IMAGING OF GENITOURINARY SYSTEM TREATMENT-RELATED DAMAGE

OVERVIEW

- 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

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


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


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**SABR of adrenal metastasis by Cyberknife**

*From Bouillet, Bull Canc 2012 99:389-395*
- 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 and neutrophil adhesion
  - 6-10 weeks: Massive tubular epithelial cell necrosis
  - >10 weeks: Interstitial fibrosis

 ultrastructural damage to the glomerular endothelium + neutrophil adhesion
 massive tubular epithelial cell necrosis
 interstitial fibrosis

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

- 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

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

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<th>GRADE 1</th>
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<td>Transient albuminuria; no hypertension; mild impairment of renal function; urea 25-35 mg/dL; creatinine 1.5-2.0 mg/dL; creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea &gt; 36-60; creatinine clearance 50-74%</td>
<td>Severe albuminuria; severe hypertension; persistent anemia (&lt; 10); severe renal failure; urea &gt; 60; creatinine &gt; 4.0; creatinine clearance &lt; 50%</td>
<td>Malignant hypertension; uremic coma; urea &gt; 100</td>
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- 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*
- 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 contralateral kidney may occur.

_Iyer, Cancer Imaging 2006; 6: S131-139_

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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_
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

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
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

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

-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


CLINICAL CONTEXT

- 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
- 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

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-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
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

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
- 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 cumulative incidence may rise due to increased expectancy of life

  Herschorns, Urology. 2014;83:S59-70

- 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
- 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*

**RADIOLOGIC SEMIOLOGY**

Stenosis on implanted brachy therapy seeds

*From Kawashima Radiographics. 2004;24:S195-216*
SUGGESTED WORK-UP

- Imaging should be reserved for cases in which complete cystourethroscopy cannot be 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_
- 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

- 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
ACUTE TOXICITY

-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..)

RADIOLOGIC SEMIOLOGY

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
- 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

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

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

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

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
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

CONCLUSION

- Interpretation of post-treatment genitourinary imaging following can prove a challenge for the radiologist (poor clinical presentation, sequelae mimicking malignant disease and vice versa, 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