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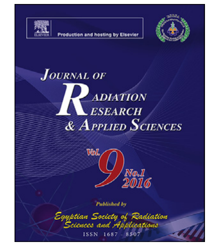

Functional and clinical evaluation of renal injury in patients treated with adjuvant chemoradiotherapy for gastric cancer: Low dose and comorbidity considerations

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ABSTRACT

Aim: To analyze the dosimetric factors affecting long-term renal function in patients with gastric cancer following postoperative radiotherapy with concomitant chemotherapy to the upper abdomen.

Methods: Between January 2005 and July 2010, 13 patients treated with three-dimensional conformal radiotherapy and concurrent fluorouracil-based chemotherapy (CRT) were included in this analysis. After a median follow-up of 55 months, creatinine, glomerular filtration rate (GFR), total kidney and left kidney volumes, before and after CRT and mercaptoacetyltriglycine (MAG3) scintigraphy, were used to evaluate the renal function and were correlated with the dosimetrics data.

Results: Significant correlations were found in the loss of left kidney volume and V35 (20.6%) ($p = 0.035$) and V40 (15.7%) ($p = 0.031$) and in the loss of relative functional contribution of the main kidney and V35 Gy ($p = 0.027$) and V40 Gy ($p = 0.019$). In patients with a slightly low basal GFR ($n = 6$), the relative functional contribution of the left kidney significantly decreased, regardless of the dosage.

Conclusion: Functional renal impairment without any clinical signs or symptoms can be observed in low doses after radiotherapy. Careful treatment planning and a detailed evaluation of the functional renal capacity before treatment may help to reduce late renal toxicity.

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1. Introduction

The kidney is one of the main dose-limiting organs during abdominal irradiation in cancer patients. Radiation-induced clinical renal injury to this late-responding tissue has been previously described (Cassady, 1995; Flentje, Hensley, Gademann, Menke, & Wannenmacher, 1993; Helal, Fick-Brosnahan, Reed-Gitomer, & Schrier, 2012; Kost et al., 2002; Verheij, Dewit, Valdes Olmos, & Arisz, 1994). The kidney has a physiological compensatory capacity, and many clinical signs and symptoms cannot be observed until the glomerular filtration rate (GFR) significantly decreases (Cassady, 1995). The tolerance limits for defining the probability of serious insufficiency were also described (Emami, Lyman, Brown, & Cola, 1991). However, the patient-related (i.e., diabetes, hypertension, liver or heart failure and previous kidney insufficiency), treatment-related (i.e., chemotherapy, low doses of radiotherapy) and organ-specific (spatial variation in radiosensitivity, compensatory capacity for both kidneys) effects remain unclear and need to described (Dawson et al., 2010).

We aimed to analyze the functional changes in the kidney over time and to examine their correlations with dose-volume results in gastric cancer patients receiving adjuvant chemoradiotherapy.

2. Materials and methods

This retrospective study was approved by the Ethical Committee of Marmara University School of Medicine with the protocol number of 09.2011.0031. Between January 2005 and June 2010, 13 (12 male: 1 female) patients who had histologically proven, locally advanced (AJCC IB-IIIB) gastric cancer and who had undergone an operation were recruited for the analysis (Edge et al., 2010). Their median age was 61 (range, 48–74 years), and all of the patients followed were disease-free, with no clinically diagnosed kidney insufficiency. There were two patients had comorbidities (hypertension and diabetes) diagnosed before adjuvant radiotherapy.

2.1. *Chemoradiotherapy*

All patients underwent our center's routine procedure for upper abdominal region tumors. The patients first underwent a simulation in the supine position and then a treatment-planning computed tomography scan (CT) with images taken at 5-mm slice intervals. The data were transferred to a treatment planning system (Eclipse v8.0 Varian Medical Systems, Palo Alto, USA), and 3D planning was performed for all patients. Two opposite and equally weighted anterior–posterior fields were used. Treatment was administered with photons (18 MV) using a linear accelerator (Saturne 42, 800 series, General Electric, Buc, France). A total median dose of 45 Gy (range, 45–50.4 Gy) in 25–28 daily fractions of 1.8 Gy was delivered to the target (primary tumor site and regional lymphatics). Concurrent chemotherapy was administered as an IV bolus of 5-fluorourasil 400 mg/m^2/day and leucovorin 20 mg/m^2/day during the first four and last three fractions of radiotherapy (Macdonald et al., 2001). Chemotherapy was administered to 84.6% of patients without any interruption due to any toxicity. All patients had one cycle of chemotherapy before radiotherapy and one more cycle after concurrent treatment.

2.2. *Kidney anatomy and function analysis*

Kidney volumes were calculated for the CT-simulation images and last follow-up abdominal CT images using a standardized formula (V = p/6 × height × width × length). The percentages of difference between the two images were also calculated. Creatinine clearance was calculated using the Cochroft formula of glomerular filtration rate (GFR) [(140–age) × kg/72 × creatinine] (www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Serum creatinine was measured using the kinetic color test (Jaffé method) for the quantitative determination of creatinine in human serum on Beckman Coulter analysers. Reference intervals for serum creatinine were as follows:

Male <50 years 74–110 μmol/L (0.84–1.25 mg/dL)
Male >50 years 72–127 μmol/L (0.81–1.44 mg/dL)
Female 58–96 μmol/L (0.66–1.09 mg/dL)

Patient serum samples were used to compare this Creatinine OSR6178 assay on the AU2700 against a commercially available enzymatic creatinine assay which has demonstrated equivalence to the IDMS reference method.

Renal insufficiency grading was performed according to the recommendations of the American Kidney Society (www.kidney.org/professionals/KDOQI/guidelines_commentaries.cfm).

2.3. *Dynamic renal scintigraphy with mercaptoacetyltriglycine (MAG3)*

Each patient was asked to drink a minimum of 500 ml of water 15–30 min before the scan. After the i.v. bolus injection of 2 mCi Tc-99m MAG3 (Technescan MAG3™ Kit, Mallinckrodt Pharmaceuticals, Ireland), images were acquired every second for 60 s in the perfusion phase and every 30 s for 23 min in the extraction and excretion phases (Symbia® E Gamma Camera System, Siemens, USA) according to European Association of Nuclear Medicine dynamic renography guideline (Gordon, Piepsz, & Sixt, 2011). The images were evaluated both visually and semiquantitatively (split function, time to peak and time from maximum activity to 1/2 maximum activity) by drawing regions of interest around each kidney, both of which were assumed to contribute equally to the total renal function (the split function was 50% for both) before radiotherapy. According to these terms, a split function of the left kidney was calculated after therapy and was correlated with the other findings.

2.4. *Dose-volume analysis*

Dose volume histograms were derived from the treatment plans for each patient. The percentages receiving 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), maximum dose (Dmax) and mean dose (Dmean) volumes for the total (combined) kidney and for