confine telehealth services to rural patients and prevent patients from connecting with their health care providers from the comfort of their homes. If this were to happen, we would likely witness an immediate and significant drop in telehealth usage.

The “slow death” of telehealth post-December 31, 2024, presents a more subtle yet equally concerning threat. This gradual decline could occur if patients and providers become increasingly frustrated with complex regulatory and billing rules, leading to disincentives to use telehealth services. To prevent this slow death, there are 4 key factors for Medicare and Congress to consider:

1. Coverage alignment across insurers: Medicare's stance on telehealth coverage significantly influences other insurers. If Medicare treats expanded telehealth coverage as temporary, it will lead commercial payers to reduce or eliminate their telehealth services.
2. Cover audio-only services: The impact of the digital divide, particularly in rural and underserved areas, highlights the necessity of audio-only telehealth. Eliminating this option could disproportionately affect these communities, depriving them of essential health care access.
3. Ensure payment parity: There's a common misconception that telehealth visits, particularly video visits, are less costly than in-person consultations. However, unless a practice is entirely virtual, overhead expenses for maintaining a physical office remain unchanged. Equitable reimbursement for telehealth services is vital to prevent a financial disincentive for providers.
4. Remove guardrails lacking clinical evidence: An example of an un-



Figure. Dr Chad Ellimoottil presents compelling testimony before the US Senate Committee on Finance, emphasizing the need for permanent telehealth coverage and outlining specific steps that Congress and the Centers for Medicare & Medicaid Services must take to achieve this goal.

necessary guardrail is the recently postponed Medicare requirement for mental health providers to have in-person visits at specific intervals with patients they see virtually. This requirement lacks clinical evidence supporting its necessity. It's crucial to evaluate and eliminate such guardrails that are not grounded in clinical efficacy.

During the hearing, we delved into the state of evidence regarding telehealth's impact on access, quality, and costs for Medicare beneficiaries. In my written testimony, accessible on the hearing's webpage,¹ I presented data illuminating the findings researchers have gathered over the past 3 years. While no single study can comprehensively capture telehealth's entire impact on costs, quality, and access, there is a general consensus among researchers on these key points:

- Costs: The expansion of telehealth services over the last 3 years has not resulted in excessive health care spending or overutilization.
- Quality: The impact of telehealth on the quality of care varies depending on the condition, the telehealth modality, and the specific quality measures used. Generally, telehealth does not undermine the quality of care for patients.
- Access: Telehealth significantly

“In the end, making telehealth expansion permanent is about ensuring that Medicare beneficiaries have choices in their care, whether it's in-person, via video, or through a phone call.”

improves access to health care services.

In the end, making telehealth expansion permanent is about ensuring that Medicare beneficiaries have choices in their care, whether it's in-person, via video, or through a phone call. As we move forward, the insights and advocacy of groups like the AUA Telehealth Task Force will be invaluable in shaping a telehealth landscape that is beneficial for all—patients, providers, and the broader health care community. ■

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ROBOTICS

Emerging Trends That Herald the Future of Robotic Surgical Simulation

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Robotic surgery is one of the most technically demanding fields that warrants a high level of expertise. In the present context of high societal expectations regarding quality of patient care and medicolegal and financial constraints, there are fewer opportunities to achieve competency in robotic urology operative techniques. Practice on cadavers as “the ultimate anatomical simulator” has been a trend since development of the first generation of surgical robots; however, ethical concerns, rising costs, operating in a bloodless field, and the need for specialized facilities has relegated it to footnote status for robotic simulation. The development of sophisticated virtual reality (VR) simulators with their automated computer-generated metrics was thought to be the final panacea; however, their lack of realistic surgical interfaces and tissue modeling, poor signal processing for complex events associated with surgery, and clinically irrelevant metrics have limited them to the initial phase of robotic training. This conundrum has left stakeholders with limited options on the ideal platform for robotic simulation that can realistically mitigate the burden of operative patient training. This article will focus on current emerging trends; three-dimensional printing including patient specific simulation, automatically generated clinically relevant metrics, and single-port (SP) robotic training.

The development of realistic physical models with strategic modifications at the Patrick C. Walsh Discovery and Learning Laboratory, Johns Hopkins Brady Urological Institute have given simulation education a new dimension.¹ A technique combining image segmentation, 3D printing technology, and polymer molding to create an immersive, procedural simulation platform for robotic urologic procedures

has opened a wide arena for the development of high-fidelity models for robotic urology training. This molding technique allows different materials replicating the various mechanical properties of human tissue to be layered into a single model.² For full immersion, the fabrication process also incorporates full procedure practice by the addition of surrounding organs and reproducing genuine operative metrics of performance (blood loss, tumor margins, ischemia time, urine leak, and the potential for complications), enabling practicing surgeons to obtain feedback and track performance. These features, which we have collectively referred to as “physical reality,” set this approach apart from any other simulation platforms that create realistic models to be used in training of complex urologic procedures.

Recently, the concept of patient-specific simulation as a strategy marks a distinct shift in the use of simulation from a platform that allows practice of a specific skill (ie,

training) to one that allows cognitive and/or physical rehearsal of a specific event (ie, a patient’s operation). Patient-specific simulation in any form allows surgeons to cognitively or physically practice, plan, and address potential problems related to a specific patient’s case, thus optimizing the real intervention.³ The benefits of this concept were demonstrated for robotic management of complex renal masses that would otherwise not undergo a nephron-sparing approach⁴ and is currently being developed for robot-assisted radical prostatectomy (RARP; Figure 1).

One of the most important advantages of surgical simulators is the opportunity they afford to acquire skills, gain confidence, and experience success before working with real patients, especially when the user’s clinical exposure is limited. However, if the simulator does not provide useful instructional feedback to the user, this advantage is significantly blunted by the need for an instructor to supervise and tutor

the trainee while using the simulator. Thus, the incorporation of relevant, intuitive metrics is essential for the development of efficient simulators. Equally as important is the presentation of such metrics to the user in such a way so as to provide constructive feedback that facilitates independent learning and improvement. From design to conception, clinically relevant objective metrics pertinent to the procedure were incorporated into the Walsh lab RARP⁵ and partial nephrectomy⁶ models as a means of quantitative method for assessment of surgical performance. Metrics included positive tumor margins, blood loss, and sensors that measure degree of tension on sensitive tissues (eg, neurovascular bundle) that could differentiate between various experience levels. Uniquely, a data set of these metrics collected from 35 expert urologists at the 2022 AUA conference were analyzed using a supervised machine learning and

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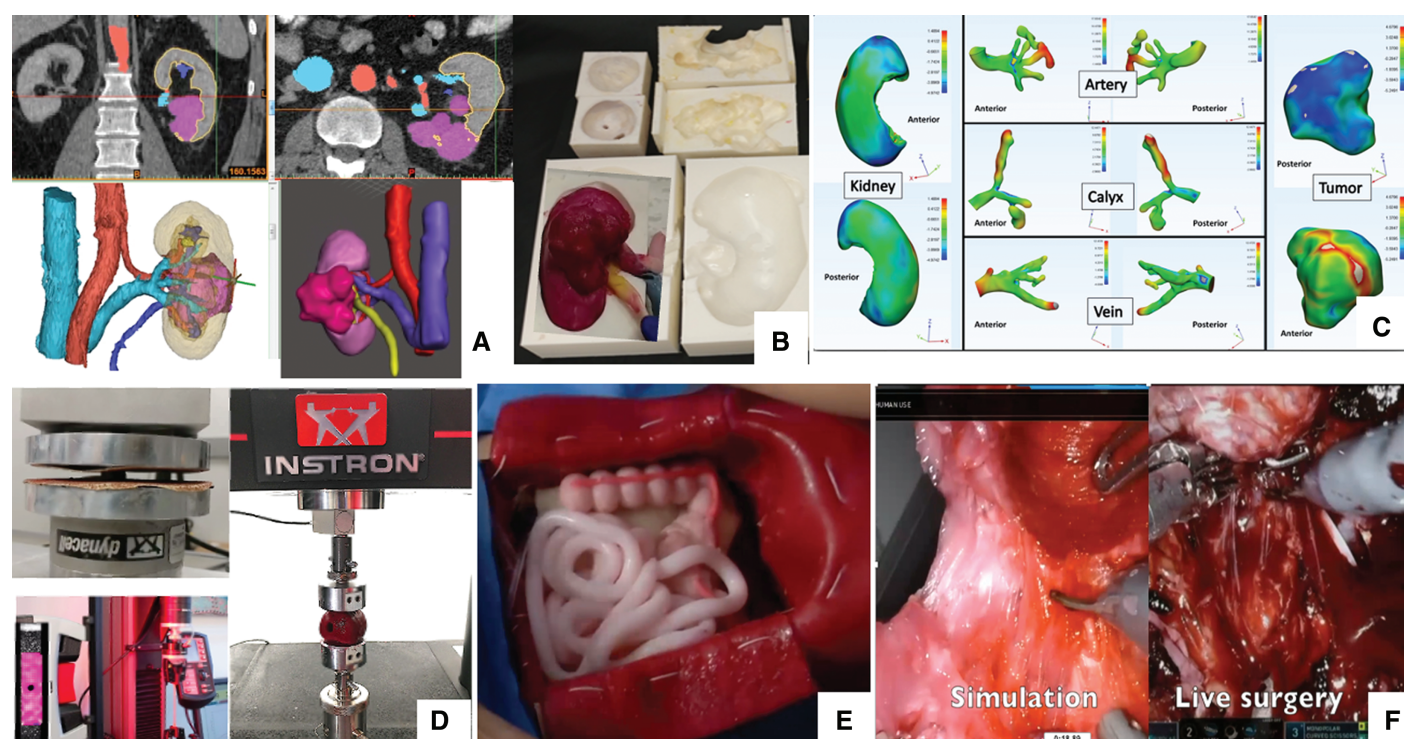


Figure 1. Patient-specific partial nephrectomy perfused hydrogel model. Computer design resulting from segmentation of patient CT scan (A); serial 3D-printed casts (tumor, renal hilum, renal parenchyma) with hydrogel kidney model containing tumor, renal vasculature, and major vessels (B); verification of the anatomical accuracy of the model in comparison to patient CT scan (C); mechanical testing of hydrogel to replicate human tissue (D); full procedure practice platform by the addition of surrounding organs (E); patient-specific simulation demonstrates excision of a tumor with bleeding (F; left live surgery, right simulated rehearsal).

EMERGING TRENDS THAT HERALD THE FUTURE OF ROBOTIC SURGICAL SIMULATION

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“This molding technique allows different materials replicating the various mechanical properties of human tissue to be layered into a single model.² For full immersion, the fabrication process also incorporates full procedure practice by the addition of surrounding organs and reproducing genuine operative metrics of performance (blood loss, tumor margins, ischemia time, urine leak, and the potential for complications), enabling practicing surgeons to obtain feedback and track performance.”

could accurately predict caseload with 96% AUC.⁷ This dataset is currently part of a mastery registry used to extract the essence of an expert's skillful maneuvers during nerve-sparing radical prostatectomy as a roadmap for novice learners. Crucially, researchers have demonstrated a correlation between VR simulation performance and live surgical RARP performance in the real operative environment thereby increasing its validity as a training modality. One study of 20 surgeons (14 of whom were experts) demonstrated a statistically significant correlation between VR needle driving scores and contingency recovery

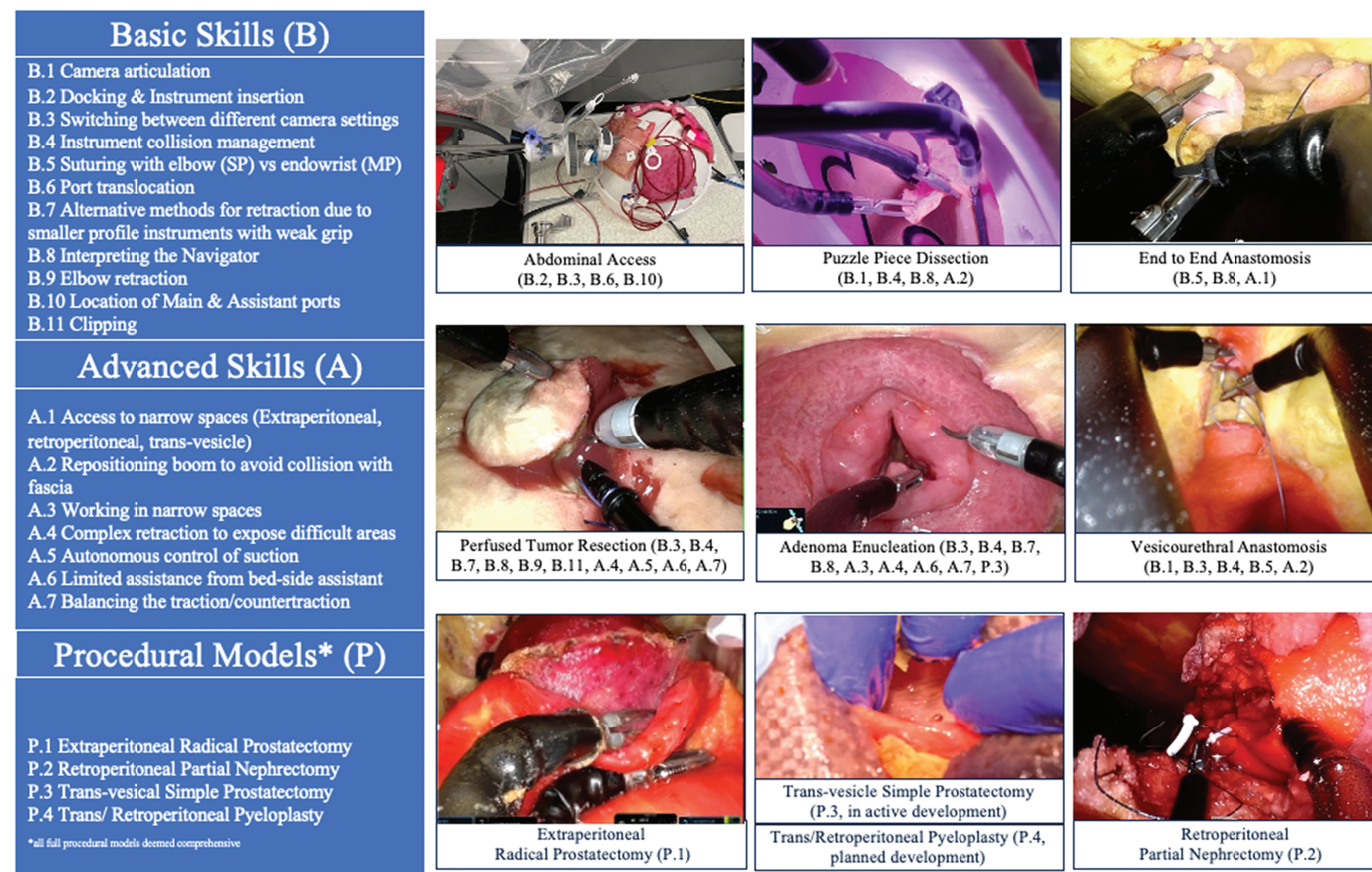


Figure 2. Fabricated models corresponding to the consensus-driven single-port (SP) specific skills. MP indicates multiport robotic surgery.

at 24 months after real RARP cases, with needle driving scores on the simulator correlating with live operative needle driving scores.⁸ Another study reported similar findings⁹ noting a positive association for expert surgeons for VR needle hold angle and driving smoothness skills and continence recovery at 3 months. Given that such technical skills influence postoperative outcomes, these findings could point towards VR being not only a training tool but also a key assessor of technical performance.

To date, there has been no coordination of available curricula, and the result is that many different curricula (with different outcome measures) exist for the same procedures. In addition, there is no uniform method for developing a curriculum. Why a trainee at one institution should have a completely different education and different assessment criteria than another at a different institution for the same surgical procedures is incomprehensible in the current data-sharing digital era. Using an Educational Design Framework,¹⁰ Kern's 6-step framework for curriculum development, a comprehensive curriculum for recently introduced SP robot

was developed. Twenty-two experts were invited to participate in a Delphi consensus-building approach regarding a needs assessment, components of a simulation-based SP curriculum, and assessment of surgical performance. The final curriculum included an online didactic platform with a video library, skills training platforms, post-curriculum proctoring, and evaluation to assess the transfer of skill to live cases. Expert consensus identified 11 basic and 7 advanced SP-specific skills critical to adoption of SP robotics. Using 3D printing and hydrogel casting, 6 hydrogel partial tasks and 4 procedures¹¹ were fabricated to address SP-specific skills and provide comprehensive skills training (Figure 2). Following preliminary validation this comprehensive curriculum will be implemented at the first SP masterclass hands-on training, May 2, 2024, at the AUA Annual Meeting in San Antonio, Texas, for the first 20 registrants. ■

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CASE REPORT

Video Endoscopic Inguinal and Simultaneous Pelvic Lymph Node Dissection in Penile Cancer

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Introduction

Penile cancer (PeC) is a disease that occurs rarely in northern countries. Inguinal dissemination is the most important prognostic factor in PeC. The number of lymph nodes removed and lymph node density are emerging prognostic factors in urologic cancers; however, evidence in PeC is provocative but poor. Patients with nonpalpable nodes with a risk for dissemination have about a 25% risk of metastatic dissemination; however, when lymph nodes are palpable, the incidence of metastasis rises above 50%.¹

Considering recent European Association of Urology guidelines, immediate inguinal lymph node dissection (ILND) after resection of the primary tumor is indicated in high-risk patients with nonpalpable nodes and for patients with palpable nodes and clinical stage < cN3 or skin invasion.² For patients with bulk inguinal disease, neoadjuvant chemotherapy with salvage surgery is the current recommendation. Pelvic lymphadenectomy is indicated in patients with more than 2 positive inguinal metastases without bulk pelvis disease.²

Due to the high morbidity reported in the open surgery era, few centers perform inguinal and prophylactic pelvic lymphadenectomy in the same operative act.³

Video endoscopic inguinal lymphadenectomy (VEIL) is becoming a popular option as it reduces surgical morbidity as compared to open ILND. There have been very few



Figure 1. Surgical room positioning. A, The surgical teams for inguinal and pelvic operations are ready to perform surgery on the right side. The video cart for the inguinal procedure is placed near the left limb, while the video cart for the pelvic procedure is placed near the right limb. B, Pelvic trocar marks and video endoscopic inguinal lymphadenectomy landmarks.

cases of severe morbidity when performing pelvic lymphadenectomy using laparoscopic or robotic approaches,^{4,5} and severe morbidity appears to be associated with N stage disease.⁴

We explore the possibility of performing simultaneous video endoscopic inguinal and pelvic lymphadenectomies, evaluating the efficacy and morbidity of this procedure.

Case Report and Preparation

A 54-year-old male has been diagnosed with penile squamous cell carcinoma at an advanced stage (cT3).

Initial examination showed the presence of 3 palpable nodes on 1 side of the groin, each measuring less than 2 cm in diameter (cN2). However, there were no adhesions to the skin and the nodes were mobile. A pelvic MRI scan was performed, which did not show any enlargement of the pelvic lymph nodes. Bilateral VEIL and simultaneous bilateral pelvic ILND (p-VEIL) were performed 1 month after partial penectomy (pT3 grade 3).

First-generation cephalosporin prophylactic intravenous antibiotics were administered routinely during hospital stays.

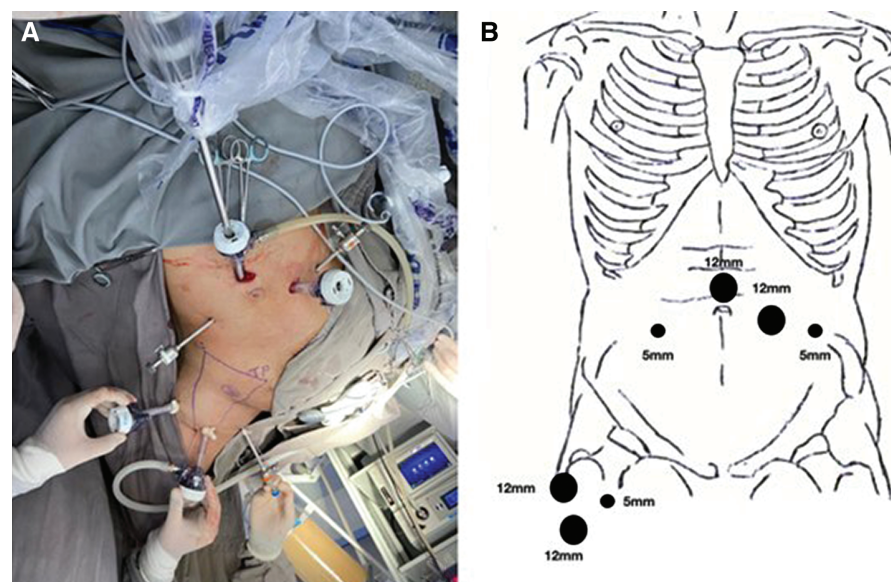


Figure 2. Trocar placement. A and B, Three trocars for the inguinal procedure and 4 for the pelvic procedure.

Relevant surgical steps of the p-VEIL procedure: one team is prepared for VEIL operation, and the other is prepared to perform laparoscopic pelvic lymphadenectomy (Figure 1).

Preoperative Workup

Palpable nodes were marked with ink on the skin. When nodes are difficult to find, such as in obese patients, the node is marked guided by ultrasound (Figure 1).

Patient Positioning and Lower Limb Preparation

VEIL: supine position with both lower limbs externally rotated, abduction of 45 degrees, and the knee joint slightly flexed. The video system must be placed on the opposite side of the limb under intervention at the level of the patient's waist. The surgeon stood on the right side of the leg, and the assistant stood on the left (Figure 1, A).

Pelvic lymph node dissection (PLND): standard laparoscopic transperitoneal PLND with Trendelenburg position.

Trocar Placement

VEIL: a 3-trocar configuration distal to the femoral triangle (Figure 2, B).

PLND: standard W-shape trocar placement (Figure 2, B).

Lymph Node Dissection and Evaluation

All VEIL steps were performed according to a previously reported study.⁵ Superficial and deep inguinal node resection (zones 1 and 2) were performed simultaneously to ipsilateral PLND (zone 3; Figure 3). Vacuum drainage was left in each inguinal region and will be removed when output is less than 50 mL. The patient was recommended to start

VIDEO ENDOSCOPIC INGUINAL AND SIMULTANEOUS PELVIC LYMPH NODE DISSECTION IN PENILE CANCER

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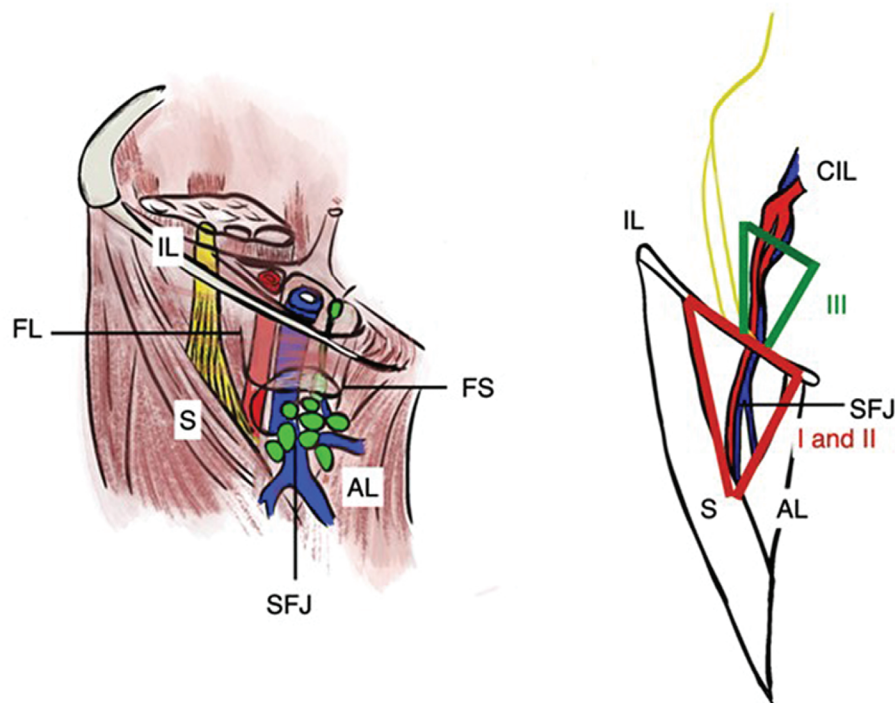


Figure 3. The illustration depicts the surgery templates and lymph node zones. Zone 1 pertains to the superficial femoral area, above the femoral sheath (FS) and fascia lata (FL). Zone 2 corresponds to the deep lymph node template, located near the saphenous femoral junction (SFJ). Zone 3 represents the standard extended pelvic lymph node dissection (LND) template (comparable to the extended LND technique used for prostate cancer). AL indicates adductor longus; CIL, common iliac vessels; IL, inguinal ligament; S, sartorius muscle.

walking early after the procedure and to wear antiembolic socks. Post-operative antibiotics were not prescribed.

A uropathology expert assigned the staging according to the 17th American Joint Committee on Cancer tumor-node-metastasis cancer staging system.

Results and Follow-Up

The procedure had an operative time of 180 minutes and blood loss of 150 mL. The hospital stay lasted 20 hours with no complications. Drainage was removed on the seventh postoperative day.

A total of 40 lymph nodes were removed (Figure 4). The histopathological evaluation confirmed 2 positive nodes with extracapsular extension in 10 retrieved at the right inguinal, and 1 positive in 12 retrieved at the right pelvic. On the left side, only 1 out of 8 inguinal nodes were positive without extracapsular extension, and 0 out of 10 were positive in the pelvic area. The pathological stage was 3 (pT3N3M0). Evidence of lymphocele or inferior members lymphedema was not observed.

Thirty days after the primary treatment, taxane-based adjuvant

chemotherapy was conducted. No radiation was applied.

Follow-ups were performed according to the European Association of Urology guidelines.² No progression was observed at 3 years of follow-up.

Discussion

Lymphatic spread to inguinal lymph nodes is the preferable dissemination route after local invasion and remains the most important prognostic factor in patients with penile cancer.⁶ Long-term survival worsens in superficial inguinal, deep inguinal, and pelvic involvement.

Lymph node dissection remains the gold standard staging and is potentially curative for lymphatic metastasis in PeC.²

The goal of lymphadenectomy is to remove the lymph nodes and achieve regional control staging, guide adjuvant treatment decisions, and improve survival. However, open ILND has a high incidence of complications, as high as 70%.⁶⁻⁸ Most are wound-related or lymph-related complications. Reduced skin morbidity is the most robust advantage observed in VEIL compared to open surgery series,⁷⁻¹⁰ followed by 3 times less lympho-

edema.¹ Over the past few decades, endoscopic inguinal lymphadenectomy has shown similar oncological outcomes to the open approach, with reduced morbidity in patients with palpable and mobile lymph nodes.⁷

The evidence supporting pelvic lymphadenectomy for PeC is weak, given that PeC is a rare disease. Professor Horenblas from Germany conducted the only retrospective study measuring the impact of prophylactic pelvic lymphadenectomy on patients with palpable 2 or more inguinal lymph nodes due to a high risk of metastasis.⁵ The probability of pelvic metastasis is 44% in patients with palpable inguinal lymph nodes, whereas pT2-4 represent a likelihood of metastasis of 30.3%, 44.2%, and 58.2%, respectively.⁶

In the era of open surgery, inguinal and pelvic procedures were performed in sequential stages due to morbidity. In the era of minimally invasive surgery, morbidity reduction allows both procedures to be performed simultaneously with better lymph node staging and morbidity no higher than the procedures performed separately. It is worth noting that the present work does not bring any new information about the indication of pelvic lymphadenectomy. However, it suggests that both procedures, pelvic lymphadenectomy and VEIL, can be performed simultaneously. This approach can lead to better lymph node staging in patients who are often difficult to follow up with due to social and cultural reasons. Compared to the laparoscopic approach, the advantages of robotics are still in study, with very few studies in PeC.¹¹

Long-term survival for stage 3 PeC is dismal. Fast multimodality treatment with surgery, systemic medications, and radiation is the best chance to improve survival in these patients. The IMPACT trial is ongoing to help provide better decision-making in these complex advanced cases.³

This preliminary experience suggests that p-VEIL is feasible.

The potential advantages may include: (1) removing more nodes with better identification of metastatic disease, (2) standardizing positive nodes in different areas: zone 1

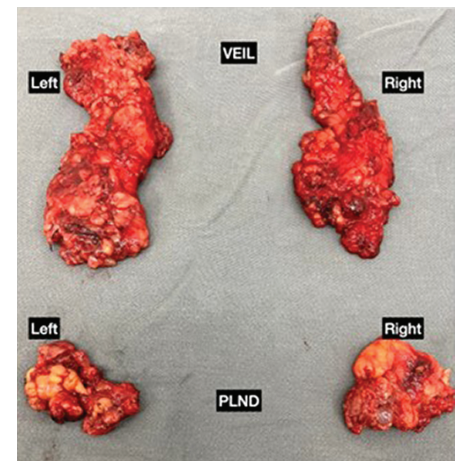


Figure 4. Specimens obtained from inguinal and pelvic surgical lymph node dissection. PLND indicates pelvic lymph node dissection; VEIL, video endoscopic inguinal lymphadenectomy.

(superficial inguinal, above fascia lata), zone 2 (deep inguinal, under fascia lata), and zone 3 (pelvic) to estimate prognosis²; this approach is justified in patients with a high risk for pelvic lymph node disease risk, and (3) offering 1-shot nodal staging, good recovery, and faster application of adjuvant treatments, especially for noncompliant patients or in cases of difficult access to health services. ■

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ROBOTICS

Robotic-Assisted Upper Urinary Tract Reconstruction: Tips and Tricks

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Upper urinary tract reconstruction was traditionally performed through an open approach. The integration of robotics in urology has revolutionized the field of upper urinary tract reconstruction, providing improved visualization, dexterity, as well as use of near-infrared fluorescence to aid in ureteral identification and assess tissue perfusion.

The key to successful upper urinary tract reconstruction is an extensive preoperative workup to understand the location and length of the ureteral defect (eg, cystogram, antegrade nephrostogram, retrograde pyelogram). The surgical approach is guided by the location, length, and etiology of disease as well as various patient factors including surgical history and prior radiation therapy. We outline common surgical options in the management of upper tract stricture disease (Figure). Despite thorough preoperative workup, surgeons may encounter unforeseen intraoperative findings, necessitating multiple techniques in their armamentarium to adapt to the variety of possible presentations.

In many cases of upper urinary

tract reconstruction, patients exhibit significant periureteral and retroperitoneal tissue reaction, increasing the difficulty of ureteral identification. Here we outline techniques that can be utilized intraoperatively to identify the ureter in such complex cases.

The patient positioning and port placement are largely dependent on the location and size of the stricture. The patient should be positioned to allow access to the urethra and the nephrostomy tube site, when applicable. Indocyanine green (ICG) is a fluorescent tracer that can be ad-

ministered intraluminally in a retrograde or antegrade fashion to aid in ureteral identification. When coupled with the near-infrared fluorescence (NIRF) imaging properties of the Firefly system, ICG can assist in the identification of the ureter when placed intraluminally and can help delineate the proximal and distal portions of the stricture.^{1,2} The benefits of ICG include its high signal to noise ratio, safety profile, and tissue penetration.³

In cases of dense scar surrounding the ureter, the ICG fluorescence may be difficult to visualize. Alternatively, the surgical assistant can perform retrograde ureteroscopy or antegrade pyeloscopy (through an existing nephrostomy tube tract) to assist with identification of the ureter. The Firefly system can be utilized to identify the light from the ureterscope. If the surgeon is unable to visualize the light from the ureterscope, the surgical assistant can gently deflect the ureterscope back and forth to aid in ureteral identification. The TilePro feature of the da Vinci surgical system can also be used to allow the surgeon on the console to simultaneously visualize the live images from the ureterscope as well as the robotic camera.⁴

A crucial factor in a successful reconstruction is ensuring the entire diseased portion of the ureter is identified and treated. Prior to com-

“The TilePro feature of the da Vinci surgical system can also be used to allow the surgeon on the console to simultaneously visualize the live images from the ureterscope as well as the robotic camera.”⁴

pleting the repair, the proximal and distal portions of the ureter should be evaluated. A ureterscope can be placed through the assistant trocar to evaluate the proximal and distal portions of the ureteral defect. Alternatively, each end can be cannulated to ensure there is no narrowing of the repaired segments of the ureter (eg, 10F red rubber catheter).

Common principles for any urologic reconstructive procedure include a tension-free anastomosis with well-perfused tissue. The previously described near-infrared fluorescence properties of the robotic system can also be used to evaluate tissue perfusion.⁵ Anastomotic tissue perfusion can be evaluated after intravenous administration of indocyanine green coupled with the NIRF properties of the Firefly system to help ensure healthy vascularized tissue is utilized (signified by a fluorescent color) to better prevent surgical complication/failure. In cases where there is concern of the viability of the tissue, adjunct maneuvers can be performed such as an omental/peritoneal flap wrap to improve vascularity.⁶

Numerous techniques have been described in the field of upper urinary tract reconstruction

“The Firefly system can be utilized to identify the light from the ureterscope. If the surgeon is unable to visualize the light from the ureterscope, the surgical assistant can gently deflect the ureterscope back and forth to aid in ureteral identification.”

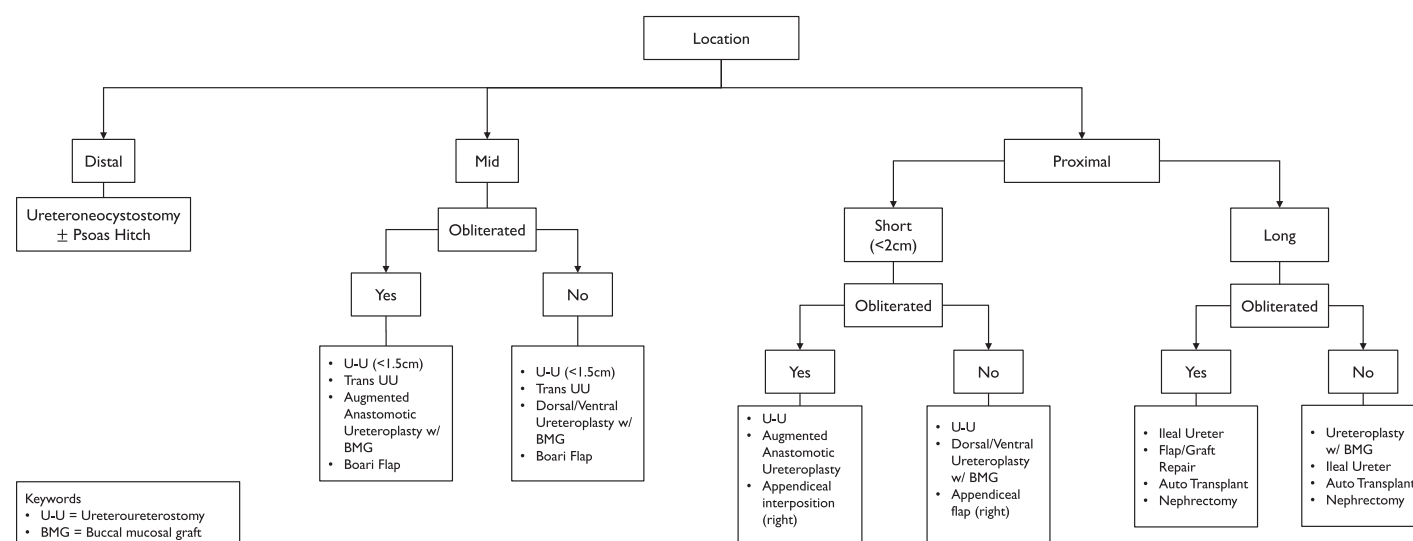


Figure. Decision-tree model outlining common management options for upper urinary tract stricture disease.

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ROBOTIC-ASSISTED UPPER URINARY TRACT RECONSTRUCTION: TIPS AND TRICKS

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including ureteroneocystostomy, ureteroureterostomy, appendiceal interposition, Boari flap, ileal interposition, etc. Novel techniques include the utilization of buccal mucosal graft in the reconstruction of complex ureteral strictures.⁷ Our technique using buccal mucosal graft in upper urinary tract reconstruction, which is currently under review, has yielded favorable outcomes. A total of 21 patients

underwent upper urinary tract reconstruction with buccal mucosal graft. Nine patients (42.9%) had prior abdominal/pelvic surgeries, and 6 patients (29.6%) with prior abdominal/pelvic radiation. Only 2 patients (9.5%) required subsequent procedures (percutaneous nephrostomy tube and revisional surgery).

The field of upper urinary tract reconstruction is constantly evol-

ing. Minimally invasive technology allows the utilization of NIRF to help identify ureteral strictures and assess tissue perfusion. Surgical techniques largely depend on the stricture location and length. Novel techniques have been described including the use of buccal mucosal graft in the repair of complex ureteral strictures. Continued research is needed to understand how to incorporate new

technological advancements in the field of upper urinary tract reconstruction. ■

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Missing Voices: Thematic Analysis and How It Can Inform Surgeons in Reconstructive Urology

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You are in pretty good shape compared to a lot of people, unless you want more surgery.

Anonymous¹

To a patient wearing 1 to 2 pads per day following curative prostatectomy, the statement above may have been accurate and intended to be reassuring advice coming from one's urologist. To the patient hearing it, however, it came across as a message of hopelessness and a lifetime of pads. That same man quoted above went on to undergo surgical intervention for stress urinary incontinence (SUI) with substantial improvement in quality of life (QoL) measures.¹

As reconstructive urologists, we are typically treating patients for QoL issues, making it vital to understand what is impacting the patients' QoL now and what options are on the table to improve it. This requires deep and individual insights into the patient's perspective. Patient perspectives can—at times frustratingly—be incredibly diverse and dynamic. A “win” for one patient may be worst case scenario for another, and may not be the same now as it will be in 6 months. Historically in reconstructive urology, we have utilized objective outcome measures (stricture-free based on 17F cystoscopy, pad-free after incontinence

surgery), but this view of outcomes is not necessarily patient centered. In order to understand patient-oriented outcomes, help inform the shared decision-making process, and ultimately provide patient-centered care, it is critical for us as reconstructive urologists to hear and understand the patient voice.

Qualitative and mixed methods (combination of quantitative and qualitative) research in reconstructive urology offers one avenue to capture patient perspectives in an otherwise clinician-oriented quantitative landscape. Specifically, thematic analysis is a type of qualitative research that seeks to identify common threads or themes collected from controlled patient interviews. Typically, cohorts of participants are interviewed to obtain their experience in the area of study (eg, men living with incontinence after prostate cancer treatment). These interviews are typically semistructured. All participants get the same questions but are also free to expand on topics or thoughts relevant to them. Interviewers are trained to allow and promote this loose structure to extract relevant dialogue, which is transcribed word for word. These transcriptions are then analyzed by trained personnel and given “codes” that emerge through an iterative process. Through an iterative 6-step process, representative thoughts from participants are grouped and analyzed.² The result is a cogent and understandable display of individual patient experiences that can also be combined with objective data

(eg, surgical outcomes) to produce high-quality, patient-centered, actionable research.

Thematic analysis and qualitative (including mixed methods) research informs and improves quantitative research by driving patient-centered quantitative research questions and lines of inquiry. For example, a recent review of 5 qualitative studies in pediatric urology highlights previously underexplored sexual and fertility challenges in the congenitalism population.³ Giving the patient a voice—particularly on sensitive issues (eg, financial toxicity, sexual health, fertility)—offers new avenues of study that can both expand existing research questions and better serve patients. Additionally, qualitative research may offer insight into gaps in existing quantitative research which may not be able to be answered with quantitative results. This may be particularly true in health care disparities work. Why are certain groups more likely to experience negative outcomes? What factors are we missing? These may be questions best answered, or at least initially explored, through qualitative data.

In addition, qualitative research can make an immediate impact. An improved understanding of the patient experience through thematic analysis may allow for a better understanding of the patient experience. Hearing that incontinence “impacts QoL,” for example, is different from reading a patient's take on this: “And being incontinent is terrible when you are wet all the time.... It totally affected

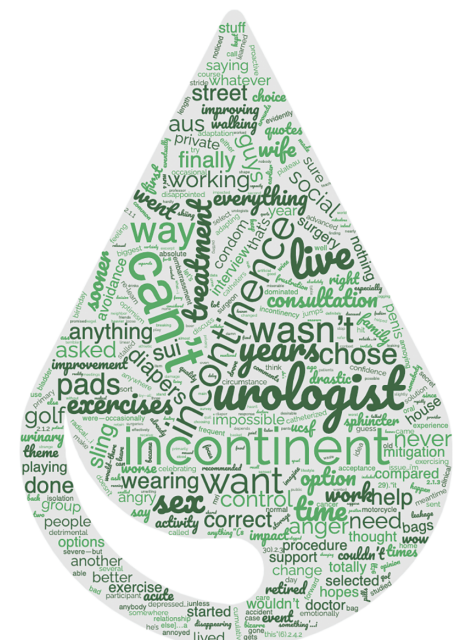


Figure. Word cloud from qualitative interviews for men with stress urinary incontinence when asked about their lived experience with incontinence.

my life. I didn't want to go out, I couldn't do anything. So, it was very disabling for me, being incontinent. It was horrible (Figure)."⁴ In addition, qualitative analysis can help us understand patients' perspectives on drivers of treatment decisions, which can help us as providers to improve shared decision-making in treatment discussion with patients. It can even help incorporate the patient perspective into the measures we use to measure treatment success.

Arguably one of the most important impacts of this type of

→ Continued on page 21

MISSING VOICES: THEMATIC ANALYSIS AND HOW IT CAN INFORM SURGEONS IN RECONSTRUCTIVE UROLOGY

→ Continued from page 20

work to the practicing urologist is the immediate clinical applicability of qualitative research to daily practice. The results of thematic analysis can be thought of as deconstructed patient counseling. If a reconstructive urologist can hear the organized and often harrowing patient experience through qualitative research, it can be immediately clinically actionable in counseling, patient decision-making assistance, and normalizing challenging topics. Direct patient quotes are “talk tracks” for patient counseling—you can provide your patients a voice on lived experience by proxy. For example, we ask all patients living with SUI about SUI and sex, particularly oral sex, because of the following quote: “No, I wouldn’t say [sex and incontinence] were separate at all. Oral sex is impossible for me to receive while I have urinary incontinence. I mean only in the most bizarre circumstance would that be possible, right?”¹ One can imagine that even a patient with low objective measures of incontinence could be tremendously bothered if it precluded important aspects of life like continued sexual intimacy. These patient perspectives can result in implementation of clinical practice changes that benefit patients.

Qualitative research offers an alternate and complimentary path, particularly in spaces where not all wins look alike. However, given the general lack of experience of researchers in analyzing, interpreting, and reviewing qualitative research, it can be difficult to get qualitative research published. As such, it is critical that we provide training to emerging investigators and clinicians about qualitative research methodologies so that we can promote the incorporation of qualitative research into the reconstructive urologists’ armamentarium. This training will also benefit reconstructive urologists applying for research funding, given that grant submissions are increasingly focused on incorporating a qualitative component in order to ensure that research is patient facing. We encourage investigators to include qualitative analyses in their research portfolios, and call

for journals to increase review and publication of qualitative and mixed methodology studies in order to provide this critical perspective. We hope patient-centered research efforts will become more commonplace, giving a voice to the patient, and leading to

improved patient-centered care in the process. ■

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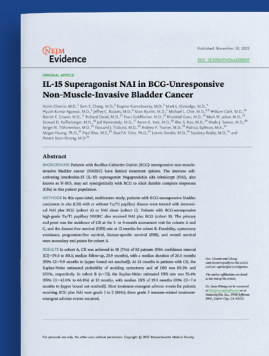
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SCAN ME

ROBOTICS

Robotic Surgery and Artificial Intelligence: A Synergistic Nexus

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Artificial intelligence (AI) continues its march into the mainstream of clinical urology, with new applications regularly appearing in different facets of patient care. As robotic-assisted surgery (RAS) has become ubiquitous in our specialty, our horizons have broadened to see this platform as a “jumping-off point” for future disruptive and digital technology in surgical care. The exponential growth of AI capabilities seen in other high-reliability industries has only been minimally integrated into daily patient care, its pace appropriately slowed by concerns around transparency and accountability. As with autonomous vehicles, the immediate impact on human safety in this space cannot be overstated, and any steps toward bringing AI into the operating room must be approached with an abundance of caution. Despite these concerns, a monumental shift in how we provide surgical care to patients with urological conditions has appeared on the horizon, and AI’s incursion into the world of RAS is now inevitable.

RAS is the perfect medium to facilitate AI’s introduction to the operating room (Figure). Originally designed as a means of providing surgeons with the ability to carry out minimally invasive surgery with advanced dexterity, control, and visualization, the robotic platform’s embrace of innovation is entwined in its very DNA. The interface between human and machine provides the ideal setting for the utilization of

machine learning as a tool to enhance surgical education, patient safety, and operative efficiency. Early successful integration into these fields has been widely published and celebrated in the academic community. Evidence demonstrates that AI can accurately classify surgeons by their level of skill, matching expert surgeon evaluations with a high level of accuracy.¹ This has important implications for important educational initiatives such as competency-based medical education, an approach to residency training that demands high volume, frequent assessments of performance.² The use of AI to reliably provide an appraisal of a trainee’s surgical skill using only audiovisual inputs will provide a level of objectivity and scalability that has been identified as a limitation of reliance on human-expert evaluation alone. Beyond identification of trainees in need of remediation, AI also has shown promise as a vehicle for providing objective, performance-based feedback to trainees in the simulation lab,³ an undoubtedly underutilized educational resource at most institutions. While these efforts originally used machine learning trained on kinematic data derived from the robotic console or physical instrument trackers,⁴ there has been a shift toward computer-vision AI approaches in this area that rely solely on video data taken from the robotic endoscope to make predictions. This unencumbered approach to AI-augmented skills assessment appears to be generalizable across different surgical techniques and procedures, and the near-complete lack of reliance on human data labeling will facilitate the dissemination of this technology.

Perhaps the most compelling use of AI in this space is its potential to improve and even standardize patient outcomes; specifically, the real-time recognition of threats to patient safety intraoperatively. Recognition of surgeon errors is becoming possible in real-time, providing surgical teams with the ability to correct deviations in procedural steps

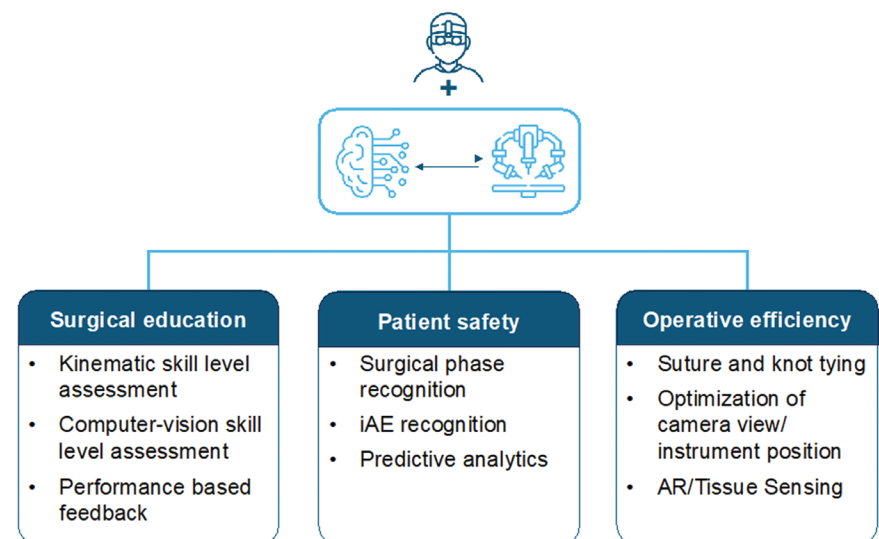


Figure. Artificial intelligence applications for robotic surgery. AR indicates augmented reality; iAE, intraoperative adverse events.

that may go otherwise overlooked, but also mitigate the potential harm that results from intraoperative adverse events through immediate recognition.⁵ Perhaps even more remarkable is the demonstration that algorithms using computer vision can accurately identify surgical phases using video data alone.⁶ When intraoperative adverse events mitigation and surgical phase detection are aligned, it seems we are close to the advent of real-time, predictive analytics in the operating room—that is, the ability for AI to guide surgeons through an operation, a true “second set of eyes” that can help surgeons with complex intraoperative decision making.⁷

While still in its infancy, automation of robotic tasks using AI is being explored as both a means of reducing human error and increasing surgical efficiency. While the idea of a surgical robot carrying out multiple steps of an operation has not yet been realized, there are examples in the literature of robotics and AI being married to allow for the execution of simple tasks such as suturing and knot tying.⁸ It is important to remember that while many would imagine a scene from science fiction, with an autonomous machine carrying out unsupervised advanced procedures with impossible speed, there are more subtle surgical actions whose automation is a

more realistic endeavor in the near future. These include optimization of instrument position and camera view to allow for more precise and efficient surgeon movements, integration of patient imaging with augmented reality, and tissue interaction sensing (ie, tension, torque, etc).⁸ The most immediate uses of AI in RAS do not need to involve surrendering control of the operation to a machine, but rather using this technology to improve our ability to carry these operations out consistently and safely.

The future is bright for RAS, and the permeation of AI into our daily lives in and out of the operating room will only grow. Robotic surgery is now becoming the new standard for many surgical procedures,⁹ and the shift from “robotic-assisted” to “AI-assisted” surgery is just a matter of time (and clear regulations!!). It is imperative that as clinicians we are the stewards of this technology, questioning not only the accuracy and precision of these algorithms, but the ethical aspects of introducing what is essentially another decision-maker into the sacred physician-patient relationship. There are obvious barriers that need to be overcome on the path to implementing AI into routine surgical care on a wide scale, least of which

ROBOTIC SURGERY AND ARTIFICIAL INTELLIGENCE: A SYNERGISTIC NEXUS

→ Continued from page 22

are the medicolegal ramifications of any reliance on these algorithms to determine how we perform in the operating room or make determinations related to the competency of a fellow surgeon or trainee.¹⁰ It is our hope that our early forays into this space are thought provoking and hypothesis generating, and as this technology becomes more tangible for all clinicians, we can continue

to explore how AI can improve the well-being of both our patients and ourselves. ■

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Developing an Algorithm on Multiport and Single Port Use for Robotic Prostate and Kidney Surgery

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Introduction

With the advent of the da Vinci Single Port (SP) platform, robotic surgeons now have a new tool in their arsenal to individualize approach in a variety of procedures. The versatility of the SP robot has been demonstrated by numerous surgeons, with descriptions of prostatectomy, partial and radical nephrectomy, reconstructive ureteral procedures, as well as cystectomy, inguinal lymph node dissection, and retroperitoneal lymph node dissection.¹⁻⁵ SP has allowed for fur-

ther regionalization of surgery and reclaiming of spaces that were previously standard areas of surgery for urologists, namely the retroperitoneum and extraperitoneal space.⁶

Currently there are no society-based guidelines on indications for SP vs multiport (MP) robotic platforms. While there has been a robust interest in adopting the former for both facile and challenging cases, for the early career urologist or early SP adopter, navigating the SP system may prove to have a significant learning curve.^{7,8} As such, we believe that it is prudent to establish an algorithm on when to perform surgery with the SP platform vs MP, as well as whether to approach the target organ transperitoneally, retro-/extraperitoneally, or transvesically. We describe our decision tree below.

Radical Prostatectomy

There are 2 main factors determining whether to perform MP or SP prostatectomy for prostate

cancer: prostate size and risk stratification (Figure 1). For patients with high-risk disease based on AUA guidelines, MRI findings, or higher Gleason scores (Grade Group [GG] 4, Gleason score ≥ 8), preferentially opt for the traditional MP transperitoneal radical prostatectomy to enable careful dissection of the prostate, but more importantly, to facilitate the appropriate lymph node dissection. Patients with higher-risk disease, regardless of prostate size, merit more radical surgery due to lymphadenectomy, which is more appropriately rendered through the MP transperitoneal approach during this early phase of adoption.

For patients with low- and intermediate-risk disease, prostate size becomes the primary driver for robotic approach. In men with glands smaller than 80 g, the SP extraperitoneal or transvesical approach is appropriate for GG1 and GG2 disease, as the need to perform a lymph node dissection is based on surgeon's own personal practice patterns, but typically less common. The SP extraperitoneal approach is preferred for GG3 disease to enable lymph node dissection. In men with larger prostate glands (>80 g), a history of prior abdominal surgery dictates SP extraperitoneal approach. In patients with larger glands and no significant prior abdominal surgery, the MP transperitoneal approach is preferred.

Simple Prostatectomy

The SP platform has allowed for direct docking into the blad-



Figure 2. Air docking for robotic simple prostatectomy.

der for prostate surgery (Figures 2 and 3).⁹ As such, the preferred approach for simple prostatectomy is SP transvesical, reserving the MP transperitoneal approach for patients with very high BMIs or larger prostate sizes (Figure 4). Additionally, for those surgeons starting off with SP, beginning with prostates that have larger intravesical components is recommended for ease of handling with the more delicate SP instruments.

Partial and Radical Nephrectomy

Since the first comparisons of SP and MP partial nephrectomy from SPARC (the Single Port Advanced Research Consortium), uptake of SP for renal surgery has increased tremendously over the last year.¹⁰ As the kidney is a retroperitoneal organ, there has been increased interest in utilizing the SP platform to better exploit this space. There have been numerous described approaches, including the traditional

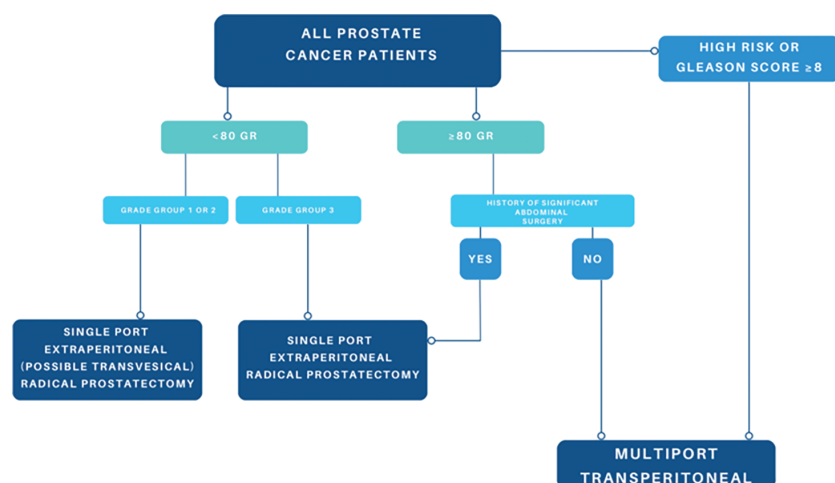


Figure 1. Robotic radical prostatectomy algorithm. GR indicates grams.

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DEVELOPING AN ALGORITHM ON MULTIPORT

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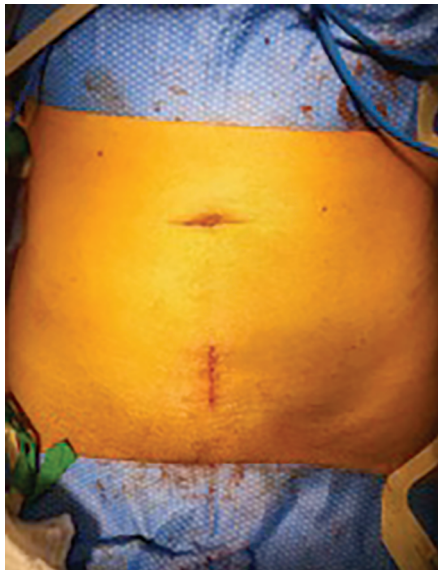


Figure 3. Location of suprapubic incision for transvesical prostatectomy.

flank approach. However, more recently, a low anterior access (LAA) has been described using multiple acronyms (modified Gibson, SARA, SPAM, STAB). Located where one might find a classic mini Gibson or McBurney incision (Figure 5), the LAA allows flexibility to approach both the peritoneal cavity and the retroperitoneum (Figure 6).

As per the above algorithm (Figure 7), the primary driver dictating approach for renal masses is tumor

complexity as well as volume of visceral fat around the kidney. In patients undergoing radical nephrectomy, we uniformly perform the standard MP transperitoneal approach given ease and efficiency. The SP approach, however, has been described for radical nephrectomy as well, particularly for surgeons proficient with the SP platform.¹¹

For partial nephrectomy, we examine tumor complexity using R.E.N.A.L. (for radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, location relative to polar line) and PADUA (Preoperative Aspects and Dimensions Used for Anatomical Classification) nephrometry scores. If a tumor is determined to be high complexity, then an MP transperitoneal approach is preferred. For low- and intermediate-complexity tumors, the presence of significant visceral or retroperitoneal fat then determines whether SP can be performed. MP is preferred in patients with significant perirenal fat due to stronger axial rigidity of the robotic arms and wider retraction capabilities, as compared to the SP counterparts. In patients with low-/intermediate-complexity

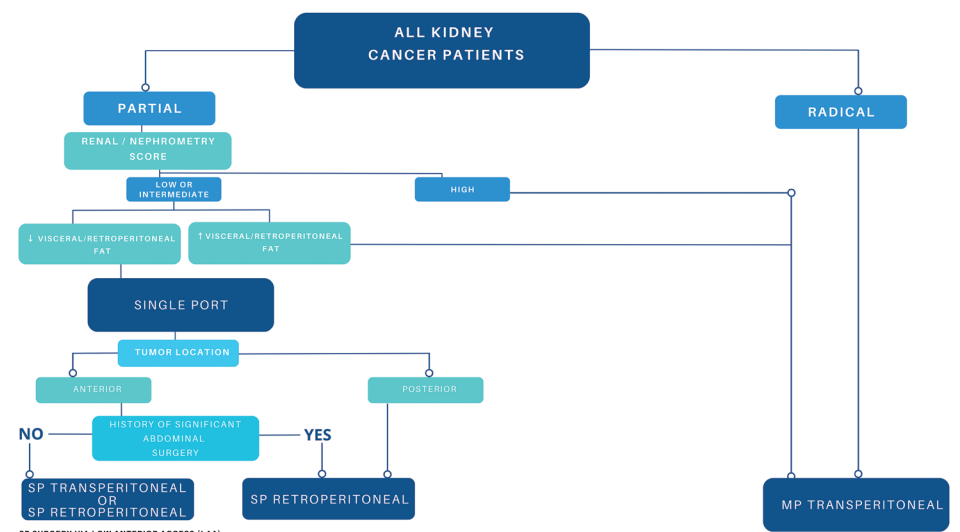


Figure 7. Robotic partial and radical nephrectomy algorithm. MP indicates multiport; RENAL, radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, location relative to polar line; SP, single port.

tumors with less visceral and retroperitoneal fat, tumor location (anterior or posterior) and history of prior abdominal surgery dictates transperitoneal vs retroperitoneal approach. Although LAA can easily access anterior tumors via a retroperitoneal approach, in the early learning phase the same access for transperitoneal approach is an excellent option. For posterior tumors, the SP retroperitoneal approach is preferred. For anterior tumors with no prior abdominal surgeries, then both SP transperitoneal and retroperitoneal approaches can be performed. For anterior tumors with prior abdominal surgeries, then the SP retroperitoneal approach should be preferentially performed.

While we presented a current algorithm on decision-making for patients between robotic platforms and approaches, these represent our unique practice guidelines more than dogma. There are numerous factors to consider when evaluating a patient with a renal mass, or high-risk prostate cancer, or even a complex ureteral stricture. Our aim is not to find ways to supplant MP with SP. Rather, as the market expands with newer models of the da Vinci robotic platform, or even novel competitor robotic systems, we should be ready to customize the care of our patients utilizing the strengths of all available technologies and the unique clinical characteristics of our patients. Whereas in the past we only had 1 tool to help perform robotic surgery, now looking toward the future there will be a multitude of options that

urologists must critically appraise for the well-being of their patients. We hope this paper will serve as a blueprint for early adopters of SP, as well as other robotic platforms, to help them navigate the tumor and patient characteristics that ultimately dictate appropriate surgery. ■

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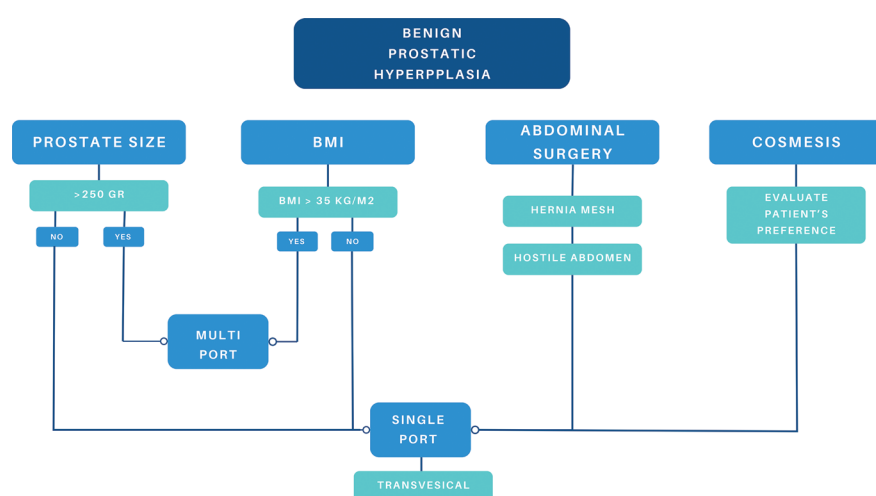


Figure 4. Robotic simple prostatectomy algorithm. GR indicates grams.

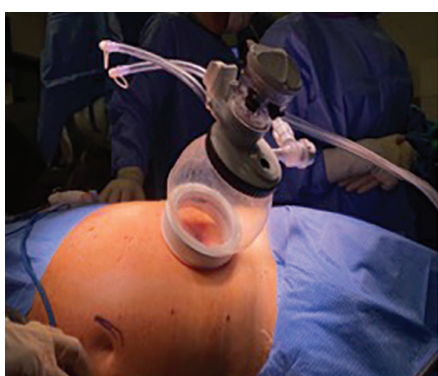


Figure 5. Air docking for low anterior access.

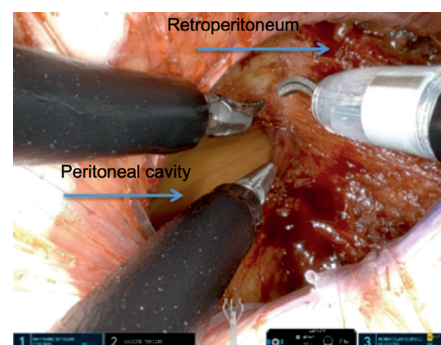


Figure 6. Low anterior access allows for entry into peritoneal cavity and retroperitoneum.