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Original Article

Vascular enhancement pattern of mass in computed tomography may predict chemo-responsiveness in advanced pancreatic cancer

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ABSTRACT

Introduction: Chemo-responsiveness in pancreatic cancer is known to be dependent on fibrosis and vascularity. The purpose of this study was to assess vascular enhancement in advanced pancreatic adenocarcinoma with or without liver metastasis in computed tomography (CT) and to analyze the correlation between enhancement patterns and chemo-responsiveness.
Methods: Patients were assigned to either a responder group (partial response or stable disease) or a non-responder group (progressive disease) according to chemo-responsiveness assessed by CT before and after gemcitabine-based chemotherapy. Hounsefield unit (HU) was measured in pancreatic mass and the largest metastatic liver mass using region of interest (ROI). HU differences (ΔHU) between arterial and pre-contrast phase were calculated.
Results: Of the 101 study subjects, 78(77.2%) were assigned to the pancreas responder group {mean ΔHU (±SD), 36.7(±21.6)} and 23(22.8%) to the pancreas non-responder group {mean ΔHU (±SD), 20.6(±9.9)} ($p = 0.001$ for ΔHUs). Of the 46 study subjects with liver metastasis, 25(54.3%) were assigned to the liver metastasis responder group {mean ΔHU (±SD), 36.9(±21.0} and 21(45.7%) to the liver metastasis non-responder group {mean ΔHU (±SD), 17.1 (±24.0)}, ($p = 0.005$ for ΔHUs).
Conclusion: CT determined mass vascular enhancement patterns may predict chemoresponse in advanced pancreatic cancer.

1. Introduction

Pancreatic ductal adenocarcinoma (PDA) is one of the most intractable malignancies with a 5-year survival rate of less than 5% [1]. The devastating prognosis of PDA has been ascribed to the ineffectiveness of chemotherapy as well as its intrinsic aggressive biological nature [2]. One of the explanations offered for poor response to chemotherapy is that chemotherapeutic agents are poorly delivered to PDA tissues because blood vessels are compressed by dense stromal matrix. This matrix is a prominent histological hallmark of PDA and an abundance of stromal matrix is

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usually referred to as desmoplasia or a desmoplastic reaction [3,4]. Recently, several studies on systemic chemotherapy in PDA focused on the desmoplastic reaction as a predictor of chemo-responsiveness [5]. Provenzano et al. reported that enzymatic ablation of stromal hyaluronic acid by PEGPH20 can increase intratumoral perfusion and therapeutic delivery of gemcitabine in murine PDA [6].

Although pancreatic cancer has considerably lower microvessel densities than normal pancreatic parenchyma [7], the induction of angiogenesis is known to be an important factor of growth, progression, and metastasis in PDA [8–11]. Furthermore, elevated VEGF (vascular endothelial growth factor) expression has been associated with poor prognosis in pancreatic cancer [12–14], and intra-tumoral blood flow measured by contrast-enhanced ultrasonography has been reported to be correlated with prognosis in unresectable pancreatic cancer [15].

Contrast-enhanced computed tomography (CT) is the standard diagnostic imaging modality for PDA, and it has been suggested that the pathologic features of PDA can be estimated using enhanced CT findings. In a retrospective study, it was found the extent of CT enhancement is inversely proportional to the degree of malignancy of PDA [16]. Yuki et al. reported that dynamic CT enhancement patterns are related to vascularity and may be modified by the extent of fibrosis. In this study, attenuation differences between arterial and pre-contrast phases were found to be positively correlated with vascularity and negatively correlated with extent of fibrosis [17].

Taken together, the chemotherapeutic resistance of PDA appears to be partly dependent on desmoplastic reaction, which is correlated with tumor vascularity that can be estimated using CT enhancement patterns. Building on these studies, we shifted focus from the relation between CT enhancement patterns and vascularity/fibrosis to the relation between CT enhancement patterns and chemo-responsiveness. Therefore, the purpose of the current study was to assess vascular enhancement patterns of pancreatic and liver metastatic masses by CT and to analyze the relation between enhancement patterns and chemo-responsiveness.

2. Methods

2.1. Patients

One hundred and ninety one consecutive patients with histologically confirmed PDA treated from January 2007 to March 2015 at four tertiary referral centers were initially considered for this retrospective study. The inclusion criteria applied were as follows: (1) unresectable stage (stage III or IV), (2) the availability of a CT scan, including pre-contrast and arterial phases, before chemotherapy, and (3) at least 3 cycles of gemcitabine-based chemotherapy plus a single follow-up CT scan conducted to evaluate chemo-responsiveness. Of the 191 patients, 152 met the inclusion criteria. The study exclusion criteria applied were as follows: (1) surgical resection as a primary therapy for PDA (n = 21), (2) concurrent chemotherapy and radiotherapy (n = 13), and (3) chemotherapy without gemcitabine (n = 17). Resultantly, 101 patients were enrolled in the present study and constituted the study cohort (Fig. 1). This study protocol was reviewed and approved by the Institutional Review Board of our institution, which waived the requirement for informed consent (IUH-IRB 14-106).

2.2. Chemotherapeutic regimens

All 101 study subjects were administered gemcitabine-based chemotherapy. The chemotherapy regimens used were as follows: (1) 25 patients received gemcitabine (1000 mg/m^{2}administered by 30-min intravenous infusion) once weekly for 3 consecutive weeks every 4 weeks, (2) 25 patients were treated with a combination of gemcitabine (1200 mg/m^2, administered by 30-min intravenous infusion on days 1 and 8) and 5-fluorouracil (1200 mg/m^2, administered as a 10-h continuous infusion on days 1,2,3 and 4) of a 21-day schedule, (3) 3 patients received a combination of gemcitabine (1200 mg/m^2 by 30-min intravenous infusion on days 1 and 8) and cisplatin (60 mg/m^2 by 15-min intravenous infusion on day 1) every 3 weeks, and (4) 48 patients were treated with a combination of gemcitabine (1000 mg/m^{2}by 30-min intravenous infusion on days 1, 8, and 15) and erlotinib (100 mg, daily) using a 4 week schedule.

2.3. Contrast-enhanced CT

CT was performed using a 16-slice MDCT scanner or a 64-slice MDCT scanner using pancreas CT protocols. For the 16-slice MDCT scanner, data were acquired using 16 detector rows and a beam collimation of 1.25 × 32 mm, a rotation time of 0.6 s, a section reconstruction thickness of 5 mm (pre/portal phase) or 2.5 mm (arterial phase), and an image reconstruction interval of 5 mm (pre/portal phase) or 2.5 mm (arterial phase). For the 64-slice MDCT scanner, scan data were acquired using a beam collimation of 0.75 × 16 mm, a rotation time of 0.5 s, a section reconstruction thickness of 5 mm (pre/portal phase) or 2 mm (arterial phase), and an image reconstruction interval of 5 mm (pre/portal phase) or 2 mm (arterial phase). In our country, CT technique of pancreas protocol use 'fixed scan delay'. After the acquisition of the pre-contrast phase, taking the pancreatic arterial phase is started 35 s after contrast administration. Then pancreas portal phase acquisition is started 35 s after completion of pancreatic arterial phase. All patients received a nonionic contrast medium at 2 ml/kg, which was administered using a mechanical power injector at 3 ml/s through an 18-gauge intravenous catheter inserted in an arm vein. Acquisition of the pancreatic arterial phase was started 35 s after contrast administration.

2.4. Determination of delta HU (ΔHU) values and the assessment of chemo-responsiveness

In each patient, Hounsfield unit (HU) values were obtained for the pancreatic mass and if liver metastatic masses were present, from the largest liver mass, by placing a 1 × 1 cm of region of interest (ROI) on most enhanced tumor areas in the arterial phase, taking care to exclude cystic areas, necrotic areas, and adjacent pancreatic parenchyma. HUs were measured throughout the study by an experienced radiologist (Y.S.J.). The measurements were performed three times, and the average data were recorded. Initially, ROIs were drawn on pre-contrast and arterial phase CT scans before commencing chemotherapy, delta HU (ΔHU) values were calculated by subtracting the HUs of ROIs in pre-contrast phase from the same ROIs in arterial phase (Figs. 2 and 3). After at least 3 chemotherapy cycles, a follow-up CT scan was performed to evaluate objective tumor response in accord with the RECIST criteria (version 1.1). Partial response (PR) was defined as ≥50% decrease in the product of the two greatest perpendicular tumor diameters; progressive disease (PD) was defined as a ≥25% increase in the product of the two greatest perpendicular tumor diameters; stable disease (SD) was defined as not PR or PD. Patients that achieved PR or SD were classified as responders to chemotherapy and the patients showing PD were classified as non-responders.

2.5. Statistical analysis

Patient demographic and laboratory data are expressed as

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