CT Texture Analysis of Ductal Adenocarcinoma Downstaged After Chemotherapy

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Abstract. *Background/Aim:* Re-staging of ductal adenocarcinoma using computed tomography (CT) scan can be problematic so new imaging techniques and evaluation parameters are required. The aim of the study was to evaluate the added value of CT texture analysis in estimation of tissue changes in ductal adenocarcinoma downsized and resected after chemotherapy. *Materials and Methods:* Patients with ductal adenocarcinoma downstaged after neoadjuvant treatment, and resected, were included. A pre- and post-treatment CT was obtained. In comparison, patients with disease progression were included for texture analysis evaluation at CT pre- and post-treatment. CT texture analysis results were compared. *Results:* A total of 17 patients affected by un-resectable or borderline ductal adenocarcinoma reached the resectable stage after treatment. The comparison between Kurtosis pre- and Kurtosis post-treatment showed a statistically significant difference. On the contrary, in the comparison group composed of 14 patients with disease progression there was no statistical difference regarding this parameter. *Conclusion:* This evaluation may represent an added value in tumor tissue changes judgment and can be extremely useful to diagnose downstaging in those cases with no evident downsizing after chemotherapy.

Pancreatic ductal adenocarcinoma is the fourth most common cause of cancer death. It is the most common

primary malignancy of the pancreatic gland (about 80%) and it is highly aggressive with incidence and mortality increasing year by year. The related estimated overall 5-year survival rate is less than 5%. These features can be explained by tumor aggressive biological behavior and by delayed diagnosis at an un-resectable stage in most of cases. The only potentially curative treatment with radical intent is surgery with a complete excision of tumor, reserved only in cases without vascular invasion or metastases. At the present only about 15%-20% of patients have potentially resectable disease at time of symptoms presentation (1, 2). Therefore, treatment of pancreatic adenocarcinoma, and consequently prognosis, depend on tumor resectability or non-resectability, usually linked with time of diagnosis, with an important role of diagnostic imaging, because an accurate staging defines the best suitable treatment option for patients (3, 4).

The National Comprehensive Cancer Network (NCCN) criteria, defining resectability status of these tumors, are based on the American Hepato-Pancreatic-Biliary Association consensus report (1, 2, 5-7). In absence of metastases, pancreatic ductal adenocarcinoma is classified into three main categories: resectable, borderline resectable, and locally advanced or un-resectable, depending on tumor location and vessels involvement.

In case of borderline resectable or locally advanced un-resectable diseases, treatment of choice at first line is neoadjuvant chemotherapy and/or radiation therapy trying to downstage the tumor to a resectable grade. In fact, for locally advanced pancreatic ductal adenocarcinoma with invasion of peri-pancreatic vessels, it has been proved that neoadjuvant combined chemotherapy and radiation therapy allows a downstaging in approximately 30% of patients (8, 9). The re-staging at imaging of ductal adenocarcinoma during or at the end of the chemotherapy treatment is still a hard challenge (1, 2).

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Due to difficulties in re-staging ductal adenocarcinoma using a computed tomography (CT) scan, new imaging techniques and evaluation parameters are required to better assess treatment response over the evaluation of resectability, judging, in presence of uncertain downsizing, possible downstaging.

New imaging analysis has been introduced and used for oncologic evaluations and response to therapy in recent time. In particular, computed texture analysis is a new tool that evaluates every pixel's value, variations and distribution (10-14).

The aim of this study was to evaluate results of texture computed analysis of pancreatic ductal adenocarcinoma downsized and judged suitable for surgery after chemotherapy and/or radiation therapy.

Materials and Methods

Patient population. Patients with a histologically-proven locally advanced or borderline resectable ductal adenocarcinoma, judged suitable for surgical evaluation after chemotherapeutic and/or radiotherapeutic treatment, and then resected, were included for texture analysis. In comparison, patients with histologically proved locally advanced adenocarcinoma with disease progression after treatment were included. Tumor downstaging was defined at CT study with a conversion from a locally advanced or borderline resectable lesion to a potentially resectable one after neoadjuvant treatments, due to a betterment in vascular encasement, with or without tumor size reduction. Tumor progression was defined at CT study with increasing of lesion dimensions and/or metastatic disease development.

Patients included in this study must have at least two CT studies, with at least three months distance from each other and with the CT pre-surgery done within one month before surgery, for those patients that underwent surgery.

In the surgical group after resection, all surgical specimens were histologically analyzed and resection margins were evaluated.

Data collection was circumscribed in a time period of about 1 year, searching in Verona University Pancreas Institute database all patients that satisfied inclusion criteria, for both groups.

Inclusion criteria for first group were histologically confirmed ductal adenocarcinoma classified as non-metastatic and locally advanced or borderline resectable at time of diagnosis with the first CT in patients who had been referred for neoadjuvant treatment. Another inclusion criterion was tumor downstaging after neoadjuvant therapy that allows surgical evaluations.

Inclusion criteria for second group were histologically confirmed ductal adenocarcinoma classified as un-resectable at time of diagnosis in patients who had been referred for treatment with chemotherapy or radiation therapy. Another inclusion criterion was tumor local or distant progression during therapy that did not permit a surgical treatment.

For all patients two CT scans were considered, the first one (named CT 1) before starting chemotherapy or radiation therapy and the second one (named CT 2) during or at the end of the treatment, with an interval between these two scans of at least 3 months.

Multi-detector CT technique and image interpretation. All CT studies were performed by using a CT multi-slice equipment 64 detectors row (Brilliance 64; Philips Healthcare, Best, The Netherlands). After a minimum fast of 6 h, CT was performed with

patients in supine position. Scans were obtained both before and after 1.5 ml per kilogram of body weight intravenous injection of nonionic contrast media (Ultravist 370, Schering, Berlin, Germany) by using a power injector (Medrad, Stellant, Bayer Healthcare Medical care), with a flow rate of 3 ml/sec, immediately followed by 50 ml saline solution intravenous injection.

Every CT study included an un-enhanced phase of superior abdomen, a contrast material-enhanced pancreatic parenchymal phase of superior abdomen, a portal phase of abdomen and pelvis, and a late phase of superior abdomen. Utilizing the bolus tracking method, pancreatic phase imaging was performed by adding 15 sec to time of peak aortic enhancement calculated at the hepatic hilum; portal venous phase imaging was obtained by adding 60-70 sec; and late phase imaging was obtained by adding 5 min. The following parameters were applied for all scans: section thickness 2 mm, pitch 1, kV 120 and mAs 125-250.

Both in CT 1 and in CT 2 tumor diameters (large and small axes) and tumor resectability were evaluated.

Imaging computed analysis. From the archive and communication system (PACS) all CT studies were download and saved. For texture analysis only pancreatic phase was used, due to better conspicuity of ductal adenocarcinoma in this phase, choosing for every CT study done before treatment the slice where the tumor was better visible. Then same slices, at the same point, were chosen in CT 2 done during or after neoadjuvant treatment. Selected slices, from CT 1 and CT 2, were then saved as DICOM files, and later analyzed with software MaZda version 4.6. Texture parameters were obtained on digital images by drawing a region of interest (ROI) inside the tumor, covering all the tumor surface, avoiding structures outside the tumor. All the ROI were manually drawn approximately of the same size inside the tumor on CT 1 and CT 2. By using MaZda ver 4.6 the following parameters were obtained for both CT: Mean value, variance, skewness, kurtosis and entropy. These values were recorded for all studies and subsequently analyzed. Texture features were correlated with resectability of tumor and with pathologic data in patients with downsized tumors.

Chemotherapy and radiation therapy. Due to the retrospective type of the study, there is heterogeneity in the type of neoadjuvant treatment and chemotherapy that were administered to patients.

The most commonly used was the Folfirinox chemotherapy regimen, composed by folinic acid, 5-fluorouracil, irinotecan, oxaliplatin, in various numbers of administration.

Other chemotherapy regimens were Folfiri, composed by folinic acid, 5-fluorouracil, irinotecan; Gemox, composed by gemcitabine with oxaliplatin; GemCap, composed by gemcitabine and capecitabine. Gemcitabine was also administrated alone, or with different chemotherapy drugs such as cisplatin, capecitabine, adriamycin, trastuzumab, docetaxel, paclitaxel albumin-stabilized.

A combined radio-chemotherapy protocol was administrated in some other cases.

Histopathological analysis. Previously, cytological or histopathological analyses were done to diagnose the tumor with fine needle aspiration (FNA) or with fine needle biopsy (FNB) done with an endoscopic approach with ultrasound guide in case of borderline resectable tumors or with percutaneous approach with transabdominal ultrasound guide in case of un-resectable tumors.

Pathologic evaluation as then performed on surgical specimens. During surgery an extensive tissue sampling, including the tumor and the adjacent circumferential resection limits, was done.

Data analysis. CT texture analysis results including mean value, variance, skewness, kurtosis and entropy, obtained on CT 1 and on CT 2 for each patient of both groups were compared by using Wilcoxon correlation test. Statistical analysis was performed by using software Analyse-it for Microsoft Excel (Analyse-it Software, version 4.51, Ltd, <http://www.analyse-it.com/>; 2009). A p -value<0.05 was considered statistically significant.

Results

In this retrospective study 17 patients with pancreatic ductal adenocarcinoma histologically-proven, judged un-resectable or borderline resectable at time of diagnosis, then downsized after neoadjuvant treatment and surgically resected, were included. In the comparison group 14 patients with un-resectable pancreatic adenocarcinoma at time of diagnosis, followed by progression of disease during or after chemotherapy and/or radiation therapy, were included.

Tumor-downsized group. Patients included in the downstaged group were composed by 10 men and 7 women, with a mean age of 61.35 years (range=49-75 years).

In 14 patients (8 men and 6 women), tumor was located in pancreatic head, included 1 in isthmus and 3 involved uncinate process; whereas 3 patients (2 men and 1 woman) had a body-tail tumor.

At least two CT studies before surgical resection were done in all 17 patients, with a mean time distance among them of 6 months (range=3-13 months), and with a last CT study done before surgery within 1 month before the surgical procedure.

Tumor volume reduction was obtained in all cases in this group (Figure 1). The mean of the largest tumor axis at CT 1 (Figure 1a) was 33.12 mm (range=24-57 mm), the mean of shortest tumor axis at CT 1 was 27.06 mm (range=16-52 mm) and the mean sum of largest and smallest axes at CT 1 was 60.18 mm (range=41-109 mm). The mean of largest tumor axis at CT 2 (Figure 1b) was 23.53 mm (range=16-37 mm), the mean of shortest tumor axis at CT 2 was 18.53 mm (range=10-28 mm) and the mean sum of largest and smallest axes at CT 2 was 42.06 mm (range=30-65 mm).

In 2 patients, tumors were classified as borderline resectable at time of diagnosis at CT 1, whereas in 15 patients the tumors were classified as locally advanced un-resectable at CT 1.

All 17 included patients were candidates for neoadjuvant treatment of different regimen, in particular: 1 patient underwent 2 cycles of gemcitabine alone; 1 patient underwent 9 cycles of Gemox chemotherapy regimen then linked with radiation therapy plus sensitizing chemotherapy;

a

b

Figure 1. CT study of pancreatic adenocarcinoma before and after chemotherapy. a. CT1: CT study of locally advanced ductal adenocarcinoma of the pancreatic head. b. CT2: CT control after chemotherapy.

1 patient underwent GemCap chemotherapy regimen; 1 patient underwent 4 cycles of cisplatin, adriamycin, gemcitabine and capecitabine, then 6 cycles of gemcitabine, docetaxel and trastuzumab, then 3 cycles of gemcitabine, docetaxel, trastuzumab and paclitaxel albumin-stabilized, then linked with radiation therapy; 13 patients underwent 9.70 mean cycles of Folfirinox chemotherapy regimen

(range=5-12 cycles), which 2 patients that then underwent radiant therapy plus sensitizing chemotherapy and 1 patient then underwent 2 cycles of Folfiri chemotherapy regimen.

After the tumor downstaging, all the patients had surgery. Tumor resection was performed in all cases. In particular 14 patients had a pancreaticoduodenectomy; 3 patients had a distal spleno-pancreatectomy.

At pathology, in 14 (82%) patients resection margins were free from tumor, in 2 patients retroperitoneal margins were focally infiltrated and in 1 patient pancreatic slice was infiltrated.

At tumor texture analysis the following parameters, both for CT 1 and for CT 2, were obtained: mean value; variance, skewness, kurtosis and entropy.

Computed texture analysis values were recorded for each study and subsequently compared. In particular, median values of computed texture analysis parameters of CT 1 were: Mean Value 1082.70; Variance 876.3100; Skewness -0.23362000; Kurtosis 0.3407900; Entropy 0.552000 (Table I). Median values of computed texture analysis parameters of CT 2 were: Mean Value 1081.10; Variance 828.1400; Skewness -0.09995700; Kurtosis -0.5135100; Entropy 0.552000 (Table II).

The values obtained from texture analysis of CT 1 were compared with the ones obtained for CT 2 by using Wilcoxon correlation test. From all the comparisons, between CT 1 and CT 2, only Kurtosis were statistically different ($p=0.0046$) in respect to mean value ($p=0.2842$), variance ($p=0.5477$), skewness ($p=0.3060$), and entropy ($p=0.2069$).

Progression-disease group. Patients included in the group with disease progression are composed by 7 men and 7 women, with a total mean age of 63.36 years (range=39-77 years).

In 11 patients (6 men and 5 women) the tumor was located in the pancreatic head, 2 involved the uncinate process; whereas 2 patients (1 man and 1 woman) had a body tumor and in 1 patient (woman) the tumor was localized in the tail.

At least two CT studies were done in all 14 patients, with a mean time distance among them of 7 months (range=3-19 months).

Disease progression was present in all cases, with local tumor progression and/or metastatic spread. The mean of the largest tumor axis at CT 1 was 34.28 mm (range=17-60 mm), and the mean of shortest tumor axis at CT 1 was 27.86 mm (range=15-37 mm). The mean of the largest tumor axis at CT 2 was 41.86 mm (range=26-54 mm), and the mean of shortest tumor axis at CT 2 was 34.57 mm (range=22-53 mm).

All the 14 included patients were candidates to chemotherapy and/or radiation therapy, with different regimens.

Computed texture analysis values were recorded for each study and subsequently compared. In particular, median

values of computed texture analysis parameters of CT 1 were: Mean Value 1081.75; Variance 485.320; Skewness -0.013894580; Kurtosis -0.261285; Entropy 0.500880 (Table III). Median values of computed texture analysis parameters of CT 2 were: Mean Value 1080.45; Variance 423.215; Skewness 0.131505000; Kurtosis -0.264600; Entropy 0.527865 (Table IV).

The values obtained from texture analysis of CT 1 were compared with the ones obtained for CT 2 by using Wilcoxon correlation test and from all the comparisons there was no statistical difference among the analyzed parameters: Mean value ($p=0.9032$), Variance ($p=0.2958$), skewness ($p=0.3575$), kurtosis ($p=0.5416$), and entropy ($p=0.9515$).

Discussion

Neoadjuvant therapy is commonly accepted as the first step in the management of patients with pancreatic ductal adenocarcinoma, due to its presentation at diagnosis that is only in few cases immediately resectable. Unfortunately, the re-staging at imaging of ductal adenocarcinoma during or at the end of the chemotherapy treatment is still a challenge (1, 2).

The positive predictive value of CT in determining unresectability is very high (89-100%), but it is lower when predicting resectability (45-79%) (1, 2). Pre-operative treatments create necrotic, fibrous, and inflammatory areas, causing an increase in the amount of fibrosis within the tumor compared to the number of viable tumor cells. CT imaging has some difficulties and limited value in differentiating residual viable tumor from fibro-inflammatory tissue replacement derived to chemotherapy and radiation therapy, probably explaining why the usual criteria for tumor response to neoadjuvant treatment, based entirely on tumor size, are not sufficient to assess the oncologic response of this cancer type (8, 15-17). Therefore, following neoadjuvant chemotherapy and radiation therapy, the solid tumor's vascular contact may be replaced by perivascular haziness or fat stranding that can be due to post-treatment fibrosis or a viable tumor, making assessment of tumor resectability on cross-sectional images difficult (1, 2, 18-20).

Several studies have empathized the difficulty of CT in reassessing local-regional tumor extension after conclusion of pre-operative neoadjuvant chemotherapy and radiation therapy (8, 18-20).

Cassinotto *et al.* (20) affirmed that the ability of CT to evaluate operability, T-staging, and histological resectability is reduced after neoadjuvant therapy, chiefly due to an overestimate of the tumor size and vascular contacts after preoperative treatment, and to the presence of diffuse peri-pancreatic inflammation. Moreover, they asserted that radiotherapy, infections, biliary drainage, complications due to biliary derivation or biopsy may participate into the overestimation of tumor infiltration and local extension.

Table I. *Parameters of computed texture analysis of CT 1 in tumor-downsized group.*

CT 1 parameters	Minimum	First quartile	Median	Third quartile	Maximum	Inter-quartile range
Mean value	1,046.6	1,079.53	1,082.70	1,089.43	1,137.9	9.90
Variance	230.490	559.6333	876.3100	1,141.2667	2,323.900	581.6333
Skewness	-1.3311000	-0.65247000	-0.23362000	0.11145067	0.7184200	0.76392067
Kurtosis	-0.768740	0.1026537	0.3407900	0.8355967	2.276700	0.7329430
Entropy	0.36811	0.522133	0.552000	0.679313	0.77216	0.157180

Table II. *Parameters of computed texture analysis of CT 2 in tumor-downsized group.*

CT 2 parameters	Minimum	First quartile	Median	Third quartile	Maximum	Inter-quartile range
Mean value	1,050.7	1,073.97	1,081.10	1,086.57	1,117.4	12.60
Variance	95.514	569.0767	828.1400	1,174.8667	23,302.000	605.7900
Skewness	-6.7595000	-0.21532667	-0.09995700	0.15062667	0.5177900	0.36595333
Kurtosis	-1.129500	-0.8076700	-0.5156200	-0.3129833	-0.066097	0.36595333
Entropy	0.12375	0.472940	0.552000	0.636630	0.77178	0.4946867

Table III. *Parameters of computed texture analysis parameters of CT 1 in progression-disease group.*

CT 1 parameters	Minimum	First quartile	Median	Third quartile	Maximum	Inter-quartile range
Mean value	1,055.0	1,076.88	1,081.75	1,093.53	1,1141.1	16.65
Variance	131.54	327.250	485.320	587.488	1,899.90	260.238
Skewness	-0.46170000	-0.059628333	-0.013894580	0.253720833	0.67796000	0.313349167
Kurtosis	-0.70370	-0.409043	-0.261285	-0.149657	-0.11358	0.259387
Entropy	0.24872	0.419161	0.500880	0.589437	0.95781	0.170276

Table IV. *Parameters of computed texture analysis parameters of CT 2 in progression-disease group.*

CT 2 parameters	Minimum	First quartile	Median	Third quartile	Maximum	Inter-quartile range
Mean value	1,062.6	1,071.93	1,080.45	1,091.12	3,3874.0	19.19
Variance	228.13	336.888	423.215	592.012	1,632.70	255.124
Skewness	-0.17073000	-0.004018208	0.131505000	0.263201667	0.44953000	0.267219875
Kurtosis	-0.45423	-0.412976	-0.264600	-0.111538	-0.07926	0.301438
Entropy	0.00000	0.398882	0.527865	0.648668	0.95781	0.249786

Cassinotto *et al.* then concluded in a prospective study done on patients with locally advanced non-metastatic cephalo-pancreatic adenocarcinoma resected after chemotherapy and radiation therapy treatment (CRT) (8) that, at CT study done after CRT treatment, a partial regression of tumor-vessel contact indicates suitability for surgical exploration, irrespective of the degree of decrease in tumor size or the degree of residual vascular involvement, demonstrating that criteria based on the extent of contact between the tumor and peri-pancreatic vessels are useful in assessing the tumor response of pancreatic adenocarcinoma in the head of the

pancreas. But this could mean that radiologists try to find any pretext to let surgeons attempt a surgery resection. However, in patient's follow-up, for detection of recurrent disease CA 19-9 shows a high sensitivity and specificity, so it remains an *in vivo* marker during treatment (21).

Since the discussed difficulties in re-staging ductal adenocarcinoma at CT images exist, new imaging techniques and evaluation parameters are required to improve the assessment of resectability following chemotherapy or radiation therapy in the tumors, in order to diagnose a possible downstaging.

New imaging analysis has been introduced and used for oncologic evaluations and response to therapy in the recent time. In particular, computed texture analysis is a new tool that evaluates every pixel's value, variations and distribution by showing parameters, such as mean value, variance, skewness, kurtosis and entropy. Texture analysis supplies an evaluation of tumor heterogeneity at imaging analyzing pixel or voxel-gray levels distribution and relationship in the image (10, 11) and there is a suggestion that texture analysis also gives information on tumor microenvironment (10, 12-14).

In the present study we evaluated results of texture computed analysis of locally advanced pancreatic ductal adenocarcinoma downsized and judged suitable for surgery after chemotherapy and/or radiation therapy. The result of the resections was characterized by free resection margins in 82% of the cases. The analysis performed in these cases represents to our knowledge the first report of CT texture parameters of downstaged pancreatic ductal adenocarcinoma. The study shows that a modification of Kurtosis with a statistically significant difference between the first and the pre-resection CT is obtainable during neoadjuvant therapy and this modification in the present series is indicative of downstaging of locally advanced pancreatic ductal adenocarcinoma. It can be argued that cellularity and architecture changes can be detected by more sophisticated evaluation than subjective observation of the aspects of the tumor on dynamic CT study. These parameter modifications could be of some help during chemotherapy to assess the correct timing for surgery together with the more important clinical (such as performance status) and laboratory (such as tumoral markers) data. In particular, considering together the results of this study, significant changes in Kurtosis parameter obtained from CT texture analysis of locally advanced pancreatic ductal adenocarcinoma could suggest the tumor treatment and this change is present in tumor with free resection margins in the present series.

Moreover, in the present study patients with histologically-proven locally advanced ductal adenocarcinoma with disease progression after chemotherapeutic and/or radiotherapeutic treatment were also evaluated for comparison. In this group, differently from the downstaged group, all the comparisons among the texture analysis parameters showed no statistically significant difference.

In literature, CT tumor texture analysis has however shown promising results in a variety of tumor types in predicting pathologic features, overall survival, and response to therapy (10, 22-29).

This study had certain limitations. First, the retrospective nature of the study. Second, the small number of patients. To confirm and extend the present preliminary results and to prospectively assess the clinical relevance of CT tumor texture analysis in the downstaging of pancreatic ductal adenocarcinoma, further studies are necessary.

Conclusion

At CT texture analysis of locally advanced ductal adenocarcinoma during chemotherapy, kurtosis parameter changed significantly in downstaging while there was no statistically significant difference among the CT texture analysis parameters in patients with disease progression.

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