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Original Research

CT texture analysis and delta radiomics in predicting R0 resection after preoperative chemotherapy in resectable pancreatic ductal adenocarcinoma

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ABSTRACT

Purpose: To evaluate the predictive performance of CT-based radiomic delta-features for predicting R0 resection in resectable pancreatic ductal adenocarcinoma (PDAC) following NALIRIFOX neoadjuvant chemotherapy.
Materials and methods: This prospective study included 107 consecutive patients with resectable PDAC treated with NALIRIFOX. After applying strict selection criteria for imaging quality and timing, 55 patients underwent comprehensive radiomic analysis. Radiomic features were systematically extracted from pre-treatment and post-treatment CT scans, with delta-features calculated as percentage variations between timepoints. Features demonstrating inter-observer intraclass correlation coefficient greater than 0.90 in both arterial and venous phases were selected. Following correlation analysis to remove redundant features (absolute correlation greater than 0.80), three predictive models were developed based on pre-treatment, post-treatment, and delta-features. Model validation was performed using 1000-replication bootstrap methodology.
Results: Surgical resectability was achieved in 80.0% of cases, with R0 resection margins in 56.8% of operated patients. Seven radiomic features met reproducibility criteria: VolumeNum, Sphericity, Entropy, Contrast, Energy, SmallAreaEmphasis, and RunLengthNonUniformity. Energy was excluded due to high correlation with Contrast, resulting in six features. The delta-features model demonstrated superior performance (AUC=0.85, 95% CI: 0.78–0.91) compared to pre-treatment (AUC=0.76, $p = 0.008$) and post-treatment models (AUC=0.82, $p = 0.042$) for predicting R0 margins. Δ-VolumeNum emerged as the strongest independent predictor (OR=3.14, 95% CI: 1.89–5.21, $p < 0.001$), followed by Δ-Entropy (OR=2.45, 95% CI: 1.56–3.85, $p < 0.001$) and Δ-Contrast (OR=1.92, 95% CI: 1.24–2.97, $p = 0.003$).
Conclusion: Radiomic delta-features analysis provides a robust and non-invasive tool for predicting R0 resection following NALIRIFOX therapy, with dynamic measurements significantly outperforming static assessments in resectable PDAC.

Key Points:

1.Delta-radiomics features (volume, entropy, and contrast changes) predicted R0 margins with AUC of 0.85, significantly outperforming pre-treatment (AUC=0.76, $p = 0.008$) and post-treatment models (AUC=0.82, $p = 0.042$) in patients with resectable PDAC treated with NALIRIFOX.

2.Volume reduction greater than 50% was observed in 72% of patients achieving R0 resection versus only 8% with low reduction, with Δ-VolumeNum demonstrating the strongest predictive value (OR=3.14, 95% CI: 1.89–5.21, $p < 0.001$) in multivariate analysis.

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3.The predictive nomogram incorporating Δ-VolumeNum, Δ-Entropy, and Δ-Contrast showed excellent calibration (slope=0.98) and maximum net benefit of 0.45 at threshold probability of 0.4, with superior performance in tumors measuring 3 cm or smaller.

Introduction

Surgical resection is the only potentially curative treatment for pancreatic ductal adenocarcinoma (PDAC); R0 resection is associated with improved overall survival (OS) compared to R1 [1]. Nevertheless, up to 80% of patients develop disease recurrence within 2 years after surgery, highlighting the aggressive biological behavior of this malignancy [2]. Neoadjuvant therapy is the standard treatment for initially unresectable PDAC. The high recurrence rate in PDAC has driven increasing interest in applying preoperative treatment strategies, which have the potential to improve R0 resection rates and treat micro-metastatic disease, also in primarily resectable tumors [3,4]. It is well known that imaging response criteria based on tumor size and tumor-to-vessel interface have significant limitations in assessing treatment response in PDAC, and imaging modalities tend to overestimate tumor resectability [5]; the most important reason for that is related to tumor histology: PDAC is composed of extensive fibrous stroma with few neoplastic cells; when effective, chemotherapy decreases or eliminates tumor cells, having no or poor effect on tumor fibrosis [6]. This highlights the need for advanced imaging analysis approaches when assessing PDAC response to chemotherapy. Radiomics extracts quantitative features from medical images and offers a promising approach to capture subtle tissue features that are not visible to the human eye [7,8]. Quantitative features extracted through radiomics have the potential to be used as noninvasive biomarkers of treatment response. Delta radiomics is the process of analyzing changes in radiomic features from pre- to post-treatment imaging and has emerged as a valuable tool for response assessment [9]; this can be of relevance in PDAC, where conventional criteria often fail to capture treatment-induced changes and do not predict the chance of R0 resection [10]. The aim of this study was to evaluate the effectiveness of computed tomography (CT) radiomic and delta-radiomic features in predicting R0 resection in patients with resectable PDAC who received preoperative chemotherapy.

Materials and methods

Patients potentially eligible for this study were part of a prospective study approved by the ethics committee of the Azienda Ospedaliera Universitaria Integrata di Verona (approval No 2610-CESC). All patients provided written informed consent. The study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki of 1975, as revised in 1983 (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/doh-oct1983/ date last accessed 18/04/2025). This study is compliant with Regulation (European Union) 2016/679 of the European Parliament and of the Council of April 27, 2016, and according to Italian law (resolution March 1, 2012, Gazzetta Ufficiale No 72 of March 26, 2012) on the use and protection of personal data. Raw data for the dataset is not publicly available to preserve individuals' privacy under the European General Data Protection Regulation.

Study population

Between May 2018 and May 2022, 107 patients with histologically confirmed and surgically resectable PDAC according to the NCCN criteria [11] were enrolled in a prospective phase II trial that assessed the safety and the activity of the NALIRIFOX perioperative treatment [4]. The inclusion criteria of the present study were: a) surgical exploration after preoperative treatment; b) availability of pre- and post-treatment contrast-enhanced CT examinations. The exclusion criteria were a) post-treatment CT performed ≥4 months after the start of preoperative treatment; b) inconsistent study protocol between pre- and post-treatment CT; c) poor tumor visibility in post-treatment CT. Based on a priori sample size calculation, it was determined that a minimum of 55 patients would be required to detect a clinically meaningful difference (ΔAUC≥0.10) between predictive models with 85% power at an alpha level of 0.05. This sample size accounted for potential variations in effect size (±20%) and possible drop-out rates up to 15%.

CT acquisition protocol

All CT examinations were performed on a 64-slice scanner (Brilliance 64, Philips; Eindhoven, The Netherlands). The scan protocol varied upon the clinical setting (baseline or post-treatment CT). For this study, only patients having late arterial and portal phase scans in both pre- and post-treatment CT were included. For post-contrast imaging, patients received intravenously a weight-based amount of iodinated contrast medium (Ultravist 370, 1.5 mL/kg). Timing for post-contrast scans was determined by bolus tracking technique. Late arterial phase imaging was acquired 15 s after reaching the aortic threshold enhancement of 150 HU, while portal phase images were acquired 65–75 s after contrast injection. Technical parameters were: 120 kV, 125–250 mAs, pitch=1, 2 mm reconstruction thickness.

Radiomic workflow

Two radiologists with 4 and 3 years of experience independently performed tumor segmentation on late arterial and portal phase images of pre- and post-treatment CT images using an open-source software (3D Slicer, ver. 5.6.2; https://www.slicer.org/) [12]. Segmentations were reviewed by a senior radiologist with 10 years of experience in pancreatic imaging. 107 radiomic features were extracted using the PyRadiomics library, ver. 3.0 (https://pyradiomics.readthedocs.io/en/latest/) [13], following image standardization according to the Image Biomarker Standardization Initiative (IBSI) guidelines. Image standardization included intensity normalization (μ=300, σ=100), isotropic resampling to 1 × 1 × 1 mm, and discretization to 64 gray levels. Inter-observer reproducibility was assessed by calculating the intraclass correlation coefficient (ICC) for each feature. Features with ICC ≥0.90 in both late arterial and portal phases were retained for further analysis. Segmentation reproducibility was quantitatively evaluated using the Dice coefficient (DSC) and Hausdorff Distance (HD) between the segmentations of both operators. Correlation analysis was performed to evaluate redundancy between features; features with high correlation were excluded from further analysis. For the selected features, delta-features were calculated as the percentage change between pre- and post-treatment values using the formula

$$\text{Delta}-\text{feature}\ (\%) = [(\text{post}-\text{treatment value} - - \text{pre}-\text{treatment value}) \ / \ \text{pre}-\text{treatment value}] \times 100$$

Statistical analysis

The collection and management of clinical data were centralized through REDCap (Research Electronic Data Capture). After feature selection and reduction, as described above, LASSO regression with 10-fold cross-validation was conducted to identify the optimal subset of predictors for R0 resection while avoiding overfitting. Three logistic regression models were developed: a) model A, based only on pre-treatment features; b) model B, using post-treatment features; and c) model C, based on delta-features. The performance of each model was evaluated through receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) as the primary metric. Comparisons between models were performed using DeLong's test for correlated

Table 1
Demographic and clinical characteristics of the study population.

Characteristic	Value
Sex	
Male	30 (54.5%)
Female	25 (45.5%)
Age (ys)	65 (45–78)
Surgical resection	
No	11 (20%)
Yes	44 (80%)
Margin status	
R0	25 (56.8%)
R1	19 (43.2%)

Categorical variables are reported as the number of cases (percentage); numerical variables are reported as the median (range). Legend: ys, years.

ROC curves, with p-values adjusted for multiple testing using the Bonferroni-Holm method. To assess the clinical usefulness of the predictive models, decision curve analysis (DCA) was conducted, quantifying the net benefit (true positives minus weighted false positives) across various threshold probabilities for clinical decision-making. A predictive nomogram incorporating the most significant delta-features for R0 prediction was developed, with "most significant" defined as features demonstrating statistical significance ($p < 0.05$) after Bonferroni-Holm correction in multivariate analysis and selected through LASSO regression with cross-validation. Model calibration was assessed using the Hosmer-Lemeshow test and calibration plots. The reproducibility (ICC) and collinearity filters, being outcome-independent, were applied once to the complete dataset. LASSO selection was likewise performed once on the development dataset; bootstrap resampling with 1000 replications was then employed to obtain internally validated estimates of model performance and to construct 95% confidence intervals for AUC values. Because the selection step was not re-executed within each bootstrap replicate, the resampling was not fully nested. Exploratory, secondary subgroup analyses were conducted to assess model performance across different tumor sizes (≤3 cm vs. >3 cm), CT phases (arterial vs. venous), tumor locations (head vs. body-tail), and patient sex; p-values were adjusted using the Bonferroni-Holm method. Statistical analysis was performed using R (ver. 4.1.2) and adhered to TRIPOD guidelines.

Results

Study population

86 patients who received preoperative NALIRIFOX treatment and surgical exploration with available pre- and post-operative CT examinations were retrospectively identified. 31 patients were excluded owing to the following reasons: post-treatment CT performed ≥4 months after the start of preoperative treatment (n = 14), inconsistent study protocol between pre- and post-treatment CT (n = 9), and poor tumor visibility in post-treatment CT (n = 8). The final study cohort comprised 55 patients (30 males, 25 females), with a median age of 65 years (range, 45–78 years). The demographic and clinical characteristics of the study population are presented in Table 1. Surgical resection was achieved in 44/55 cases (80%); among them, 25 patients (56.8%) had R0 resection.

Feature selection and reduction

7 radiomic features had ICC ≥0.90 in both late arterial and portal phases: VolumeNum, Sphericity, Entropy, Contrast, Energy, GLSZM SmallAreaEmphasis, and GLRLM RunLengthNonUniformity. The mean DSC was 0.82±0.06 for the late arterial phase and 0.83±0.05 for the portal phase, confirming high inter-operator concordance. A threshold of $|r| \geq 0.80$ was applied to identify problematic collinearity in the correlation analysis. Energy showed a strong inverse correlation with Contrast ($r = -0.82$, $p < 0.001$) and was therefore excluded. Other statistically significant correlations were observed (VolumeNum and Entropy, $r = 0.72$, $p < 0.001$; VolumeNum and SmallAreaEmphasis, $r = -0.67$, $p < 0.001$; Contrast and Entropy, $r = 0.76$, $p < 0.001$; Entropy and SmallAreaEmphasis, $r = 0.71$, $p < 0.001$), but r values were below the collinearity threshold, and the features were retained. Other feature pairs did not show significant correlations ($p > 0.05$). Feature stability was assessed through controlled perturbations (±2 voxels), revealing coefficients of variation ranging from 2.8% to 5.4%, with morphological features showing the highest stability (mean CV 3%) and texture features showing acceptable stability (mean CV 4.9%). Fig. 1

Predictive performance for R0 resection

At LASSO regression three features were selected for model A: VolumeNum ($\beta = 0.45$, $p = 0.004$), Sphericity ($\beta = 0.32$, $p = 0.018$), and Entropy ($\beta = 0.28$, $p = 0.001$); model B included four features: VolumeNum ($\beta = 0.41$, $p = 0.002$), Entropy ($\beta = 0.35$, $p < 0.001$), Contrast ($\beta = 0.29$, $p = 0.003$), and SmallAreaEmphasis ($\beta = 0.22$, $p = 0.011$); model C retained six features, with standardized coefficients ranging from Δ-VolumeNum ($\beta = 0.68$) to Δ-RunLengthNonUniformity ($\beta = 0.17$). At pairwise comparison of ROC curves, model C demonstrated significantly higher predictive performance for R0 status (AUC= 0.85, 95% CI: 0.78–0.91) compared to models A (AUC= 0.76, 95% CI: 0.68–0.84, $p = 0.008$) and B (AUC=0.82, 95% CI: 0.74–0.89, $p = 0.042$), as shown in Fig. 2. These p-values remained significant after Bonferroni-Holm correction for multiple testing.

The bootstrap validation (1000 replications) confirmed the robustness of these findings, with minimal variability in AUC estimates (<5% across iterations). Calibration assessment using the Hosmer-Lemeshow test showed no significant deviations from ideal calibration for the delta-features model ($p = 0.82$). Decision Curve Analysis (Fig. 3) demonstrated that model C provided consistently superior net benefit throughout the clinically relevant threshold probability range (0.2–0.8). The maximum net benefit of 0.45 was achieved at a threshold probability of 0.4, substantially higher than both the pre-treatment and post-treatment models.

Delta-features were categorized into three groups based on the magnitude of change: high reduction (>75th percentile), moderate reduction (25th-75th percentile), and low reduction (<25th percentile). As shown in Table 2, specific patterns emerged for R0 outcomes. For tumor volume reduction, 72% of patients achieving R0 resection demonstrated volume reduction >50%, compared to only 8% showing low reduction. Similar patterns were observed for entropy reduction (64% high reduction in R0 patients) and contrast changes (60% high reduction in R0 patients).

Multivariate analysis identified Δ-VolumeNum as the strongest predictor of R0 resectability (OR= 3.14, 95% CI: 1.89–5.21; $p < 0.001$), followed by Δ-Entropy (OR= 2.45, 95% CI: 1.56–3.85; $p < 0.001$) and Δ-Contrast (OR=1.92, 95% CI: 1.24–2.97; $p = 0.003$).

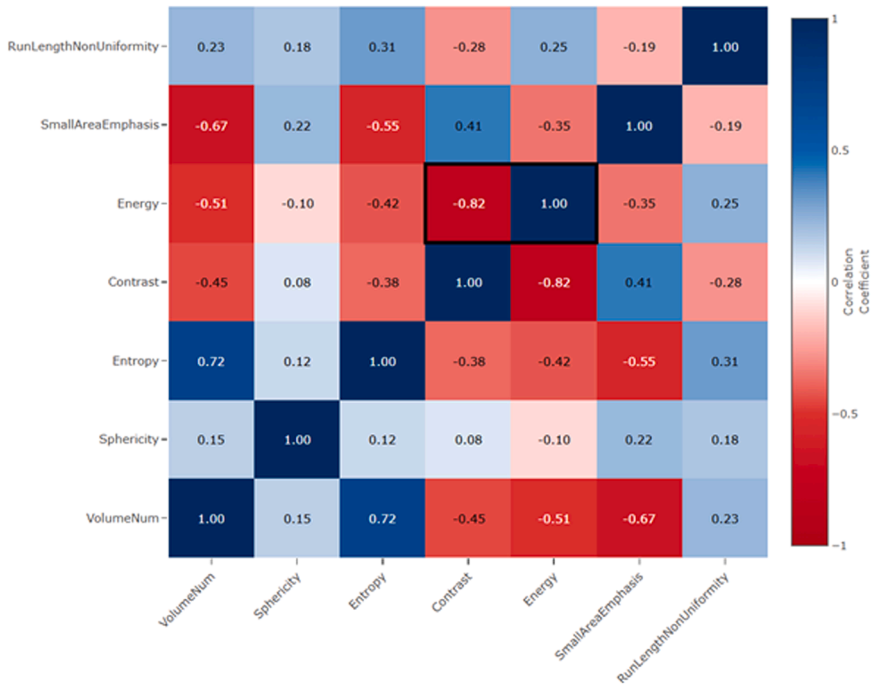

Fig. 1. Correlation matrix of selected radiomic features. Heatmap illustrating the correlations between radiomic features with ICC ≥0.90. Blue indicates positive correlations, red indicates negative correlations, with intensity reflecting correlation strength.

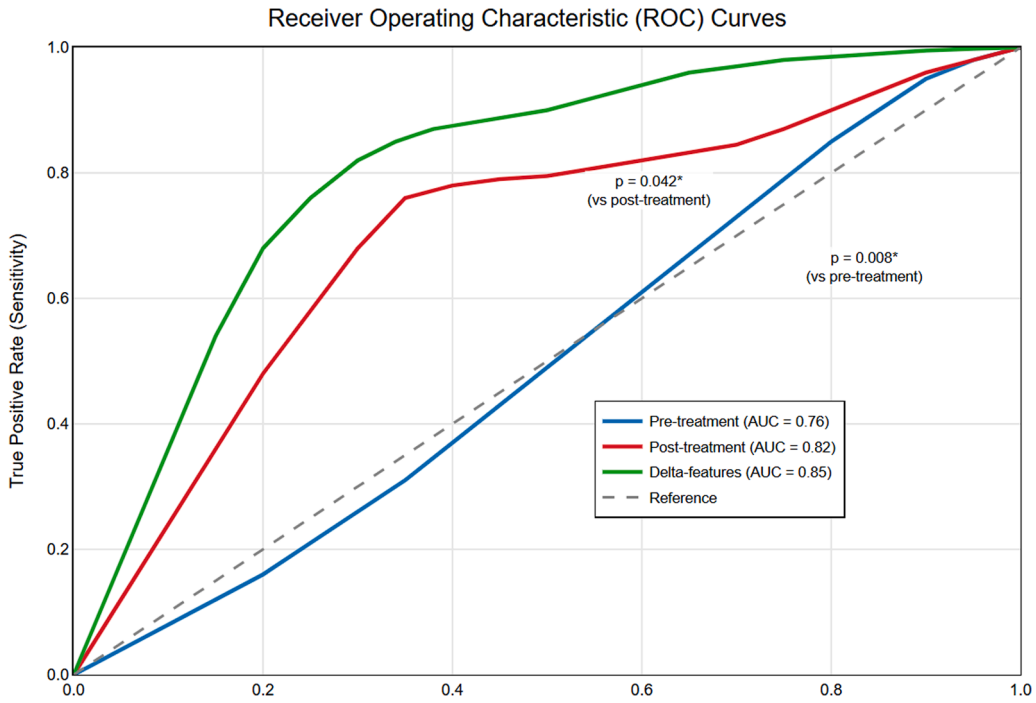

Fig. 2. ROC curve comparison for R0 prediction. Model C showed significantly better performance compared to model A (p = 0.008) and model B (p = 0.042). P-values adjusted using the Bonferroni-Holm method for multiple comparisons.

SmallAreaEmphasis (p = 0.061), Δ-Sphericity (p = 0.412), and RunLengthNonUniformity (p = 0.082) were non-significant. The forest plot of odds ratio for R0 prediction is shown in Fig. 4.

Based on these results, a nomogram incorporating the three features with statistical significance after multiple testing correction was developed (Fig. 5).

The calibration plot (Fig. 6) demonstrated excellent agreement between predicted and observed probabilities for the delta-features model (intercept=0.02, slope=0.98).

Subgroup analyses (Table 3) revealed that model C performed significantly better in tumors ≤3 cm compared to those >3 cm (AUC= 0.87 vs. 0.81; p = 0.046 after Bonferroni-Holm correction). No

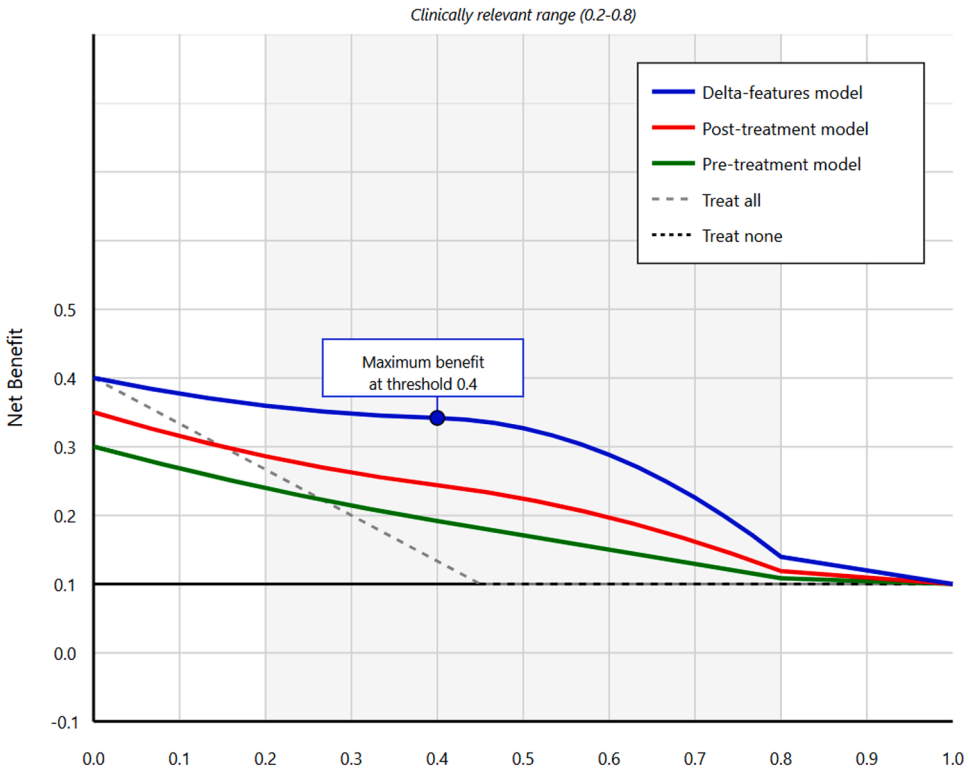

Fig. 3. Decision curve analysis. Net benefit curves across different threshold probabilities for the three predictive models. Model C (blue line) showed consistently higher net benefit in the clinically relevant threshold range (0.2–0.8), with maximum benefit of 0.45 at threshold 0.4.

Table 2
Association between delta-features reduction and R0 status.

Delta features	R0 (n = 25)	R1 (n = 19)	p-value
Δ-Volume			<0.001
>50% reduction	18 (72%)	3 (15.8%)	
30–50 reduction	5 (20%)	7 (36.8%)	
<30% reduction	2 (8%)	9 (47.4%)	
Δ-Entropy			<0.001
High reduction (>75th)	16 (64%)	4 (21.1%)	
Moderate reduction (25–75th)	7 (28%)	8 (42.1%)	
Low reduction (<25th)	2 (8%)	7 (36.8%)	
Δ-Contrast			0.002
High reduction (>75th)	15 (60%)	5 (26.3%)	
Moderate reduction (25–75th)	8 (32%)	8 (42.1%)	
Low reduction (<25th)	2 (8%)	6 (31.6%)	

Data are number of cases (percentage).

significant differences in AUC were observed between late arterial and portal phase feature (AUC= 0.86 vs. 0.83, p = 0.312), pancreatic head and body-tail tumors (AUC= 0.84 vs. 0.82, p = 0.628), and male and female patients (AUC= 0.86 vs. 0.83, p = 0.481).

Discussion

This study demonstrated that radiomic delta-features analysis may provide a robust and non-invasive approach for predicting R0 resection following preoperative therapy in resectable PDAC. The higher performance of delta-features compared to pre- and post-treatment features (AUC= 0.85 vs. 0.76 and 0.82, respectively) highlights the value of quantifying dynamic structural changes during treatment. The identification of Δ-VolumeNum as the strongest independent predictor (OR=3.14) aligns with the conventional understanding of treatment response assessment. However, the significant predictive value of Δ-Entropy (OR=2.45) and Δ-Contrast (OR=1.92) indicates that texture changes capture biological modifications not apparent through conventional metrics. This is particularly relevant given the recognized limitations of RECIST criteria in pancreatic cancer response assessment [14]. The ability to predict R0 resection is of paramount clinical importance, as achieving negative surgical margins significantly impacts overall survival in PDAC patients [1]. Traditional imaging approaches, which rely primarily on size measurements and morphological criteria, have shown limited accuracy in predicting resectability after neoadjuvant therapy [5,10]. The desmoplastic reaction characteristic of pancreatic cancer, with its extensive fibrotic stroma, often persists despite effective tumor cell elimination by chemotherapy [6]. This biological phenomenon explains why conventional imaging criteria frequently fail to capture true treatment response. Our delta-radiomics approach addresses this limitation by quantifying subtle texture changes that reflect underlying biological modifications [8,9]. The specific radiomic features identified in our analysis— GLSZM SmallAreaEmphasis and GLRLM RunLengthNonUniformity— are quantitative measures of tumor heterogeneity. SmallAreaEmphasis quantifies the distribution of small homogeneous zones within the tumor, while RunLengthNonUniformity measures the variability in consecutive pixels with the same gray level. The high reproducibility of these features (ICC ≥0.90) supports their potential clinical implementation. These texture metrics reflect spatial organization patterns within the tumor that change in response to effective chemotherapy [16]. The observed reductions in entropy and contrast in patients achieving R0 resection suggest transformation from heterogeneous viable tumor to more uniform fibrous tissue, representing a favorable treatment response pattern [15]. The observed R0 resection rate of 56.8% in our cohort, while lower than the 65.3% reported in the broader nITRO trial [4], likely reflects our strict selection criteria focusing on cases with adequate imaging for radiomic analysis. This difference underscores the importance of patient selection in radiomic studies and suggests that our cohort may represent a more challenging subset of patients. Given that long-term survival in PDAC remains disappointing even after successful resection [2], identifying patients most likely to benefit from surgical intervention is

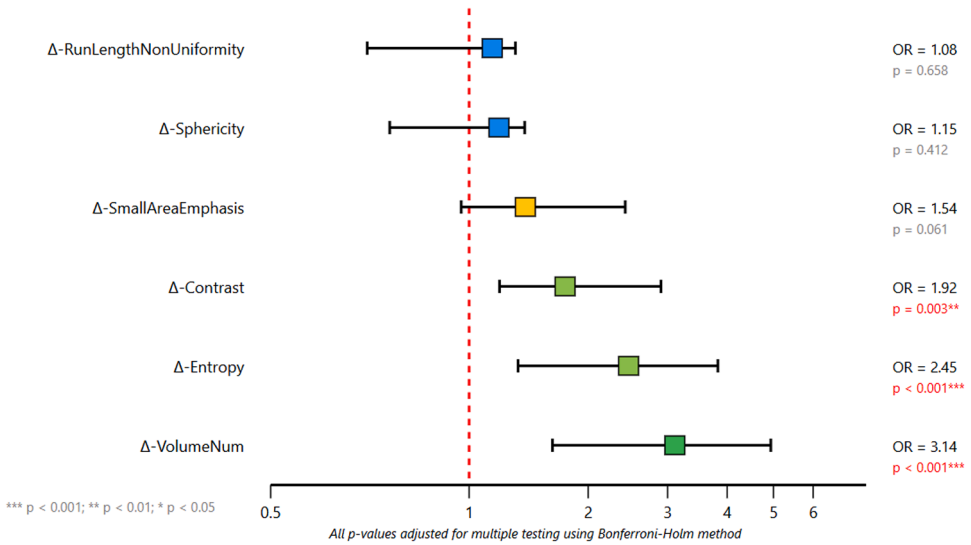

Fig. 4. Forest plot of odds ratios for R0 prediction. Multivariate analysis results showing odds ratios with 95% confidence intervals for delta-features predictors of R0 status.

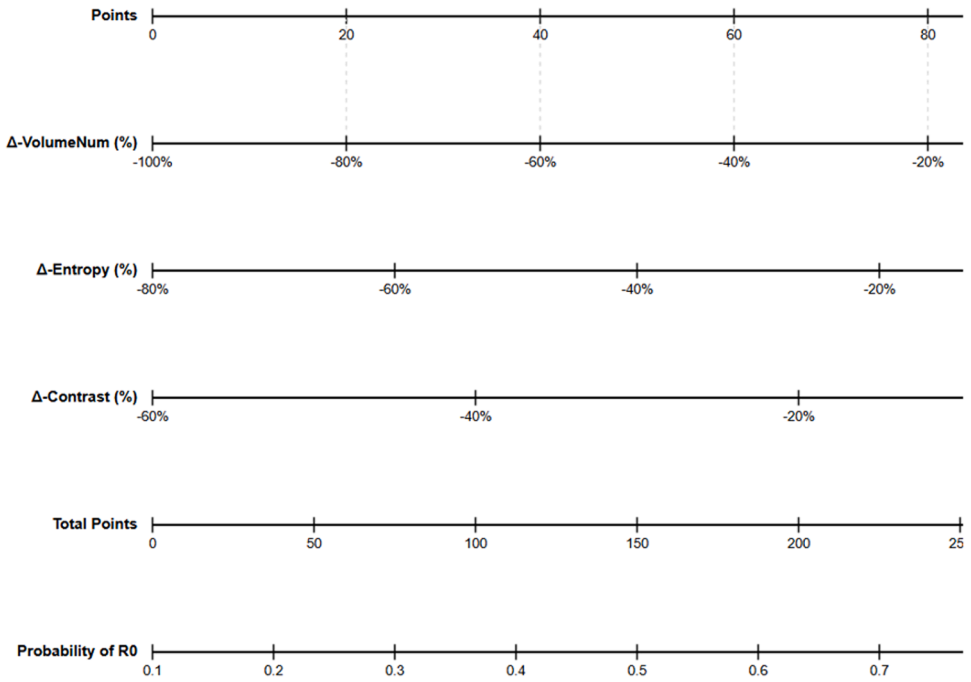

Fig. 5. Predictive nomogram for R0 resection. The nomogram included the three significant delta-features (Δ-VolumeNum, Δ-Entropy, and Δ-Contrast) for individualized prediction of R0 probability after NALIRIFOX treatment. The % probability of R0 resection (lower line) is given by the sum of the points associated to changes of the three variables.

crucial for optimizing therapeutic strategies. The exclusion of Energy due to high correlation with Contrast (r=−0.82) exemplifies the importance of addressing feature redundancy in radiomic analyses. This methodological rigor, implemented using validated open-source tools [12,13], helps ensure that the predictive model is not confounded by collinear variables and improves its interpretability and generalizability. The strong association between delta-features and R0 resection supports the radiomic hypothesis proposed by Lambin et al. [7], suggesting that macroscopic imaging features can reflect underlying genomic and proteomic patterns. The observed associations between texture changes and clinical outcomes align with previous studies linking radiomic heterogeneity to histological characteristics in PDAC [15,16]. Compared to previous radiomic studies in PDAC, our model based on NALIRIFOX therapy demonstrated superior performance. Studies using FOLFIRINOX have reported lower predictive accuracy (AUC 0.77–0.79) [17], while gemcitabine-based studies have shown limited predictive capacity for R0/R1 status [18]. These differences likely reflect the distinct mechanisms of action and efficacy profiles of these regimens [3]. NALIRIFOX, as an evolution of standard chemotherapy regimens for pancreatic cancer [4], may induce more consistent and predictable tissue changes that are captured by radiomic analysis. The clinical implications of these findings are substantial. The developed predictive nomogram (Fig. 5)

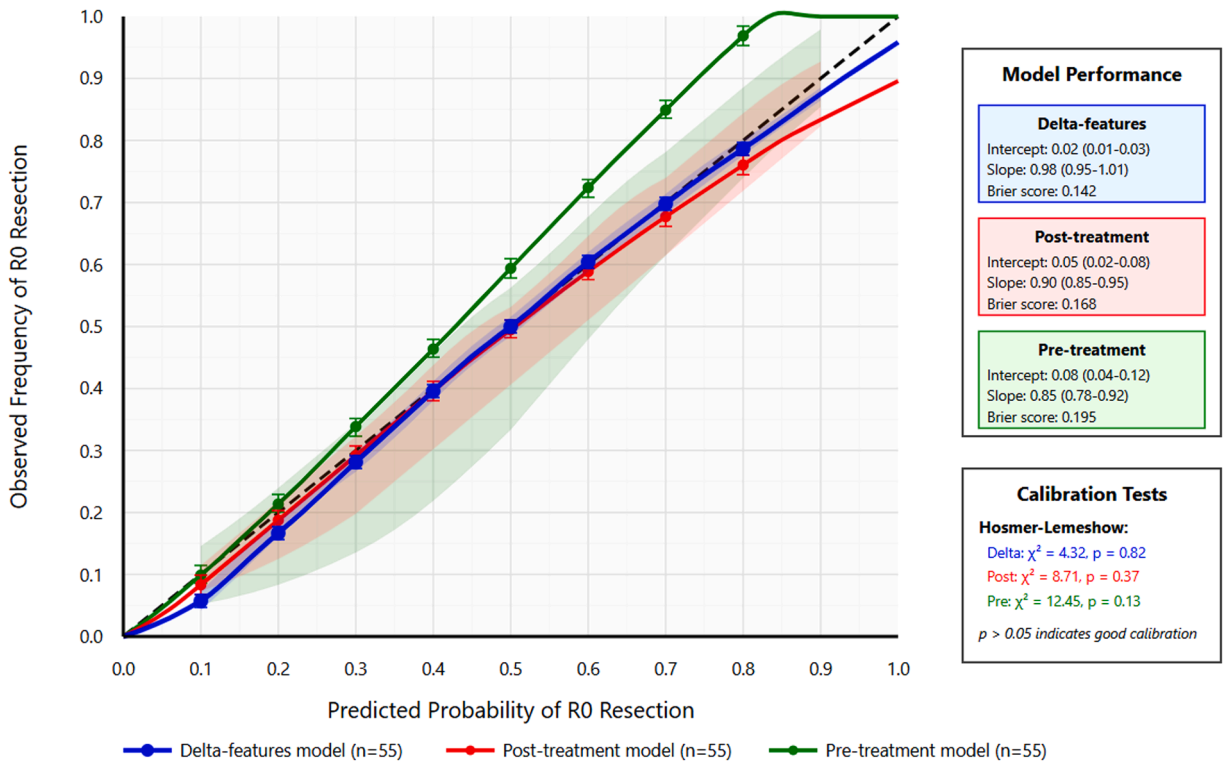

Fig. 6. Calibration plot. Agreement between predicted probabilities of R0 resection (x-axis) and observed frequencies of R0 resection (y-axis) for the three models. Model C (blue line) showed excellent calibration (intercept 0.02, slope 0.98), with observed frequencies closely matching predicted probabilities. The diagonal line represents perfect calibration.

Table 3
Subgroup analysis of model C performance.

Subgroup	N	AUC (95% CI)	P value*
Tumor size			0.046
≤3 cm	26	0.87 (0.80–0.94)	
>3 cm	18	0.81 (0.73–0.89)	
CT phase			0.312
Late arterial	44	0.86 (0.78–0.92)	
Portal	44	0.83 (0.76–0.90)	
Tumor location			0.628
Head	28	0.84 (0.77–0.91)	
Body-tail	16	0.82 (0.72–0.92)	
Sex			0.481
M	24	0.86 (0.78–0.93)	
F	20	0.83 (0.74–0.91)	

* adjusted using the Bonferroni-Holm method. Legend: CT, computed tomography; M, male; F, female; N, number of cases; AUC, area under the curve; CI, confidence interval.

provides a practical tool for estimating R0 probability after NALIRIFOX treatment. This could facilitate more informed surgical planning and potentially identify patients who may benefit from intensified neoadjuvant treatment or alternative therapeutic strategies, in accordance with current guidelines for resectable PDAC management [11]. For patients with favorable radiomic profiles predicting high R0 probability, surgical planning can proceed with confidence. Conversely, patients with unfavorable profiles might benefit from additional therapy cycles or consideration of alternative approaches [3]. The superior performance in smaller tumors (≤3 cm) suggests that radiomic analysis may be particularly valuable in early-stage disease, where treatment decisions are most critical. The consistency of performance across CT phases and anatomical locations supports the robustness of the approach. The delta-radiomics methodology offers advantages over static single-timepoint assessments by capturing the temporal evolution of tissue characteristics [9]. This dynamic approach better reflects the biological response to treatment than snapshot evaluations. The integration of quantitative imaging biomarkers into clinical decision-making represents a shift toward more personalized and data-driven oncology care [8]. The observed pattern of texture normalization in responding tumors—characterized by decreased entropy and contrast—suggests that radiomic features capture the biological transformation from heterogeneous viable malignancy to more homogeneous fibrous tissue [15,16]. This imaging manifestation of treatment effect provides complementary information to traditional size-based metrics and anatomical criteria [6,10]. The practical implementation of radiomic analysis in clinical workflows requires standardized protocols and validated software tools [12,13], emphasizing the importance of methodological rigor in translating research findings into clinical practice. This study has several limitations. Despite adequate statistical power, the single-center design limits generalizability. Differences in CT acquisition protocols and scanner characteristics across institutions may affect radiomic feature reproducibility [8]. External validation in multicentric cohorts with standardized imaging protocols is necessary before clinical implementation. In addition, feature selection (LASSO) was performed once on the development dataset rather than being embedded within each bootstrap iteration; consequently, the internal validation does not fully account for selection-induced optimism, and the reported discrimination may overestimate performance in independent data. Fully nested resampling, with the selection step repeated within each iteration, represents the more rigorous approach and should be adopted in the planned external validation. The relatively modest sample size, while adequate for our primary analyses, limited statistical power within subgroups; the subgroup analyses were therefore secondary and exploratory, and the observed differences — including the apparently superior performance in tumors ≤3 cm — should be regarded as hypothesis-generating and require confirmation in larger, adequately powered cohorts. Integration

with molecular markers and clinical parameters might further enhance predictive accuracy. Future studies should investigate whether combining radiomic features with biomarkers such as CA 19–9 levels and circulating tumor DNA could create more comprehensive predictive models. The temporal limitation to two imaging timepoints (pre- and post-treatment) represents another constraint; serial imaging throughout treatment might capture evolving response patterns with greater precision [9]. Additionally, the requirement for adequate tumor visibility on post-treatment imaging excluded some patients, potentially introducing selection bias that may affect the generalizability of our findings to the broader PDAC population undergoing neoadjuvant therapy.

Conclusions

In conclusion, this study provided evidence that radiomic delta-features may represent robust biomarkers for predicting R0 resection after preoperative treatment in resectable PDAC. The superior performance of dynamic feature changes compared to static evaluations emphasizes the importance of quantifying treatment-induced modifications. While further validation is required, these findings suggest that quantitative imaging analysis could contribute to the multidisciplinary management of pancreatic cancer, potentially supporting patient selection for surgery and treatment planning.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the Ethics Committee of the Azienda Ospedaliera Universitaria Integrata di Verona, Italy. All patients provided written informed consent prior to enrolment in the prospective phase II trial and to the use of their anonymized imaging and clinical data for research purposes. Data handling complied with Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of personal data and with applicable Italian regulations (resolution March 1, 2012, Gazzetta Ufficiale No 72 of March 26, 2012); raw data are not publicly available in order to safeguard participants' privacy under the European General Data Protection Regulation.

CRediT authorship contribution statement

Riccardo De Robertis: Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Nicolò Cardobi:** Writing – original draft, Validation, Supervision, Software. **Flavio Spoto:** Writing – original draft, Software, Methodology, Conceptualization. **Beatrice Mascarin:** Validation, Resources, Investigation. **Anna Garofano:** Software, Methodology, Investigation, Formal analysis, Data curation. **Simona Casalino:** Resources, Investigation, Data curation. **Alberto Quinzii:** Resources, Investigation, Data curation. **Giuseppe Malleo:** Validation, Supervision. **Davide Melisi:** Validation, Supervision, Resources, Data curation. **Mirko D'Onofrio:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflicts of interest to disclose in relation to this manuscript. No financial support or other benefits from commercial sources were received for the work described in this article. The authors have no financial interests that may be directly or indirectly related to the work submitted for publication.

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