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Long-Term Effect of Chemoradiotherapy At Gastric Cancer on Pancreas

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Abstract: *Local or regional disease recurs or distant metastasis occur after resection in a significant proportion of those with gastric cancer.The reduce the risk of recurrence and mortality, adjuvant chemoradiotherapy has been proved to increase relapse-free survival and overall survival importantly.there is no knowledge about pancreas even it's effected by most of the radiotherapy dose since it's in close vicinity of stomach and dose levels which may adversely effect the pancreatic function are not defined. Therefore, the purpose of this study patients who referred to our clinic with opere gastric cancer and underwent adjuvant chemoradiotherapy were appraised prospectively and effects of pancreatic RT doses and outcomes were studied. The association among pancreatic functions, fasting blood glucose, glycosylated hemoglobin, insulin and amylase, pancreas volume and adjuvant chemoradiotherapy was determined.Before the initiation, after the first session and at the 1th, 3th, 6th, 12th and 24th months of radiotherapy, difference between serum Fasting blood glucose (p:0.209), insulin (p:0.276), HbA1c (p:0.528) and amylase levels (p:0.109) levels were not statistically significant but there is statistically significant decrease in pancreatic volume after treatment (p:0.002).Local or regional disease recurs or distant metastasis occur after surgery in a significant proportion of those with gastric cancer. Adjuvant chemoradiotherapy is able to prolong survival and decrease recurrence in operated gastric cancer patients. We could not identify any statistically significant finding related to pancreatic toxicity or its presentation on biochemical parameters except pancreas atrophy in 24 months period. Although we haven't found any DMs in our sudy, it would be useful to continue the follow-up and perform more extensive studies.*

Keywords*: Chemoradiotherapy, Gastric cancer, Pancreatic enzymes, Pancreas volume*

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I. Introduct on

Gastric cancer is an aggressive disease and the fourth most common malignity [1], being the third leading cause of death among men and the fifth leading cause of cancer death among women worldwide [2]. Surgical resection is the primary therapy used, but palliative treatment is given for metastatic disease [3]. Gastric cancer with locally advanced stage disease, radiotherapy (RT), chemotherapy (CT) or chemoradiotherapy (CRT) are main treatment options. Surgical treatment alone reasons high recurrence rates [4], patients with a more advanced stage disease experience locoregional, peritoneal systemic recurrences or distant metastasis after receiving curative gastrectomy alone [5]. Clinical trials have been conducted to reduce the risk of recurrence and mortality, adjuvant chemoradiotherapy has been proved to increase relapse-free survival (RFS) and overall survival (OS) importantly [6]. The Intergroup 0116 (INT-0116) trial, the largest phase III trial comparing CRT versus observation, showed that adjuvant CRT prolonged OS and RFS for curatively resected gastric cancer [7,8]. But, final data from ARTIST and CRITICS trials showed that there was no important survival benefit in the CRT group over chemotherapy alone for D2 resected patients [9, 10].Different a study have shown that chemoradiotherapy is beneficial after D2 surgery [11].

Currently, standard dose of RT for gastric cancer is generally 45-50.4 Gy (in the absence of residual disease), 1.8 Gy per fraction [12]. Chemotherapy with 5-fluorouracil and calcium folinate is the mostly used regimen, although other agents such as capecitabine are being used in an increasing fashion [13]. Adjuvant radiotherapy is necessarily associated with side effects and the normal tissue toxicity is the major obstacle to administer effective radiation dose. Advanced RT techniques (eg. Intensity modulated radiotherapy (IMRT)) are likely to deliver radiation dose more exactly and reduce radiation toxicity significantly.In radiotherapy guidelines, kidney, liver, spinal cord, lung and heart are definited to be the organs at risk, and dose restrictions for each of them are detected. Otherwise, there is no knowledge about pancreas even it's effected by most of the

RT dose since it's in close vicinity of stomach and dose levels which may adversely effect the pancreatic function are not defined.Therefore, the purpose of this study patients who referred to our clinic with opere gastric cancer and underwent adjuvant CRT were appraised prospectively and effects of pancreatic RT doses and outcomes were studied. The association among pancreatic functions, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), insulin and amylase, pancreas volume and adjuvant CRT was determined.

II. Materials And Methods

Patients were eligible for analysis if they were diagnosed with gastric cancer, underwent gastrectomy during the study and referred to our clinic for adjuvant CRT were included in this prospective study, Diabetic patients were extracted from study. For researching the effects of RT over pancreas, HbA1c (%), FBG (mg/dl), amylase (U/L) and insulin (uIU/mL) levels were evaluated at the initiation. On the treatment planning, pancreas was contoured the organ.The computerized tomography (CT) scans at the control visit in 12th and 24 th month after RT and pancreas volume was contoured again to measure the difference. HbA1c, FBG, amylase and insülin levels were evaluated before RT and re-evaluated at the end of RT and at 1th, 3th, 6th, 12th and 24th months of RT. This study was approved by intuitional ethical committee, project no: 2015/9.

Patients Characteristics

Seventy one of gastric cancer patients who underwent gastrectomy were examined and the patients had stage I-IIIC. There were female to male ratio was 1/1.7 and 48 (68%) males and 23 (32%) females. Mean age at presentation was 55±9.2 (36-75) years. Of those tumors, 6 (8%) were detected in the pylorus, 24 (34%) in the antrum, 31 (44%) in the corpus and 10 (14%) in the cardia. Total excision was applied in 42 (59%) patients and subtotal excision was performed in 29 (41%) patients. 20 (28%) patients had undertake D1 dissection and 51 (73%) patients had D2 dissection.The surgical margin was negative in 53 (75%) and positive in 18 (25%) cases. In terms of pathological stage: 2 (3%) patients were diagnosed as stage IA, 2 (3%) patients as stage IB, 6 (8%) patients as stage IIA, 13 (18%) patients as stage IIB, 19 (27%) patients as stage IIIA, 13 (18%) patients as stage IIIB, and 16 (23%) patients as stage IIIC andgrade I was seen in 18 (25%), grade II was seen in 19 (27%) and grade III was seen in 34 (48%) patients respectively. The most common histologic subtype was adenocarcinoma (87%), followed by signet ring cell carcinoma (13%). 53 patients (75%) were treated with 45Gy, 16 patients (23%) were treated with 50.4Gy and 2 patients (3%) were treated 54Gy. Capecitabine was given to 7 (10%) patients and FUFA was given to 64 (90%) patients.The characteristics of gastric cancer patients who underwent gastrectomy are showed in table 1.

Adjuvant Treatment

Intensity-Modulated Radiation Therapy (IMRT) or Three-dimensional conformal RT (3D-CRT) technique, were performed at fractions of 1.8 Gy daily for a gross of 45-54 Gy which was gived by using 6-18 MV photons. 53 patients (74%) were treated 45 Gy dose, 16 patients (23%) were treated 50.4 Gy dose and 2 patients (3%) were treated 54 Gy dose.Treatment design involved the tumor bed or the remaining stomach, as well as regional nodes (perigastric, pancreaticoduodenal, porta hepatic, paraaortic, celiac, splenic and suprapancreatic) and extended 2 cm beyond the proximal and distal margins of resection.CT (leucovorin, 20 mg/m^2/day and fluorouracil, 425 mg/m^2/day) was begun on day 1 and was followed by CRT 28 days after the beginning of the initial cycle of CT. The second course of CT including fluorouracil (400 mg/m^2/day) and leucovorine (20 mg/m^2/day) was given on the first four and the last three days of RT. Capecitabine 825 mg/m^2 added to the therapy on days 1-5 weekly for 5 weeks.

Follow-up

Visits to reexamination were carried out at the first month after completion of RT and then three months during the first two years, after this process the follow up visits were applied at six months intervals. Physical examination, a complete blood count (FBG, HbA1c, insulin and amylase including) were repeated in each visit and thoracic and upper abdominal computed tomography scanning were administrated when clinically indicated. Follow-up visits continued from the initial diagnosis to the last follow-up or date of death. Statistical analysis of the data was done with SPSS Software (version 13.0 for Windows). For interaction analysis Repeated Measures test was used.

III. Results

Twenty five patients (35%) are still alive and, forty-six (65%) patients are dead. Mean survival time of all patients was 31.40±3.03 (95% CI, 25.44-37.35) months, and the median overall survival time was 20.0±3.27 (95% CI, 13.57-26.42) months. 1 and 2 year survival rates were 77.5% and 42.3% respectively. Regular blood levels of FBG, insulin, amylase and HbA1c were 74-106 mg/dL, <29.1 uIU/mL, 28-100 U/L and 4.5-6.0% respectively. Before the beginning of RT, thereafter the first session of RT and 1th, 3th, 6th, 12th and 24th

month later RT, insulin levels were 10.89±7.19 (2.00-33.70), 13.25±9.41 (2.08-38.20), 11.90±8.64 (2.28-29.30), 11.86±11.53 (2.59-46.0), 12.92±8.94 (2.30-29.30), 13.37±11.16 (2.59-29.50) and 12.28±9.26 (2.39-32.50) respectively. Among the seven assessments in the insülin phase, there was no statistically significant difference (p:0.276). Before the beginning of RT, thereafter the first session of RT and 1th, 3th, 6th, 12th and 24th month afterwards RT, FBG levels were 89.87±10.94 (62.0-105.0), 88.25±12.14 (54.0-112.0), 87.45±13.18 (45.0-108.0), 87.55±11.40 (52.0-109.0), 87.11±13.22 (46.0-110.0), 82.45±14.36 (52.0-105.0) and 84.48±14.36 (52.0-108.0) respectively. Among the seven evaluation in terms of FBG, there was no statistically significant difference (p:0.209). Before the beginning of RT, thereafter the first session of RT and 1th, 3th, 6th, 12th and 24th month later RT, HbA1c levels were 5.39±0.54 (4.30-6.50), 5.41±0.48 (4.20-5.90), 5.40±0.52 (4.30-5.90), 5.53±0.56 (4.10-6.0), 5.49±0.58 (4.30-5.90), 5.70±0.26 (5.50-6.0) and 5.45±0.26 (4.50-6.0) respectively. Among the seven assessments in terms of HbA1c, there was no statistically significant difference (p:0.528). Before the beginning of RT, thereafter the first session of RT and 1th, 3th, 6th, 12th and 24th month afterwards RT, amylase levels were 57.62±22.56 (10.0-99.0), 51.04±21.52 (8.0-101.0), 49.75±22.37 (11.0-107.0), 47.19±20.43 (10.0-91.0), 49.56±22.34 (11.0-107.0), 47.58±26.44 (10.0-109.0) and 48.16±25.42 (10.0-108.0) respectively. Until 3rd month after RT, amylase levels were decreased (p:0.0001) yet, after 1 and 2 year of RT, no statistically significant difference (p:0.109). Although temporary reduction of amylase levels to be seen in most patients, RT was not associated to a pathologic level in the early term. Nevertheless anyone of the patients were not diagnosed as diabetes mellitus at the end of the follow-up. Plasma levels of insulin, FBG, amylase and HbA1c are summarized in table 2.

All of the patients's mean pancreatic volume was found to be 55.79±21.71 cm^3. A wide content of pancreatic volume designated from 26.14-153.12 cm^3 were observed. In the group of 45 Gy RT mean value was calculated as 55.59±22.19 cm^3 (26.14-153.12) and in the group ofv ≥50.40 Gy RT mean value was found to be 56.92±22.59 cm^3 (30.60-104.43). All of the patients had CT scans when they came at the control visit in 12th and 24th month afterward RT and pancreas was contoured again for assessment the difference. All of the patients's mean pancreatic volume was measured as 21.97±6.85 cm^3 (12.46-32.41) afterward 1 year of RT and 21.78±6.75 cm^3 (12.06-33.01) afterward 2 year of RT (p:0.0001). In the group of 45 Gy RT, mean pancreatic volume was 21.56±6.39 cm^3 (13.84-32.41) (p:0.0001) and in the group of ≥50.40 Gy RT it was 22.66±8.15cm3 (12.46-30.80) (p:0.002) afterward 1 year of RT. In the group of 45 Gy RT, mean pancreatic volume was 21.08±6.75 cm^3 (12.06-32.01) (p:0.0001) and in the group of ≥50.40 Gy RT it was 21.98±8.05 cm^3 (12.54-30.65) (p:0.002) afterward 2 year of RT. All of the patients who passed on RT were demonstrated a 38% and 37% reduction in pancreatic volume at first and second year respectively. Volume degradation was 38% and 39% in the 45Gy RT group and ≥50.40 Gy RT group respectively. These worth were found to be statistically significant. The volumes of pancreas were showed in table 3.

IV. D □scuss □on

Local or regional disease recurs or distant metastasis occur after resection in a significant proportion of those with gastric cancer. To prevent such recurrences postoperative chemoradiation therapy have been studied. Chemoradiation is known to improve survival, based on the results of the INT-0116 trial [7]. On condition that gastric cancer patients live long, an opportunity of studying the radiation related late toxicity. In guidelines, kidney, spinal cord, heart and liver are defined as the organs at risk and dose restriction for each of them are defined. However, there is no knowledge about pancreas even it's effected by most of the RT dose since it's in close vicinity of stomach and dose levels which may adversely effect the pancreatic function aren't defined.Pancreas as an organ at risk for radiation related to late toxicity isn't investigated; also underlying procedure of the damage isn't determined.

FBG and HbA1c levels are necessary for the showing of diabetes. Some studies noticed pancreatic radiation toxicity as well as diabetes mellitus was higher in survivors of childhood cancers (leukemia, Wilm's tumor, renal tumors, soft tissue sarcoma, lymphoma, neuroblastoma) who had undergone upper gastrointestinal system RT [14]. Relationship between gastric cancer and diabetes was shown in animal model and it was mostly related with chemical induction of carcinogenesis [15]. Diabetes mellitus (DM) is associated with some type of cancers including liver, breast endometrial, bladder, colorectal and pancreatic cancer [16] and some prospective studies reported that determination of DM was associated with gastric cancer [17]. İn a study investigated the evaluation of late radiation induced endocrine functional disturbance of the pancreatic tissue in operated gastric cancer patients treated with adjuvant RT [18]. In evaluation of HbA1c and FBG, there didn't emerge any difference between the control and study groups at 12th months comparing the last phase and initial levels. In our study, there was no difference between plasma FBG and HbA1c levels at 12th months [19] and 24 months.

İnsulin is produced in Langerhans cells. In a animal study, exocrine pancreatic insufficiency has occurred after RT and Intraoperative electron beam radiotherapy (IORT). Evidence of gastrointestinal injury has been present in postradiation therapy in approximately 10% of patients, a figure which might be higher if more patients had a longer survival (average 10 months). Some patients need pancreatic enzyme

supplementation because of pancreatic deficiency treatment [17]. Heijmanns et al. in the study a significant decrease within insulin secretion in dogs treated with 30-35 Gy IORT. This study suggests that 25 Gy IORT to the pancreas may be used clinically, and that higher IORT doses may induce endocrine pancreatic insufficiency in the long-term. Moreover, there has been no evidence of radiation damage to the islets of Langerhans [16]. In our study plasma insulin levels didn't altered in patients treated with 45-54 Gy RT.

Amylase is secreted by both the pancreas (acinus sacs) and salivary glands, differing in molecular weight, carbohydrate content and electrophoretic mobility and they have identical enzyme activities. The enzyme content of pancreatic secretion is decreased by exposure of pancreas to radiation. The acinar cells of the pancreas are relatively sensitive to radiation and this finding has been described clearly after RT performs. [22]. In a study, early and late effects of intraoperative radiation on the exocrine and endocrine functions of the residual pancreas were examined in patients with pancreatic head resection. The results suggest that intraoperative radiation causes significant deterioration of pancreatic exocrine function at the early postoperative period [23]. In our study, exposure of pancreas to radiation decreases plasma amylase levels in early effect. In addition to, decreased in plasma amylase levels was found with radiation dose of 5 Gy (V5) in pancreas (p:0.001). Latter doses beyond 5 Gy (V10, V20 and V40) were not associated with decrease in such biochemical levels.

Stefanovic et al. reported the volume of the pancreas showed a range from 37.4 to 168.2 cm^3 and an average pancreas volume of 79.2±24 cm^3 in 220 individuals [24]. In our study, mean pancreatic volume of all the patients was 55.79±21.71 cm^3. It was detected the fact that a wide range of the pancreatic volume values from 26.14 to 153.12 cm^3. Mean pancreatic volume was measured as 55.59±22.19 cm^3 (26.14-153.12) in 45 Gy RT group and 56.92±22.59 cm^3 (30.60-104.43) in ≥50.40 Gy RT group.Ahmadu-Suka et al.reported RT dose-response relationships were observed for the injury to the pancreas as a whole, for pancreatic fibrosis and decrease in normal acinar cells [25]. In our study, mean pancreatic volume of all the patients was measured as 21.78±6.75 cm^3 (12.06-33.01) after 24th months of RT (in 45 Gy RT group, mean pancreatic volume was 21.08±6.75 cm^3 (12.06-32.01) and in ≥50.40 Gy RT group it was 21.98±8.05 cm^3 (12.54-30.65)). Acinar cells of the pancreas, which are more sensitive to radiation induced injury more than islet cells and chronic vascular injury is the main way for radiation damage such as fibrosis and atrophy. Finally, pancreatic volumes of all the patients who underwent RT demonstrated a statistically significant decrease.

V. Conclusion

Local or regional disease recurs or distant metastasis occur after surgery in a significant proportion of those with gastric cancer. Adjuvant chemoradiotherapy is able to prolong survival and decrease recurrence in operated gastric cancer patients. We could not identify any statistically significant finding related to pancreatic toxicity or its presentation on biochemical parameters except pancreas atrophy in 24 months period. Although we haven't found any DMs in our sudy, it would be useful to continue the follow-up and perform more extensive studies.

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Table 1. Patient characteristics and pancreas doses

	n (%)	**Pancreas Mean Dose**
General	71	4456.88±204.55 (3760-4767)
Sex		
Female	23 (32)	443.33±235.21 (3760-4767)
Male	48 (68)	4503.70±105.57 (4246-4676)
Anatomical Site		
Cardia	10 (14)	4522.86±117.45 (4358-4700)
Corpus	31 (44)	4508.68±167.23 (4021-4676)
Antrum	24 (34)	4417.48±229.94 (3760-4630)
Pylorus	6 (8)	4503.33±66.51 (4436-4569)
T Stage		
T1	3 (4)	4338.33±312.98 (3977-4525)
T2	4 (6)	4271.67±490.57 (3786-4767)
T3	31 (44)	4493.43±133.81 (4092-4700)
T4	33 (46)	4478.25±178.96 (3847-4686)
N Stage		
N0	9 (13)	4423.22±211.08 (3977-4700)
N1	17 (24)	4419.13±257.10 (3786-4657)
N2	17 (24)	4511.19±147.60 (4157-4676)
N3	28 (39)	4490.48±152.38 (4021-4686)
Stage		
IA	2 (3)	3786.0
IB	2 (3)	4413.0
IIA	6 (8)	4478.11±74.07 (4406-4643)
IIB	13 (18)	4405.56±281.44 (3760-4686)

IIIA	19 (27)	4541.47±117.39 (4200-4700)
IIIB	13 (18)	4457.24±157.03 (4092-4657)
IIIC	16 (23)	4428.75±263.68 (3847-4767)
Histology		
Adenocarcinoma	62 (87)	4462.13±201.61 (3786-4767)
Signet Cell	9 (13)	4504.83±106.38 (4262-4686)
RT Dose		
45 Gy	53 (75)	4457.16±218.20 (3760-4700)
50.4 Gy	16 (23)	4488.88±165.87 (4021-4686)
54 Gy	2 (3)	4483.50±400.93 (4200-4767)
Grade		
I	18 (25)	4468.31±123.47 (4157-4657)
II	19 (27)	4468.69±209.94 (3786-4700)
III	34 (48)	4560.08±109.07 (4383-4676)
Surgical margins		
Negative	53 (75)	4447.55
Positive	18 (25)	4536.00
Dissection		
D1	20 (28)	4446.06±216.08 (3847-4676)
D2	51 (73)	4478.16±179.04 (3786-4767)
Surgery		
Total	42 (59)	4498.20±163.57 (3786-4700)
Subtotal	29 (41)	4426.33±216.95 (3847-4767)
Chemotherapy		
FUFA	64 (90)	4454.45±215.00 (3760-4767)
Capecitabine	7 (10)	4480.67±125.10 (4246-4604)

Table 2. Plasma diabetic biomarkers (FBG, insulin, HbA1c and amylase)

	FBG (mg/dL)	**□nsulin (uIU/mL)**	**HbA1c (%)**	**Amylase (U/L)**
Before RT	89.87±10.94 (62.0-105.0)	10.89±7.19 (2.00-33.70)	5.39±0.54 (4.30-6.50)	57.62±22.56 (10.0-99.0)
After RT	88.25±12.14 (54.0-112.0) p:0.246	13.25±9.41 (2.08-38.20) p:0.247	5.41±0.48 (4.20-5.90) p:0.600	51.04±21.52 (8.0-101.0) p:0.008
1th month After RT	87.45±13.18 (45.0-108.0) p:0.261	11.90±8.64 (2.28-29.30) 0.371	5.40±0.52 (4.30-5.90) p:0.802	49.75±22.37 (11.0-107.0) p:0.007
3th month After RT	87.55±11.40 (52.0-109.0) p:0.226	11.86±11.53 (2.59-46.0) p:0.209	5.53±0.56 (4.10-6.0) p:0.784	47.19±20.43 (10.0-91.0) p:0.0001
6th month After RT	87.11±13.22 (46.0-110.0) p:0.234	12.92±8.94 (2.30-29.30) p:0.334	5.49±0.58 (4.30-5.90) p:0.837	49.56±22.34 (11.0-107.0) p:0.125
1th year After RT	82.45±14.36 (52.0-105.0) p:0.179	13.37±11.16 (2.59-29.50) p:0.296	5.70±0.26 (5.50-6.0) p:0.468	47.58±26.44 (10.0-109.0) p:0.069
2th year After RT	84.48±14.36 (52.0-108.0) p:0.209	12.28±9.26 (2.39-32.50) p:0.276	5.45±0.26 (4.50-6.0) p:0.528	48.16±25.42 (10.0-108.0) p:0.109

	Pancreas Volume			p
	Before RT	**12th month After RT**	**24th month After RT**	
All patients	55.79±21.71cm^3 (26.14-153.12)	21.97±6.85cm^3 (12.46-32.41)	21.78±6.75 cm^3 (12.06-33.01)	0.0001
45 Gy	55.59±22.19 (26.14-153.12)	21.56±6.39 (13.84-32.41)	21.08±6.75 cm3 (12.06-32.01)	0.0001
50.4 Gy	56.92±22.59 (30.60-104.43)	22.66±8.15 (12.46-30.80)	21.98±8.05cm3 (12.54-30.65)	0.002

Table 3. Before RT and 2th year after RT Pancreas volüme

*Mustafa Kandaz. "Long-Term Effect of Chemoradiotherapy At Gastric Cancer on Pancreas." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.11 (2017): 45-51