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컴퓨터 단층 촬영 조직 분석을 통한 췌장 선암종의 절제 가능성 평가와 예후 예측

CT prediction of resectability and prognosis in patients with pancreatic cancer after neoadjuvant treatment using image findings and texture analysis

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Abstract

CT prediction of resectability and prognosis in patients with pancreatic cancer after neoadjuvant treatment using image findings and texture analysis

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Purpose: To assess the utility of CT findings and texture analysis for predicting resectability and prognosis after neoadjuvant therapy in patients with surgery for pancreatic cancer.

Materials and Methods: From 2013 to 2016, among 308 patients, forty-five patients with pancreatic cancer underwent both neoadjuvant therapy and surgery were included. They underwent neoadjuvant concurrent chemoradiation therapy (CCRT, n=27) or neoadjuvant chemotherapy (ChoT, n=18). All patients performed baseline and preoperative CT. Two reviewers assessed CT findings and resectability (resectable, borderline resectable, unresectable). Residual tumor categorized into no residual tumor (R0) and residual tumor (R1 or R2). We analyzed the relationship between CT findings and R classification.

CT texture analysis was performed by PC-based in-house software using baseline and preoperative CT. Texture values obtained by subtracting preoperative CT from baseline CT were analyzed using multivariate Cox/logistic regression analysis to identify significant parameter for prediction of resectability and prognosis.

Results: There were 30 patients without residual tumor (CCRT, n=20; ChoT, n=10) and 15 patients with residual tumor (CCRT, n=7; ChoT, n=8). Overall accuracy for R0 resectability was better when considering borderline as resectable tumor [68.9% (31 of 45) for both readers] than when considering borderline as unresectable tumor [55.6% (25 of 45) for reader 1 and 51.1% (23 of 45) for reader 2] ($P<0.001$). Considering borderline as resectable tumor, CCRT group has better accuracy than chemotherapy group (77.8% vs 55.6%, P=0.545 for reader1, 74.1% vs 61.1% P=0.279 for reader 2). On the contrary, considering borderline as unresectable tumor, chemotherapy group has better accuracy than CCRT group (61.1% vs 51.9% P=0.119 for reader1, 61.1% vs 44.4% P=0.363 for reader 2). In CT texture analysis, three subtracted texture values were found to be independent predictors of R0 resection; surface area (OR 1.077, P=0.011), GLCM IDM (OR 0.000, P=0.005) and GLCM contrast (OR 0.982, P=0.012) and two subtracted texture values were associated with overall survival; entropy (HR 0.159, P=0.005) and

GLCM entropy (HR 10.235, P=0.036).

Conclusion: After neoadjuvant therapy, considering borderline as resectable tumor have better accuracy for R0 resectability, particularly in CCRT group and CT with texture analysis can be useful to predict patient's outcome after neoadjuvant therapy in pancreatic cancer.

Keywords: pancreatic adenocarcinoma, neoadjuvant therapy, resectability, texture analysis

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Table of contents

List of tables

List of figures

Introduction

Despite all efforts to develop a better treatment strategy for the pancreatic ductal adenocarcinoma (PDAC), prognosis remains poor. The 5-year survival rate is 8% for pancreas cancer, even after successful surgical resection, the 5-year survival rate does not exceed 20% [1; 2]. Moreover 30% of resected PDAC having positive resection margin [2]. The resection margin status is essential for determining patient's prognosis. Patients who undergo R1 resection, which is gross total resection with histologically positive margin, or R2 resection, which is resection with residual gross tumor, have worse survival than that undergo R0 resection, which is gross total resection with histologically negative margin, with better survival outcome [3-5].

After emerging concept of borderline resectable pancreatic cancer as a potentially resectable tumor, several studies reported that neoadjuvant treatment could down staging the tumor and give an opportunity for surgery and potential of R0 resection in patients with PDAC [6-8]. In this sense accurate imaging based assessment of resectability before and after the neoadjuvant treatment is crucial to therapeutic management. Multi-detector row computed tomography

(MDCT) is the image of choice for preoperative tumor staging and resectability assessment in PDAC. [9]. However, achieving a sufficient accuracy for precise assessment was challenging, furthermore, neoadjuvant treatment significantly reduces diagnostic performance of CT for prediction of resectability because of changes after neoadjuvant treatment, including pancreatitis, necrosis or fibrous scar [10-13].

Recently, CT texture analysis has garnered much attention as quantitative imaging biomarkers in oncologic imaging, providing important information about tumor characterization and prognosis by quantifying tissue heterogeneity and assessing the distribution of texture coarseness [14-16]. According to previous studies, texture analysis is helpful for predicting prognosis or assessing therapeutic response in variable cancer [15; 17; 18].

To our knowledge, there has been no reports regarding the usefulness of CT texture analysis for predicting resectability and prognosis after neoadjuvant treatment in patients with PDAC. The purpose of our study is to assess the utility of CT findings and texture analysis for predicting resectability after neoadjuvant therapy in patients with PDAC. We also assessed the utility of CT texture analysis for predicting prognosis after surgery.

Material and methods

This retrospective study received our institutional review board approval and the requirement for patients' informed consent was waived.

Study Population

From January 2013 to February 2016, a total of 308 patients with pathologically proven PDAC underwent surgery. Among them 48 patients received neoadjuvant treatment because the tumor was considered as borderline resectable or locally advanced on the baseline CT images. Exclusion criteria were as follows: (a) patients who did not have preoperative CT performed after completion of neoadjuvant treatment (n=1); (b) reconstruction technique mismatch between baseline and preoperative CT (n=2). Thus, a total of 45 PDAC patients (23 men, 22 women; mean age, 64.8 ± 8.7 years) who received concurrent chemoradiation therapy (CCRT, n=27) or neoadjuvant chemotherapy (n=18) were included in our study population (Fig. 1). Chemotherapy was performed using the following regimens: oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) in 7 patients; gemcitabine

based chemotherapy in 11 patients (Gemcitabine alone [n=3], gemcitabine and cisplatin [n=3], gemcitabine and xeloda [n=2], gemcitabine and oxaliplatin [n=1], gemcitabine and tarceva [n=2]). Neoadjuvant CCRT consisted of 45Gy/25fx + 9Gy/5fx (n=18) or 45Gy/25fx + 5.4Gy/5fx (n=9) of external-beam radiation and weekly gemcitabine (n=22) or fluorouracil (n=3) or capecitabine (n=2) based chemotherapy.

Surgery was underwent by using a pylorus-preserving pancreaticoduodenectomy (n = 25); Whipple operation (n=8); distal pancreatectomy (n=11), total pancreatectomy (n=4); palliative operation (n=3); or opening and closure (n=5)..

MDCT Examination

CT examination were performed with either quadruple-phase CT (n=45), which consisted of unenhanced, early arterial, pancreatic, and venous phases, or triple-phase CT (n=9), which consisted of unenhanced, arterial, and venous phases. All patients were performed baseline and follow-up preoperative CT after neoadjuvant treatment. CT scans were obtained using one of the following commercially available MDCT scanners: 16-MDCT scanners (Sensation 16; Siemens Medical Systems,

Erlangen, Germany [n=8]), 64-MDCT scanners (Brilliance 64; Philips Healthcare, Best, the Netherlands [n=8]; SOMATOM Definition; Siemens Medical Systems [n=5]; Discovery CT750 HD; GE Healthcare, Milwaukee, Wis [n=3]),128-MDCT scanner (Ingenuity, Philips Healthcare [n=5]) or 320-MDCT scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan [n=16]). The scanning parameters for the 16-, 64-, 128- and 320- detector CT examinations, detector collimations of 0.75, 0.625 mm, 0.5 mm and a pitch of 1.25, 0.9-1.2, 1.172 and 0.813 were used. MDCT images were acquired using 2.5–3.2-mm thick sections and 3 mm section thickness with a 3-mm reconstruction interval, 300–370 mm field of view, 0.5 -0.75 second gantry rotation time, 150–200 mAs tube current–time product and 120 kVp peak voltage. A total of 1.5 mL of nonionic contrast material (iopromide solution containing 370 mg of iodine per milliliter) per kilogram of body weight was administered with a power injector (Multilevel CT; Medrad, Pittsburgh, Pa) at a rate of 3 mL/sec with an 18 gauge intravenous catheter in the antecubital vein, followed by a 20-mL saline flush. For image acquisition, an automatic bolus tracking technique was used. The trigger threshold was 100 HU at the abdominal aorta. Early arterial phase images were obtained 6 seconds after the trigger threshold was achieved, and pancreatic phase

images were obtained 5–9 seconds later. The average imaging time delay was 23 seconds for the early arterial phase, 37–45 seconds for the pancreatic phase, and 70 seconds for the venous phase.

CT Image Analysis

For each patient, baseline and preoperative CT images were reviewed by two radiologists (I.J.J and S.J.A with ten and eight years of experience in abdominal imaging). Both reviewers were blinded to the history of neoadjuvant treatment and operative and histological findings, but were aware that patients had PDAC. Two reviewers assessed CT imaging findings and classified tumors as resectable, borderline resectable, unresectable. We categorized tumor-vessel interface as four grade; absence, abutment (≤180 degrees of the circumference), encasement (>180 degrees of the circumference and luminal irregularity) and occlusion. The tumor with 1 or more of following criteria was classified as borderline resectable PDAC: (a) short segment narrowing or occlusion of the superior mesenteric vein (SMV) or portal vein (PV) that is amenable to resection and venous reconstruction; (b) Abutment or short segmental encasement of the hepatic artery or branches; (c) abutment of the SMA; (d) abutment of celiac axis (CA).

Moreover, the tumor with 1 or more of following criteria was classified as unresectable PDAC: (a) aorta, inferior vena cava invasion or encasement; (b) SMA encasement; (c) CA encasement (d) unreconstructible SMV/PV occlusion; (e) distant organ metastasis; (f) peritoneal seeding [19-21]. All imaging assessments were performed using picture archiving and communication system workstation monitors (INFINITT PACS; INFINITT Healthcare, Seoul, Korea)

The reference standard for determining the accuracy of resectability was histopathologic and surgical findings. We used the R classification for residual tumors, according to the International Union Against Cancer: no residual tumor (R0), microscopic residual tumor (R1), macroscopic residual tumor (R2) [22]. Lesions that were interpreted as resectable tumors were regarded as pathologic R0 resection. Borderline resectable tumors in CT based interpretation were analyzed in two different aspects as considering borderline as resectable tumor and considering borderline as unresectable tumor.

Computerized CT Texture Analysis

CT Texture analysis was performed by using computer-based in-house software (MISSTA, Medical Imaging Solution for Segmentation and

Texture Analysis) with fully automated quantification of the texture features implemented using dedicated C + + language (Microsoft Foundation Classes; Microsoft, Redmond, Wash). To maintain the consistency of the texture analysis variables, venous phase images were applied for texture analysis. To overcome the limitation of defining the boundary of PDAC, a radiologist (I.J.J), who did not involve the texture analysis, drew a region of interest (ROI) along the margin of the tumor on the baseline and preoperative CT, prior to texture analysis. Subsequently, other radiologist (B.R.K) performed segmentation of the tumor by consensus drawing ROI using the texture analysis software program (Fig 2). After the lesion was segmented, the program automatically calculated following texture parameters: histogram parameters including (a) mean attenuation, (b) standard deviation and variance of grey level, (c) skewness, (d) kurtosis, (e) entropy, (f) homogeneity, (g) surface area, (h) sphericity and (i) discrete compactness; and second-order texture parameters based on a grey level co-occurrence matrices (GLCM) including (a) GLCM moments, (b) GLCM angular second moment (ASM), (c) GLCM inverse difference moment (IDM), (d) GLCM contrast, and (e) GLCM entropy, which characterize the spatial distribution of grey levels in images. In order to

minimize measurement errors, we used mean texture value of three measurements obtained on different day and of the same representative lesion.

Statistical analysis

Categorical data were expressed as numbers (percentages) and compared using the Chi-squared test or Fisher's exact test. Quantitative data were expressed as mean ± standard deviation and compared using independent sample t-tests. McNemar test and Chi-squared test was used to compare difference of diagnostic accuracy. Logistic regression analysis were used to identify significant predictors of R0 resection. Paired T test and Wilcoxon signed rank test were performed for comparison of baseline CT texture parameters and preoperative CT texture parameters after Shapiro–Wilk test. Subtracted texture values by subtracting baseline CT from preoperative CT texture parameters were calculated. The Cox proportional hazards regression model was utilized to evaluate the effect of subtraction texture parameters and clinico-pathologic variables on patient's overall survival (OS). To assess inter-observer agreement, we performed a simple κ analysis. The degree of interobserver agreement in the range

of 0.81–1.00 was interpreted as excellent, 0.61–0.80 as substantial, 0.41–0.60 as moderate, 0.21–0.40 as fair, and 0.00–0.20 as poor. SPSS 21.0 software package (SPSS, Chicago, IL, USA) was used for all statistical analyses in our study and P-value of <0.05 was considered statistically significant difference.

Results

Patient clinical, demographic and pathological characteristics are shown in Table 1. Twenty cases were classified as R0 and one as R1 and six as R2 in neoadjuvant CCRT group; and 10 cases were classified as R0, four as R1, and four as R2 in neoadjuvant chemotherapy group. Most of the tumors were located at the pancreas head or neck (71.1%, 32/45), T3 stage (64.4%, 29/45) and moderately differentiated (70.3%, 26/37). The mean CA 19-9 was decreased after neoadjuvant treatment from 1317.4 ± 2394.2 U/mL to 572.3 ± 1955.0 U/mL and tumor size was also decreased from 30.9 ±9.7 mm to 22.2 ±8.7 mm. During the follow up period, tumor recurred in 33 patients (73.3%) and 12 cases (26.7%) were early recurred within 1 year.

Accuracy of CT findings for predicting resectability after neoadjuvant therapy

Post neoadjuvant tumor-vessels relationships were summarized in the Table 2. The celiac axis and tumor relationship on image analysis was significantly different between R0 resection group and R1 & R2 resection group (P=0.032). However, other vessels showed no significant

differences of tumor-vessels relationships between the two groups (P > 0.05). Interreader agreement of tumor- vessels relationship evaluation between the two radiologists was moderate to substantial (0.559-0.664). Overall accuracy for R0 resectability was better when considering borderline as resectable tumor [68.9% (31 of 45) for both readers] than when considering borderline as unresectable tumor [55.6% (25 of 45) for reader 1 and 51.1% (23 of 45) for reader 2] (P < 0.001). In particular, CCRT group exhibits superior accuracy (77.8% vs. 51.9% for reader 1; 74.1% vs. 44.4% for reader 2) (P < 0.001), sensitivity (90.0% vs. 40.0% for reader 1; 80.0% vs. 30.0% for reader 2) (P = 0.002) for resectability assessment when considering borderline as resectable than as unresectable with statistically significant difference (Fig 3). Considering borderline as resectable tumor, CCRT group has better accuracy than chemotherapy group (77.8% vs 55.6%, P = 0.545 for reader1, 74.1% vs 61.1% P = 0.279 for reader 2). On the contrary, considering borderline as unresectable tumor, chemotherapy group has better accuracy than CCRT group (61.1% vs 51.9% P = 0.119 for reader1, 61.1% vs 44.4% P = 0.363 for reader 2). Though no significant difference was observed between CCRT group and Chemotherapy group. Table 3 summarizes the diagnostic performance of CT for prediction of

resectability after neoadjuvant therapy in pancreatic cancer.

Accuracy of CT texture analysis for predicting resectability after neoadjuvant therapy

Table 4 describes mean values of CT texture parameters and comparison results obtained from baseline and preoperative CT images in R0 resection group and R1 or R2 resection group. In R0 resection group, several parameters including surface area, sphericity, discrete compactness, GLCM ASM and GLCM entropy showed significant difference between baseline and after neoadjuvant treatment ($p<0.05$). In R1 or R2 resection group, same parameters (surface area, sphericity, discrete compactness, GLCM ASM and GLCM entropy) showed significant difference between baseline and after neoadjuvant treatment ($p<0.05$). In terms of subtracted texture values, which was subtracted baseline CT texture parameter from preoperative CT texture parameter after neoadjuvant therapy, subtracted surface area was larger in the R1 or R2 resection group than R0 resection group (-19.6 vs -12.4 mm2, P=0.273) and subtracted GLCM contrast was higher in the R0 resection group (24.9 vs -86.5, P=0.09). In multivariate logistic regression analysis

using subtracted texture values, the following features attained statistical significance for predicting the R0 resection: lower subtracted value of surface area (Hazard ratio [HR] 1.077, P=0.011), higher subtracted values of GLCM IDM (HR 0.000, P=0.005) and GLCM contrast (HR 0.982, P=0.012).

Important CT texture analysis for predicting overall survival after surgery

The median survival of the entire 45 patients was 23.9 ± 2.1 months. The median survival of neoadjuvant chemotherapy group (24.7 ± 6.3 months) was longer than the CCRT group (22.9 ± 2.1 months), although difference of medial survival of two groups were not statistically significant (P=0.772). The entropy value decreased after neoadjuvant treatment from 4.37 ± 0.22 to 4.27 ± 0.22 (P=0.026) and GLCM Entropy value also decreased from 3.24 ± 0.18 to 3.05 ± 0.22 (P=0.000). We applied the subtracted value of the texture parameters, which showed significant differences before and after treatment, as input variables for multivariate Cox proportional analysis for OS. In multivariate analysis, higher subtracted value of entropy (HR 0.159,

P=0.005) and lower subtracted value of GLCM entropy (HR 10.235, P= 0.036) were associated with better outcome (Table 5, Fig 4). The optimal cut-off values were 0.03 in the subtracted value of entropy and -0.35 in the subtracted value of GLCM entropy.

Discussion

In our study, after neoadjuvant therapy, considering borderline as resectable tumor have better accuracy for R0 resectability than considering borderline as unresectable tumor (68.9% for both readers vs 55.6% for reader 1 and 51.1% for reader 2). In particular, our result suggested that neoadjuvant CCRT group provide better accuracy (77.8%, 74.1% for each reader) for resectability assessment when considering borderline as resectable tumor than as unresectable tumor.

Previous studies [10-13; 23; 24] demonstrated decreased diagnostic performance of CT for the evaluation of resectability after neoadjuvant treatment. Katz et al[23] suggested radiographic downstaging was uncommon; only 1 patient (0.8%) was downstaged to resectable status among the 112 borderline resectable PDAC patient with neoadjuvant treatment, and 95% R0 resection was achieved in 85 patients who underwent pancreatectomy with favorable median survival (33 vs 22 months). These authors finally concluded that borderline PDAC patients should undergo surgery after neoadjuvant treatment in the absence of metastasis. Cassinotto et al. [11; 13] identified that CT accuracy of R0 resectability determination in neoadjuvant group was lower than that in

control group (58% vs 83%, P= 0.039) due to the overestimation of vascular invasion and suggested that partial regression of tumor-SMV/PV contact was suitable for surgical treatment with 100% positive predictive value for R0 resection. Applying lenient criteria for vascular contact assessment could give superior accuracy of resectability assessment after neoadjuvant treatment. Therefore, it is useful to extend the range of criteria for CT image based resectability evaluation after the neoadjuvant treatment. As in our study result, interpreting the borderline resectable tumor as a resectable tumor can provide superior accuracy of R0 resection in the clinical setting after completion of neoadjuvant treatment.

Our CT texture analysis results revealed that subtracted values of CT texture parameter can be useful to predict patient's outcome including R0 resectability and prognosis after neoadjuvant therapy in pancreatic cancer although role of CT texture evaluation of resectability was not satisfied because of lower statistical significance of HR of subtracted texture parameters, except lower subtracted values of GLCM IDM (HR 0.000, P=0.005).

However, CT texture parameters can be useful to predict patient's prognosis after neoadjuvant therapy in pancreatic cancer. In

our study, higher subtracted value of entropy (optimal cut-off values were 0.03, HR 0.159, P=0.005) and lower subtracted value of GLCM entropy (optimal cut-off values were -0.35 HR 10.235, P= 0.036) are important parameters for prediction of longer OS in PDAC patients after neoadjuvant treatment. The entropy is the first order statistics from gray-level histogram, which reflects how uniform the gray level distribution is, that is texture irregularity. Higher entropy represent increased heterogeneity [25; 26]. According to previous studies, heterogeneous tumor which tend to have greater entropy showed tumor aggressiveness, poor treatment response or poor patient prognosis [25; 27-29]. Focusing on changes before and after treatment of tumor, Yip et al. [30] suggested that tumor texture of primary esophageal cancer became more homogeneous after neoadjuvant chemotherapy with a significant decrease in entropy. And in subsequent study of Yip et al [15] suggested that entropy showed a decrease after CCRT and lower post-treatment entropy on contrast-enhanced CT images was associated with improved OS time in patients who completed CCRT for primary esophageal cancer (median OS, 33.2 vs 11.7 months; P = .0002). Additionally, Goh et al [18] reported that tumor entropy decreased by 3%–45% after administration of tyrosine kinase inhibitor in metastatic

renal cell carcinoma and baseline entropy (≤2.33) correlated with time to progression (P=0.02). However, in our study results, higher subtracted value of entropy; higher preoperative tumor entropy after neoadjuvant treatment was associated with longer OS. Even though mean tumor entropy was decreased after treatment from 4.37 to 4.27, our results regarding relation between survivals and subtracted entropy differ from the results of previous published studies. This discrepancy might result from the different underlying tumor biology of different organs that determine response to the neoadjuvant treatment. According to published histologic grading schemes of PDAC [31; 32], 3 variables are in consideration for evaluate treatment response of PDAC: viable tumor cell mass, fibrosis and necrosis. In marked-response group, the residual cancer cells are fewer, but more tumor is replaced by fibrosis or necrosis and more tumor cells are with cytopathic effect than in the poor response group. This kinds of heterogeneous changes may have contributed to association higher subtracted value of entropy and longer survival outcome. However, further studies for relationships between texture parameters and histologic change in post neoadjuvant treatment clinical setting are warranted.

Whereas GLCM is second order statistics that are gray-level co-

occurrence matrix calculated the spatial distribution of grey levels. The GLCM texture features represent how often a pixel with specific grey level finds itself within a certain relationship to another pixel with another specific grey level [28; 33]. Because GLCM offset was decided to be 1 pixel for the spatial relationship between adjacent pixels, gradual change of grey level in adjacent pixels tend to contribute to a lower GLCM feature than the radical change. So far, there have been few studies on GLCM texture parameter changes after neoadjuvant treatment, and most of them have focused on GLCM texture and tumor biology relation. In previously published studies, GLCM entropy of malignant pulmonary nodules demonstrated to be higher in comparison to those of benign pulmonary nodules (3.800 vs.3.560, P=0.001) [28], and GLCM Entropy was significantly higher in high-grade gliomas than low-grade glioma (6.861 vs.6.261, P=0.006), based on the ADC map [29]. We suggested lower subtracted GLCM entropy that is related to lower preoperative tumor GLCM entropy as the important parameter for prediction of longer OS. GLCM entropy is not simply a representation of heterogeneity but a randomness of the matrix. For this reason, a smooth pattern will have low GLCM entropy and checkerboard pattern which is not textually uniform pattern will also have low GLCM entropy,

even though these GLCM imaging features are not visible with ease on the conventional grey scale CT images [34; 35]. Therefore, our results on lower preoperative GLCM entropy may have some relevance to the increased heterogeneity seen in association with higher preoperative entropy. Further study is required to evaluate relationship between GLCM entropy change and histologic change and to confirm the role of GLCM entropy in survival of PDAC patients.

Several limitations of our study need to be mentioned. First, as retrospective study design, there may be potential selection bias. Second, we performed manual segmentation by the radiologist. As infiltrative feature of PDAC margin, especially after neoadjuvant treatment, automatic segmentation was technically challenging. And manual segmentation technique is widely used in current texture analysis studies. Moreover, to minimize influence of manual segmentation, consensus drawing and repetitive drawing of ROI was performed. Finally, MDCT were performed using a number of different scanners in our study. Inter-scanner difference might affect the texture analysis result. Thus further studies for inter-scanner variation of texture analysis need to be established.

In conclusion, after neoadjuvant therapy, considering borderline as

resectable tumor have better accuracy for R0 resectability, particularly in neoadjuvant CCRT group. In addition, CT texture analysis can be useful to predict patient's prognosis after neoadjuvant therapy in PDAC. Higher subtracted value of entropy and lower subtracted value of GLCM entropy were important parameters for prediction of better prognosis after surgery.

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Table 1. Characteristics of study population

Characteristics	Values (n=45)	R0 resection (n=30)	R1 or R2 resection (n=15)	P value*	Overall survival	
					Hazard Ratio	P value†
Age (y)	64.8±8.7	62.5±8.3	69.5±7.8	0.009	1.016 (0.977, 1.056)	0.435
No. of men	23 (51.1%)	15 (50.0%)	8 (53.3%)	0.916	0.787 (0.390, 1.590)	0.505
CA 19-9 (U/mL)						
Baseline	1317.4±2394.2	1585.1±2862.0	781.9±766.6	0.294	1.000 (1.000, 1.000)	0.512
Post-neoadjuvant	572.3±1955.0	595.7±2253.9	525.4±1218.9	0.911	1.000 (1.000, 1.000)	0.695
Tumor location				0.490		
Head/neck	32 (71.1%)	23 (76.7%)	9 (60.0%)		3.273 (0.966, 11.083)	0.057
Body	6 (13.3%)	3 (10.0%)	3 (20.0%)		3.475 (0.797, 15.158)	0.097
Tail	7 (15.6%)	4 (13.3%)	3 (20.0%)		Reference category	
Tumor largest diameter (mm)						
Baseline	30.9±9.7	31.7±9.7	29.4±9.8	0.459	0.775 (0.511, 1.177)	0.232
Post-neoadjuvant	22.2±8.7	22.4±8.7	21.7±9.1	0.803	0.948 (0.630, 1.426)	0.798
T stage				<0.001		
T1	4 (8.9%)	4 (13.3%)	0 (0.0%)		Reference category	

T2	1 (2.2%)	1 (3.3%)	0 (0.0%)		0	0.987
T3	29 (64.4%)	23(76.7%)	6 (40.0%)		3.781 (0.507, 28.223)	0.195
T4	3 (6.7%)	2 (6.7%)	1 (6.7%)		24.054 (2.310,250.488)	0.008
Palliative Op./O&C‡	8 (17.8%)	0 (0.0%)	8 (53.3%)		12.547 (1.545, 101.862)	0.018
Differentiation grade (n=37)				0.477		
Well (G1)	6 (16.2%)	5 (16.2%)	1 (14.3%)		Reference category	
Moderately (G2)	26 (70.3%)	20 (66.7%)	6 (85.7%)		1.393 (0.405, 4.793)	0.6
Pooly (G3)	5 (13.5%)	5 (16.7%)	0 (0.0%)		3.046 (0.713, 13.013)	0.133
Presence of LVI (n=37)	19 (51.4%)	15 (50.0%)	4 (57.1%)	0.936	1.492 (0.682, 3.264)	0.317
Presence of PNI (n=37)	27 (73.0%)	23 (76.7%)	4 (57.1%)	0.565	5.199 (1.539, 17.566)	0.008
Presence of LN invasion (n=37)	10 (16.2%)	7 (23.3%)	3 (42.9%)	0.565	1.245 (0.539,2.874)	0.608
Patient outcome (n=45)						
Early recurrence	12 (26.7%)	5 (16.7%)	7 (46.7%)	0.007	7.914 (3.381,18.523)	0
recurrence	33 (73.3%)	21 (70.0%)	12 (80.0%)	0.005	2.705 (1.044, 7.010)	0.04
deaths	35 (77.8%)	21 (70.0%)	14 (93.3%)	0.163		

Note. – * P values were determined by independent t –test or Pearson’s chi-square test or Fisher’s exact test for comparison between R0 group and R1&R2 group

† P values were determined by Cox proportional hazard model for overall survival

‡ O& C = open and closure operation

Table 2. Post-neoadjuvant tumor-vascular relationship in R0 resection group and R1& R2 resection group

Post-neoadjuvant vessel relationship		R0 Resection Group (n = 30)	R1&R2 Resection Group (n = 15)	P value*	kappa†
Celiac axis				0.032	0.599
	absence	29	11		
	abutment	0	3		
	encasement	1	1		
HA				0.117	0.608
	absence	26	10		
	abutment	2	3		
	encasement	2	2		
SMA				0.419	0.664
	absence	20	7		
	abutment	8	6		
	encasement	2	2		
SMV-PV				0.890	0.530
	absence	9	4		
	abutment	14	8		
	encasement	6	2		
	occlusion	1	1		

Note. – HA = hepatic artery, SMA = superior mesenteric artery, SMV-PV = superior mesenteric vein – portal vein
* P values were determined by Pearson's chi-square test for comparison between R0 group and R1&R2 group
† κ values were determined by inter-observer agreement between readers

Table 3. Diagnostic performance of CT for prediction of resectability after neoadjuvant therapy in pancreatic cancer.

	Neoadjuvant treatment	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)
Considering borderline resectable tumors as unresectable						
Reader 1	Chemotherapy	61.1 (11/18)	60.0 (6/10)	62.5 (5/8)	66.7 (6/9)	55.6 (5/9)
	CCRT	51.9 (14/27)	40.0 (8/20)	85.7 (6/7)	88.9 (8/9)	33.3 (6/18)
	Overall	**55.6 (25/45)**	46.7 (14/30)	73.3 (11/15)	77.8 (14/18)	40.7 (11/27)
Reader 2	Chemotherapy	61.1 (11/18)	40.0 (4/10)	87.5 (7/8)	80.0 (4/5)	53.8 (7/13)
	CCRT	44.4 (12/27)	30.0 (6/20)	85.7 (6/7)	85.7 (6/7)	30.0 (6/20)
	Overall	**51.1 (23/45)**	33.3 (10/30)	86.7 (13/15)	83.3 (10/12)	39.4 (13/33)
Considering borderline resectable tumors as resectable						
Reader 1	Chemotherapy	55.6 (10/18)	90.0 (9/10)	12.5 (1/8)	56.3 (9/16)	50.0 (1/2)
	CCRT	**77.8 (21/27)**	90.0 (18/20)	42.9 (3/7)	81.8 (18/7)	60.0 (3/5)
	Overall	**68.9 (31/45)**	90.0 (27/30)	26.7 (4/15)	71.1 (27/38)	57.1 (4/7)
Reader 2	Chemotherapy	61.1 (11/18)	80.0 (8/10)	37.5 (3/8)	61.5 (8/13)	53.8 (3/5)
	CCRT	**74.1 (20/27)**	80.0 (16/20)	57.1 (4/7)	84.2 (16/19)	50.0 (4/8)
	Overall	**68.9 (31/45)**	80.0 (24/30)	46.7 (7/15)	75.0 (10/12)	53.8 (7/13)

Table 4. Comparison of CT texture parameters between baseline and after neoadjuvant therapy in R0 resection group and R1 or R2 resection group.

	Study group (n=45)			R0 resection group (n=30)			R1 or R2 resection group (n=15)		
	Baseline	Preoperative	P value	Baseline	Preoperative	P value	Baseline	Preoperative	P value
Mean HU	76.74±17.34	75.76±16.88	0.708	77.46±18.37	76.35±15.81	0.723	75.27±15.48	74.52±19.40	0.880
SD (HU)	21.88±5.21	21.97±5.15	0.919	21.11±4.24	22.11±5.18	0.418	23.43±6.62	21.69±5.28	0.240
Variance (HU)	505.30±255.08	509.84±253.85	0.925	462.87±191.90	516.37±248.96	0.360	590.19±341.50	496.79±271.78	0.281
Skewness	-0.02±0.31	0.15±0.84	0.376	-0.01±0.31	0.26±0.96	0.169	-0.02±0.31	-0.04±0.53	0.881
Kurtosis	0.29±0.56	1.06±5.76	0.87	0.30±0.60	1.37±7.06	0.398	0.25±0.47	0.34±0.75	0.706
Entropy	4.37±0.22	4.27±0.22	0.026	4.35±0.19	4.25±0.21	0.052	4.40±0.26	4.26±0.24	0.061
Homogeneity	0.02±0.01	0.02±0.01	0.524	0.02±0.08	0.02±0.01	0.476	0.02±0.01	0.02±0.01	0.538
Surface area	63.35±21.14	46.12±18.07	0.000	65.66±22.46	46.01±17.79	0.000	58.73±18.06	46.33±19.24	0.009
Sphericity	-2.57±0.65	-2.14±0.68	0.000	-2.57±0.67	-2.19±0.68	0.003	-2.56±0.68	-2.14±0.69	0.039

Discrete compactness	1.88±0.17	2.06±0.25	0.000	1.86±0.15	2.06±0.22	0.000	1.92±0.19	2.06±0.24	0.005
GLCM Moments	0.62±0.27	0.60±0.26	0.000	0.62±0.27	0.64±0.29	0.836	0.60±0.24	0.59±0.31	0.875
GLCM ASM	0.00±0.00	0.00±0.00	0.000	0.00±0.00	0.00±0.00	0.036	0.00±0.00	0.00±0.00	0.012
GLCM IDM	0.09±0.02	0.10±0.03	0.094	0.00±0.03	0.00±0.05	0.713	0.09±0.03	0.09±0.03	0.732
GLCM Contrast	246.38±164.19	234.14±165.45	0.453	223.63±117.86	248.51±187.57	0.515	291.92±229.38	205.43±108.74	0.110
GLCM Entropy	3.24±0.18	3.05±0.22	0.000	3.25±0.17	3.05±0.19	0.000	3.31±0.18	3.05±0.22	0.006

Note. – GLCM = grey level co-occurrence matrices, ASM = angular second moment, IDM = inverse difference moment

Table 5. Multivariate Cox Proportional Hazards Regression analysis for overall survival

Parameter	Hazard Ratio	P Value*
Entropy_subtraction	0.159 (0.044, 0.575)	0.005
GLCM Entropy_subtraction	10.235 (1.159, 90.409)	0.036

Note. – * P values were determined by Cox proportional hazard model for overall survival

Figure Legends.

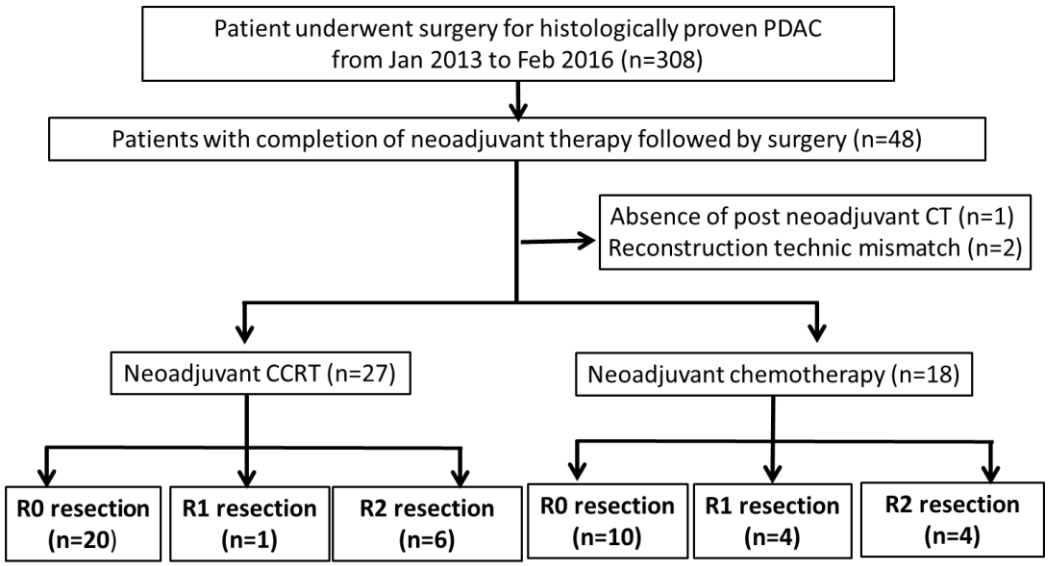

Figure 1. Flow chart schematizing the patient selection process.

PDAC = pancreatic ductal adenocarcinoma, CT = computed tomography, CCRT = concurrent chemoradiation therapy

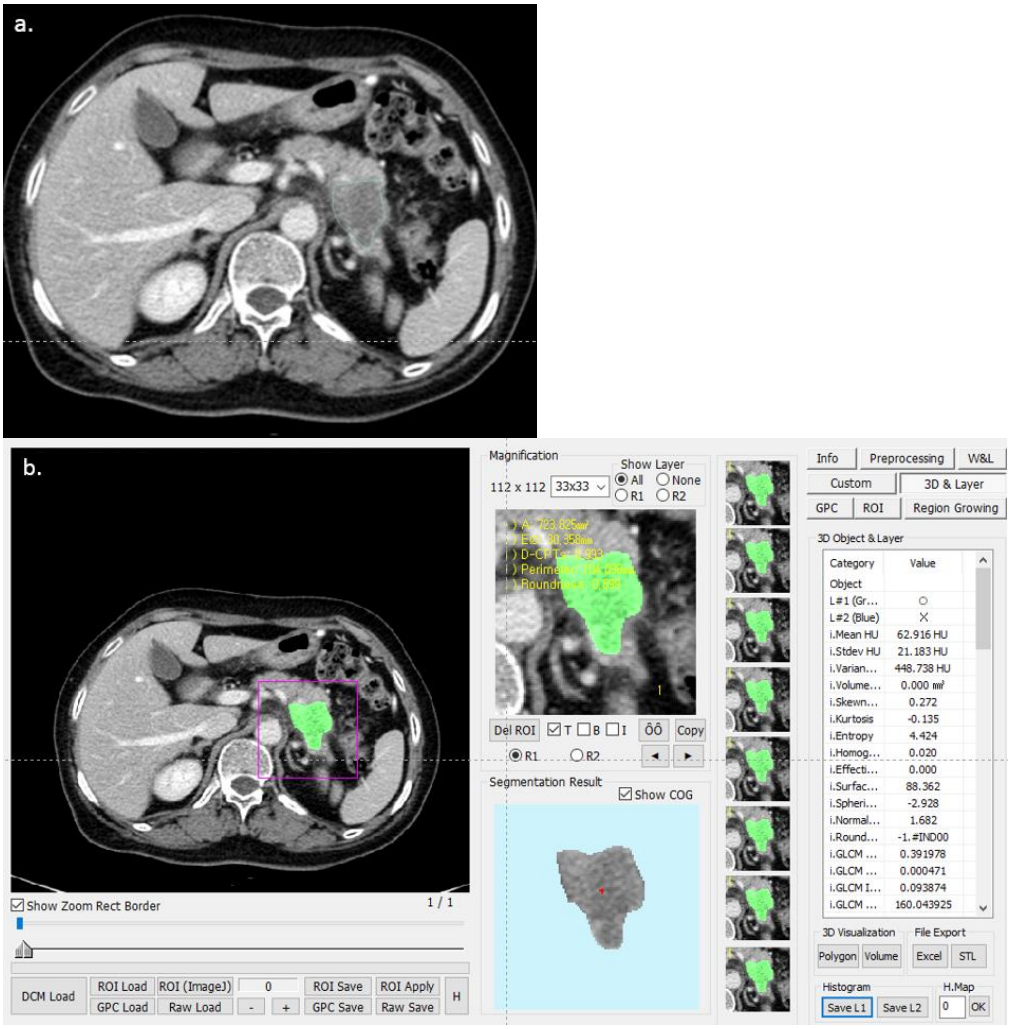

Figure 2. CT texture analysis software program on 2D. The outlining of pancreatic adenocarcinoma was manually conducted, prior to texture analysis (a). Subsequently segmentation was performed with consensus manner, by using computer-based in-house texture analysis software program and texture features of the nodules were automatically extracted and calculated (b).

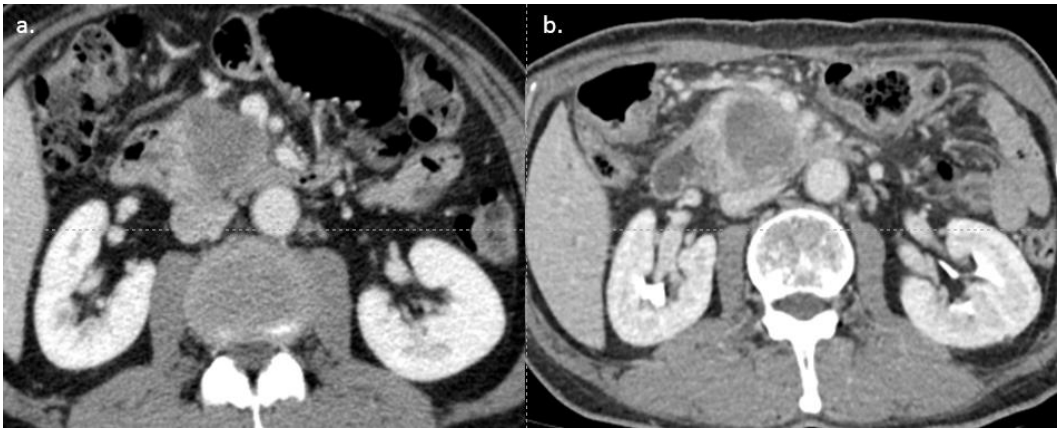

Figure 3. Baseline CT (a) image of a 4cm pancreatic ductal adenocarcinoma in a 62-year-old man before neoadjuvant CCRT shows pancreas head cancer encasing superior mesenteric vein (SMV). After completion of neoadjuvant CCRT, preoperative CT (b) shows abutment with superior mesenteric artery and encasement of SMV with increased peri-tumoral and perivascular infiltration. Tumor was classified as borderline resectable tumor by both readers in preoperative CT. However, postoperative histological examination revealed that R0 resection was performed without microscopic residual tumor

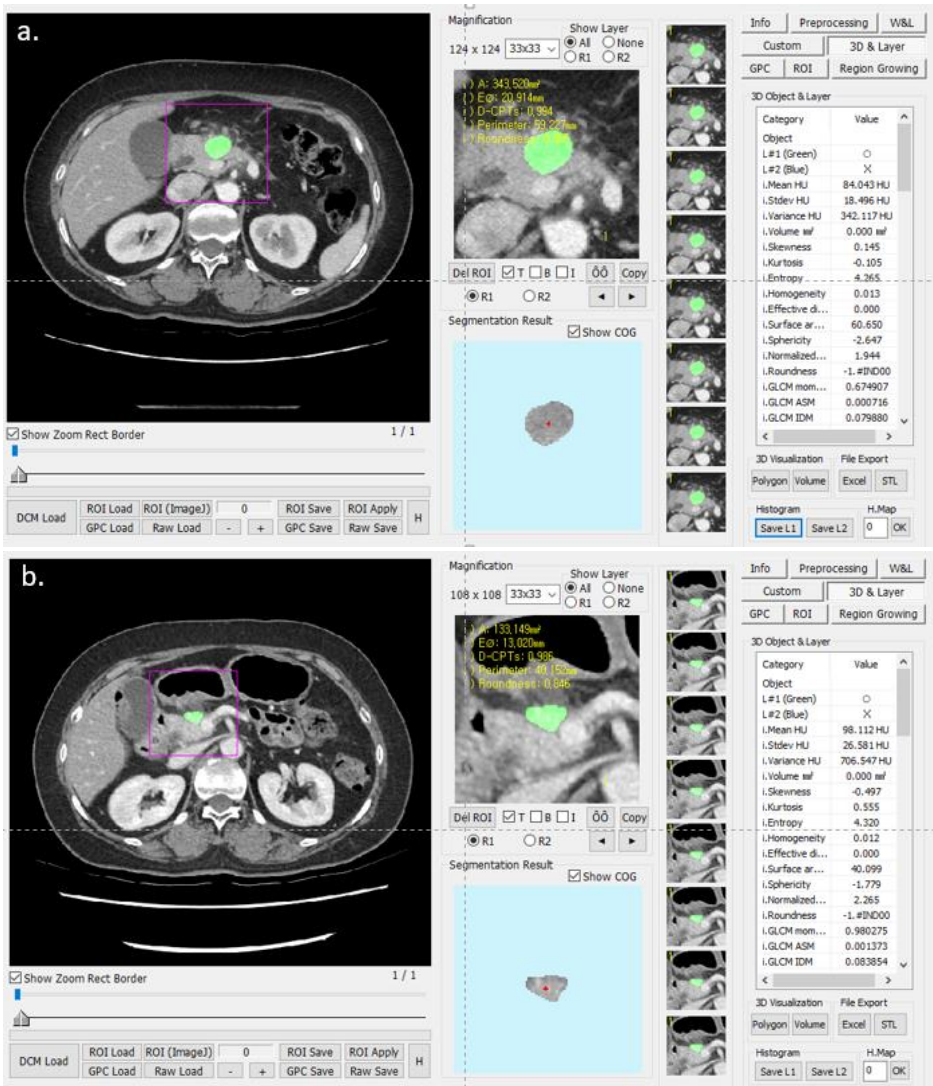

Figure 4. Segmentation and their texture feature was extracted from baseline and preoperative CT images. Subtracted value of entropy of pancreas head cancer was 0.0554 and subtracted value of GLCM entropy was -0.3983. Overall survival of a 52-year-old man was 35.3 month, longer than median survival.

논 문 초 록

목적: 췌장선암(pancreatic ductal adenocarcinoma)으로 수술을 받은 환자에서 신보조(neoadjuvant) 요법 후 절제 가능성과 예후를 예측하기 위한 전산화 단층(CT) 촬영 영상 소견과 조직 분석의 유용성을 평가하고자 한다.

대상 및 방법: 2013 년부터 2016 년까지 308 명의 환자 중 신 보조 요법과 수술을 받은 췌장암 환자 45 명이 포함되었다. 그들은 신보조동시화학방사선 요법(CCRT, n = 27) 또는 신보조화 요법(ChoT, n = 18)을 받았다. 모든 환자는 기준 CT 및 수술 전 CT 를 시행 하였으며, 2 명의 영상의학과 의사가 CT 소견과 절제 가능성을 세 그룹(절제 가능, 경계 절제 가능, 절제 불가능)으로 평가 하였다. 환자들은 잔여 종양 없는 그룹(R0)과 잔여 종양이 있는 그룹으로 (R1 또는 R2)으로 분류되었으며, CT 영상 소견과 절제 후 병리 소견과의 관계를 분석하였다. CT 조직 분석은 컴퓨터 기반의 자체 소프트웨어로 수행되었으며, 기준 CT 에서 수술 전 CT 에서 추출된 조직 분석 변수들의 값의 차이를 이용하여, 다중 변수 Cox / Logistic 회귀 분석을 통해 절제 가능성과 예후 예측에 중요한 인자를 확인 하였다.

결과: 잔류 종양이 없는 30 명의 환자 (CCRT, n = 20, ChoT, n = 10)와 잔류 종양이 있는 15 명의 환자 (CCRT, n = 7, ChoT, n = 8)로 분류되며, 경계 절제 가능 종양을 절제 가능하다고 평가할 때, R0 절제 가능성에 대한

전반적인 정확도는 68.9 %으로 절제 불가능한 종양으로 평가할 때의 전반적 정확도인 55.6 %보다 우수하였다 (P < 0.001). 경계성 절제 가능 종양을 절제 가능하다고 평가할 때, R0 절제 가능성에 대한 정확도는 ChoT 군보다 CCRT 군에서 높았으며 (77.8% vs 55.6%, P = 0.545 for reader 1, 74.1% vs 61.1% P = 0.279 for reader 2), 반대로, 절제 불가능한 종양으로 평가하였을 때는 CCRT 군보다 ChoT 군의 정확도가 높은 경향을 보였다 (61.1% vs 51.9% P = 0.119 for reader1, 61.1% vs 44.4% P = 0.363 for reader 2). CT 조직 분석에서, 3 개의 감산된 조직 분석 변수 값 (surface area [OR 1.077, P = 0.011], GLCM IDM [OR 0.000, P = 0.005]과 GLCM contrast [OR 0.982, P = 0.012] 은 R0 절제술의 독립적인 예측 인자로 밝혀졌고, 2 개의 감산 된 entropy(HR 0.159, P = 0.005) 및 GLCM entropy (HR 10.235, P = 0.036) 값은 전체 생존과 관련이 있었다.

결론: 신 보조 항원 치료 후 CT 영상 평가에서 경계 절제 가능 종양을 절제 가능하다고 평가하는 것이 R0 절제 가능성 평가의 정확성을 높일 수 있으며, CT 를 이용한 조직 분석은 신 보조 항원 치료 후 췌장암 환자의 예후를 예측하는 데 유용한 지표로 사용될 수 있다.

주요어: 췌장 선암, 신 보조 요법, 절제 가능성, 조직 분석

학번: 2016-21950