

Received:
14 January 2022

Revised:
19 May 2022

Accepted:
27 May 2022

Published online:
23 June 2022

<https://doi.org/10.1259/bjr.20220072>

Cite this article as:

Marti-Bonmati L, Cerdá-Alberich L, Pérez-Girbés A, Díaz Beveridge R, Montalvá Orón E, Pérez Rojas J, et al. Pancreatic cancer, radiomics and artificial intelligence. *Br J Radiol* (2022) 10.1259/bjr.20220072.

REVIEW ARTICLE

Pancreatic cancer, radiomics and artificial intelligence

^{1,2}LUIS MARTI-BONMATI, ¹LEONOR CERDÁ-ALBERICH, ²ALEXANDRE PÉREZ-GIRBÉS, ³ROBERTO DÍAZ BEVERIDGE, ⁴EVA MONTALVÁ ORÓN, ⁵JUDITH PÉREZ ROJAS and ^{1,6}ANGEL ALBERICH-BAYARRI

¹GBI230 Research Group on Biomedical Imaging, Instituto de Investigación Sanitaria La Fe, Valencia, Spain

²Department of Radiology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

³Department of Oncology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

⁴Department of Surgery, Hospital Universitario y Politécnico La Fe, Valencia, Spain

⁵Department of Pathology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

⁶Quantitative Imaging Biomarkers in Medicine, Quibim SL, Valencia, Spain

Address correspondence to: Dr Luis Marti-Bonmati

E-mail: luis.marti@uv.es; marti_lui@gva.es

ABSTRACT

Patients with pancreatic ductal adenocarcinoma (PDAC) are generally classified into four categories based on contrast-enhanced CT at diagnosis: resectable, borderline resectable, unresectable, and metastatic disease. In the initial grading and staging of PDAC, structured radiological templates are useful but limited, as there is a need to define the aggressiveness and microscopic disease stage of these tumours to ensure adequate treatment allocation. Quantitative imaging analysis allows radiomics and dynamic imaging features to provide information of clinical outcomes, and to construct clinical models based on radiomics signatures or imaging phenotypes. These quantitative features may be used as prognostic and predictive biomarkers in clinical decision-making, enabling personalised management of advanced PDAC. Deep learning and convolutional neural networks also provide high level bioinformatics tools that can help define features associated with a given aspect of PDAC biology and aggressiveness, paving the way to define outcomes based on these features. Thus, the prediction of tumour phenotype, treatment response and patient prognosis may be feasible by using such comprehensive and integrated radiomics models. Despite these promising results, quantitative imaging is not ready for clinical implementation in PDAC. Limitations include the instability of metrics and lack of external validation. Large properly annotated datasets, including relevant semantic features (demographics, blood markers, genomics), image harmonisation, robust radiomics analysis, clinically significant tasks as outputs, comparisons with gold-standards (such as TNM or pretreatment classifications) and fully independent validation cohorts, will be required for the development of trustworthy radiomics and artificial intelligence solutions to predict PDAC aggressiveness in a clinical setting.

INTRODUCTION

A steady worldwide increase in the age-adjusted incidence of pancreatic ductal adenocarcinoma (PDAC) and of its mortality has been observed in recent decades, mainly due to a rise in the prevalence of lifestyle related risk factors, such as age, tobacco smoking, alcohol consumption and obesity.^{1,2} PDAC displays significant genetic heterogeneity, and molecular alterations to *KRAS*, *CDKN2A/p16*, *TP53* and *SMAD4/PDC4* are frequent in this disease, with the tumours in each patient having a specific genomic and molecular signature.^{1,3–6} PDAC is a biologically aggressive tumour, establishing a low oxygen and nutrient poor microenvironment, limited vascularity and an intensely desmoplastic stroma.^{1,2} Most patients with PDAC are diagnosed when the clinical manifestations reflect an advanced-stage disease, whereas much less frequently the tumours are detected as incidental findings in a radiological examination

performed for another reason, or in patients with elevated CA 19–9 levels in blood analysis.

Standard-of-care medical imaging allows lesions to be located and a differential diagnosis to be established, not least by defining the shape, size, infiltration and extension of the tumour, information that guides the therapeutic strategy to be adopted. Although pancreatic lesions can be visualised through ultrasound and magnetic resonance (MR) images, contrast-enhanced computer tomography (CECT) is the principal modality used to evaluate these tumours due to its ability to define the local extent of tumour infiltration (of surrounding planes, major blood vessels and surrounding organs) and the existence of metastases (mainly in the lymph nodes and liver parenchyma). Spectral CECT imaging might even outperform standard CT to detect lesions and define tumour conspicuity in

low-keV virtual monoenergetic reconstructed images.⁷ Multi-modality positron emission tomography (PET) and CT (PET/CT) imaging provide high spatial resolution and metabolic resolution, although their role is mainly restricted to detect tumour recurrence in the follow-up period after adjuvant therapy. Pre-operative MR with diffusion-weighted and contrast-enhanced hepatobiliary phase images are mainly used prior to surgery to depict synchronous liver metastases, which are evident in at least 10% of patients with a negative liver CECT evaluation.^{8,9}

Following contrast administration, CECT images obtained at both the arterial and early venous pancreatic phases (around 6 and 18 s after bolus arrival, respectively) can be used to report on the most important features that define risk, and that are used to assign a therapy, such as tumour size, surrounding arterial and venous invasion, regional node involvement, and distant metastases (mainly in the liver, peritoneum and lung).¹⁰ The accurate assessment of tumour resectability (resectable, borderline resectable, locally advanced unresectable) and metastatic stage is essential to guide therapeutic decision-making (neoadjuvant treatment, surgery, chemoradiation, palliative chemotherapy, actionable genetic targeted approaches and immunotherapy).^{11,12} It is hoped that these therapeutic strategies, as well as the patients' outcomes, will soon be improved by incorporating approaches that specifically target the malignant cells, immunosuppressive immune check-points, the tumour microenvironment and the desmoplastic stroma with fibrosis.^{12,13}

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines CE-CECT criteria have been shown to accurately stratify patients with PDAC undergoing initial surgery, with R0 resection rates of 73%, 55%, and 16% for resectable, borderline resectable, and unresectable tumours, respectively.¹⁴ In a systematic review and meta-analysis, the NCCN criteria for post-neoadjuvant surgery showed resectability rates with lower sensitivity (28%) but higher specificity (90%).¹⁵ Unmet clinical needs are therefore present. As important deficiencies persist in the precise staging of PDAC lesions, more accurate assessment of the biological aggressiveness of the tumour and disease staging will be needed to improve decision-making and treatment allocation in individual cases.^{2,5,13,16,17} For example, early arterial invasion status and minimal distant metastases are both features ultimately related to cancer aggressiveness and should be defined in all cases. Best treatment options should consider the predicted tumour response to neoadjuvant chemotherapy and chemoradiation, a more precise tumour downsized-resectability status, responses to targeted therapies and immunotherapy, and possible chemoresistance. Patient performance and expected long-term prognosis must be based on accurate expectations of the time to local recurrence and distant metastases, as well as on progression-free survival (PFS) and overall survival (OS), which will also influence treatment decisions.

To help estimate these precision medicine needs, both quantitative imaging and genomic analysis of the tumour and their distant sites have been employed. Quantitative imaging allows radiomics and dynamic imaging features to be considered, alone or in combination, enabling clinical prediction models to be

constructed based on radiomics signatures or imaging phenotypes, and permitting clinical outcomes associated to the tumour biology to be estimated.¹⁸ Furthermore, artificial intelligence (AI) tools can be used to train predictive models based on radiomics, genomics and clinical data, and to extract deep radiomics features from the images to aid better patient management.¹⁹ However, studies on radiomics and PDAC have a low median quality score, highlighting the need to improve both the methodology and sample sizes.²⁰

This review will focus on the different radiomics and AI approaches available that can complement current structured radiology reports, fostering the incorporation of quantitative imaging into clinical decision-making protocols in real-world practice.

RADIOMICS AS IMAGING BIOMARKERS

Quantitative image processing is the science of extracting relevant and reproducible objective metrics from acquired images. Tissue properties are extracted after applying different computational models and processing techniques, screening large parameter spaces to find sensitive markers for outcome prediction.²¹⁻²³ These metrics can be related to the pixel/voxel distribution within the image (radiomics features) or to signal modification by changing the acquisition parameters (dynamic parameters). Both these approaches can be used to obtain numeric dimensional descriptors (such as the mean and standard deviation), or parametric images with spatial resolution. The properties extracted can be expressed globally for the whole tumour or locally for each partial image or tumour subregion when heterogeneity is expected.^{21,23}

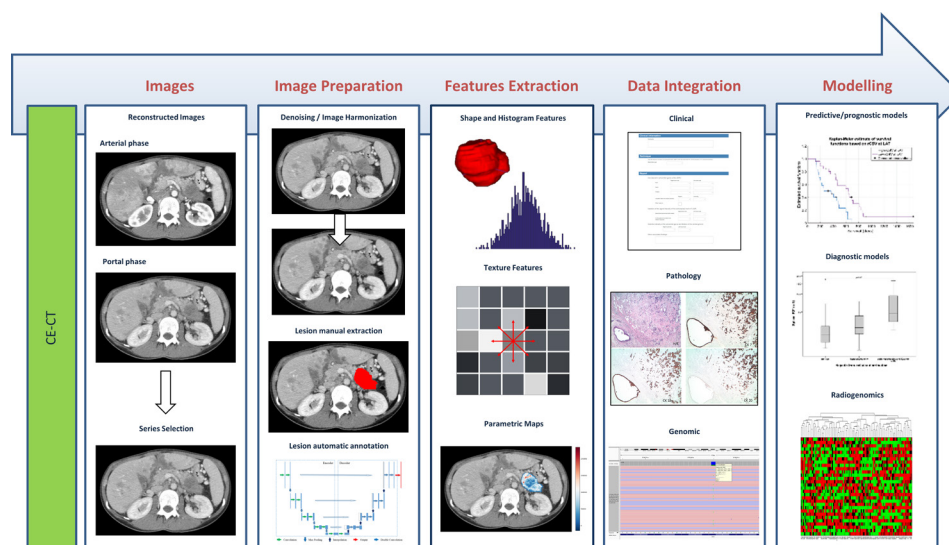
Radiomics is intrinsically a data-driven process allowing biological processes to be tracked spatially. The metrics can be consistently linked to different tumour behaviours, genomic profiles or particular clinical outcomes, and they can be considered as imaging biomarkers.²⁴ These phenotypic markers explore, quantify, and represent a tissue specific property, such as a surrogate indicator, related in magnitude and direction with a relevant biological tumour hallmark. To be clinically useful, they should be actionable to improve on the outcomes delivered by standard-of-care oncological assessments.

Biomarkers can also be combined in multivariable models to better estimate the outcomes, expressing relevant biological mechanisms in the form of nosological images. In most clinical situations, these multidimensional clinical predictions will improve upon simpler models since biology is commonly too complex to be represented as a single surrogate property. To ensure robust decision-making based on radiomics, the following aspects must be taken into account when extracting information (Figure 1).^{22,25}

Image preparation

In the real world, CECT images are obtained on different equipment, using distinct acquisition protocols (energy, modulation, filters) and contrast administration settings (contrast agent, iodine concentration, dose, flow rate, dynamic phases). Before

Figure 1. Flowchart of the image processing pipeline for pancreatic cancer, including image reconstruction and preparation (denoising, harmonisation, segmentation), feature extraction, data integration and modelling to predict clinical outcomes and diagnostic/prognostic factors.



images can be assessed as “data”, the images must be prepared to improve the reliability and reproducibility of radiomic extraction. This process involves feature domain methods (identification of reproducible features, denoising, resizing, normalisation techniques) and advanced harmonisation processes or image domain solutions (standardisation of image acquisition, post-processing of raw sensor-level image data, data augmentation techniques and style transfer based on AI tools to synthesise common framework images).^{26,27} Deep learning solutions have the potential to address the variability across multicentric radiomics studies, especially when using generative adversarial networks (GANs), neural style transfer (NST) techniques or a combination of both.^{28,29}

Tumour segmentation

Tumour segmentation can be performed in three different ways: manually, semi-automatically, or automatically. Manual segmentation is usually performed by an experienced radiologist, slice-by-slice, either encircling the tumour or annotating the voxels of interest. This expert knowledge-based method is usually considered as the ground truth, although it is time-consuming and prone to interobserver variability. Semi-automatic segmentation tries to solve some of the problems associated with manual segmentation by complementing the process with algorithms, such as region growing or segmentation expansion to other slices, to reduce the effort and time required from the user. Automatic segmentation methods do not rely on user interaction and these solutions are usually based on convolutional neural network (CNN) algorithms. Tumour segmentation performed on 2D images suffers from the lack of information regarding adjacent slides, while segmentation on 3D series need a larger sample size to train the algorithm but will obtain better results. One example is the 3D nnU-Net deep learning-based segmentation framework that automatically configures itself, and that includes preprocessing, network architecture, training, and post-processing for any new task.³⁰ This framework was used to

automatically carry out 10 different image segmentation tasks (Medical Segmentation Decathlon) with a Dice score on the testing set of 0.82 for pancreas segmentation but of only 0.53 for the whole tumour.³¹ To improve tumour segmentation metrics, transfer and continuous learning methods have been explored to train a network model on a unique source dataset available at a single clinical site, then deploying it at another target site without sharing the original images or labels. As network models trained on data from a single source suffer from a loss of quality due to the domain shift, a semi-supervised domain adaptation method was proposed to refine the model's performance in the target domain. A paper on prostate segmentation using domain adaptation showed a generalisation capability for pancreas segmentation in CT scans.³² For pancreas segmentation, this domain shift was not only limited to differences in image appearance but also, it covered the different distributions of the healthy (source domain) and cancerous pancreas (target domain). The resulting domain adaptation method managed to combine transfer learning and uncertainty guided self-learning based on deep ensembles, achieving a tumour Dice score of 0.73 with only five labelled target cases as training data.³²

Feature extraction and dimensionality reduction

Extraction of radiomics features from medical images and their corresponding segmented tumours may be performed using either commercially available software (*e.g.* MaZda³³ and LIFEx,³⁴) open-source libraries (most notably Pyradiomics³⁵) or in-house software developed *ad hoc*.

Radiomics features can be classified into three main classes.³⁶

- Shape features that describe semantic (*e.g.* the shape of the region of interest traced) and/or geometric properties (*e.g.* volume, maximum diameter in different orthogonal directions, maximum surface, tumour compactness and sphericity).

- First-order statistics features that describe the distribution of individual voxel values without any concern for their spatial relationships. These are histogram-based properties that report the mean, median, maximum and minimum values of the voxel intensities of the image, as well as their skewness (asymmetry), kurtosis (flatness), uniformity and randomness (entropy).
- Second-order statistics features that describe the statistical relationships between neighbouring voxels. They provide a measure of the spatial arrangement of the voxel intensities and hence, of intralesion heterogeneity. Such features can be derived from the grey-level co-occurrence matrix (GLCM—quantifying the incidence of voxels with the same intensities at a predetermined distance along a fixed direction) or from the Grey-level run-length matrix (GLRLM—quantifying consecutive voxels with the same intensity in fixed directions).

First- and second-order classes can be calculated on either the original or a derived image obtained by applying filters. These descriptors usually receive the name of higher order statistical features, and they are obtained by applying mathematical transformations to the images with the aim of identifying patterns, suppressing noise or highlighting details. These include methods such as fractal analysis, Minkowski functionals, wavelet and Laplacian transformations of Gaussian-filtered images.

A lack of standardisation among feature extraction approaches has been identified as a potential issue that may affect the comparability of radiomics studies and their correlation to clinical endpoints.³⁷ In this regard, the Image Biomarker Standardisation Initiative (IBSI) has led valuable efforts to establish uniform feature calculations, definitions, and nomenclatures. The use of IBSI-compliant feature extraction methods is strongly encouraged to ensure the robustness and reproducibility of the results, and to improve statistical reliability.³⁸

Computational processing in high-dimensional spaces can become difficult due to the complexity of the data, which can lead to what is referred to as the “curse of dimensionality” and that can lead to model overfitting. Radiomics variables need to be reduced to avoid those that lack repeatability or that are highly redundant, while still preserving the most important information. Dimension reduction techniques are based on feature selection approaches (relief, stepwise, statistical selection), multivariate projection algorithms (Principal Component Analysis—PCA, Linear Discriminant Analysis—LDA, constrained Non-Negative Matrix Factorisation—cNMF) or manifold learning techniques (Isomap, Locally Linear Embedding—LLE, Semi-definite Embedding).^{39,40} Other reduction algorithms are based on linear methods that aim to discover a significant low-dimensional space, or on non-linear complex applications. Some of the most common linear techniques include PCA, LDA, Singular Value Decomposition (SVD), Latent Semantic Analysis (LSA), Locality Preserving Projections (LPP), Independent Component Analysis (ICA) and Project Pursuit (PP). Some relevant non-linear techniques include Kernel Principal Component Analysis (KPCA), Multidimensional Scaling (MDS), Isomap, LLE, Self-Organising Map (SOM), Latent Vector Quantisation (LVQ), t-Stochastic neighbour embedding (t-SNE) and Uniform

Manifold Approximation and Projection (UMAP).^{41,42} Beyond these dimension reduction techniques, other approaches rely on feature robustness, and they are insensitive to multivendor and multicentre variability. Alternatively, they may retain all the features and harmonise their statistical properties so that they can be pooled during the modelling step, as with ComBat methodology.⁴³

Radiogenomics might allow the genomic heterogeneity of PDAC to be evaluated *in vivo*. As treatment responses to therapies vary widely when administered to unselected patient populations, profiling the inter- and intratumoral genomic heterogeneity, and any variability in molecular expression, might help to identify responder and chemoresistant patients before initiating therapy.⁴

Model development

The learning methods used to study the relationship between features and outcomes can be further categorised into supervised, unsupervised, and semi-supervised methods. Supervised classification implies the identification of a relationship between observations and a set of known labelled categories, such that biomarkers can be assigned to an expected class label by multivariate logistic regression statistical analysis, pattern-recognition, or machine learning (ML) approaches. The standard linear or least squares methods perform poorly when using a large multivariate data set with variables that exceed the number of samples. A better alternative is to create a linear regression model that is penalised for including too many variables by adding a constraint in the equation. These penalised regression methods include ridge regression, lasso regression and elastic net regression, and have been extensively used in radiomics analyses for PDAC in combination with a multivariate Cox analysis.^{44,45}

The Cox (proportional hazards or PH) model is the most used multivariate approach for analysing censored survival time data in medical research. It is a survival analysis regression model, which describes the relation between the event incidence, as expressed by the hazard function, and a set of covariates.

The unsupervised classification is based on obtaining associative voxel segmentation by applying clustering techniques to unlabelled data sets, which may lead to the discovery of tumour habitats that provide insights into any existing biological heterogeneity.⁴⁶ Clustering of radiomics features through unsupervised learning algorithms have been used to assess the differentiation of PDAC from normal control cases.⁴⁷ These algorithms can also be combined with some of the aforementioned dimensionality reduction techniques, such as the PCA, LPP, KPCA, MDS, PP, t-SNE and LDA methods.⁴⁰

Radiomics has shown potential prognostic ability in multiple types of cancer, including PDAC. A new radiomic signature has shown prognostic value for OS in a small series of patients with resectable PDAC,⁴⁸ and a recent pre-operative model has been shown, although not validated, to accurately stratify upfront resectable patients according to the risk of early distant disease relapse after surgery (<12 months from index procedure).⁴⁹ However, the traditional radiomics pipelines that are based on hand-crafted radiomics features alone have limited prognostic

value.⁵⁰ The implementation of CNN-based transfer learning models can potentially achieve reasonable performance and outperform radiomics models using small data sets. A transfer learning-based prognostic model for OS in PDAC patients was associated with an area under the receiver operating characteristic curve (AUC) of 0.81 on the test cohort, which was significantly higher than that of the traditional radiomics model (0.54), and with a significantly higher prognostic value (hazard ratio—HR—of 1.86, 95% Confidence Interval—CI—1.15–3.53; *p*-value 0.04).⁵¹ These results suggest that transfer learning-based models may significantly improve prognostic performance when dealing with the typical small sample size of medical imaging studies.

Biological and clinical validation

Radiomics has moved quickly towards high-throughput, agnostic ML analyses, resulting in increasingly large feature sets. This represents a trend towards enhanced predictive power of the models and a movement away from a biological understanding of the findings, highlighting the need for external validation. To expand the clinical translation of radiomics, efforts to reintroduce biological meaning into radiomics are gaining traction, with distinct approaches emerging that include genomic correlates, local microscopic pathological image textures and macroscopic histopathological marker expression. Integrated holistic analyses may increase the predictions accuracy. The integration of non-imaging data in the models is pivotal since end points estimations have been observed to improve when relevant factors beyond radiomics are included.⁵² Semantic analyses are among the relevant methods, *i.e.* combining multiple semantic features (radiologist-defined accepted metrics that describe characteristic tumour morphology and location) with more complex signatures (*e.g.* gene expression prediction). Indeed, studying the relationship between radiogenomics and gene expression, based on combining a data-driven image feature extraction process with genetic analysis, can provide more information on mutation status, exceeding survival, and tumour grade prediction.⁴

Radiomics signatures can be defined as the model drawn from a radiomics analysis of a tumour that can be used to predict a particular outcome. To be reproducible and trustworthy, the predicted model needs to be validated, demonstrating either the performance of the outcomes with balanced independent data not used in the fitting model, or through a statistical relationship with relevant pathological information like a biological context correlate.^{23,25} These methods allow us to achieve biological and clinical validation, a procedure that is quickly becoming standard practice in the field, further increasing the potential contribution of radiomics to clinical decision-making.⁵³ The performance of the model using a hold-out test set from the same institutions by time acquired (internal temporal validation) or, preferable, using a fully independent data from different centres, scanners, and protocols (external validation) is mandatory to assess accuracy and reproducibility.⁵² To be considered of clinical utility, generalisable and transferable, the developed models require independent evaluations.⁵⁴ Finally, large multicentre international studies, incorporating pre-operative clinical variables and radiomics, will be required for validation of clinically useful prognostic models in PDAC.⁵⁵

In the following section, some recently proposed Radiomics and AI imaging candidates will be considered based on their level of evidence and quality assurance. The evidence obtained from studies can only be considered strong if metaanalyses or systematic reviews are used, or they have been the focus of large observational studies with external multicentre validation, well-defined reference standards and controls of bias.^{23,56} All other publications should be considered as pilot studies in need of further research, which is the situation of most publications to date. The development of guidelines for the use of AI in medical imaging through FUTURE-AI, assesses Fairness, Universality, Traceability, Usability, Robustness and Explainability, which will help to provide trustworthy AI solutions for clinical practice.⁵⁷

SOME RELEVANT RADIOMICS AND AI CANDIDATES

Although no approved medical device solutions currently exist on the market, both AI and radiomics solutions have been developed to achieve pancreatic and tumour segmentation, and to perform radiomics and deep radiomics end-to-end feature extraction to be used in research into lesion detection, characterisation, staging and outcome prediction.⁵⁸ Interactive CNNs applied to CECT images provide very accurate pancreas segmentation and good sensitivity in terms pancreatic cancer detection, even for small tumours.⁵⁹ Here, we will focus on the characterisation of tumour behaviour and biological risk that complements the structural radiological information to make better treatment decisions. We emphasise where these studies followed IBSI-compliant feature extraction (Table 1) to account for comparability, as occurred in approximately half of the studies analysed.^{48,49,53,60–68,76} However, some recent studies make use of deep learning algorithms for deep feature extraction that did not comply to IBSI guidelines.^{71,77}

Among these studies, a multivariate logistic regression model was generated using portal venous phase CECT radiomics features that was able to accurately assess superior mesenteric vein invasion in patients who underwent surgical resection (AUC = 0.75). The study involved 181 patients and 1029 radiomics features, and it outperformed the standard approaches to assess resectability-based extent of tumour–vascular contact, although the model was not validated.⁶²

In a retrospective CECT study of 194 patients, radiomics was applied to the PDAC perivascular space surrounding the superior mesenteric artery (SMA) but not the hepatic artery and celiac axis.⁶⁰ The two main prognostic features identified were spatial derived maximum hugging angle (degree of circumferential vascular involvement) and minimum distance (tumour more than 1 mm from the perivascular region). The final model incorporated five radiomic features (maximum hugging angle, maximum diameter, minimum distance, log robust mean absolute deviation and square GLCM correlation representing the heterogeneity of the perivascular tissue) and it performed a significantly better than the radiologist's assessment to assess SMA vascular involvement (AUC = 0.71 vs 0.54), with a sensitivity of 62% (33 of 53 patients) and a specificity of 77% (108 of 141 patients).⁶⁰ If validated, these results could improve the

Table 1. Details of various software packages used in the studies of radiomics feature extraction analysed and their compliance with the IBSI initiative guidelines

Feature extraction software	IBSI compliant	References
LIFEx	Yes	60,61
Pyradiomics	Yes	48,49,59,62–67
3D Slicer radiomics module (based on Pyradiomics)	Yes	68
Custom Matlab code	Yes	53
IBEX	No	69,70
MaZda	No	71
Direct Gray Level Non-Uniformity (GLN) formula calculation	No	72
TexRAD	Unknown	58,73,74
Artificial Intelligence Kit, GE Healthcare	Unknown	75
Deep Learning algorithms	N/A	76,77
Only radiological features	N/A	78

IBSI, Image Biomarker Standardisation Initiative.

performance in predicting complete resection (R0), even after neoadjuvant chemotherapy.

In a series of 131 patients with hypovascular PDAC tumours in the pancreas, several features that can be extracted from CECT texture analysis were associated with relevant high-risk diagnostic phenomena, such as post-operative margin status, nodal disease, high tumour grade, lymphovascular invasion and perineural invasion.⁶³ Lymph node involvement constitutes one of the most important independent predictors of survival, yet standard CECT images have low sensitivity and poor positive-predictive value in detecting the status of lymph nodes. In a single centre series of 225 patients with pathologically confirmed PDAC, CECT and 1029 tumour radiomics features from the arterial phase were used to construct a multivariate logistic regression model. The rad-score constructed with 12 of these features was significantly associated with lymphatic involvement, although no validation was performed.⁶⁴ In a different single centre study on 155 tumours evaluated with pre-operative dual-energy CECT, a single radiomics feature (wavelet energy with rows and columns filtered using low pass and high pass frequency bands with scale factors = 2: WavEnLH_s-2) was able to discriminate lymph node metastases with a likelihood ratio of 2.08 and an AUC of 0.63.⁷⁹ Elsewhere, 15 radiomics features were selected from the pre-operative CECT images of 159 patients to construct a combined prediction model (radiomics signature, CT reported lymph enlargement and pathological grade) that was able to discriminate lymphatic metastases (AUC = 0.94 for training and 0.91 for internal validation).⁷⁸ To further reinforce the role of radiomics, another study on 130 patients showed that 4 radiomics features were closely associated with lymph node metastasis ($p < 0.01$), with this radiomics signature having a strong AUC (0.80 for the training and 0.78 for the validation cohort).⁶⁵

In terms of estimating the development of metastases, a retrospective series of 147 patients with internal validation showed that integrating a biochemical marker (serum CA19-9 levels), a semantic radiological finding (necrosis) and a radiomics feature

(Surface to Volume ratio as a major determinant of tumour and cell size) in a ML tool is significantly associated with the early appearance of metastases. As such, this tool identified patients at a high risk (50% chance) of developing metastases within 12 months after surgery and who may benefit from neoadjuvant chemotherapy as opposed to upfront surgery.⁴⁹

Predicting OS is challenging as PDAC is a biologically aggressive disease even in patients with localised tumours, and there is an imperfect correlation between disease stages and long-term survival rates. When evaluating prognostic outcomes, any AI and radiomics model should improve over the subjective reading of a radiologist. From a series of 168 patients, it was recommended that some standard predictors of OS could be used in standardised reporting templates, including tumour arterial contact of any kind (HR = 1.89), tumour contact with the common hepatic artery (HR = 2.33), portal vein deformity (HR = 3.22), larger tumour size (HR = 2.30) and venous collaterals (HR = 2.28).⁷³ Several studies evaluated the relationship between size, intensity and edge-based radiomics features of PDAC tumours and clinical end points.¹⁶ Pre-treatment portal venous phase CE-CT texture features, like large tumour size, hypoattenuation, homogeneity, standard deviation, and skewness, have been associated with poorer PFS and lower OS in patients with unresectable lesions treated with chemotherapy. Although this was studied on a small series of patients and without independent validation, this combination of parameters has the potential to perform better in survival models than individual imaging biomarkers.⁷² In a similar manner, a multicentre study involving 98 patients showed that CECT Sum Entropy and Cluster Tendency radiomics GLCM features, and the combined radiomics signature, had good prognostic value for OS in validation cohorts (HR = 1.56–1.35).⁴⁸ These two CECT prognostic radiomics features were evaluated in an independent data set of 108 patients with unresectable PDAC, and only Cluster Tendency of the tumour, lymph nodes and metastasis had a significant prognostic relationship with OS and time to progression (HR = 1.27 and 1.25, respectively).⁶⁶

The impact of CECT heterogeneity in GLRLM features on survival was confirmed in a series of 116 patients, where a GLN135 (Grey-level non-uniformity 135 angle) higher than the mean values was associated with poor prognosis.⁶⁹ In a different CECT study on 207 patients, a Random Forest ML algorithm indicated the PDAC molecular subtype (quasi-mesenchymal *vs* non-quasi-mesenchymal) and survival were predicted from the tumour's radiomics features. When applied to histopathological unclassifiable tumours, the ML tool defined two groups with significantly different survival times (8.9 and 39.8 months, HR = 4.33), allowing pre-operative patient stratification.⁶¹ In a larger study on 401 patients (151 for training, 150 for testing and 100 for external validation), a pre-operative CECT radiomics signature coupled to a support vector machine model showed moderate predictive accuracy to differentiate low-grade from high-grade PDACs with a shorter survival (AUC = 0.96, 0.91 and 0.77, training, testing and validation cohorts, respectively).⁷⁴ Incorporating this evaluation into the radiology report might help better grade pathologically heterogeneous tumours and unclassified lesions after biopsy.

Finally, CECT features at presentation from 60 patients were able to predict the OS of unresectable pancreatic cancer treated with chemoradiotherapy.⁵⁹ Higher parameters at a mean value of positive pixels (>31.6) and kurtosis (>0.56) obtained using a medium spatial filter were linked significantly with a worse median OS. However, the best prognostic factors linked with improved OS were semantic findings, such as the presence of metastatic disease, venous invasion, and arterial invasion. However, these results have yet to be validated.⁵⁹

Also, aiming to improve response by better patient selection for neoadjuvant therapy, a large series of 352 patients showed that a mixed clinical and radiomic model had a significant association with OS (HR 3.78) and disease-free survival (DFS, HR 2.81).⁵⁵ The association was also found in an independent external series of 215 patients with OS (HR 2.87) and DFS (HR 5.28). However, it was found that this prognostic model had a low discriminative ability for treatment decisions, probably related to the CECT images heterogeneity.⁵⁵

Although MR is less frequently used, several radiomics features extracted from T_2 weighted images can also estimate DFS and OS based on tumour size, skewness, kurtosis and entropy.⁷⁵ In a larger data set of 303 patients with resectable PDAC evaluated with T_1 -, T_2 - and CET_1 weighted images, a combined radiomics signature had a large AUC to predict early recurrence (0.80 for the training cohort, 0.81 for the internal validation cohort and 0.78 for the external validation cohort). Moreover, when CA 19-9 levels and clinical stage were incorporated, the radiomics nomogram gave even higher AUC values (0.87 training cohort, 0.88 internal validation cohort and 0.85 external validation cohort).⁷⁰

A radiomics signature derived from unenhanced CT images from 100 patients with locally advanced PDAC, which included age and features of homogeneity, was able to differentiate patients with a longer (14 months) or shorter (9 months) OS after

stereotactic body radiation therapy (AUC of 0.81 for training and 0.73 for internal validation).⁶⁸ In another study, 800 radiomics features we extracted from pre-radiation CE-CT of 74 patients with PDAC undergoing stereotactic body radiotherapy, showing that a radiomics signature can outperform clinical models in predicting OS (AUC = 0.78 *vs* 0.66, no external validation).⁶⁷ The use of deep radiomics has also been defined and deep radiomics CECT features obtained with a CNN and through transfer learning were extracted from 111 patients. The deep features were strongly correlated with survival time, although this relationship was not validated, and they were also correlated to HMGA2 (AUC = 0.91) and C-MYC (AUC = 0.90) gene expression.⁷⁷

ML models might help to predict OS through both unsupervised and supervised learning approaches, defining patient risk groups that can be used in prescriptive analyses.⁵⁰ Moreover, the implementation of ML algorithms can improve our understanding of cancer progression. A random forest supervised ML model trained on radiomics features obtained from pre-operative diffusion-weighted (DW) apparent diffusion coefficient maps was able to predict the survival of 102 PDAC patients above and below median OS, with an AUC of 0.90 in a validation cohort of 30 independent patients.⁷⁶

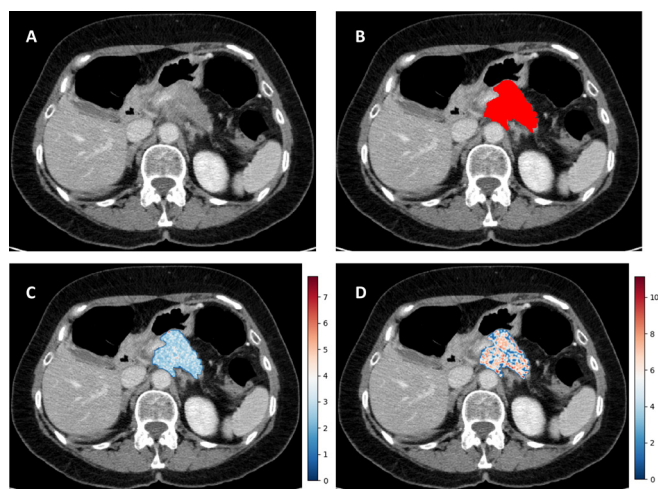
Neoadjuvant therapy is associated with lower rates of PDAC nodal involvement and perineural invasion, and higher rates of negative margin resection, although determining the imaging response and resectability can be difficult. Radiomics, delta-radiomics and iodine concentration maps from CECT might have the potential to identify a rapid response to chemotherapy and early down-staging to a surgically resectable tumour.¹⁶

A CNN DL model based on the LeNet architecture applied to pre-operative post-chemotherapy CE-CT data from patients with PDAC yielded an AUC of 0.74 when distinguishing patients with a pathological response (35 patients with tumour regression grades 0–2) from those with no response (46 patients with tumour regression Grade 3; $p < 0.001$). If the model incorporated the semantic features of a 10% decrease in CA19-9, the AUC increased significantly (AUC = 0.79).⁷¹ These results were not validated in an independent series. However, if it does prove to be useful, this DL model might be retrained and implemented to limit the duration of pre-operative treatment and the need for additional radiotherapy, sparing patients from unnecessary surgery.

A series of 2520 CT examinations from 50 patients receiving chemoradiation therapy were used to longitudinally extract radiomics features (delta-radiomics) to create a ML outcome prediction model of response. Significant changes were detected following 2–4 weeks of treatment using 13 delta-radiomics features (normalised-entropy-to-standard-deviation-difference, kurtosis, and coarseness). Moreover, the ML tool differentiated good from poor responders (AUC 0.94) in the validation cohort of 40 patients.⁸⁰

MR (0.35 T)-guided stereotactic radiotherapy requires accurate evaluations to define early responses that may allow better

Figure 2. A 65-year-old female with locally advanced unresectable pancreatic adenocarcinoma (Stage III, T4N0M0). CECT showed a large mass within the pancreatic body with arterial vascular invasion. The patient was treated with gemcitabine plus Nab-paclitaxel and with radiotherapy after local progression. Overall survival was 1799 days. (A) Portal venous phase (35s delay after pancreatic phase); (B) Manual tumour segmentation; (C) Kurtosis parametric map (tumour value of 13.87); (D) Grey Level Run Length Matrix—Non-uniformity parametric map (tumour value of 1098.54). Our in-house dedicated image processing pipeline (image denoising, tumour segmentation, radiomic feature extraction, feature selection with factor analysis and data clustering: unpublished results) successfully identified this patient as high survival, with the most predictive features being tumour Elongation and Range, Grey Level Non-uniformity, Grey Level, Grey Level Small Area Emphasis, and tumour Kurtosis. CECT, contrast-enhanced CT.



prescription. After signal intensity normalisation, tumour histogram skewness defines changes in treatment groups reflected as an asymmetric distribution of the modifications, which were significantly associated with PFS in a small series of 26 locally advanced and borderline resectable PDAC patients.⁵³

SUGGESTED PIPELINE FOR PDAC

Endoscopic ultrasound (EUS)-guided fine needle aspiration of the pancreatic mass is usually performed to achieve a diagnosis before any treatment option is proposed. EUS is also used to assess the resectability of the tumour during the diagnostic evaluation, particularly those who are equivocal on CECT, and it might even be used to apply local therapies, such as the direct injection of cytotoxic agents and radiofrequency ablation.¹⁶ Patients with advanced PDAC should undergo molecular tumour profiling to detect somatic alterations that can be targeted therapeutically.⁵ For example, patients with homologous recombination repair (HRR) mutations and cell-free DNA abnormalities could benefit from aggressive medical interventions.^{16,81} Any additional information coming from images could help further grade and properly stage PDAC tumours.

In this sense, tumours with an early aggressive behaviour may benefit from neoadjuvant chemotherapy instead of upfront surgery to avoid early recurrence after surgery, securing a radical

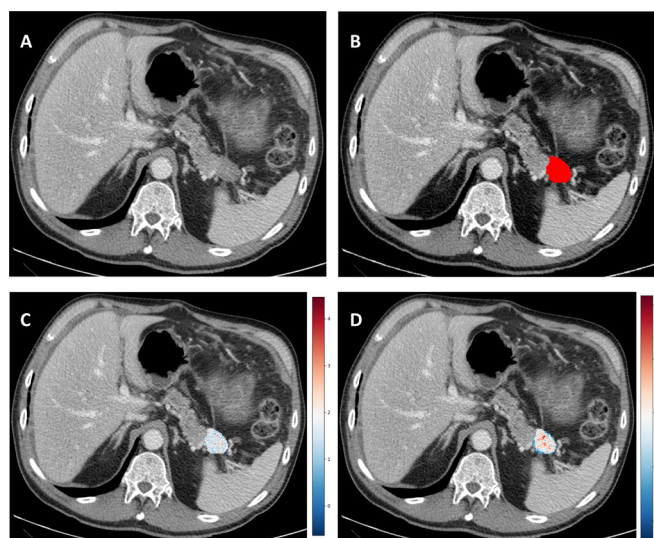
R0 curative resection. Some recent guidelines included biological factors when defining unresectable tumours, such as an elevated CA 19-9 ($>500\text{IU l}^{-1}$) and poor patient performance.¹¹ Staging and restaging after PDAC treatment are key roles of radiologists, yet they are not their only roles.⁸ Aggressive phenotypes might be extracted from radiomics features and identifying these tumours may allow chemotherapy and chemoradiation, as well as targeted genomic and immunotherapy to be better tailored to each case, enhancing patient survival.^{17,82}

Digital image processing extracts radiomics and dynamic variables from the tumour to better estimate relevant tumour characteristics and resolve an unmet clinical need. If a causal inference is observed, these imaging metrics might be linked to the probability of reaching relevant clinical end points, such as the development of metastases, recurrence, or survival (Figures 2 and 3). The imaging biomarkers extracted will help to define a new taxonomy of the disease, driven by advances in imaging, as well as enhancing our understanding of the genomics and the molecular pathways driving the disease. This prognostic phenotyping might help grade lesions (aggressiveness, molecular pathways), and predict the response to treatment and the development of complications. Imaging phenotypes might also offer rapid read-outs of treatment effects, facilitating prompt shifts from ineffective to effective therapies, and the rapid abandonment of ineffective therapies. Image processing also allows distinct tumour areas and cell subpopulations to be identified through the combination of relevant multidimensional parameters, known as habitat imaging.²³ Therefore, information provided by images (radiomics and signal models) can be linked to the pathology and to genomic data to achieve more precise evidence-based medicine that can guide clinical trials and therapeutic decisions.

The peritumoral space is relevant to define resectability. Tumour contact of at least 180° and vessel deformity, are common criteria of a locally advanced unresectable tumour. Tumour aggressiveness is usually assessed by increased CA19-9 levels, along with radiological evidence of nodal and metastatic extension. Any information from the radiomics analysis of PDAC that enables aggressive tumours to be identified might be incorporated into radiological reports. Lymph node and liver parenchyma radiomics data might also help identify the frequent cases with possible microscopic nodal or distant metastatic liver extension. Poor performance status might also be a relevant factor to avoid unnecessary treatments, significantly increasing the risk for morbidity or mortality after surgery.⁸² In this sense, sarcopaenia assessed using a neural network that quantifies the muscle index at CT and showed it to be significantly associated with mortality in PDAC patients (HR = 1.58).⁸³ It is currently necessary to improve the definition of tumour response to treatment. Treatment response after neoadjuvant chemotherapy, with and without chemoradiation, might be difficult to assess as DCE-CT and MR cannot usually distinguish viable tumours from inflammation/fibrosis. However, a lower metabolic standard uptake value (SUV) might identify good responders.⁸²

The main limitations regarding radiomics studies in patients with PDAC are associated with the low incidence, high mortality,

Figure 3. A 70-year-old male with metastatic pancreatic adenocarcinoma (Stage IV, T1NOM1). CECT showed a small pancreatic mass located in the pancreatic tail. The patient was treated with gemcitabine plus Nab-paclitaxel and his overall survival was 150 days. (A) Portal venous phase (35 s delay after pancreatic phase); (B) Manual tumour segmentation; (C) Kurtosis parametric map (tumour value of 4.56); (D) Grey Level Run Length Matrix–Non-uniformity parametric map (tumour value of 457.15). Our dedicated image processing clustering analysis was successful in differentiating the patient as low survival with tumour Elongation and Range, Grey Level Non-uniformity, Grey Level, Grey Level Small Area Emphasis, and tumour Kurtosis features. CECT, contrast-enhanced CT.



and large variability of the disease. Studies incorporating radiomics analyses of the tumour, regional lymph nodes and liver parenchyma should produce benefits in patient management over conventional decision-making approaches. As prospective randomised trials might be difficult to carry out due to ethical issues and the lengths of the follow-up periods, observational non-interventional emulated trials might help recruit real-world cohorts that are of sufficient quality and size, made up of patients (positive for the imaging biomarkers) and controls (negative for the biomarker).⁸⁴ Similarly, large meta-analysis pooling existing evidence and extracting the most meaningful set of radiomics features in PDAC would help to establish reliable evidence. To

develop clinically useful imaging biomarkers, high quality and consistently labelled data sets, with varied feature combinations, will be needed to train and test computational solutions.^{58,85} If they prove to be useful, promising results from observational trials must be validated to obtain biological and clinically meaningful outcomes, producing real-world evidence in patients treated outside the discovery phase.^{55,86}

CONCLUSIONS

The increase in the number of radiomics publications focusing on PDAC should soon translate into the clinical implementation of new companion diagnostic tools. Radiomics and dynamic imaging features should be validated as prognostic and predictive biomarkers to be used in clinical decision-making, enabling personalised management of advanced PDAC. AI more efficiently transforms big data into clinically insights that can improve diagnostic accuracy and make real-time predictions. DL solutions identify high level computer vision features that are significantly associated with a given biological and aggressiveness profile, offering further information on outcomes.⁵⁸ The paucity of large, properly annotated, multicentre data sets that include relevant semantic features (demographics, blood markers, genomics), image harmonisation and robust radiomics analysis, as well as clinically significant read outs, comparisons with gold standards (such as TNM or pre-treatment classification) and fully independent validation cohorts, are currently the main limiting factors to the implementation of trustworthy radiomics and AI solutions to predict PDAC aggressiveness in a clinical setting.^{20,87} Although models integrate multilevel genomic, transcriptomic and radiomics data to explain and estimate the biological behaviour of PDAC, further research is needed to establish the relationship between the radiomics signatures extracted, pathological findings and genetic profiles as biological drivers of patient outcomes.²³

CONTRIBUTORS

Conceptualization, L.M.B., L.C.A., and A.A.B.; methodology, L.M.B., L.C.A., A.P.G., and A.A.B.; writing—original draft preparation, L.M.B., L.C.A.; writing—review and editing, L.M.B., L.C.A., A.P.G., R.D.B., E.M.O., J.P.R. and A.A.B.; visualization, L.M.B., L.C.A., A.P.G., R.D.B., E.M.O., J.P.R. and A.A.B.; supervision, L.M.B., L.C.A., A.P.G., R.D.B., E.M.O., J.P.R. and A.A.B. All authors read and agreed to the published version of the manuscript.

REFERENCES

- Gupta N, Yelamanchi R. Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management. *World J Gastroenterol* 2021; 27: 3158–81. <https://doi.org/10.3748/wjg.v27.i23.3158>
- Pekarek L, Fraile-Martinez O, Garcia-Montero C, Alvarez-Mon MA, Acero J, Ruiz-Llorente L, et al. Towards an updated view on the clinical management of pancreatic adenocarcinoma: current and future perspectives. *Oncol Lett* 2021; 22(5). <https://doi.org/10.3892/ol.2021.13070>
- Visani M, Acquaviva G, De Leo A, Sanza V, Merlo L, Maloberti T, et al. Molecular alterations in pancreatic tumors. *World J Gastroenterol* 2021; 27: 2710–26. <https://doi.org/10.3748/wjg.v27.i21.2710>
- Gutiérrez ML, Muñoz-Bellvis L, Orfao A. Genomic heterogeneity of pancreatic ductal adenocarcinoma and its clinical impact. *Cancers (Basel)* 2021; 13: 4451. <https://doi.org/10.3390/cancers13174451>
- O'Kane GM, Ladak F, Gallinger S. Advances in the management of pancreatic ductal adenocarcinoma. *CMAJ* 2021; 193: E844–51. <https://doi.org/10.1503/cmaj.201450>
- Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, et al. Oncogenic signaling pathways in the cancer genome

- atlas. *Cell* 2018; **173**: 321–327. <https://doi.org/10.1016/j.cell.2018.03.035>
7. Nagayama Y, Tanoue S, Inoue T, Oda S, Nakaura T, Utsunomiya D, et al. Dual-layer spectral CT improves image quality of multiphasic pancreas CT in patients with pancreatic ductal adenocarcinoma. *Eur Radiol* 2020; **30**: 394–403. <https://doi.org/10.1007/s00330-019-06337-y>
8. Vernuccio F, Messina C, Merz V, Cannella R, Midiri M. Resectable and borderline resectable pancreatic ductal adenocarcinoma: role of the radiologist and oncologist in the era of precision medicine. *Diagnostics (Basel)* 2021; **11**: 2166. <https://doi.org/10.3390/diagnostics11112166>
9. Jhaveri KS, Babaei Jandaghi A, Thipphavong S, Espin-Garcia O, Dodd A, Hutchinson S, et al. Can preoperative liver MRI with gadoxetic acid help reduce open-close laparotomies for curative intent pancreatic cancer surgery? *Cancer Imaging* 2021; **21**: 45. <https://doi.org/10.1186/s40644-021-00416-4>
10. Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the american pancreatic association. *Gastroenterology* 2014; **146**: 291–304. <https://doi.org/10.1053/j.gastro.2013.11.004>
11. Heckler M, Hackert T. Surgery for locally advanced pancreatic ductal adenocarcinoma—is it only about the vessels. *J Gastrointest Oncol* 2021; **12**(5). <https://doi.org/10.21037/jgo-20-313>
12. Schlick K, Kiem D, Greil R. Recent advances in pancreatic cancer: novel prognostic biomarkers and targeted therapy—a review of the literature. *Biomolecules* 2021; **11**(10). <https://doi.org/10.3390/biom11101469>
13. Lellouche L, Palmieri L-J, Dermine S, Brezault C, Chaussade S, Coriat R. Systemic therapy in metastatic pancreatic adenocarcinoma: current practice and perspectives. *Ther Adv Med Oncol* 2021; **13**. <https://doi.org/10.1177/17588359211018539>
14. Hong SB, Lee SS, Kim JH, et al. Pancreatic cancer CT: prediction of resectability according to NCCN criteria. *Radiology* 2018; **289**: 710–18. <https://doi.org/10.1148/radiol.2018180628>
15. Yang HK, Park MS, Choi M, Shin J, Lee SS, Jeong WK, et al. Systematic review and meta-analysis of diagnostic performance of CT imaging for assessing resectability of pancreatic ductal adenocarcinoma after neoadjuvant therapy: importance of CT criteria. *Abdom Radiol (NY)* 2021; **46**: 5201–17. <https://doi.org/10.1007/s00261-021-03198-2>
16. Zeeshan MS, Ramzan Z. Current controversies and advances in the management of pancreatic adenocarcinoma. *World J Gastrointest Oncol* 2021; **13**: 472–94. <https://doi.org/10.4251/wjgo.v13.i6.472>
17. Taboada AGM, Lominchar PL, Roman LM, et al. Advances in neoadjuvant therapy for resectable pancreatic cancer over the past two decades. *Ann Hepatobiliary Pancreat Surg* 2021; **25**: 179–91. <https://doi.org/10.14701/ahbps.2021.25.2.179>
18. Bartoli M, Barat M, Dohan A, et al. CT and MRI of pancreatic tumors: an update in the era of radiomics. *Jpn J Radiol* 2020; **38**: 1111–24. <https://doi.org/10.1007/s11604-020-01057-6>
19. Hayashi H, Uemura N, Matsumura K, et al. Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma. *World J Gastroenterol* 2021; **27**: 7480–96. <https://doi.org/10.3748/wjg.v27.i43.7480>
20. Abunahel BM, Pontre B, Kumar H, Petrov MS. Pancreas image mining: a systematic review of radiomics. *Eur Radiol* 2021; **31**: 3447–67. <https://doi.org/10.1007/s00330-020-07376-6>
21. Limkin EJ, Sun R, Dercle L, Zacharaki EI, Robert C, Reuzé S, et al. Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology. *Ann Oncol* 2017; **28**: 1191–1206. <https://doi.org/10.1093/annonc/mdx034>
22. Larue R, Defraene G, De Ruysscher D, Lambin P, van Elmpt W. Quantitative radiomics studies for tissue characterization: a review of technology and methodological procedures. *Br J Radiol* 2017; **90**: 1070. <https://doi.org/10.1259/bjr.20160665>
23. Tomaszewski MR, Gillies RJ. The biological meaning of radiomic features. *Radiology* 2021; **298**: 505–16. <https://doi.org/10.1148/radiol.2021020553>
24. Alberich-Bayarri Á, Hernández-Navarro R, Ruiz-Martínez E, García-Castro F, García-Juan D, Martí-Bonmatí L. Development of imaging biomarkers and generation of big data. *Radiol Med* 2017; **122**: 444–48. <https://doi.org/10.1007/s11547-017-0742-x>
25. Shur JD, Doran SJ, Kumar S, Ap Dafydd D, Downey K, O'Connor JPB, et al. Radiomics in oncology: A practical guide. *Radiographics* 2021; **41**: 1717–32. <https://doi.org/10.1148/rg.2021210037>
26. Mali SA, Ibrahim A, Woodruff HC, et al. Making radiomics more reproducible across scanner and imaging protocol variations: a review of harmonization methods. *J Pers Med* 2021; **11**(9). <https://doi.org/10.3390/jpm11090842>
27. Fernández Patón M, Cerdá Alberich L, Sangüesa Nebot C, Martínez de Las Heras B, Veiga Canuto D, Cañete Nieto A, et al. MR denoising increases radiomic biomarker precision and reproducibility in oncologic imaging. *J Digit Imaging* 2021; **34**: 1134–45. <https://doi.org/10.1007/s10278-021-00512-8>
28. Wei L, Lin Y, Hsu W. Using a Generative Adversarial Network for CT Normalization and Its Impact on Radiomic Features. 2020 IEEE 17th International Symposium on Biomedical Imaging (ISBI); Iowa City, IA, USA. ; April 2020. <https://doi.org/10.1109/ISBI45749.2020.9098724>
29. Fetty L, Bylund M, Kuess P, Heilemann G, Nyholm T, Georg D, et al. Latent space manipulation for high-resolution medical image synthesis via the stylegan. *Z Med Phys* 2020; **30**: 305–14. <https://doi.org/10.1016/j.zemedi.2020.05.001>
30. Isensee F, Jaeger PF, Kohl SAA, Petersen J, Maier-Hein KH. NnU-net: a self-configuring method for deep learning-based biomedical image segmentation. *Nat Methods* 2021; **18**: 203–11. <https://doi.org/10.1038/s41592-020-01008-z>
31. Simpson AL, Antonelli M, Bakas S, et al. A large annotated medical image dataset for the development and evaluation of segmentation algorithms. arXiv:190209063 [cs, eess]. Available from: <http://arxiv.org/abs/1902.09063>
32. Meyer A, Mehrtash A, Rak M, Bashkanov O, Langbein B, Ziaei A, et al. Domain adaptation for segmentation of critical structures for prostate cancer therapy. *Sci Rep* 2021; **11**: 1–14. <https://doi.org/10.1038/s41598-021-90294-4>
33. Szczypiński PM, Strzelecki M, Materka A, Klepaczek A. MaZda—a software package for image texture analysis. *Comput Methods Programs Biomed* 2009; **94**: 66–76. <https://doi.org/10.1016/j.cmpb.2008.08.005>
34. Nioche C, Orlhac F, Boughdad S, Reuzé S, Goya-Outi J, Robert C, et al. LIFEx: A freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity. *Cancer Res* 2018; **78**: 4786–89. <https://doi.org/10.1158/0008-5472.CAN-18-0125>
35. van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, et al. Computational radiomics system to decode the radiographic phenotype. *Cancer Res* 2017; **77**: 104–7. <https://doi.org/10.1158/0008-5472.CAN-17-0339>
36. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. *Radiology* 2016; **278**: 563–77. <https://doi.org/10.1148/radiol.2015151169>
37. Fornacon-Wood L, Mistry H, Ackermann CJ, Blackhall F, McPartlin A, Faivre-Finn C, et al.

- Reliability and prognostic value of radiomic features are highly dependent on choice of feature extraction platform. *Eur Radiol* 2020; **30**: 6241–50. <https://doi.org/10.1007/s00330-020-06957-9>
38. Zwanenburg A, Vallières M, Abdalah MA, Aerts H, Andrearczyk V, Apte A, et al. The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. *Radiology* 2020; **295**: 328–38. <https://doi.org/10.1148/radiol.2020191145>
 39. Tharwat A, Gaber T, Ibrahim A, Hassanien AE. Linear discriminant analysis: a detailed tutorial. *AIC* 2017; **30**: 169–90. <https://doi.org/10.3233/AIC-170729>
 40. Siblini W, Kuntz P, Meyer F. A review on dimensionality reduction for multi-label classification. *IEEE Trans Knowl Data Eng* 2019; **33**. <https://doi.org/10.1109/TKDE.2019.2940014>
 41. Nanga S, Bawah AT, Acquaye BA, Billa M-I, Baeta FD, Odoi NA, et al. Review of dimension reduction methods. *JDAIP* 2021; **09**: 189–231. <https://doi.org/10.4236/jdaip.2021.93013>
 42. Blum MGB, Nunes MA, Prangle D, Sisson SA, et al. A comparative review of dimension reduction methods in approximate bayesian computation. *Statist Sci* 2013; **28**: 189–208. <https://doi.org/10.1214/12-STS406>
 43. Da-Ano R, Masson I, Lucia F, Doré M, Robin P, Alfieri J, et al. Performance comparison of modified combat for harmonization of radiomic features for multicenter studies. *Sci Rep* 2020; **10**(1). <https://doi.org/10.1038/s41598-020-66110-w>
 44. Zhang Y, Lobo-Mueller EM, Karanicolas P, Gallinger S, Haider MA, Khalvati F, et al. Improving prognostic performance in resectable pancreatic ductal adenocarcinoma using radiomics and deep learning features fusion in CT images. *Sci Rep* 2021; **11**(1). <https://doi.org/10.1038/s41598-021-80998-y>
 45. Zhou H-F, Han Y-Q, Lu J, Wei J-W, Guo J-H, Zhu H-D, et al. Radiomics facilitates candidate selection for irradiation stents among patients with unresectable pancreatic cancer. *Front Oncol* 2019; **9**. <https://doi.org/10.3389/fonc.2019.00973>
 46. Cerdá Alberich L, Sangüesa Nebot C, Alberich-Bayarri A, et al. A confidence habitats methodology in MR quantitative diffusion for the classification of neuroblastic tumors. *Cancers (Basel)* 2020; **12**: 12–3858. <https://doi.org/10.3390/cancers12123858>
 47. Chu LC, Park S, Kawamoto S, et al. Utility of CT radiomics features in differentiation of pancreatic ductal adenocarcinoma from normal pancreatic tissue. *AJR Am J Roentgenol* 2019; **213**(2):349–357. <https://doi.org/10.2214/AJR.18.20901>
 48. Khalvati F, Zhang Y, Baig S, et al. Prognostic value of CT radiomic features in resectable pancreatic ductal adenocarcinoma. *Sci Rep* 2019; **9**(1). <https://doi.org/10.1038/s41598-019-41728-7>
 49. Palumbo D, Mori M, Prato F, et al. Prediction of early distant recurrence in upfront resectable pancreatic adenocarcinoma: a multidisciplinary, machine learning-based approach. *Cancers (Basel)* 2021; **13**: 19–4938. <https://doi.org/10.3390/cancers13194938>
 50. Bakasa W, Viriri S. Pancreatic cancer survival prediction: A survey of the state-of-the-art. *Comput Math Methods Med* 2021. <https://doi.org/10.1155/2021/1188414>
 51. Zhang Y, Lobo-Mueller EM, Karanicolas P, Gallinger S, Haider MA, Khalvati F. Prognostic value of transfer learning-based features in resectable pancreatic ductal adenocarcinoma. *Frontiers in Artificial Intelligence* 2020; **3**: 77. <https://doi.org/10.3389/frai.2020.550890>
 52. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017; **14**: 749–62. <https://doi.org/10.1038/nrclinonc.2017.141>
 53. Tomaszewski MR, Latifi K, Boyer E, et al. Delta radiomics analysis of magnetic resonance guided radiotherapy imaging data can enable treatment response prediction in pancreatic cancer. *Radiation Oncology* 2021; **16**(1). <https://doi.org/10.1186/s13014-021-01957-5>
 54. Halligan S, Menu Y, Mallett S. Why did european radiology reject my radiomic biomarker paper? how to correctly evaluate imaging biomarkers in a clinical setting. *Eur Radiol* 2021; **31**: 9361–68. <https://doi.org/10.1007/s00330-021-07971-1>
 55. Healy GM, Salinas-Miranda E, Jain R, et al. Pre-operative radiomics model for prognostication in resectable pancreatic adenocarcinoma with external validation. *Eur Radiol* 2021; **32**: 2492–2505. <https://doi.org/10.1007/s00330-021-08314-w>
 56. Marti-Bonmati L. Evidence levels in radiology: the insights into imaging approach. *Insights Imaging* 2021; **12**: 45. <https://doi.org/10.1186/s13244-021-00995-7>
 57. Lekadir K, Osuala R, Gallin C, et al. FUTURE-AI: guiding principles and consensus recommendations for trustworthy artificial intelligence in medical imaging. Available from: <http://arxiv.org/abs/2109.09658>
 58. Barat M, Chassagnon G, Dohan A, Gaujoux S, Coriat R, Hoeffel C, et al. Artificial intelligence: a critical review of current applications in pancreatic imaging. *Jpn J Radiol* 2021; **39**: 514–23. <https://doi.org/10.1007/s11604-021-01098-5>
 59. Sandrasegaran K, Lin Y, Asare-Sawiri M, Taiyini T, Tann M. CT texture analysis of pancreatic cancer. *Eur Radiol* 2019; **29**: 1067–73. <https://doi.org/10.1007/s00330-018-5662-1>
 60. Rigioli F, Hoyer J, Lerebours R, Lafata KJ, Li C, Meyer M, et al. CT radiomic features of superior mesenteric artery involvement in pancreatic ductal adenocarcinoma: a pilot study. *Radiology* 2021; **301**: 610–22. <https://doi.org/10.1148/radiol.2021210699>
 61. Kaissis GA, Ziegelmayr S, Lohöfer FK, Harder FN, Jungmann F, Sasse D, et al. Image-based molecular phenotyping of pancreatic ductal adenocarcinoma. *J Clin Med* 2020; **9**(3). <https://doi.org/10.3390/jcm9030724>
 62. Bian Y, Jiang H, Ma C, Cao K, Fang X, Li J, et al. Performance of CT-based radiomics in diagnosis of superior mesenteric vein resection margin in patients with pancreatic head cancer. *Abdom Radiol (NY)* 2020; **45**: 759–73. <https://doi.org/10.1007/s00261-019-02401-9>
 63. Kulkarni A, Carrion-Martinez I, Jiang NN, Puttagunta S, Ruo L, Meyers BM, et al. Hypovascular pancreas head adenocarcinoma: CT texture analysis for assessment of resection margin status and high-risk features. *Eur Radiol* 2020; **30**: 2853–60. <https://doi.org/10.1007/s00330-019-06583-0>
 64. Bian Y, Guo S, Jiang H, Gao S, Shao C, Cao K, et al. Relationship between radiomics and risk of lymph node metastasis in pancreatic ductal adenocarcinoma. *Pancreas* 2019; **48**: 1195–1203. <https://doi.org/10.1097/MPA.0000000000001404>
 65. Liang X, Cai W, Liu X, Jin M, Ruan L, Yan S. A radiomics model that predicts lymph node status in pancreatic cancer to guide clinical decision making: A retrospective study. *J Cancer* 2021; **12**: 6050–57. <https://doi.org/10.7150/jca.61101>
 66. Salinas-Miranda E, Khalvati F, Namdar K, Deniffel D, Dong X, Abbas E, et al. Validation of prognostic radiomic features from resectable pancreatic ductal adenocarcinoma in patients with advanced disease undergoing chemotherapy. *Can Assoc Radiol J* 2021; **72**: 605–13. <https://doi.org/10.1177/0846537120968782>
 67. Parr E, Du Q, Zhang C, Lin C, Kamal A, McAlister J, et al. Radiomics-based outcome prediction for pancreatic cancer following stereotactic body radiotherapy. *Cancers (Basel)* 2020; **12**(4). <https://doi.org/10.3390/cancers12041051>

68. Cozzi L, Comito T, Fogliata A, Franzese C, Franceschini D, Bonifacio C, et al. Computed tomography based radiomic signature as predictive of survival and local control after stereotactic body radiation therapy in pancreatic carcinoma. *PLOS ONE* 2019; **14**(1). <https://doi.org/10.1371/journal.pone.0210758>
69. Kim HS, Kim YJ, Kim KG, Park JS. Preoperative CT texture features predict prognosis after curative resection in pancreatic cancer. *Sci Rep* 2019; **9**(1). <https://doi.org/10.1038/s41598-019-53831-w>
70. Tang T-Y, Li X, Zhang Q, Guo C-X, Zhang X-Z, Lao M-Y, et al. Development of a novel multiparametric MRI radiomic nomogram for preoperative evaluation of early recurrence in resectable pancreatic cancer. *J Magn Reson Imaging* 2020; **52**: 231–45. <https://doi.org/10.1002/jmri.27024>
71. Watson MD, Baimas-George MR, Murphy KJ, Pickens RC, Iannitti DA, Martinie JB, et al. Pure and hybrid deep learning models can predict pathologic tumor response to neoadjuvant therapy in pancreatic adenocarcinoma: a pilot study. *Am Surg* 2021; **87**: 1901–9. <https://doi.org/10.1177/0003134820982557>
72. Cheng S-H, Cheng Y-J, Jin Z-Y, Xue H-D. Unresectable pancreatic ductal adenocarcinoma: role of CT quantitative imaging biomarkers for predicting outcomes of patients treated with chemotherapy. *Eur J Radiol* 2019; **113**: 188–97. <https://doi.org/10.1016/j.ejrad.2019.02.009>
73. Dickinson SM, McIntyre CA, Schilsky JB, Harrington KA, Gerst SR, Flynn JR, et al. Preoperative CT predictors of survival in patients with pancreatic ductal adenocarcinoma undergoing curative intent surgery. *Abdom Radiol (NY)* 2021; **46**: 1607–17. <https://doi.org/10.1007/s00261-020-02726-w>
74. Chang N, Cui L, Luo Y, Chang Z, Yu B, Liu Z. Development and multicenter validation of a CT-based radiomics signature for discriminating histological grades of pancreatic ductal adenocarcinoma. *Quant Imaging Med Surg* 2020; **10**: 692–702. <https://doi.org/10.21037/qims.2020.02.21>
75. Choi MH, Lee YJ, Yoon SB, Choi J-I, Jung SE, Rha SE. MRI of pancreatic ductal adenocarcinoma: texture analysis of T2-weighted images for predicting long-term outcome. *Abdom Radiol (NY)* 2019; **44**: 122–30. <https://doi.org/10.1007/s00261-018-1681-2>
76. Kaissis G, Ziegelmayer S, Lohöfer F, Algül H, Eiber M, Weichert W, et al. A machine learning model for the prediction of survival and tumor subtype in pancreatic ductal adenocarcinoma from preoperative diffusion-weighted imaging. *Eur Radiol Exp* 2019; **3**: 41. <https://doi.org/10.1186/s41747-019-0119-0>
77. Li K, Xiao J, Yang J, Li M, Xiong X, Nian Y, et al. Association of radiomic imaging features and gene expression profile as prognostic factors in pancreatic ductal adenocarcinoma. *Am J Transl Res* 2019; **11**: 4491–99.
78. Li K, Yao Q, Xiao J, Li M, Yang J, Hou W, et al. Contrast-enhanced CT radiomics for predicting lymph node metastasis in pancreatic ductal adenocarcinoma: a pilot study. *Cancer Imaging* 2020; **20**: 12. <https://doi.org/10.1186/s40644-020-0288-3>
79. Fang WH, Li XD, Zhu H, Miao F, Qian XH, Pan ZL, et al. Resectable pancreatic ductal adenocarcinoma: association between preoperative CT texture features and metastatic nodal involvement. *Cancer Imaging* 2020; **20**: 17. <https://doi.org/10.1186/s40644-020-0296-3>
80. Nasief H, Zheng C, Schott D, Hall W, Tsai S, Erickson B, et al. A machine learning based delta-radiomics process for early prediction of treatment response of pancreatic cancer. *NPJ Precis Oncol* 2019; **3**: 25. <https://doi.org/10.1038/s41698-019-0096-z>
81. Milin-Lazovic J, Madzarevic P, Rajovic N, et al. Meta-analysis of circulating cell-free DNAs role in the prognosis of pancreatic cancer. *Cancers (Basel)* 2021; **13**: 14–3378. <https://doi.org/10.3390/cancers13143378>
82. Nappo G, Donisi G, Zerbi A. Borderline resectable pancreatic cancer: certainties and controversies. *World Journal of Gastrointestinal Surgery*. 2021; **13**(6):516–528. <https://doi.org/10.4240/wjgs.v13.i6.516>
83. Hsu T-MH, Schawkat K, Berkowitz SJ, et al. Artificial intelligence to assess body composition on routine abdominal CT scans and predict mortality in pancreatic cancer—A recipe for your local application. *Eur J Radiol*. 2021; **142**:109834. <https://doi.org/10.1016/j.ejrad.2021.109834>
84. Hernán MA, Robins JM. Using Big Data to emulate a Target trial when a randomized trial is not available. *Am J Epidemiol*. 2016; **183**(8):758–764. <https://doi.org/10.1093/aje/kwv254>
85. Suman G, Patra A, Horiatis P, et al. Quality gaps in public pancreas imaging datasets: Implications & challenges for AI applications. *Pancreatol*. 2021; **21**(5):1001–1008. <https://doi.org/10.1016/j.pan.2021.03.016>
86. Blomstrand H, Batra A, Cheung WY, Elander NO. Real-world evidence on first- and second-line palliative chemotherapy in advanced pancreatic cancer. *World J Clin Oncol* 2021; **12**: 787–99. <https://doi.org/10.5306/wjco.v12.i9.787>
87. Yamashita R, Perrin T, Chakraborty J, Chou JF, Horvat N, Koszalka MA, et al. Radiomic feature reproducibility in contrast-enhanced CT of the pancreas is affected by variabilities in scan parameters and manual segmentation. *Eur Radiol* 2020; **30**: 195–205. <https://doi.org/10.1007/s00330-019-06381-8>