Chapter IX. Acute Radiation Effects: Organ Specific Organs Dose and Species Differences:

Section I. Ionizing Irradiation Damage to Kidney

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Introduction:

The parameters governing injury to the kidney from medical radiotherapy and diagnostic procedures (1-5) are very different from those encountered in the setting of radiation terrorism or a nuclear reactor accident.

The primary difference between these forms of injury is the magnitude of irradiation sustained from an event, and the mechanism by which the damage occurs. In a clinical setting of Radiation Oncology, radiotherapy doses to the kidney based upon volume of kidney treated, whether radiation is delivered to both kidneys or just one, and the fractionation scheme by which radiation is delivered.

In the modern era with the availability of CT scanning and 3-dimensional contouring techniques for establishing a treatment plan and with the availability of Intensity Modulated Radiotherapy, 3-dimensional treatment site planning, and capacity to deliver boost high radiation doses to very small volumes (Stereotactic radiotherapy), and finally, the availability of better chemotherapy protocols for clinical diagnosis in which abdominal radiation was previously used, plus the settings of renal toxicity. However, it is useful to understand the literature on prior radiotherapy techniques by which toxicity to the kidney was originally discovered (1-2), and how techniques to avoid renal radiation were developed.

Prior to the availability of CT scanning, renal treatment volumes were identified by intravenous pyelogram (IVP). A radiation dense dye, renografin, was injected intravenously, and a renal nephogram (Ability to visualize the entire kidney, and the dye is cleared through vasculature, and the kidney glomeruli into the collecting tubules, and then the pyelogram (later stage of clearance of the dye) in which the renal calysex and renal pelvis as well as ureters can be visualized.) (1-2).

Radiation oncologists deliver total abdominal irradiation, for the treatment of ovarian cancer, and in some cases to palliate symptoms from disease spread of recurrent colorectal cancer, and rarely endometrial cancer would block the kidneys using 10 half value layers of lead or similarly dense materials placed on a lucite tray above the patient and attached to the gantry. The portal films taken on the radiotherapy machine would be matched to treatment planning films using conventional diagnostic orthovoltage x-ray, and the contours of the kidney verified to be outside of the radiation field for the treatments. Typical fractionation for whole abdominal irradiation (which is now rarely used) would typically be doses of 1.5 – 2.0 Gy per day usually delivered by multiple static fields (2 or 4 fields). Doses sustained by the kidney would be less than 10 Gy over the entire treatment course, which might be 20 or 30 treatments (1).

Renal tolerance is defined in early studies in which the kidney was irradiated to doses well above the current standard of 10 Gy total dose in fractionated radiotherapy (1).

Baring a portion of one kidney (renal pole) often allowed delivery of higher doses to tumor volumes that encompassed a lower part of one kidney. Most importantly in treatment planning, radiation oncologists identified from the I.V.P. those patients who had a single pelvic kidney, often called horse-shoe kidney, and in these cases, placed protecting renal blocks in that area.

Information about renal toxicity from radiation came from historic cases in which these precautions were not carried out, and in rare cases, in which a single pelvic kidney was irradiated without proper treatment planning. Renal injury from ionizing irradiation delivered in a clinical setting can be classified as acute and chronic radiation damage, as with many other organs and tissues. These syndromes will be described below.

Renal toxicity from delivery of radiation emitting isotopes is very rare in the clinical setting. While case reports might be available on overdose of radiation emitting isotopes including: colloidal chromic phosphate (originally used as an abdominal bath, injected intraperitoneally in attempts to treat ascites containing ovarian cancer cells) or in rare cases from overdose of radioisotopes naturally cleared by the kidney, are very rare cases and can be identified from case reports (1). The issue of radioisotope damage to the kidney is very relevant in the scenario of radiation terrorism.

Radiation exposure to the kidney in a setting of total body irradiation (used for bone marrow transplantation in clinical settings)(3-5, 7-8, 10, 12) is quite rare for two different reasons. In clinical radiotherapy, outline of the kidneys is described as indicated above, and if radiation doses are to be boosted to particular areas along with total body radiation (very rare clinical protocols), the kidneys would be blocked. Furthermore, toxicity from total body irradiation, the bone marrow and intestine are usually those organs, which govern sub-lethal or lethal toxicity, long before the appearance of renal toxicity as a cause of a clinical problem. All of the above information on the history of clinical radiotherapy involving kidney volumes, led to the classic descriptions of acute radiation nephritis and chronic radiation fibrosis (6).

A common factor in radioisotope induced renal damage follows those radioisotopes cleared by the kidney and likely to be nephrotoxic if renal clearance is decreased allowing isotope dwell time in the kidneys. In a setting of radiation terrorism, such a situation might evolve from inhalation, ingestion, or topical penetration of significant levels of radioisotopes that would naturally be cleared from the circulation by the kidney. In order for significant radiation to be sustained by the kidney, there must either be a very large dose of isotope cleared rapidly by the kidney such that bone marrow or GI toxicity would not take precedence, or there would of necessity have to be an obstructing lesion either in the renal calux ureters of an individual with only one kidney to produce a high enough radiation dose in that kidney, or comorbid renal disease (a pre-existing condition) would couple with the administration of a radioisotope cleared by the kidney to produce acute radiation nephritis (6-17).

Acute Kidney Injury

The pathophysiology of acute renal injury follows the principles common to all other organs in general with a few specific modifications based on renal physiology. Acute renal injury is characterized in two categories. Radiation-induced glomerulo-nephritis, arterial stricture (stenosis) (3, 9), and radiation-induced vasculitis. In experimental animal systems, high dose external beam radiation to the kidneys results in sequella common to infections or toxic metal (Cadmium) toxicity. The pathology demonstrates swelling of endothelial cells and swelling of cells in the glomerular filtration system. Normal renal physiology is critically dependent upon both the glomerular filtration apparatus in which blood flow through the kidney results in

clearance of high concentrations of salts principally sodium, potassium, and calcium in the urine. An intact endothelial/renal epithelial barrier in the glomerular is critical to prevent blood cell components (red cells, white cells, platelets) from "leaking" into the urine (18). The renal filtration system begins in the glomeruli and radiation damage to these structures (There are typically thousands in each kidney in the renal cortex (outside areas of the kidney on the lateral aspects in the human I.V.P. to those highlighted in the nephrogram stage of the I.V.P.), such that following of either endothelial cells or renal epithelial cells in the glomeruli would lead to cases between the cells and transit of cellular blood components into the urine collecting system.) (19-21). The proximal convoluted tubules, which are the first part of the renal collecting system, further concentrate salts and any toxic materials into the urine. Breakdown products of natural physiology leading to creatinine from normal metabolism concentration in the urine, and blood urea nitrogen (BUN) also natural breakdown products of metabolism, move through the proximal tubules into the distal convoluted tubules or the distal collecting system. These distal collecting tubules feed into the renal calyx (visualized during the pyelogram stage of the I.V.P. as described above), and then into the ureters leading down into the bladder for eventual excretion during urination.

The contents of the urine in both quantity and quality can often determine the first signs of damage to the kidney by irradiation. A separate chapter in this web-based textbook dealing with metabalomics (Amundson and Brenner and Fornace) deals with the ability to use urine components as a biomarker for total dose of irradiation since the kidney will be clearing breakdown products that have been altered by irradiation to other sites.

In the setting of direct renal damage from either external beam irradiation or high concentrations of radioisotopes, the common factor of acute damage is endothelial cell swelling, increased spacing between cells, and in the case of the kidney, leakage of blood components into the urine collecting system. The clinical diagnosis of radiation nephritis relies upon diagnoses of events common to glomerulonephritis from all causes, namely red blood cells in the urine indicative of the leakage of blood components across endothelial cells, and an absence of infectious organisms, which would rule out other causes of nephritis. Analysis of the urine for toxic components including Cadmium, and other metals, which can poison the renal collecting systems also rules out these causes of glomerulonephritis. Such diagnostic techniques would be important in the setting of clandestine dispersal of radioisotopes or clinical setting, overdose of one or both kidneys by improper radiotherapy treatment planning. In a setting of radiation terrorism, the one source of irradiation in a setting of a nuclear fission bomb or dirty bomb would alert personnel to a likelihood of radiation as the cause of glomerulonephritis. Acute radiation injury to the kidneys would be treated identically to acute glomerulonephritis from other causes with several caveats.

First, a patient demonstrating signs of radiation nephritis from external beam radiation would likely suffer from predominant signs and symptoms of radiation damage to the intestine. The target volume would naturally be in the irradiation field and due to the greater organ sensitivity to irradiation, symptoms associated with bowel damage would precede renal damage. In a setting of radioisotope clearance by the kidneys causing the damage, isotope would be detected in the urine by Geiger counter or by scanning the patient in the kidney areas.

An exception would be the treatments caused by alpha-emitting radioisotopes. Undetectable by external Geiger counter or other ionization chamber detectors, collection of blood, urine, and feces from an individual thought to have experienced Plutonium 210 poisoning would be required. In the radiation terrorism case of Alexander Litvinenko (New York City, 2005?), multiple other organ system failures from systemic distribution of isotope preceded any indication of renal damage. This individual, who consumed Plutonium 210 orally, demonstrated bone marrow and immune system toxicity that preceded any signs of renal damage.

Patients with acute radiation nephritis would be treated with hemodialysis to maintain normal physiology until the kidney was allowed to heal (18-21).

In severe renal damage, situations in which renal recovery is not detectable by analysis of urine as a marker of recovery, kidney transplantation might be considered. Factors influencing the severity of acute radiation nephritis include those found in the general medical population. Individuals of pre-existing renal conditions, chronic glomerulonephritis, chronic pyelonephritis, and previous clinical radiotherapy, or previous exposure to nephrotoxic agent could lead to detection of the acute signs and symptoms of nephritis after lower irradiation doses from the incident event being evaluated. Hospitalization, careful monitoring of intake and output, serial analysis of urine are critical to determining whether the renal system is healing, and patients can be discontinued from bi-weekly hemodialysis. The technique of peritoneal dialysis is also possible in hospital settings, particularly in a situation in which there would be large numbers of casualties from radiation terrorism. However, as indicated above, patients would more likely suffer toxicity from bone marrow or gastrointestinal system damage before any specific problems to the kidney had appeared.

Late Radiation Damage to the Kidney (Renal Fibrosis)

Late radiation damage would be detected in situations in which one kidney received a high radiation dose. These clinical case reports are rare and usually follow the treatment of abdominal cancers that require a high radiation dose, and in situations in which nephrectomy on the involved side is not possible. In radiotherapy treatment plans in which total dose is planned to exceed renal tolerance (30 Gy) and in which the entire kidney must be treated, would require a careful consideration of whether nephrectomy is indicated prior to radiotherapy. Most settings in which high radiotherapy doses to a renal volume prescribed would require two conditions: The patient would be judged a poor candidate for surgical removal of the kidney and a functioning contralateral kidney with documented and known to be sacrosanct from any radiation in the treatment planning. These conditions would be quite rare. Abdominal soft tissue sarcomas in which gross disease must be treated usually require doses that exceed the tolerance by small intestine, the toxicity to which would predate any renal toxicity. In most situations, in which one kidney was irradiated to a dose high enough to produce radiation fibrosis, the condition would be preceded by renal failure from acute radiation nephritis. A non-functioning kidney would remain in situ for a long enough duration to produce radiation fibrosis. Such a clinical setting would be extremely rare.

Therefore, information on late radiation damage to the kidney comes from experimental models.

A non-functioning kidney from acute radiation nephritis would sit in situ, perfused by blood circulation, and over several months, demonstrate radiation fibrosis. Prior studies in other animal model systems (Readers should consult the sub-chapter on radiation damage to the lung in the web-based textbook), demonstrate that bone marrow derived progenitors of fibroblasts, as well as proliferation of residual fibroblast progenitor cells in the organ contribute to radiation fibrosis. However, the role of bone marrow progenitor cells of fibroblast is organ specific. Other information is available on chronic fibrosis resulting from other initiating events. Experimental systems, ligating either renal artery causing organ death from ischemia, or in experimental models of ischemia/reperfusion, acute nephritis may not be a clinical problem due to normal functioning of the contralateral kidney. However, fibrosis developing in the damaged kidney would follow the same pattern.

Therapy of Radiation Fibrosis to the Kidney

Nephrectomy (surgical removal of the kidney) is recommended in any situation in which a non-functioning injury has resulted from radiation damage. In a setting in which a patient would not be a candidate for surgery, careful observation of the toxicity caused by fibrosis should be monitored. Typically, fibrotic and non-functional kidneys demonstrate shrinkage and decreased size of the organ. In the modern era, CT scanning would identify small size of the kidney and absence of collecting systems.

Research Methodologies and Study of Radiation Damage to the Kidney

Scientists interested in studying the effects of ionizing irradiation on the kidney have at their disposal a plethora of techniques (22-32). Renal physiology in rodent animal models is highly developed and investigators should consult textbook on renal physiology and model systems. Areas of research in Radiation Biology of the kidney are quite interesting and timely for a number of reasons. There are few systems in which physiologic changes induced by irradiation can be studied better than that of radiation damage to the glomerulonephritis filtration apparatus. Studying effects of ionizing irradiation on physiologic functions of the kidney can be carried out both in vivo and in vitro. Recent techniques for explant and study of individual glomeruli in culture have been published. Renal perfusion injuries and modification by irradiation can be quantitated in such systems. In rodent models, the study of clearance of radioisotopes through renal filtration and collection systems can be carried out and such laboratory facilities are available at many universities and government research facilities such as the Armed Forces Radiation Research Institute (AFRRI), Department of Energy (DOE), Department of Defense (DOD), and, of course, the American Society of Nephrology.

Recent investigations on radiation kidney damage have focused on renal podocytes (32) to explain the mechanism of acute proteinuria and glomerulonephritis. These phenomena can lead to chronic radiation nephropathy, reduced kidney size, and renal failure after irradiation. The role of podocytes may be critical since lipid peroxidation is a clear mechanism, forming in ceremides in the kidney. New radioprotection drugs (20) may target these capital cells in the effect to ameliorate radiation damage to the kidney.

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