Editorial

Predicting, preventing, treating and understanding radiation nephropathy

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In the current issue of the *Journal of GI Oncology*, May and colleagues present data on the longitudinal measurement of biochemical and imaging parameters that define radiation nephropathy.[1] Since the total nephron volume dictates global renal function, it is understandable that injuries resulting from partial kidney irradiation result in decrease of nephron number to impact global renal function. However, detection of global renal dysfunction by clinical or biochemical parameters often requires substantial reductions in nephron number/volume. Furthermore, the long latency for development of clinically or biochemically detectable renal dysfunction and the multiple confounding factors that contribute to these changes result in under-appreciation, under-diagnosis and under-reporting of radiation nephropathy. Early markers of renal function that are more sensitive than typical serum creatinine measurements include creatinine clearance and glomerular filtration rate (GFR) – however, these require 24 hour urine collections or mathematical estimations using other variables and do not provide information on differential renal function. Another surrogate measure of renal function is Technetium^{99m} renal scintigraphy which not only allows early and accurate detection of renal function but also allows determination of the relative function of each kidney. In turn, this offers the possibility of greater correlation with traditional radiation dose-volume parameters.

May and colleagues examined changes in renal function as measured by scintigraphy in the months following concurrent chemoradiation therapy for a variety of gastrointestinal malignancies, comparing imaging characteristics in the kidney receiving a higher radiation dose to that in the kidney receiving a lower radiation dose.[1] They also measured biochemical parameters of renal function (creatinine clearance) after treatment. As one might expect, imaging changes signifying decreased renal function preceded the appearance of biochemical markers of kidney dysfunction. Furthermore, significant reduction of relative function (by scintigraphy) of the primarily irradiated kidney and reduction of global function (by creatinine clearance) were detectable as early as 6 months after treatment. Lastly, the authors correlated dosimetric characteristics with poorer renal function. Specifically the relative volume of kidney receiving either 25 Gy (V25) or 40 Gy (V40) were correlated with poorer renal function, with mean kidney dose trending toward statistical significance in this context. It is unclear if any threshold effect was present in regards to specific dosimetric parameters and any of the renal toxicity outcomes measured.

The most widely used guidelines enumerating the tolerance of normal tissues to radiation were those originally published by Emami and colleagues.[2] More recently, Dawson and colleagues[3] have also offered specific recommendations and general treatment guidelines. In regards to whole kidney radiation tolerance, the threshold dose for any radiation-induced injury is estimated at 15 Gy. However, much of this data is based largely on retrospective chart reviews and clinical observations. Similarly, individual experiences of clinical groups form the basis for partial kidney tolerance estimates noted above. Objective data regarding toxicity, particularly in the current era with the increased use of concurrent chemoradiation, is sparse. This study presents some important findings regarding renal toxicity in the era of chemoradiation therapy. First, the fact that post-treatment outcome endpoints can be correlated with pre-treatment radiation dose-volume parameters offers the possibility of preventing radiation nephropathy. Second, even if renal dysfunction could not have been predicted *a priori*, the early detection of dysfunction offers the possibility of early

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intervention to reduce long-term consequences of radiation nephropathy.

On both these fronts, preventing radiation nephropathy and intervening early as a means of prophylaxis from late renal damage, recent advances in radiation oncology and biology provide some future directions. Based on dosimetric parameters predicting renal dysfunction, it is conceivable that more conformal radiotherapy techniques (intensity modulation, charged particles, etc), image-guided radiotherapy, and respiratory-gating or breath-hold treatments may allow significant sparing of the kidney(s) while still adequately encompassing the large geographical areas at risk for recurrence of many gastrointestinal tumors. Recognizing that dose per fraction is one of the key predictors of all late toxicities, lower fractional doses may also offer some relative renal sparing. What is less clear is the role of the spatial heterogeneity of dose within each kidney on renal function and whether this offers the option of conformal avoidance of a more critical area of the kidney. It seems reasonable to speculate that the collecting system (e.g. within the renal pelvis) is less critical than the renal cortex with its glomerular and tubule-interstitial networks. In addition to these physical means of preventing radiation nephropathy, there may be biological methods to mitigate this side-effect if its risk is known *a priori*. Furthermore, if radiation associated nephropathy is detected early, prompt and effective treatment may reduce long-term sequelae. Indeed, there is an expanding body of literature that suggests that radiation nephropathy can be mitigated and treated with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists.[4] Beginning with experimental radiation nephropathy models where ACE inhibitors and angiotensin receptor antagonists were effective in the mitigation of radiation nephropathy, sequential studies have confirmed that these agents exert variable effects in mitigation and treatment scenarios, with the anti-hypertensive effects contributing more in treatment scenarios and the suppression of the renin-angiotensin system contributing in both scenarios. Importantly, in a randomized trial comparing captopril or placebo administered during and following engraftment in patients undergoing total body irradiation for hematopoietic stem cell transplants, patients who received captopril had higher GFRs at 1 year than those who received placebo, although this did not reach statistical significance.[5] These results validate the early observations by Fajardo and colleagues that endothelial cell damage progressing to extensive thrombosis of glomerular capillaries contribute to radiation nephropathy.[6]

As noted by the authors, there are many confounding factors that can cause renal damage, making the interpretation of any study of renal dysfunction challenging. Among the most common causes for renal dysfunction are underlying renal insufficiency, atherosclerotic disease, cardiomyopathy, diabetes, hypertension, smoking, and nephrotoxic/antihypertensive medications. In this cohort of patients, particularly one comprised of patients with pancreatic (60%) or periampullary malignancies (15%), one would expect a large number of patients with new-onset and less than optimally controlled diabetes mellitus, which is a significant confounder in examining early markers of renal toxicity. Other common confounders in this cohort of patients are the frequent use of potentially nephrotoxic contrast agents for computed tomography scans, increasing use of cisplatin-containing regimens, particularly in the treatment of pancreatic cancers, and the use of non-steroidal anti-inflammatory agents for pain control. One additional challenge with the interpretation of split renal function by scintigraphy is that this does not differentiate between decreased functioning of the irradiated kidney and any potential compensatory increase in renal function of the unirradiated kidney. It is also not clear whether a low dose delivered to a larger volume in intensity modulated plans compared with simpler plans might reduce the possibility of a compensatory increase in kidney function. Nevertheless, a decrease in relative function of the irradiated kidney concurrent with a reduction in global renal function is probably a reasonable indicator of accumulating renal dysfunction.

In summary, this report provides important evidence that radiation nephropathy can be predicted *a priori* based on dosimetric parameters and can be documented early using scintigraphic and biochemical parameters. In the absence of either conclusive and validated dosimetric parameters or pharmacologic radiation mitigators/protectors, the primary driver in regards to sparing renal toxicity is the clinical judgment of the treating physician. The data presented here will serve to guide the treating physician.

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