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Pancreatic ductal adenocarcinoma and local staging with MDCT: Effect of tube voltage and iodine load on assessment of vascular involvement

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ABSTRACT

***Purpose*:** In patients with pancreatic ductal adenocarcinoma (PDAC) a low-tube-voltage, high-iodine-load multidetector computed tomography (MDCT) protocol has been shown to increase tumour conspicuity compared to normal-tube-voltage, normal-iodine-load (standard) protocol. The aim of this study was to prospectively compare a low-tube-voltage with high- or normal-iodine-load MDCT protocol with a standard protocol regarding vascular involvement in patients with PDAC.

Material and Methods: Thirty consecutive patients (16 women-14 men; mean age 67 and 65 years, respectively) with PDAC, deemed primary resectable at the multidisciplinary board, underwent twice preoperative triple-phase MDCT according to: (i) 120-kV standard protocol (PS; 0.75g iodine (I)/kg body weight, *n*=30) and (ii) 80-kV protocol A (PA; 0.75g I/kg, *n*=14) or protocol B (PB; 1g I/kg, *n*=16). Two independent readers evaluated vascular involvement and accuracy per protocol was calculated. A third reader calculated the ves-

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sel-to-tumour contrast-to-noise ratio (CNR). Statistical analysis was performed with the Chi-square test. Standard of reference was surgical and histopathological findings.

***Results*:** For readers 1/2, the accuracy of PS, PA, and PB was 91/91, 92/94, and 92/90%, respectively (P>0.05). Compared to PS, PA and PB showed significantly higher artery-to-tumour CNR in the parenchymal phase (P=0.015 and 0.0016, respectively) and vein-to-tumour CNR in the portal-venous phase (both, P<0.001). PB had significantly higher artery-to-tumour CNR compared to PA in parenchymal phase (P=0.049).

***Conclusions*:** In primary resectable PDAC, vascular involvement was assessed with similarly high accuracy with all protocols. Low-tube-voltage protocols, particularly with high-iodine-load, increase the vessels-to-tumour CNR compared to standard protocol and may prove beneficial in patients with locally advanced tumours where assessment of vascular invasion may be challenging.

KEY WORDS

pancreatic neoplasm/ductal; tumour staging; multidetector CT/protocols; contrast media

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a disease with dismal prognosis and an incidence that closely parallels the mortality rate [1]. Surgical removal of the tumour is the only potential curative therapy [2]. Approximately 15-20% of patients benefit from upfront surgery [3] but the majority present with a non-resectable tumour [4]. For a third group of patients, neoadjuvant therapy increases the likelihood of surgical resection with negative margins and offers upfront treatment of potentially coexisting microscopic distant tumour spread. For these reasons, and given the fact that pancreatic cancer surgery bears a significant risk for severe postoperative complications [5], it is of utmost importance to assign each patient to the appropriate group [6].

A critical aspect in the evaluation of patients with PDAC is the assessment of the local tumour extent. Many classification systems have been introduced over the last two decades [7, 8]. The most important criterion is the description of the interface between the tumour and the major peripancreatic vessels. Lu et al. [9] were the first to describe that a radiographic interface between the tumour and the adjacent vessel measuring at least 180 degrees of the vessel's circumference is a specific indicator of vessel wall infiltration, which necessitates vascular resection in order to remove the tumour without macroscopic residual disease.

The wide availability of multidetector computed tomography (MDCT) and recent technical advances that permit high spatial resolution, have made MDCT the preferred modality for the investigation of patients with a suspicion of PDAC [10, 11]. Accordingly, the International Study Group of Pancreatic Surgery (ISGPS) suggests that the preoperative evaluation of tumour resectability should be based on MDCT [12]. The pancreatic parenchymal phase (PPP) is the optimal phase for the detection of PDAC because of the higher attenuation difference between the hypovascular tumour and the surrounding structures. Two parameters that influence this difference are the dosage (g of iodine) of the intravenous injected contrast medium (CM) and the scanner's tube voltage. Since 1995 it has been established that the dosage of the intravenously administered CM should be at least 0.52 g iodine (I)/kg body weight for optimal detection of hypovascular liver metastasis [13] and that 0.75 g I/kg body weight is superior to 0.6 g I/kg and 0.45 g I/kg body weight for liver and pancreatic imaging, respectively [14]. Tube voltage at 120 kV is considered standard in abdominal imaging [15, 16]. By reducing the tube voltage to 80 kV, the mean photon energy of the X-ray beam lies closer to the k-edge of iodine (33.2 keV), which leads to higher attenuation of the iodine-containing structures [17].

The purpose of this prospective randomised study was to compare a low-tube-voltage with high- or normal-iodine-load MDCT protocol with a normal-tube-voltage, normal-iodine-load (standard) protocol regarding vascular involvement in patients with PDAC.

2. Materials and Methods

This prospective randomised study was fully approved by the regional ethics review board and performed according to the ethical standards as described by the Declaration

Table 1. The three different MDCT examination protocols

Protocol	*Standard*	*A*	*B*
Oral contrast	1,000 ml tap water, 30 min prior to examination		
Intravenous contrast	iomeprol 400 mg/ml* or iodixanol 320 mg/ml**		
Volume (g I/kg body weight)	0.75	0.75	1
Injection duration*** (s)	25	25	25
NaCl flush	50 ml at 5 ml/s	50 ml at 5 ml/s	50 ml at 5 ml/s
Scan start & range			
NCP	Upper abdomen		
PPP	Upper abdomen; 20 s after bolus tracking reached 160 HU in the aorta at the level of the first lumbar vertebra		
PVP	Abdomen and pelvis; 25 s after the end of PPP		
Scanning parameters PPP			
Tube voltage (kV)	120	80	80
Tube current (mA)	ATCM	ATCM	ATCM
Section collimation (mm)	64 x 0.625	64 x 0.625	64 x 0.625
Table feed (mm)	20	20	20
Rotation time (s)	0.6	0.6	0.6
Noise index	22	10	10
Scanning parameters PVP			
Tube voltage (kV)	120	80	80
Tube current (mA)	ATCM	ATCM	ATCM
Section collimation (mm)	64 x 0.625	64 x 0.625	64 x 0.625
Table feed (mm)	39	39	39
Rotation time (s)	0.6	0.6	0.6
Noise index	40	10	10
Reconstructions	Axial, coronal and sagittal		
Slice thickness	5 mm (and 3 mm with narrower FOV focused on pancreas)		
Interval	2.5 mm (and 1.5 mm with narrower FOV focused on pancreas)		

** Iomeron-400, Bracco Imaging S.p.A, Milan, Italy*
*** Visipaque-320, GE Healthcare, Chalfont St. Giles, UK*
**** Given the body weight-adjusted volume and fixed injection duration, the iodine injection rate was variable*
NCP non-contrast phase, PPP pancreatic parenchymal phase, PVP portal venous phase, ATCM automatic tube current modulation, FOV field of view

of Helsinki. All patients provided their written informed consent.

Study population

Between February 2010 and September 2014, 235 consecutive patients, who were referred to our institution's weekly multidisciplinary tumour board (MTB) and diagnosed at MDCT (performed at either our institution or outside centres) with a potentially resectable, hypovascular solid pancreatic tumour according to imaging criteria described elsewhere [18], were invited to participate in the study. This is the same study population as used previously [19]. Of these patients, 30 (16 women and 14 men; mean age 67 and 65 years, respectively) were enrolled in the study. The tumour was located in the pancreatic head in 25 patients and in the body/tail in 5 patients.

Image acquisition

All patients included in the study were examined on a 64-channel MDCT scanner (LightSpeed VCT or LightSpeed VCT XTE, GE Healthcare, Milwaukee, WI, USA). Following a CT examination according to the institution's standard CT protocol (PS, *n*=30), patients were randomised to 2 groups: protocol A (PA, *n*=14) and protocol B (PB, *n*=16). The mean time interval between the CT examinations was 15 days (range: 3-28).

Scanning protocols

Our institution's standard protocol (PS) and the study protocols (PA and PB) are described in **Table 1**. Portal venous phase (PVP) images from 6 patients (2 from PA and 4 from PB) were excluded from the image analysis due to the fact that, for technical reasons related to suboptimal compli-

ance with the study protocol, the tube voltage of 80 kV was not used. In 5 examinations from PA and 4 from PB, the rotation time in PPP was set at 1 s. Data from these 9 patients were included in all analyses.

Imaging assessment

Imaging assessment was performed using a picture archiving and communicating system workstation (Sectra, Linköping, Sweden). For the purpose of the study, all evaluations were performed after collection of all data. For the clinical decision-making by the MTB, only the PS CT examinations were considered during the study period (i.e. 2010-2014) by several in-house specialists with experience in pancreatic imaging.

Qualitative analysis

Two radiologists (with 15 and 6 years' experience in abdominal imaging, respectively), who were blinded to the examination protocols as well as to the surgical and histopathological findings, assessed all cases independently in random order. This assessment was performed on a separate occasion later than the MTB. Readers were allowed to adjust the window level and width.

For each protocol, each reader rated the tumour involvement of the major peripancreatic vessels (superior mesentericoportal axis, SMV/PV; coeliac artery, CA; hepatic artery, HA; superior mesenteric artery, SMA) as well as of the mesenteric venous or arterial branching in both imaging phases. Based on the criteria defined by Lu et al. [9], if tumour involvement of the vessel circumference was ≤180 degrees or >180 degrees, the vessel was classified as abutted or encased, respectively. The results were correlated with the surgical and histopathological findings. Sensitivity, specificity, accuracy, positive and negative predictive values and the respective 95% confidence intervals (CI) were calculated.

Quantitative analysis

A third radiologist (with 3 years' experience in abdominal imaging) measured the attenuation of the tumour, SMV and SMA in both PPP and PVP by manually drawing in the axial plane 3 circular regions of interest (ROIs) in each structure such that as much of the tumour and vessels as possible were included in the axial plane. Areas of necrosis and cystic changes were avoided during measurements. For each patient, measurements were performed simultaneously and at the same level during both protocols (i.e. PS and PA; PS and PB) and imaging phases to ensure consistency. The 3 measurements of tumour and each vessel (i.e. SMV/SMA) were averaged and the mean values were used to calculate the signal-to-noise ratio (SNR) and the vessel-to-tumour contrast-to-noise ratio (CNR) for each vessel. For the calculation of the SNR, and CNR the following formulas were used:

SNR=mean vessel attenuation /noise,

CNR=(mean vessel–mean tumour attenuation)/noise,

whereby noise represents the mean value of the standard deviation (SD) of the subcutaneous fat attenuation in the anterior abdominal wall. This was obtained by manually drawing 3 circular ROIs in a homogeneous area of the anterior abdominal wall.

Surgical procedures

All patients underwent surgical exploration with curative intent. Experienced and fully trained pancreatic surgeons familiar with the techniques of major vascular resection and reconstruction performed all the operations: 23 pancreatoduodenectomies (of which 8 patients underwent SMV/PV resection and 1 patient combined SMV/PV and HA resection), 2 distal pancreatectomies (of which 1 patient underwent SMV/PV resection and en-bloc CA resection) and 5 palliative operations due to the presence of occult liver metastases and/or peritoneal carcinomatosis detected at surgery. The mean time interval between MDCT examination and surgery was 19 days (SD=9).

Histopathological analysis

All the specimens were evaluated in a standardised manner [20]. For the purpose of the study, the histopathological reports were analysed; in cases where additional relevant information for the assessment of vascular involvement were required, an experienced pancreatic pathologist (CV) re-evaluated the microscopic slides. Mean tumour size in the axial plane was 3.6 cm (SD=1.6).

The resected vascular segments were evaluated for presence of wall infiltration. The vascular wall was shown to be involved in 8 of 10 patients undergoing SMV/PV resection, in 1 patient undergoing HA and in 1 patient undergoing CA resection (in both patients with arterial resections, the SMV/PV was also resected and the wall of the venous segments were shown to be infiltrated). As stated above, detection of liver and/or peritoneal metastases during laparotomy in 5 of 30 patients led to the intraoperative deci-

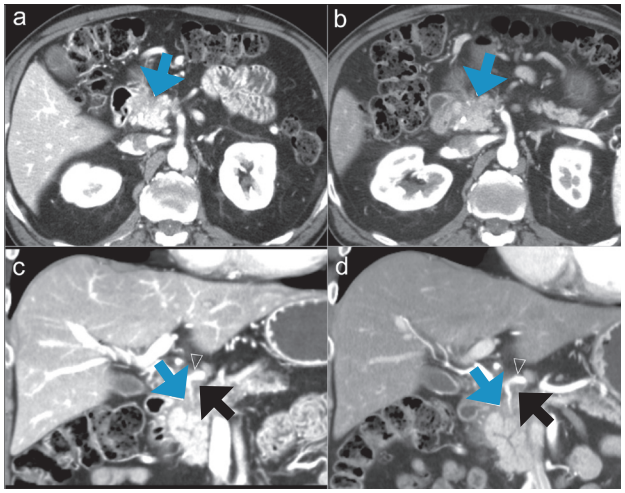

Fig. 1. *Axial (a, b) and coronal (c, d) MDCT images of a 63-year-old patient with ductal adenocarcinoma (blue arrow) in the ventral aspect of the pancreatic head during the pancreatic parenchymal phase. Images (a) and (c) were obtained at 80-kV (normal-iodine-load; protocol A), whereas (b) and (d) were taken at 120-kV (standard protocol; PS). Both readers reported hepatic artery (HA) (arrowhead) encasement by the tumour at the origin of the gastroduodenal artery (black arrow) in both the 80- and 120-kV examinations. During surgery, no signs of infiltration of the HA were present, and arterial resection was not performed, which indicates the radiological overestimation of the HA engagement probably due to fibrotic and/or inflammatory changes [12]. Regarding venous engagement, both readers identified superior mesenteric/portal vein encasement (not shown), which was confirmed by histology*

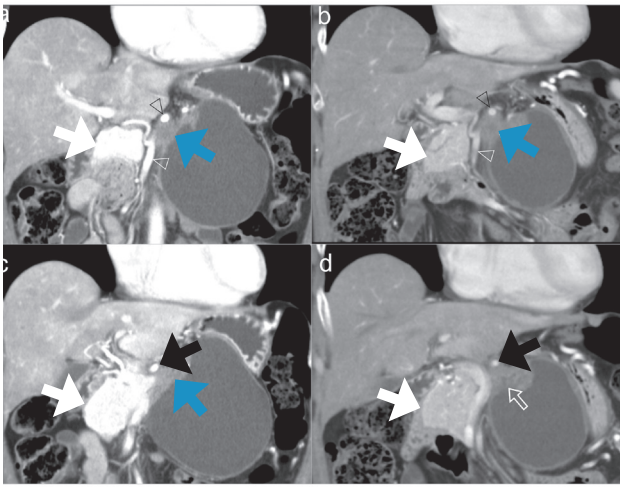

Fig. 2. *Coronal MDCT images of a 54-year-old patient with a histologically verified pancreatic adenocarcinoma in the body of the pancreas (blue arrow) during the pancreatic parenchymal imaging phase. Images (a) and (c) are obtained at 80-kV (normal iodine-load; protocol A) while (b) and (d) at 120-kV (standard protocol). Both readers reported encasement of the coeliac artery (CA; open black arrowhead at a and b) and superior mesenteric artery (SMA; open white arrowhead at a and b) at both the 80- and 120-kV. During surgery, there was involvement of the CA but not the SMA, which resulted in true positive findings for both readers regarding CA and false positive findings regarding SMA involvement. Regarding the hepatic artery (HA; black arrow at c and d), one of the readers reported encasement at 120-kV (d) but not at 80-kV (c), whereas the other reader did not report encasement with either protocol. At surgery there were no signs of infiltration around the HA, indicating a false positive result for one reader at 120-kV. Superior contrast-enhancement of the non-tumorous pancreatic parenchyma in the head (solid white arrow) with the 80-kV (a, c) compared to the 120-kV protocol (b, d) is also observed*

sion not to resect the tumour. As the assessment of vascular wall involvement was not possible in these 5 patients, their data were excluded from the qualitative analysis. The resection was considered R1, if the microscopic distance of the tumour to the circumferential resection margin in the surgical specimen was smaller than 1 mm. In 20 out of the 25 patients whose tumours were surgically removed, the resection was deemed R1, and R0 for the remaining 5 patients. There were no R2-resections.

Statistical analysis

Multiple comparisons of continuous data were performed by analysis of variance. If there was a statistically significant result, statistical comparisons were made by using the post-hoc test to control for multiplicity as proposed by Fisher [21]. Differences between two independent groups were assessed by Student's t-test for uncorrelated means, following validation for normal distribution by use of the Shapiro-Wilk test. In order to evaluate hypotheses of variables in contingency tables, the Chi-square test was used. Sensitivity, specificity, accuracy, PPV and NPV were calculated with corresponding 95% confidence intervals. In addition, descriptive statistics were used to characterise the data. All analyses were performed out by using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was considered significant.

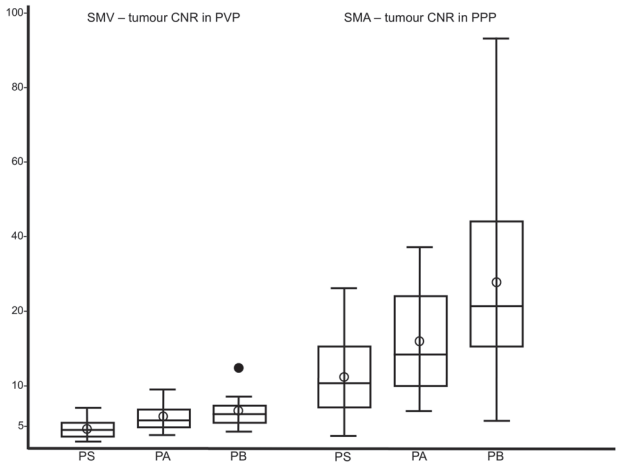

Fig. 3. *Box plot representing the superior mesenteric vein (SMV)-to-tumour contrast-to-noise ratio (CNR) in the portal venous phase (PVP) and superior mesenteric artery (SMA)-to-tumour CNR in the pancreatic parenchymal phase (PPP). SMV-to-tumour CNR in PVP was significantly higher for PB and PA compared to PS while SMA-to-tumour CNR in PPP was significantly higher for PB compared to PA and PB. The white round dots represent the mean values, the black round dot an outlier*

3. Results

Qualitative analysis

The results of the assessment of the parameter "vascular involvement" per protocol and reader, and correlation with the surgical and histopathological findings are presented in **Table 2.** Sensitivity, specificity, accuracy, PPV, and NPV and their 95% CI per reader and protocol are shown in **Table 3.** For Readers 1/2, the accuracy of PS, PA, and PB for vascular assessment was 91/91 %, 92/94 %, and 92/90 %, respectively (no statistically significant differences observed). There was statistically significant difference in PPV of PB (*vs.* PA and PS) for Reader 1 and in sensitivity of PA (*vs.* PB and PS) for Reader 2.

All three protocols resulted in a slight overestimation of HA involvement. In 4 patients (1 from reader 1, 2 from reader 2 and 1 from both readers), the HA was assessed as encased with PS. In only 1 patient, a short segment of HA was resected and vascular involvement was observed microscopically. In 1 patient examined with PA (both readers) and a further patient who underwent examination with PB (reader 2), the HA was assessed as encased, but none of these patients required a HA resection (**Fig. 1**).

In 6 patients (2 from reader 1 and 4 from reader 2), there was disagreement in venous assessment between the protocols. More specifically, in these 6 patients, PS underestimated venous involvement in 3 and overestimated in 1, whereas PB overestimated in 2 and underestimated in 1. In 2 patients (2 from each reader), there was disagreement in the HA assessment between the protocols: in both cases, PS overestimated the HA involvement. In 2 patients (1 from each reader), both PA and PB overestimated the SMA involvement. A further example of the assessment of local vascular involvement is presented in **Fig. 2.**

Quantitative analysis

The results concerning tumour, SMA and SMV mean attenuation as well as the mean vessel SNR and vessel-to-tumour CNR are presented in **Table 4.** Box plots of SMV-to-tumour CNR in PVP and SMA-to-tumour CNR in PPP are shown in **Fig. 3.**

In the PPP, both PA and PB resulted in significantly higher SMA-attenuation/-SNR and SMA-to-tumour CNR compared to the PS. In the PVP, both PA and PB protocols showed significantly higher SMV-attenuation/-SNR and SMV-to-tumour CNR compared to the PS. Furthermore, PB was superior to PA regarding the SMA-attenuation and the SMA-to-tumour CNR in the PPP. An imaging example of the quantitative analysis in 2 patients is presented in **Fig. 4.**

4. Discussion

This prospective randomised study of 30 patients with a preoperatively resectable PDAC revealed the superiority of low-tube-voltage protocols regarding the opacification of the main peripancreatic vessels and the vessel-to-tumour CNR compared to the PS. More specifically, in the PPP both low-tube-voltage protocols resulted in statistically significantly higher SMA-to-tumour CNR compared to the PS, whereas in the PVP, both protocols showed significantly higher SMV-to-tumour CNR compared to the PS. Furthermore, when the low-tube-voltage was combined with high-iodine-load (PB) it was shown to be superior to normal-iodine-load (PA) regarding the SMA-to-tumour CNR in the PPP.

The results of the qualitative analysis did not show any statistically significant differences in the accuracy of the three protocols regarding local vascular assessment. However, this is most probably due to the patient population

Table 2. Assessment of the parameter "vascular involvement" per protocol and reader, and correlation with the surgical and histopathological findings

	Standard			*PA*			*PB*		
Surgical and histopathological findings									
	No vasc. involvement	**Vasc. involvement**	**Total**	**No vasc. involvement**	**Vasc. involvement**	**Total**	**No vasc. involvement**	**Vasc. involvement**	**Total**
Reader 1									
Tumour vessel contact ≤180°	87 (TN)	5 (FN)	92	46 (TN)	1 (FN)	47	42 (TN)	4 (FN)	46
Tumour vessel contact >180°	4 (FP)	4 (TP)	8	3 (FP)	2 (TP)	5	0 (FP)	2 (TP)	2
Total	91	9	100	49	3	52	42	6	48
Reader 2									
Tumour vessel contact ≤180°	86 (TN)	4 (FN)	90	46 (TN)	0 (FN)	46	40 (TN)	3 (FN)	43
Tumour vessel contact >180°	5 (FP)	5 (TP)	10	3 (FP)	3 (TP)	6	2 (FP)	3 (TP)	5
Total	91	9	100	49	3	52	42	6	48

TP true positive, TN true negative, FP false positive, FN false negative
Vascular involvement was assessed for veins and arteries in both imaging phases, according to the criteria proposed by Lu et al. [9]

selected for this study. In order to have the most reliable standard of reference for the assessment of vascular involvement (i.e. the combination of surgical and histopathological findings), we selected patients with tumours that were deemed at the MTB to be primary resectable, in whom there is by definition no or very limited vascular engagement. Hence, it is possible that for more locally advanced tumours, i.e. tumours that engage the superior mesenteric vessels and/or their branches as well as CA/HA, the results of a similar qualitatively analysis could have been in favour of the low-tube-voltage protocols. The reason for that is that the higher vessel opacification and, more importantly, the consequent higher vessel-to-tumour CNR in both the PPP (dedicated imaging phase for arterial assessment) and PVP (dedicated imaging phase for venous assessment), as observed in our study, may potentially allow a more clear delineation of the tumour borders in relation to the adjacent vessels and, therewith, facilitate the distinction between primary resectable and borderline/non-resectable tumours in equivocal cases. Interestingly, by combining low-tube-voltage with high-iodine-load in PB, the artery-to-tumour CNR increased to an even greater extent, which can potentially further improve the assessment of arterial engagement. These, together with the observed higher tumour conspicuity in PB compared to PA or PS [19] indicate that the low-tube-voltage high-iodine-load protocol is the preferred option for the investigation of patients with a suspicion of PDAC. Furthermore, it has been shown that hypovascular liver metastases have similar [22] or higher [23] CNR at low-tube-voltage protocols compared to normal-tube-voltage protocols, which implies that the former allow at least a similar evaluation of the liver compared to the latter. As described previously [19], the superior performance of the low-tube-voltage protocols was combined with significantly lower radiation exposure, which is an additional factor in favour of the low-tube-voltage protocols.

As shown in **Table 3**, there were statistically significant differences in PPV of PB vs. PA and PS (100% vs 40% and

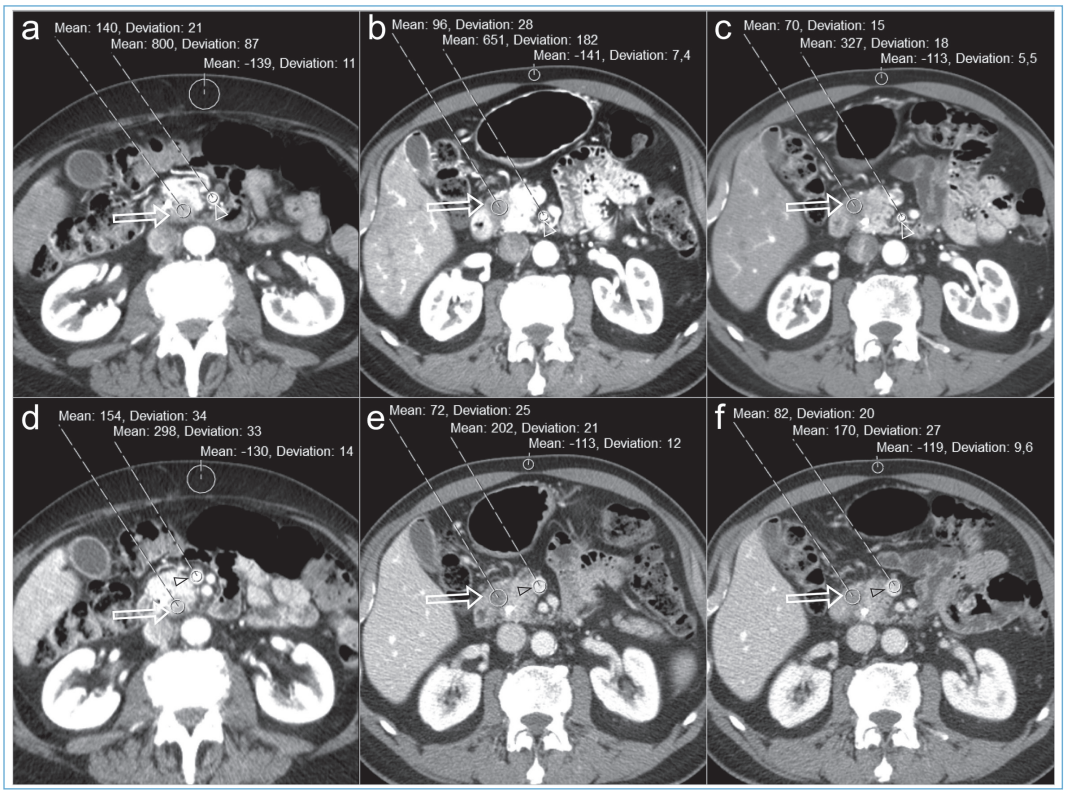

Fig. 4. *Axial MDCT images of a 75-year-old (a, d) and 67-year-old (b, c, e, f) with histologically verified pancreatic adenocarcinomas in the head of the pancreas (open white arrow) during the pancreatic parenchymal (a, b, c) and portal venous (d, e, f) imaging phases. Images (a) and (d) are obtained at 80-kV (normal iodine-load; protocol A), (b) and (e) at 80-kV (high iodine-load; protocol B) while (c) and (f) at 120-kV (standard protocol; PS). The open white arrowheads point at the superior mesenteric artery (SMA) and the open black arrowheads at the superior mesenteric vein (SMV). For these two particular patients, the SMA-to-tumour contrast-to-noise (CNR) in (a), (b), and (c) was 60, 75, and 47, respectively, while the SMV-to-tumour CNR in (d), (e), and (f) was 10.3, 10.8, and 9.1, respectively. For the whole patient cohort, it was shown that SMA-to-tumour CNR in PPP was significantly higher for PB compared to PA and PS, whereas SMV-to-tumour CNR in PVP was significantly higher for PB and PA compared to PS*

50%) for Reader 1 and in sensitivity of PA *vs.* PB and PS (100% vs. 50% and 56%) for Reader 2. With the above two exceptions, sensitivity and PPV values were rather low (33%-67%) and their respective 95% CI very wide for both readers and all protocols. Once again, this is the result of the chosen study design, namely the selection of patients with primary resectable tumours –and consequently the inclusion of relatively few tumours with true vascular infiltration– in order to obtain the most reliable standard of reference (combination of surgical and histopathological findings). Thus, as observed in our study, misdiagnosis of even solitary vascular segments may lead to significant differences in the respective comparisons. Values of specificity and NPV for both readers and all protocols ranged from 93% to 100% and their respective 95% CIs were very narrow, findings that confirm the value of CT for the exclusion of vascular engagement.

For the sake of simplicity, the measurements for the quantitative analysis were performed on one main peripancreatic artery (SMA) and one vein (SMV). All the main peripancreatic arteries (SMA, CA, HA) are branches of the abdominal aorta and their opacification occurs simultaneously and to the same grade. Thus, the measurements of the SMA can be safely extrapolated for the other peripancreatic main arteries and their branches. Regarding the vein measurements, we selected the SMV, which opacifies essentially to the same grade as the PV during the PVP of pancreatic imaging.

The definition of resectability of PDAC has changed in recent decades [7, 24]. This is mainly due to the introduction of new, more aggressive surgical techniques allowing vascular resection and reconstruction with survival rates that are comparable to those of patients with tumours that have no vascular engagement and do not require vascular resection. Potential strategies to increase the possibil-

Table 3. Evaluation of sensitivity, specificity, accuracy, positive predictive values (PPV) and negative predictive value (NPV) per protocol and reader

	Standard	*PA*	*PB*
Reader 1			
Sensitivity	44 (12-77)	67 (13-100)	33 (0-71)
Specificity	96 (91-100)	94 (87-100)	100
Accuracy	91 (85-97)	92 (85-100)	92 (84-99)
PPV	50 (15-85)	40 (0-83)	100
NPV	95 (90-99)	98 (94-100)	91 (83-99)
Reader 2			
Sensitivity	56 (23-88)	100	50 (1-90)
Specificity	95 (90-99)	93 (87-100)	95 (89-100)
Accuracy	91 (85-97)	94 (88-100)	90 (81-98)
PPV	50 (19-81)	50 (1-90)	60 (17-100)
NPV	96 (91-100)	100	93 (85-100)

All presented values are percentages. The values within parentheses represent 95% confidence intervals.

Table 4. Comparison between the three protocols [standard, protocol A (PA) and protocol B (PB)] for the parameters "tumour attenuation", "vessel attenuation", "vessel SNR", "vessel-to-tumour CNR" for SMA and SMV in both PPP and PVP

	Standard	*PA*	*PB*	*P-value*		
				PS vs PA	*PS vs PB*	*PA vs PB*
PPP (SD)						
Tumour (in HU)	90 (24)	125 (23)	140 (47)	<0.0001	<0.0001	0.26
SMA (in HU)	259 (68)	448 (176)	620 (151)	0.0003	<0.0001	0.007
SMA SNR	34 (12)	45 (15)	61 (27)	0.007	0.0018	0.06
SMA–tumour CNR	22 (11)	32 (14)	48 (26)	0.015	0.0016	0.049
SMV (in HU)	221 (49)	321 (141)	429 (83)	0.003	<0.0001	0.015
SMV SNR	28 (8)	34 (17)	41 (10)	0.2	0.2	0.0001
SMV–tumour CNR	17 (8)	21 (17)	27 (10)	0.33	0.0004	0.2
PVP (SD)						
Tumour (in HU)	86 (18)	121 (38)	145 (40)	0.0002	<0.0001	0.14
SMA (in HU)	161 (15)	259 (49)	330 (34)	<0.0001	<0.0001	0.0005
SMA SNR	14 (3)	18 (4)	21 (6)	0.0006	0.001	0.13
SMA–tumour CNR	7 (2)	10 (4)	12 (5)	0.0005	0.0005	0.23
SMV (in HU)	182 (17)	289 (43)	357 (29)	<0.0001	<0.0001	0.0002
SMV SNR	16 (3)	20 (4)	22 (6)	0.0006	0.0012	0.18
SMV–tumour CNR	8 (2)	12 (4)	13 (5)	0.0003	0.0004	0.3

PS standard protocol, PA protocol A, PB protocol B, SNR signal-to-noise ratio, CNR contrast-to-noise ratio, SMA superior mesenteric artery, SMV superior mesenteric vein, PPP pancreatic parenchymal phase, PVP portal venous phase, SD standard deviation, HU Hounsfield units

ity of negative resection-margins include resection of the superior mesentericoportal axis or of a short segment of the HA for tumours in the pancreatic head, as well as CA resection in selected tumours of the pancreatic body or tail [12]. However, the classification system proposed by Lu et al. [9], which takes into consideration the circumference of the vessel that is contiguous to the tumour, remains the cornerstone of the most widely used and accepted classification systems for the assessment of the main peripancreatic vascular involvement [7, 25]. In our study, the assessment of vascular involvement yielded comparable results across the three protocols. An overestimation in the extent of arterial involvement, predominantly of the HA, was observed, a finding which is in agreement with the results from another recent study [26]. For this reason, the ISGPS recommends surgical exploration in cases where the HA appears encased on preoperative imaging [12]. In our study the percentage of patients with R0-resection, as analysed by standardised histopathological analysis, is 20 % (5 out of 25 patients). This is consistent with other studies showing that the proportion of R1-resections exceeds 75%, even in experienced centres [27, 28].

A potential limitation of our study is the risk of overestimation of the accuracy of all three protocols regarding the assessment of vascular involvement. The reason for this is that all patients included in the study were deemed at the MTB to be candidates for surgical treatment with curative intent. Thus, the anticipated extent of the vascular involvement in our series is much lower compared to the majority of patients with PDAC and, therefore, our results regarding the absolute values of accuracy of the three protocols in assessing vascular involvement must be interpreted with caution. However, we consider this limitation to have a very low impact on the comparison of the protocols that were tested. Furthermore, as previously observed [19], a technical limitation of the study is the inclusion in the analysis of nine patients in whom the rotation time during the acquisition of PPP at 80 kV was 1 s instead of the predetermined level of 0.6 s. This could potentially increase the radiation dose and consequently decrease the image noise, a factor that could have been in favour of the low-tube-voltage protocols. However, during PPP the radiation dose levels at 80 kV never reached those of the 120 kV protocols and therefore there was no decrease in image noise at the low-tube-voltage protocols despite the increase in the rotation time. This indicates that this limitation had limited, if any, impact on the comparison of the protocols.

In conclusion, in patients with primary resectable PDAC, low-tube-voltage protocols, particularly with high-iodine-load, increase significantly both the opacification of the main peripancreatic vessels and the vessels-to-tumour CNR compared to standard protocol. The accuracy in the assessment of vascular involvement is similarly high across the three protocols (>90 %). Potentially, the increased vessel opacification and vessel-to-tumour CNR observed with low-tube-voltage protocols may prove beneficial in patients with locally more advanced tumours. R

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Conflict of interest
The authors declared no conflicts of interest.

References

1. Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. *Lancet* 2016; 388 (10039): 73-85.
2. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; 7(4): e1000267.
3. Conroy T, Bachet JB, Ayav A, et al. Current standards and new innovative approaches for treatment of pancreatic cancer. *Eur J Cancer* 2016; 57: 10-22.
4. Heinemann V, Haas M, Boeck S. Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer. *Ann Oncol* 2013; 24(10): 2484-2492.
5. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; 220(4): 530-536.
6. Datta J, Vollmer CM Jr. Advances in surgical management of pancreatic diseases. *Gastroenterol Clin North Am* 2016; 45(1): 129-144.
7. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Bor-

derline resectable pancreatic cancer: Definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006; 13(8): 1035-1046.
8. Tempero MA, Malafa MP, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2014: Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2014; 12(8): 1083-1093.
9. Lu DS, Reber HA, Krasny RM, et al. Local staging of pancreatic cancer: Criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am J Roentgenol* 1997; 168(6): 1439-1443.
10. Brennan DD, Zamboni GA, Raptopoulos VD, et al. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. *Radiographics* 2007; 27(6): 1653-1666.
11. Raman SP, Fishman EK. Advances in CT Imaging of GI Malignancies. *Gastrointest Cancer Res* 2012; 5 (3 Suppl 1): S4-9.
12. Bockhorn M, Uzunoglu FG, Adham M. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; 155(6): 977-988.
13. Heiken JP, Brink JA, McClennan BL, et al. Dynamic incremental CT: Effect of volume and concentration of contrast material and patient weight on hepatic enhancement. *Radiology* 1995; 195(2): 353-357.
14. Yamashita Y, Komohara Y, Takahashi M, et al. Abdominal helical CT: Evaluation of optimal doses of intravenous contrast material-a prospective randomized study. *Radiology* 2000; 216(3): 718-723.
15. McNulty NJ, Francis IR, Platt JF, et al. Multi-detector row helical CT of the pancreas: Effect of contrast-enhanced multiphasic imaging on enhancement of the pancreas, peripancreatic vasculature, and pancreatic adenocarcinoma. *Radiology* 2001; 220(1): 97-102.
16. Kidoh M, Nakaura T, Nakamura S. Low-dose abdominal CT: comparison of low tube voltage with moderate-level iterative reconstruction and standard tube voltage, low tube current with high-level iterative reconstruction. *Clin Radiol* 2013; 68(10): 1008-1015.
17. Schindera ST, Nelson RC, Mukundan S Jr. Hypervascular liver tumors: Low tube voltage, high tube current multi-detector row CT for enhanced detection-phantom study. *Radiology* 2008; 246(1): 125-132.
18. Loizou L, Albiin N, Ansorge C, et al. Computed tomography staging of pancreatic cancer: A validation study addressing interobserver agreement. *Pancreatology* 2013; 13(6): 570-575.
19. Loizou L, Albiin N, Leidner B, et al. Multidetector CT of pancreatic ductal adenocarcinoma: Effect of tube voltage and iodine load on tumour conspicuity and image quality. *Eur Radiol* 2016; 26(11): 4021-4029.
20. Campbell F, Verbeke CS. Pancreatic pathology - a practical approach. Springer London 2013.
21. Daniel WW. Biostatistics: A foundation for analysis in the health sciences, 6th edn. John Wiley & Sons, New York 1995.
22. Nattenmüller J, Hosch W, Nguyen TT, et al. Hypodense liver lesions in patients with hepatic steatosis: Do we profit from dual-energy computed tomography? *Eur Radiol* 2015; 25(12): 3567-3576.
23. Robinson E, Babb J, Chandarana H, et al. Dual source dual energy MDCT: Comparison of 80 kVp and weighted average 120 kVp data for conspicuity of hypo-vascular liver metastases. *Invest Radiol* 2010; 45(7): 413-418.
24. Loyer EM, David CL, Dubrow RA, et al. Vascular involvement in pancreatic adenocarcinoma: Reassessment by thin-section CT. *Abdom Imaging* 1996; 21(3): 202-206.
25. McIntyre CA, Winter JM. Diagnostic evaluation and staging of pancreatic ductal adenocarcinoma. *Semin Oncol* 2015; 42(1): 19-27.
26. Fong ZV, Tan WP, Lavu H. Preoperative imaging for resectable periampullary cancer: Clinicopathologic implications of reported radiographic findings. *J Gastrointest Surg* 2013; 17(6): 1098-1106.
27. Verbeke CS. Resection margins and R1 rates in pancreatic cancer-are we there yet? *Histopathology* 2008; 52(7): 787-796.
28. Esposito I, Kleeff J, Bergmann F. Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 2008; 15(6): 1651-1660.

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