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The integration of artificial intelligence models to augment imaging modalities in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a limited number of effective treatments. Using emerging technologies such as artificial intelligence (AI) to facilitate the earlier diagnosis and decision-making process represents one of the most promising areas for investigation. The integration of AI models to augment imaging modalities in PDAC has made great progression in the past 5 years, especially in organ segmentation, AI-aided diagnosis, and radiomics based individualized medicine. In this article, we review the developments of AI in the field of PDAC and the present clinical position. We also examine the barriers to future development and more widespread application which will require increased familiarity of the underlying technology among clinicians to promote the necessary enthusiasm and collaboration with computer professionals.

Keywords: Artificial intelligence, Deep learning, Imaging modality, Machine learning, Pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with no effective treatment when surgical resection is not appropriate. The prognosis hasn't significantly improved in the past 3 decades[1] and in China, the incidence of PDAC ranks 9th among all cancers, with more than 100,000 patients diagnosed each year. The mortality from PDAC ranks 6th and it has become one of the leading causes of tumour related death.[1] Presently the therapeutic strategies for PDAC remain limited and surgery remains the only effective treatment with 5-year survival rates only 8% for patients following potentially curative surgery.[2] A number of different therapeutic options have been investigated but the benefits of more recent treatments such as immunotherapy, neoadjuvant chemotherapy and chemoradiotherapy remain uncertain.[3] As a consequence, research into novel approaches continues and it is recognised that the use of emerging technologies to facilitate earlier diagnosis represents one of the most promising areas for investigation. Recent developments in the field of artificial intelligence applied to the augmentation of imaging modalities are encouraging and it is appreciated that we need to appreciate the potential and take full advantage of the opportunities for interdisciplinary research to improve the prognosis of patients with PDAC.

The idea of AI was originally suggested by McCarthy et al in 1955[4] and it was initially meant to allow machines to replicate activities traditionally associated with human intellect including logical reasoning, learning, pattern recognition, intuition and deduction. Since AI and machine learning was envisaged the concept has significantly expanded and the potential for application in myriad fields, appreciated. Research facilitated the development and expansion of AI from the original rule-based models which could only pursue simple tasks to statistical and learning based models which can investigate and recognize patterns in massive data sets. AI has emerged as a mature discipline with the goal of achieving human-like capabilities, in particular autonomous development and learning. The progress in AI has also occurred in parallel with developments in the acquisition and management of "big data" and the hardware and technology required for its application. The potential for the integration of AI and big data and the subsequent applications in healthcare are now widely appreciated and it is believed to offer opportunities for a paradigm shift with a new era for clinical practice in areas including health and well-being, early detection, diagnosis, decision making, treatment, end of life care, research, and training.

Definitions of AI are broad and are generally divided into narrow AI which includes areas such as the interpretation of video feeds, visual inspection and co-ordination with other intelligent systems and general AI, which is the type of flexible, adaptable intelligence capable of learning found in humans. AI is now accepted as an overarching term for systems including machine learning, neural networks and deep learning.

Traditional machine learning is often regarded as the "shallow-layer learning method" which is where large amounts of data are used by computer systems to learn how to carry out specific tasks such as speech recognition. Traditional machine learning relies on pattern recognition or statistical methods and requires structured and historic data with prior knowledge of outcomes. The common models and algorithms of machine learning include

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logistics regression, random forest (RF),[5] support vector machine (SVM),[6] expectation-maximization (EM)[7] and *k*-nearest neighbour (KNN).[8]

Deep learning is a more recent AI development and often referred to as a "deep-layer learning method" and is based on artificial neural networks (ANN). ANNs were developed to recognise patterns in data and are loosely modelled on the human brain. They consist of a set of algorithms, based on a collection of connected units or nodes referred to as artificial neurons. The artificial "neurons" loosely model biological neurons and they interpret sensory data which they then categorise and collate. More complex neural networks contain more hidden layers and as a consequence, more connections. The increasing complexity which results from these additional layers, together with the statistical weights and biases within the system enable the networks to "learn" and identify complex patterns in large data sets.

For the application of ANNs in image recognition, each "neuron" of the input layer is responsible for extracting the information contained in a specific region, while the weight of its output will affect the activation of neurons in the next layer. All neurons of a given layer are generating an output for the next layer and if the output weight is low (for the overall picture) then it will mean less for the overall picture and will be partially or completely muted. The information gathered will be abstracted into feature vectors by multiple transformations and nonlinear mappings via a multi-layer structure, and finally condensed and displayed in the output layer. ANNs are generally trained end-to-end by iteratively optimizing a loss function which is one of the important components of neural networks and is used to update the weights of the neural net allowing an ANN to be trained.

Convolutional neural networks are a class of deep neural networks most commonly applied to analysing visual imagery. Convolutional networks are neural networks that use convolution in place of general matrix multiplication in at least one of their layers. The name "Convolutional neural networks (CNN)" is a consequence of the mathematical operation called convolution (an operation which has 2 functions as input but a single function, describing how the input functions influence each other, as the output) utilised by the networks. Fully convolutional networks (FCNs) owe their name to their architecture, which is built only from locally connected layers. The absence of a dense layer in FCNs reduces the number of parameters and computation time and the network does not requiring any fixed number of units at any stage so the original image size is not important.[9,10] The field of deep learning and neural networks is complex and rapidly expanding and is discussed in a comprehensive review by Litjens et al.[9]

There has been a rapid expansion of the applications of AI to medical images analysis over the last 5 years including the investigation of pancreatic cancer using multi-organ segmentation based on spatially-divided probabilistic atlases of 3D abdominal CT images for the detection and differential diagnosis of PDAC, therapeutic effect monitoring and the prediction of prognosis in individual patients. All of these techniques may also be applied in image reconstruction, disease screening, endoscopic navigation, conformal radiotherapy, individualized therapy, and patient surveillance.

The application of AI in pancreas segmentation

The segmentation of pancreas and pancreatic lesions is one of the most popular applications of AI in medical images and part of the foundation of computer-aided diagnosis (CAD), tumour staging, and radiotherapy contouring. To date the performances of segmentation on liver, kidney, and spleen have exceeded 90% on Dice Similarity Coefficient (DSC) (also called the Sørensen-Dice coefficient a statistical method used to assess the similarity of 2 samples).[11,12] Although the pancreas is one of the most difficult organs for parenchymal segmentation the accuracy is presently approximately 74% on DSC and 60% of Jaccard Index (JI, also known as the Jaccard similarity coefficient which is a statistical model used to compare the similarities between sample sets) (Table 1).

The anatomical and imaging features of the pancreas are responsible for the preclusion of greater diagnostic accuracy. The adjacent organs and adipose tissues surrounding the pancreas have a similar attenuation to the gland itself resulting in indistinct boundaries and the shape of pancreas is irregular with considerable variation in size and anatomical disposition between individuals. Lesions in the pancreas are also morphologically diverse and frequently result in deformation of the gland further confounding accurate and reproducible automated segmentation.

Multi-atlas registration and label fusion (MALF) is one of the most popular strategies to achieve organ segmentation on medical images (also called atlas-based segmentation). The "atlas" is constructed from spatially aligned images with the region of interest (ROI) identified and defined by physicians. The labels on atlases are then used to guide the acquisition of estimations on each voxel (a unit of graphic information which defines a point in 3-dimensional space) and the labels are then transferred to target images. The accuracy of MALF is excellent but the process is complex and the production of the atlases and required computational complexity limit the clinical application of this technique.

Shimizu et al presented one of the earliest studies of pancreas segmentation in 2007 and demonstrated a 35% JI by using the atlas guided segmentation incorporating with an extended EM algorithm. Subsequently in 2009 the same group improved the results significantly achieving an average 57.9% JI.[13] In the 2009 study Shimizu et al improved the localization of the pancreas via a 2-stage segmentation strategy, guided with a patient-specific probabilistic atlas and the utilization of a classifier ensemble to boost segmentation performance. During the evolution of algorithms for MALF based strategies, Wolz et al[11] introduced a coarse-to-fine weighting scheme on global, organ and voxel level, and combined the multi-atlas registration with a patch-based segmentation. Wang et al[14] employed geodesic distances in patch selection during a KNN search process (k-nearest neighbour algorithms work by calculating distances between a query and all the examples in the data, selecting the specified number examples [K] closest to the query), which improved the tolerance in respect of registration errors. In addition, Tong et al[12] improved the segmentation performance by modifying the atlas selection process, proposing a voxel-wise atlas selection strategy to capture the information from the target image, and used a discriminative dictionary learning for a segmentation (DDLS) method to deal with the high inter-subject variation on abdominal CT images.

Limitations of the conventional intensity-based atlas relate to the similar attenuation of surrounding structures and the complex and crowded retroperitoneal space in which the pancreas is located. In 2015, Okada et al[15] proposed a prediction-based priors for pre-segmentation and an organ correlation graph for spatial correction. Using this approach, the

Table 1

Studies and performances about pancreas segmentation.

		Model/algorithm/method	DSC (%)	JI (%)	Image source
Shimizu[60]	2007	MALF, extended EM		About 35	CT
Shimizu[13]	2010	MALF, MadaBoost		57.9	CT
Chu[61]	2013	MALF	69.1±15.3	54.6	CT
Wolz[11]	2013	MALF, graph-cuts	69.6±16.7	55.5±17.1	CT
Okada[62]	2013	MALF, PLSR	71.8	59.2	CT
Wang[14]	2014	MALF, KNN	65.5±18.6		CT
Tong[12]	2015	MALF, DDLS	71.1±14.7	56.9±15.2	CT
Roth[17]	2015	CNN	68±10		CT
Roth[19]	2015	CNN	71.8±10.7		CT
Okada[15]	2015	MALF, PLSR	73.3±14.1	60.0±15.9	CT
Oda[63]	2016	MALF, regression forest	75.1±15.4	62.1	CT
Roth[20]	2016	HNN	78.01±8.2		CT
Cai[28]	2016	CNN	76.1±8.7		MRI
Shen[27]	2016	MALF	67.2±15.5		MRI
Saito[64]	2016	SSM	74.4±20.2	62.3±19.5	CT
Farag[18]	2017	CNN	70.7±13.0	57.9±13.6	CT
Cai[29]	2017	CNN, LSTM	82.4±6.7(CT) 80.5±6.7(MRI)	70.6±9.0(CT) 67.9±8.9(MRI)	CT+MRI
Karasawa[16]	2017	MALF, EM	78.5±14.0	66.3±15.5	CT
Fu[65]	2018	RCF	76.4±14.3	63.7±17.1	CT
Gibson[23]	2018	DenseVNet	78		CT
Roth[21]	2018	HNN	81.27±6.27	68.87±8.12	CT
Bobo[32]	2018	FCN	69.1		MRI
Oktay[25]	2018	U-net with attention gate	84±8.7, 83.1±3.8		CT
Yu[22]	2018	RNN	84.5±4.97		CT
Isensee[26]	2019	U-net-based	82		CT
Boers[24]	2020	Interactive U-net	78.1±8.7(automatic); 86.0(semi-automatic)		CT
Zheng[31]	2020	U-net	73.9(MRI); 84.4(CT)		CT+MRI
He[66]	2020	CNN, MCMC	78.13		CT
Bagheri[67]	2020	CNN	78±8		CT
Liang[30]	2020	CNN	73±9		MRI

DenseVNet = dense V-network FCN; EM = expectation-maximization; HNN = holistically-nested convolutional neural networks; LSTM = long short-term memory network; MCMC = Markov chain Monte Carlo; PLSR = partial least square regression; RFC = richer feature convolutional network; SSM = statistical shape model.

estimation was set free from supervised intensity information and also achieved an accuracy of 73% on DSC. In a similar study in 2017, Karasawa et al[16] proposed a structure-based atlas selection strategy in which the vessels around pancreas, including the splenic and mesenteric veins, were used as landmarks. The method employs a non-rigid registration and utilizes vessel structure around the pancreas to select atlases with high pancreatic resemblance to the unlabelled volume. Coarse-to-fine pancreas segmentation was realized with EM algorithm and the model was evaluated using 150 CT sets and achieved 78.5% in DSC and 66.3% in JI, but unfortunately even with this technique the runtimes were still 2 to 4 hours per case.

Due to the complexity of MALF atlas generation and the required computing power, methods based on artificial neural networks (ANN) have become increasingly popular in the last 5 years[10] and ANNs (vide supra) underpin approaches to pancreas segmentation. Roth et al[17] were one of the first groups to apply CNN to pancreas segmentation and made significant progress in automating the process. In his study, superpixel (groups of pixels considered together based on similarities of colour and other low-level properties) candidates of abdominal regions were generated via feature extraction and random forest classifier, and the retained superpixels were put into a 5-layer CNN. The probability map was output and smoothed by using a Gaussian kernel. Roth et al achieved a performance of 68% in DSC and revealed the potential of CNN in pancreas segmentation and a similar approach has been used by Farag et al.[18] A major problem of CNN is that the feature maps size of target image will be condensed during convolution and pooling, which caused the loss of detailed information and clarity of the boundaries of the ROI.

To address the loss of detail and edge of organ definition the FCN architecture was proposed. FCN achieves semantic segmentation via full convolutionalisation which is used to maintain the features dimension, the up-sampling to regain the image size, and the skip connection architecture to restore the lost information. Roth et al subsequently proposed a holistically nested convolutional network (HNN) architecture, which combined the FCN with deep supervision and demonstrated enhanced performance on edge detection. Roth's model has undergone considerable development and following a number of iterations the DSC rose from 71.8%[19] to 78.01%,[20] and finally 81.3%.[21] There are other approaches to the problems produced when confusion is caused by complex and variable backgrounds and Yu et al have describe a technique using a Recurrent Saliency Transformation Network with a course-to-fine approach using a prediction from the first stage to identify a smaller input region for the second stage.[22]

U-Net and V-Net are further adaptations of FCN and in 2018 Gibson et al[23] developed a deep FCN based registration-free algorithm which achieved segmentation in a number of organs including the pancreas. The dense connections and the multi-scale

V-net structure improve the performance of pancreas segmentation to 78% in DSC and achieved promising accuracy for the digestive tract and associated organs. Consequently, Gibson et al demonstrated the potential value of their model in supporting intra-procedural navigation during interventions such as endoscopic retrograde cholangiopancreatography (ERCP). In a further iteration an interactive 3D U-net method (iUnet) was proposed by Boers et al,[24] in which the initial segmentation was provided via U-net. The iUnet was fully trained to produce the best possible initial segmentation. In interactive mode it was additionally trained on a partial set of layers on user generated scribbles and initial segmentation performance of iFCN and iUnet compared on a 100CT dataset using dice similarity coefficient analysis. Labelled voxels and the nearby regions of uncertainty were re-weighted and put into the model for retraining. The performance of iUnet surpassed the similar approaches such as FCN and normal U-net. Moreover, the interactive amendments not only achieved outstanding accuracy of 86% in DSC, but also dramatically reduced the time required to 8 minutes, compared with the 87% DSC in 15 minutes for manual segmentation. The interactive method proposed by Boers et al confirmed that prior knowledge from expert physicians is required to improve the efficiency of the model, facilitate model training and boost the performance of any AI applied to pancreatic imaging. Different groups have further refined the ability of a model to focus on target structures of varying shapes and dimensions and Oktay et al describe a novel "Attention Gate Model". Models trained with AGs implicitly learn to suppress irrelevant regions in an input image while highlighting salient features useful for a specific task.[25] The design of solutions is highly dependent on the properties of the dataset and the hardware conditions. Isensee et al have developed an approach which they have made publicly available as an open source tool. nnU-Net is a deep learning framework that condenses current domain knowledge and is able to autonomously takes the key decisions needed to transfer a basic architecture to different datasets and segmentation tasks.[26]

Progress has also been made in AI-based pancreas segmentation based on MRI images. Although MRI has not been widely used for the diagnosis of pancreatic disease and pathology due to the cost and time required, it is better suited for the identification and delineation of peri-pancreatic adipose tissues, which is often the major factor limiting the segmentation accuracy of imaging modalities. Shen et al,[27] employed a MALF based strategy to perform pancreas segmentation based on MRI images (67.2% in DSC) but the overwhelming majority of studies were based on an approach using ANN.

In 2016, Cai et al[28] used a 2-step CNN based method to perform tissue detection and boundary delineation separately, and achieved 76.1% DSC on MRI images. Later, they improved the model and hybridized a convolutional long short-term memory network to CNN in order to perform contextual learning and smooth the neighbouring 2D images. Further studies suggested that this novel architecture achieved a superior accuracy using both MRI and CT images.[29] Subsequently, Liang et al[30] analysed 37 sets of MRI from pancreatic cancer patients and by using a square-window based CNN architecture which reduced the time of gross tumour volume delineation to 10 seconds and also achieved comparable accuracy to experts. These very promising results are likely to see this approach investigated further and in particular to facilitate its application in MRI-guided online adaptive radiation therapy for PDAC. Other groups including Zheng et al[31] and Bobo et al[32] have also investigated the use of U-net or FCN for MRI analysis and achieved similarly promising accuracy.

The application of AI in the diagnosis of pancreatic cancer

Pancreatic cancer is by far the most common malignancy of the pancreas with the highest mortality. The retroperitoneal anatomical position, relationship to adjacent organs and the surrounding and intra-pancreatic vessels make accurate and reliable imaging notoriously difficult. For this reason, the application of AI to augment traditional expert analysis and improve efficiency is very attractive particularly for the detection of pancreatic cancer and the differential diagnosis of benign pancreatic diseases.

Imaging of the pancreas is an essential pre-requisite for the diagnosis of pancreatic cancer and similar to tumours in the lung or liver, lesions in the pancreas often have a low attenuation and lack a clear margin and separation from surrounding structures making early detection extremely difficult even for experienced radiologists. The majority of PDACs occur in the head and uncinate process, which unfortunately is the most complicated area anatomically and where adjacent tissues are most likely to be invaded. It is this combination of factors which complicates the preoperative assessment especially as pancreatic cancer can be associated with other, often concomitant pancreatic diseases such as intraductal papillary mucinous neoplasms (IPMN) which further reduces the potential accuracy of any imaging modality. Other benign conditions, particularly post-inflammatory problems such as mass forming pancreatitis which can also be associated with PDAC can also reduce the potential diagnostic accuracy. This complexity makes the assessment of pancreatic imaging an ideal area to consider the use of AI to enable the reliable, early identification of pancreatic cancer.

Typically, radiologists will consider tumour characteristics revealed by any imaging modality holistically, including the size, shape, location, Grayscale level, attenuation and uniformity and considering all the characteristics together decide on the most likely diagnosis based on their previous experience. Diagnostic AI functions are generally implemented through texture and radiomic analysis,[33] which simulates the workflow of a clinical radiologist. The textural features of an image are characterized by the spatial distribution of Gray levels in a neighbourhood, and are extracted via structural, statistical, or modelling methods. The role of radiomics is to contextualise the process by providing high-dimensional and quantitative information on images and decoding the radiomic biomarkers and phenotypes of tumours.

The early algorithms developed for PDAC recognition were based on traditional machine learning methods, and support vector machine algorithms (SVM) were the most popular. In 2012, He et al[34] used SVM to detect PDAC biomarkers from spectrometry data and a 3 years later, Jiang et al[33] used an SVM based model for PDAC classification where the Grayscale and fractal dimension features from pancreatic images were extracted and condensed to tensors. The tensors were then put into the SVM which was optimized by the improved fruit fly optimal algorithm (algorithms based on swarm intelligence are an effective way of solving complex optimisation problems and compared with traditional algorithms improve simplicity and effectiveness) and a better classification performance of 97.14% accuracy was achieved within 31 seconds. In 2019, Hussein et al[35] were able to accurately identify and diagnose IPMN by SVM in a unsupervised manner and for the first time, Ren et al[36]

combined imaging features and textural analysis to differentiate mass forming pancreatitis (MFP) from PDAC. In this study, conventional imaging features such as tumour location, shape, and enhancement pattern, as well as the textural features such as voxel intensities distribution, geometric features, and high-order Gray information from the ROI were extracted and evaluated. Further studies were able to demonstrate that, the textural features conferred an improved better accuracy (96%) when compared with conventional imaging features (84%), while the multi-phase feature-combined model achieved the highest accuracy (98%) in classifying these 2 pancreatic pathologies. In addition to pancreatic cancer a number of groups have explored the application of AI for the identification of pancreatic cystic masses using traditional machine learning and demonstrated that it was possible to achieve average accuracies and AUC of 66% to 93% and 0.75 to 0.837.[37–41]

Deep learning methods such as CNN have also been employed for PDAC detection and diagnosis. Liu et al[42] employed a faster region-based CNN and analysed more than 6000 CT images from 338 PDAC patients. Labelled CT images were converted into convolutional feature maps for regression and classification via a pre-trained VGG16 model (a model which achieves 92.7% top-5 test accuracy in ImageNet, which is a dataset of over 14 million images belonging to 1000 classes) and the parameters were adjusted and iterated continuously. Eventually, Liu's model was validated in a relatively large cohort and achieved 0.9632 in AUC for PDAC detection, and the duration of diagnosis was only 20 seconds for each patient. Unfortunately, the perception of CNN (black-box characteristics) and the difficulty in understanding the underlying concepts have limited CNNs acceptance by physicians. To address these issues Dmitriev et al[43] focused on the decision making processes of an AI model and presented a comparative eye-tracking experiment comparing AI and radiologists, in order to ensure that the features which influenced the decision making process were explicit and transparent. In this way Dmitriev and colleagues who achieved a 91.7% accuracy in classifying different pancreatic lesions were also able to reveal and explain the features of random forest and CNN models used in the decision-making process. In addition, and more importantly, the decision-process visualized CAD system is easier to interpret and consequently confers increased accessibility for physicians.

PET/CT and MRI based AI models have also proved to be effective in augmenting the diagnosis of PDAC and Li et al[44] extracted major structure and location information from the ROI on CT and PET images, and also incorporated metabolic features such as standard uptake value (SUV) mean and variance. Those features were further refined using a dual threshold principal component analysis (DT-PCA) method in order to reduce the feature dimension, and the hybrid SVM-RF algorithm was used to fulfil the identification. By doing this, Li et al achieved a 96.47% accuracy for PDAC classification in 80 cases with a 95.23% sensitivity and 97.51% specificity. Zhang et al[45] performed a radiomic analysis to differentiate PDAC from autoimmune pancreatitis (AIP) and 251 features containing pixel/voxel intensity, ROI morphological, and textural information were extracted from both 2D and 3D PET and CT images. Results demonstrated that 3D features were significantly more accurate when compared with 2D features and that anatomical information contained in CT scans was more discriminative than metabolic features on PET scans. The best performance was achieved via SVM-RFE feature selection (recursive feature elimination) and Linear SVM classifier, in which the AUC was 0.93 and the diagnostic accuracy was 85% which was comparable to expert clinical radiologists. For MRI, Gao et al[46] analysed enhanced MRI images from 504 patients with 7 categories of pancreatic diseases which had been diagnosed by radiologists. Lesion obtained MRI patches were prepared based on the pathological results, and synthetic images of ROI from each disease group used to train the CNN model. Finally, with the help of the generative adversarial network and InceptionV4 (both are CNN architectures), the AUC of pancreatic cancer and other pancreatic diseases was 0.91 and 0.72 to 0.93 in validation.

The application of AI in individualized medicine of pancreatic cancer

The considerable inter-tumour heterogeneity due to variations of the genotype and phenotype is considered to be one of the main factors contributing to the quite different biological behaviour. These differences also underpin the rationale behind individualized medicine and the belief that significant advances will result from an approach that bases treatments on a comprehensive understanding of this heterogeneity. Variations in tumours resulting from gene mutations together with the genetic makeup of patients determine the behaviour of the tumours and individualised medicine relies on "multi-omics" data, which generally refers to the genomic, transcriptomic, and proteomic characteristics of tumours and patients. Unfortunately, the cost and time pressures which these approaches impose on any healthcare system are barriers to the widespread availability and uptake of themselves.

A number of studies have demonstrated that the information contained in radiomics may be the macroscopic expression of tumours characteristics and that by analysing the information contained in the images augmented with a variety of recent AI techniques that sufficient data will not only facilitate appropriate therapeutic response evaluation, and prognosis analysis but also improve access to individualised medicine by ensuring it is cost effective.

Qiu et al[47] conducted a machine learning based quantitative texture analysis on the CT images from patients with PDAC. They used the SVM to classify cases based on their textural features and found that 18 features were significantly different between patients with pathological high-grade and low-grade PDAC while the clinical characteristics were less distinctive. Qiu et al achieved an accuracy of 86% when make a pathological prediction of PDAC according to radiomic information, which may be used as a method for non-invasive preoperative pathological evaluation to assist clinicians to formulate treatment plans.

Kambakamba et al[48] adopted a similar approach and used radiomics in an attempt to predict the risk of developing a postoperative pancreatic fistula (POPF). They performed a textural analysis on preoperative CT images from 110 patients who had undergone a pancreatoduodenectomy. The textural features were further condensed and demonstrated the ability to detect fibrosis, lipomatosis, and intraoperative pancreatic hardness. Comparing the predictive value, Kambakamba et al concluded that texture analysis was more accurate (AUC=0.95) than the original and alternative fistula risk scores (AUC=0.76 and 0.72, respectively) in predicting POPF and would provide a superior guide, alerting clinicians to the need for postoperative interventions in targeted patients.

AI has also been shown to a valuable aid when evaluating the therapeutic effect and predicting the prognosis of PDAC patients,

potentially guiding clinicians to ensure optimal treatment and better surveillance. Cui et al[49] were one of the first groups to perform a quantitative feature analysis of PET/CT to predict the overall survival (OS) of PDAC patients. They reviewed the pre-treatment PET/CT results from 139 patients with locally advanced PDAC who had received stereotactic radiation therapy and defined and extracted 5 categories of 173 radiomic features and correlated these with OS and used the findings to propose a prognostic imaging signature (imaging biomarker). When validating their findings Cui et al found that only the proposed signature was significant correlated with OS, contrasting with conventional imaging modalities and clinical factors. Kaissis et al[50] also developed an accurate model to predict OS (AUC= 0.9) based on information about a patients prognosis and their radiomic features on MRI. They demonstrated that their machine learning model based on preoperative diffusion-weighted imaging for the prediction of survival correlated with the tumour histopathological subtype in PDAC explaining the model's ability to predict prognosis. The results from these studies demonstrated to clinicians that radiomic analysis could be used as an accurate, non-invasive method to acquire basic pathological information. In addition, the necessary comprehensive preoperative assessment will reassure physicians that they are safely able to perform less aggressive treatments in certain patients, ensuring the important balance that is so important in patients with PDAC, between OS and quality of life.

Nasief et al[51] analysed CT images from 90 patients who had received CT-guided-chemoradiation therapy, and extracted the baseline radiomic features and the changes induced by treatment. By employing a machine learning based model, Nasief et al found that variations in 13 radiomic features were significantly correlated with the pathological response. Further validation revealed that the optimized model performed well (AUC=0.9) and was able to accurately predict whether the patient would derive benefit from chemoradiation therapy, and the AUC reached 0.94. These findings allow physicians to employ novel radiomic biomarkers to select the patients who will benefit maximally from individualised risk-adaptive therapy.

Barriers to acceptance and the future of AI in pancreatic cancer

The development of AI architectures and algorithms together with the clinical demand for better tools to investigate, diagnose and monitor the treatment of patients with PDAC has been one of the main drivers for the investigation of the clear potential of AI systems in clinical practice. Studies have clearly demonstrated the value of AI-based radiomic analysis, the information from which, through quantitative and weighted analytical methods can significantly augment even expert clinical opinion. The added value from the AI input improves the accuracy of diagnoses in patients with PDAC in an efficient manner and provides invaluable prognostic data.

A number of factors have contributed to the dramatic progress of AI in the management of patients with PDAC including the optimisation of algorithms, increasing computing power, the expansion of training sets and the processing speed and accuracy of AI analysis. Nevertheless, when dealing with complex systems, all decisions are associated with a degree of uncertainty. This is an issue widely recognised in medical applications and the principle sources of these uncertainties are often categorised as epistemic or aleatoric.

Epistemic uncertainty (derived from the Greek for knowledge and -logy concerned with knowledge) is due to the physical attributes of the system being analysed. It derives from a lack of knowledge resulting from inadequate understanding of the underlying processes, incomplete knowledge of the phenomena, or imprecise evaluation of the related characteristics. Epistemic uncertainty is generally caused by limited training data, and it arises when a model encounters input data that differs from training set. It is possible to reduce epistemic uncertainty with increased amounts of training data but never eradicate it completely. Aleatoric uncertainty (derived from the Latin *alea* meaning dice alludes to the chance nature of the problem) refers to unknown effects that influence an experiment each time it is performed. The aleatoric uncertainty is the result of inherent data noise and cannot be reduced even if more data is available. In real-life epistemic and aleatoric uncertainty can occur together in a single model and it can be difficult to identify their individual contributions. To date, most state-of-the-art models studying the pancreas only report variance of model performance over multiple runs rather than investigating such uncertainties on model outputs, but it is an active research area and methods such as Bayesian statistics have shown promising results in assessing and analysing them.[52,53] Epistemic uncertainty is the main concern for current DL-based models used for imaging in the medical field, as the quantity of data in both image and text modalities is much less than other disciplines.[54,55]

Although there are rapidly increasing demands on radiology services it is presently not possible to consider the use of AI as a stand-alone service. Nevertheless, if progress continues at the present rate AI models will become more anthropomorphic increasing clinical acceptance and as a consequence utilisation. This will inevitably improve clinical efficiency but should also reduce the inter-individual differences among physicians caused by different levels of personal experience and exposure to disease spectra and hopefully facilitate the ultimate goal of individualized medicine.

The clinical application of AI should be problem orientated, reflecting the continued need for close cooperation between clinicians and computer professionals involved in the development and implementation of AI technologies. Barriers, particularly to the integration and implementation of AI in the management of all tumours including PDAC remain and one of the most difficult to overcome is the mistrust of AI systems that result primarily from clinicians lack of understanding of the underlying technology.

A number of studies have demonstrated the potential for AI based systems to provide non-invasive information reliably and cost effectively. Coroller et al[56] performed radiomic analysis to obtain phenotypic information of tumours and to predict the likelihood of distant metastasis in patients with lung cancer and Aerts et al[57] found that the gene-expression patterns of tumours could also be revealed from radiomic features conferring decision-support at reduced cost. Springer et al[58] developed a machine learning based comprehensive system, which would spare the unnecessary resection of cystic pancreatic lesions and Pan et al[59] used fluorescent signals from cancer cells to define the organotrophic pattern of PDACs, and evaluated the biodistribution of therapeutic antibodies. These approaches are encouraging, and clinicians are increasingly looking for those clinical areas which will benefit from the incorporation of the new and rapidly evolving AI models.

Continued development clearly also requires the continued enthusiasm and collaboration of computer professionals who are

able to understand the underlying clinical issues and the sensitivity required of AI imaging modalities to address the nuances of cancer management particularly in patients with PDAC. Computer professionals and software engineers are essential to implement the necessary iterations and adaptations in algorithms used in AI models and many problems can only be overcome using mathematical and statistical methods. The practical effects of lab-validated models remain uncertain, and the complete replacement of human physicians by AI might still be unacceptable in the present ethical and medico-legal environment.

The potential value of AI in all fields of medicine is enormous and models and approaches which were ubiquitously believed to be highly subjective are increasingly accepted and recognised as valuable tools in the armamentarium of clinicians dealing with patients with malignancies particularly those where imaging is generally complex and requires time and considerable resources. In these patients by definition a definitive diagnosis is often delayed which limits the opportunity for potentially curative treatment. The development of increasingly sensitive, reliable and cost-effective AI models is not possible without sufficiently large and accurate data sets but fortunately these are becoming more widely available and national and international collaborative projects continue to expand the breadth and detail of the data available to train AI models. It is inevitable that developments in AI will change clinical practice supporting clinicians in their decision-making processes, allowing them to work more efficiently and ensuring patients receive individualised treatment and better surveillance to ensure an optimal management and outcome.

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Author contributions

Ashley R. Dennison designed and directed the project; Xianze Wang and Wen Yuan Chung draft the manuscript; Yi Zhu, Elon Correa and Eyad Issa made critical revisions of the manuscript; Ashley R Dennison made final approval of the manuscript.

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Conflicts of interest

There is no conflicts of interest among authors.

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