Comparing Cystatin C Changes as a Measure of Renal Function before and after Radiotherapy in Patients with Stomach Cancer

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Abstract- The objective of this study was to determine and compare Cystatin C changes before and after radiotherapy in patients with stomach cancer who were candidate for radiotherapy. This study was conducted as a prospective cohort one. Eighteen patients with definite diagnosis of stomach cancer under treatment by radiotherapy who presented to Radiotherapy-Oncology Center of Imam Hossein Hospital, Tehran-Iran, and the treatment in all cases was simultaneous chemoradiation with Xeloda were included. In all patients before radiotherapy and after radiotherapy serum creatinine (Cr) and Cystatin C were measured simultaneously. Mean cystatin level before treatment (1.2±0.4) was significantly lower than that of post-treatment (1.6±0.36), (*P*=0.001). Serum Cr level before treatment was 1.15±0.33 and after radiotherapy was 1.08±0.24 and did not show significant difference. Glomerular filtration rate (GFR) of the patients before radiotherapy was -46.8 ± 21.0 and after radiotherapy was 43.8±15.8 that did not have significant difference (*P*=0.146) and also blood urea nitrogen (BUN) before radiotherapy was 20.72±3.7 and 20±6.38 after radiotherapy that did not have significant difference (*P*=0.6). Comparison of the Cystatin C difference with total radiation dose of the kidneys that are put in three dose groups in radiotherapy field had association that in dose of less that 18 gray (Gy) the Cystatin C change showed significant and positive association (*P*=0.027; r=0.52) and about 18-24 Gy the Cystatin C difference showed significant and negative association (*P*=0.023, r=-0.53). It seems that for evaluating the renal function, serum Cystatin C measurement is preferable than serum Cr. level.

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Keywords: Cystatin C; Radiotherapy; Stomach neoplasms

Introduction

Using radiotherapy in abdominal cavity can cause radiation of the kidneys and induce impairment in the kidneys function. If the kidney injuries are discovered in early stages, appropriate treatment can delay the progress of these lesions. Therefore, workup the renal function in these patients is essential (1,2). The routine technique for stomach cancer radiotherapy is using AP-PA fields and the minimum dose applied is 45 CY/25 F (3,4). In tumors of upper parts of the stomach, at least 50% of the left kidney is inside the radiotherapy field and in the tumors of lower parts of the stomach nearly the same size of the right kidney is inside the field (4,5). Radiotherapy has acute and chronic effects on the kidneys (6,7). Decrease in creatinine (Cr) clearance depends on the percentage of kidney which goes under radiotherapy and does not happen until 6 months after radiotherapy (5). In early diagnosis of renal dysfunction, serum Cr has limited value and can not detect early stages of renal dysfunction. The serum Cr level does not change until its clearance reaches less than 70 ml/minute and due to its secreted and filtered to the circulation after complete glomerular filtration, it underestimates renal function (6-9). Also, serum Cr level is affected by different factors such as age, gender, protein consumption, muscular mass, muscle metabolism, hydration, and some medications (10).

Also, during acute changes of glomerular filtration, serum Cr does not reflect actual renal function until it reaches a stable state (11).

One of the methods for early diagnosis of renal dysfunction and decreased glomerular filtration is the serum Cystatin C measurement that due to not having

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renal secretion and not reabsorbing to the circulation after filtration is closer to an ideal endogenous marker and gives us an accurate estimation of GFR. Cystatin C is not affected by exogenous factors (10-14).

Cystatin C is a reliable marker for the diagnosis of renal diseases especially in early stages when serum urea and Cr are still normal (14).

Cystatin C, a low molecular weight protein (13 kDa), freely crosses the glomerular filtration structure composed of capillary endothelium, glomerular basement membrane, and glomerular visceral epithelial cell and is almost completely reabsorbed by cells of the proximal tubule. This protein might, therefore, not only offer an ideal serum marker of glomerular filtration rate (GFR), but also prove useful in assessing the initial stages of renal impairment (5,15).

Early diagnosis of kidney damages and using appropriate medications can cause some degrees of symptom improvement or at least slowing the renal failure progress in these patients (6,7).

Since there has not been any study about Cystatin C changes in patients with stomach cancer who undergo radiotherapy, and Cystatin C changes is an early predictor of renal failure**,** the aim of this study was to determine Cystatin C levels before and after radiotherapy in patients with stomach cancer.

Materials and Methods

This study was done as a before and after clinical trial. All the patients who had the definite diagnosis of stomach cancer according to histo-pathology report with indication of radiotherapy and presented to radiotherapy-oncology department of Imam Hossein Hospital, Tehran-Iran, from 2008 to 2009 in case of meeting the inclusion criteria were entered into the study. The treatment in all patients was simultaneous chemoradiation with Xeloda. Radiation consisted of 45 Gy in 5 fractions per week during 5 weeks.

Inclusion criteria were cancer patients who were candidate for radiotherapy in the age range of 35-70 years with normal serum urea and Cr levels and having consent to participate in the study. Exclusion criteria were age more that 70 years, renal failure with Cr clearance equal to or less than 60 CC/min, usage of diuretic, cimetidine, trimetoprim and triamterene, combined chemotherapy regimen with cisplatin and a nephrotoxic agent, history of kidney radiotherapy, patients with metastasis and those who did not have consent for the study.

After selection of patients and completing the information form, before radiotherapy 5cc clot was obtained from patients and its serum was separated by centrifuge and was kept inside freezer in -20ºC. On the day of last session of radiotherapy, 5 cc clots with a pre-determined method was taken from patients. On the test day, the sample melted and its degree reached the laboratory temperature and serum urea, Cr, and Cystatin C were measured. In all patients before radiotherapy and after radiotherapy serum Cr and Cystatin C were simultaneously assayed. Blood samples were transferred to the laboratory with standard conditions and serum Cr was measured by Pars Azmoon kit and RI instrument Cobasmira 1000. Cystatin C was assayed by Dako cystatin C PET kit using PETIA (Particle-Enhanced Turbidimetry-Biovendor) nephlometry method. GFR calculated by MDRD formula.

Obtained data were documented in pre-designed information forms. All the figures were coded and inserted to the computer memory with SPSS statistical software.

Serum Cr, Cystatin C and BUN levels before and after radiotherapy were analyzed by the paired samples T test. Comparing the difference of Cystatin C, BUN, and Cr before and after treatment in two categorical groups was done by the independent samples T test. For assessment of association between quantitative variables, Pearson correlation test was applied. Also, $P<0.05$ was considered statistically significant.

Results

Eighteen patients with mean age of 62.7±9.6 were studied. Mean weight was 60.7±15.8. Eleven patients were male (61.1%) and 7 were female (38.9%). Fourteen patients (77.8%) received adjuvant and 4 (22.2%) received neoadjuvant therapy.

Comparison of Cystatin C, BUN, and Cr before and after treatment showed significant difference regarding Cystatin C. Mean Cystatin C before treatment (1.2±0.4) was significantly higher than after treatment (1.6±0.36) (P=0.001).

Serum Cr before radiotherapy was 1.15±0.33 and after treatment was 1.08±0.24 and did not have significant difference (P=0.1).

GFR before radiotherapy was 46.8±21.0 and after radiotherapy was (43.8±15.8) and did not have significant difference (P=0.146). Also, serum Bun levels before and after treatment were 20.72±3.7 and 20±6.38, (P=0.6). Comparing the differences of Cystatin C, BUN, Cr, and GFR before and after treatment was not significant in either gender (P>0.05). Comparing the differences of Cystatin C before and after treatment in three groups of dose showed in figures 1,2,3.

Table 1. Comparing the difference of Cystatin C with total dose of the kidneys that in three groups of dose are inside radiotherapy field showed association.

		Age	Weight	<18 Gy	18-24 Gy	>24 Gy
Cr change (after-before)	r	0.297	-0.307	0.036	-0.010	0.191
	P	0.232	0.216	0.889	0.967	0.448
BUN change (after-before)	r	-0.090	0.403	0.126	-0.156	0.136
	P	0.722	0.097	0.619	0.536	0.592
Cystatin C change (after-before)	r	0.165	0.216	0.521	-0.534	-0.104
	P	0.512	0.390	0.027(*)	0.023(*)	0.680
GFR change (after-before)	r	0.282	-0.321	0.034	0.011	0.108
	P	0.257	0.193	0.892	0.964	0.671

Spearman's rho Correlation, * *P*, statistical significant value

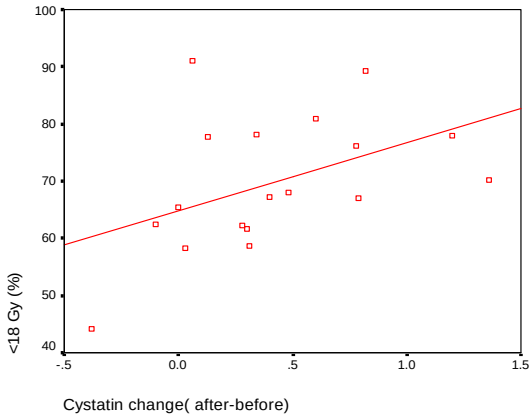

Figure 1. Comparing the difference of Cystatin C with total dose of the kidneys in dose of less than 18 Gy, (*P*<0.05) ststistical significant value.

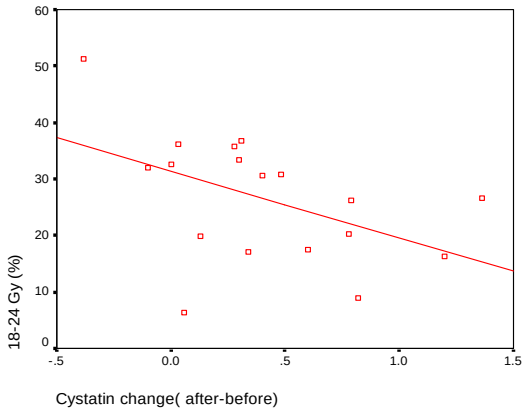

Figure 2. Comparing the difference of Cystatin C with total dose of the kidneys in dose of 18-24 Gy, (*P*<0.05) ststistical significant value.

Comparing the differences of Cystatin C, BUN, creatinine, and GFR before and after treatment did not have association with age nor with weight. Comparing the difference of Cystatin C with total dose of the kidneys that in three groups of dose are inside radiotherapy field showed association and in dose of less than 18 Gy cystatin C difference showed significant and positive association (*P*=0.027, r=0.52). In dose of 18-24 Gy, Cystatin C had significant and negative association (*P*=0.023, r=-0.53), (Table 1).

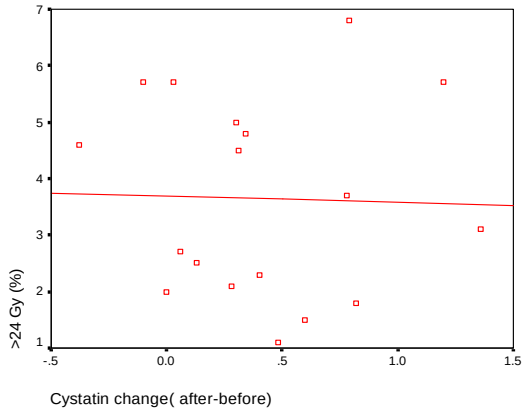

Figure 3. Comparing the difference of Cystatin C with total dose of the kidneys in dose of more than 24 Gy, (*P*>0.05) no ststistical significant value.

Discussion

It was seen in this study that Cystatin C, BUN, Cr, and GFR before and after treatment, between males and females and in two groups of adjuvant and neoadjuvant did not have significant differences.

In this study, for the first time significant increase in Cystatin C following abdominal cavity radiotherapy, especially stomach cancer was seen. But significant change was not observed regarding GFR, Cr, and BUN. In this study, Cystatin C changes showed association to the dose and the size of the kidney which was under radiotherapy in a way that these changes for dose of 18 Gray was significant. As the average size of the kidney that received radiation doses less than 18 Gy increased, Cystatin C changes were more and significant. As the volume that received radiation doses more than 18 Gy increased, Cystatin C changes were less and in doses more than 24 Gy, there were no changes. It seems that in doses more than 18 Gy especially more than 24 Gy renal function failure occurs and this part of the kidney that

has no function can not cause more changes in Cystatin C. Therefore, increasing radiation dose more can not have effect on this part of kidney which has not function and can not increase Cystatin C changes.

For doses more than 24 Gy that no changes in Cystatin C was observed it is likely that due to kidney size difference that received doses more than 24 Gy that was very little and started from 1.1% and was maximum 6.8%. Also in this study, GFR changes after radiotherapy had increase which was not significant.

Stubuc *et al.* (2000) with the objective of determining the strength of Cystatin C for the prediction of Cr clearance decrease in patients under chemotherapy with cisplatin performed a study in 60 patients. In this study it was revealed that Cystatin C had more powerful relationship with GFR compared to Cr (P=0.01, r=0.74) and according to ROC analysis the Cystatin C sensitivity was higher. According to the obtained results Cystatin C for prediction of Cr.cl < 76 has higher power and was preferable than serum Cr (16).

Tabatabaeifar *et al.* (2008) study showed that serum Cystatin C of patients before chemotherapy was 1.31±0.37 and after chemotherapy was 1.28±0.35 that this difference was not significant (P=0.6). Serum Cr before chemotherapy was 1.13±0.33 and after chemotherapy was 1.1±0.31 that did not have significant difference (P=0.6). Also, Cr clearance of 24-hour urine before chemotherapy was 80±16 and after chemotherapy was 79±15 that did not have significant difference (17).

This study may be the first in the world in its kind because there has not been an exact marker that can reflect the rate of kidney damage in acute phase.

Regarding the results of the current study, although BUN, Cr, and GFR of the patients who underwent radiotherapy have no significant changes and the patients have no symptoms, but Cystatin C has significant increase. Therefore, this study suggests evaluating the renal function by Cystatin C measurement in these patients. Since we need more studies in this field, it is recommended that for confirming the obtained results and definite clinical recommendations, more studies with larger sample sizes should be conducted.

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