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Imaging-based biomarkers: Changes in the tumor interface of pancreatic ductal adenocarcinoma on CT scans indicate response to cytotoxic therapy

Ahmed M. Amer, MD[1], **Mohamed Zaid, MD**[1], **Baishali Chaudhury, PhD**[1], **Dalia Elganainy, MD**[1], **Yeonju Lee, PhD**[1], **Christopher T. Wilke, MD**[1], **Jordan Cloyd, MD**[1], **Huamin Wang, MD, PhD**[2], **Anirban Maitra, MBBS**[2], **Robert A. Wolff, MD**[3], **Gauri Varadhachary, MD**[3], **Michael J. Overman, MD**[3], **Jeffery E. Lee, MD**[4], **Jason B. Fleming, MD**[5], **Ching Wei Tzeng, MD**[4], **Matthew H. Katz, MD**[4], **Emma B. Holliday, MD**[1], **Sunil Krishnan, MD**[1], **Bruce D. Minsky, MD**[1], **Joseph M. Herman, MD**[1], **Cullen M. Taniguchi, MD, PhD**[1], **Prajnan Das, MD**[1], **Christopher H. Crane, MD**[6], **Ott Le, MD**[7], **Priya Bhosale, MD**[7], **Eric P Tamm, MD**[7], and **Eugene J. Koay, MD, PhD**[1]

[1]Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA

[2]Department of Pathology, MD Anderson Cancer Center, Houston, TX, USA

[3]Department of GI Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

[4]Department of Surgical Oncology, MD Anderson Cancer Center, Houston, TX, USA

[5]Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa Bay, FL, USA

[6]Department of Radiation Oncology, Memorial Sloan Cancer Center, New York, NY, USA

[7]Department of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background—Assessment of pancreatic ductal adenocarcinoma response to therapy remains challenging. We investigated whether changes in the tumor/parenchyma interface were associated with response.

Corresponding author: Dr. Eugene J. Koay, MD, PhD, Assistant Professor, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1220 Holcombe Blvd, MS97, Houston, TX 77030, ekoay@mdanderson.org.

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Methods—We reviewed the pre- and post-therapy CT scans in four cohorts: (1) 99 patients with stage I/II PDAC who received neoadjuvant chemoradiation and surgery, (2) 86 patients with stage IV PDAC who received chemotherapy, (3) 94 patients with stage I/II PDAC who received protocol-based neoadjuvant gemcitabine chemoradiation, (4) 47 patients with stage I/II PDAC who received neoadjuvant chemoradiation and were prospectively followed in a registry. We visually classified the tumor/parenchyma interface as a type I (interface remained or became well-defined) or type II (interface became poorly defined) response after therapy. Consensus (cohorts 1–3) and individual (cohort 4) visual scoring were performed. We quantified the changes in enhancement at the interface using Philips platform.

Results—In cohort 1, type I responders had a higher probability of achieving a complete or near-complete pathologic response (21% vs 0%, p=0.01). For cohorts 1–3, type I responders had significantly longer disease-free survival (DFS) and overall survival (OS), independent of traditional covariates of outcomes, baseline and normalized CA19-9. In cohort 4, two senior radiologists achieved a kappa of 0.8, and the interface score associated with OS. The quantitative method showed high specificity and sensitivity in classifying patients as type I or type II responders (AUC of 0.92 [cohort 1], 0.96 [cohort 2], and 0.89 [cohort 3]).

Conclusion—Changes at the PDAC/parenchyma interface may serve as an early predictor of response to therapy.

Keywords

Imaging biomarker; pancreatic cancer; response; RECIST; cytotoxic therapy

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 Food and Drug Administration (FDA) approved biomarker for the disease, CA19-9, is often used to track disease response or recurrence, but it is limited to patients with Sialyl Lewis a-positive genotype (~90% of patients). Further, proper interpretation of CA19-9 levels require a normal bilirubin, and the performance of the test can be highly variable [1]. To date, a reliable radiographic measurement of response has also been elusive, as changes in tumor size on diagnostic imaging (e.g., RECIST 1.1) do not predict outcomes [2].

This lack of progress in the past may have been partly attributed to a dearth of active agents for the disease. In the modern era, however, responses are seen with combination chemotherapy regimens, including FOLFIRINOX [3] and gemcitabine/nab-paclitaxel [4], leading to improved survival compared to gemcitabine monotherapy for advanced disease. Defining radiographic responses to chemotherapy and radiation in a rigorous manner remains a challenge, however [2,5].

The goal of this study was to determine if changes in the tumor interface on CT imaging could indicate response of PDAC to cytotoxic therapies. Based on 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

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parenchyma after cytotoxic therapy would have a worse response to therapy than tumors with a well-defined (or sharpening) interface between tumor and parenchyma.

Methods

Patients

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

CT analysis for interface response

The pancreatic protocol CT scan is a diagnostic test for patients with pancreatic cancer, where iodine-based contrast is injected intravenously at a fixed rate [6]. The test usually consists of a pre-contrast, 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 by response evaluation criteria in solid tumors (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 an interface that remains or becomes distinct (type I response), or as having an interface that becomes less distinct (type II response). We had three radiologists score all of the cases in this study. Consensus visual scoring was reached when at least two of the three radiologists reported the same visual score. The radiologists performed the visual scoring for all cases independently. They conducted joint sessions to review a random sampling of 20% of cases from cohorts 1–3 to ensure consistency in the method. This consensus aproach 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 kappa statistic. The radiologists were blinded to the outcomes of all the patients while doing the scoring. Our radiologists excluded patients with peripancreatic fat stranding (pancreatitis), beam hardening artifacts obscuring the tumor interface, contrast injection that was incorrectly timed (i.e., contrast in renal collecting system on portal venous images), and IPMNs.

We also evaluated a quantitative metric of the interface using the qEASL feature in the Multi-Modality Tumor Tracking (MMTT) application (Philips Healthcare, Intellispace Portal 8) 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 non-contrast scan. Enhancement at the tumor/pancreas interface was compared to the enhancement in the spinous muscle at the level of the pancreas. The software provides a measure of change in enhancement, called tumor

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"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 with baseline and follow-up scans that included a non-contrast 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 (i.e, 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 Chi square test or Fisher's test for categorical data. A logistic regression model was constructed to evaluate the potential association of chemoradiation and postoperative outcomes, variables with a p value <0.25 on univariate analysis were incorporated into the final multivariate model. We also considered known or established variables into the multivariate model to fully evaluate the performance of the response readout in the context of these variables. A p value <0.05 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 pathological and clinical associations of the observed response patterns using consensus visual scoring by 3 radiologists using 3 retrospective cohorts: (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 (Supplementary Table 1).

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 prior to resection and enrolled on a prospective registry (Fig. 1B). The patient characteristics of cohort 4 are described in Supplementary Table 1.

A type I response at the interface associates with pathological response in cohort 1

We correlated consensus scoring of the interface response with pathological response to neoadjuvant therapy for 99 patients who underwent induction chemotherapy and concurrent chemoradiation to 50.4 Gy in 28 fractions, followed by surgical resection (cohort 1, Supplementary Table 1). The median interval between completion of neoadjuvant treatment to follow up imaging was 5.7 weeks (range, 1.6 to 17.7). We have previously reported that patients who achieve a major pathological 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 to patients who had a type II interface response, and patients who had a type I interface

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response were more likely to achieve a major pathological response to therapy than patients with a type II interface response (Fig 2A).

Another marker of response that has been reported to associate with outcomes of PDAC is normalization of CA19-9 after neoadjuvant therapy [10]. In cohort 1, we observed an association between normalization of CA19-9 with achieving a major pathological response (Fig. 2B, Pearson P=0.005), whereby patients who had an elevated CA19-9 at baseline and achieved normalization of CA19-9 after neoadjuvant therapy were more likely to achieve a major response compared to patients who did not achieve normalization of CA19-9. However, only 47 out of 99 patients were evaluable for CA19-9 normalization; others had an elevated bilirubin at baseline (>= 2 mg/dl) or lack of production of CA19-9.

Additionally, 7 of 17 patients in cohort 1 who achieved a partial radiographic response by RECIST 1.1 criteria were more likely to achieve a major pathological response than patients who had stable or progressive disease (10 of 72 patients, Fisher's Exact Test P=0.009).

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 (standard chemoRT group, Supplementary Table 1). Compared to patients with a type II interface response, patients who were classified as having a type I interface response demonstrated an improved median disease-free survival (DFS, 17.6 vs 5.6 mos., p<0.0001), and overall survival (OS, 38.7 vs 14.5 mos., p<0.0001, Fig. 3A). As previously reported [9], normalization of CA19-9 also associated with OS, but only 47 of 99 of the patients were evaluable for normalization as mentioned in the previous section. There was no correlation between interface response and achieving R0 resection (p=0.52). Univariate results are in Supplementary Table 2. Interface response was an independent predictor of DFS and OS on multivariate analysis (Table).

Cohort 2: Patients with metastatic PDAC at diagnosis—We evaluated the interface response in cohort 2, which included 86 patients with stage IV disease (metastatic group, Supplementary Table 1). Compared to patients with a type II response, patients with a type I response after initial follow-up had a trend for longer median progression free survival (PFS, 5 vs 3.7 mos., P=0.08) and significantly longer OS (12 vs 8 mos., p=0.04, Fig. 3B). Univariate results are shown in Supplementary Table 2. Consensus visual scoring of the changes in the interface showed a trend for improved PFS on multivariate analysis (Table). For OS, a type I response was an independent predictor on multivariate analysis (Table). A response as measured by RECIST 1.1 criteria and CA19-9 values (at baseline or with normalization) did not associate 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 (gemRT group, Supplementary Table 1). The median interval from completion of neoadjuvant therapy to follow up imaging was 5.9 weeks (range, 3.3 to 17.7).

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Patients who were classified as having a type I response had improved median DFS (30.7 vs. 14.5 mos., P=0.004), and OS (27.6 vs. 13.8 mos., P=0.003, Fig. 3C). Normalization of CA19-9 was associated with OS on univariate analysis, but CA19-9 was evaluable in only 41 out of 94 patients in cohort 3 who had an elevated CA19-9 and normal bilirubin at baseline. There was no correlation between interface response and achieving R0 resection (p=0.91). Univariate survival results are shown in Supplementary Table 2. Interface response was an independent predictor of DFS and OS on multivariate analysis (Table).

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 undergoing therapy for PDAC. We analyzed patients in this study who had resectable or borderline resectable PDAC and received neoadjuvant therapy (Supplementary Table 1). Two senior radiologists (>10 years of experience) independently scored the changes in the interface for these patients and were blinded to the outcomes of the patients and the scoring of the other person. 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 survival analysis interpretation. Nevertheless, both radiologists' scoring of the interface response showed a clear pattern of separation between good and bad prognosis groups (Fig. 3D). Normalization of CA19-9 in this cohort was not associated with RFS or OS. A junior radiologist (<5 years experience) was also recruited to evaluate the changes in the interface on the CT scans of this cohort and demonstrated moderate concordance with the two senior radiologists (kappa= 0.5, kappa=0.5). Detailed analysis of the 10 discrepant cases showed that 7 of the 10 cases did not have a clear interface at baseline. Eight of the 10 discrepant cases had an endobiliary stent in place for head of pancreas tumors. Notably, the baseline conspicuity of the PDAC tumors was not associated with the interface score in 2 of the 3 retrospective datasets (Supplementary Table 3).

Application of a quantitative metric to define interface response

The measurement of "viability" was confined to patients who had pre- and post-therapy scan sets that included a portal venous phase and a non-contrast phase, reducing the number of patients evaluable for each of the 3 retrospective datasets. Using the percentage change in viability as a continuous variable yielded an AUC of 0.92 for the standard chemoradiation group, with the consensus interface response by the radiologists as the gold standard (n=88, Fig. 4A, P=0.0006). In the metastatic PDAC group (cohort 2), the percentage change in viability had an AUC of 0.96 (n=32, Fig. 4B, P=0.01). In cohort 3, the percentage change in viability had an AUC of 0.89 (n=82, Fig. 4C, P=0.0001).

Discussion

We have identified a radiographic predictor that associates with pathological response nd clinical outcomes in localized and metastatic PDAC after cytotoxic therapies. This non-invasive metric of response uses standard of care CT images and differentiates prognosis of patients with a strong effect size (average hazard ratios of death from 2 to 4 comparing type

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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 CA19-9, which is the only FDA-approved biomarker to monitor response to therapy in this disease. The establishment of a radiographic predictor of response can aid multiple efforts to improve outcomes for 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 naïve PDAC enhancement patterns. It was found that lower relative enhancement change of tumor tissue compared to 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 II trials, we found that lower ratios of area under the enhancement curve (AUC) on pancreatic protocol CT scans of PDAC was correlated with poorer patient outcome[12]. Baseline avidity on positron emission tomography with fluorodeoxyglucose has also been associated with prognosis[13]. However, these 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, as clinicians are unable to provide information to patients regarding whether therapy is working except by following CA19-9 levels. However, this biomarker can be challenging to interpret when the bilirubin is high at presentation, or when a patient presents with a normal CA19-9 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/OS as endpoints. These clinical outcome endpoints limit the ability to rapidly evaluate the efficacy of new therapies due to the time needed for adequate follow up of patients. Our radiographic scoring of interface response can be interpreted at the first restaging scan following initial chemotherapy, providing an early readout of response. With further validation, this radiographic indicator of response may allow for rapid evaluation of new therapies for PDAC, overcoming the challenge in this disease of not being able to assess pathological response in the majority of patients due to its propensity for advanced disease presentation. Encouragingly, early prediction of response combined with innovative clinical trial designs have been successful for breast cancer drug development, especially in targeted populations [14,15].

This study’s main limitation is its reliance on retrospective cohorts that spanned over one decade, including an era where chemotherapy was not as effective as in the modern era. Our prospective evaluation of patients on the registry trial, however, indicates that the interface

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response readout applies to contemporary regimens like FOLFIRINOX and gemcitabine/nab-paclitaxel. It is notable 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]. Further, all images were reviewed using 2.5 mm CT image slice thickness. Our radiologists reviewed all scans and excluded exams if the timing of contrast was clearly incorrect or confounding factors like pancreatitis were present. Despite changes in the technologies and techniques over time, our results consistently showed that this morphological 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, as our data indicate that certain morphologies of PDAC and 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 (Supplementary Table 3). Further analysis will be required to understand if 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 reduction of metal artifacts, dual energy CT may mitigate this problem with 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 in 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 associate with pathological response, DFS/PFS, and OS across disease stages. Further development of this imaging-based biomarker of response to therapy may aid clinical decision following induction therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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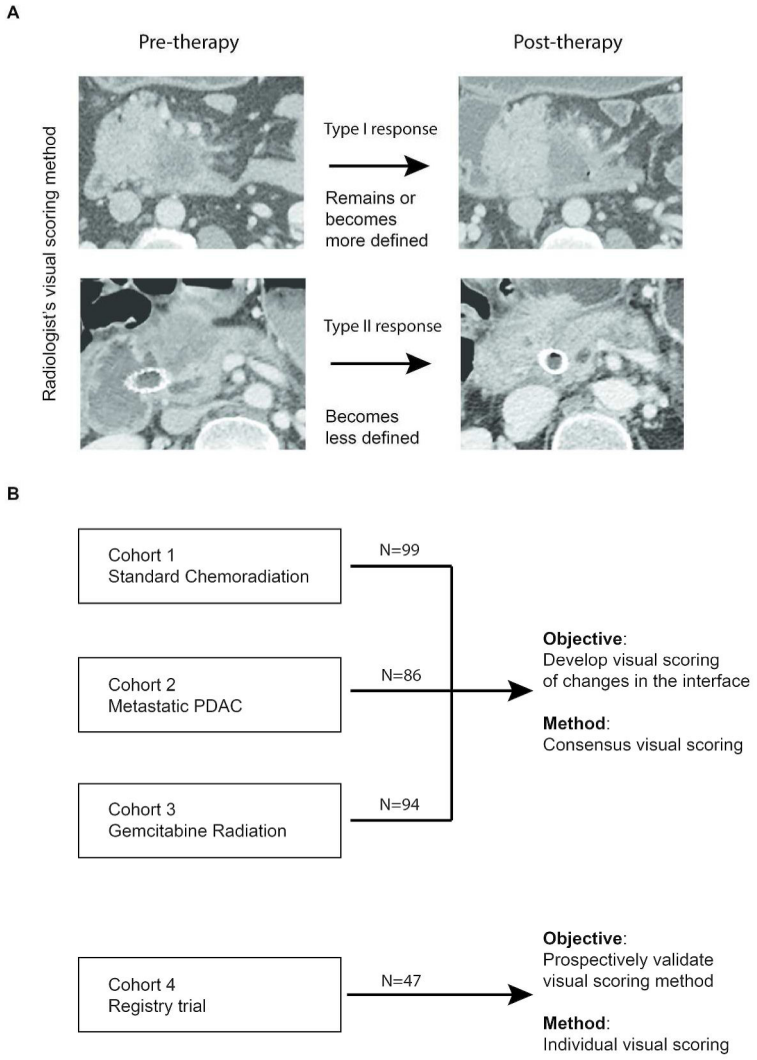

Figure 1.
Visual scoring of changes in PDAC interface (A) and study design (B)

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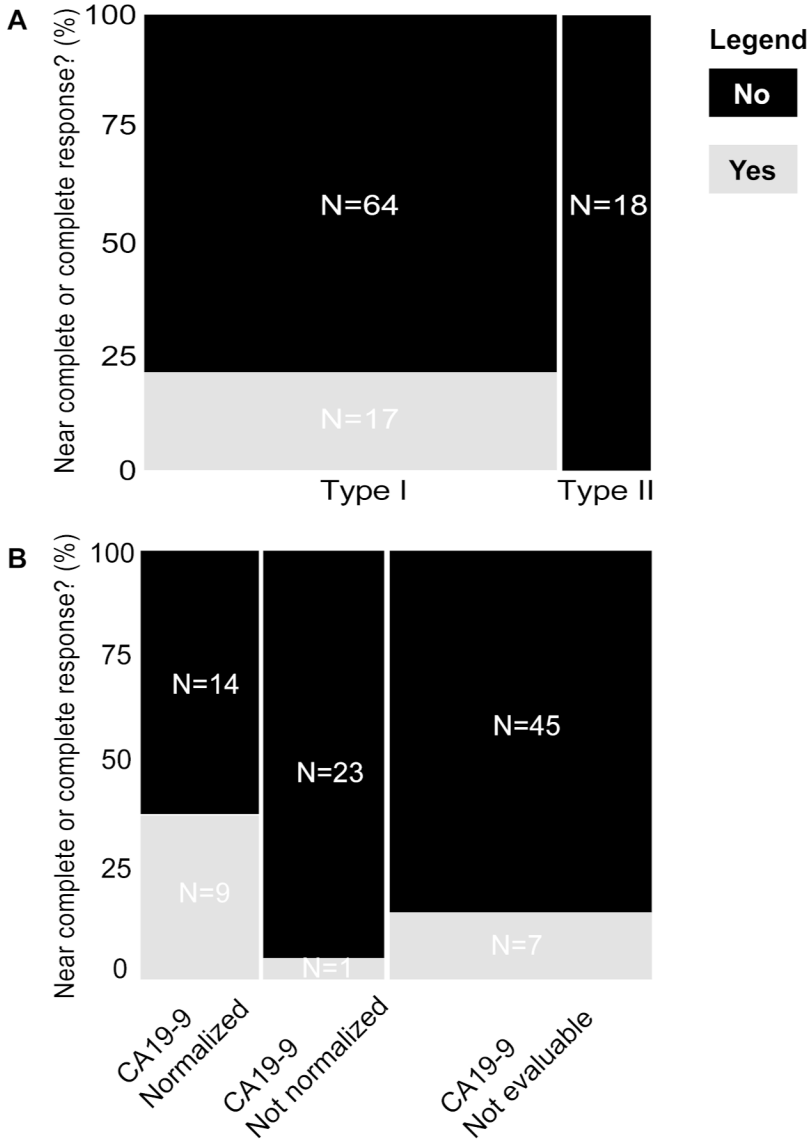

Figure 2.

Associations of near complete or complete pathological response with radiographic response (A) and CA 19-9 (B) in cohort 1

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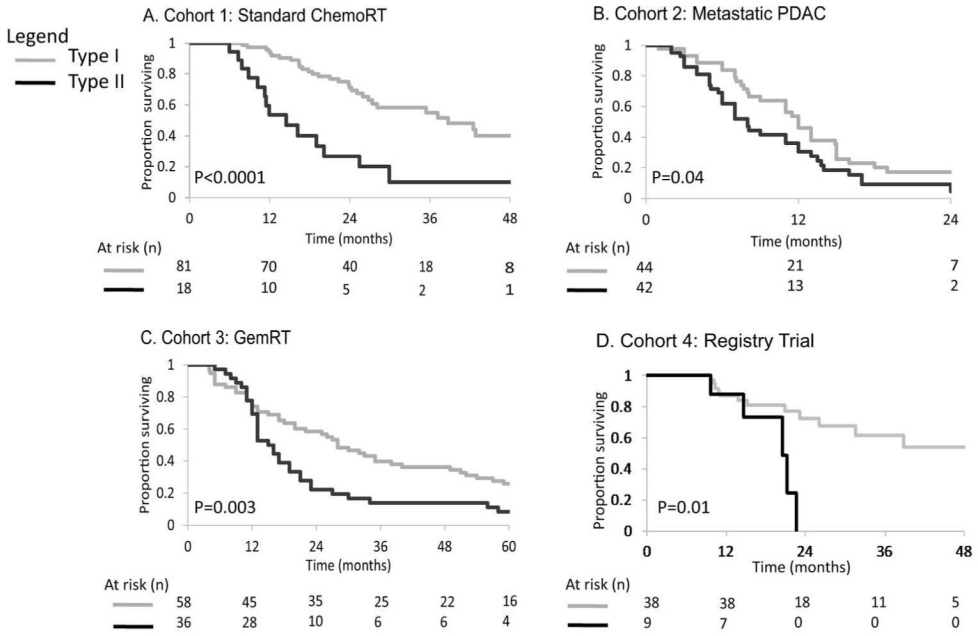

Figure 3.
Survival stratified by radiographic response in cohorts 1–4

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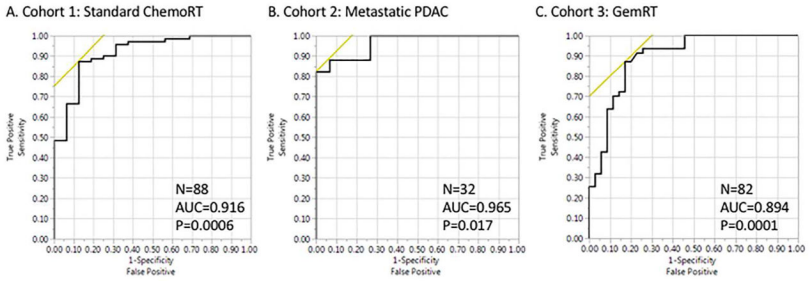

Figure 4.

Receiver operator characteristic curves for quantitative changes in enhancement as compared to consensus radiographic response

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Table

Multivariate survival analyses for cohorts 1, 2, and 3 for DFS and OS

Cohort 1: Standard Chemoradiation				
	Disease Free Survival		**Overall Survival**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Interface response				
Type I	Reference	0.002	Reference	0.0003
Type II	2.88 (1.51–5.23)		4.18 (1.98–8.59)	
Age	1.02 (0.99–1.05)	0.09	1.05 (1.01–1.08)	0.01
Sex				
Male	Reference	0.21	Reference	0.13
Female	0.72 (0.43–1.21)		0.63 (0.34–1.15)	
Margins				
Negative	Reference	0.11	Reference	0.18
Positive	Undefined		Undefined	
Lymph nodes				
ypN0	Reference	0.96	Reference	0.71
ypN1	0.99 (0.57–1.68)		0.88 (0.44–1.72)	
CA19-9 evaluation				
Normalized	Reference	0.12	Reference	0.41
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				
	Disease Free Survival		**Overall Survival**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Interface response				
Type I	Reference	0.12	Reference	0.04
Type II	1.45 (0.92–2.32)		1.61 (1.01–2.60)	
Sex				
Male	Reference	0.21	Reference	0.11
Female	0.67 (0.41–1.08)		0.67 (0.41–1.09)	
Cohort 3: Gemcitabine radiation				
	Disease Free Survival		**Overall Survival**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Interface response				
Type I	Reference	0.018	Reference	0.005
Type II	2.18 (1.14–4.18)		2.15 (1.25–3.65)	
Surgical resection				
Yes	Reference	<0.0001	Reference	<0.0001
No	4.20 (2.10–8.15)		8.46 (4.51–15.8)	

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Cohort 1: Standard Chemoradiation				
	Disease Free Survival		**Overall Survival**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CA19-9 evaluation				
Normalized	Reference	0.92	Reference	0.067
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)	