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Radiation induced pancreatic damage

Radiation-induced injury of the exocrine pancreas after chemoradiotherapy for gastric cancer

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ABSTRACT

Background and purpose: The pancreas is located almost entirely within the treatment area for radiotherapy of gastric cancer. The aim of this study was to analyze radiation-induced injury of the exocrine pancreas.

Material and methods: The study included 127 gastric cancer patients, who underwent preoperative or postoperative chemoradiotherapy. A total dose of 45 Gy was given in 25 fractions. Concurrent chemotherapy was 5-fluorouracil-based. Lipase and α-amylase were assayed before, during and after treatment.

Results: Lipase and α-amylase deficiencies were found in 48.2% and 19.7% of patients, respectively. In the univariant analysis, age and pretreatment α-amylase and lipase activities influenced on risk of injury of the exocrine pancreas ($p < 0.05$). Younger patients (<65 years) had a lower risk of hypoamylasemia than older patients. The probability of insufficiency was lower than 0.2 for patients with pretreatment α-amylase and lipase activities above 50 U/L and 55 U/L, respectively. The multivariate analyses of the time to hypolipasemia showed that only pretreatment lipase activity was significant.

Conclusions: Gastric cancer patients have an increased risk of exocrine pancreatic insufficiency after chemoradiotherapy. Thus, the pancreas should be regarded as an OAR. Measuring lipase activity should be the standard for assessing radiation-induced pancreatic injury.

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Radiotherapy is an important component of combined modality treatment for tumors located in the abdomen, especially gastric, pancreatic and biliary tract cancers. The effectiveness of radiation therapy depends on the total dose and the fractionation scheme. Knowledge regarding radiation-induced injury of organs at risk (OAR) is necessary to modify current treatment schemes. Of the abdominal organs, the radiosensitivity of the liver, kidney, bowel duodenum and stomach has been accurately assessed [1–4]. The pancreas lies almost entirely within the treatment area for postoperative and preoperative radiotherapy of gastric cancer, and the endocrine and exocrine functions of this organ are well known. Recently, a published study assessed the risk of damage to the endocrine pancreas [5]. However, no systematic studies have provided data on exocrine pancreatic function. The NCI Common Terminology Criteria for Adverse Events (CTCAE) only describes pancreatitis as a possible consequence of pancreatic radiation injury [6]. Furthermore, the Quantitative Analyses of Normal Tissue Effects Found in the Clinic (QUANTEC) guidelines do not include the pancreas as an OAR [7]. However, radiation-induced pancreatic insufficiency can be expected to be similar to radiation-associated salivary gland injury. Based on our previous study data, our goal was to analyze early and late radiation-induced injury of the exocrine pancreas after pre- or postoperative chemoradiotherapy for gastric cancer [8,9].

Materials and methods

Patient population

Patients with biopsy-proven, locally advanced gastric adenocarcinoma, with no evidence of distant metastases, were treated with pre- or postoperative chemoradiotherapy. All the patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2, serum creatinine levels <1.5 mg/dl, serum bilirubin levels <2.0 mg/dl, a granulocyte count >1,500 cells/μl and a platelet count >100,000 cells/μl. Pretreatment staging included a complete physical examination, esophagogastroscopy

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with biopsies, and a chest X-ray or computed tomography (CT) of the abdomen. The patients did not undergo laparoscopic staging. This staging process focused on identifying patients with operable gastric cancer who were eligible for surgery. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The study included 127 patients, including 35 females (27.6%) and 92 males (72.4%), with a mean age of 58 years and an age range of 25–74 years. Patients were enrolled in the study between 2008 and 2013. Patient characteristics are listed in Table 1 (Supplementary Material 1).

Chemoradiotherapy

The treatment regimen consisted of radiotherapy and chemotherapy, given over 33 days. A total dose of 45 Gy was given in 25 fractions (5 fractions per week for 5 weeks). The tumor location or gastric bed was defined based on CT scans of the abdomen and upper gastrointestinal endoscopy reports. The treatment fields encompassed the stomach or gastric bed and regional lymph nodes (gastric, celiac, gastroduodenal, porta hepatis, splenic, peripancreatic, pancreaticoduodenal and lower esophageal). The longitudinal margins of the esophagus or duodenum (5 cm) were included when the tumor involved the cardia or the gastroduodenal junction [10]. Radiation therapy was delivered with a high-energy linear accelerator (Clinac 23EX; Varian Medical Systems, Palo Alto, CA, USA), using 6–20 MV photons. Radiotherapy was administered using intensity-modulated radiation therapy or a three- or four-field isocentric conformal technique. In these techniques, the almost whole pancreas is irradiated. The concurrent chemotherapy regimen was based on 5-fluorouracil (5-FU). Chemotherapy was administered at least 1 h prior to starting irradiation. 5-FU was administered intravenously as a 10-min bolus injection. Patients routinely received prophylactic antiemetic support. Bolus infusions of 5-FU (325 mg/m^2 of body surface area) were administered intravenously on days 1–5 and 29–33. Complete blood cell (CBC) counts and liver, renal and pancreatic function tests were monitored prior to each course. Adjuvant chemotherapy for up to 6 cycles was planned for all patients who underwent R0/R1 resection. For that group of patients after neoadjuvant chemoradiotherapy, adjuvant chemotherapy was started as soon as possible after surgery. Chemotherapy consisted of four 5-day cycles. Bolus infusions of 5-FU (425 mg/m^2/day) as well as bolus infusions of LV (20 mg/m^2/day) were administered intravenously. Chemotherapy courses were repeated every 28 days.

Toxicity criteria

Treatment-related toxicity was classified according to the Common Terminology Criteria for Adverse Events, version 3.0 [6]. Nausea, vomiting, diarrhea, leukopenia, granulocytopenia, lymphocytopenia and thrombocytopenia were assessed weekly during chemoradiotherapy.

Laboratory assays

Serum enzyme levels in participating patients were assayed before, during and after treatment. Peripheral venous blood samples were obtained using a standard procedure with a Becton Dickinson Vacutainer System (Becton, Dickinson and Company; Plymouth, UK). Blood samples were collected into plastic vacuum tubes containing a separation gel without anticoagulant. The serum specimens were processed by centrifugation for half an hour (2000 g/10 min) at room temperature. The α-amylase and lipase levels were determined by a spectrophotometric technique known as absorption photometry using reagent kits and the biochemical analyzer Architect ci8200 by Abbott Laboratories (Abbott Park, IL 60064, USA). The α-amylase assay method involves using a nitrophenyl derivative of maltosaccharide as a substrate. The assay measures the rate of formation of free 2-chloro-4-nitrophenol, which is detected spectrophotometrically at 404 nm to give a direct measurement of the α-amylase activity in the sample. The lipase assay is based on the hydrolysis of a natural substrate 1,2-diglyceride to produce a 2-monoglyceride, which in turn releases glycerol and free fatty acid. Glycerol is then assayed by a sequence of enzymatic actions (glycerol kinase, glycerol phosphate oxidase, and peroxidase) that produce a quinone monoimine dye. The rate of formation of the dye, measured as an increase in absorbance at 548 nm, is proportional to the lipase concentration in the sample. The reference ranges for lipase and α-amylase were 8–78 U/L and 25–125 U/L, respectively. In the 127 patients, α-amylase and lipase were assayed 674 times (mean 5, range from 2 to 17) and 512 times (mean 4, range from 2 to 17), respectively. Mean time of last assay of amylase and lipase was 424 days (range, 24–2223) and 435 days (range, 18–2223), respectively.

Follow-up

Each patient was periodically assessed after treatment for at least 5 years or until death. The follow-up evaluations included a physical examination, esophagogastroscopy, chest X-ray, transabdominal ultrasonography or CT scans of the abdomen, CBC count, CEA and CA 19–9 levels, and liver, pancreatic and renal function tests.

Statistical analysis

The time to exocrine pancreatic insufficiency was estimated using the Kaplan–Meier method. The groups were compared using the log-rank test. Additionally, a logistic regression was used to analyze the pretreatment activity of pancreatic enzymes. Receiver operating characteristic (ROC) analysis was also used. Computations were performed in the R platform [11].

Results

During and after treatment, α-amylase deficiency occurred in 19.7% (25/127) of the patients, and lipase deficiency occurred in

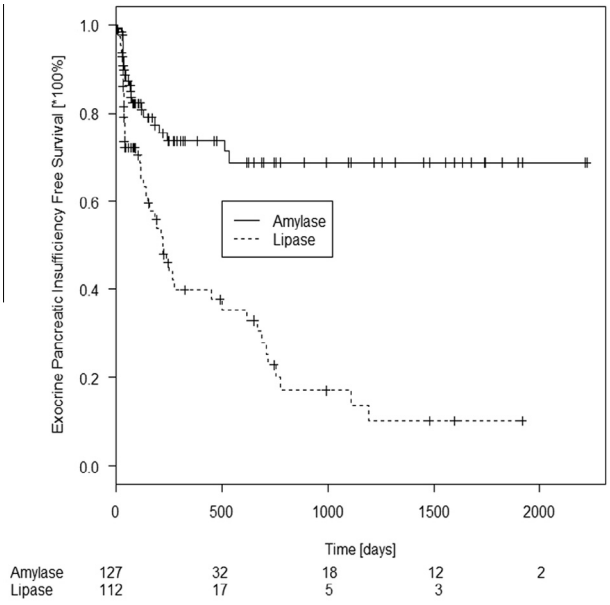

Fig. 1. Exocrine pancreatic insufficiency after chemoradiotherapy for gastric cancer.