IMAGING OF GENITOURINARY SYSTEM TREATMENT-RELATED DAMAGE

OVERVIEW

Azienda Ospedaliero Universitaria Careggi

- Radiation therapy is commonly used to treat pelvic or retroperitoneal cancers

- The price for effectiveness in this setting is a considerable impact on genito-urinary system

-Short-term side effects are frequent with usually a complete regression of symptoms

-Nevertheless, incidence of major complications is about 12% and is probably underestimated due to latency between radiation therapy and diagnosis of some adverse events

Fiorino, Radiother Oncol 2009;93:153–67

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi

- **<u>TOTAL BODY IRRADIATION(bilateral irradiation)</u>**
- **5%-nephropathy risk dose: 9.8 Gy/1# or 16 Gy in standard fractionation**
- **++ exposure to nephrotoxic drugs (CDDP, aminoglicosides)**

Kal , Int J Radiat Oncol Biol Phys 2006 ;65: 1228-32

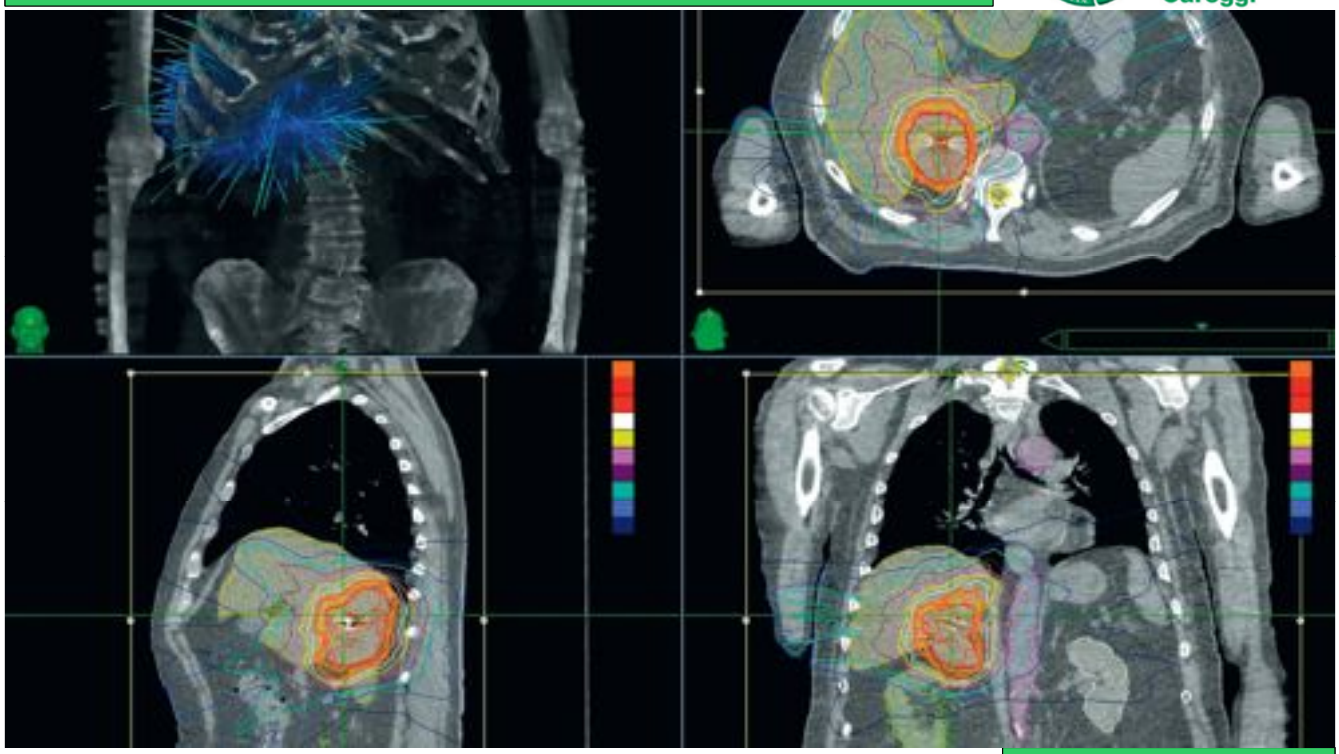
- **<u>ABDOMINAL IRRADIATION (partial irradiation)</u>**
- **5%-nephropathy risk dose: 18-23 Gy in standard fractionation**
- **Area receiving >25 Gy: functional loss**

Dawson , Int J Radiat Oncol Biol Phys 2010 ;76: S108-15

KIDNEY

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi



SABR of adrenal metastasis by Cyberknife

From Bouillet, Bull Canc 2012 99:389-395

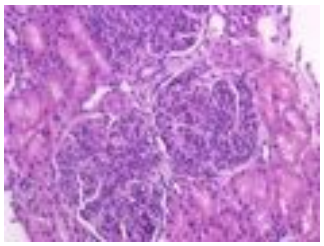
KIDNEY

PATHOPHYSIOLOGY

Azienda Ospedaliero Universitaria Careggi

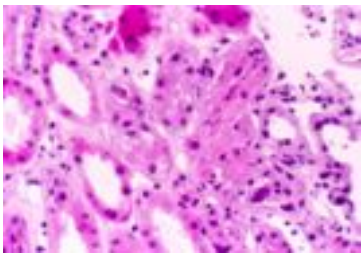
- Poorly understood
- Results of complex, dynamic interactions between glomerular, tubular, interstitial cells
-Involvement of the Renine-Angiotensin System and oxydative stress
-After a 10 Gy local kidney irradiation:

3 weeks



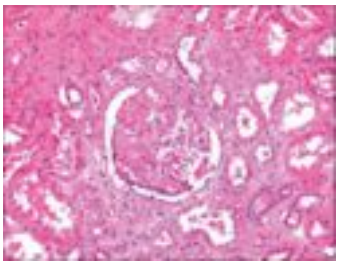
Ultrastructural damage to the glomerular endothelium+ neutrophil adhesion

6-10 weeks



Massive tubular epithelial cell necrosis

>10 weeks



Interstitial fibrosis

Cohen, Semin Nephrol. 2003;23:486-99

KIDNEY

ACUTE TOXICITY

Azienda Ospedaliero Universitaria Careggi

-Within 3 months after irradiation

-Unfrequent, ++ following bilateral irradiation (i.e. Total Body Irradiation)

-Functional impairment (creatinine clearance decline, increased serum B2-microglobulin)

- Progression to Uremic Hemolytic Syndrome reported in Bone Marrow Transplantation patients

Cheng, Int J Radiat Oncol Biol Phys 2008;71:436–443

KIDNEY

LATE TOXICITY

Azienda Ospedaliero Universitaria Careggi

-Chronic parenchymal injury (>18 months) is characterized by benign or malignant hypertension, elevated creatinine levels, anemia, and renal failure

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Transient albuminuria; no hypertension; mild impairment of renal function; urea 25-35 mg/dL; creatinine 1.5-2.0 mg/dL; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36-60; creatinine clearance 50-74%	Severe albuminuria; severe hypertension; persistent anemia (< 10); severe renal failure; urea > 60; creatinine > 4.0; creatinine clearance < 50%	Malignant hypertension; uremic coma; urea > 100

Dawson , Int J Radiat Oncol Biol Phys 2010 ;76: S108-15

KIDNEY

LATE TOXICITY

Azienda Ospedaliero Universitaria Careggi

- Radiation-related arterial stenosis should be considered apart

- Development of hypertension+++

- Rare complication (incidence 0.5 cases per 1,000 at a median time from irradiation to referral of about 9 years).

Fakhouri Am J Kidney Dis 2001;38:302–9

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

-In acute radiation nephritis, the kidney remains normal in size and shape, although glomerular damage is present histologically

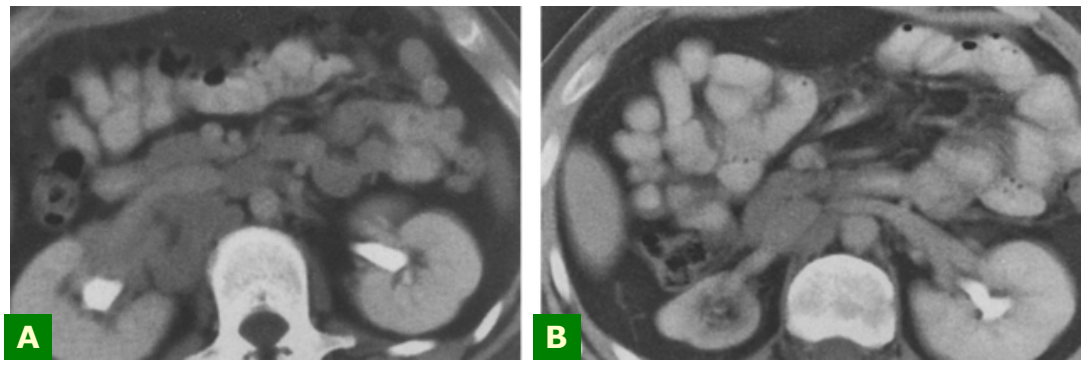
-Late toxicity results in atrophic, poorly functioning but non-obstructed kidneys with smooth outlines. Compensatory hypertrophy of the controlateral kidney may occur

Iyer, Cancer Imaging 2006; 6: S131-139

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



Shrunken kidney 2 years following 4000 cGy for recurrent retroperitoneal lymphoma
A) Preradiotherapy CT scan showing recurrent lymphoma in the right renal hilus and right para-aortic area.
B) Atrophic right kidney+ contralateral compensatory hypertrophy 2 years later

From Libshitz, Eur. Radiol. 1998 6, 786-795

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

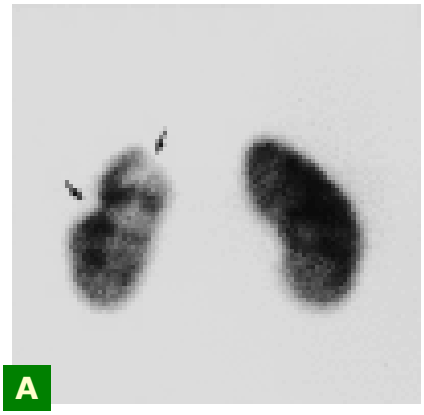
CT of the abdomen shows atrophy of the left kidney and asymmetric uptake of IV contrast after radiation therapy 3 years earlier for gastric lymphoma

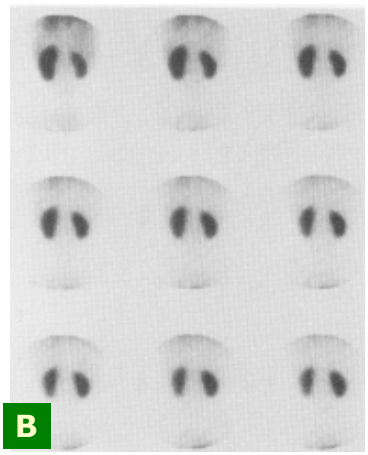
From Iyer, Cancer Imaging 2006; 6: S131-139

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi





A) 99mTc-DMSA scan (posterior view): cortical defects (arrows) at upper pole and lateral margin of left kidney → reduced tubular function

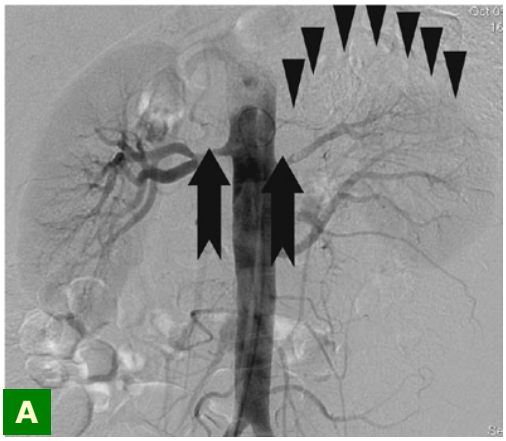
B) 99mTc-DTPA scan : small size and decreased uptake of the right kidney → reduced glomerular function

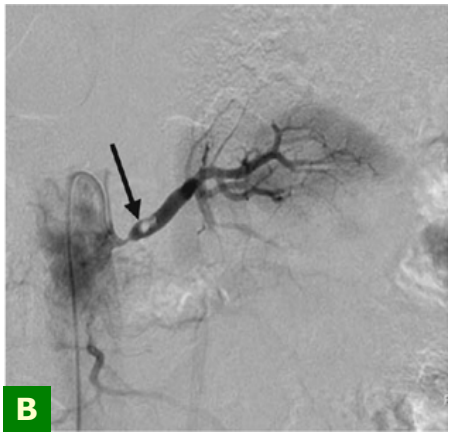
From Prvulovich, BMJ, 1998; 316: 1140-1146

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi





Patient treated by mantle + inverted Y RT for Hodgkin Lymphoma: development of hypertension 6 years later
A) Angiography showing bilateral renal artery stenosis
B) 90% stenosis of the left followed by an intraluminal thrombus

From Izzedine, Kidney Int. 2007;71:1188

KIDNEY

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

MRI: Dynamic contrast-enhanced acquisition (GRE) in coronal plane at different time points → NO concentrating ability of gadolinium in the right kidney

KIDNEY

SUGGESTED WORKUP

Azienda Ospedaliero Universitaria Careggi

-Biological surveillance of renal function is mandatory during the 2 years following irradiation

-In the event of previously undetected renal dysfunction : US (chronic kidney disease vs reversible kidney injury) → CT to detect postrenal etiology (++disease relapse!!)

- Future techniques for detecting renal function may include dynamic MRI with Gado- DTPA

Dawson , Int J Radiat Oncol Biol Phys 2010 ;76: S108-15

Remer , ACR Appropriateness Criteria(®) on Renal Failure. Am J Med. 2014

KIDNEY

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi

- Radiation-related ureter fibrosis is a rare complication following radiation therapy for prostate, bladder, colorectal, and cervical cancer

- Incidence range from 1-3% after cervical brachytherapy and 1.1% after radical external beam RT for prostate cancer

McIntyre, Cancer 1995; 75: 836–843
Arcangeli, Int J Radiat Oncol Biol Phys 1991 ;20:439-446

URETER

PATHOPHYSIOLOGY

Azienda Ospedaliero Universitaria Careggi

- Ureter is fairly radioresistant (up to 20 Gy/1# intraoperatively)

- Preclinical experiences suggest risk increase in dose-dependent, time-dependent and volume dependent manner

Iyer, Cancer Imaging 2006; 6: S131-139

van Kampen Radiology. 2003; 228:139-43

URETER

DIAGNOSTIC WORKUP

Azienda Ospedaliero Universitaria Careggi

-Ureteral stenosis results in loin pain, recurrent upper urinary tract infection up to hydronephrosis → Radiation stenosis is smoothly tapered and can be clearly visualized on delayed CT scans obtained after administration of intravenous contrast material, which opacifes the ureter

NEVER MISTAKE A LOCAL RELAPSE FOR A POST-RADIATION FIBROTIC STRICTURE!!!

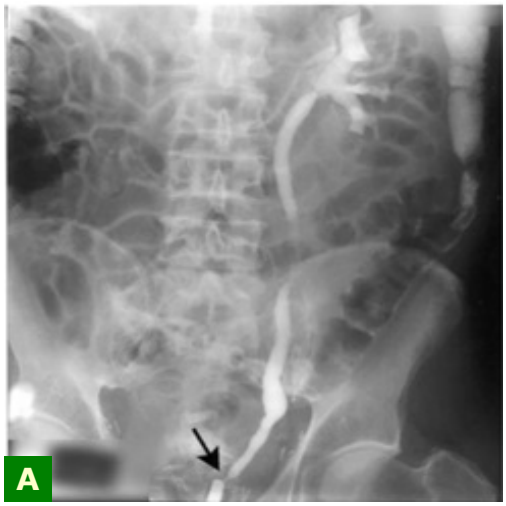
-+++ if early onset (median 16 vs 45 months), previous N+ stage and/or locally avanced stage, concurrent lower limbs edema, stenosis outside radiation field

McIntyre, Cancer 1995; 75: 836–843

URETER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



Retrograde pyelography (A) and contrast-enhanced CT (B) show distal left ureteral benign stricture in prostate cancer patients treated by IMRT

From Cohen, Am J Clin Oncol 2010; 33:108

URETER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

Uretero-iliac artery fistula (as seen in arteriography) are rare rare but potentially life-threatening sequelae due to massive hematuria

From Mitterberger, Cases J. 2009; 2: 6266

URETER

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi

- Radiation-related urethral fibrosis is mainly related to treatment of prostate cancer

- Stenosis occur in 4% to 9% of men after brachytherapy and 1%-13% after external beam radiotherapy (NB 5-10% for radical surgery)

- Postradiotherapy stenoses have longer latency than surgery-related (>2 years) and cumulate incidence may rise due to increased expectance of life

Herschorns, Urology. 2014;83:S59-70

URETHRA

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi

- Stenosis rate will be greater after combination therapy (3 fold for EBRT+BT vs BT)

- Previous surgery is the main risk factor for radiation stenosis (15% rate following TURP+RT vs 6% for RT alone) and incidence can exceed 40% after salvage prostatectomy

-Longer half-life, permanent seeds (low-dose-rate BT [LDR-BT]) shows lower incidence of stenosis (0.5-5%) compared to short-acting nonpermanent seeds (high-dose rate BT [HDR-BT])

Herschorns, Urology. 2014;83:S59-70

URETHRA

PATHOPHYSIOLOGY

Azienda Ospedaliero Universitaria Careggi

- Stenosis are secondary to chronic fibrosis and progressive endarteritis in poorly oxygenated submucosal and muscular tissues, followed by tissue scarring

- Bulbomembranous urethra is the most common site of stricture (92.1%)

- Dose to prostatic apex is predictive according to some authors

- Unfrequent complete obstruction (+++Lower Urinary Tract Symptoms)

Sullivan, Radiother Oncol 2009 91:232-236

URETHRA

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

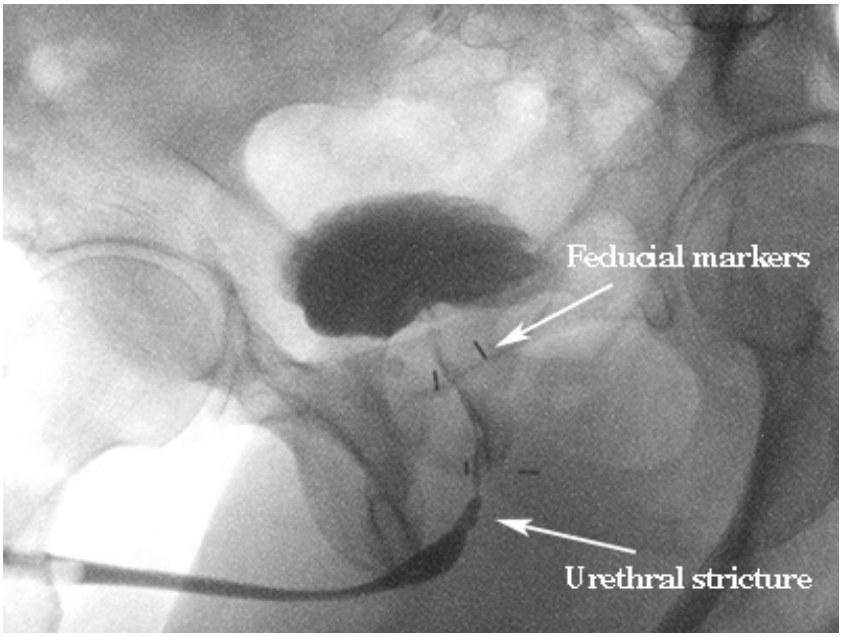
Stenosis on implanted brachy therapy seeds

From Kawashima Radiographics. 2004;24:S195-216

URETHRA

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



Stenosis after EBRT + HDR-BT

From Kawashima Radiographics. 2004;24:S195-216

URETHRA

SUGGESTED WORK-UP

Azienda Ospedaliero Universitaria Careggi

-Imaging should be reserved for cases in which complete cystourethroscopy cannot performed for various reasons (multiple strictures encountered, complete urethral obliteration, patient unwilling to undergo procedure in ambulatory setting)

-Aim: to delineate the length, location, severity, and complexity of the stenosis

→Retrograde urethrography and, possibly, voiding cystography
+/- Renal and/or ureteral US if clinically indicated
+/- Prostate transrectal US to exclude abscess, calcification, recurrence
+/- TC/RMN if extended disease

Herschorns, Urology. 2014;83:S59-70

URETHRA

CLINICAL CONTEXT

Azienda Ospedaliero Universitaria Careggi

- Bladder toxicity is common during the course of radiation treatment for pelvic cancer (++prostate, cervix, rectum, bladder,anus)

-Bladder injury is divided into acute reactions (during or within 3-6 months of radiation), and late reactions (3-6 months following radiation).

Marks , Int J Radiat Oncol Biol Phys 1995 ;31: 1257-80

BLADDER

PHYSIOPATHOLOGY

Azienda Ospedaliero Universitaria Careggi

-Acute inflammatory phase followed by smooth detrusor muscle degeneration, fibrosis, ischemia leading to loss of compliance

- Bladder injury correlates to delivered dose, in particular above 60 Gy (in particular in the event of bladder urothelial cancer)

De La Taille, Ann Urol 2003 ;37:345-57

BLADDER

ACUTE TOXICITY

Azienda Ospedaliero Universitaria Careggi

-Acute symptoms (dysuria, hematuria) usually subside several weeks following radiation

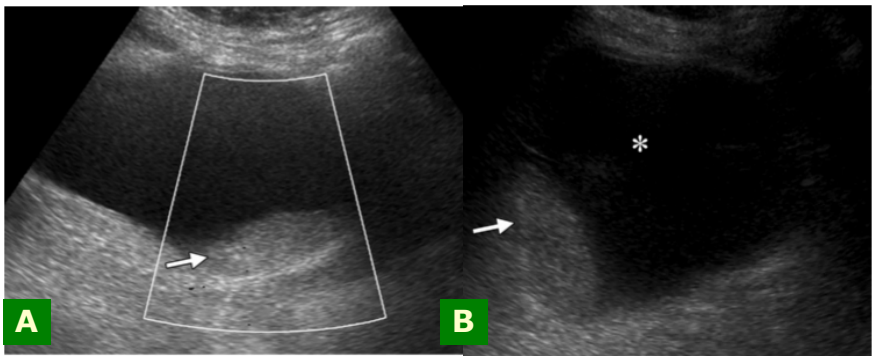
-These early reactions are self-limited and therapy is generally geared toward symptomatic relief

-Imaging is required in exceptional cases (acute urine retention, massive hematuria..)

BLADDER

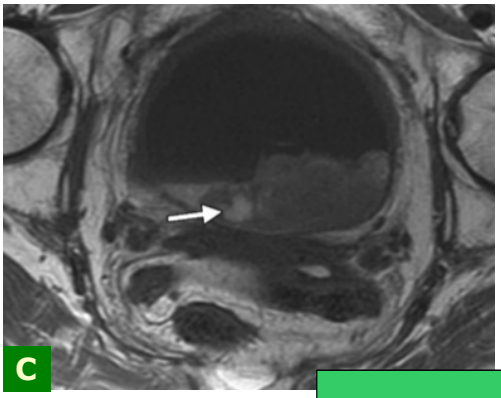
RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



Mobile clot at US
A) Supine, echogenic filling defect
B) Right side, echogenic mass in a dependent position

C)Axial T1-weighted MR image shows increased signal intensity within the clot (arrow), a finding that represents hemorrhage



From Addley, Radiographics, 2010; 30:1843-56

BLADDER

LATE TOXICITY

Azienda Ospedaliero Universitaria Careggi

-In the chronic phase, bladder has a small volume and cannot be fully distended because of fibrosis→ detrimental urodynamic impact

-Incidence of late radiation cystitis varies widely according to the site of treatment

-Fistulae to vagina or bowel occur in 2% of cases, mainly with a latency of 2 years from irradiation

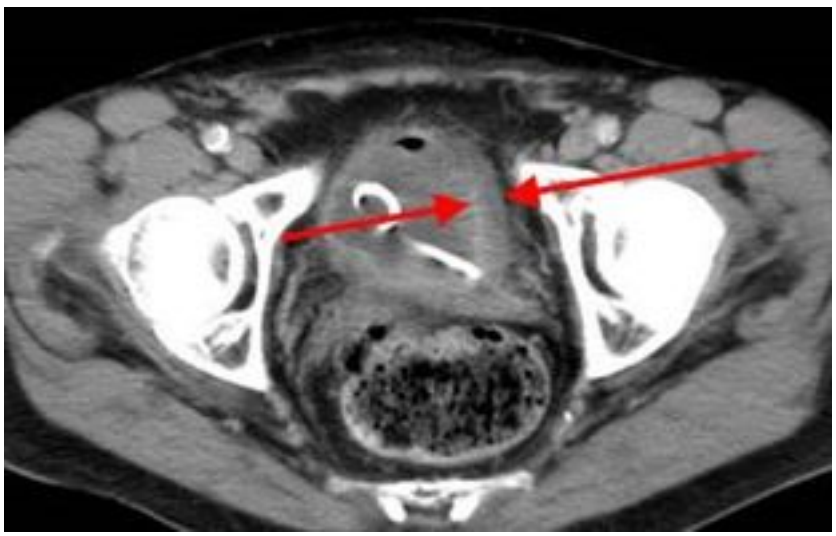
-Spontaneous rupture of the bladder, a rare and menacing event, has been reported following decades from treatment

De La Taille, Ann Urol 2003 ;37:345-57

BLADDER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



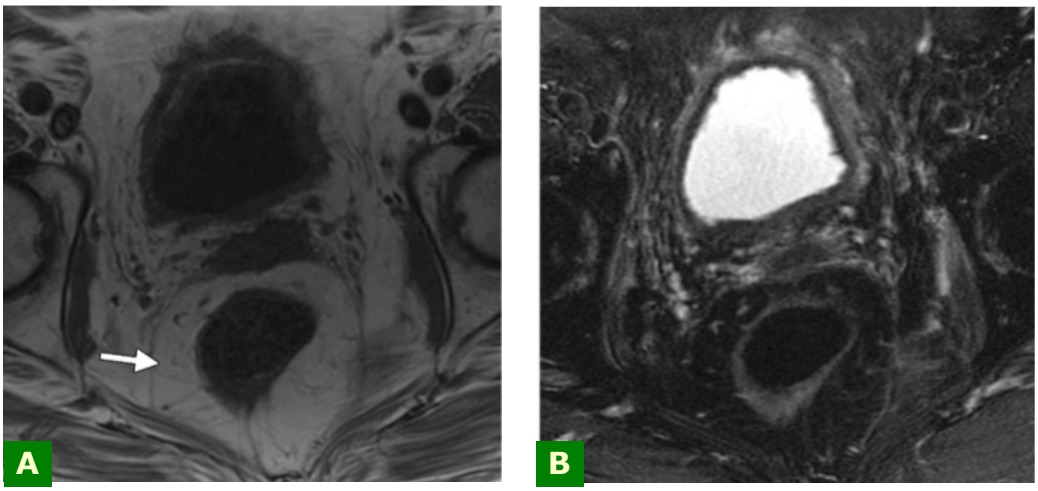
CT scan: thickening in the left lateral bladder wall from radiation induced cystitis after pelvic irradiation for non-bladder cancer

From Addley, Radiographics, 2010; 30:1843-56

BLADDER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



MRI shows small-volume bladder with thick walls
A) T1-weighted: increased perirectal space due to fat deposition (white arrow)
B) T2-weighted: high intensity signal of outer layer

From Addley, Radiographics, 2010; 30:1843-56

BLADDER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi

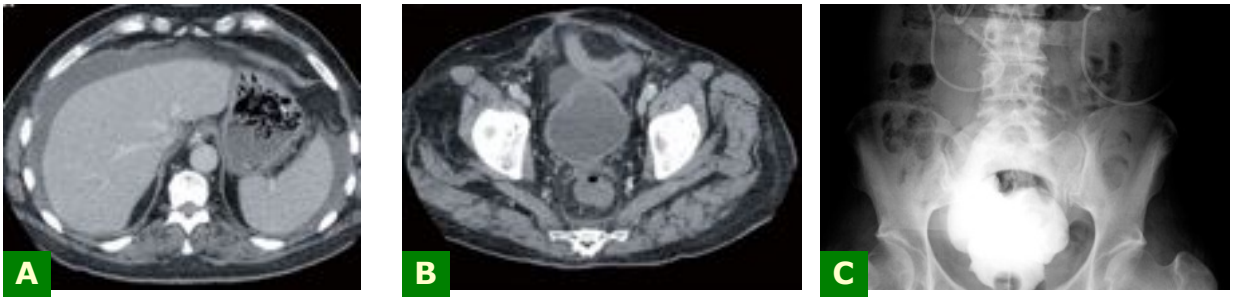
Fistula 3 years after chemotherapy–radiation therapy for stage IIB cervical carcinoma. CT scan +IV contrast shows indirect evidence of a fistula, with gas in the urinary bladder (white arrow) and a fistulous tract (black arrow).

From Addley, Radiographics, 2010; 30:1843-56

BLADDER

RADIOLOGIC SEMIOLOGY

Azienda Ospedaliero Universitaria Careggi



Patient with prior prostate irradiation 17 years before.
Contrast-enhanced computed tomography revealing (A) intra-abdominal free fluid and (B) no direct nor indirect signs of fistula. (C) Cystography shows intraperitoneal leakage of contrast material, in favour of spontaneous bladder rupture

From Ketata , Clin Genitourin Cancer. 2007;5:287-90

BLADDER

CONCLUSION

Azienda Ospedaliero Universitaria Careggi

-Interpretation of post-treatment genitourinary imaging following can prove a challenge for the radiologist (poor clinical presentation, sequelae mimicking malignant disease and viceversa, scarce predictive criteria)

-Understanding of the findings commonly seen after chemotherapy and radiation therapy helps in making the correct interpretation and avoiding possible pitfalls

- Radiologists should be acquainted with the common immediate and long-term post- treatment appearances of involved organs, complications that are specifically related to the therapy, and differentiation of these findings from recurrent tumor