Original Article

Imaging-Based Biomarkers: Changes in the Tumor Interface of Pancreatic Ductal Adenocarcinoma on Computed Tomography Scans Indicate Response to Cytotoxic Therapy

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BACKGROUND: The assessment of pancreatic ductal adenocarcinoma (PDAC) response to therapy remains challenging. The objective of this study was to investigate whether changes in the tumor/parenchyma interface are associated with response. **METHODS:** Computed tomography (CT) scans before and after therapy were reviewed in 4 cohorts: cohort 1 (99 patients with stage I/II PDAC who received neoadjuvant chemoradiation and surgery); cohort 2 (86 patients with stage IV PDAC who received chemotherapy), cohort 3 (94 patients with stage I/II PDAC who received protocol-based neoadjuvant gemcitabine chemoradiation), and cohort 4 (47 patients with stage I/II PDAC who received neoadjuvant chemoradiation and were prospectively followed in a registry). The tumor/parenchyma interface was visually classified as either a type I response (the interface remained or became well defined) or a type II response (the interface became poorly defined) after therapy. Consensus (cohorts 1-3) and individual (cohort 4) visual scoring was performed. Changes in enhancement at the interface were quantified using a proprietary platform. **RESULTS:** In cohort 1, type I responders had a greater probability of achieving a complete or near-complete pathologic response (21% vs 0%; $P = .01$). For cohorts 1, 2, and 3, type I responders had significantly longer disease-free and overall survival, independent of traditional covariates of outcomes and of baseline and normalized cancer antigen 19-9 levels. In cohort 4, 2 senior radiologists achieved a κ value of 0.8, and the interface score was associated with overall survival. The quantitative method revealed high specificity and sensitivity in classifying patients as type I or type II responders (with an area under the receiver operating curve of 0.92 in cohort 1, 0.96 in cohort 2, and 0.89 in cohort 3). **CONCLUSIONS:** Changes at the PDAC/parenchyma interface may serve as an early predictor of response to therapy. ***Cancer* 2018;124:1701-9**.

KEYWORDS: cytotoxic therapy, imaging biomarker, pancreatic cancer, response, Response Evaluation Criteria in Solid Tumors (RECIST).

INTRODUCTION

Decades of research in pancreatic ductal adenocarcinoma (PDAC) have failed to produce a reliable biomarker of response to cytotoxic therapy that can be applied to any patient. The only US Food and Drug Administration-approved biomarker for the disease, cancer antigen 19-9 (CA 19-9), is often used to track disease response or recurrence, but it is limited to patients with a Sialyl-Lewis^A-positive genotype (approximately 90% of patients). Furthermore, proper interpretation of CA 19-9 measurements requires a normal bilirubin level, and the performance of the test can be highly variable.[1] To date, a reliable radiographic measurement of response has also been elusive, because changes in tumor size on diagnostic imaging (eg, Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) do not predict outcomes.[2]

This lack of progress in the past may have been attributed in part to a dearth of active agents for the disease. In the modern era, however, responses are observed with combination chemotherapy regimens, including combined folinic acid

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(leucovorin), 5-fluorouracil, irinotecan, plus oxaliplatin (FOLFIRINOX)[3] and combined gemcitabine plus albumin-bound paclitaxel (gemcitabine/nab-paclitaxel),[4] leading to improved survival compared with gemcitabine monotherapy for advanced disease. However, defining radiographic responses to chemotherapy and radiation in a rigorous manner remains a challenge.[2,5]

The objective of the current study was to determine whether changes in the tumor interface on computed tomography (CT) imaging can indicate a response of PDAC to cytotoxic therapies. On the basis of our clinical intuition about changes in enhancement of these tumors after therapy, we hypothesized that tumors exhibiting an infiltrative pattern (or blurring) of the interface between tumor and parenchyma after cytotoxic therapy would have a worse response to therapy than tumors with a well defined (or sharpening) interface between tumor and parenchyma.

MATERIALS AND METHODS

Patients

In the development of our response metric, we retrospectively studied patients with resectable, borderline resectable, and metastatic disease. We recorded clinical and pathologic variables for each patient under an Institutional Review Board-approved protocol (PA14-0646). For prospective validation, we studied patients who were enrolled on an Institutional Review Board-approved registry trial of PDAC at our institution (PA14-0319). All patients had pancreatic protocol CT scans obtained at baseline before treatment.

CT Analysis for Interface Response

The pancreatic protocol CT scan is a diagnostic test for patients with pancreatic cancer in which iodine-based contrast is injected intravenously at a fixed rate.[6] The test usually consists of a precontrast phase, an arterial phase (35-40 seconds after starting contrast infusion), and a portal-venous phase (65-70 seconds after starting contrast infusion). All tumors were assessed according to RECIST 1.1.[7]

We developed a visual scoring of the interface response using the baseline pancreatic protocol and the follow-up CT scan after chemotherapy or chemoradiation (Fig. 1A). The response metric depends on the assessment of how the tumor/parenchyma interface changes after therapy. Our scoring system describes tumors as having either an interface that remains or becomes distinct (type I response) or an interface that becomes less distinct (type II response). We had 3 radiologists score all patients in this study. Consensus visual scoring was reached when at least 2 of the 3 radiologists reported the same visual score. The radiologists performed the visual scoring independently for all patients. They conducted joint sessions to review a random sampling of 20% of patients from cohorts 1, 2, and 3 to ensure consistency in the method. This consensus approach was used to establish the visual scoring method and investigate its associations. Independent visual scoring was used in a prospective registry (cohort 4) to validate the visual scoring method and to measure concordance between the radiologists using the κ statistic. The radiologists were blinded to the outcomes of all patients during the scoring. Our radiologists excluded patients who had peripancreatic fat stranding (pancreatitis), beam-hardening artifacts that obscured the tumor interface, incorrectly timed contrast injection (ie, contrast in the renal-collecting system on portal-venous images), and intraductal papillary mucinous neoplasms.

We also evaluated a quantitative metric of the interface using the qEASL feature in the Multi-Modality Tumor Tracking application (Intellispace Portal 8; Philips Healthcare, New York, NY) to measure changes in enhancement on the same scans.[8] The regions of interest at the interface were volumetrically segmented on the baseline and follow-up scans on the portal-venous phase after registration to a noncontrast scan. Enhancement at the tumor/pancreas interface was compared with enhancement in the spinous muscle at the level of the pancreas. The software provides a measure of change in enhancement (called tumor *viability* in the manufacturer's software). This is calculated as the number of voxels in the region of interest with enhancement values measuring 1 standard deviation over the mean enhancement in the reference region. Only patients who had baseline and follow-up scans that included a noncontrast phase and a portal-venous phase were evaluated with the quantitative method. The portal-venous phase was chosen for quantification because most follow-up scans were routine CT scans (ie, not pancreatic protocol), and routine CT scans are generally acquired at a portal-venous phase.

Statistics

Variables were compared between cohorts using a Mann-Whitney test for quantitative data and a chi-square test or Fisher test for categorical data. A logistic regression model was constructed to evaluate the potential association of chemoradiation and postoperative outcomes, and variables with P values $< .25$ on univariate analysis were

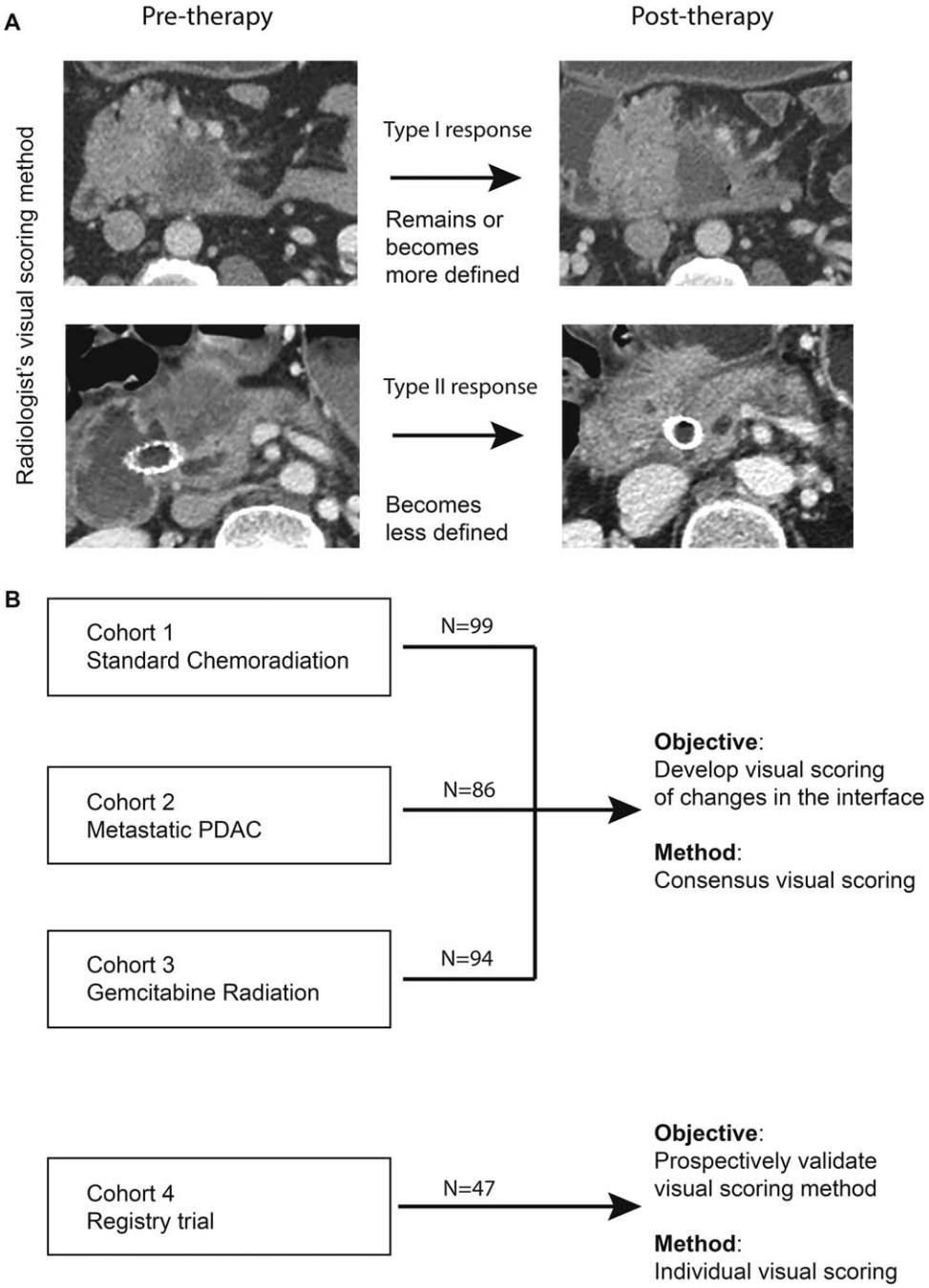

Figure 1. Visual scoring of changes is illustrated (A) at the pancreatic ductal adenocarcinoma (PDAC) interface and (B) in the study design.

incorporated into the final multivariate model. We also considered known or established variables in the multivariate model to fully evaluate the performance of the response readout in the context of these variables. A P value $< .05$ was considered statistically significant. All statistical analysis was performed using JMP (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

We studied patients with localized and metastatic PDAC for the initial development of our technique. Our first objective was to determine the pathologic and clinical associations of the observed response patterns using consensus visual scoring by 3 radiologists using 3 retrospective cohorts:

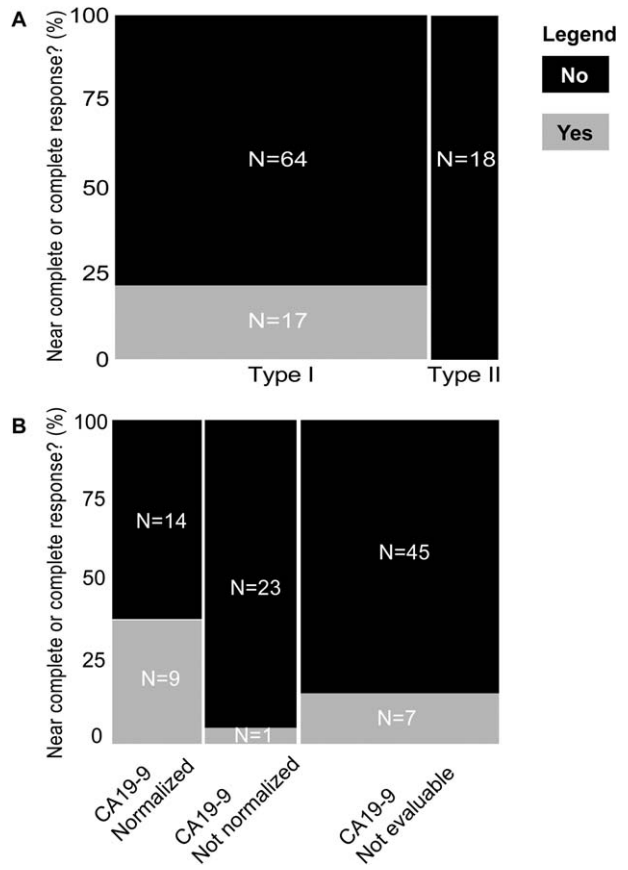

Figure 2. Associations of near-complete or complete pathologic response with (A) radiographic response and (B) cancer antigen 19-9 (CA 19-9) response are illustrated in cohort 1.

cohort 1 (99 patients with stage I/II PDAC who received neoadjuvant chemoradiation), cohort 2 (86 patients with stage IV PDAC who received chemotherapy), and cohort 3 (94 patients with stage I/II PDAC who received protocol-based neoadjuvant gemcitabine chemoradiation (Supporting Table 1; see online supporting information).

After determining the clinical significance of the changes in the interface with the consensus approach, we sought to validate the findings through individual scoring by radiologists using a cohort of 47 consecutive patients with stage I/II PDAC who received neoadjuvant therapy before undergoing resection and were enrolled on a prospective registry (cohort 4) (Fig. 1B). Characteristics of the patients in cohort 4 are described in Supporting Table 1 (see online supporting information).

A Type I Response at the Interface Associates With Pathologic Response in Cohort 1

We correlated consensus scoring of the interface response with the pathologic response to neoadjuvant therapy in 99 patients who received induction chemotherapy and concurrent chemoradiation (50.4 grays in 28 fractions), followed by surgical resection (cohort 1) (Supporting Table 1; see online supporting information). The median interval between the completion of neoadjuvant treatment and follow-up imaging was 5.7 weeks (range, 1.6-17.7 weeks). We previously reported that patients who achieve a major pathologic response (<5% viable tumor cells) after neoadjuvant therapy have an excellent prognosis.[9] Patients who had a type I interface response after neoadjuvant therapy had significantly fewer viable tumor cells compared with those who had a type II interface response, and patients who had a type I interface response were more likely to achieve a major pathologic response to therapy than those with a type II interface response (Fig. 2A).

Another marker of response that reportedly is associated with outcomes of PDAC is normalization of CA 19-9 after neoadjuvant therapy.[10] In cohort 1, we observed an association between normalization of CA 19-9 and achieving a major pathologic response (Pearson $P = .005$) (Fig. 2B), in which patients who had an elevated CA 19-9 level at baseline and achieved normalization of CA 19-9 after neoadjuvant therapy were more likely to achieve a major response compared with those who did not achieve normalization of CA 19-9. However, only 47 of 99 patients were evaluable for CA 19-9 normalization; and others had elevated bilirubin levels at baseline ($\geq$2 mg/dL) or lacked of production of CA 19-9.

In addition, 7 of 17 patients in cohort 1 who achieved a partial radiographic response according to RECIST 1.1 were more likely to achieve a major pathologic response than those who had stable or progressive disease (10 of 72 patients; Fisher exact test; $P = .009$).

Changes in the Interface Associate With Clinical Outcomes in All Stages of Disease

Cohort 1: Patients who underwent neoadjuvant therapy and surgery

We evaluated the clinical outcome correlations for interface response in cohort 1, which included patients with localized PDAC who received neoadjuvant therapy (the *standard chemoradiation group*) (Supporting Table 1; see online supporting information). Compared with patients who had a type II interface response, those who had a type I interface response demonstrated improved median disease-free survival (DFS) (17.6 vs 5.6 months; $P < .0001$), and overall survival (OS) (38.7 vs 14.5 months; $P < .0001$) (Fig. 3A). Normalization of CA 19-9, as previously reported,[9] also was associated with OS, but only 47 of 99 of patients were evaluable for normalization, as noted

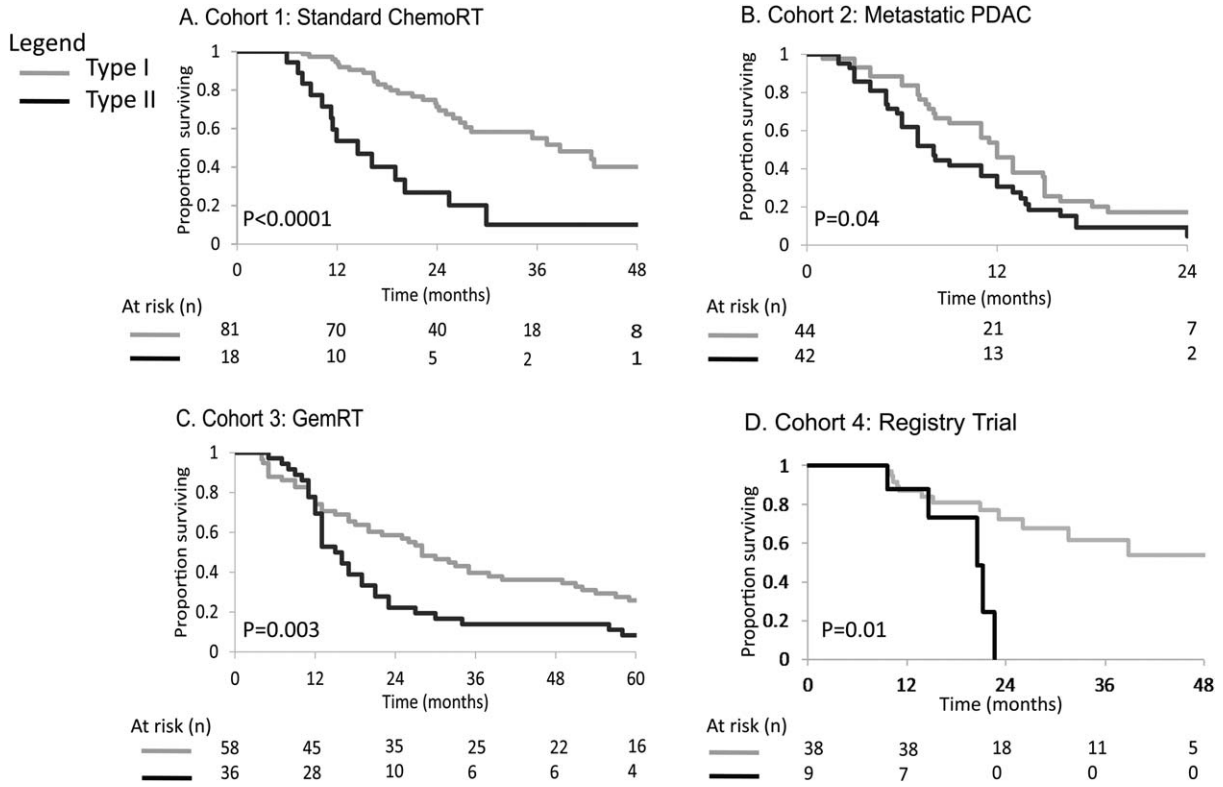

Figure 3. Survival stratified by radiographic response is illustrated in (A) cohort 1 (standard chemoradiation [ChemoRT]), (B) cohort 2 (metastatic pancreatic ductal adenocarcinoma [PDAC]), (C) cohort 3 (protocol-based gemcitabine plus chemoRT [GemRT]), and (D) cohort 4 (registry trial).

above. There was no correlation between interface response and achieving complete (R0) resection ($P = .52$). Univariate results are provided in Supporting Table 2 (see online supporting information). Interface response was an independent predictor of DFS and OS on multivariate analysis (Table 1).

Cohort 2: Patients with metastatic PDAC at diagnosis

We evaluated the interface response in cohort 2, which included 86 patients with stage IV disease (the *metastatic group*) (Supporting Table 1; see online supporting information). Compared with patients who had a type II response, those who had a type I response after initial follow-up had a trend toward longer median progression-free survival (PFS) (5 vs 3.7 months; $P = .08$) and significantly longer OS (12 vs 8 months; $P = .04$) (Fig. 3B). Univariate results are provided in Supporting Table 2 (see online supporting information). Consensus visual scoring of the changes in the interface revealed a trend toward improved PFS on multivariate analysis (Table 1). For OS, a type I response was an independent predictor on multivariate analysis (Table 1). A response measured according to RECIST 1.1 and CA 19-9 values (at baseline or with normalization) was not associated with clinical outcomes.

Cohort 3: Patients who received protocol-based gemcitabine chemoradiation for potentially resectable PDAC

We performed retrospective-prospective validation in cohort 3, a group of 94 patients who received protocol-based chemotherapy and chemoradiation (the *gemcitabine-chemoradiation group*) (Supporting Table 1; see online supporting information). The median interval from completion of neoadjuvant therapy to follow-up imaging was 5.9 weeks (range, 3.3-17.7 weeks). Patients who were classified as having a type I response had improved median DFS (30.7 vs 14.5 months; $P = .004$) and OS (27.6 vs 13.8 months; $P = .003$) (Fig. 3C). Normalization of CA 19-9 was associated with OS on univariate analysis, but CA 19-9 was evaluable in only 41 of 94 patients in cohort 3 who had elevated CA 19-9 and normal bilirubin levels at baseline. There was no correlation

TABLE 1. Multivariate Survival Analyses for Cohorts 1, 2, and 3 for Disease-Free and Overall Survival

Characteristic	Disease-Free Survival		Overall Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Cohort 1: Standard chemoradiation				
Interface response				
Type I	Reference	.002	Reference	.0003
Type II	2.88 (1.51-5.23)		4.18 (1.98-8.59)	
Age	1.02 (0.99-1.05)	.09	1.05 (1.01-1.08)	.01
Sex				
Men	Reference	.21	Reference	.13
Women	0.72 (0.43-1.21)		0.63 (0.34-1.15)	
Margins				
Negative	Reference	.11	Reference	.18
Positive	Undefined		Undefined	
Lymph nodes				
ypN0	Reference	.96	Reference	.71
ypN1	0.99 (0.57-1.68)		0.88 (0.44-1.72)	
CA 19-9 evaluation				
Normalized	Reference	.12	Reference	.41
Not normalized	1.88 (0.85-4.25)		1.82 (0.73-4.97)	
Not evaluable	1.68 (0.88-3.49)		1.60 (0.72-4.07)	
Cohort 2: Metastatic PDAC				
Interface response				
Type I	Reference	.12	Reference	.04
Type II	1.45 (0.92-2.32)		1.61 (1.01-2.60)	
Sex				
Men	Reference	.21	Reference	.11
Women	0.67 (0.41-1.08)		0.67 (0.41-1.09)	
Cohort 3: Gemcitabine radiation				
Interface response				
Type I	Reference	.018	Reference	.005
Type II	2.18 (1.14-4.18)		2.15 (1.25-3.65)	
Surgical resection				
Yes	Reference	< .0001	Reference	< .0001
No	4.20 (2.10-8.15)		8.46 (4.51-15.8)	
CA 19-9 evaluation				
Normalized	Reference	.92	Reference	.067
Not normalized	0.89 (0.38-2.27)		2.16 (1.01-5.10)	
Not evaluable	1.01 (0.45-2.51)		2.29 (1.11-5.23)	

Abbreviations: CA 19-9, cancer antigen 19-9; CI, confidence interval; HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma; ypN, residual invasive cancer or lymph node status.

between interface response and achieving R0 resection ($P = .91$). Univariate survival results are provided in Supporting Table 2 (see online supporting information). Interface response was an independent predictor of DFS and OS on multivariate analysis (Table 1).

Prospective validation and concordance in cohort 4: Patients who received neoadjuvant therapy on a registry

We opened a prospective registry trial to validate our imaging biomarker in patients who were receiving therapy for PDAC. We analyzed patients in the study who had resectable or borderline resectable PDAC and received neoadjuvant therapy (Supporting Table 1; see online supporting information). Two senior radiologists (>10 years' experience) independently scored changes in the interface for these patients and were blinded to the patient outcomes and the scoring of the other radiologist. There was high concordance between the senior radiologists ($\kappa = 0.8$). This cohort had a median follow-up of 2 years, and there were 13 deaths among the 47 patients, limiting the survival analysis interpretation. Nevertheless, both radiologists' scoring of the interface response revealed a clear pattern of separation between good and bad prognosis groups (Fig. 3D). Normalization of CA 19-9 in this cohort was not associated with recurrence-free survival or OS. A junior radiologist (with <5 years' experience) also was recruited to evaluate changes in the interface on the CT scans for this cohort and demonstrated moderate concordance with the 2 senior radiologists ($\kappa = 0.5$ for both). A detailed analysis of the 10 patients who had discrepant results revealed that 7 of the 10 patients did not have a clear interface at baseline. Eight of the 10 patients with discrepant results had endobiliary stents in place for tumors of the pancreatic head. Notably, the baseline conspicuity of the PDAC tumors was not associated

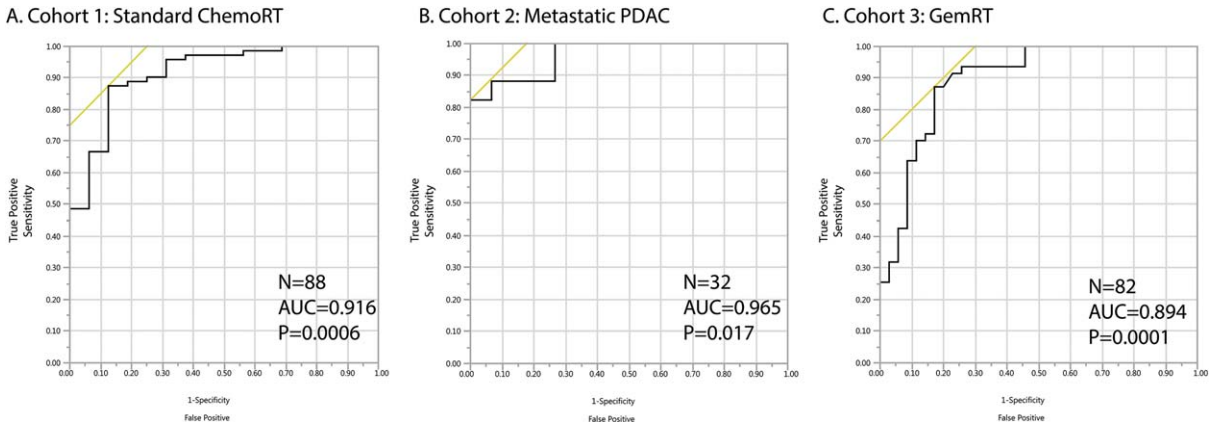

Figure 4. Receiver operating characteristic curves for quantitative changes in enhancement are compared with consensus radiographic response in (A) cohort 1 (standard chemoradiation [ChemoRT]), (B) cohort 2 (metastatic pancreatic ductal adenocarcinoma [PDAC]), and (C) cohort 3 (protocol-based gemcitabine plus chemoRT [GemRT]). AUC indicates area under the enhancement curve.

with the interface score in 2 of the 3 retrospective data sets (Supporting Table 3; see online supporting information).

Application of a Quantitative Metric to Define Interface Response

The measurement of *viability* was confined to patients who had pretherapy and post-therapy scan sets that included a portal-venous phase and a noncontrast phase, reducing the number of patients who were evaluable for each of the 3 retrospective data sets. Using the percentage change in viability as a continuous variable yielded an area under the enhancement curve (AUC) of 0.92 for the standard chemoradiation group, with the consensus interface response by the radiologists as the gold standard (n = 88; $P = .0006$) (Fig. 4A). In the metastatic PDAC group (cohort 2), the percentage change in viability had an AUC of 0.96 (n = 32; $P = .01$) (Fig. 4B). In cohort 3, the percentage change in viability had an AUC of 0.89 (n = 82; $P = .0001$) (Fig. 4C).

DISCUSSION

We have identified a radiographic predictor that associates with pathologic response and clinical outcomes in patients with localized and metastatic PDAC after cytotoxic therapies. This noninvasive metric of response uses standard-of-care CT images and differentiates the prognosis of patients with a strong effect size (average hazard ratios of death ranged from 2 to 4 comparing type I and type II responses). The survival associations for the radiographic readout can be applied to more patients and performs better in terms of differentiating prognosis than CA 19-9 measurement, which is the only US Food and Drug Administration-approved biomarker for monitoring the response to therapy in this disease. The establishment of a radiographic predictor of response can aid multiple efforts to improve outcomes for patients with PDAC.

Because PDAC often does not change in size as an indication of response to chemotherapy, a radiographic assessment has been elusive. Previous work has focused on baseline radiographic markers for prognostication. For example, Zhu et al investigated treatment-naive PDAC enhancement patterns. Those authors observed that a lower relative change in enhancement of tumor tissue compared with pancreatic parenchymal tissue was associated with shorter PFS after curative surgery.[11] Similarly, in 110 patients with potentially resectable tumors who received gemcitabine-based neoadjuvant therapy in 2 phase 2 trials, we observed that lower ratios of the area under the enhancement curve (AUC) on pancreatic protocol CT scans of PDAC were correlated with poorer patient outcome.[12] Baseline avidity on positron emission tomography with fluorodeoxyglucose also has been associated with prognosis.[13] However, those studies did not assess the value of changes in these measurements as predictors of response after cytotoxic therapy.

This lack of a radiographic predictor of response has been a major challenge in the clinical management of patients with PDAC, because clinicians are unable to provide information to patients regarding whether therapy is working except by following CA 19-9 levels. However, this biomarker can be challenging to interpret when the bilirubin is high at presentation or when a patient presents with a normal CA 19-9 level. In the context of evaluating the interface response for a patient with borderline

resectable or locally advanced disease and deciding about surgical resection, it is important to note that there was no association between the response and achievement of an R0 resection (the vast majority of patients achieved R0 status). Instead, our interface response readout may be interpreted as a predictor of early disease progression and death, and future trials may investigate tailored treatments based on the interface response.

To date, clinical research with experimental drugs for PDAC has relied on PFS, DFS, and OS as endpoints. These clinical outcome endpoints limit the ability to rapidly evaluate the efficacy of new therapies because of the time needed for adequate patient follow-up. Our radiographic scoring of interface response can be interpreted at the first restaging scan after initial chemotherapy, providing an early readout of response. With further validation, this radiographic indicator of response may allow for the rapid evaluation of new therapies for PDAC, overcoming the challenge in this disease of not being able to assess pathologic response in the majority of patients because of the propensity for advanced disease presentation. It is encouraging to note that the early prediction of response, combined with innovative clinical trial designs, has been successful for breast cancer drug development, especially in targeted populations.[14,15]

The current study's main limitation is its reliance on retrospective cohorts that spanned over 1 decade, including an era during which chemotherapy was not as effective as in the modern era. Our prospective evaluation of patients on the registry trial, however, indicates that the interface response readout applies to contemporary regimens like FOLFIRINOX and gemcitabine/nab-paclitaxel. It is noteworthy that CT imaging has also evolved over the study period, but the timing of the arterial and portal-venous images has remained essentially unchanged.[16] Furthermore, all images were reviewed using 2.5-mm CT image slice thickness. Our radiologists reviewed all scans and excluded examinations if the timing of contrast was clearly incorrect or if confounding factors like pancreatitis were present. Despite changes in the technologies and techniques over time, our results consistently demonstrated that this morphologic assessment of the interface maintained clinical relevance throughout. We acknowledge that further validation is needed in patients for whom uniform therapy was applied in a prospective fashion. We also acknowledge that the qualitative nature of the visual scoring is a limitation of our approach. This likely contributed to the low concordance between the senior radiologists and the junior radiologist, because our data indicate that certain morphologies of PDAC and the presence of beam-hardening artifacts make the assessment more difficult. Regarding the morphologies, it is notable that, in the 3 retrospective cohorts, the baseline conspicuity did not correlate with the interface response, except in cohort 3 (Supporting Table 3; see online supporting information). Further analysis will be required to determine whether there are associations between the baseline conspicuity of the tumors and how they respond. This may help achieve higher concordance in the visual readout. Regarding the reduction of metal artifacts, dual-energy CT may mitigate this problem with the use of higher energies.[17,18]

For future implementation of the interface readout in clinical trials, consensus reading or reading by senior radiologists may be necessary. Our quantitative data using changes in enhancement (or *viability*) measurements builds on our previous work[12] and indicates that a quantitative method may be feasible for assessing response. Ongoing work is focused on external/prospective validation of our quantitative metric.

In conclusion, our results indicate that changes in the interface of PDAC and the surrounding pancreatic parenchyma are associated with pathologic response, DFS/PFS, and OS across disease stages. Further development of this imaging-based biomarker of response to therapy may aid clinical decision making after induction therapy.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Ahmed M. Amer: Conceptualization, methodology, investigation, formal analysis, and writing–original draft. **Mohamed Zaid:** Investigation and formal analysis. **Dalia Elganainy:** Methodology and investigation. **Baishali Chaudhury:** Writing–review and editing. **Yeonju Lee:** Writing–review and editing. **Christopher T. Wilke:** Writing–original draft. **Jordan Cloyd:** Writing–review and editing. **Huamin Wang:** Writing–review and editing. **Anirban Maitra:** Writing–review and editing. **Robert A. Wolff:** Writing–review and editing. **Gauri Varadhachary:** Writing–review and editing. **Michael J. Overman:** Writing–review and editing. **Jeffery E. Lee:** Writing–review and editing. **Jason B. Fleming:** Conceptualization, methodology, and writing–review and editing. **Ching Wei Tzeng:** Writing–review and editing. **Matthew H. Katz:** Writing–review and editing. **Emma B. Holiday:** Writing–review and editing. **Sunil Krishnan:** Writing–review and editing. **Bruce D. Minsky:** Writing–review and editing. **Joseph M. Herman:** Writing–review and editing. **Cullen M. Taniguchi:** Writing–review and editing. **Prajnan Das:** Writing–review and editing. **Christopher H. Crane:** Writing–review and editing. **Ott Le:** Investigation and methodology. **Priya Bhosale:** Conceptualization, methodology, and investigation. **Eric P. Tamm:** Conceptualization, methodology, and investigation. **Eugene J. Koay:** Conceptualization, methodology, investigation, writing–original draft, supervision, and project administration.

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