American Urological Association

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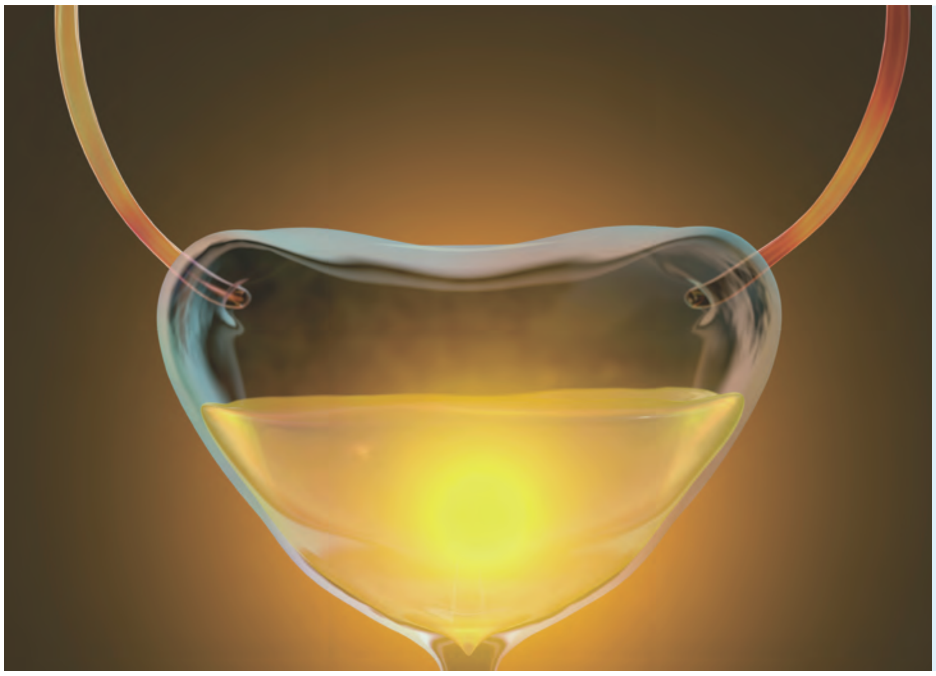

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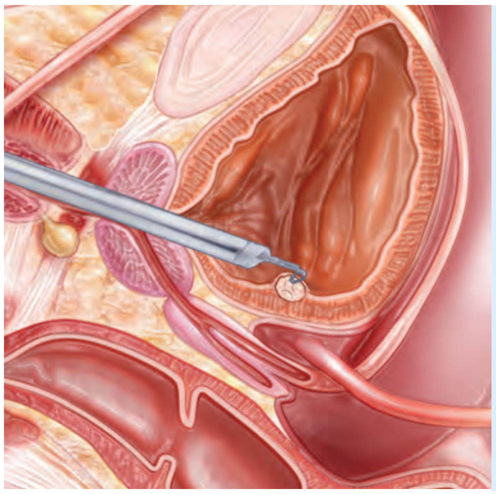

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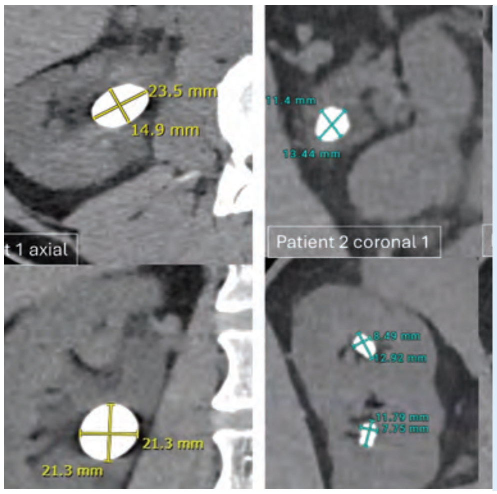


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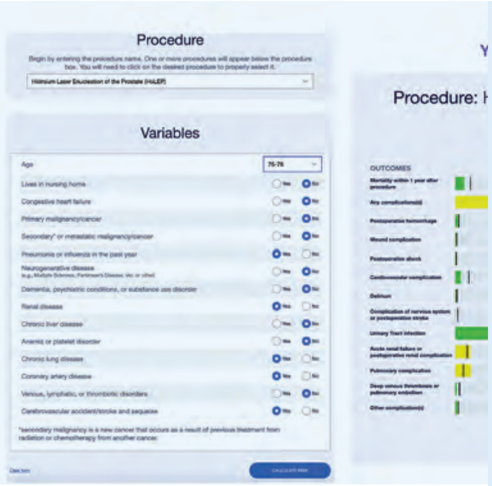


## Bridging the Gap: Frailty and the Future of Age-Friendly Urologic Care

Anne M. Suskind, MD, MS, FACS, URPS

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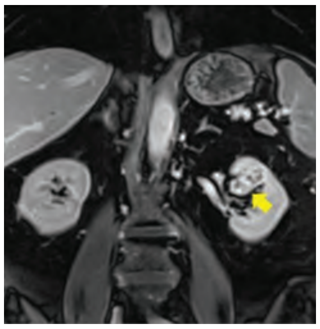



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XTANDI is indicated for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR), metastatic castration-sensitive prostate cancer (mCSPC), or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

**XTANDI is the first and only ARi approved for patients with nmCSPC with high-risk BCR[1]**

# NEW DATA

## in nmCSPC with high-risk BCR can help empower treatment decisions

**Visit XtandiHCP.com for the latest trial data**

**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 ≥ 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 neoadjuvant/adjuvant therapy to treat prostate cancer ≤ 36 months in duration and ≥ 9 months before randomization or a single dose or a short course (≤ 6 months) of hormonal therapy given for rising PSA ≥ 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]

**Metastasis-free survival was defined** as the time from randomization to whichever the following occurred first: 1) radiographic progression per BICR or 2) death.[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.

**Dysphagia or Choking** Severe dysphagia or choking, including events that could be life-threatening requiring medical intervention or fatal, can occur due to XTANDI product size. Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Consider use of a smaller tablet size of XTANDI in patients who have difficulty swallowing. Discontinue XTANDI for patients who cannot swallow capsules or tablets.

### Adverse Reactions (ARs)

In the data from the five randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 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 (≥ 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®
(enzalutamide)
40 mg tablets | 80 mg tablets

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

# Harness the power of XTANDI + GnRH therapy*

## XTANDI + GnRH therapy* significantly improved metastasis-free survival vs placebo + GnRH therapy*[1]

**METASTASIS-FREE SURVIVAL** (primary endpoint): 58% reduction in the risk of metastasis or death with XTANDI + GnRH therapy* (n = 355) vs placebo + GnRH therapy* (n = 358) (HR = 0.42 [95% CI, 0.30-0.61]; *P* < 0.0001)[1]

- 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* arm[1]

**New data: OVERALL SURVIVAL** (prespecified, alpha-protected, key secondary endpoint; not included in the US Full Prescribing Information for XTANDI): 40% reduction in the risk of death with XTANDI + GnRH therapy* (n = 355) vs placebo + GnRH therapy* (n = 358) (HR = 0.60 [95% CI, 0.44-0.80]; *P* = 0.0006)[4]

- Number of events: 73 (20.6%) with XTANDI + GnRH therapy* and 111 (31.0%) with placebo + GnRH therapy*[4]
- Median overall survival was not reached in the XTANDI + GnRH therapy* arm (95% CI: NR, NR) and 117.5 months in the placebo + GnRH therapy* arm (95% CI: 109.8, NR)[4]

**In the EMBARK trial, the adverse reactions** that occurred at ≥ 5% (Grade 1-4) or ≥ 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]

## Scan the QR code for NEW overall survival data

**ARi**, androgen receptor inhibitor; **BICR**, blind 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.

***Leuprolide.**[1]

†Includes multiple terms.[1]

## Important Safety Information (Cont'd)

### Adverse Reactions (ARs) (Cont'd)

placebo-controlled study of chemotherapy-naive 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-naive 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 ≥ 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, hypophosphatemia, 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; 2025. **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):1453-1465. **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 [published online August 12, 2021]. BMJ Open. 2021. Accessed February 5, 2025. https://bmjopen.bmj.com/content/bmjopen/11/8/e046588.full.pdf. **4.** Astellas. XTANDI. Data on File.

astellas
Pfizer Oncology


MAT-US-XTD-2025-00489 10/25

Xtandi®
(enzalutamide)
40 mg tablets | 80 mg tablets

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.

#### Dysphagia or Choking

Severe dysphagia or choking, including events that could be life-threatening requiring medical intervention or fatal, can occur due to XTANDI product size. Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Consider use of a smaller tablet size of XTANDI in patients who have difficulty swallowing. Discontinue XTANDI for patients who cannot swallow capsules or tablets.

### 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 |

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

| | XTANDI (N = 800) | | Placebo (N = 399) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **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 |
| **Infections and Infestations** | | | | |
| Upper Respiratory Tract Infection[5] | 11 | 0 | 6 | 0.3 |
| Lower Respiratory Tract And Lung Infection[6] | 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 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 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **General Disorders** | | | | |
| Asthenic Conditions[2] | 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** | | | | |
| Dizziness[3] | 11 | 0.3 | 7 | 0 |
| Headache | 11 | 0.2 | 7 | 0.4 |
| Dysgeusia | 8 | 0.1 | 3.7 | 0.0 |
| Mental Impairment Disorders[4] | 6 | 0 | 1.3 | 0.1 |
| Restless Legs Syndrome | 2.1 | 0.1 | 0.4 | 0 |
| **Respiratory Disorders** | | | | |
| Dyspnea[5] | 11 | 0.6 | 8 | 0.6 |
| **Infections and Infestations** | | | | |
| Upper Respiratory Tract Infection[6] | 16 | 0 | 11 | 0 |
| Lower Respiratory Tract And Lung Infection[7] | 8 | 1.5 | 4.7 | 1.1 |

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

| | XTANDI (N = 871) | | Placebo (N = 844) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **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 |
| **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 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **Overall** | 94 | 39 | 94 | 38 |
| **General Disorders** | | | | |
| Asthenic Conditions[2] | 32 | 1.6 | 23 | 1.1 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Back Pain | 19 | 2.7 | 18 | 1.6 |
| Musculoskeletal Pain[3] | 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 Infection[4] | 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 Nonmetastatic 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 |

**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 (%) |
| **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 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Fractures[4] | 6 | 1.0 | 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.

**EMBARK: XTANDI versus Placebo in Nonmetastatic CSPC Patients with High-Risk BCR**

EMBARK 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 Treatment[1]** | | | |
| 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 | 18.0 | 16.6 | 9.4 |
| Range, months | 1.4 – 87.9 | 3.4 – 83.0 | 2.0 – 77.7 |
| **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 a 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, dysphagia (including choking related to XTANDI product size)

*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 strong CYP3A4 inducers. If the coadministration of XTANDI with a strong CYP3A4 inducer 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] ≥ 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 ≤ 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 (≥ 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 ≥ 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 ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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# Benign Prostatic Hyperplasia and Overactive Bladder: Prostate Surgery or Sacral Neuromodulation?

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*Two roads diverged in a wood, and I–*
*I took the one less traveled by,*
*And that has made all the difference.*
**Robert Frost**, The Road Not Taken

The optimal treatment of overactive bladder (OAB) in men remains a persistent and underaddressed challenge in urology. When the underlying cause of a man's refractory lower urinary tract symptoms (LUTS) is not clearly obstruction from benign prostatic hyperplasia (BPH), we often find ourselves navigating in uncertainty. Each clinician may approach this population differently, with most steering patients toward BPH surgeries and others toward procedural OAB management. Treatment selection is influenced by a combination of clinical inputs, symptom profiles, and comorbidities as we struggle to navigate complex clinical scenarios with limited data to guide decision-making.

> "In the era of minimally invasive surgical therapies, waterjet ablation, and laser enucleation of the prostate—alongside traditional transurethral resection of the prostate—we can offer tailored options that prioritize sexual function, recovery time, or durability."

## Rationale for a BPH-First Approach

It is no surprise that prostate procedures are the path most traveled. In the era of minimally invasive surgical therapies, waterjet ablation, and laser enucleation of the prostate–alongside traditional transurethral resection of the prostate–we can offer tailored options that prioritize sexual function, recovery time, or durability. Across these approaches, 70% to 75% of men report meaningful symptom improvement, highlighting their efficacy.[1]

Among men who remain symptomatic after prostate surgery, outlet reduction may not have been the wrong treatment, it may simply have been an insufficient one. Regret after BPH surgery has been reported in 10% to 33% of men with dissatisfaction driven by lack of efficacy, de novo symptoms, or procedural complications.[2] However, rates are lowest following enucleation, a therapy typically reserved for men consistently with the most to gain from outlet reduction, given their larger prostates, worse baseline symptoms, and more profound obstruction. These data suggest that insufficient benefit from BPH surgery may be related to suboptimal procedure choice (eg, minimally invasive surgical therapies when transurethral resection of the prostate or laser enucleation of the prostate may be warranted). In other dissatisfied men, BPH surgery may have been necessary but not adequate absent "adjuvant" OAB therapy.

This is not to imply that every patient needs a well-selected BPH surgery with or without OAB therapy. Some men clearly fail to benefit because they would have been better off without an operation. Yet BPH outcome studies may steer more patients and providers toward BPH surgery, overestimating real-world benefit due to exclusion of patients with neurologic disease, catheter-dependent urinary retention, history of radiation therapy, or limited surgical fitness.[3]

> "BPH outcome studies may steer more patients and providers toward BPH surgery, overestimating real-world benefit due to exclusion of patients with neurologic disease, catheter-dependent urinary retention, history of radiation therapy, or limited surgical fitness.[3]"

## Patients Who May Benefit From an OAB-First Approach

Once a prostate procedure is performed, it cannot be undone. The introduction of new symptoms or the exacerbation of storage dysfunction may limit therapeutic flexibility. In practice, we aim to select patients who may be better suited for an OAB-first intervention by identifying those men at high risk for (1) poor functional outcomes, (2) perioperative or long-term surgical complications, or (3) dissatisfaction from surgery related to anticipated side effects.

1. Greater risk of persistent LUTS or retention[3-5]:
   a. Age >70 years
   b. Prostate size <40 to 50 mL, particularly when paired with bladder contractility index <100
   c. Postvoid residual >250 mL
   d. Detrusor overactivity amplitude >40 $cmH_2O$, particularly at volumes <250 to 350 mL
   e. Bladder compliance <20 $mL/cmH_2O$
2. Greater risk of surgical complications[4,6]:
   a. Frailty
   b. Neurologic disease
   c. History of pelvic radiation
   d. Stricture disease
   e. Mandatory anticoagulation
3. High risk of dissatisfaction, even with a successful outcome[2]:
   a. Professed aversion to de novo urinary incontinence or sexual dysfunction

In a subset of men, proceeding with a BPH-first approach could lead to additional treatment, exacerbation of symptoms, or procedural dissatisfaction. We must therefore do our best to identify patients for whom an OAB-targeted approach will offer durable symptom relief–or at the very least, identify those patients for whom the downsides of BPH surgery are not acceptable.

## Procedural OAB Management in Men With BPH/LUTS

Unfortunately, treatment options and data remain limited for men with BPH/LUTS who have failed low-risk OAB therapies–such as behavioral modifications, medications, or tibial nerve stimulation–yet may be better served by an OAB-first approach.

### *Chemodenervation*

OnabotulinumtoxinA injection in men with BPH has been associated with urinary retention, UTI, gross hematuria, and dysuria, with high discontinuation rates.[7,8] However, onabotulinumtoxinA may be an effective treatment in men with lesser degrees of outlet obstruction or who are willing to accept intermittent catheterization with improved storage symptoms as a desirable alternative to accepting the potential negative outcomes and morbidity of BPH surgery.[9]

### *Sacral Neuromodulation*

Most men bristle at the concept of needing to catheterize, even as they struggle to cope with fairly severe symptoms. Therefore, sacral neuromodulation (SNM) may be a

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more appealing option than chemodenervation for those who are not solid candidates for BPH-first approaches. Although men have lower initial success rates with SNM than women, more than 50% may nevertheless experience sustained benefit beyond 1 year.[10] Furthermore, in contrast to prostate surgery, SNM via percutaneous nerve evaluation allows for trialing therapy without an incision or potentially even anesthesia. Although clearly limited by lack of data and the inevitable "what if" of forgoing BPH surgery, SNM does represent a compelling option for those with LUTS with uncertain contributions from prostatic obstruction or heightened intolerance to BPH surgery risks and side effects.

### Conclusion

The dominant paradigm of BPH surgery for male LUTS is effective for many patients. However, in men without obvious contributions from prostatic obstruction to symptom bother or with predictors of poor response to prostate procedures, OAB-directed therapies such as SNM may offer a more appropriate path forward. Often being less invasive and reversible, OAB-first therapies should be considered for selected men with storage-symptom predominant BPH/LUTS. As our diagnostic tools and treatment options evolve, so too must our willingness to explore "the road less traveled" for this complex patient population. ■


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# Enhanced Recovery After Surgery Pathways for Transurethral Resection of Bladder Tumor Surgery


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Transurethral resection of a bladder tumor (TURBT) is a surgery commonly performed by urologists for both diagnosis and treatment of bladder cancer. It is utilized repeatedly in management of nonmuscle-invasive bladder cancer, which comprises 75% to 80% of all bladder cancer cases.[1] While TURBT is generally thought to be a minimally invasive, "well-tolerated" surgery, many patients experience symptoms such as pain, urinary dysfunction, or anxiety from the procedure.[2,3] Due to the need for repeated surgeries, living with bladder cancer can pose significant deterioration of health-related quality of life, impacting not only physical but also psychological, social, and financial domains (Figure).[4,5]

Given the profound impacts on patients in multiple areas of life, TURBT can benefit from a streamlined patient-centric intervention. Enhanced recovery after surgery (ERAS) protocols have been utilized widely in cystectomy care and even ambulatory ureteroscopy; however, they have not been implemented previously for TURBT.[6,7] For this reason, our group performed a 159-patient prospective needs assessment, proposed the first ever ERAS protocol for ambulatory TURBT, and executed a randomized clinical trial on 100 patients to validate this protocol.[8,9]

### Needs Assessment to Characterize Toxicity of Ambulatory TURBT

A multicenter prospective cohort study enrolled 159 patients to evaluate symptom burden and defined toxicity associated with ambulatory TURBT.[8] Collecting data across 5 perioperative time points, the assessment found substantial morbidity in a subset of patients, particularly among women and those with ≥ T2 disease. Suprapubic pain, dysuria, and genital pain were significantly elevated in the highest symptom tertile and persisted up to 1 week post-operatively. Post-TURBT hematuria occurred in 79.3% of patients, and bladder spasms, incontinence, constipation, and anxiety were common. Notably, 10.1% of patients required unplanned postoperative care, and qualitative feedback underscored gaps in patient education and perioperative support. These findings highlight the need for enhanced recovery pathways and tailored preoperative counseling.

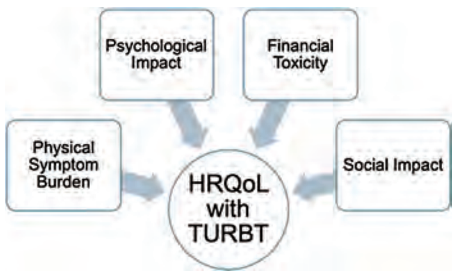


**Figure.** Factors influencing health-related quality of life (HRQoL) for patients undergoing transurethral resection of bladder tumor (TURBT).

### ERAS Protocol Development

The ERAS protocol for ambulatory TURBT was designed based on patient and provider input. Specifically, we utilized the results of the needs assessment, a review of literature, and our institutional experience with prior ambulatory TURBT protocols.[8-10] The protocol aimed at enhancing the perioperative experience in 3 phases: preoperative, intraoperative, and postoperative interventions. In the preoperative period, patients were given a detailed patient-centered handbook on TURBT perioperative care. It includes clear explanations of bladder cancer, the TURBT procedure, recovery expectations, catheter care (with photos and QR codes), medication guidance, follow-up instructions, and patient tips—with links to trusted bladder cancer resources for further support.

In addition to the handbook and preoperative education, key interventions included both medical and surgical considerations. Medically speaking, a bowel regimen was given preoperatively and intraurethral lidocaine and other analgesic interventions were given intraoperatively, and deep extubation was requested from the anesthesia provider to reduce bleeding risk. Surgical considerations included minimizing the number of times the scope is passed through the urethra,

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## ENHANCED RECOVERY AFTER SURGERY PATHWAYS

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assessing for excess compression of the urethral meatus by resectoscope, and examining resection sites carefully for bleeding while the bladder was draining. Postoperatively, for patients discharged with a catheter, the protocol ensures hands-on instruction and written materials for at-home catheter care and removal, with extended teaching compared with standard of care. Throughout the process, implementation instructions were provided to anesthesia, nursing, the surgical resident, and the attending physician in the surgery.

### Validation: The ERAS for Ambulatory TURBT: Enhancing Bladder Cancer Care Trial

EMBRACE (Enhancing Bladder Cancer Care) is a prospective, randomized controlled trial that enrolled 100 patients undergoing ambulatory TURBT, randomized to "usual care" vs the ERAS protocol.[11] The primary outcome was the Quality of Recovery-15 (QoR-15) questionnaire administered on the day of surgery and postoperative day 1, which evaluates recovery in multiple domains: pain, physical comfort, functional anatomy, emotions, and psychological support. Secondary outcomes included the UTI-symptom questionnaire, pain scores (numeric rating scale), incontinence rates and degree of hematuria on postoperative day 1, and 30-day complications.

Patients in the ERAS group had a 14-point higher mean QoR-15 score on the day of surgery and postoperative day 1 (136.9 vs 125.0; $P < .001$). Pain and urinary symptoms were also reduced: ERAS patients reported lower rates of urethral pain (2.4 vs 4.0), penile/vulvar pain (1.3 vs 2.7), dysuria (2.6 vs 4.4), and urinary incontinence (14% vs 41%, $P = .02$). Additionally, ERAS participants had fewer outpatient visits within 30 days and lower UTI-symptom questionnaire scores (5.8 vs 12.0, $P < .001$). These improvements were sustained even in first-time TURBT patients.

### Conclusions

The EMBRACE trial represents a pivotal step forward in optimizing the perioperative experience for patients undergoing ambulatory TURBT. By addressing a previously overlooked gap in bladder cancer care, this ERAS protocol demonstrated measurable improvements in recovery and symptom burden for patients. Notably, the implementation of simple, scalable interventions—such as patient education, multimodal analgesia, and structured care pathways—resulted in higher QoR-15 scores, reduced pain, and fewer unplanned encounters. In summary, ERAS for TURBT offers a compelling evidence-based strategy to enhance quality of life across the bladder cancer continuum. Broader adoption may not only improve patient recovery but also reduce the cumulative burden of repeat TURBT procedures on patients and health systems alike. ■


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## RADIOLOGY CORNER

# Identification of Renal Segmental Vein Invasion


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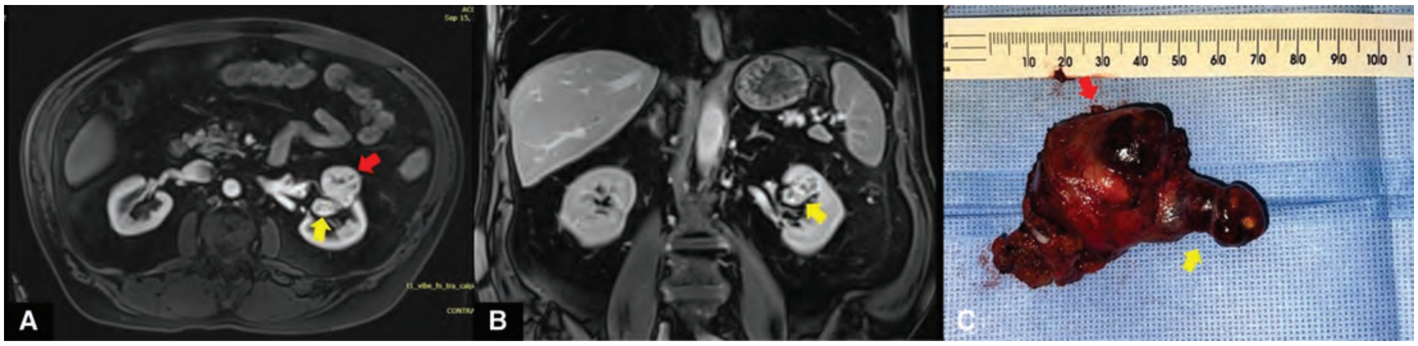


**Figure.** MRI scan and gross specimen. A, Axial T1 postcontrast arterial phase showing the mass (red arrow) and the knuckle extending into deeper vascular structures (yellow arrow). B, Coronal T1 postcontrast arterial phase. C, Gross examination showing 5.6-cm mass with tumor thrombus extension.

### Case Presentation

A 60-year-old man was incidentally found with a 3.9-cm left renal mass during a metastatic workup of T-cell lymphoma in the left groin. He had a history of gastroesophageal reflux disease, hypertension, and obesity (BMI of 39 kg/m$^2$). He underwent radiation for the lymphoma and was placed on active surveillance for the renal mass. In 14 months, the mass grew to 5.6 cm, and he was referred for surgical evaluation. The left upper pole renal mass was moderately complex (nephrometry score of 8a). On the T1 postcontrast phase, there was clear extension of a knuckle of the tumor into the renal sinus fat vs a segmental vein branch, with effacement of the upper pole calyces (parts A and B of Figure). Metastatic workup was negative. With the anticipated need for future chemotherapy for lymphoma and a baseline renal function of 1.3 mg/dL (estimated glomerular filtration rate of 56 mL/min), the patient was offered a robotic-assisted left partial nephrectomy to maximally preserve his renal function.

Intraoperatively, the patient was positioned in the lateral decubitus position for a standard intraperitoneal approach. The gonadal vein and adjacent lumbar veins were taken to allow for identification and skeletonization of the renal artery. Dissection within Gerota's fascia was performed, and the tumor was demarcated using ultrasound, which also confirmed extension into a deeper vascular structure. An off-clamp approach with a broad dissection was performed initially to find the edge of the tumor pseudocapsule before diving deeper. Two bulldog clamps were placed on the renal artery, but with an anticipated entry into a major vascular sinus, a third bulldog clamp was placed on the vein. With an enucleative resection, the tumor was followed deep into a large open vascular channel. A wide approach freed all but the vascular extension. Lifting up on the mass, the deeper sinus was

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## IDENTIFICATION OF RENAL SEGMENTAL VEIN INVASION

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opened to allow us to completely pull out an intact ~2-cm segmental renal tumor thrombus (part C of Figure). The segmental vein was closed with 3-0 V-loc sutures before coming off clamp at 39 minutes. After hemostasis was confirmed, a renorrhaphy was performed. The patient was discharged on postoperative day 1. Final pathology revealed a stage pT3aN0 clear cell renal cell carcinoma (RCC) with negative surgical margins. Postoperatively, renal function was preserved, with the creatinine level unchanged at 1.3 mg/dL. The patient was offered but declined adjuvant pembrolizumab because he was more focused on the likely need for further therapy for his lymphoma. He had no recurrence of his RCC on surveillance imaging for 1 year. He unfortunately had relapse of his T-cell lymphoma and was treated with brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone, and he subsequently received a bone marrow transplant 14 months after his partial nephrectomy. He died 2 years postoperatively from septic shock in the setting of neutropenic fever.

### Discussion

In this index case, renal segmental vein invasion was suspected on MRI due to a phallic-like extension off the tumor into the deeper sinus. The identification of venous invasion has traditionally been a difficult aspect of accurately staging cT3a tumors. Various studies have attempted to quantify the sensitivity of identifying segmental renal vein invasion tumors on CT scans, reporting sensitivities ranging from 59% to 88%[1] and 86%.[2] Conversely, another study notes that in a population of patients receiving partial nephrectomy for pT3a tumors with venous extension, in only 25% of cases was the venous component identified preoperatively.[3] Renal vein enlargement in itself is not a specific finding for tumor thrombus because the hypervascularity of RCC as opposed to mass effect can contribute to enlargement, and alternatively, tumor thrombus does not necessarily cause enlargement of the vein.[4] Given the excellent resolution of MRI, it may particularly

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> "Despite improvements in imaging, high suspicion is needed for cases with central extension. Using intraoperative ultrasound can confirm this suspicion, and an enucleative resection can follow the tumor extension into vascular spaces."

## IDENTIFICATION OF RENAL SEGMENTAL VEIN INVASION

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be employed to assess venous involvement to define the presence and extent of tumor thrombus.[4] The sensitivity of tumor thrombus detection is higher with MRI at up to 89%, with 1 study demonstrating 100% sensitivity of MRI detecting tumor thrombus invading the distal renal vein.[5,6] Because MRI may be more sensitive than CT for detecting perinephric and renal sinus fat invasion, the staging accuracy of MRI for T3a tumors is generally superior to the CT modality.[5] Despite improvements in imaging, high suspicion is needed for cases with central extension. Using intraoperative ultrasound can confirm this suspicion, and an enucleative resection can follow the tumor extension into vascular spaces. We advocate for clamping the main renal vein during these cases to allow a near bloodless field for confirmation of complete tumor removal. ■


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# Bridging the Gap: Frailty and the Future of Age-Friendly Urologic Care

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Chronological age and comorbidity have long been the standard tools used for assessing whether a patient is "fit" for surgery. However, this basic formula fails to account for the confounds of older adulthood, a highly heterogeneous population that spans a wide spectrum of physical and cognitive phenotypes, wherein age and comorbidity alone have been shown to be poor predictors of surgical outcomes.

Incorporation of frailty can help to address the discrepancy in this unbalanced equation. Frailty is defined as a physiologic state or condition describing a multisystem reduction in reserve capacity that results in a vulnerability to external stressors that leads to an increased risk of adverse health outcomes including falls, decreased mobility, loss of independence, hospitalization, disability, and death.[1] It is important to appreciate that frailty is a distinct concept from disability or comorbidity. While these concepts may overlap in certain individuals, frailty in and of itself is a complex, multidimensional, and even cyclical state[2] that should be considered an important independent factor for morbidity. It is additionally important to note that frailty is not a binary condition. The term "prefrail," which describes a state between frail and not frail, is often overlooked but may be extremely significant. The prefrail state acknowledges that frailty exists as a spectrum and further supports the multidimensionality of this condition.[1]

There is a growing body of literature that strongly endorses the link between frailty and increased postoperative complications specifically among urological patients. One study of 95,108 individuals undergoing 21 different types of urological procedures–spanning from cystectomy to hydrocele repair–used the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to examine the impact of frailty on postoperative outcomes. It found that increasing levels of frailty, as measured by the NSQIP Frailty Index (FI), were associated with a higher likelihood of 30-day postoperative complications; the adjusted odds ratio was 1.28 (95% CI 1.21-1.36) for NSQIP FI 0.09, and the adjusted odds ratio was 1.74 (95% CI 1.64-1.85) for NSQIP FI ≥ 0.18 compared with NSQIP FI 0 (no frailty).[3] These findings were echoed in another study using NSQIP data involving patients undergoing cystectomy and applying the modified FI, whereby those who were frail demonstrated increased rates of 30-day postoperative complications and 30-day mortality; a modified FI of ≥ 2 (indicative of frailty) had rates of 14.6% vs 8.3% for Clavien grade 4 or 5 complications and 3.5% vs 1.8% for 30-day mortality, respectively.[4] Several additional studies in oncology patients (including breast,

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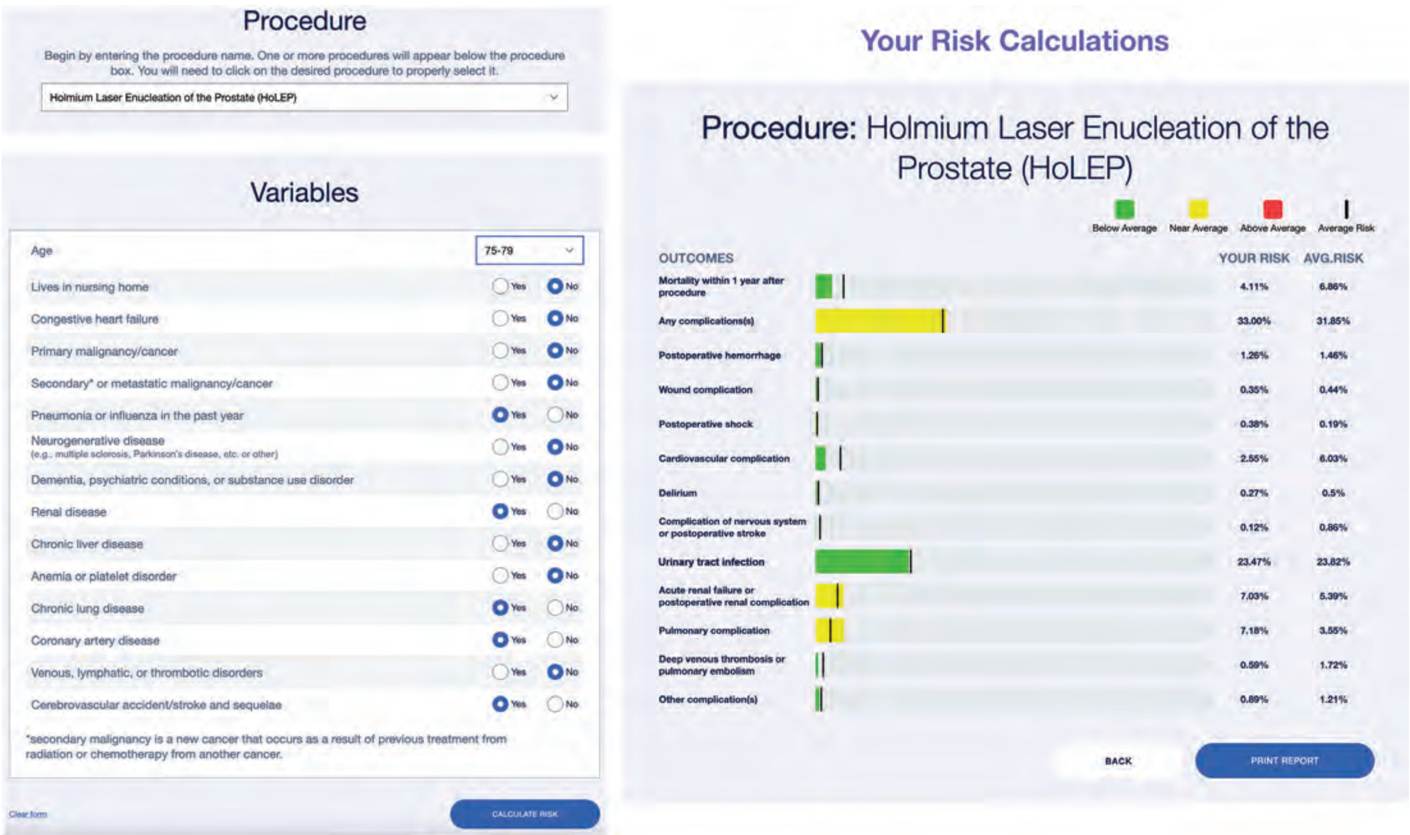


**Figure.** Example input and output from the Urologic Surgery for Older Adults Risk Calculator for a hypothetical patient considering undergoing holmium laser enucleation of the prostate. Avg. indicates average.

## BRIDGING THE GAP: FRAILTY AND THE FUTURE OF AGE-FRIENDLY UROLOGIC CARE

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colorectal, gynecologic, head and neck, pancreas, gastrointestinal, and urological) also demonstrated that frailty is a well-established risk factor for postoperative complications, chemotherapy intolerance, disease progression, and death.[2]

Despite its apparent utility in predicting postoperative complications and mortality, frailty is seldom systematically measured in clinical practice. As urologists, this is of critical importance, since approximately 45% of patients seeking urological care demonstrate prefrail or frail phenotypes, which otherwise may go unmeasured and unnoticed and yet have the potential to negatively impact outcomes.[5] While > 70 different measures of frailty exist for both research and clinical use,[2] measures such as the Timed Up and Go Test are scalable for use in everyday clinical practice to measure frailty in real time, enabling it to be incorporated into individualized clinical decision-making. The Timed Up and Go Test is a parsimonious measure of physical function and frailty, which captures multiple dimensions of frailty. It requires no special equipment or training, and it takes less than a minute to complete in the office setting.[5] Additional tools that can be used to measure frailty in the clinical setting include, but are not limited to, the Clinical Frailty Scale,[6] Fried Frailty Index, and the Edmonton Frail Scale.

Surgical risk calculators that incorporate measures of frailty can further assist in preoperative evaluation of urological patients. Our laboratory developed the Urological Surgery for Older Adults Risk Calculator, which is a novel and publicly available risk calculator for adults > 65 years of age undergoing commonly performed urological procedures including surgery for bladder outlet obstruction in men,[7] pelvic organ prolapse and stress urinary incontinence in women,[8] and suprapubic tube placement (http://uroarc.ucsf.edu).[9] This calculator was built using a 100% sample of Medicare claims data for patients undergoing these procedures in the United States and incorporates components of frailty into an individualized risk assessment that can be used in clinical practice to assist in perioperative risk stratification and decision-making (Figure). More tools that are focused on urological patients and procedures are needed to further inform these important treatment decisions.

> "The Timed Up and Go Test is a parsimonious measure of physical function and frailty, which captures multiple dimensions of frailty. It requires no special equipment or training, and it takes less than a minute to complete in the office setting.[5]"

As urologists, there is an opportunity not only to incorporate measures of frailty into the daily clinical care of older adults but also to become more educated and adept in caring for the growing aging population in general. Research on age-friendly care has shown that the most important attributes to consider in caring for older adults are the 4 *M*'s: what Matters (the patient's articulation of their goals, wishes, needs, and experiences), Medication (understanding side effects and polypharmacy in this population), Mentation (understanding the risk factors for dementia, depression, and delirium), and Mobility (physical function, activities, improving strength, and physical "fitness").[10] Measurement of frailty aligns with the mobility aspect of the 4 *M*'s, and collectively, this useful framework emphasizes the importance of a more holistic approach to caring for older adults undergoing urological care.

Ultimately, as urologists, we occupy an important space at the convergence of surgical and nonsurgical care for this important patient population, many of whom are frail and all of whom would benefit from a more individualized and holistic approach. To this effect, not only do we need to re-evaluate how we deliver care to older adults, but there is also a need to incorporate frailty measures into our daily practice and to move beyond only studying 30-day complications and mortality to incorporating outcomes that matter most to patients. Collectively, these steps are essential to move the field of urology forward as an age-friendly specialty equipped to care for a growing population of older adults. ■


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# Stone Volume: Is It the Future or Just Fancy Software?

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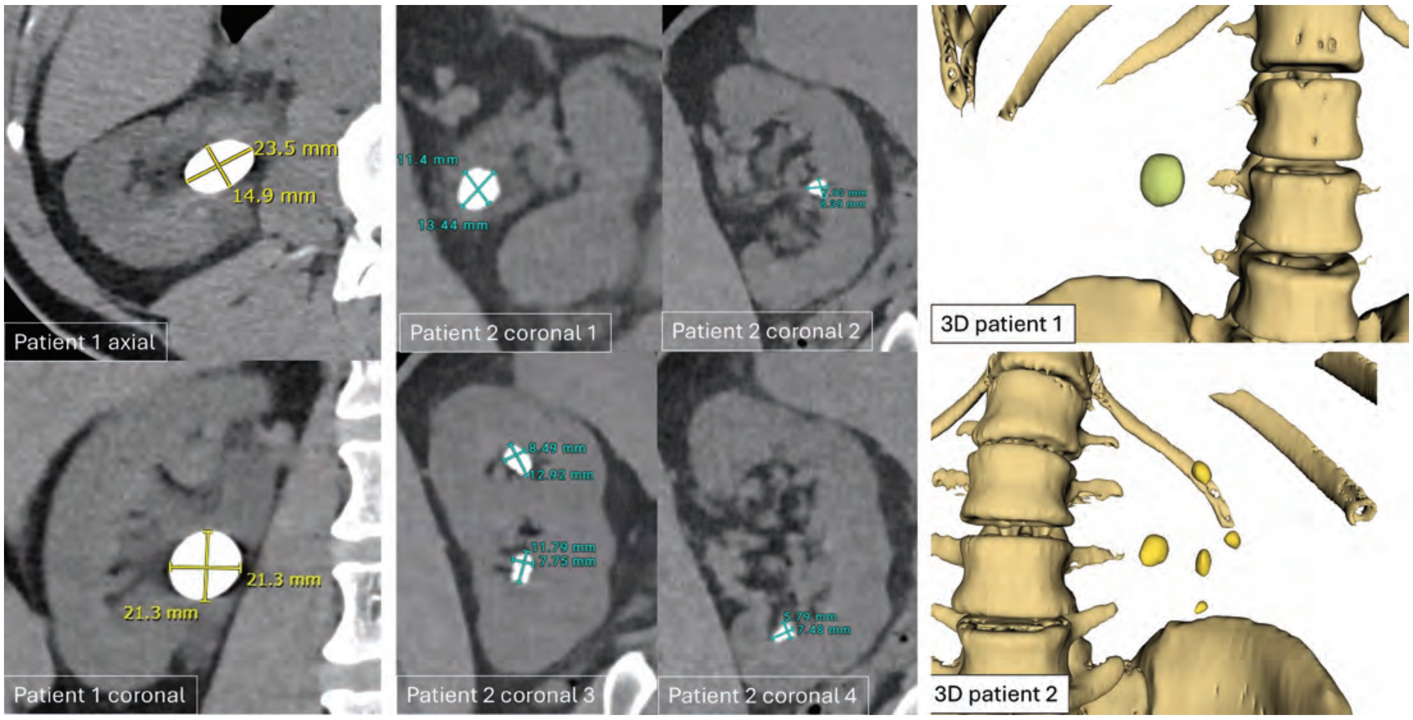


**Figure.** Noncontrast CT images (left and center panels) and 3D rendering (right panels) of 2 patients with renal stones.

Kidney stones are 3D shapes, and both scientifically and intuitively we know that volume is the most accurate representation of a 3D shape. Historically, stones could only be identified by ultrasound or fluoroscopic images, and thus, only linear measurements of stones were available. As clinicians, we have therefore always relied on a linear measure of stone burden to decide on the most appropriate intervention for each of our patients. This is reflected in our guidelines, which still use a linear measure when discussing and recommending stone treatments.[1,2] The implementation of CT for urinary stone disease assessment, which has been the gold standard for urinary stone disease management for over 2 decades, has allowed us to measure stones in multiple dimensions and measure or calculate the stone volume.[3,4] Despite these advancements, a decade ago, volume was the least-used measure of stone burden in published literature on stone treatments, used in only 4% of the manuscripts.[5] Today this has improved slightly, but remains underutilized with only approximately 20% of papers using volume to report stone burden (T. Tailly, unpublished data). Although volume is very likely the best metric to represent stone burden, whether or not it is also a better predictor of the treatment outcomes was, until recently, insufficiently known.

Geraghty et al[6] conducted a systematic review of the published literature comparing the predictive accuracies of different stone burden metrics on clinically meaningful outcomes for all stone procedures. The meta-analysis identified that, across the models assessed, stone volume is more accurate at predicting stone-free status overall and specifically for stones treated by extracorporeal shock wave lithotripsy (ESWL) or retrograde intrarenal surgery (RIRS). For percutaneous nephrolithotomy (PCNL), however, this could not be demonstrated. While the AUCs for volume and linear size may be statistically significantly different for ESWL and RIRS, the values are quite close and may not hold a clinical significance (0.69 vs 0.66 and 0.79 vs 0.75, respectively). Unfortunately, there were not enough data to evaluate the predictive accuracy of different stone burden metrics for operative time and complications. Interestingly, while stone burdens are usually largest for PCNL, the association between volume and patient outcomes was the least researched for this treatment modality, and the AUC values demonstrating its predictive accuracy for stone-free status were lowest. This is likely due to the increased impact of stone complexity and other parameters on the procedure outcomes. While we so strongly believe that volume is a better measurement than linear size, why are these differences not larger? Why do the data not support that volume is in fact a better predictor of stone-free status than size?

To demonstrate that stone burden alone is insufficient as a predictor of the treatment outcomes, the left and center panels of the Figure show the CT images with commonly reported linear measurements of 2 patients with different stone burdens, and the right panels of the Figure show the same stone burdens in 3D renderings of those CT images. One patient has a solitary stone of approximately 4000 mm³, while the other patient has multiple stones for a total stone burden of approximately 2000 mm³, with cumulative stone diameters (CSD) of 23 and 54 mm, respectively. In contrast to the stone burden in the first case, the stone burden in CSD of the second case is more than double, while it is only half the volume of the first case. Based on CSD, the second case should be the longer case with the lower probability of becoming stone free, while based on volume it should be the opposite.

> "Maybe we are caught in a vicious cycle: we do not use volume because we struggle to think in terms of volume, while we cannot think in volume because we are not routinely using it."

Stone burden, whether measured in volume or size, is of course not the only parameter that influences the outcomes of stone treatment. This is nicely demonstrated by the myriad nomograms and scoring systems that are currently available to predict the outcomes of ESWL, RIRS, and PCNL.[7] While a measure of stone burden is the most commonly included parameter in these models, volume is the least commonly used metric. But why is volume not incorporated in these nomograms more often? What is holding us back from using volume in nomograms or in clinical practice?

Perhaps we are lacking the tools to quickly, accurately, and reliably measure stone volume. Panthier

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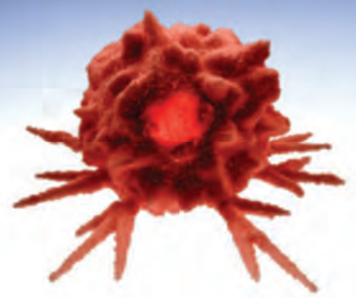
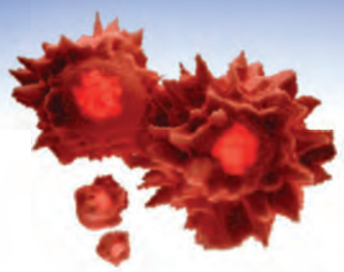
# How high are the stakes in high-risk NMIBC?

BCG monotherapy is essential to help protect against recurrence and progression, but many patients do not achieve lasting remission[1-6]



**UP TO 50%**

of patients with high-risk NMIBC are at risk of recurrence within 1 year of treatment[1,7*]



**~20%**

of patients with high-risk NMIBC may progress to MIBC within 4 years of diagnosis[5,8†]

**~50%**

of patients with MIBC may progress to metastatic disease, which has a 5-year survival rate of 9%[6,9,10]

**Preventing recurrence and progression is critical in high-risk NMIBC**

Scan to visit HighRiskNMIBC.com to learn more about the stakes

*Based on a combined analysis of individual patient data from 7 EORTC clinical trials including 2,596 patients. All of the included studies evaluated patients post-TURBT, at which point they received variable treatments.[1]

†Based on a systematic review of 19 clinical trials that included a total of 3,088 patients.[8]

BCG, bacillus Calmette-Guérin; EORTC, European Organisation for Research and Treatment of Cancer; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle–invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

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Pfizer

## STONE VOLUME: IS IT THE FUTURE OR JUST FANCY SOFTWARE?

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> "What is holding us back from using volume in nomograms or in clinical practice?"

et al[3] summarize the different methods for measuring or calculating stone volume, demonstrating that volume measurement is available, feasible, and should not be overly time-consuming with the currently available (not too fancy) software. With the help of artificial intelligence and machine learning, stone detection and volumetric assessment can even be automated, reducing the workload of getting stone volumes from CT images, and may hopefully soon be available at just the click of a button.

Or perhaps, while we can calculate or measure stone volume, we have difficulties in thinking in terms of volume rather than linear size.[8] We can easily visualize a solitary 2-cm stone, or 3 stones with a cumulative size of 4 cm. But can we as easily picture a 3000-mm$^3$ solitary stone? Or a 23,000-mm$^3$ staghorn stone? Apparently not. Maybe we are caught in a vicious cycle: we do not use volume because we struggle to think in terms of volume, while we cannot think in volume because we are not routinely using it.

We do not lack the tools. We do not lack the ability of using volume routinely, yet we simply do not use it. As is so often the case, changing practice takes time as well as more and more evidence to support that change. We are confident that volume will find its way into clinical practice in the (near) future. All we and our colleagues need to do is start using it—if not in clinical practice yet, at least in clinical research. May this be a call to all investigators to report both linear sizes and volume in future papers on stone treatment to help us move the needle. Then, someday in the future, urologists may exclaim "Eureka" like Archimedes did when realizing that volume was the answer. ■


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# Risk-Adapted Screening With MRI for Early Detection of Clinically Significant Prostate Cancer


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Prostate cancer is not only the most common male malignancy and a leading cause of male cancer deaths, it is also one of the most heritable conditions.[1] Individuals with strong family history[2] or Black/African ancestry[3] carry nearly double the risk of developing prostate cancer (and lethal disease in particular). Recent work has demonstrated that germline rare pathogenic variants in high-risk genes (eg, *BRCA2*)[4] as well as polygenic risk scores derived from hundreds of common single nucleotide polymorphisms can further distinguish high-risk populations that might benefit from targeted screening efforts.[5,6]

Universal screening with serum PSA has been fraught with controversy over low specificity and concerns regarding overdiagnosis and overtreatment of indolent tumors that are unlikely to cause harm.[7] Using prostate multiparametric MRI (mpMRI) to triage patients with an elevated PSA has improved specificity for detecting clinically significant prostate cancer (ie, grade group ≥2),[8] but the utility of MRI as a primary screening tool is unknown. Still, many individuals at high risk of dying of prostate cancer do not undergo any or adequate prostate cancer screening. Thus, there is a critical need to address the gap in prostate cancer screening to improve outcomes for individuals at high risk of developing clinically significant prostate cancer, particularly among genetically predisposed populations and individuals of Black/African ancestry.

There is growing evidence and enthusiasm for moving from a one-size-fits-all approach to risk-adapted screening, where testing is intensified for high-risk individuals and de-intensified (or even omitted) for low-risk individuals.[9] The goal of risk-adapted screening is to facilitate early detection of clinically significant cancers among individuals at greatest risk of dying of prostate cancer, while avoiding overdiagnosis and overtreatment of indolent tumors. Two key components of a risk-adapted screening strategy are (1) identifying individuals at high risk of developing potentially lethal prostate cancer (ie, using the aforementioned risk factors) and (2) utilizing screening tests that can reliably distinguish individuals likely to harbor significant cancers from those with

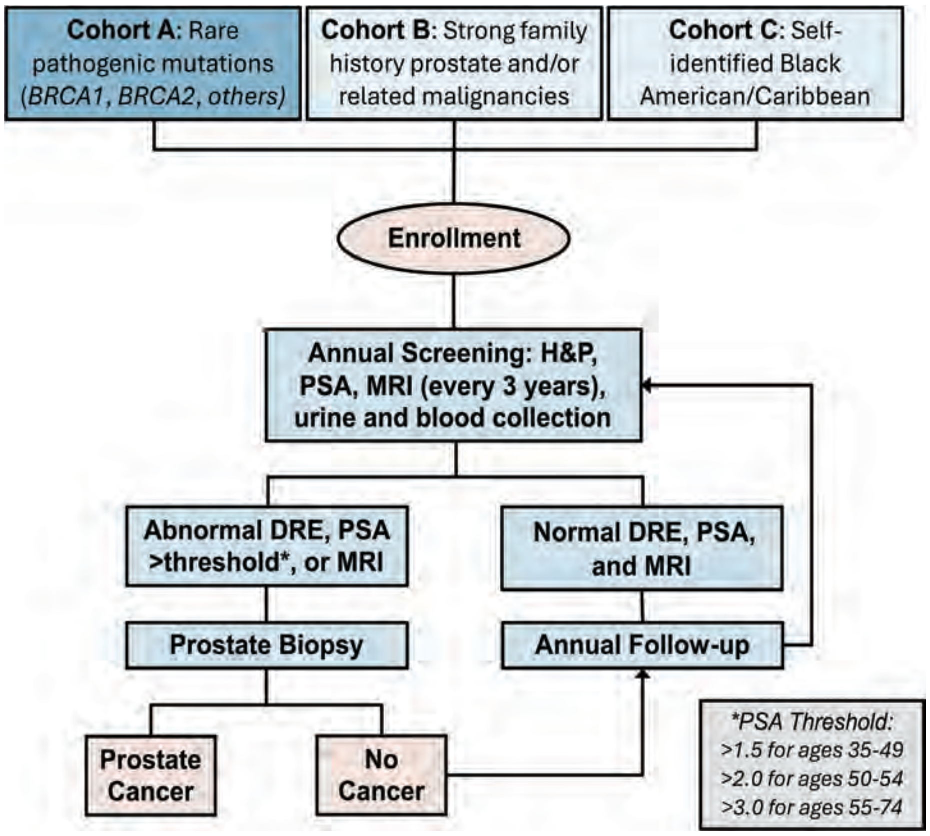


**Figure 1.** Prostate Cancer Genetic Risk Evaluation and Screening Study (PROGRESS) schema. DRE indicates digital rectal examination; H&P, history and physical.

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## RISK-ADAPTED SCREENING WITH MRI FOR EARLY DETECTION OF CLINICALLY SIGNIFICANT PROSTATE CANCER

→ Continued from page 18

insignificant or no cancer. The clinical utility of modern prostate cancer screening approaches integrating mpMRI among high-risk individuals is now the subject of investigation among several ongoing and recently completed clinical trials.

The Prostate Cancer Genetic Risk Evaluation and Screening Study (PROGRESS) is a prospective prostate cancer early detection study among males from 3 populations considered to be high risk for developing aggressive prostate cancer (Figure 1; NCT05129605): (1) rare germline pathogenic variant carriers, (2) individuals with strong family history of prostate cancer and/or genetically related malignancies, and (3) individuals of self-reported Black American or Black Caribbean background. Participants ages 35 to 74 years are screened with an annual PSA and digital rectal examination (DRE) as well as an mpMRI of the prostate every 3 years. PSA is considered elevated based on age-adjusted cutoffs corresponding to approximately the 90th percentile for each age bracket: > 1.5 ng/mL (35-49 years), > 2.0 ng/mL (50-54 years), and > 3.0 ng/mL (55-74 years). If an abnormality is detected by DRE, PSA (above age-adjusted cutoffs), or mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] ≥3 lesion), a prostate biopsy is recommended in accordance with clinical decision-making of the treating clinician. The primary end point of the study is detection rate of clinically significant prostate cancer, defined as grade group ≥ 2 prostate adenocarcinoma on prostate biopsy or radical prostatectomy pathology. The secondary end point is detection rate of any prostate cancer.

We recently reported interim results from 101 germline rare pathogenic variant carriers in PROGRESS Cohort A who completed the first round of screening, where we observed a 9% overall cancer detection rate and 7% clinically significant cancer detection rate.[10] In our updated analysis presented at the 2025 AUA Annual Meeting, the cancer detection rate has remained steady among 170 Cohort A participants who have completed at least 1 round of screening: 17/170 (10%) for overall prostate cancer and 12/170 (7.1%) for clinically significant prostate cancer. Thirty-three participants had an abnormal screening MRI, and 41 participants underwent a prostate biopsy, over half of whom (24/41) were indicated for an abnormal MRI in the setting of normal PSA and DRE (Figure 2, A). For detection of clinically significant prostate cancer, abnormal MRI (PI-RADS ≥4) demonstrated 83% sensitivity with a positive predictive value of 56%, whereas elevated age-adjusted PSA had 58% sensitivity with a positive predictive value of 41%. Of 6 screening strategies evaluated in decision curve analysis, MRI-based screening achieved superior net benefit at all threshold probabilities compared with PSA screening (Figure 2, B). Compared with age-adjusted PSA, the MRI PI-RADS ≥ 4 strategy detected ~1 additional significant cancer per 12 patients, without an increase in unnecessary biopsies. Conventional PSA screening (cutoff >4.0 ng/mL) would have missed more than 75% of these cases.

In addition to PROGRESS, other ongoing clinical trials are investigating targeted screening strategies for high-risk germline pathogenic variant carriers using

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## RISK-ADAPTED SCREENING WITH MRI FOR EARLY DETECTION OF CLINICALLY SIGNIFICANT PROSTATE CANCER

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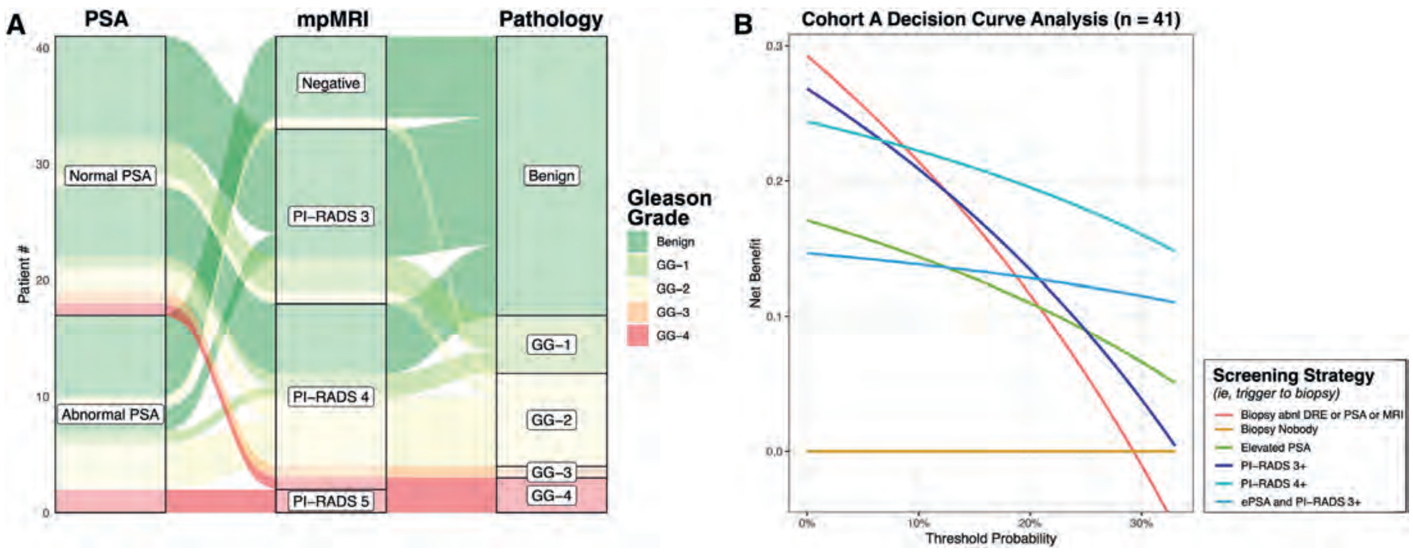


**Figure 2.** A, Screening and biopsy results for 41 participants biopsied in the Prostate Cancer Genetic Risk Evaluation and Screening Study. B, Decision curve analysis comparing screening strategies for detection of clinically significant prostate cancer. DRE indicates digital rectal examination; ePSA, elevated PSA; GG, Gleason grade group; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System.

mpMRI and/or age-adjusted PSA (eg, NCT03805919, PATROL [NCT04472338]), as well as evaluating how polygenic risk scores can be used to identify high-risk individuals for mpMRI- and PSA-based detection of clinically significant prostate cancer (eg, BARCODE1,[6] NCT06398639). Together, these approaches, if successful, have the potential to shift our screening paradigm from a one-size-fits-all approach to a risk-adapted approach with the goal of improving early detection of prostate cancers most likely to cause harm while avoiding the harms of overdiagnosis and overtreatment. ■


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# Contrast-Enhanced Voiding Ultrasound in Videourodynamics

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Contrast-enhanced voiding urosonography (ceVUS) has increasingly played a role in pediatric urologic imaging in the United States since the ultrasound contrast agent Lumason (sulfur hexafluoride lipid-type A microspheres; Bracco Diagnostics, Princeton, New Jersey) was approved by the Food and Drug Administration for intravesical use in children in 2016. ceVUS, which has been used in Europe for decades, involves intravesical administration of contrast agent and real-time ultrasound, allowing for dynamic monitoring of urinary structures. One of the most studied applications in urology has been the detection of vesicoureteral reflux (VUR), and a phase 1 trial in 2018 using Lumason demonstrated the high sensitivity and specificity of ceVUS compared with gold standard fluoroscopy in detection and grading of VUR in a pediatric population.[1]

The principal benefit of ceVUS compared with fluoroscopy is the reduced exposure to radiation. In the pediatric population, the reduction of radiation exposure becomes particularly important. One study in which ceVUS offers the potential to greatly reduce radiation exposure is urodynamics (UDS), because video UDS with voiding cystourethrogram can provide radiation exposure of up to 10 mGy per study.[2] Spinal dysraphism is one of the most common indications for pediatric UDS, and although the average number of studies these patients undergo has not been defined, guidelines recommend studies yearly for the first 3 years of life and as indicated for clinical change thereafter.[3] Risks related to radiation, including the development of malignancy, are dose dependent, and therefore, care should be taken to avoid exposure whenever possible.[4]

"Risks related to radiation, including the development of malignancy, are dose dependent, and therefore, care should be taken to avoid exposure whenever possible.[4]"

Three institutions, including ours, have investigated the feasibility of using ceVUS with UDS in place of fluoroscopy with comparable results.[5-7] In our study, patients were placed in a supine position and set up for UDS according to standard practice. Concurrently, a licensed ultrasonographer performed ultrasound imaging at the time of the UDS (Figure 1). Our ceVUS protocol includes scanning of the bladder early, mid, and late fill to evaluate shape and structure. Kidneys are imaged for assessment of VUR early, mid, and late fill. Otherwise, the focus of the imaging is primarily on the bladder neck and urethra to monitor configuration and activity during the study. In all cases, we achieved confident interpretation of the studies by both a pediatric radiologist and urologist, and no study required repeat imaging. These findings support the growing body of evidence that ceVUS can be seamlessly integrated into UDS protocols as a reliable radiation-free alternative to fluoroscopic imaging.

"These findings support the growing body of evidence that ceVUS can be seamlessly integrated into UDS protocols as a reliable radiation-free alternative to fluoroscopic imaging."

Diagnostically, ceVUS has been shown to have equal or better sensitivity for VUR than fluoroscopy.[8] In part, this may be attributed to the fact that ceVUS can provide continuous and dynamic imaging since the length of the study confers no increased radiation risk to the patient. We have found that this is also a benefit for the use of ceVUS with UDS where continuous monitoring can be achieved. While we mostly rely on the UDS tracing to predict the start of voiding, we are able to visualize the bladder neck opening to initiate voiding prior to the detrusor pressure changes (Figure 2, A and B). When comparing ceVUS and fluoroscopic imaging during UDS, our institution found no statistically significant differences in bladder shape, VUR, bladder neck, or urethral appearance among 75 pediatric patients who underwent both studies (Figure 2, C and D).[9] However, we did appreciate some difficulty assessing subtle trabeculations, small diverticula, and urethral pathologies with ceVUS (Figure 2, E). In an unpublished

"Diagnostically, ceVUS has been shown to have equal or better sensitivity for VUR than fluoroscopy.[8] In part, this may be attributed to the fact that ceVUS can provide continuous and dynamic imaging since the length of the study confers no increased radiation risk to the patient."

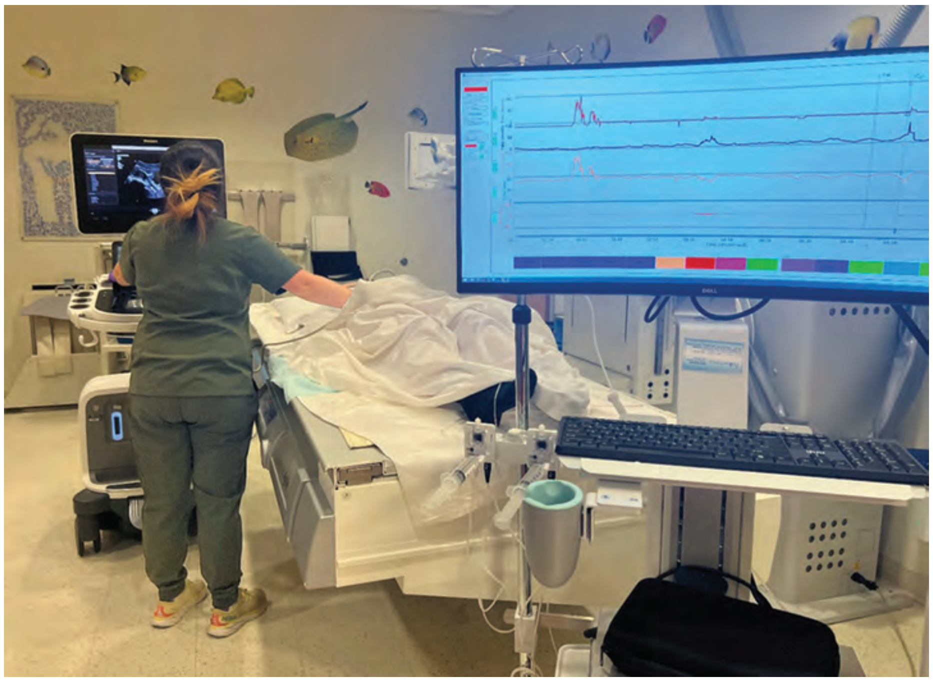

**Figure 1.** A pediatric sonographer performs contrast-enhanced voiding urosonography while a patient undergoes urodynamics. © 2024 Kennady E, et al.[9] *Neurourology and Urodynamics* published by Wiley Periodicals LLC. Novel use of contrast enhanced ultrasonography with urodynamics in children: a comparison study to fluoroscopy. Wiley Online Library. https://onlinelibrary.wiley.com/doi/epdf/10.1002/nau.2542. Creative Commons CC-BY-NC license 4.0.

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## CONTRAST-ENHANCED VOIDING ULTRASOUND IN VIDEOURODYNAMICS

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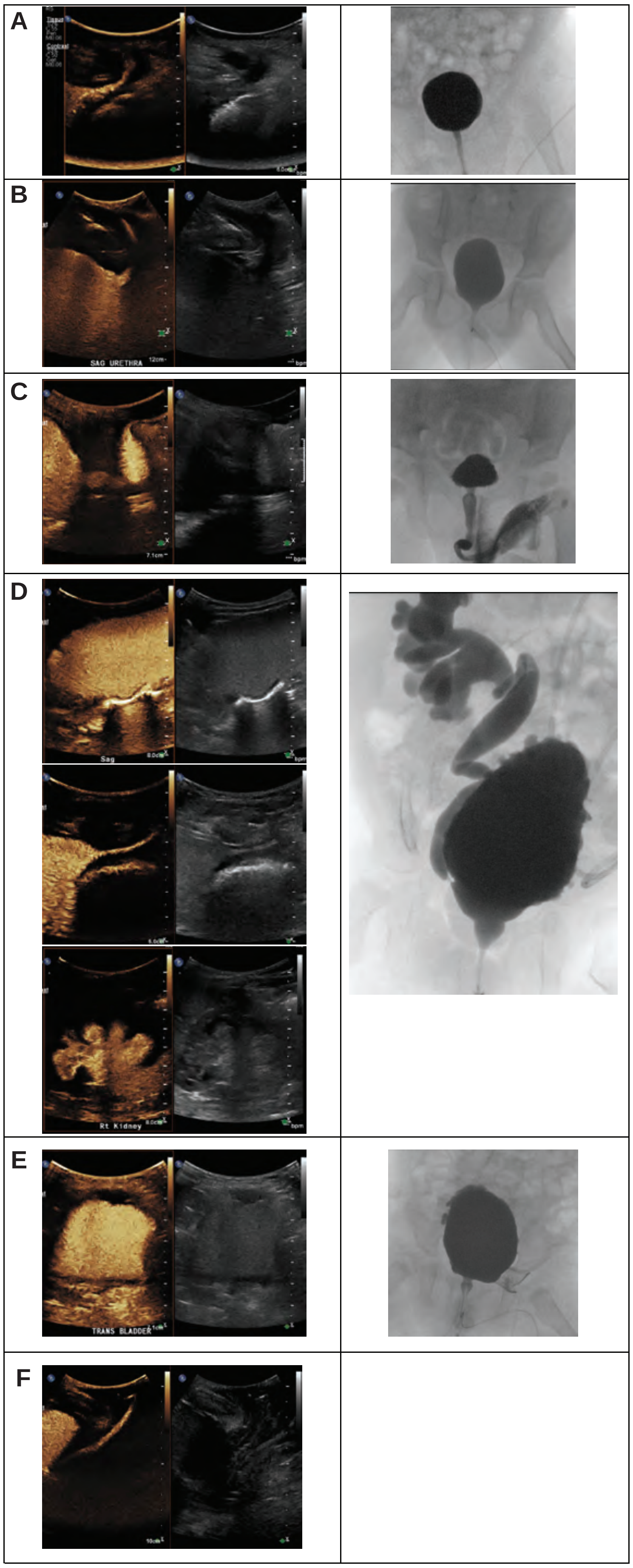


**Figure 2.** Comparison of imaging with contrast-enhanced voiding urosonography (left panels) vs fluoroscopy (right panels). A, Normal urethra with voiding. B, Open bladder neck without voiding. C, Voiding with bladder neck hypertrophy and narrowed proximal urethra. D, Trabeculated bladder with open bladder neck and high-grade vesicoureteral reflux. E, Trabeculated bladder (difficult to appreciate on contrast-enhanced voiding urosonography). F, Layering of contrast on top of urine due to nonmixing, making bladder neck visualization inadequate. © 2024 Kennady E, et al.[9] *Neurourology and Urodynamics* published by Wiley Periodicals LLC. Novel use of contrast enhanced ultrasonography with urodynamics in children: a comparison study to fluoroscopy. Wiley Online Library. https://onlinelibrary.wiley.com/doi/epdf/10.1002/nau.2542. Creative Commons CC-BY-NC license 4.0.

> "The principal benefit of ceVUS compared with fluoroscopy is the reduced exposure to radiation."

study conducted by our institution, we specifically evaluated urethral pathologies including detrusor sphincter dyssynergia and posterior urethral valve and found lower interrater reliability on ceVUS compared with fluoroscopy.[10] Because of this, we would suggest selecting fluoroscopy over ceVUS when more granular details are desired or seeking a first-time diagnosis of a specific urethral pathology. Otherwise, for follow-up UDS studies where imaging is desired, ceVUS can largely replace fluoroscopy with similar diagnostic ability. Another limitation with ceVUS UDS is that the bladder neck is unable to be visualized if there is residual urine in the bladder (Figure 2, F). To mitigate this, the urine should be fully evacuated, or contrast can also be injected through the catheter to force mixing of the contrast with residual urine for better visualization.

An additional benefit of ceVUS UDS compared with fluoroscopic UDS is parental preference.[11] In a survey of 53 parents, 91% indicated that they preferred ceVUS to fluoroscopy, primarily citing the decreased exposure to radiation. Patient and parental comfort was another factor; the fluoroscopic unit is large and caused anxiety in some children, and no radiation meant no lead and an increased perception of closeness between parent and child.

ceVUS offers a safe and patient-centered alternative to fluoroscopic imaging during pediatric UDS. With comparable diagnostic utility for most scenarios, ceVUS UDS is a well-suited option for follow-up imaging and for patients requiring serial studies. While fluoroscopy remains preferred for certain urethral pathologies, ceVUS UDS offers a valuable adjunct that has the potential to meaningfully reduce radiation exposure while preserving diagnostic value in pediatric urology. ■

> "With comparable diagnostic utility for most scenarios, ceVUS UDS is a well-suited option for follow-up imaging and for patients requiring serial studies."


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