The impact of radiomics in diagnosis and staging of pancreatic cancer

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Abstract

Introduction: Pancreatic cancer (PC) is one of the most aggressive tumours, and better risk stratification among patients is required to provide tailored treatment. The meaning of radiomics and texture analysis as predictive techniques are not already systematically assessed. The aim of this study is to assess the role of radiomics in PC.

Methods: A PubMed/MEDLINE and Embase systematic review was conducted to assess the role of radiomics in PC. The search strategy was 'radiomics [All Fields] AND ("pancreas" [MeSH Terms] OR "pancreas" [All Fields] OR "pancreatic" [All Fields])' and only original articles referred to PC in humans in the English language were considered.

Results: A total of 123 studies and 183 studies were obtained using the mentioned search strategy on PubMed and Embase, respectively. After the complete selection process, a total of 56 papers were considered eligible for the analysis of the results. Radiomics methods were applied in PC for assessment technical feasibility and reproducibility aspects analysis, risk stratification, biologic or genomic status prediction and treatment response prediction.

Discussion: Radiomics seems to be a promising approach to evaluate PC from diagnosis to treatment response prediction. Further and larger studies are required to confirm the role and allowed to include radiomics parameter in a comprehensive decision support system.

Keywords: decision supporting system, pancreatic cancer, radiomics

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Introduction

Pancreatic cancer (PC) is one of the most aggressive tumours, representing the fourth cause of cancer-related deaths with 132,600 estimated new diagnoses, 128,000 deaths per year and accounting for 3.4–6.6% of all cancer cases, respectively.[1,2] The incidence and mortality are slightly increasing during the years with a 5-year overall survival (OS) rate lower than 10%.[3] Males are more frequently affected than females and incidence in both sexes increases with age, reaching its peak in people older than 70 years.[4]

Primary prevention is of utmost importance as there is currently no effective method of screening for the general population. Nevertheless, molecular or imaging tests can help early diagnosis in high-risk cohorts; for example, endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) allowed to detect precursor or invasive pancreatic neoplasms in asymptomatic people with an inherited predisposition (5–10% of all patients), thus increasing the resectability of the tumours and the overall prognosis of these patients.[5] Further data are needed to establish the most adequate approach and to select patients who could benefit the most from screening programmes.

Signs and symptoms are indeed not disease-specific and usually appear when it has already become unresectable or distantly spread.

Computed tomography (CT) is the most commonly used imaging diagnostic tool, supported

by EUS with fine needle biopsy or aspiration in the identification of small lesions and in providing a definitive diagnosis.[6] MRI and positron emission tomography (PET) may also contribute to the systemic staging of the disease and in characterizing the primary tumour as resectable, borderline resectable or unresectable.

PC is a heterogeneous group of diseases; nearly 90% of the total are adenocarcinomas. Exocrine tumours are known to have a more aggressive behaviour compared with endocrine ones, with a median survival of about 4 *versus* 27 months, as reported in a large population-based study.[7] Pancreatic adenocarcinoma can progress from different types of precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia (IPMN), under the push of consecutive genetic alterations whose significance is frequently unknown.[8] Some of these mutations have been recognized as having a role in different steps of carcinogenesis or even a prognostic significance, such as SMAD4 loss, which is linked to metastatic spread and lower survival rates.[9] These alterations may have, therefore, the potential to identify precursor lesions and serve as targets for new therapies. Currently, the first treatment option for PC is represented by radical surgery. Unfortunately, few more than 10% of patients are amenable to curative-intent surgery and prognosis remains poor even in this cluster of patients, with 5-year survival rates around 20%.[10]

The quantitative analysis of medical images data and the extraction of imaging features, also called 'radiomics', represent an emerging approach in personalized medicine and advanced diagnostics, especially for disease characterization or outcome prediction.[11–13] The interest towards radiomics is rapidly growing in the multidisciplinary cancer community as it shows an interesting pertinency and efficacy to answer several clinical questions arising in the management of patients affected by other gastrointestinal tumours.[14–21]

The aim of this study is to systematically assess and summarize evidence published in the scientific literature about the different applications of radiomics in PC.

Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[22] A systematic PubMed/MEDLINE and Embase search was performed using the following search strategy: 'radiomics [All Fields] AND "pancreas" [MeSH Terms] OR "pancreas"[All Fields] OR "pancreatic" [All Fields])'.

Only original articles regarding radiomics applications in PC characterization were selected. Papers published between 1 January 2005 and 2 January 2021 were considered for this analysis. The exclusion criteria were as follows: (1) not original articles (e.g. reviews, editorials, letters, congress communications or posters, book chapters); (2) papers not referred to PC in humans (e.g. benign lesions, atrophy); (3) papers not referred to radiomics and (4) articles that were not in English, French, Spanish, Italian or German.

All the papers were selected and analyzed by a board of five radiation oncologists (ROs; CC, AD, FP, SM, AP), followed by an independent validation of three experts in PC (two ROs, GCM and FC, and one gastroenterologist, IB) and three experts on radiomics (two ROs, ND and LB, for the clinical point of view, and one physicist, DC, for the technical point of view). The whole process, the results and the discussion about potential discrepancies were validated by the other two different independent expert ROs (MAG and VV).

Results

A total of 123 studies were obtained using the mentioned search strategy on PubMed/MEDLINE, and 183 articles were obtained on Embase. Of these, 68 papers were selected based on the title according to the previously described criteria. The selection process, shown in Figure 1, led to the identification of 58 potentially eligible studies according to the abstract (two papers discarded according to the exclusion criterion 1; seven papers discarded for the exclusion criterion 2, and one paper discarded according to the exclusion criterion 3). After full-text analysis, one paper was discarded for the exclusion criterion 1 and one paper according to criterion 2. After the complete selection process, a total of 56 papers were considered eligible for the analysis of the results. All the studies included in the analysis are retrospective; the range of publication year is from 2017 to 2021. The participant centres' nations were China ($n = 26$; 46.4%), the United States ($n = 13$; 23.2%), Italy ($n = 6$;

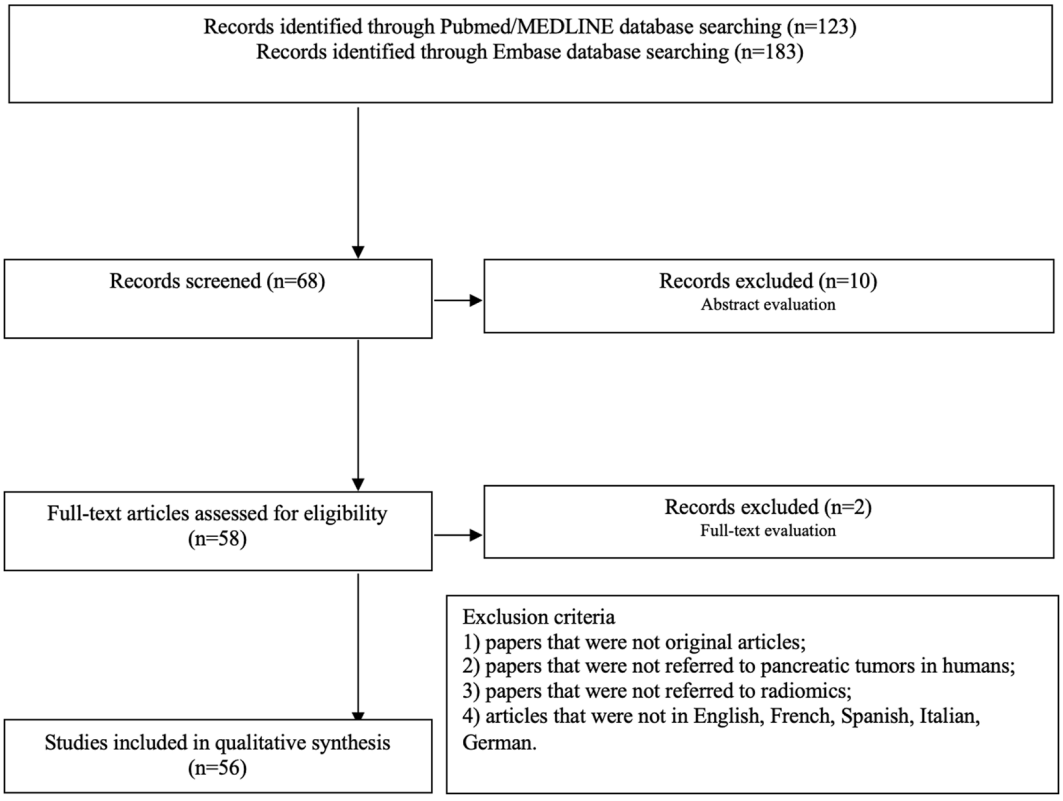

Figure 1. Flowchart of the systematic literature search process.

10.7%), Canada and Germany ($n=3$; 5.4%), Japan ($n=2$; 3.6%), France, Russia and South Korea ($n=1$; 1.78%). The radiomics analysis was performed on CT ($n=43$; 76.8%), PET-CT ($n=6$; 10.7%) or MR ($n=7$; 12.5%) images. The median number of patients involved in the analysis was 110 (range 10–422); the median number of features analyzed was 410 (range 1–3328). Radiomics, as resulted from the analyzed works, plays a role in many aspects of PC management.

Diagnostic imaging features were found to correlate with diagnosis and differentiation of pancreatic ductal adenocarcinoma (PDAC) from noninvasive diseases in 10 studies (17.9%).[23–32]

CT-based features were found able to distinguish PC from normal pancreatic tissue[23,28] and to detect cancer in the context of intraductal papillary mucinous neoplasm (IPMN)[27,30]; CT- and PET-CT-based radiomics could discriminate PC from pancreatitis,[24–26,31,32] while MRI was able to discriminate pancreatic neuroendocrine tumours (pNETs) from solid pseudopapillary tumours in one study.[29] Six studies (10.7%) analyzed technical feasibility and reproducibility aspects of radiomics analysis. Yamashita *et al.*[33] demonstrated that the variation between contrast-enhanced CT scans (e.g. scanner model, pixel spacing and contrast administration rate) affects radiomic feature reproducibility more significantly than the variation in segmentation. Mori *et al.*[34] confirmed the minimal impact of delineation uncertainty of pancreatic neuroendocrine neoplasms (panNEN) on CT radiomics features extraction. Plautz *et al.*[35] observed statistically significant changes over the radiotherapy course time in patients' radiomics feature values, describing interesting delta-radiomics applications also in PC. Chu *et al.*[36] compared the diagnostic performances between a commercial and an in-house radiomic software. Loi *et al.*[37] evaluated the impact of interpolation and discretization on the robustness of radiomics features. The reproducibility of radiomics features in patients affected by pNETs was analyzed by Gruzdev *et al.*[38]

A correlation between cancer imaging features and treatment response prediction was found in seven studies (12.5%).[39–45] Cozzi *et al.*[39] analyzed CT-based radiomic features and found a

significant correlation with local control (LC) and OS after stereotactic body radiation therapy (SBRT). Nasief *et al.*[42] investigated the additional predictive power of combining delta-radiomics features with CA 19-9 levels in patients undergoing concomitant chemoradiation therapy, with this combination resulting in an earlier prediction of good and bad responders. Simpson *et al.*[43] investigated the role of 0.35T MRI-based delta radiomics in the prediction of treatment response. Parr *et al.*[44] predicted clinical outcomes (OS and recurrences) using a CT-based radiomics model. Cusumano *et al.*[45] built a 0.35T MRI-based delta radiomics to predict LC. Yue *et al.*[40] evaluated the prognostic value of PET-CT texture variations in predicting treatment response. Nasief *et al.*[41] predicted pathologic response to the treatment using CT delta radiomics.

Overall, 15 studies (26.8%) were focused on radiogenomics, correlating image phenotype with specific gene expression, mutations, molecular or pathological findings.[46–60] Of these, 8 studies found correlations between CT or MRI features and pNETs grading.[50–54,57–59] One study conducted by Chang *et al.*[60] defined and validated a radiomic model able to predict histological grade in patients affected by PDAC. Ren *et al.*[46] developed a CT-based radiomic model to perform differential diagnosis between pancreatic adenosquamous carcinoma and PDAC. Attiyeh *et al.*[49] demonstrated the possibility to predict SMAD4 status and tumour stromal content using CT-based features. Two studies assessed the role of machine learning algorithms, derived from both CT and MRI analysis, in correlating clinical outcomes predictions with molecular and pathological tumour pathways.[47,48] Other two studies proposed PET-CT- or CT-based radiomics to predict mutational status or PD-L1 expression.[55]

In total, 21 studies (37.5%) described the application of radiomics in PC risk group stratifications, mainly in preoperative setting.[40,47,48,61–78]

Within this heterogeneous group of papers, four articles[62,66,72,74] analyzed the role of CT-based radiomics in lymph nodes (LNs) metastasis risk assessment before surgery. The preoperative evaluation of the risk of a positive resection margin using CT-based radiomics analysis was the aim of three papers.[58,69,76] Zhang *et al.*[61] evaluated the risk of occurrence of pancreatic fistula using a CT-based radiomic model. Overall, 13 articles [40,47,48,63–65,68,70,71,73,75,77,78] analyzed the role of radiomics to predict clinical outcomes, such as OS, progression-free survival (PFS) and early relapse.

Table 1 summarizes the main characteristics of the analyzed studies, including aim, conclusion and the cluster area of radiomic correlation.

Discussion

Radiomics seems to be an effective approach to evaluate patients affected by PC in several clinical settings and in different clinical contexts, from diagnosis to risk stratification, from biologic or genomic status prediction to treatment response evaluation or assessment. Figure 2 shows an example of clinical implementation of a delta radiomic model during a stereotactic radiotherapy treatment prescribed in five fractions.

The common lack of technical standardization of the features extraction process and the necessity of external independent validation for each proposed predictive model hamper the feasibility of extensive radiomics studies in PC and impose the involvement of multidisciplinary research teams and the enrolment of larger patient samples.

Another limitation that reduces the generalizability of these observations is represented by the multiple kinds of image modalities and, for each of them, the variability of acquisition protocols. Moreover, the huge heterogeneity of features analyzed in the different studies poses a limitation in the possibility of creating a cluster of significant features for radiomics in this pathology. The same number of features analyzed, study by study, is very variable (from 1 to 3328 features per study) documenting that the resulting models are very much linked to the analysis experience of each centre.

Despite the above limitations, radiomics could potentially have an important role in providing reliable risk stratification (for both outcomes or complications), facilitating surgical choices, predicting clinical response after treatments, allowing differential diagnosis between cancer and other benign pancreatic abnormalities and predicting histological examination, disease differentiation grade or specific gene mutations.

The multidisciplinary management of these patients by dedicated teams of different specialists

Table 1. Quantitative synthesis of the 56 selected articles.

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Chu *et al.* (China)[23]	380	To determine the utility of RF in differentiating CT cases of PDAC from normal pancreas	Diagnosis	Retrospective	CT	40	RF extracted from whole pancreas can be used to differentiate between CT cases from patients with PDAC and healthy control subjects with normal pancreas.
Zhang *et al.* (China)[24]	111	To investigate the value of radiomics method for noninvasively differentiating autoimmune pancreatitis from PDAC	Diagnosis	Retrospective	PET-CT	251	The quantified radiomics method could aid the noninvasive differentiation of autoimmune pancreatitis and PDAC in 18F-FDG PET-CT images and the integration of multidomain features is beneficial for the differentiation.
Park *et al.* (USA)[25]	182	To determine if machine learning of radiomics features could distinguish autoimmune pancreatitis from PDAC	Diagnosis	Retrospective	CT	431	The model obtained an accuracy of 95.2% and an AUC of 0.975 in distinguishing autoimmune pancreatitis from PDAC.
E *et al.* (China)[26]	96	To build a radiomics model able to distinguish PDAC from focal-type autoimmune pancreatitis	Diagnosis	Retrospective	CT	1160	The prediction model identifies PDAC from autoimmune pancreatitis with a sensitivity, specificity and accuracy of 93.3%, 96.1% and 94.8%, respectively.
Polk *et al.* (USA)[27]	29	To predict PC in patients with IPMNs	Diagnosis	Retrospective	CT	39	The model achieved an AUC of 0.93 and 0.90 for the training dataset and for the fivefold cross-validation, respectively.
Qiu *et al.* (China)[28]	312	To identify patients affected by PDCA against patients with healthy pancreas using a CT-based radiomics model	Diagnosis	Retrospective	CT	26	The proposed texture analysis architecture achieved an AUC of 0.88 and an accuracy of 81.19%.
Shi *et al.* (China)[29]	66	To identify patients affected by pNET from patients with solid pseudopapillary tumours using an MRI-based radiomics model	Diagnosis	Retrospective	MRI	195	The model achieved an AUC of 0.97 and 0.86 on the primary and validation cohort, respectively.

(Continued)

Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Tobaly *et al.* (France)[30]	408	To assess the performance of radiomic analysis to predict malignancy in IPMNs of pancreas	Diagnosis	Retrospective	CT	85	The radiomics model provided an AUC of 0.84 and 0.71 for training and external validation, respectively.
Ziegelmayer *et al.* (Germany)[31]	86	To evaluate the performance of deep convolutional neural network-assisted feature extraction against traditional radiomic features to predict the differentiation between autoimmune pancreatitis and PDAC	Diagnosis	Retrospective	CT	1411	Deep convolutional neural network-assisted feature extraction achieved a higher sensitivity, specificity and AUC in comparison with traditional radiomic features.
Ren *et al.* (China)[32]	109	To distinguish mass-forming pancreatitis from PDAC using radiomics	Diagnosis	Retrospective	CT	396	The model obtained a mean sensitivity, specificity and accuracy of 82.6%, 80.8% and 82.1%, respectively, at the leave group out cross-validation method.
Yamashita *et al.* (USA)[33]	37	To measure the reproducibility of radiomic features in pancreatic parenchyma and PDAC in patients who underwent consecutive CECT scans	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	266	Variations between CECT scans (e.g. scanner model, pixel spacing and contrast administration rate) affected radiomic feature reproducibility to a greater extent than variation in segmentation. A smaller number of pancreatic tumour-derived radiomic features were reproducible compared with pancreatic parenchyma-derived radiomic features under the same conditions.
Mori *et al.* (Italy)[34]	31	To quantify the impact of CT delineation uncertainty of panNEN on RF	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	69	The impact of inter-observer variability in delineating panNEN on RF was minimum, except for the neighbourhood intensity difference family and asphericity, showing a moderate agreement.

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Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Plautz *et al.* (USA)[35]	10	To show that the values of texture features extracted from phantoms are stable over clinical timescales; that changes in patients' feature values over the course of RT are treatment-induced and statistically significant	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	50	The changes observed in features extracted from longitudinal patient CT data may be treatment-induced and demonstrate their potentiality for early assessment of treatment response.
Chu *et al.* (USA)[36]	380	To compare diagnostic performance between a commercial and an in-house radiomics software	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	478	Similar diagnostic performances were achieved between commercially available and in-house radiomics softwares.
Loi *et al.* (Italy)[37]	39	To evaluate the impact of image interpolation and discretization in a radiomics-based prediction analysis of tumour grade, positive LNs, distant metastases and vascular invasion in patients affected by pancreatic neuroendocrine neoplasms	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	69	The role of radiomic features is relatively invariant against image interpolation and discretization.
Gruzdev *et al.* (Russia)[38]	12	To evaluate reproducibility of radiomics features in patients affected by pNET	Technical feasibility and reproducibility aspects of radiomics analysis	Retrospective	CT	52	This study showed a high reproducibility of the results of the textural analysis of pNET.
Cozzi *et al.* (Italy)[39]	100	To appraise the ability of a radiomics signature to predict clinical outcome after SBRT for pancreas carcinoma	Treatment response prediction	Retrospective	CT	41	A CT-based radiomic signature was identified, which correlated with OS and LC after SBRT and allowed to identify low- and high-risk groups of patients.
Yue *et al.* (USA)[40]	26	To stratify risks of pancreatic adenocarcinoma patients using pre- and post-RT PET-CT images and to assess the prognostic value of texture variations in predicting therapy response of patients	Risk stratification and treatment response prediction	Retrospective	PET-CT	48	Locoregional metabolic texture response provides a feasible approach for evaluating and predicting clinical outcomes following the treatment of pancreatic adenocarcinoma with RT.

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Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Nasief *et al.* (USA)[41]	90	To develop a delta-radiomic process based on ML to predict treatment pathologic response	Treatment response prediction	Retrospective	CT	1300	The results show that 13 DRFs passed the tests and demonstrated significant changes following 2–4 weeks of treatment.
Nasief *et al.* (USA)[42]	24	To investigate the predictivity power of combining different biomarkers (DRFs or CA19-9) in patients undergoing chemoRT	Treatment response prediction	Retrospective	CT	>1300	The combination of CT delta radiomics and the clinical biomarker CA19-9 leads to improved prediction of treatment responses for chemoRT of PC, as compared with radiomics or CA19-9 alone.
Simpson *et al.* (USA)[43]	20	To predict treatment response in patients with PDAC who underwent SBRT using 0.35T MRI-based delta radiomics	Treatment response prediction	Retrospective	MRI	42	The model obtained an AUC of 0.81 in predicting treatment response.
Parr *et al.* (USA)[44]	74	To predict clinical outcomes (OS and recurrence) after SBRT	Treatment response prediction	Retrospective	CT	841	The combined clinical and radiomics model obtained an AUC of 0.68 in OS prediction and an AUC of 0.76 in recurrence prediction.
Cusumano *et al.* (Italy)[45]	35	To predict LC in patients affected by PDAC using 0.35T MRI-based delta-radiomics features	Treatment response prediction	Retrospective	MRI	92	This study demonstrates that low tesla MRI-based delta radiomics is adequate in 1-year LC prediction (AUC = 0.78, $p = 0.005$).
Ren *et al.* (China)[46]	112	To develop a model able to perform a differential diagnosis between pancreatic adenosquamous carcinoma and PDAC	Radiogenomics	Retrospective	CT	792	The proposed radiomics signature predicted the correct histology with 94.5% accuracy (76.4% accuracy in 10-times leave group out cross-validation method).
Kaissis *et al.* (Germany)[47]	207	To develop a ML CT-based algorithm capable to correlate preoperative CT to histopathological and molecular subsets and OS	Radiogenomics and risk stratification	Retrospective	CT	1474	ML enables radiomic phenotyping of PDAC and the correlation with clinical outcomes.

(Continued)

Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Kaissis *et al.* (Germany)[48]	132	To develop supervised ML algorithm predicting above-*versus* below-median OS from DWI-derived radiomic features in patients with PDAC	Risk stratification and radiogenomics	Retrospective	MRI	504	ML application to ADC radiomics allowed OS prediction with a high diagnostic accuracy in an independent validation cohort.
Attiyeh *et al.* (USA)[49]	35	To determine whether radiomic analysis could accurately predict the genotype of PDAC driver genes and to use radiomics to predict stromal content in these tumours.	Radiogenomics	Retrospective	CT	255	RF extracted from clinical CT images is associated with genotype, the number of altered genes and stromal content in PDAC.
He *et al.* (China)[50]	147	To develop and validate an effective model to differentiate NF-pNET from PDAC	Radiogenomics	Retrospective	CT	7	The nomogram achieved an optimal preoperative, noninvasive differential diagnosis between atypical pNET and PDAC.
Gu *et al.* (China)[51]	138	To develop and validate a radiomics-based nomogram for preoperatively predicting grade 1 and grade 2/3 tumours in patients with pNET	Radiogenomics	Retrospective	CT	853	The proposed nomogram integrating the clinical predictor tumour margin and fusion radiomic signature had a powerful predictive capability for grade 1 and grade 2/3 in pNET patients.
Liang *et al.* (China)[52]	137	To develop and validate a nomogram model combining radiomics features and clinical characteristics to preoperatively differentiate grade 1 and grade 2/3 tumours in patients with pNET	Radiogenomics	Retrospective	CT	467	The combined nomogram model developed could be useful in differentiating grade 1 and grade 2/3 tumours in patients with pNETs.
McGovern *et al.* (USA)[53]	121	To identify imaging characteristics in patients with known pNET that predict the ALT phenotype by blinded retrospective review of preoperative multiphasic CT scans	Radiogenomics	Retrospective	CT	n.a.	Several preoperative CT features of pNET are associated with the ALT phenotype. CT findings of intratumoral calcifications and metastases predicted poor survival independent of the ALT status.

(Continued)

Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Zhao *et al.* (China)[54]	99	To establish a tumour grade prediction model for preoperative grade 1/2 NF-pNETs using radiomics for multislice spiral CT image analysis	Radiogenomics	Retrospective	CT	585	Radiomics developed with a combination of nonenhanced and portal venous phases shows good discrimination and calibration of preoperatively predicting tumour grading in patients with grade 1/2 NF-pNETs.
Lim *et al.* (South Korea)[55]	48	To determine if major gene mutations in KRAS, SMAD4, TP53 and CDKN2A were related to FDG PET-based radiomic features in PDAC	Radiogenomics	Retrospective	PET-CT	35	Genetic alterations of KRAS and SMAD4 had significant associations with FDG PET-based radiomic features in PDAC.
Iwatate *et al.* (Japan)[56]	107	To predict p53 status, PD-L1 expression and prognosis using radiomics	Radiogenomics	Retrospective	CT	1037	Radiomics could predict p53 mutation (AUC = 0.795) and PD-L1 expression (AUC = 0.683). Radiomics prediction of p53 mutation was associated with poor prognosis ($p = 0.015$).
Bian *et al.* (China)[57]	102	To predict nonfunctioning pNET grade using a CT-based radiomics score	Radiogenomics	Retrospective	CT	1029	The CT-based radiomics score was able to identify pNET grade with an AUC of 0.86.
Bian *et al.* (China)[58]	157	To predict pNET grades using an MRI-based radiomics score	Radiogenomics	Retrospective	MRI	1409	The MRI-based radiomics score identified grade 1 *versus* grade 2/3 nonfunctioning pNETs with an AUC of 0.775.
Bian *et al.* (China)[59]	139	To predict nonfunctional pNET grades using MRI-based radiomics features	Radiogenomics	Retrospective	MRI	3328	The model obtained an AUC of 0.769 and of 0.729 in the training and in the validation cohort, respectively.
Chang *et al.* (China)[60]	401	To define and validate a radiomics model to predict histological grade in patients affected by PDAC	Radiogenomics	Retrospective	CT	1452	The radiomics signature obtained an AUC of 0.961, 0.910 and 0.770, respectively, for training dataset, testing dataset and external validation dataset.

(Continued)

Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Zhang *et al.* (China)[61]	117	To develop and validate a radiomics-based formula for the preoperative prediction of POPF in patients undergoing pancreaticoduodenectomy	Risk stratification	Retrospective	CT	1219	A novel radiomics-based formula was developed and validated for predicting POPF in patients who underwent pancreaticoduodenectomy.
Li *et al.* (China)[62]	159	To develop a computational model integrating clinical data and imaging features extracted from CECT images to predict LN metastasis in patients with PDAC	Risk stratification	Retrospective	CT	2041	A noninvasive radiomics signature, extracted from CECT images, can be conveniently used to predict preoperative LN metastasis in patients with PDAC.
Tang *et al.* (China)[63]	303	To develop a preoperative radiomic nomogram to help identify patients with increased risk of ER	Risk stratification	Retrospective	MRI	427	The radiomic nomogram can effectively evaluate ER risks in patients with resectable PC preoperatively.
Xie *et al.* (China)[64]	220	To identify a CT-based radiomics nomogram for survival prediction in patients with resected PDAC	Risk stratification	Retrospective	CT	330	Rad-score was an independent prognostic factor in PDAC patients.
Zhang *et al.* (Canada)[65]	520 (422 pz NSCLC)	Using transfer learning, a CNN-based survival model was built and tested on preoperative CT images of resectable PDAC patients.	Risk stratification	Retrospective	CT	1428	The proposed CNN-based survival model outperforms traditional CPH-based radiomics and transfer learning pipelines in PDAC prognosis.
Bian *et al.* (China)[66]	225	To explore the relationship between the arterial rad-score and LN metastasis in PDAC	Risk stratification	Retrospective	CT	1029	The arterial rad-score is independently and positively associated with the risk of LN metastasis in PDAC.
Bian *et al.* (China)[67]	181	To identify the relationship between a portal rad-score and SMV resection margin and to evaluate the diagnostic performance in patients with pancreatic head cancer	Risk stratification	Retrospective	CT	1029	The portal rad-score is significantly associated with the pathologic SMV resection margin, and it can accurately and noninvasively predict the SMV resection margin in patients with PC.

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Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Khalvati *et al.* (Canada)[68]	98	To establish the prognostic value in terms of OS of CT-based radiomic features contoured by two human readers in patients affected by PDAC	Risk stratification	Retrospective	CT	410	The radiomic features predictive role was confirmed (hazard ratio = 1.56, $p = 0.05$ and hazard ratio = 1.35, $p = 0.022$ for the first and the second reader, respectively).
Hui (China)[69]	86	To predict, using preoperative CT radiomics, the resection margin after pancreaticoduodenectomy for pancreatic head PDAC	Risk stratification	Retrospective	CT	n.a.	The model obtained an AUC of 0.8614 in predicting margin status.
Mapelli *et al.* (Italy)[70]	61	To predict clinical outcomes and tumour aggressiveness in patients affected by pancreatic neuroendocrine neoplasms using Ga-DOTATOC and fluorine-18-fluorodeoxyglucose PET	Risk stratification	Retrospective	PET-CT	9	Specific texture features could noninvasively predict specific tumour characteristics and patients' outcomes.
Mori *et al.* (Italy)[71]	176	To predict distant relapse FS in patients with locally advanced PDAC who underwent radiochemotherapy	Risk stratification	Retrospective	PET-CT	198	Distant relapse FS could be predicted by a PET-based radiomics model, p-value of 0.0005 and 0.03 for the training and the internal validation dataset, respectively.
Gao *et al.* (China)[72]	172	To build a radiomics-based nomogram to predict the risk of LN metastasis	Risk stratification	Retrospective	CT	396	The nomogram performances were AUC = 0.92 and AUC = 0.95 for training and internal validation cohort, respectively.
Toyama *et al.* (Japan)[73]	161	To evaluate the role of PET-based radiomics with machine learning in the prediction of prognosis in patients with PC	Risk stratification	Retrospective	PET-CT	42	It is possible to define patients' risk category according to the radiomics feature.
Liu *et al.* (China)[74]	85	To develop a model able to predict preoperatively LN status in resectable PDAC	Risk stratification	Retrospective	CT	1124	The proposed model achieved an AUC of 0.841.

(Continued)

Table 1. (Continued)

First author (country)	No. of patients	Objectives	Cluster area	Study design	Imaging modality	No. of features	Conclusions
Salinas-Miranda *et al.* (Canada)[75]	108	To validate two previously published radiomic features as predictive of OS and time to progression	Risk stratification	Retrospective	CT	2	The predictive role was confirmed (hazard ratio of 1.27 and 1.25, p-value of 0.039 and 0.047, respectively).
Chen *et al.* (China)[76]	146	To develop a radiomics signature for predicting portal vein-superior mesenteric vein involvement in patients affected by PDAC	Risk stratification	Retrospective	CT	869	The radiomics signature achieved an AUC of 0.848 in the validation cohort.
Zaid *et al.* (USA)[77]	207	To evaluate if a quantitative score of CT contrast enhancement is comparable to previously published qualitative classification of patients affected by PDAC	Risk stratification	Retrospective	CT	1	This study showed that quantitative analysis is predictive of qualitative one and could be correlated to patients' outcomes.
Zhou *et al.* (China)[78]	106	To develop a model to select appropriate candidates for irradiation stent placement among patients with UPC-MBO	Risk stratification	Retrospective	CT	620	The radiomics-based model had good performance for RFS prediction in patients with UPC-MBO who received an irradiation stent. Patients with slow progression should consider undergoing irradiation stent placement for a longer RFS.

18F-FDG-PET/CT, 18 F-fluorodeoxyglucose positron emission tomography/computed tomography; ADC, apparent diffusion coefficient; ALT, alternative lengthening of telomeres; CECT, contrast-enhanced computed tomography; CNN, convolutional neural network; CPH, Cox proportional hazard model; CT, computed tomography; DRFs, delta-radiomic features; DWI, diffusion-weighted imaging; ER, early recurrence; LC, local control; LN, lymph node; ML, machine learning; MRI, magnetic resonance imaging; NF-pNET, nonfunctional neuroendocrine tumours; OS, overall survival; panNEN, pancreatic neuroendocrine neoplasms; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumours; POPF, postoperative pancreatic fistula; rad-score, radiomics score; RF, radiomic features; RFS, restenosis-free survival; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SMV, superior mesenteric vein; UPC-MBO, unresectable pancreatic cancer with malignant biliary obstruction.

Figure 2. Example of clinical implementation of a delta radiomic model during a stereotactic radiotherapy treatment prescribed in five fractions. Before the start of the treatment, a radiomic model able to predict the LC 1 year from the end to the treatment was trained and tested on a retrospective cohort of patients. The model was based on the radiomic analysis of the MR images acquired during simulation and during fractions 1 and 2. Using the radiomic model, the RO can have a prediction of 1 year LC at the end of the fraction 2, so having the possibility to modify the radiation treatment for the remaining three fractions, increasing the dose or moving towards alternative approaches.
MR, magnetic resonance.

has proven to be a promising approach in terms of treatment quality and outcomes.[79]

Radiation therapy (RT) can play a role in all possible scenarios, being particularly relevant in reducing the risk of relapse of resected cancer (adjuvant setting) and in pursuing LC in locally advanced disease (definitive setting).

Chemotherapy is also part of the management in all stages, and is administered in association with other treatment modalities (neoadjuvant, adjuvant therapy) or as a main part of the treatment for metastatic disease.

An important role to improve diagnostic and therapeutic options for PC patients is represented by the innovative approach of personalization through risk stratification, aiming to better define patients risk category and choose therapeutic patterns accordingly.[80,81]

Patients' stratification is mainly performed based on the genotype, but the lack of a convergency in genomics models seems to reveal that the understanding of biological and clinical heterogeneity of PC is still far from completely understood.[82,83] Recently, advances in imaging with the possibility of combining endoscopic modalities with image fusion techniques have provided new ways of approaching the diagnosis and stratification of PC.[84–86]

As part of an omics-guided care pathway, the integration of these modalities with artificial intelligence and deep-learning methods would seem to be a compelling prospect for pursuing personalized care in a highly heterogeneous disease.[87–89] In this framework, radiomics is a promising method to be investigated that could provide more information about PC patients and its future integration in multiomics clinical support systems will allow more personalized and efficacious cancer care.

Author contributions

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