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Survival Prediction in Pancreatic Ductal Adenocarcinoma by Quantitative Computed Tomography Image Analysis

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Abstract

Background.—Pancreatic cancer is a highly lethal cancer with no established a priori markers of survival. Existing nomograms rely mainly on post-resection data and are of limited utility in directing surgical management. This study investigated the use of quantitative computed tomography (CT) features to preoperatively assess survival for pancreatic ductal adenocarcinoma (PDAC) patients.

Methods.—A prospectively maintained database identified consecutive chemotherapy-naïve patients with CT angiography and resected PDAC between 2009 and 2012. Variation in CT enhancement patterns was extracted from the tumor region using texture analysis, a quantitative image analysis tool previously described in the literature. Two continuous survival models were constructed, with 70% of the data (training set) using Cox regression, first based only on preoperative serum cancer antigen (CA) 19–9 levels and image features (model A), and then on CA19–9, image features, and the Brennan score (composite pathology score; model B). The remaining 30% of the data (test set) were reserved for independent validation.

Results.—A total of 161 patients were included in the analysis. Training and test sets contained 113 and 48 patients, respectively. Quantitative image features combined with CA19–9 achieved a c-index of 0.69 [integrated Brier score (IBS) 0.224] on the test data, while combining CA19–9, imaging, and the Brennan score achieved a c-index of 0.74 (IBS 0.200) on the test data.

Conclusion.—We present two continuous survival prediction models for resected PDAC patients. Quantitative analysis of CT texture features is associated with overall survival. Further

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work includes applying the model to an external dataset to increase the sample size for training and to determine its applicability.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer that carries a poor prognosis, with a 5-year survival rate of approximately 7%.¹ Diagnosis is usually made at an advanced stage of disease, and current treatment regimens offer relatively little survival improvement. For the minority of patients identified at an early stage of disease (10–20%), surgery remains the best chance of a cure, with a post-resection 5-year survival rate of 20–30%.^{2,3} However, most of these patients recur locally and/or with distant metastasis.⁴ While the mortality associated with a pancreatic resection performed at a high-volume institution is relatively low (3.8%), the short-term morbidity remains high at 30–40%.^{5,6} Thus, improving patient selection remains critical, with the aim of offering surgery to those who would most likely benefit while sparing others with a low chance of long-term survival from a highly morbid procedure.

Previous studies have described clinical and pathological factors prognostic of overall survival in PDAC. In 2004, Brennan et al. developed a clinical nomogram based on 555 pancreatic resections for adenocarcinoma.⁷ In Cox multivariate analysis, pathological variables such as tumor differentiation, margins, T stage, and number of negative/positive nodes were most prognostic for survival. The final nomogram achieved a c-index of 0.64, an improvement over traditional TNM staging. More recent studies have similarly concluded that these markers correlate with overall survival, especially in long-term survivors.⁸

While pathological biomarkers enhance our understanding of the biology of these tumors, a preoperative model is needed to identify patients for whom surgery can offer the best chance of long-term survival. Within the last decade, studies investigating preoperative clinical markers, such as tumor and inflammatory markers, circulating tumor cells, and gene signatures, have shown promise in reliably predicting the chance of survival.^{9–14} Similarly, tumor size was found to be an independent predictor of poor prognosis in a 2016 study.¹⁵ The authors concluded that tumors seen on imaging that measure > 2.0 cm should be considered for neoadjuvant chemotherapy. This finding highlights the potential of imaging data for additional prognostic information. In other cancer types, computer-based quantitative assessment of tumor appearance on diagnostic imaging has been reported and is increasingly demonstrating the potential to describe underlying tumor biology.^{16–19} Texture analysis, an established technique that describes spatial variations in pixel intensities in images, is one method for quantitative assessment. Whereas a radiologist may qualitatively describe PDAC enhancement patterns as homogeneously isoattenuating or heterogeneously hypoattenuating, texture analysis may capture more subtle underlying differences that reflect important pathologic differences to help predict patient survival.²⁰ The purpose of our study was to assess whether texture analysis of preoperative contrast-enhanced computed tomography (CT) predicts overall survival for PDAC patients following resection.

METHODS

Patient Cohort

With the approval of our Institutional Review Board, a prospectively maintained database was queried for patients who underwent resection for PDAC between 2009 and 2012. Patients who had preoperative CT angiography of a chemotherapy-naïve pancreas were included. Cases where an underlying intraductal papillary mucinous neoplasm (IPMN) was found on pathological review were excluded, as were cases where a diagnostic radiologist could not clearly delineate the tumor on pancreas CT, for example due to excessive artifacts.

Clinical and Pathological Variables

Demographic, clinical, and laboratory variables including preoperative CA19–9 were collected from the database and the electronic medical record. The Brennan nomogram score was calculated for each patient in the cohort from the following variables: sex, portal vein resection or splenectomy performed, margin of resection, tumor location, grade of differentiation, posterior margin status, nodal status, presence of back pain or weight loss, and T stage.⁷

Computed Tomography (CT) Image Acquisition

Contrast-enhanced CT images were utilized in quantitative image analysis. The post-contrast CT images were acquired following the administration of 150 mL iodinated contrast (Omnipaque 300, GE Healthcare, Princeton, NJ, USA) at 4.0 mL/s, on multidetector CT (Lightspeed 16 and VCT, GE Healthcare, Madison, WI, USA). The scan parameters were as follows: pitch/table speed 0.984–1.375/ 39.37–27.50 mm; autoMA 220–380; noise index 12.5–14; rotation time 0.7–0.8 ms; scan delay 80–85 s. Axial slices reconstructed at 2.5 mm intervals were used.

Quantitative Computed Tomography Image Analysis

Using Scout Liver (Pathfinder Technologies Inc., Analogic Corporation, Peabody, MA, USA) and with the help of a diagnostic radiologist with 7 years of post-fellowship experience, the tumor region was segmented manually on every axial slice in which it appeared (Fig. 1). Necrotic areas in heterogeneous tumors were included in the region of interest. Based on the tumor segmentation, a 3D model of the tumor was generated and the tumor size was calculated. A set of 255 texture features representing different aspects of image heterogeneity were extracted from the tumor region. Briefly, extracted features were based on gray-level co-occurrence matrices (GLCMs; 19 features),²¹ run-length matrices (RLMs; 11),²² local binary patterns (LBPs; 127),²³ fractal dimensions (FDs; 54),²⁴ intensity histograms (IHs; 5), and angle co-occurrence matrices (ACMs; 38).²⁵ The matrices encode the spatial variation in pixel values. Image features are statistics extracted from the matrix. For example, GLCM-based features encode the variation of pixel intensities within an area surrounding a particular pixel (repeated across the entire image), whereas RLM-based features encode pixel similarity in a row of pixels. Texture features were extracted from the tumor region in each CT slice and averaged across all the slices to provide a single value for the entire tumor. The set of quantitative image features included tumor volume and the set of

255 texture features, for a total of 256 features. All image analysis was implemented in Matlab 2015a (MathWorks, Natick, MA, USA). A list of all features is provided in Appendix 1.

Model Building and Evaluation

The cohort was randomly split into training (70% of cohort) and test (30% of cohort) groups. Texture features significant for overall survival by univariate analysis assessed with Cox proportional hazards model on the training set (P value < 0.1) were included in multivariate analysis. Two multivariate continuous survival models were designed using Cox proportional hazards model from the training data. Model A was designed to predict survival of PDAC patients prior to resection using CA19–9 values and image features, while Model B combined CA-19–9, image features, and the Brennan score (composite pathology score) into a second model to predict survival following resection (Fig. 2). Concordance indices (c-indices) and integrated Brier scores (IBS; mean squared prediction error), measures of model discrimination and accuracy, assessed model performance. IBS was evaluated for 0–5 years. The final multivariate models underwent independent validation using the test data. All statistical analyses were performed in R 3.3.1.²⁶

RESULTS

A total of 391 patients underwent resection for PDAC between 2009 and 2012. A preoperative pancreas CT was available for 194 patients, of whom 23 patients had undergone neoadjuvant chemotherapy prior to their pancreas CT and were therefore excluded due to chemotherapy-induced changes of the appearance of PDAC on imaging. Finally, an additional 10 patients were excluded due to the presence of artifact or the absence of a measurable mass on imaging. The remaining 161 patients constituted our study group (Fig. 3).

Sex was equally distributed [male: 82 (51%), female: 79 (49%)]. Median age was 67 years [interquartile range (IQR) 59–74], and median OS was 24 months (IQR 13–45). Nearly all CT scans were performed 6 months prior to surgery (95%).

Training and Test Subgroups

The training and test sets contained 113 (70%) and 48 (30%) patients, respectively. No clinical or pathological variables were statistically different between the training and test sets, suggesting similarity in the cohorts. Complete demographic and pathological results stratified by training and test subgroups can be found in Table 1.

Model Performance

Model A (the preoperative model based on CA19–9 and image features) achieved a c-index of 0.68 (IBS 0.141) on the training data. Evaluation of Model A on the test set yielded a c-index of 0.69 (IBS 0.224). For completeness, a survival model based solely on preoperative CA19–9 was built on the training set; however, the c-index was 0.51 (only slightly better than chance), with an IBS of 0.165. Based on the training data, the c-index was 0.73 (IBS 0.125) for model B (the postoperative model based on CA19–9, image features, and the

Brennan score); with test data, the result remained consistent, with a c-index of 0.74 (IBS 0.20). A summary of the model performance results is provided in Table 2. Comparison of model performance with only CA19–9 and the Brennan score is provided for completeness. Representative images of patients with good and poor overall survival are shown in Fig. 4. Quantitative image analysis demonstrates that heterogeneously hypoattenuating tumors are prognostic of poor survival.

DISCUSSION

Currently, our ability to predict survival in patients with resectable PDAC is imperfect. Existing nomograms rely on post-resection data such as margin status, differentiation, and lymph node ratio. Pathological features provide an important insight into the biology of a tumor and are central to an established TNM staging system used in many cancer types, but their applicability is limited to resected patients. The development of a stronger preoperative survival model that relies on non-invasive methods is needed and could be a valuable adjunct in the management of resectable patients with PDAC.

In the current study, we developed and independently validated two separate continuous survival models for PDAC: a preoperative model based on both quantitative CT analysis and CA19–9 levels (model A), and a model that includes pathological variables in the form of the Brennan nomogram score (model B). The c-indices for models A and B on validation data were 0.69 and 0.74, respectively. For comparison, the published Brennan nomogram achieved a c-index of 0.64.⁷ These results demonstrate that the models are able to predict overall survival based on quantitative image features and clinical variables. The strengths of this study include the relatively large sample size and the use of an independent validation dataset. Validation on an independent dataset decreases the risk of overfitting; in both model A (training: 0.67; test: 0.69) and model B (training: 0.73; test: 0.74), the c-indices remained consistent, suggesting that these models are likely applicable in other cohorts.

Clinicians rely on CT imaging in PDAC patients to determine the extent of disease and resectability. A small minority of patients will be deemed resectable, but survival remains difficult to predict, and many patients will undergo a highly morbid procedure for relatively little gain. As shown above, a prognostic model based solely on CA19–9 levels was comparable to chance. While this may suggest that CA19–9 is a poor prognostic marker, thereby conflicting with previous studies, the study was limited to patients undergoing surgery and was likely underpowered to detect a significant difference in survival between patients with low and high levels.¹⁰ Model A showed significant improvement when image features were added to the CA19–9-only model, as measured by a higher c-index (from 0.52 to 0.69 on validation data). Future studies including applying external validation will be needed to confirm these results. Furthermore, including data from unresected patients would expand the applicability of the model to a greater population.

In addition to size, radiologists often describe a tumor using terms such as ‘isodense’ or ‘heterogeneously necrotic’. Smaller isodense-appearing tumors are thought to represent less aggressive disease, while larger and more heterogeneous or necrotic tumors may represent more advanced disease.^{27,28} The link between qualitative image features and stage of disease

has been previously described and results suggest a positive correlation between CT imaging and histopathological findings.^{15,28–30} This association may be largely based on the tumor perfusion, which could be affected by growth rate, resulting in a more heterogeneous quality on CT. The appearance of such a tumor and its association with disease stage and therefore survival may explain the positive results obtained with our model. While this study did not attempt to demonstrate a direct relationship between quantitative image features and pathology, it is conceivable image analysis is able to predict overall survival indirectly by detecting biologically meaningful pathologic differences. Another possibility is that image analysis detects underlying genetic or epigenetic changes, which may alter tumor appearance on imaging. The relationship between imaging features and tumor mutational profile, termed radiogenomics, is currently being investigated by our group, as is the relationship between imaging features and pathology. Our current work explores the relationship of imaging features extracted from the normal pancreas and cystic lesion, with high-risk disease in resected IPMN.

A secondary goal of this study was to determine whether the inclusion of the Brennan score (a composite pathology score) would improve overall survival prediction. A preliminary model combining preoperative CA19–9 and the Brennan score was built, with a resultant c-index of 0.65 on both the training and test data. This result is consistent with the result reported in the original study (0.64).⁷ After the addition of imaging features, the c-index increased from 0.65 to 0.74 on validation data. This result suggests that image features are informative in terms of predicting survival and may be a useful tool in stratifying resectable patients into potential short- and long-term survivors.

While previous studies have shown a correlation between ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake on positron emission tomography (PET)/CT and overall survival, the current study relied exclusively on contrast-enhanced CT imaging.^{31–33} CT scanning is generally accepted to be the first-line imaging test for patients with suspected pancreatic cancer and is therefore available in many patients. At most institutions, a multi-phase ‘pancreatic protocol’ CT angiogram is commonly obtained in patients with confirmed pancreatic cancer to assess resectability and stage of disease. Current studies are ongoing to determine the feasibility of applying our methods to CT scans from outside institutions.

The present study has several weaknesses. First, our protocol for acquiring image features relies on manual segmentation of the tumor. This step relies on the presence of a visible distinct mass, which can be challenging in the setting of an isoattenuating tumor. In addition, segmentation of the tumor is currently a rigorous time-consuming process. Recent studies have demonstrated the possibility of automatically segmenting abdominal organs with acceptable accuracy in both CT and magnetic resonance imaging (MRI).^{34–36} Future work will involve incorporating these new techniques into our protocol to streamline the analysis. Second, as stated previously, our study cohort only included patients with multiphase CT angiography of the pancreas. While this methodology ensures the use of a standardized imaging protocol, the applicability to patients who undergo other types of abdominal CT examinations remains to be seen. Finally, our study did not include external validation using imaging data from outside institutions that may have differing imaging protocols.

CONCLUSIONS

For patients with resectable PDAC, we present two independently validated models for predicting post-resection survival using preoperative factors in one model, and both preoperative and pathological data in the other. The former may be useful to stratify resectable patients to aid in optimizing management; the latter is a more robust predictive model due to the inclusion of pathological data. Future work will be needed to incorporate other preoperative biomarkers of survival (e.g. CA19–9, inflammatory markers) and include external data to help standardize our model.

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APPENDIX 1: LIST OF 255 TEXTURE FEATURES

A. GLCM (19 Features)²¹

1. Energy
2. Contrast
3. Correlation
4. Sum of squares
5. Inverse difference moment
6. Sum average
7. Sum variance
8. Entropy
9. Difference variance
10. Sum entropy
11. Difference entropy
12. Information-theoretic measures of correlation 1
13. Information-theoretic measures of correlation 2
14. Maximum correlation coefficient
15. Inertia
16. Cluster shade
17. Cluster prominence
18. Renyi entropy
19. Tsallis entropy

B. RLM (11 Features)²²

1. Short run emphasis
 2. Long run emphasis
 3. Gray-level nonuniformity
 4. Run length nonuniformity
 5. Run percentage
 6. Low gray-level run emphasis
 7. High gray-level run emphasis
 8. Short run low gray-level emphasis
 9. Short run high gray-level emphasis
 10. Run low gray-level emphasis
 11. Long run high gray-level emphasis
- C. LBP (128 Features)²³**
1. 59 unique output levels of uniform LBP (ULBP)
 2. 10 unique output levels of rotation invariant (RI) ULBP
 3. Standard deviation (SD), skewness, kurtosis, and entropy of ULBP histogram
 4. SD, skewness, kurtosis, and entropy of RI-ULBP histogram
 5. Mean, SD, skewness, kurtosis, and entropy of LBP histogram
 6. SD, skewness, kurtosis, and entropy of efficient RI-LBP histogram
 7. SD, skewness, kurtosis, and entropy of rotated LBP histogram
 8. 38 Fourier descriptors of RI-ULBP histogram
- D. FD (54 Features)**
1. FD from 16 binary images created from the image
 2. Mean gray value from each of the 16 binary images
 3. Pixel count from each of the 16 binary images
 4. Maximum of mean of FD
 5. Maximum of standard deviation of FD
 6. Maximum of lacunarity of FD
 7. Average of mean of FD
 8. Average of standard deviation of FD
 9. Average of lacunarity of FD
- E. IH (5 Features)**

1. Mean
 2. Standard deviation
 3. Skewness
 4. Kurtosis
 5. Entropy
- F.** ACM1 and ACM2 (Total 38 Features, 19 From Each)²⁵
1. Energy
 2. Contrast
 3. Correlation
 4. Sum of squares
 5. Inverse difference moment
 6. Sum average
 7. Sum variance
 8. Entropy
 9. Difference variance
 10. Sum entropy
 11. Difference entropy
 12. Information-theoretic measures of correlation1
 13. Information-theoretic measures of correlation2
 14. Maximal correlation coefficient
 15. Inertia
 16. Cluster shade
 17. Cluster prominence
 18. Renyi entropy
 19. Tsallis entropy

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FIG. 1.

Left Extraction of the tumor from preoperative CT angiography of the pancreas. *Middle* Appearance of the segmented tumor with magnified area with grayscale pixels (black box). *Right* List of image features extracted from the tumor region. *GLCM* gray-level co-occurrence matrix, *RLM* run-length matrix, *LBP* local binary pattern, *FD* fractal dimension, *IH* intensity histogram, *ACM* angle co-occurrence matrix, *CT* computed tomography

FIG. 2.

Model building and evaluation. The cohort was randomly split into training and testing groups. Univariate analysis was performed on the training group to select features significant for overall survival. Two multivariate continuous survival models were built on the training data and assessed using c-indices and IBS. The two models were then validated on the testing group and assessed similarly using c-indices and IBS. *IBS* integrated Brier scores, *pre-op* preoperative, *post-op* postoperative, *CA* cancer antigen, *c-indices* Concordance indices

FIG. 3.
Study cohort. PDAC pancreatic ductal adenocarcinoma, *pre-op* preoperative, *CT* computed tomography

FIG. 4. Representative images of patients with good and poor overall survival. The magnified tumor region supports our hypothesis that heterogeneously hypoattenuating tumors are prognostic of poor survival

TABLE 1
Univariate analysis of differences in patient characteristics in the training and test groups ($n = 161$)

	Training set ($n = 113$)	Test set ($n = 48$)	<i>P</i> value
Age, years	66 (58–74)	70 (60–78)	0.27
Sex			
Male	84 (48)	28 (58)	0.23
Female	59 (52)	20 (42)	
Weight loss			
Yes	56 (50)	25 (52)	0.86
No	57 (50)	23 (48)	
CA19–9	62 (29–244)	87 (28–198)	0.54
Neoadjuvant therapy			
Yes	26 (23)	7 (15)	0.29
No	87 (77)	41 (85)	
Adjuvant therapy			
Single-agent gemcitabine	83 (73)	35 (73)	0.95
Combination therapy	13 (12)	5 (10)	
None or unknown	17 (10)	8 (17)	
Op to adjuvant Txp, days ^a	51 (43–64)	53 (48–61)	0.50
Overall survival, months	22 (11–40)	28 (16–47)	0.12
T stage			
0	1 (1)	0 (0)	0.40
1	2 (2)	0 (0)	
2	1 (1)	0 (0)	
3	109 (96)	47 (98)	
4	0 (0)	1 ^b (2)	
N stage			
0	32 (28)	14 (29)	1.00
1	81 (72)	34 (71)	
Tumor size, cm (path)	2.8 (2.3–3.5)	3.0 (2.3–3.5)	0.74

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	Training set (<i>n</i> = 113)	Test set (<i>n</i> = 48)	<i>P</i> value
Location (path)			
Head	88 (78)	41 (85)	0.71
Uncinate	1 (1)	0 (0)	
Neck	1 (1)	1 (2)	
Body	10 (9)	4 (8)	
Distal	2 (2)	1 (2)	
Tail	10 (9)	1 (2)	
None	1 (1)	0 (0)	
Margin (path)			
Negative	85 (75)	39 (81)	0.54
Positive	28 (25)	9 (19)	
Grade (path)			
Well	1 (1)	0 (0)	0.55
Moderate	79 (70)	31 (65)	
Poor	31 (27)	17 (35)	
Unknown	2 (2)	0 (0)	

Data are expressed as mean (interquartile range) or *N*(%) CA cancer antigen

^aNumber of days between the date of surgery and adjuvant therapy initiation

^bThe tumor in this patient was abutting the SMV but was still deemed resectable by the surgeon

TABLE 2
C-index and Brier score for each model evaluated on both the training and test groups

	Training set (<i>n</i> = 113)		Test set (<i>n</i> = 48)	
	C-index (95% CI)	IBS	C-index (95% CI)	IBS
CA19-9 only	0.51 (0.49–0.54)	0.165	0.52 (0.48–0.57)	0.203
+ Image features (Model A)	0.68 (0.62–0.73)	0.141	0.69 (0.62–0.77)	0.224
CA19-9 + Brennan score	0.65 (0.59–0.70)	0.145	0.65 (0.59–0.71)	0.191
+ Image features (Model B)	0.73 (0.68–0.78)	0.125	0.74 (0.68–0.81)	0.200

C-index Concordance index, *CI* confidence interval, *IBS* integrated Brier score, *CA* cancer antigen
Model A = Preoperative CA19-9 and image features
Model B = Preoperative CA19-9, Brennan score (post-resection pathological variables), and image features