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Apparent diffusion coefficient of pancreatic adenocarcinoma: is there any congruity with tumor resectability?

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Abstract

Background: The accurate determination of resectability in patients with pancreatic cancer is a main goal of preoperative imaging after diagnosis. With advances in surgical techniques, the definition of resectability is in evolution, and it is crucial for radiologists to have an understanding of findings that are relevant to the determination of resectability. The parallel advancements in imaging technology are aiming to improve the ability of imaging modalities to predict resectability. Fifty patients with pancreatic ductal adenocarcinoma (PDAC) were analyzed for capability of apparent diffusion coefficient (ADC) values to predict possible tumor resectability. The patients were classified into resectable and unresectable groups based on magnetic resonance (MR) imaging criteria. Logistic regression analysis was used. Receiver operator characteristic (ROC) curve was reconstructed.

Results: Out of different prognostic variables, tumor size was the only significant predictor of tumor resectability. ROC curve analysis showed that ADC value is not a discriminator of tumor resectability (area under the curve (AUC) = 0.5, *P* value = 0.452).

Conclusions: In patients with pancreatic adenocarcinoma, ADC values might be unreliable for prediction of tumor resectability in clinical practice. Low ADC value in such tumors is more attributed to fibrotic nature rather than grade of the tumor.

Keywords: ADC, Pancreatic adenocarcinoma, Resectability

Background

Ductal adenocarcinomas account for most pancreatic malignancies. Despite recent advances in imaging and management strategies, pancreatic adenocarcinoma continues to be one of the most common causes of cancer-related mortality worldwide [1, 2]. Due to the lack of early specific symptoms and tendency of pancreatic adenocarcinoma to invade adjacent structures or to metastasize at an early stage, many patients with pancreatic cancer already have advanced disease at the time of diagnosis resulting in a high mortality rate [3].

Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, > 80% of patients present with disease that cannot be cured with surgical resection [4]. High-quality multiphase imaging can help to preoperatively distinguish between patients eligible for curative resection and those with an unresectable disease [4].

MRI is a well-established reliable imaging modality for evaluation of patients with pancreatic neoplasms that has a great advantage of excellent soft-tissue contrast for focal lesion detection. It allows a comprehensive analysis of the morphological changes of pancreatic parenchyma and pancreatic duct. However; due to adverse effects and contraindications of contrast media, there is a great need for another imaging modality that can give the same valuable information [3].

Diffusion-weighted (DW) MRI is a recently introduced abdominal MR sequence that expanded MRI capabilities, bringing functional aspects into conventional morphologic MRI evaluation. Modifications of water diffusion induced by different factors acting on the extracellular and intracellular spaces, such as increased cell density, edema, fibrosis, or altered functionality of cell membranes, can be

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Table 1 Descriptive and imaging characteristics of studied patients

	Group I (resectable) ($N = 15$)	Group II (non-resectable) ($N = 35$)	P value
Age (mean ± SD)	63 ± 8	64 ± 9	0.7
Sex (male, %)	10/15 (67%)	22/35 (63%)	0.4
Site (head, %)	11 (73%)	30 (85 %)	0.1
Size (mean ± SD)	2.8 ± 2.01	3.4 ± 1.4	0.8

detected using DWI sequence. Diffusion restriction can be also quantified through calculation of ADC values within specific regions of interest [5].

In this study, we attempted to justify whether ADC of pancreatic adenocarcinomas can predict the status of tumor resectability which will be ultimately reflected upon the plan of patient management.

Methods

This is a retrospective study that was conducted upon 50 patients with pathologically proven pancreatic adenocarcinoma during the period from January 2016 to December 2018. Patients who received CTH or RTH before the MRI study time were excluded from the study.

MRI examination

The patients were examined on a 1.5 Tesla MRI scanner (Philips Achieva, Philips Medical Systems, the Netherlands). Phased array body coil was used. The following pulse sequences were obtained for all patients: T1WI: axial plane, TR/TE 992/10 ms, slice thickness 7 mm with inter-slice gap of 1 mm and 248 × 384 matrix; T2WI: axial or coronal plane, TR/TE 1448/100 ms, slice thickness 7 mm with inter-slice gap of 1 mm and 128 × 384 matrix; T2 SPIR (fat sat): axial or coronal plane, TR/TE460/80, slice thickness 5 mm with inter-slice gap of 1 mm and 128 × 288 matrix; DWI: free-breathing single-shot spin-echo-based diffusion-weighted images in axial plane, TR/TE 2500/123 ms, slice thickness 7 mm with inter-slice gap of 1 mm and 182 × 192 matrix: at b values (0, 500, 1000) followed by computer-generated ADC mapping of the pancreas.

Table 2 Comparison between detection of the lesion at conventional and DWI

Detection of the lesions	Size of the lesion	Lesions		Detection rate (%)
At conventional image	2–7 cm	37 identified	13 not identified	74
After adding DWI		50 identified		100

Table 3 The associated MRI findings of unresectable lesions

	Frequency	Percent
Bone metastasis	4/35	11.4
Liver metastasis	6	17.1
Biliary obstruction (dilated CDB, IHBD)	27	77.1
Vascular encasement	26	74.3
Infiltration of surrounding tissue left kidney	3	8.5
LN	10	25.8

Image interpretation

In the beginning, qualitative assessment for conventional and diffusion-weighted MR images was done. Images were assessed for the presence of abnormalities of pancreatic contour and abnormal signal intensity mass at different parts within pancreatic tissue. The site, size, and signal intensity were assessed for each identified pancreatic mass, as well as associated biliary obstruction, regional lymph nodes, vascular invasion, and distant metastasis. When the lesions with no vascular encasement (< 50%), separable from the duodenum, spleen, or left kidney, or having no distal metastasis, it is said to be resectable lesion.

This was followed by quantitative assessment: pixel-based ADC maps were generated on a dedicated workstation (PAXERA, Ultima), for precise placement of circular region of interest (ROI); ROIs were placed on the exact cut of the lesions on DWI (at b value 1000), thus pointing to the exact corresponding area on ADC map. Mean ADC values for pancreatic masses were measured.

Operative technique and details

In the resectable lesions of the pancreatic head, Whipple's operation was done (6 cases) allowing the safe removal of the pancreatic head, distal stomach, duodenum, bile duct, and gall bladder. In cases of pancreatic body and tail lesions, distal or sub-total pancreatectomy was done (3 cases). Segmental venous resection was done and the splenic vein is preserved. An interposition graft was used to repair the removed venous segment (3 cases). When the venous patch was needed, it was taken from the saphenous vein of the leg (2 cases). Also, the interposition of the venous graft was needed and taken from the left-sided internal jugular vein of the neck (one case). In unresectable lesions, palliative procedures were done. Only the resectable lesions (15 cases)

Table 4 Regression analyses for different prognostic variables

Prognostic factor	P value	OR	R^2	95% CI
Age	0.055	0.925	0.115	0.849 to 1.006
Male gender	0.367	0.812	0.078	0.634 to 1.543
Size	0.001**	1.131	0.509	0.720 to 0.974
ADC value	0.542	0.104	0.084	0.164 to 1.243

** Tumor size is the only significant predictor for tumor resectability (P-value 0.001)

were proved by surgery, while the unresectable lesions (35 cases) were proved by biopsy (either surgical 24/35 or needle biopsy 11/35).

Statistical analysis

Descriptive data were shown as mean ± SD. Two-tail Student's *t* test was used for comparison between different groups of the study. Logistic regression analyses were performed for prognostic factors of resectability. Receiver operator characteristic (ROC) curve was constructed for diagnostic performance of ADC value to discriminate between resectable and unresectable groups. The statistical analyses were performed using SPSS software. *P* value (< 0.05) was considered statistically significant.

Results

This study included 50 patients with histopathologically proved pancreatic adenocarcinoma. The majority of patients were males (60 %). The mean age of patients was 62 years (± 10). The most common clinical presentation was obstructive jaundice (33 %).

They all underwent dedicated pancreatic MRI examination for detection and characterization. The most common site for involvement was pancreatic head, representing 82 % of cases, followed by pancreatic body and tail. The maximum diameter of lesions ranged between 2 and 7 cm in diameter (4.3 cm ± 1.3). Most of the lesions were solid (73%), whereas 27% of the lesions had complex mixed solid and cystic components (Table 1).

There were 13/50 lesions that could not be detected by conventional MRI sequences (their size is from 2 to 3 cm), but could be clearly identified upon adding DW-MRI, raising the detection rate from 74% for conventional MRI to 100% after adding the DWI (Table 2).

By DWI, 37/50 lesions (74%) showed restricted diffusion, while 13/50 (26%) lesions had mixed restricted and facilitated diffusion components. The ADC values for studied lesions ranged between 0.9 and 1.4 × 10^{-3} mm^2/s (1.2 ± 0.07).

The lesions were classified into two groups according to their possible respectability, based on DW-MR imaging findings:

Resectable lesions. This included 15/50 (30%) patients who had clear fat planes around SMV and SMA with no encasement (< 180°) or infiltration to surrounding structures (spleen, left kidney, and duodenum).

Unresectable lesions. This included 35/50 (70%) patients, most of which (26/35) (74%) had an MRI evidence of vascular (mainly SMA/celiac trunk) encasement of > 180°. Meanwhile, 8/35 (23%) patients had distant (bone/liver) metastasis, and 3/35 (8.5%) patients had pancreatic mass lesion infiltrating the left kidney and duodenum.

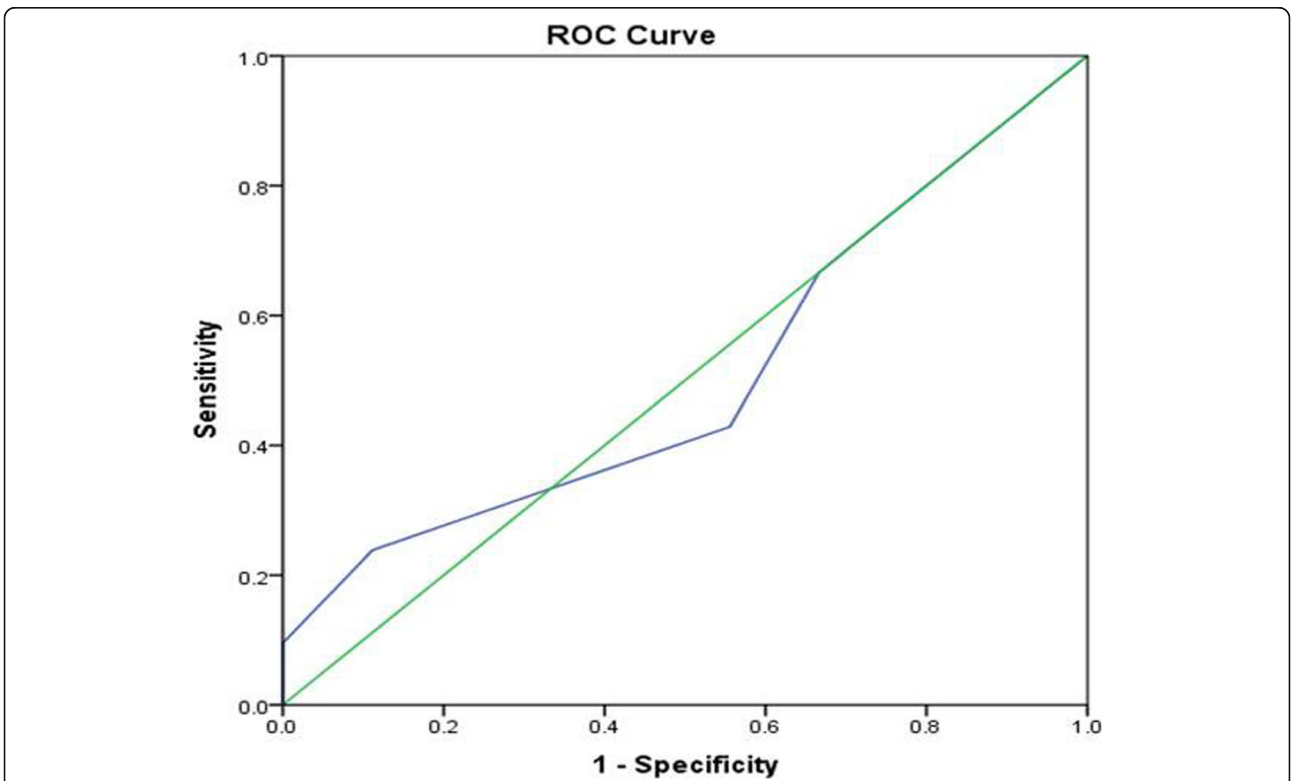

Fig. 1 ROC analysis of ADC values for predicting resectability. ADC values could not discriminate between resectable and unresectable lesions (*P* value 0.452)

There were many associated MRI findings on studied non-resectable lesions; the most common of them were biliary obstruction (27/35), followed by vascular encasement (26/35), representing 77.1% and 74.3% respectively while the least common associated finding was infiltration to surrounding organs (3/35) representing 8.5% (Table 3).

Regression analyses of different variables of resectable/unresectable groups revealed that:

- Tumor size was the only significant predictor for detection of unresectable lesions (P value = 0.0001 and R^2 = 0.5) as shown in Table 4.
- ADC values could not discriminate between resectable and unresectable lesions as shown by the ROC curve analysis (P value = 0.452) (Fig. 1). Selected cases were illustrated on Figs. 2, 3, 4, 5, and 6

Discussion

Radiology can have a major role to play not only in baseline assessment of pancreatic adenocarcinoma, but also it can potentially give more details that may be prognostically important, including prediction of surgical resection [6].

Both DWI visual analysis and ADC measurement can reliably distinguish PDAC from background pancreatic parenchyma. Pancreatic tumors, even if small in size, almost invariably show diffusion restriction, presenting as a focal high signal area on high b value DW images with low signal on ADC mapping [7].

In this study, we found that the pancreatic head is the most common site for pancreatic adenocarcinoma presented. In 41/50 cases, 11/15 are resectable lesions (73%), and in 30/35, non-resectable lesions (85%). This is also established in the study done by Greenlee. et al. [8], who found that 65% of pancreatic adenocarcinomas involved the pancreatic head and uncinate process and 15% in the body and tail. The remaining lesions were detected diffusely involving the pancreas.

In our study, males are more affected than females presented in 10/15 (67%) resectable and 22/35 (63) non-resectable lesions. Artinyan et al. 2008 [9] stated that the anatomic location of pancreatic cancer was a prognostic factor for survival. The age of resectable lesions was lower than the age of the patients having unresectable lesions.

In this study, the addition of DWI to the conventional MRI sequence increased significantly the tumor detection rate. Thirteen of fifty lesions could not be detected by conventional MRI and could clearly be

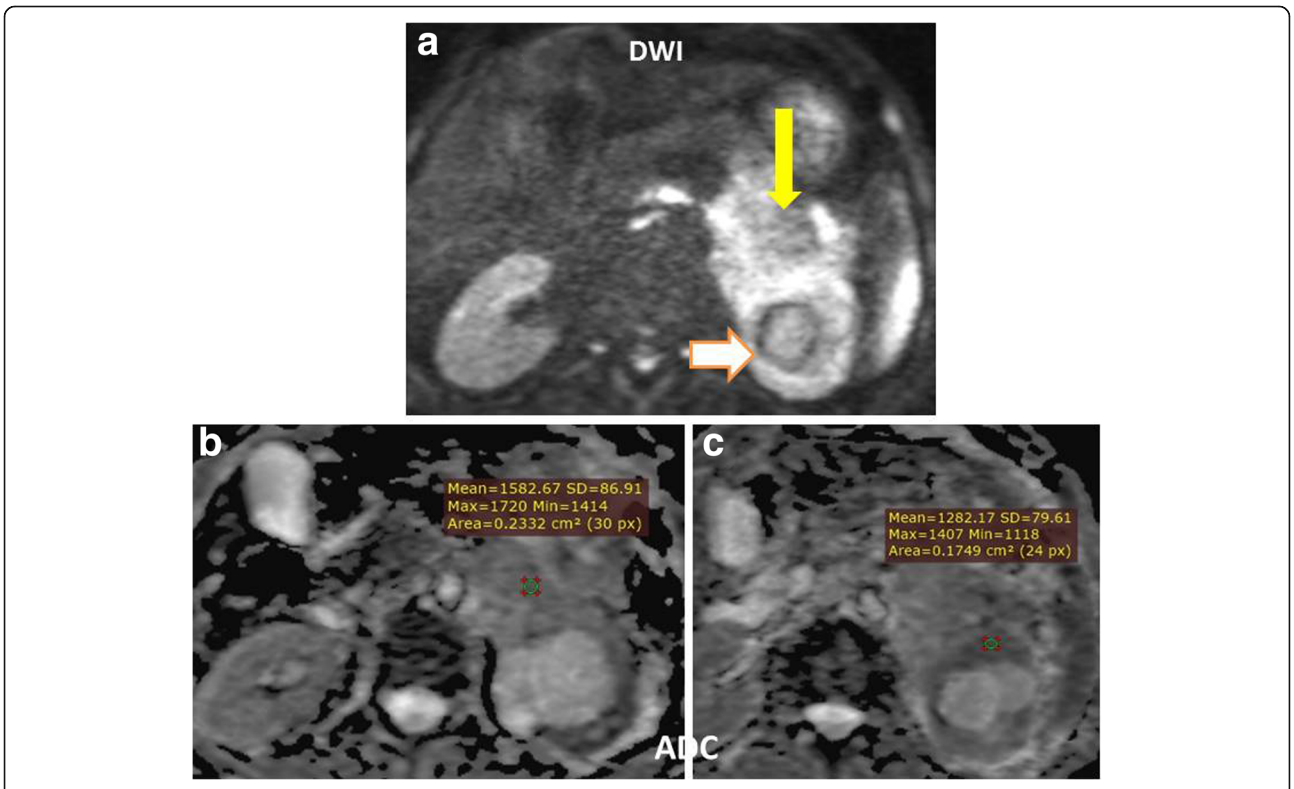

Fig. 2 A 67-year-old male patient comes complaining from left hypochondrial pain and swelling. **a**–**c** DWI and ADC maps showed truly restricted pancreatic tail lesion extending extra-pancreatic and inseparable from the left kidney. The average ADC value from this lesion was 1.2–1.5 × 10^{-3} mm^2/s) (non-resectable lesion)

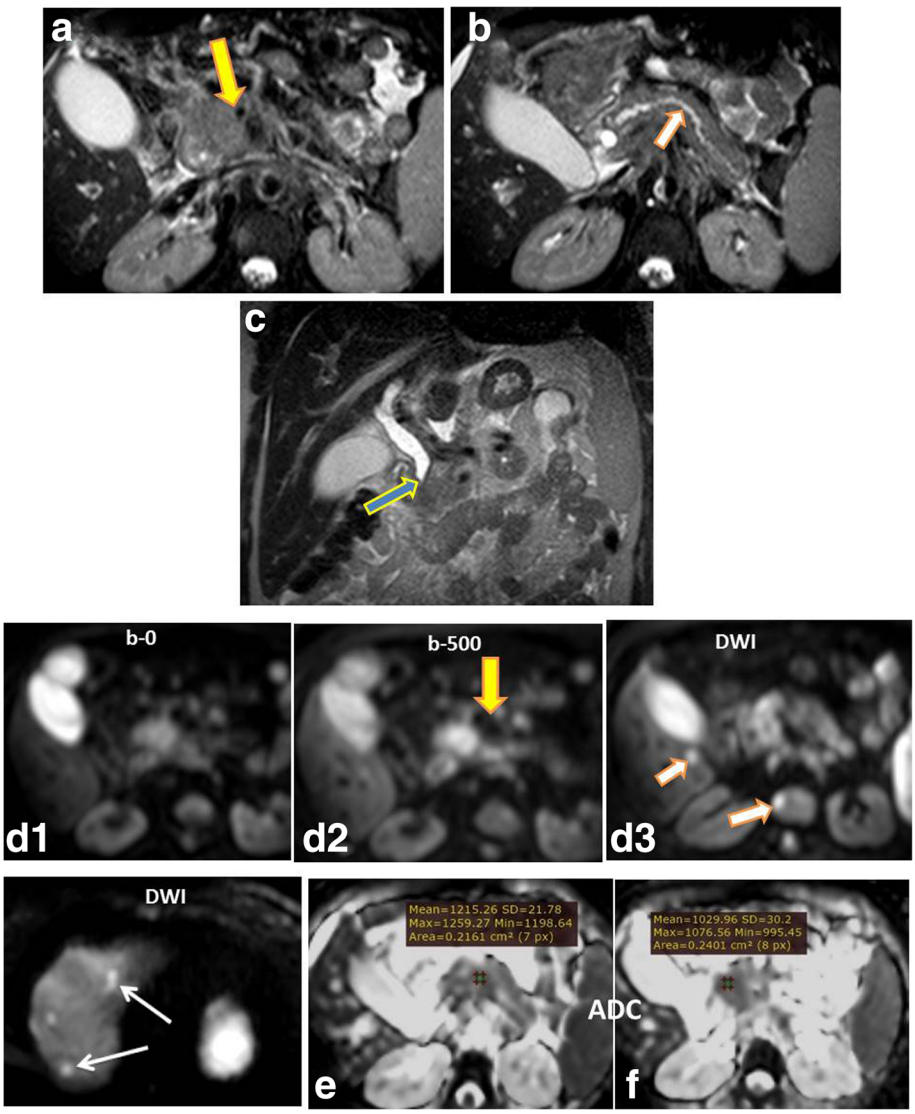

Fig. 3 A 73-year-old female patient presented by obstructive jaundice. **a**–**c** Conventional images (axial and coronal T2WI) showed isointense signal intensity lesion involving the pancreatic head with encasement of the mesenteric vessels > 180° (yellow arrow). Dilated CBD down to its lower end (arrow in **c**). **d**–**f**) DWI and ADC maps revealed truly restricted pancreatic head mass with increased brightness with increasing of the *b* value denoting its malignant nature. The vascular encasement here appeared to be < 180° (resectable lesion). Multiple hepatic (**d4**) and bone (**d3**) deposits are detected rendering the lesion unresectable. The ADC value of the lesion ranged from 1.0 to 1.2 × 10^{-3} mm^2/s

detected by the addition of DWI, and their sizes ranged between 2 and 3 cm. So, the accuracy of detection raised from 74 to 100%. Park et al. [10] demonstrated that the addition of DW-MR imaging to conventional MR sequences helps increase significantly the sensitivity of MR imaging for the detection of small pancreatic adenocarcinoma with sensitivity values rising from 75–76% to 96–98%.

In this research, we have many associated findings with the non-resectable lesions such as biliary obstruction in 27/35 (77.1%), vascular encasement in 26/36 (74.3%), distant metastasis in 8/35 (22.8%), infiltration to adjacent structures in 3/35 (8.5%), and infiltrating spleen, duodenum, and left kidney. Jun et al. [11] stated that the most frequent sites of metastasis form carcinoma of the pancreas are the lymph nodes, lung, liver, adrenal glands, kidney, and bone.

Elsayes et al. [12] found that associated lesions should be described and can affect surgical decision-making. Peritoneal nodules or the presence of ascites suggest disseminated disease that would render the patient unsuitable for a curative resection. Also, the presence of enlarged lymph nodes can also affect surgical resectability and indicate a need for additional therapy.

In our study, 15/50 (30%) lesions are resectable and 35/50 (70%) lesions are non-resectable. Whipple's

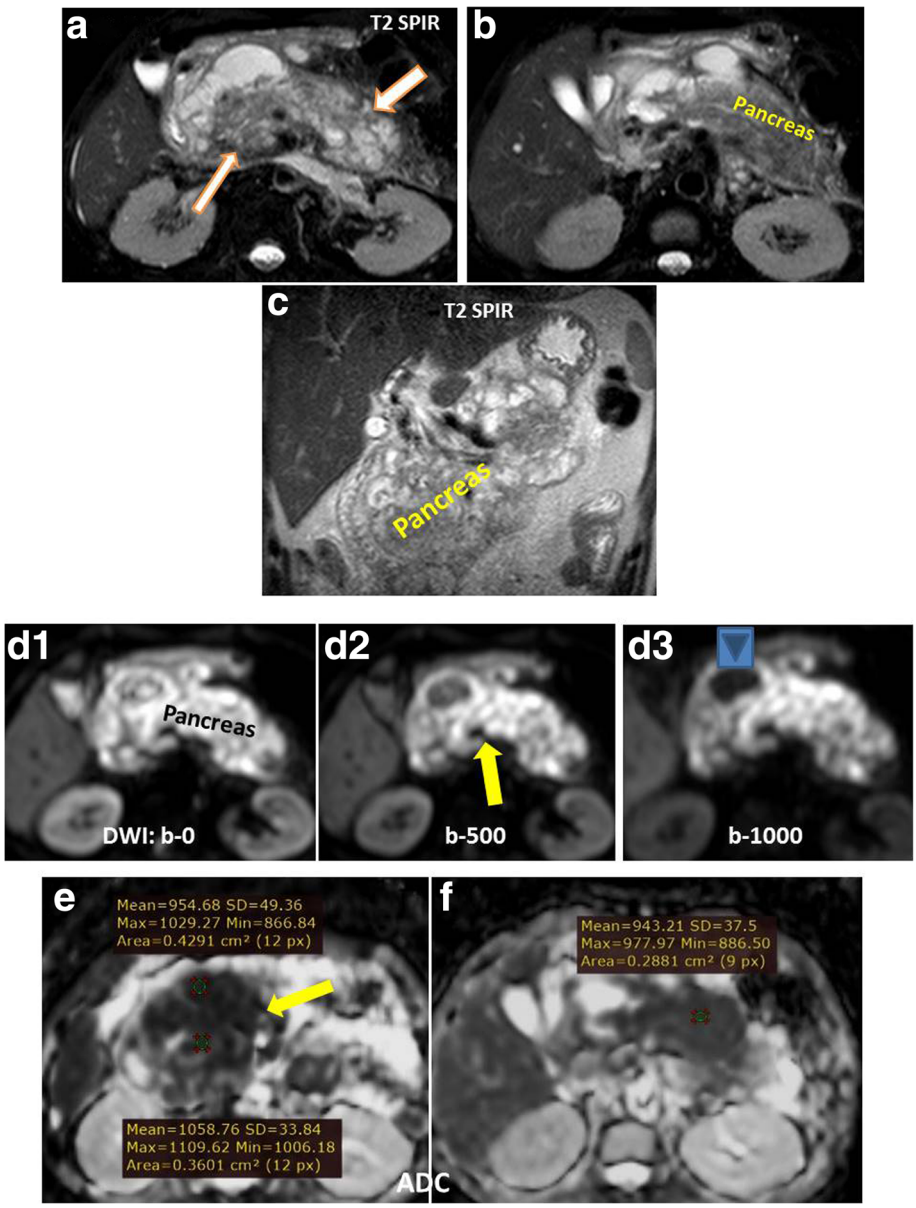

Fig. 4 A 55-year-old male patient comes by epigastric pain and discomfort. **a**–**c** Axial and coronal T2 fat saturation sequence showed diffusely enlarged swollen pancreas (head, body, and tail) with heterogeneous signals and relatively preserved peri-pancreatic fat planes. The pancreatic vessels are totally encased inside the lesion. **d1**–**d3** DWI at multiple *b* values (0, 500, and 1000 s/mm^2) demonstrates the increase of degree of lesion restriction by the increased *b* value denoting the malignant nature of the lesion apart from the facilitated cystic degenerated part of the lesion in which the signal was progressively reduced (colored arrow head). **e**, **f** ADC map of the pancreas showed low signal of the lesion and the measured ROI reflected the low ADC value (0.9–1.0 × 10^{-3} mm^2/s). Also, the mesenteric vessels are noted near totally encased within the lesion (yellow arrow at **d2** and **e**) (non-resectable lesion)

operation was done in 6 cases, subtotal pancreatectomy in 3 cases, venous graft taken from the great saphenous vein in 2 cases, and from the internal jugular vein in 1 case. In non-resectable lesions, palliative procedures were done. Chen et al. [13], on a study done on 38 patients, found that 31 lesions were in the head or uncinate process, 5 in the body, and 2 in the tail. Twenty-four lesions were resectable and underwent Whipple's (3 cases), child operation (13 cases), pylorus-preserving pancreaticoduodenectomy (7 cases), and distal pancreatectomy with splenectomy (7 cases). The lesion size is less than 2 cm in 10 patients and more than 2 cm in 14 patients (2–6 cm). Unresectable lesions underwent palliative procedures like choledechojejunostomy, gastrojejunostomy, and external biliary drainage.

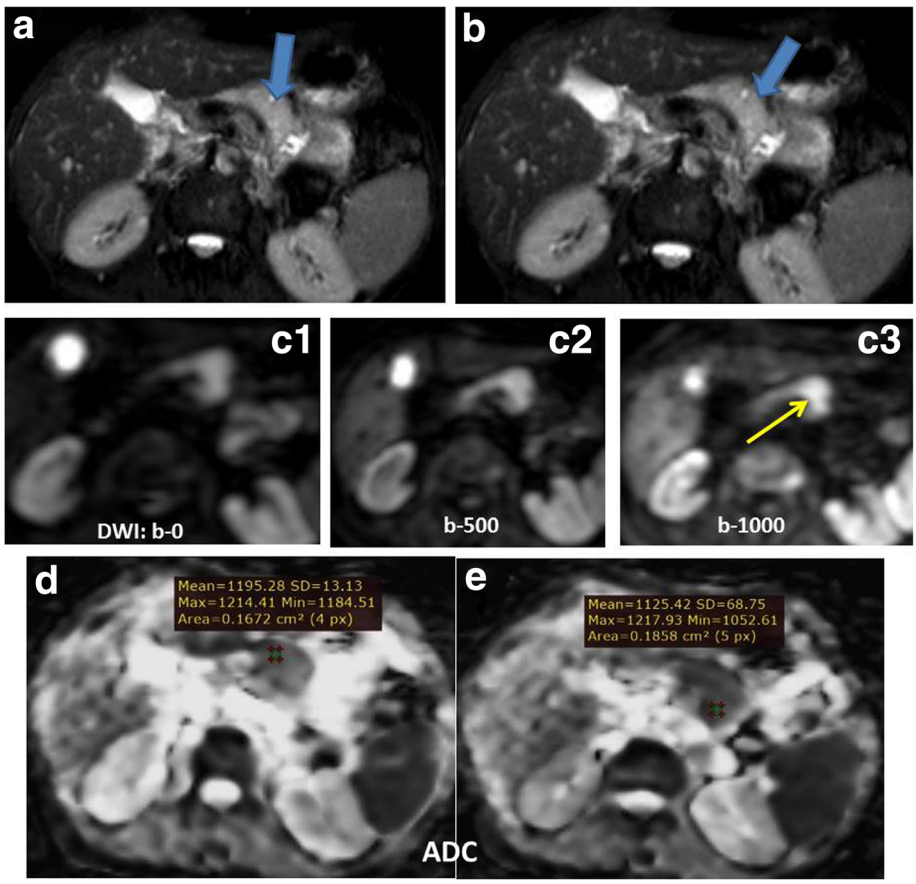

Fig. 5 A 70-year-old male patient presented with abdominal discomfort and pain. **a**, **b** Axial T2 fat saturation revealed just deformed contour of pancreatic body with no detectable abnormal signal lesions. **c1**–**c3** DWI at multiple *b* values (0, 500, and 1000 s/mm^2). The lesion appeared with increased restriction by elevating the *b* value (yellow arrow at **c3**). **d**, **e** The pancreatic lesion showed low signal at ADC map with low ADC value (1.1×10^{-3} mm^2). The lesion abuts the superior surface of the mesenteric vessels but not encase them (resectable lesion)

In our study, the ADC value of both resectable and non-resectable lesions are seen with great overlap with a wide range and insignificant *P* value of 0.452. The ADC value from examined lesions ranged between 09 and 1.4 $\times 10^{-3}$ mm^2/s.

Also, in this research, there is no significant difference between the ADC values of different grades of the pancreatic adenocarcinomas.

The mean ADC values of pancreatic adenocarcinoma extracted from published studies are 1.3×10^{-3} mm^2/s (range 0.78×10^{-3} mm^2/s to 2.32×10^{-3} mm^2/s). In general, most of the studies reported that the mean ADC values of malignant pancreatic tumors were lower than those of normal pancreatic tissues and benign lesions [14].

Barral et al. [15] and Lee et al. [16], instead, did not report significant differences in ADC values between PDACs and other solid pancreatic tumors.

In addition, a considerable overlap of ADC values in the range of malignant lesions might be present. Moreover, benign pancreatic lesions such as pseudocysts can show some degree of diffusion restriction which is thought to be due to the high viscosity of its content [17]. Thus, quantitative ADC analysis alone may be not so accurate for characterization of pancreatic lesions [18].

Rosenkrantz et al. [19] did not report a significant difference in the mean ADC between poorly and well/moderately differentiated tumors. However, some authors postulated that the cell density is proportional to tumor aggressiveness as ADC values were lower in higher than lower-grade tumors in their studies. Also, other studies suggested a relation between tumors hyper-cellularity and increased metastatic capacity [18].

In this study, tumor size was a significant predictor for tumor resectability. This is logical as large tumors become more in contact with blood vessels and lymphatics, and therefore, more chance of tumor spread. Phoa et al. reported that a tumor diameter of > 3 cm showed poor survival after resection [20].

In fact, tumor size is a particularly important prognostic factor to examine as it is included in the American Joint Committee on Cancer (AJCC) staging of pancreatic adenocarcinoma [21].

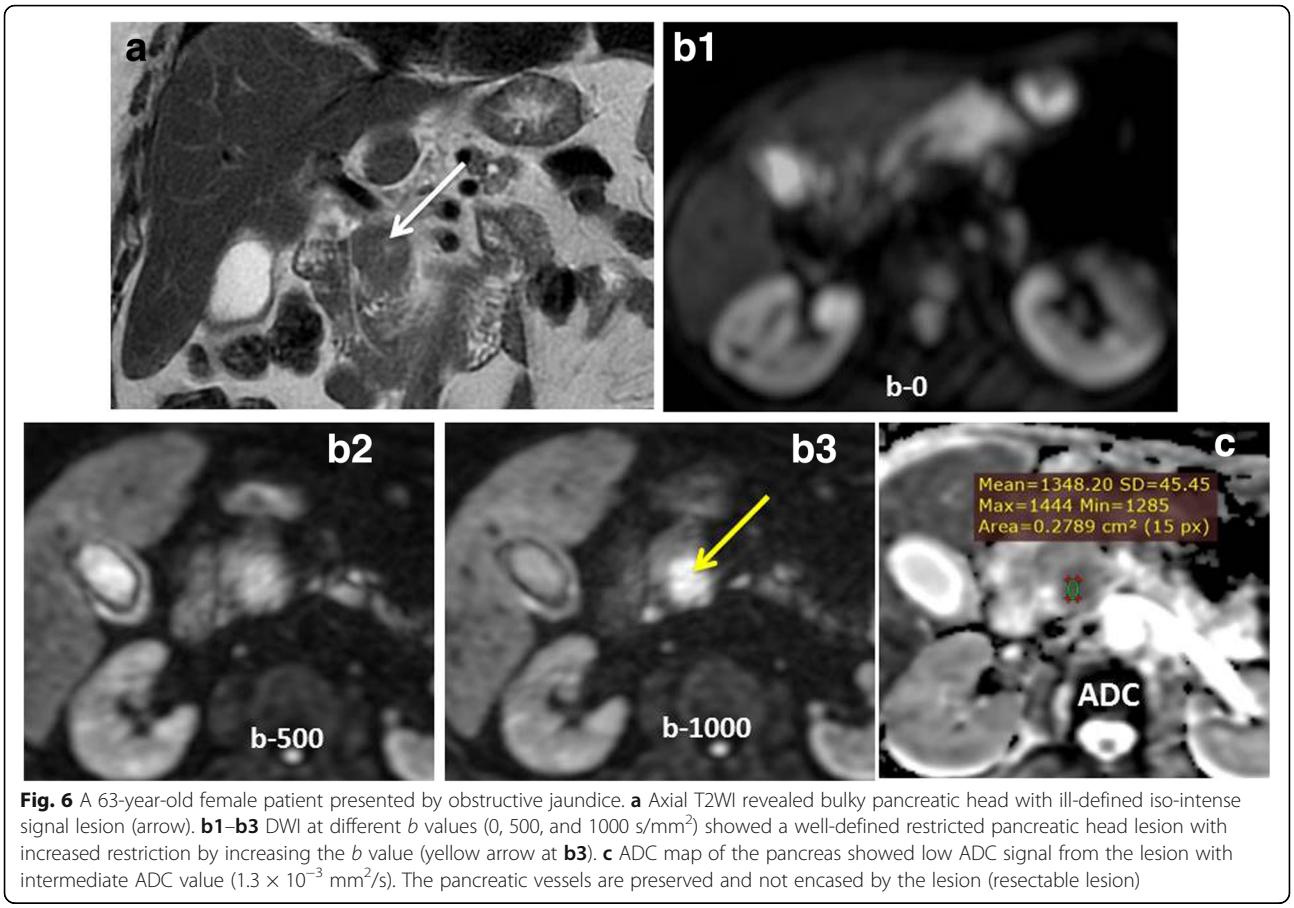

Fig. 6 A 63-year-old female patient presented by obstructive jaundice. **a** Axial T2WI revealed bulky pancreatic head with ill-defined iso-intense signal lesion (arrow). **b1**–**b3** DWI at different *b* values (0, 500, and 1000 s/mm^2) showed a well-defined restricted pancreatic head lesion with increased restriction by increasing the *b* value (yellow arrow at **b3**). **c** ADC map of the pancreas showed low ADC signal from the lesion with intermediate ADC value (1.3×10^{-3} mm^2/s). The pancreatic vessels are preserved and not encased by the lesion (resectable lesion)

However, it should be kept in mind that the effect of tumor size on prognosis is largely mediated through other biologic factors such as lymph node status and histologic differentiation rather than merely tumor size, especially when tumor size is < 5 cm [22].

This study had some limitations such as its retrospective design and the relatively small number of patients within each patient group. It is recommended to focus on clear classification of the groups, criteria of resectability, and ADC values and their relations to each other.

Conclusion

ADC values of PADCs might be unreliable for the prediction of tumor resectability in routine clinical practice. Low ADC value in such tumors is more attributed to fibrotic nature rather than grade of the tumor.

Abbreviations

ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted image; DW-MRI: Diffusion-weighted-magnetic resonance imaging; MR: Magnetic resonance; MRI: Magnetic resonance imaging; PDAC: Pancreatic ductal adenocarcinoma; ROC: Receiving operator characteristic; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SPIR: Selective partial inversion recovery; TE: Time to echo; TR: Time of repetition

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Not applicable

Authors' contributions

All authors have apprised the article and actively contributed to the work. MAK contributed to the idea, DW-MRI, ADC map evaluation, image revision, and final editing. HRA contributed to the data collection, revision, and editing. MMS contributed to the idea, surgical interference, and images. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of El Minia University. An informed oral consent from each patient was taken before enrollment into the study.

Consent for publication

A written informed consent was obtained from all individuals relevant to this research.

Competing interests

The authors declare that they have no competing interests.

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