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CT RADIOMICS AND SERUM CA19-9 FOR RESECTABILITY AND SURVIVAL IN PANCREATIC DUCTAL ADENOCARCINOMA: A SYSTEMATIC REVIEW

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) has dismal outcomes, and preoperative tools that refine resectability and survival estimates are urgently needed. Radiomics converts routine CT into quantitative features that capture tumor heterogeneity, while serum CA19-9 is the most widely used biomarker in PDAC. We systematically synthesized original studies evaluating CT-based radiomics, alone or combined with CA19-9, for predicting resectability, early recurrence, or overall survival (OS) in PDAC. Following PRISMA principles, nine original radiomics studies were included. Across cohorts (n=68–326), radiomics improved prognostication beyond clinicopathologic models: for survival, radiomics increased C-index versus clinical factors (from 0.68 to 0.74), and radiomics nomograms frequently outperformed TNM staging. Vessel-centric radiomics yielded high resectability discrimination (AUC =0.92; external sensitivity/specificity up to 100%/88%), and models predicted resectability after neoadjuvant therapy in locally advanced disease (AUC =0.85–0.94). Integrating CA19-9 with radiomics added value: preoperative nomograms (radiomics + CA19-9) exceeded CA19-9 alone, and delta-radiomics combined with CA19-9 achieved strong performance (c-index =0.87) for treatment response and survival. Limitations include retrospective designs, heterogeneous CT protocols, variable segmentation/reproducibility reporting, and scarce multi-center validation. Overall, CT radiomics, especially when combined with CA19-9, shows consistent promise for preoperative risk-stratification in PDAC and warrants prospective, standardized, multi-centric validation.

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Keywords: Pancreatic Ductal Adenocarcinoma; CT; Radiomics; CA19-9; Resectability; Survival; Early Recurrence; Nomogram.

INTRODUCTION

Only a minority of patients with PDAC are candidates for upfront resection, and many recur early despite curative-intent surgery. Contemporary preoperative risk-stratification increasingly considers “biologic resectability,” incorporating serum CA19-9, nodal status, and metabolic imaging alongside anatomic criteria to identify patients who might benefit from neoadjuvant therapy despite technically resectable disease [1]. Several groups have proposed preoperative risk scores combining CT findings, FDG-PET/CT, and CA19-9 to predict recurrence-free survival after surgery, highlighting that easily accessible biomarkers can enrich decision-making before the operating room [1]. Yet CA19-9 has important caveats: a meta-analysis concluded it is not reliable as a stand-alone determinant of surgical resectability and should not be used in isolation to deny or proceed with surgery [2].

Perioperative and postoperative CA19-9 dynamics, however, are consistently prognostic. In resected PDAC, lower preoperative CA19-9 correlates with earlier stage, and postoperative declines and normalization are independent predictors of improved survival [3]. A prospective correlative analysis from RTOG 9704 definitively validated the prognostic importance of postresection CA19-9: thresholds such as 90–180 U/mL stratified overall survival even after multi-variable adjustment [4]. Subsequent analyses from the same trial linked elevated postresection CA19-9 to higher risks of both local/regional and distant failure, underscoring its utility for recurrence risk profiling and possibly tailoring adjuvant strategies [5].

While CA19-9 provides a low-cost biologic signal, it does not capture intratumoral phenotypes or perivascular relationships that influence resectability and relapse. CT radiomics extracts high-throughput texture and shape descriptors from standard imaging and can quantitatively characterize tumor heterogeneity. This review focuses on CT radiomics for resectability, early recurrence, and survival in PDAC and examines how combining radiomics with CA19-9 might yield complementary information. We synthesize original radiomics studies and contextualize findings against clinical CA19-9 evidence to outline translational opportunities for preoperative decision-making in PDAC [1–5].

METHODS

Protocol and Question. We conducted a systematic review to answer: among adults with PDAC, how accurately do CT-based radiomics models, alone or integrated with CA19-9, predict (a) resectability (technical or realized), (b) early recurrence after surgery, and/or (c) survival outcomes?

Eligibility Criteria. Inclusion: original human studies of PDAC using computed tomography (contrast-enhanced multiphase or pancreatic protocol) with handcrafted radiomics and/or radiomics-derived signatures; endpoints including resectability (preoperative assessment or post-neoadjuvant conversion), early recurrence (typically

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≤12 months), disease-free survival, or overall survival; and clear reporting of model performance (AUC, C-index, hazard ratios) with internal and/or external validation. We included studies that integrated serum CA19-9 with radiomics in preoperative models or evaluated CA19-9 alongside radiomics-based response prediction. Exclusion: non-radiomics imaging, MRI-only radiomics, AI models without feature transparency if radiomics outcomes were not reported, pediatric populations, review/editorial pieces, and non-PDAC cohorts.

Data Items. We extracted: study design, cohort size and setting, imaging phase(s), segmentation approach (2D/3D; tumor/vessel regions), number and type of features, feature reduction/modeling method (LASSO, random survival forests), inclusion of CA19-9, endpoint definitions, validation strategy (internal/external), and reported performance metrics (AUC/C-index/HR, calibration, decision-curve analysis).

Risk of Bias and Applicability. We qualitatively assessed: retrospective vs. prospective design; sample size; segmentation reproducibility; feature harmonization; risk of overfitting (events per variable, penalization, nested CV); blinding to outcomes; handling of missing data; and presence/quality of external validation. Heterogeneity of CT acquisition, preprocessing, feature sets, and clinical endpoints precluded meta-analysis; we therefore provide a structured narrative synthesis with comparative tables.

RESULTS

Study Overview

Nine original CT-radiomics studies (2019–2024) met criteria. Cohorts ranged from 68 to 326 patients, spanning resectable and locally advanced settings. Four studies modeled OS after resection using tumor-centric radiomics (with/without clinicopathologic covariates) [6–9]; two focused on early recurrence after surgery [10,11]; and three evaluated resectability, including vessel-centric radiomics and conversion to resection after neoadjuvant therapy [12–14]. Two studies explicitly integrated CA19-9 into radiomics-based preoperative models or delta-radiomics response prediction [7,9].

Survival Prediction After Surgery

In a single-center retrospective cohort (n=153), Park et al. extracted 3D tumor features and used random survival forests: adding radiomics to clinical variables improved C-index from 0.68 to 0.74 for OS prediction, and a 10-feature panel separated low- vs high-risk groups with =82% accuracy [6]. Khalvati et al. analyzed two independent resection cohorts (n=30 training; n=68 validation) with PyRadiomics features; a two-feature signature (sum entropy, cluster tendency) was reproducibly prognostic across readers and cohorts (HR =1.35–1.56) [7]. Two nomogram studies showed radiomics outperforms or augments conventional staging: Xie et al. (n=220) found a radiomics nomogram outperformed TNM and a clinical model for DFS/OS with good calibration and clinical utility; the Rad-score remained independently prognostic [8]. Cen et al. (n=326) built clinical-radiomics nomograms to predict histological grade and to forecast OS after radical resection; the survival nomogram achieved an integrated AUC =0.80 and stratified

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outcomes by predicted grade/risk [9]. Collectively, these data indicate that CT radiomics adds discriminative signal for survival beyond standard factors and staging.

Early Recurrence After Surgery

A multicenter model by Lee et al. (n=190; external test n=40) compared radiomics-only, clinical-radiologic (CR), and combined (CRR) models to predict recurrence within 12 months after pancreatectomy. CRR outperformed radiomics alone (AUC 0.83 vs 0.69 externally) and yielded more balanced sensitivity/specificity than CR alone, suggesting complementary value of radiomics for early recurrence risk [10]. Cen et al. also linked radiomics-predicted grade to differential survival, with high-grade signatures associating with worse outcomes, consistent with early recurrence risk phenotypes [9].

Resectability (Baseline and Post-Neoadjuvant)

Resectability hinges on tumor–vessel interfaces. Litjens et al. (chemo-naïve PDAC head) explicitly segmented both tumor and adjacent arteries/veins and derived handcrafted vessel features that best predicted surgical resectability, achieving AUC =0.92 (train) and test sensitivity/specificity of 100%/88%; tumor-only models underperformed [12]. In the neoadjuvant setting, Rossi et al. (LAPC) extracted 1,655 planning-CT features and built a LASSO model that predicted conversion to resection with validated AUC =0.85–0.86 across resampling; a four-feature final model reached AUC =0.94 on the full dataset, supporting utility for surgical triage after therapy [13].

Integration With CA19-9

Two studies provided direct integration with CA19-9. Wang et al. (n=184 + external n=45) combined a LASSO-derived Rad-score with preoperative CA19-9 to construct a prognostic nomogram; the combined model's C-index (=0.69–0.71) exceeded CA19-9 or AJCC stage alone across internal and external validations, with favorable calibration/decision-curve profiles [11]. Nasief et al. (n=24, daily CT during chemoradiation) showed delta-radiomics features correlated with CA19-9 dynamics; combining DRFs with CA19-9 increased c-index from 0.57 (either alone) to 0.87 for response/survival modeling, and decreases in CA19-9 and DRFs independently predicted improved survival on multivariable analysis [14]. These results demonstrate biologic complementarity and support multimodal preoperative risk-tools.

Risk of Bias and Generalizability

Most studies were retrospective single centers with modest sample sizes; external validation was present in several (Lee, Wang, Litjens) but not universal. Segmentation reproducibility and feature harmonization varied; only some addressed inter-reader effects or scanner variability. Overfitting mitigation (penalization, nested cross-validation) was common but not uniform. While endpoints varied (OS, DFS, early recurrence, resectability), the directionality was consistent: radiomics adds signal beyond clinical variables, and vessel-aware features are crucial for resectability assessments.

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Table 1: Study characteristics of included CT-radiomics investigations

Study (year)	Setting / N	Imaging & ROI	Features / Model	Validation	Primary endpoint(s)
Park et al. 2021 [6]	Resected PDAC, n=153	Pancreatic-protocol CT; 3D tumor	478 tumor + pancreas boundary; RSF	Internal (split)	OS (C-index gain with radiomics)
Khalvati et al. 2019 [7]	Resected PDAC, n=30/68	Pre-op CT; tumor	PyRadiomics; Cox (2-feature signature)	External reader & cohort	OS (HR per signature)
Xie et al. 2020 [8]	Resected PDAC, n=220	CT; tumor	300 features; LASSO; nomogram	Internal (train/val)	DFS/OS; nomogram vs TNM
Cen et al. 2023 [9]	Resected PDAC, n=326	CECT; tumor	Radiomics grade; clinical-radiomics nomograms	External grade test	Grade prediction; OS nomogram
Lee et al. 2024 [10]	Resected PDAC, n=190 (+40)	CECT; tumor	Radiomics vs CR vs CRR; LR	External test	Early recurrence ≤12 mo (AUC)
Wang et al. 2022 [11]	Resected PDAC, n=184 (+45)	CECT; tumor	Rad-score + CA19-9; nomogram	Internal & external	OS (C-index vs CA19-9 / AJCC)
Litjens et al. 2023 [12]	Chemo-naïve PDAC head, n=101	CECT; tumor + arteries/veins	Vessel & tumor features; LASSO	Internal + small test	Resectability (AUC; sens/spec)
Rossi et al. 2022 [13]	LAPC post-NAT, n=71	Planning CT; tumor	1,655 features; LASSO	Repeated splits	Conversion to resection (AUC)
Nasief et al. 2020 [14]	CRT cohort, n=24	Daily CT; pancreas head region	Delta-radiomics + CA19-9	Internal	Response; survival (c-index)

Table 2: Key performance metrics

Study	Endpoint	Key results
Park 2021 [6]	OS	Clinical C-index 0.68 + radiomics 0.74; 10-feature panel 82% accuracy (high vs low risk).
Khalvati 2019 [7]	OS	Two-feature signature robust across readers/cohorts; HR=1.35–1.56; independent of clinical factors.
Xie 2020 [8]	DFS/OS	Radiomics nomogram outperformed TNM and clinical model; good calibration/DCA.
Cen 2023 [9]	Grade / OS	HGrad AUC=0.75–0.76 (test/validation); OS nomogram integrated AUC=0.80; risk stratification significant.
Lee 2024 [10]	Early recurrence	External AUC: CRR 0.83 vs radiomics 0.69; CRR sensitivity/specificity 0.65/0.87 (balanced vs CR).
Wang 2022 [11]	OS	Nomogram C-index =0.69–0.71; exceeded CA19-9 alone (=0.56–0.61) and AJCC stage; validated externally.
Litjens 2023 [12]	Resectability	Vessel-only model AUC=0.92; test sens/spec 100%/88%; tumor-only AUC=0.76.
Rossi 2022 [13]	Resectability post-NAT	Validated AUC =0.85–0.86; final 4-feature model AUC =0.94 on full set.
Nasief 2020 [14]	Response/Survival	CA19-9+DRFs c-index 0.87 vs 0.57 (either alone); decreases in both predicted better survival.

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DISCUSSION

This synthesis shows that CT radiomics improves preoperative and perioperative risk-stratification in PDAC and that integrating CA19-9 often augments model performance. From a clinical vantage point, preoperative risk scores that include CA19-9 and imaging-derived variables can identify high-risk patients who might benefit from neoadjuvant therapy despite anatomically resectable disease, an approach aligned with “biologic resectability” paradigms and supported by risk-score studies combining CA19-9, CT, and FDG-PET/CT [1]. At the same time, CA19-9 should not be used in isolation to decide resectability; a meta-analysis labeled it only a “fair” marker with considerable heterogeneity and explicitly cautioned against single-parameter surgical decisions [2].

Perioperative CA19-9 dynamics are strongly prognostic. Lower preoperative levels associate with earlier stage, and postoperative declines/normalization independently predict survival [3]. Prospective correlative data from RTOG 9704 validated postresection CA19-9 thresholds (90–180 U/mL) as powerful survival stratifiers [4], and secondary analyses linked elevated postresection CA19-9 to higher local/regional and distant failure risks, information that guide adjuvant intensification or surveillance [5]. Pre- and post-neoadjuvant CA19-9 also carry decision weight: after FOLFIRINOX, post-treatment thresholds around =92 U/mL predicted the likelihood of completing resection and conferred survival differences, supporting CA19-9 as part of response evaluation and surgical triage [6]. For patients with early-stage disease, preoperative CA19-9 cutoffs (=70 U/mL) correlated with early recurrence within six months after surgery, emphasizing the need for intensified systemic strategies in biomarker-high phenotypes [7]. Pooled analyses further support presurgical CA19-9 as a predictor of overall survival and failure patterns, advocating stratification by CA19-9 in trials and practice [8].

Against this biomarker backdrop, radiomics adds spatial phenotyping. Tumor-centric models reproducibly improved OS prediction beyond clinical variables and TNM staging [6–9,8], while early-recurrence models benefited when radiomics was combined with clinical-radiologic features [10]. For resectability, vessel-centric radiomics that explicitly quantify tumor–vessel relationships achieved excellent discrimination and matched multidisciplinary team performance, a particularly promising direction for avoiding futile laparotomies [12]. Importantly, integrating CA19-9 with radiomics generally outperformed either modality alone, whether in preoperative nomograms [11] or in delta-radiomics during therapy [14], highlighting complementary biologic and phenotypic information.

Limitations in studies include retrospective designs, modest sample sizes, heterogeneous CT acquisition and preprocessing, incomplete reporting of segmentation repeatability and feature harmonization, and sparse multi-center external validation. Future work should prioritize prospective, multi-institutional designs with standardized radiomics pipelines (IBSI compliance), robust feature stability testing, transparent modeling (TRIPOD), risk-of-bias assessment (PROBAST), and pre-specified integration of CA19-9 and clinically accepted risk factors. Harmonized endpoints (RECIST-independent resectability definitions, uniform early-recurrence windows) will facilitate evidence aggregation and meta-analysis.

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CONCLUSION

CT radiomics consistently improves prediction of survival, early recurrence, and resectability in PDAC beyond standard clinicopathologic models. Models that quantify tumor–vessel interfaces are particularly informative for resectability, and integrating CA19-9, preoperatively or as delta measures, adds complementary biologic signal, yielding stronger, more clinically useful nomograms. Given current heterogeneity and predominantly retrospective designs, rigorous multi-center prospective validation and standardized radiomics workflows are the critical next steps before routine clinical adoption. In the interim, multidisciplinary decisions were enhanced by combining CA19-9 with vetted radiomics tools in appropriate patients.

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