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Radiation-Induced Pancreatic and Hematologic Injury in Gastric Tumors

Gastrik Tümörlerde Radyasyona Bağlı Pankreatik ve Hematolojik Hasarlanma

Gülşen Pınar Soydemir, Esengül Koçak Uzel

Department of Radiation Oncology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: There is little information about the pancreas even though it is close to the stomach, which may be affected by radiotherapy (RT), resulting in the alteration of the pancreatic functions. We aimed to demonstrate the radiation-induced pancreatic and hematologic injury in three-dimensional conformal radiation therapy (3D-CRT) for gastric tumors by examining the data of patients with gastric cancer (GC) and who underwent chemoradiotherapy (CRT) retrospectively, comparing the pancreatic exocrine enzymes and blood parameters between pre- and post-RT.

Method: The data of 43 patients who were referred to our clinic with GC at stage II–IV and underwent CRT were evaluated retrospectively. Pancreatic exocrine enzymes and blood parameters were studied. These parameters were compared between pre- and post-RT. Correlation analysis was performed between the alterations in pancreatic enzyme concentrations and the pancreatic dose distribution.

Results: The majority of patients (95.3%) receiving RT were treated with adjuvant RT (87.8%). CRT was given to 83.7% of the cases. The mean levels of albumin, amylase, lipase, white blood cells (WBC), and platelets were significantly lowered after RT compared with pre-RT levels ($p<0.05$). No correlation was found between the pancreatic exocrine enzymes and pancreatic mean dose, volume, and V40 ($p>0.05$).

Conclusion: The function of the exocrine pancreas and the hematological parameters may be affected by CRT in GC patients, which may provide clues for the assessment of RT-induced toxicity. This toxicity for the pancreas is inevitably associated with side effects and complications in terms of pancreatic functions and hematological findings.

Keywords: Chemoradiotherapy, gastric cancer, pancreatic enzymes, radiotherapy

ÖZ

Amaç: Pankreatik fonksiyonunun değişmesine neden olabilecek, gastrik tümörlere yönelik uygulanan radyoterapiden etkilenebilecek mideye yakın konumdaki pankreas hakkında çok az bilgi vardır. Gastrik kanserli ve kemoradyoterapi uygulanan hastaların verilerini retrospektif olarak inceleme sonucunda pankreas ekzokrin enzimlerini, kan parametrelerini radyoterapi öncesi ve sonrası karşılaştırarak, gastrik tümörleri için üç boyutlu konformal radyoterapisinde (3D-CRT) radyasyona bağlı pankreatik ve hematolojik hasarı göstermeyi amaçladık.

Yöntem: Kliniğimize II-IV evresinde gastrik kanser nedeniyle başvuran ve kemoradyoterapi uygulanan 43 hastanın verileri retrospektif olarak değerlendirildi. Pankreas ekzokrin enzimleri ve kan parametreleri çalışıldı. Bu parametrelerin radyoterapi öncesi ve sonrasına değişimleri karşılaştırıldı. Ayrıca pankreatik enzim konsantrasyonlarındaki değişiklikler ile pankreas doz dağılımı arasında korelasyon analizi yapıldı.

Bulgular: Radyoterapi alan hastaların çoğu (%95,3) adjuvan radyoterapi (%87,8) ile tedavi edildi. Vakaların %83,7'sine kemoradyoterapi verildi. Radyoterapi sonrası albümin amilaz, lipaz, lökosit ve trombosit düzeylerinin, radyoterapi öncesi düzeylere kıyasla önemli ölçüde düştüğü belirlendi ($p<0,05$). Pankreas ekzokrin enzimleri ile ortalama pankreatik doz, hacim ve V40 arasında korelasyon bulunmadı ($p>0,05$).

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Address for Correspondence/Yazışma Adresi: Gülşen Pınar Soydemir, Department of Radiation Oncology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
E-mail: gulpin3528@hotmail.com **ORCID ID:** 0000-0001-7758-8760

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Sonuç: Ekzokrin pankreasın işlevi ve hematolojik parametreler, gastrik kanser hastalarında kemoradyoterapiden etkilenebilir ve bu da radyoterapiye bağlı toksisitenin değerlendirilmesi için ipucu sağlayabilir. Bu toksisite, pankreas fonksiyonları ve hematolojik bulgular açısından yan etkilerle ve komplikasyonlarla kaçınılmaz olarak ilişkilidir.

Anahtar kelimeler: Gastrik kanser, kemoradyoterapi, pankreatik enzimler, radyoterapi

INTRODUCTION

Despite the recent decrease in the incidence of gastric cancer (GC) due to the therapeutic options, GC is still a major burden for global health.[1] According to the report of the World Health Organization in 2018, GC is the fifth most common malignancy among new cases of cancers in Turkey, with an incidence of 5.7%, and the second most common cause of cancer mortality with a rate of 8.6% of all cancer-related mortalities in the Turkish population.[2] Treatments for GC are classified as curative (tumor resection/gastrectomy and lymphadenectomy) or palliative. Surgery is the main remedy in GC treatment. However, surgical treatment alone may result in a high recurrence rate in GC patients. Chemoradiotherapy (CRT), chemotherapy (CT) alone, and radiotherapy (RT) alone are the main adjuvant treatment options for GCs with locally advanced tumors.[3,4]

The developed techniques of external RT, such as image-guided radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), have successfully prevented some extent of exposure to radiation on the organs at risk (OAR), suggesting reducing RT-related toxicity, morbidity, or mortality.[5] RT guidelines define the OAR as the spinal cord, heart, lung, liver, and kidney with dose restrictions for each organ.[6,7] As the pancreas is a radiation-sensitive organ, it tends to lose its volume and function after radiation exposure; however, it is not yet considered as an organ at risk for radiation treatment planning, and there is little information about the pancreas even though it is near to the stomach, may be affected from the RT doses, resulting in the alteration of the pancreatic function.[8,9] Therefore, in the present study, we aimed to demonstrate the radiation-induced pancreatic and hematologic injury in three-dimensional conformal radiation therapy (3D-CRT) for gastric tumors by examining the data of patients who were referred to our clinic with GC and underwent CRT retrospectively, comparing the pancreatic exocrine enzymes and blood parameters between pre- and post-RT. The other aim was to find out the correlation between the alterations in pancreatic enzyme concentrations and the pancreatic dose distribution.

METHOD

Patients Characteristics

The data of 43 patients diagnosed with GCs at stage II–IV in our clinic or tertiary institute between the years 2017 and 2019 and referred to our hospital for surgery or neoadjuvant and adjuvant CT or CRT were analyzed in this retrospective study. The exclusion criteria were being unoriented or non-cooperated and older than 90 years old. The gender, age, status and type of operation, histopathological findings, and TNM staging anatomical staging of tumors were recorded for analysis.

This study was approved by the Clinical Research Ethical Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Project no.: 2019-10-03; Date: 20 May 2019). The investigation confirms the principles outlined in Helsinki Declaration approved in 1975.

Radiation Treatment

3D-CRT and IMRT techniques were performed at fractions of 1.8 Gy daily for a total of 45 Gy, which was delivered using 6–18 MV photons. Patients with positive surgical margin were treated up to 50.4 Gy dose according to risk factors. RT field included the tumor bed, the remaining stomach, and regional nodes (perigastric, celiac, local para-aortic, splenic, suprapancreatic, pancreaticoduodenal, and porta hepatic) and extended 2 cm beyond the proximal and distal margins of resection. The pancreas was also contoured among the OAR. Mean pancreatic dose and the pancreatic volume that received 40 Gy (V40) values were calculated. CT (fluorouracil: 425 mg/m^2/day; leucovorin: 20 mg/m^2/day) was initiated on day 1 and was followed by CRT 28 days after the beginning of the initial cycle of CT. Capecitabine 825 mg/m^2 per os twice daily was added to the therapy on days 1–5 weekly for 5 weeks. Upon the end of the RT course, the first course CT scheme was carried out as adjuvant therapy throughout 3 months.

Laboratory Analysis

To compare the pancreatic exocrine enzymes and blood parameters, the concentrations of albumin (g/dL), total and direct bilirubin (mg/dL), amylase (U/L), lipase (U/L), hemoglobin (g/dL), neutrophil (10^3 µL^{-1}), white blood cells (WBC) (10^3

μL^{-1}), and PLT (10^3 μL^{-1}) were evaluated before RT treatment and reevaluated at the end of RT.

Follow-Up

Follow-up visits were carried out at the first month after completion of RT and then 3 months during the first 2 years. After this procedure, the follow-up visits were applied at 6-month intervals. Physical examination, a complete blood count, and liver function tests were repeated in each visit, and thoracic and abdominal computed tomography scanning was administrated when clinically indicated. The status, location, treatment type of recurrence or metastasis, mortality, and duration of follow-up (month) was recorded. Follow-up visits continued from the initial diagnosis to the last follow-up or date of death.

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, UT, USA) program was used for all statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used in evaluating the data. The distribution of quantitative data was tested by Shapiro–Wilk test and graphical examinations. Paired samples t-test was used for the comparison of normally distributed quantitative variables for pre-RT and post-RT, and Wilcoxon signed-rank test was used for the comparison of non-normally distributed quantitative variables for pre- and post-RT.

RESULTS

Descriptive Characteristics of Patients

This study was conducted in the Department of Radiation Oncology of Bakırköy Dr. Sadi Konuk Training and Research Hospital between the years 2017 and 2019, with a total of 43 cases, of which 27.9% were female and 72.1% were male patients (Table 1). The mean age of all patients at the beginning of treatment was 63.57±8.44 (range: 41.8–82.0). Of these patients, 88.4% were operated, 47.4% of them underwent a subtotal gastrectomy, and 52.6% (n=20) underwent a total gastrectomy (Table 1).

Considering the pathological findings, most of the patients (60.5%) were diagnosed with adenocarcinoma, and the minority of them (4.7%) were diagnosed with an adenoneuroendocrine tumor (Table 1). Considering the grading of disease, most of the patients were in grade 3 (55.8%). TNM staging showed that most of the patients were in T3 and T4 stages (46.5% and 41.9%, respectively). In addition, most of the patients were in N2 and N3 stage (27.9% and 32.6%, respectively), and most did not have distant metastasis (90.7%). According to the anatomic staging, most of the cases were in stage III (65.1%) (Table 1).

Table 1. Descriptive characteristics of patients

Parameter	n (%)
Age at the beginning of treatment (years)	
Mean±SD	63.57±8.44
Min-max	41.8–82
Gender	
Female	12 (27.9)
Male	31 (72.1)
Pathology	
Adenocarcinoma	26 (60.5)
Signet-ring cell carcinoma	9 (20.9)
Adenocarcinoma+signet-ring cell carcinoma	6 (14.0)
Adenoneuroendocrine	2 (4.7)
Grade	
Grade 1	2 (4.7)
Grade 2	17 (39.5)
Grade 3	24 (55.8)
Operation status	38 (88.4)
Operation type (n=38)	
Subtotal gastrectomy	18 (47.4)
Total gastrectomy	20 (52.6)
T Stage	
T1	1 (2.3)
T2	4 (9.3)
T3	20 (46.5)
T4	18 (41.9)
N Stage	
N0	11 (25.6)
N1	6 (14.0)
N2	12 (27.9)
N3	14 (32.6)
M Stage	
M0	39 (90.7)
M1	4 (9.3)
Stage	
Stage II	11 (25.6)
Stage III	28 (65.1)
Stage IV	4 (9.3)

Treatment Outcome of Patients

Neoadjuvant CT was applied to three (7.0%) of the cases and docetaxel+5-fluorouracil+cisplatin agents were used in all of these cases. The number of cycles of neoadjuvant CT varied between 2 and 5 (Table 2).

Table 2. Distribution of treatment types

Parameter	n (%)
Neoadjuvant	
CT status	3 (7.0)
CT agent (n=3)	
D+5-FU+C	3 (100)
Number of cycle (n=3)	
Mean±SD (min-max)	3.33±1.53 (2–5)
Adjuvant	
CT status	38 (88.4)
CT agent (n=38)	
C+FU	1 (2.6)
FUFA	3 (7.9)
Others	1 (2.6)
CAPOX	26 (68.4)
FOLFOX	3 (7.9)
XELODA	4 (10.5)
Number of cycle (n=38)	
Mean±SD (min-max)	5.47±2.27 (3–15)
Radiotherapy	
RT status	41 (95.3)
Adjuvant	36 (87.8)
RT type (n=41)	
Neoadjuvant	1 (2.4)
Palliative	4 (9.8)
RT duration (days) (n=39)	
Mean±SD (min–max)	37.03±9.07 (4–67)
Chemoradiotherapy status	36 (83.7)

CT: Chemotherapy; D+5-FU+C: Docetaxel+5-fluorouracil+cisplatin; C+FU: Cisplatin+5-fluorouracil; CAPOX: Capecitabin+oxaliplatin; FOLFOX: 5-Fluorouracil+leucovorin+oxaliplatin; XELODA: Capecitabine; FUFA: 5-Fluorouracil+folinic acid (leucovorin); RT: Radiotherapy; SD: Standard deviation

The number of cases having adjuvant CT was 38 (88.4%). Most of them (68.4%) had capecitabin + oxaliplatin, only one patient (2.6%) had cisplatin+5-fluorouracil, and another one (2.6%) had other agents. The number of cycles of adjuvant CT varied between 3 and 15 (Table 2).

A high proportion of 41 patients (95.3%) receiving RT were treated with adjuvant RT (87.8%). Duration of RT varied between 4 and 67 days. CRT was given to 83.7% of the cases (Table 2).

Clinical Outcome of Patients

Recurrence of the disease was detected in 7.0% of the cases, and the location of recurrence was local in all of these cases.

Table 3. Distribution of clinical outcomes

Parameter	n (%)
Recurrence status	3 (7.0)
Recurrence place (n=3)	
Local	3 (100)
Recurrence treatment (n=3)	
Surgery	1 (33.3)
CT	1 (33.3)
CT+RT	1 (33.3)
Metastasis status	19 (44.2)
Location of metastasis	
Liver	4 (21.1)
Bone	3 (15.8)
Lung	2 (10.5)
Brain	1 (5.3)
Buccal mucosa	1 (5.3)
Others	8 (42.1)
Treatment of metastasis	
CT	11 (68.8)
RT	2 (12.5)
CT+RT	3 (18.7)
Mortality (n=43)	
Ex	16 (37.2)
Follow-up duration (months)	
Mean±SD (min–max)	16.72±9.74 (2.4–44.2)

CT: Chemotherapy; RT: Radiotherapy; SD: Standard deviation

One of these cases was operated, another was applied only CT, and the last one was treated with CT+RT (Table 3).

Metastasis was detected in 44.2% of the cases (Table 3). It was mostly located in the liver (21.1%), bone (15.8%), and other anatomical regions (42.1%). As a treatment, most of these patients received CT (68.8%), and a minority of them received RT (12.5%).

According to the last condition examined during the follow-up ranged from 2.4 to 44.2 months, 37.2% (n=16) of the patients died (Table 3).

Laboratory Findings of Patients

The mean levels of albumin, amylase, lipase, WBC, and PLT were significantly lowered after RT compared with the pre-RT levels ($p<0.05$ for albumin, amylase, and lipase; $p<0.01$ for WBC and PLT). No statistical difference was detected for total bilirubin, albumin/total bilirubin ratio, direct bilirubin, hemoglobin, and neutrophil amounts before and after RT (Table 4).

Table 4. Comparison of laboratory findings pre- and post-radiotherapy

Parameter	Mean±SD (min-max)		p
	Pre-RT	Post-RT	
Albumin (g/dL)	3.86±0.42 (2.7–4.9)	3.68±0.51 (2.1–4.6)	0.015*
Total bilirubin (g/dL)	0.52±0.20 (0.2–1.2)	0.63±0.35 (0.3–1.9)	0.141
Albumin/total bilirubin	8.62±4.19 (2.3–25.6)	7.24±3.17 (1.6–14.4)	0.101
Direct bilirubin (mg/dL)	0.16±0.11 (0–0.7)	0.18±0.13 (0–0.7)	0.318
Amylase (U/L)	63.75±28.02 (16–145)	55.05±22.54 (11–95)	0.016*
Lipase (U/L)	25.31±15.88 (4.8–81)	13.57±23.46 (1–107)	0.010*
Hemoglobin (g/dl)	11.43±1.81 (6.1–16.9)	11.37±1.61 (7.4–15.1)	0.791
WBC (10^3 μL^{-1})	6.49±2.75 (2.7–15.2)	5.31±2.23 (1.9–10.3)	0.001**
PLT (10^3 μL^{-1})	252.63±113.02 (116–550)	194.63±83.11 (66–424)	0.001**
Neutrophil (10^3 μL^{-1})	3.62±2.43 (1.1–12.2)	3.52±1.85 (1–9)	0.668

*p<0.05; **p<0.01. RT: Radiotherapy; SD: Standard deviation; WBC: White blood cells; PLT: Platelets

Pancreatic Dose Distributions

The mean pancreatic radiation dose and the mean pancreatic volume were found to be 4579.90±122.73 cGy and 74.09±16.01 cm^3, respectively (Table 5). V40 of the pancreas had received 98.47% (±6.17). No significant correlation was detected between pre-RT pancreatic enzyme concentrations, and the mean pancreatic dose, volume, and V40 values (Table 6).

DISCUSSION

Radiation-induced toxicity on OAR is a crucial burden highly examined in the RT or CRT since the cancer patients treated undergoing these therapies have encountered side effects and complications. Although the pancreas has rarely been considered as an OAR, the exact dose of radiation inducing the pancreatic complications due to radiation toxicity within 5 years remains elusive.[8,10,11] Several studies considering this toxicity have been manifested from animal experiments, retrospective studies, and clinical trials using abdominal irradiation for curable diseases like GC.[8,12,13] However, these studies are not enough to extrapolate the radiation-related side effects and complications on pancreatic functions to determine the safe dose or volume limits for OAR during RT. Therefore, in the present study, we evaluated the data of 43 patients with GC at stage II–IV, who underwent neoadjuvant CT or RT or adjuvant CT or CRT, retrospectively and compared the pancreatic exocrine enzymes and blood parameters between pre- and post-RT. We found that the pancreatic exocrine enzymes amylase and lipase and the hematological parameters albumin, WBC, and PLT significantly lowered after RT compared with the pre-RT levels. No statistical difference was detected between pre- and post-RT levels of total and direct bilirubin, hemoglobin, and neutrophil.

There is a wide range of pancreatic volume values from 26.14 to 153.12 cm^3 in the literature.[8,9] A study analyzing the effect of CRT at GC on pancreatic enzymes and pancreas volume measured the mean pancreatic volume as 55.79±21.71 cm^3, as 55.59±22.19 cm^3 (26.14–153.12) in 45 Gy radiation and 56.92±22.59 cm^3 (30.60–104.43) in ≥50.40 Gy radiation [9]. In the present study, the mean pancreatic volume was 74.09±16.01 cm^3 and V40 of the pancreas had received 98.47±6.17.

Potential late toxicity of radiation exposure on pancreatic tissues including the endocrine and exocrine functions was reported in the prospective studies.[8,13,14] In one of these studies, the endocrine capacity of the pancreas was found

Table 5. Dose distribution of pancreatic radiotherapy

Pancreatic parameter	
Mean dose	
Mean±SD (min-max)	4579.90±122.73 (3822–4675)
Volume	
Mean±SD (min-max)	74.09±16.01 (35–118)
V40	
Mean±SD (min-max)	98.47±6.17 (59.92–100)
Pancreatic location	
Distal, n (%)	18 (46.2)
Proximal, n (%)	21 (53.8)

SD: Standard deviation; V40: Pancreatic volume that received 40 Gy

Table 6. Correlation between pre-radiotherapy hematologic measurements, and pancreatic mean dose, volume, and V40 values

Parameter	Pancreatic dose	Mean pancreatic volume	Pancreatic V40
Albumin	r 0.041‡	0.136†	0.235‡
	p 0.795	0.385	0.130
Total bilirubin	r‡ –0.061	–0.156	–0.133
	p 0.695	0.318	0.394
Albumin/total Bilirubin	r‡ 0.077	0.172	0.210
	p 0.624	0.271	0.177
Direct bilirubin	r –0.070‡	–0.004†	0.223‡
	p 0.702	0.984	0.221
Amylase	r‡ 0.079	0.191	–0.029
	p 0.674	0.304	0.876
Lipase	r‡ –0.035	0.099	–0.098
	p 0.824	0.527	0.533
Hemoglobin	r 0.055‡	0.008†	–0.033‡
	p 0.725	0.960	0.834
WBC	r 0.033‡	0.098†	–0.186‡
	p 0.834	0.530	0.233
PLT	r‡ –0.106	0.005	0.001
	p 0.498	0.977	0.998
Neutrophil	r‡ 0.004	0.028	–0.167
	p 0.978	0.857	0.284

*p<0.05; **p<0.01. †r: Pearson's correlation coefficient; ‡r: Spearman's correlation coefficient; WBC: White blood cells; PLT: Platelets.

to be very sensitive to irradiation which demonstrated itself with the decrease of beta-cell function following abdominal RT for GC.[14] Another similar study revealed the exocrine functional loss of the pancreatic tissue following the abdominal irradiation, suggesting that these functional losses are due to radiation-induced atrophy of the organ.[13] In a recent study, Gemici et al.[8] found a significant decrease in pancreas volume of the irradiated patients 1 year after comparing the adjuvant abdominal RT. Although the present study did not compare the pancreatic volume and mean doses of patients depending on the duration of follow-up and although no significant correlation was found between the pancreatic dose distribution and pancreatic enzymes, the decreased levels of pancreatic enzymes after RT suggest that the function of the exocrine pancreas may be affected from RT or CRT.

Amylase levels give clues for the function of the exocrine pancreas. The enzyme content of pancreatic secretion is decreased by exposure of the pancreas to radiation. The acinar cells of the pancreas are comparatively sensitive to radiation and hence are prone to abdominal radiation toxicity in RT of gastric malignancies.[9] Chronic pancreatitis was reported even years after abdominal RT.[15] Kandaz et al.[9] found that the exposure of the pancreas to a radiation dose of 5 Gy (V5) decreased the plasma amylase levels, associated with decreased risk of GC . In our study, the radiation dose of 45 Gy on the gastric tumor may probably affect the acinar cells of the pancreas, which are sensitive to radiation-induced injury more than islet cells, resulting in a significant decrease in amylase levels right after RT.

The relationships between the treatment planning and hematological parameters are being established by recording and analyzing the dosimetric and clinical data and the incidences of secondary malignancies.[16,17] As the hematopoietic system is highly sensitive to the damage from both cytotoxic CT and RT,[18] hematologic toxicity is a common complication of CRT that can limit the delivery of the treatment planning.[19]

RT is inevitably associated with side effects and complications in terms of pancreatic functions and hematological physiology. Tissue toxicity is the main obstacle to overcome in planning an effective radiation dose.[20,21] In a recent study, Vitzthum et al.[20] compared the hematological toxicity in head/neck vs cervical cancer patients undergoing CRT. They found that the peripheral cell counts significantly declined over the course of treatment in each group of cancer. Compared with the head/neck patients, the cervical cancer patients had greater mean reduction in absolute neutrophil, lymphocyte, and platelet counts with treatment. Both patient groups exhibited different patterns of subacute compensatory response in the bone marrow, and the higher volume of active marrow irradiated in cervical cancer patients appears to be a significant independent contributor to a faster depletion of circulating neutrophil, lymphocyte, and platelet cell types.[20] To reveal the hematological damage by RT in gastric patients, we investigated and compared the blood parameters before and after the planning treatment. The hematological parameters albumin, WBC, and PLT significantly lowered after RT; however, we could not find a statistical difference for the total and direct bilirubin, hemoglobin, and neutrophil amounts probably due to the different treatment modalities and durations compared with the literature. Therefore, the total and direct bilirubin, hemoglobin, or neutrophil levels alone may not give remarkable data in terms of radiation toxicity on the pancreas and hematological findings. However, oth-

er hematological parameters albumin, WBC, and PLT may give a clue for the evaluation of radiation-induced toxicity in operated GC patients treated with adjuvant CRT.

CONCLUSION

Improved RT techniques are needed to determine more accurate radiation dose and reduce radiation-related toxicity in OAR. In this retrospective study, we could identify a statistically significant difference related to pancreatic exocrine enzymes and some hematological parameters. The function of the exocrine pancreas and the hematological parameters may be affected by CRT in GC patients, which may provide clues for the assessment of RT-induced toxicity. This toxicity for the pancreas is inevitably associated with side effects and complications in terms of pancreatic functions and hematological findings.

More advanced studies are needed to create a dose–volume histogram and determine the dose constraints for the OAR including the pancreas. Thereafter, the quality assurance and protocols for RT planning must be better standardized.

Disclosures

Ethics Committee Approval: The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (No: 2019-10-03, Date: 20/05/2019).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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