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Correlation between appearance of the retroportal fat plane at preoperative CT and pathology findings in resected adenocarcinoma of the pancreatic head

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AIM: To correlate the appearance of the retroportal fat plane at preoperative computed tomography (CT) and the pathology findings in resected adenocarcinoma of the pancreatic head (PDAC).

MATERIAL AND METHODS: Forty-eight patients with resected PDAC of the pancreatic head were included (24 men, 24 women, mean age 63 years, median BMI 24.1). All patients underwent CT <30 days before surgery. The state of the retroperitoneal resection margin and the presence of lymphatic or perineural invasion were obtained from pathology reports. CT images were reviewed independently by two radiologists for assessment of the retroportal fat plane and graded in two categories (clear/effaced). Inter-reader discrepancies were solved in consensus. Interobserver agreement was calculated and Fisher's test was used to assess the correlation between CT and pathology findings. Visceral fat areas were measured and correlated with CT findings.

RESULTS: A clear retroportal fat plane was significantly associated with a negative retroperitoneal margin at pathology with 100% specificity and PPV (p=0.0001). No association was observed between the appearance of the fat plane at CT and the presence of lymphatic or perineural invasion (p=ns). Interobserver agreement for retroportal fat plane evaluation was good (0.741). False-positive cases had a significantly lower visceral fat area than the correctly classified patients (p=0.0480).

CONCLUSIONS: A clear retroportal fat plane is significantly associated with negative retroperitoneal resection margins at pathology. The lack of visceral adipose tissue can lead to overestimation of retroportal fat plane involvement at preoperative CT.

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Introduction

Pancreatic ductal adenocarcinoma is a tumour with poor prognosis, mainly due to its late clinical presentation and limited response to chemo- and radiotherapy. Nowadays, surgical resection represents the only potentially curative treatment, increasing the 5-year overall survival from <5% to 10–20%.[1–3] Several prognostic factors have been identified for predicting long-term survival, such as preoperative levels of CA 19-9, type of resection performed, margins status after surgery, tumour stage, tumour grade, nodal involvement, and adjuvant therapy.[3–5] Ninety-five percent of tumour relapses occur in the first 2 years after resection as local recurrences, liver metastases, or peritoneal dissemination.[4]

The retroportal fat plane, also called retroportal lamina or posterior lamina, is defined as the triangular-shaped space delimited anteriorly and laterally by the posterior aspect of the pancreatic head, posteriorly by the pancreaticoduodenal fascia and medially by the superior mesenteric vessels (Fig 1). This anatomical space mainly contains fat, lymphatics, and nerves,[6–8] and its anterior aspect corresponds to the retroperitoneal/uncinate process resection margin after pancreaticoduodenectomy or total pancreatectomy. Some authors reported the micro- or macroscopic involvement (R1–R2) of this margin as an independent long-term survival prognostic factor after resection.[9,10]

The aim of the present study was to correlate the appearance of the retroportal fat plane at preoperative computed tomography (CT) with retroperitoneal margin involvement, perineural invasion, and lymphatic invasion in the histology specimen.

Materials and methods

According to the institutional guidelines, IRB approval and patient informed consent were not required for this retrospective study.

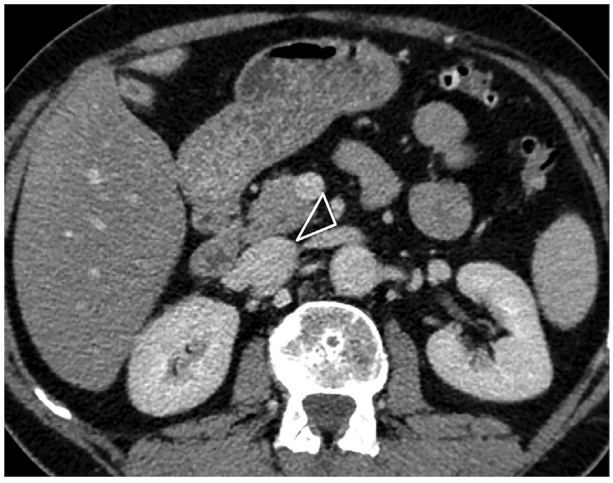

Figure 1 The retroportal fat plane is defined as the triangular-shaped space delimited anteriorly and laterally by the posterior aspect of the pancreatic head, posteriorly by the pancreaticoduodenal fascia and medially by the superior mesenteric vessels.

Study population

Every patient who underwent pancreaticoduodenectomy or total pancreatectomy for resectable pancreatic head adenocarcinoma between January 2009 and March 2013 were considered for inclusion in the present study. Fifty-one patients who underwent multiphasic preoperative CT <30 days before surgery were initially included. Exclusion criteria included poor image quality due to motion artefacts (1/51) or to high patient body mass index (BMI; 2/51). The final population included 48 patients, 24 men and 24 women, with a mean age of 65 years (range 39–79 years). The mean interval between CT and surgery was 9 days (range 0–27 days). Mean and median preoperative values of CA 19.9 were 2,514 and 194 U/ml, respectively (range 5–88,579 U/ml). Eight of these 48 patients were studied after preoperative neoadjuvant chemotherapy. All patients were deemed suitable for resection according to the NCCN guidelines. Forty-six of the 48 patients underwent pancreaticoduodenectomy whereas 2/48 patients had total pancreatectomy.

CT imaging

All examinations were performed on a 64-row MDCT (Brilliance 64, Philips Medical Systems, The Netherlands) with a multiphasic protocol, which included unenhanced, late arterial and portal–venous acquisitions, timed with a bolus-tracking technique. The patient was required to fast at least 6 hours before the examination and 500 ml of water were administered orally 10–20 min before the scan. A region of interest (ROI) of 1 cm^2 was positioned by a radiographer in the abdominal aorta at the origin of the coeliac axis and multiple low-dose scans (50–75 mA) were performed after contrast medium injection. Late arterial and portal–venous phases were acquired respectively 15 and 60 seconds after a threshold of 150 HU was reached in the ROI. All patients received a weight-based (1.5 ml/Kg) amount of high-concentration iodinated contrast agent (Ultravist 370, Bayer Schering Pharma, Germany) through an 18- or 20-gauge intravenous catheter placed in an antecubital vein, using an automatic power injector (Stellant Medrad, Indianola, PA, USA) at a flow rate of 3.5 ml/s, followed by a 50 ml saline flush. All scans were acquired craniocaudally with the patient lying supine on the table, with the arms raised over the head. Scanning parameters are listed in Table 1.

Image evaluation

The CT images were reviewed independently on a PACS workstation (Carestream Vue PACS Version 11.4, Carestream Health, Rochester, NY, USA) by two readers with 5 and 13 years of experience in abdominal imaging, respectively, using various reformatting techniques as needed. The retroportal fat plane was considered clear when there was a defined fat plane between the pancreatic head and the mesenteric vessels, with homogeneous fatty density and without peripancreatic fat stranding (Fig 2). Conversely, it was considered effaced when there was focal obliteration of

Table 1
Imaging parameters

Scanning tube voltage (kV)	120
Collimation	64×0.625
Rotation time	0.5 s
Pitch	1.4
Reconstruction thickness	2 mm
Reconstruction algorithm	FBP

the fat plane between the pancreatic head and the mesenteric vessels, when it had an inhomogeneous density, or when peripancreatic fat stranding or solid nodules were present (Fig 3). Interobserver agreement was calculated and inter-reader discrepancies were solved in consensus. This latter evaluation was used for further analyses.

The presence of biliary stents was noted, as their presence can induce a certain degree of beam-hardening artefacts and peripancreatic inflammation that might influence the retroportal fat plane evaluation. Moreover, as retroportal fat plane evaluation might be affected by patient total visceral fat volume, a third reader measured the visceral fat areas independently at a single level using a semi-automated software tool (ImageJ Version 1.8.0_112, https://imagej.nih.gov/ij/; threshold −190, −30 HU).[11] The axial level L2–L3 was used for measurements, as the visceral fat area obtained at this level has been proved to strongly correlate with the total visceral fat volume.[12–14] The visceral fat areas obtained were then correlated with patient BMIs.

Pathological evaluation

The involvement of the retroperitoneal/uncinate process resection margin by the tumour and the presence of microscopic perineural or lymphatic invasion were obtained from the pathology reports. R0 was defined by ≥1 mm tumour distance from the resection margin.[15] Pathological evaluation was considered the reference standard. All pathology findings were then compared with the CT appearance of the retroportal fat plane.

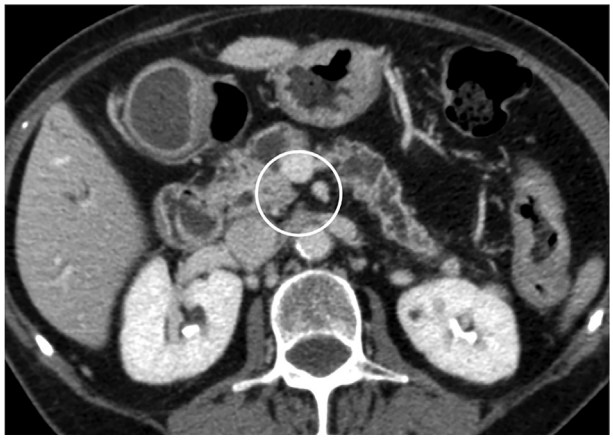

Figure 2 Clear retroportal fat plane. This 2 mm thick axial image shows a homogeneous, fat-density retroportal fat plane (circle) in a 78-year-old woman with pancreatic head adenocarcinoma. There were no signs of retroperitoneal margin infiltration at pathology.

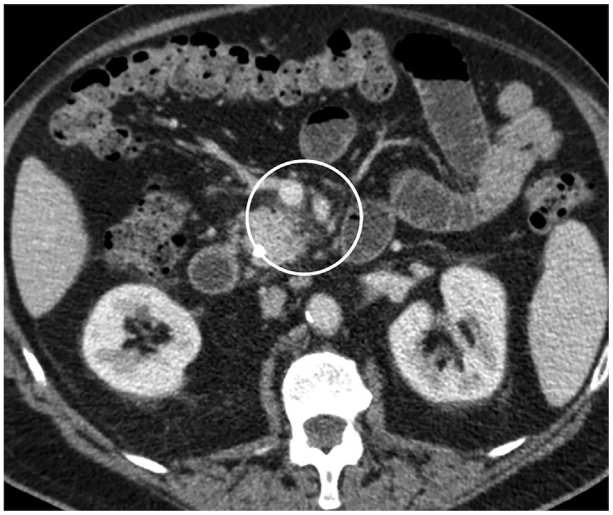

Figure 3 Effaced retroportal fat plane. This 2 mm thick axial image shows an inhomogeneous retroportal fat plane with high-density values and peripancreatic fat stranding (circle) in a 74-year-old man with pancreatic head adenocarcinoma. Pathology showed retroperitoneal margin infiltration.

Statistical analysis

Fisher's exact test, Mann–Whitney test and Spearman correlation were calculated using GraphPad Prism version 6.00 for Mac OS X (GraphPad Software, La Jolla California, USA, www.graphpad.com). Interobserver agreement for retroportal fat plane evaluation was calculated according to the weighted kappa-statistics using GraphPad QuickCalcs (www.graphpad.com). Agreement was assessed as follows: very good if $k = 0.81–1.00$, good if $k = 0.61–0.80$, moderate if $k = 0.41–0.60$, fair if $k = 0.21–0.40$, poor if $k < 0.20$.

Results

Thirty-six of the 48 patients did not present with retroperitoneal margin infiltration at pathology, whereas 12/48 patients had a R1 retroperitoneal resection margin. No R2 resections were observed. Forty-six of the 48 patients presented with perineural invasion and 45/48 showed lymphatic invasion. The mean tumour diameter at pathology was 27 mm (range 10–50 mm).

At preoperative CT, reader 1 considered 17/48 patients to have a clear retroportal fat plane and 31/48 patients to have an effaced fat plane between the pancreatic head and the mesenteric vessels. Reader 2 considered 21/48 patients to have a clear retroportal fat plane and 27/48 patients to have an effaced fat plane. After consensus, 22/48 patients were considered to have a clear retroportal fat plane and 26/48 patients to have an effaced fat plane.

None of the patients with a retroportal fat plane evaluated as clear showed retroperitoneal margin infiltration at pathology (0/22), whereas 12/26 patients with an effaced fat plane presented infiltration of the retroperitoneal resection margin. All patients (8/8) who underwent neoadjuvant chemotherapy were considered to have an effaced retroportal fat plane at preoperative CT, but none of these

actually showed retroperitoneal margin infiltration (0/8). Perineural invasion was present in 21/22 patients with a clear fat plane and in 25/26 patients with an effaced fat plane. Similarly, lymphatic invasion was present in 20/22 patients with a clear fat plane and in 25/26 patients with an effaced fat plane (Table 2).

A clear retroportal fat plane was significantly associated with the absence of infiltration of the retroperitoneal resection margin at pathology (Fisher's exact test; p=0.0001), with a sensitivity of 61% (95% CI: 44–77%), specificity of 100% (95% CI: 74–100%), positive predictive value of 100% (95% CI: 85–100%) and negative predictive value of 46% (95% CI: 27–67%). No association was found between the appearance of the retroportal fat plane at CT and the presence of perineural or lymphatic invasion (Fisher's exact test; p=ns). Interobserver agreement for retroportal fat plane evaluation was 0.741 (95% CI: 0.549–0.932) and was considered to be "good".

Twenty-two of the 48 patients had a biliary stent in place during CT. Of these, 15 presented an effaced fat plane at CT, and 7/15 had a R1 margin at pathology. No significant correlation was found between the presence of biliary stents and false-positive cases (Fisher's exact test; p=ns).

Mean and median patient BMIs were 24.6 and 24.1, respectively (range 18.5–37.7). Mean and median patient visceral fat areas at the selected level were 152 and 151.2 cm^2, respectively (range 40–354.8 cm^2). There was a moderate correlation between patient BMI and calculated visceral fat areas (Spearman correlation; r=0.457). Median patient BMI in the false-positive cases and in the correctly classified cases were 23.9 and 24.2, respectively. No significant differences were found in patient BMI between the false positive cases and the correctly classified cases (Mann-Whitney test; p=ns). Median patient visceral fat areas in the false positive cases and in the correctly classified cases were 110.6 and 168.2 cm^2, respectively. False positive cases had a significantly lower visceral fat area than the correctly classified patients (Mann–Whitney test; p=0.0480).

Discussion

Several factors can induce alterations of the density of the retroportal fat plane at preoperative CT: neoplastic factors include direct extension of the tumour, lymph node metastases, and extrapancreatic nerve invasion,[16] while non-neoplastic factors are mainly related to inflammatory changes secondary to chronic obstructive pancreatitis, which may cause oedema of the retropancreatic fat and alteration of its normal density, and fibrosis induced by the tumour itself, which may simulate neoplastic infiltration of the surrounding structures (Figs 4 and 5). This study demonstrates that the absence of CT alterations of the retroportal fat plane is significantly associated with the absence of infiltration of the retroperitoneal/uncinate process resection margin at pathology, with both specificity and positive predictive value of 100%; nevertheless, the low values observed for sensitivity (47%) and negative predictive value (39%) reflect the abovementioned heterogeneity of possible aetiologies for retroportal fat plane alterations at CT. Particular attention must be paid to the patients who undergo neoadjuvant chemotherapy, which induces local necrosis and subsequent increase of the peritumoural desmoplastic reaction (Fig 6), making the differential diagnosis with tumoural infiltration very difficult, as demonstrated by Cassinotto *et al.*[17] In the present series, all the patients who underwent neoadjuvant chemotherapy showed marked alterations of the retropancreatic fat tissue at preoperative CT, sometimes with complete obliteration of the fat plane itself and extensive vascular encasement. Nevertheless, none of these patients actually showed retroperitoneal margin or vascular infiltration at pathology, substantially confirming the findings of Cassinotto *et al.* Another possible pitfall in retroportal fat plane evaluation might be represented by the relative lack of visceral adipose tissue: in the present series the false-positive cases had a significantly lower visceral fat amount than the correctly classified ones, suggesting that in these patients the retroportal fat plane involvement may be overestimated at preoperative CT. To the authors' knowledge, this is the first paper that underlines the correlation between the quantity of visceral adipose tissue and the retroportal fat plane involvement at CT in pancreatic head adenocarcinoma.

No correlation was found between the absence of CT alterations of the retroportal fat plane and the absence of microscopic perineural or lymphatic infiltration, as they were both present in the majority of patients, independent of retroportal fat plane status.

Only two papers in the literature have focused on the correlation between the retroportal fat plane appearance at CT and the infiltration of the retroperitoneal margin after major pancreatic surgery.[18,19] The study of Mazzeo *et al.* concluded that the presence of a subverted retroportal fat plane at preoperative CT correlates with the infiltration of the retroperitoneal margin only in a minority of cases, which confirms the present results of low CT accuracy in the prediction of a positive retroperitoneal resection margin given the presence of retroportal fat plane alterations.[18] The results found by Yamamoto *et al.* are consistent with those of the present study, with high specificity and positive predictive value for the absence of retroperitoneal margin infiltration given a "normal" retroportal fat plane. Indeed, even in a larger series and with more stringent evaluation criteria, they found that the absence of CT alterations of the retroportal fat plane was never associated with a

Table 2
Correlation between the presence of retroperitoneal margin infiltration, perineural and lymphatic invasion and the appearance of the retroportal fat plane at preoperative computed tomography

		Retroportal fat plane appearance	
		Clear	Effaced
Retroperitoneal margin infiltration	Absent	22/22	14/26
	Present	0/22	12/26
Perineural invasion	Absent	1/22	1/26
	Present	21/22	25/26
Lymphatic invasion	Absent	2/22	1/26
	Present	20/22	25/26

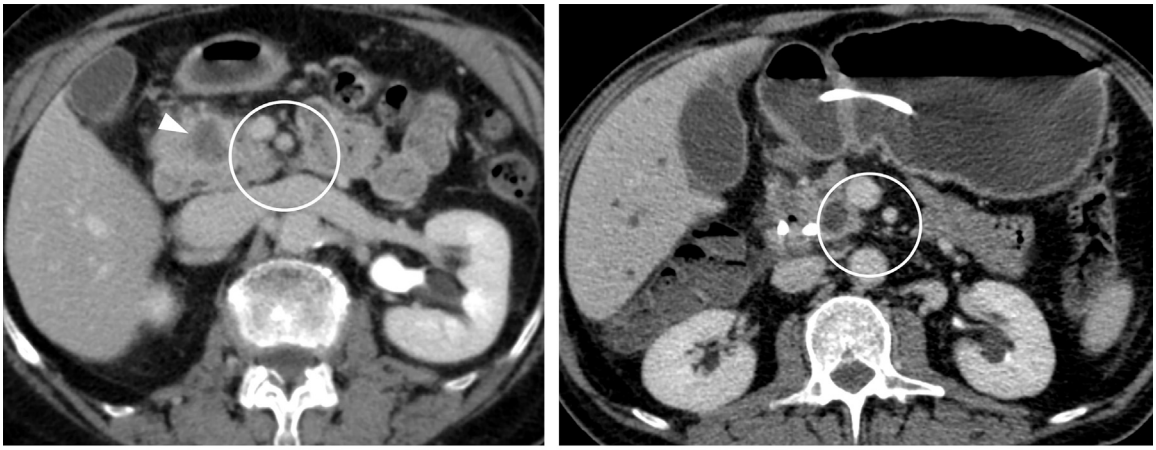

Figure 4 Two-millimetres thick axial images of a 78-year-old woman (a) and a 48-year-old man (b) with pancreatic head adenocarcinoma (arrowhead in a) and a subtle stranding of the retroportal fat plane (circles). In both cases there was a discrepancy between the readers that alternatively classified the retroportal fat plane as clear or effaced. No signs of retroperitoneal margin infiltration were observed at pathology for both patients.

retroperitoneal margin infiltration. Similarly, the presence of CT alterations had low specificity for retroperitoneal margin infiltration.[19]

Preoperative assessment of retroperitoneal margin infiltration is not considered an exclusion criterion for potentially curative surgery or an indication for neoadjuvant chemotherapy, even if its involvement at pathology is considered by some authors an independent prognostic factor after resection.[9,10] Despite this, preoperative identification of potential involvement of this margin may lead surgeons to different approaches, for example, performing a more extended resection or even a total pancreatectomy in order to achieve a clear margin and therefore a possible improvement in the overall survival.

The present study had several limitations, first of all its retrospective design, which limited the number of patients included. Despite the large number of major pancreatic resections performed every year at the University Hospital of Verona, which is a high-volume referral centre, only a minority of patients underwent preoperative CT at our Institute, as most tumours have usually already been staged in the referring centres. Second, the qualitative evaluation of the appearance of the retroportal fat plane may reduce the reproducibility of the study as it introduces a certain degree of interobserver variability, although good concordance was found between readers. Finally, the correlation was made with the pathology reports rather than with a second dedicated pathological review of the margins performed by a single reader, introducing the potential bias of inter-reader discrepancies in margin evaluation. Most pancreatic specimens in our institution, however, are evaluated by a single dedicated pathologist.

In conclusion, the presence of a homogeneous, low-density retroportal fat plane at preoperative CT is significantly associated with the absence of infiltration of the retroperitoneal/uncinate process resection margin at

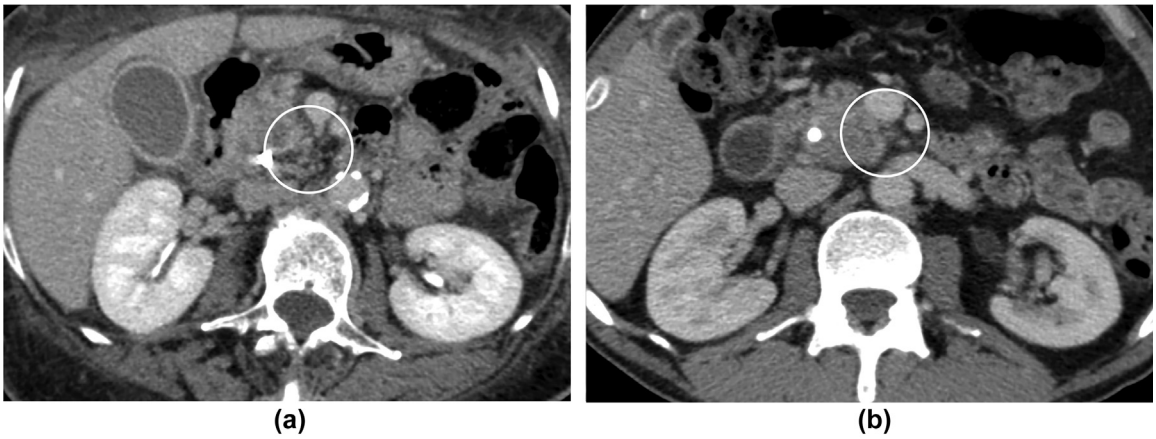

Figure 5 Two-millimetres thick axial images of 68-year-old (a) and 47-year-old (b) male patients with pancreatic head adenocarcinoma and effaced retroportal fat plane (circles). In both cases there were no signs of retroperitoneal margin infiltration at pathology (false positives), being the higher density of fat due to peripancreatic oedema.

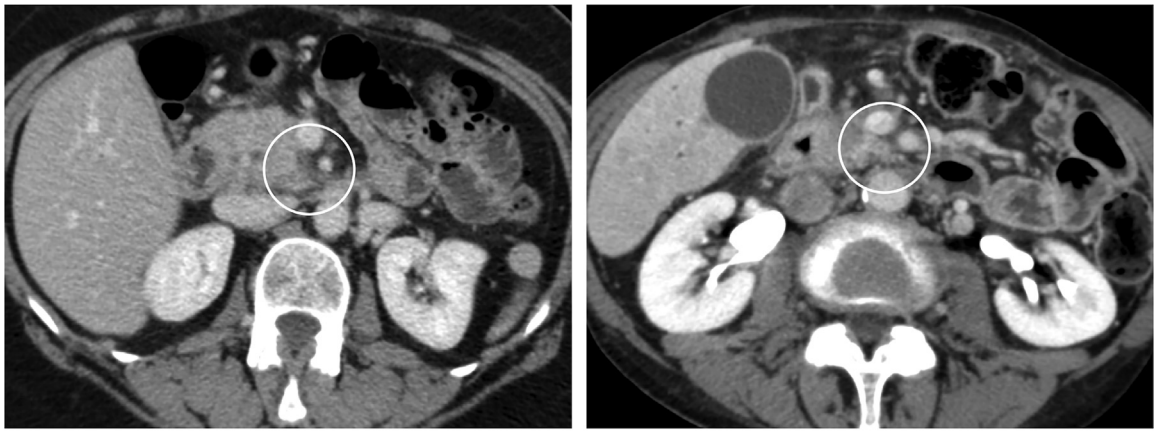

Figure 6 Two-millimetres thick axial images of 55-year-old (a) and 68-year-old (b) female patients with pancreatic head adenocarcinoma who underwent neoadjuvant chemotherapy. In both cases a markedly inhomogeneous retroportal fat plane is depicted (circles) due to desmoplastic reaction induced by necrosis. There were no signs of retroperitoneal margin infiltration at pathology.

pathology. The presence of an effaced or infiltrated plane has low accuracy in predicting actual tumour infiltration of the retroperitoneal margin, especially in patients who underwent neoadjuvant chemotherapy or have little visceral fat. No correlation was found between the CT appearance of the retroportal fat plane and the presence of microscopic perineural or lymphatic invasion.

Conflict of interest

The authors declare no conflict of interest.

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