Validation of a Proposed Tumor Regression Grading Scheme for Pancreatic Ductal Adenocarcinoma After Neoadjuvant Therapy as a Prognostic Indicator for Survival

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Abstract: Neoadjuvant therapy has been increasingly used to treat patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC). Although the College of American Pathologists (CAP) grading scheme for tumor response in posttherapy specimens has been used, its clinical significance has not been validated. Previously, we proposed a 3-tier histologic tumor regression grading (HTRG) scheme (HTRG 0, no viable tumor; HTRG 1, $<5\%$ viable tumor cells; HTRG 2, $\geq 5\%$ viable tumor cells) and showed that the 3-tier HTRG scheme correlated with prognosis. In this study, we sought to validate our proposed HTRG scheme in a new cohort of 167 consecutive PDAC patients who completed neoadjuvant therapy and pancreaticoduodenectomy. We found that patients with HTRG 0 or 1 were associated with a lower frequency of lymph node metastasis ($P = 0.004$) and recurrence ($P = 0.01$), lower ypT ($P < 0.001$) and AJCC stage ($P < 0.001$), longer disease-free survival (DFS, $P = 0.004$) and overall survival (OS, $P = 0.02$) than those with HTRG 2. However, there was no difference in either DFS or OS between the groups with CAP grade 2 and those with CAP grade 3 ($P > 0.05$). In multivariate analysis, HTRG grade 0 or 1 was an independent prognostic factor for better DFS ($P = 0.03$), but not OS. Therefore we validated the proposed HTRG scheme from our previous study. The proposed HTRG scheme is simple and easy to apply in practice by pathologists and might be used as a successful surrogate for longer DFS in patients with potentially resectable PDAC who completed neoadjuvant therapy and surgery.

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal diseases among all major human malignancies. Vast majority of the patients with PDAC present at advanced stage of disease at the time of diagnosis, and only 20% of patients are considered candidates for surgery.[1] Among patients with PDAC who underwent surgery with or without adjuvant therapy, the 5-year survival rate is approximately 15% to 20%, and the median overall survival (OS) ranges from 11 to 23.6 months.[2–6] The high mortality in these patients results from a high propensity for early recurrence and metastasis, which has been reported in up to 80% of patients after surgery, and from tumor resistance to conventional chemotherapeutic agents and radiation therapy.[7] Therefore, surgery has been considered the only curative strategy for PDAC. The current trend of therapeutic approach for patients with PDAC has become increasingly multimodality, and more patients are being treated with preoperative chemoradiation therapy followed by surgical resection, particularly in those patients who present with borderline resectable/locally advanced disease.

As with carcinomas of the esophageal/gastroesophageal junction region, stomach, and rectum, neoadjuvant therapy offers potential theoretical benefits over upfront surgery, followed by adjuvant therapy for patients with potentially resectable PDAC, including control of systemic micrometastasis, potential downstaging of the primary tumor with consequent reduction in the risks of a microscopically positive resection (R1) and locoregional failure or recurrence, and better patient selection for surgery, potentially resulting in a better clinical outcome and improved survival duration.[8] Although data regarding the use of neoadjuvant therapy for patients with potentially resectable PDAC are limited, multiple phase II studies have demonstrated that completion of neoadjuvant chemoradiation therapy and subsequent surgery is associated with an improved disease-free survival (DFS) and OS.[9–13]

The results from these studies have provided the foundation for clinical application of a neoadjuvant approach to patients with potentially resectable PDAC.[14,15]

It is important to define potential prognostic histologic factors in posttherapy pancreatic specimens. In our previous studies, we showed that several histologic parameters including tumor invasion into the muscular vessels, posttherapy tumor (ypT) stage, the number and ratio of positive lymph nodes, the distance of superior mesenteric artery margin from tumor, and histologic tumor regression grade (HTRG) are predictive of the clinical outcome in patients who received neoadjuvant therapies and underwent pancreaticoduodenectomy (PD).[9,10,16–18] Recent studies have demonstrated that HTRG of the surgical specimens after neoadjuvant therapies is a consistent and reproducible histologic factor that can help determine the effectiveness of specific neoadjuvant therapies compared with others.[15,18] Several proposed grading schemes, including the grading scheme currently used by the College of American Pathologists (CAP) Protocol[19] and Evans' grading scheme,[10] have been used for HTRG in posttherapy pancreatic specimens for PDAC. Our previous study showed that patients with no (CAP grade 0) or minimal residual tumor (< 5% of viable tumor, CAP grade 1) had better DFS and OS than those who had CAP grade 2 (partial response, residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells) or CAP grade 3 (poor or no response, extensive residual cancer with no evident tumor regression). However, we did not observe significant difference in either DFS or OS between the group with CAP grade 2 and those with CAP grade 3 responses. Therefore we proposed a modified 3-tier CAP grading scheme: HTRG 0, no viable residual carcinoma; HTRG 1, < 5% viable residual carcinoma cells (minimal residual cancer with single cells or small groups of cancer cells); and HTRG 2, ≥ 5% viable residual tumor cells.[18] The aim of this study is to validate the importance of our proposed 3-tier HTRG grading scheme as a useful predictor for clinical outcome in a new cohort of 167 consecutive patients with PDAC who received neoadjuvant therapies and PD.

MATERIALS AND METHODS

Patients and Follow-up

The study was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center (MD Anderson). One hundred sixty-seven consecutive patients were included in this study from our prospective maintained, institutional pancreatic tumor database. Our study population consists of 84 male and 83 female patients with age ranging from 34 to 85 years at the time of surgery (median age, 65 y). All patients had histologically confirmed PDAC, completed neoadjuvant therapies, and underwent PD at our institution between 2008 and 2012. We excluded from analysis the patients who underwent distal pancreatectomy for recurrent PDAC (n = 2), periampullary adenocarcinoma (n = 3), invasive adenocarcinoma arising in an intraductal papillary mucinous neoplasm (n = 2), and adenocarcinoma arising in the distal bile duct (n = 3).

Twenty-nine patients (17.4%) received neoadjuvant fluoropyrimidine-based chemoradiation (TX1), 30 patients (18.0%) received neoadjuvant gemcitabine-based chemoradiation (TX2), 22 patients (13.2%) received neoadjuvant chemotherapy, followed by gemcitabine-based chemoradiation (TX3), 68 patients (40.7%) received neoadjuvant chemotherapy followed by fluoropyrimidine-based chemoradiation (TX4), and 18 patients (10.8%) received neoadjuvant chemotherapy alone (TX5). In patients who received neoadjuvant chemotherapy only (TX5), 2 patients (1.2%) received fluoropyrimidine-based chemotherapy, and 16 patients (9.6%) received gemcitabine-based chemotherapy. After completion of neoadjuvant therapy, all patients were reevaluated by pancreatic protocol computed tomography scan, and PD was performed only in selected patients who had no disease progression or metastasis and had no contraindications to major abdominal surgery.

After PD, patients were evaluated every 6 months by physical examination, chest radiography, abdominal computed tomography scan, or positron emission tomography (PET) scan. The development of a new low-density mass or intra-abdominal lymphadenopathy in the regions of the resected pancreas or mesenteric root was considered a locoregional relapse or recurrence. Any low-density mass in the liver or lungs or other distant sites was considered distant metastasis.

Histologic Evaluation of HTRG in PD Specimens

A standardized scheme for histologic evaluation of PD specimens was set up and has been used at our institution since 1990. Histopathologic information from our standardized pathologic reports, including tumor type, location, size, differentiation, HTRG, tumor involvement of extrapancreatic tissue, presence of lymphovascular or perineural invasion, numbers of positive and total lymph nodes, margin status, and ypTNM stage, were reviewed by 3 pathologists (S.M.L., L.L., H.W.). For all PD specimens, we routinely submitted pancreatic neck/parenchymal margin (en face), bile duct margin (en face), proximal margin (gastric or duodenal, en face), distal margin (distal duodenal or jejunal, en face), and retroperitoneal (uncinate or superior mesenteric artery) margin (entirely submitted, perpendicular sections), which are the same as the current CAP protocol. The histologic grade of tumor response in PD specimens was evaluated on the basis of microscopic estimation of the overall percentage of residual viable tumor relative to the entire treated tumor bed using the 4-tiered CAP grading scheme and the proposed 3-tiered HTRG scheme as described previously: HTRG 0, no residual carcinoma with entire pancreas, bile duct and ampulla of Vater submitted for histologic examination; HTRG1, patients with minimal residual carcinoma (single cells or small groups of cancer cells, < 5% residual carcinoma); and HTRG 2, patients with 5% or more residual carcinoma.[18] For the

cases with no grossly identifiable mass lesion (HTRG 0 and/or 1), the entire pancreas, common bile duct, and ampulla of Vater in the PD specimens were submitted for histologic evaluation to confirm the absence or presence of any residual PDAC cells. Representative micrographs showing the CAP grading scheme and the proposed 3-tier HTRG scheme are shown in Figure 1. The margin status of PD specimens were documented as R0 (negative surgical margin microscopically), R1 (negative surgical margin grossly but with tumor cells present margin microscopically), or R2 (presence of grossly identifiable tumor at any margin). Posttherapy pathologic stage was grouped according to the American Joint committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.[20]

Statistical Analysis

Correlations between HTRG and categorical clinicopathologic variables including sex, sex, tumor differentiation, lymph node metastasis, recurrence, ypT, and AJCC stage and margin status were examined using the Fisher exact test or χ^2 analysis. The DFS and OS were calculated as previously described.[18] The survival curves for DFS and OS were constructed using the Kaplan-Meier method and the log-rank tests were used to compare survival outcomes between clinicopathologic variables including the HTRG category. The association between DFS or OS with HTRG category and the above clinicopathologic parameters were determined using univariate Cox regression analysis. Cox proportional hazards models were fitted for multivariate analysis. After interactions between the variables were examined, a backward stepwise procedure was used to derive the best-fitting model. A P value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL).

RESULTS

Analyses of HTRG With Clinical and Histopathologic Data

Correlations of the proposed 3-tier HTRG scheme with clinical and histopathologic data are summarized in Table 1. Posttherapy tumor size ranged from 0 to 6.0 cm, with an average of 2.4 cm. According to the World Health Organization classification standards, 104 cases (62%) were well-differentiated to moderately differentiated PDAC, and 63 cases (38%) were poorly differentiated PDAC. The

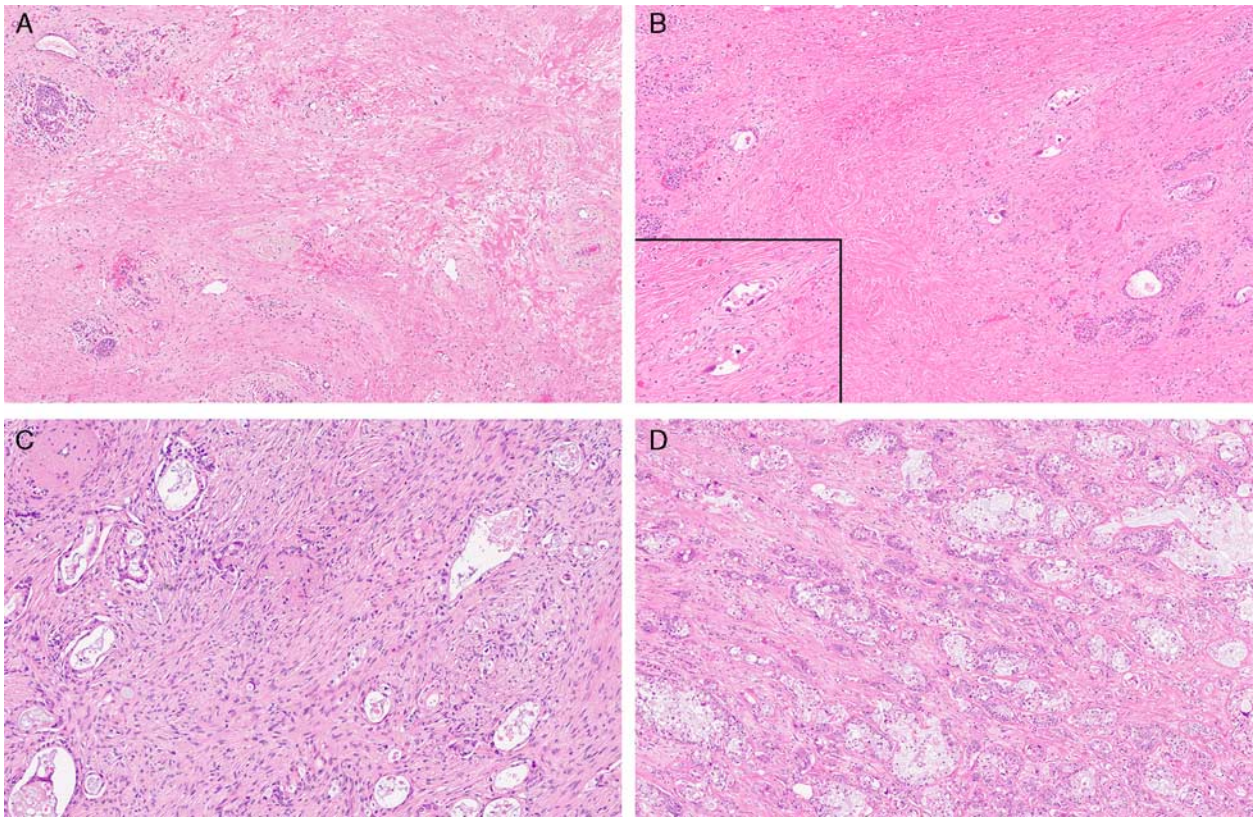

FIGURE 1. Representative micrographs show the different HTRGs after neoadjuvant therapies. A, HTRG 0 (CAP grade 0): complete pathologic response with no residual viable adenocarcinoma cells identified after histologic examination of the entire resected pancreas. B, HTRG 1 (CAP grade 1): treated tumor bed with scar, fibrosis and microscopic focus of residual tumor cells (<5% viable tumor cells). C, HTRG 2 (CAP grade 2): moderate response, residual cancer outgrown by fibrosis (approximately 30% of viable residual tumor cells). D, HTRG 2 (CAP grade 3): poor response, residual tumor cells outgrow the stroma (approximately 75% of viable residual tumor cells).

TABLE 1. Clinicopathologic Correlation of Histologic Tumor Response Grade

Variable	No. Patients	HTRG 0 or 1 (n [%])	HTRG 2 (n [%])	*P*
Sex				
Female	83	12 (7.2)	71 (42.5)	0.47
Male	84	9 (5.4)	75 (44.9)	
Age (y)	167	62.4 ± 11.3	65.3 ± 8.5	0.16
Tumor size (cm)	167	1.1 ± 1.3	2.6 ± 1.1	**< 0.001**
Tumor differentiation				
Well to moderate	104	16 (9.6)	88 (52.7)	0.16
Poor	63	5 (3.0)	58 (34.7)	
Lymph nodes				
Negative (ypN0)	84	17 (10.2)	67 (40.1)	**0.003**
Positive (ypN1)	83	4 (2.4)	79 (47.3)	
Pathologic tumor stage				
ypT0	3	3 (1.8)	0	**0.003**
ypT1	12	8 (4.8)	4 (2.4)	
ypT2	6	1 (0.6)	5 (3.0)	
ypT3	146	9 (5.4)	137 (82.0)	
Resection margin				
Negative	162	21 (12.6)	141 (84.4)	0.39
Positive	5	0	5 (3.0)	
AJCC stage				
0 or I	17	10 (6.0)	7 (4.2)	**< 0.001**
IIA	67	7 (4.2)	60 (35.9)	
IIB	83	4 (2.4)	79 (47.3)	
Recurrence				
None	56	13 (7.8)	43 (25.7)	**0.01**
Regional	33	2 (1.2)	31 (18.6)	
Distant	78	6 (3.6)	72 (43.1)	

Values in bold are statistically significant $P < 0.001$.

number of regional lymph nodes ranged from 10 to 68 with an average of 16.6. Lymph node involvement by metastatic disease was identified in 83 cases (50%), with the number of positive lymph nodes ranging from 1 to 19 nodes. Post-therapy tumor stages ypT0, ypT1, ypT2, ypT3, and ypT4 were present in 3 (1.8%), 12 (7.2%), 6 (3.8%), 146 (87.4%), and 0 (0%), respectively. Three (1.8%) patients had HTRG 0 (CAP grade 0), 18 (10.8%) had HTRG 1 (CAP grade 1), and 146 (87.4%) were HTRG 2 responses (95 [56.9%] with CAP grade 2 and 51 [30.5%] CAP grade 3 response). Among the 3 patients with HTRG 0, 1 had microscopic metastasis in 1 of 16 lymph nodes examined, and the other 2 were node negative with 18 and 26 lymph nodes examined, respectively. Pretherapy diagnosis of adenocarcinoma was confirmed in all 3 cases with HTRG 0 response. R0 resection was achieved in 162 patients (97%), and R1 resection was present in 5 patients (3%, 3 cases with positive pancreatic margin and 2 cases with positive retroperitoneal margin). Common bile duct margin was negative in all patients. Fifty-six patients (33.5%) did not show any recurrent or metastatic disease during the follow-up. Thirty-three (19.8%) patients had locoregional recurrence in the surgical bed or mesenteric root, and 78 (46.7%) patients had distant metastatic disease, predominantly in liver or lung. Patients with HTRG 0 or 1 had significantly a lower frequency of lymph node metastasis ($P = 0.003$) and recurrence ($P = 0.01$) and lower ypT ($P < 0.001$) and AJCC stage ($P < 0.001$) than those with HTRG 2. The mean tumor size was 1.1 ± 1.3 cm in HTRG 0 or 1 group compared with 2.6 ± 1.1 cm in HTRG 2 group ($P < 0.001$). However, HTRG was not correlated with other clinicopathologic features including sex, tumor differentiation, and margin status ($P > 0.05$). Similar to the results from our previous study,[18] we did not observe significant difference in HTRG among the different neoadjuvant treatment groups ($P = 0.25$).

Analyses of HTRG With Survival

The length of clinical follow-up time in this cohort ranged from 8.2 to 84.2 months with a median follow-up time of 30.5 months. At the time of last follow-up, 97 (58.1%) patients died of PDAC, 3 (1.8%) patients died of other causes, 19 (11.4%) patients were alive with PDAC, and 48 (28.7%) patients were alive with no clinical or radiographic evidence of recurrent PDAC. Median OS for the entire cohort was 33.7 months (95% confidence interval, 28.1-39.3 mo) with 1-year and 3-year OS rates of 97% and 49%, respectively.

Patients with HTRG 0 or 1 had longer DFS and OS than those with HTRG 2 (Fig. 2). The mean DFS was 44.0 ± 5.5 months for the group with HTRG 0 or 1 compared with 28.2 ± 2.6 months for those with HTRG 2 ($P = 0.004$). The mean OS was 54.0 ± 4.2 months for the group with HTRG 0 or 1 compared with 44.4 ± 2.5 months for those with HTRG 2 ($P = 0.02$). All 3 patients with HTRG 0 were alive with no evidence of recurrent or distant disease at last follow-up. However, there was no difference in either DFS or OS between patients with CAP grade 2 and those with CAP grade 3 (Fig. 3). Different chemoradiation regimens did not show any correlation with DFS or OS (data not shown).

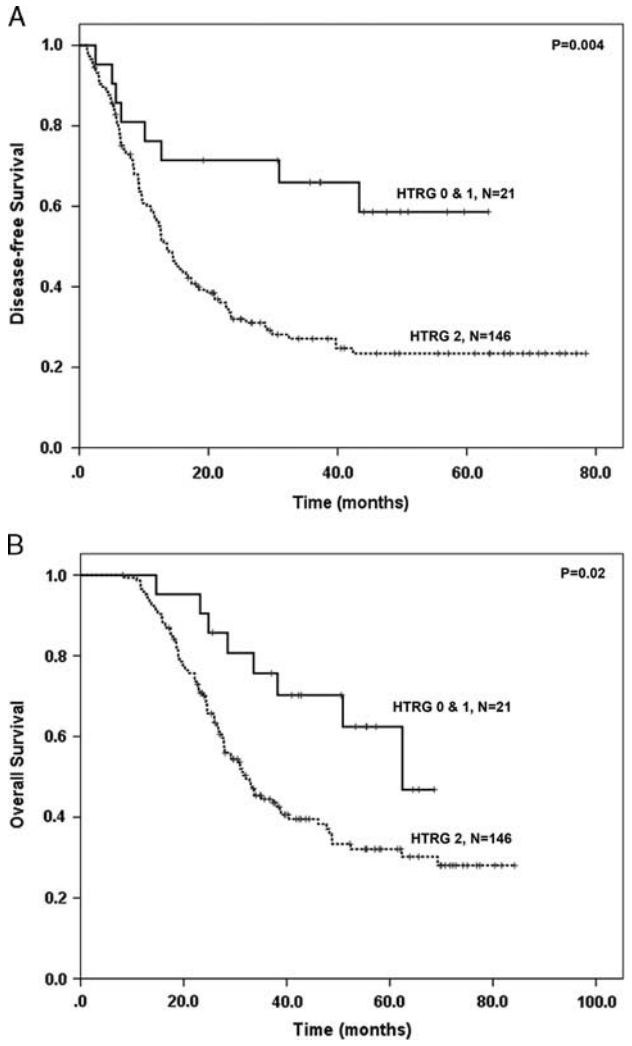

FIGURE 2. Kaplan-Meier curves of DFS (A) and OS (B) stratified by the proposed HTRG in patients with PDAC who received neoadjuvant chemoradiation followed by PD.

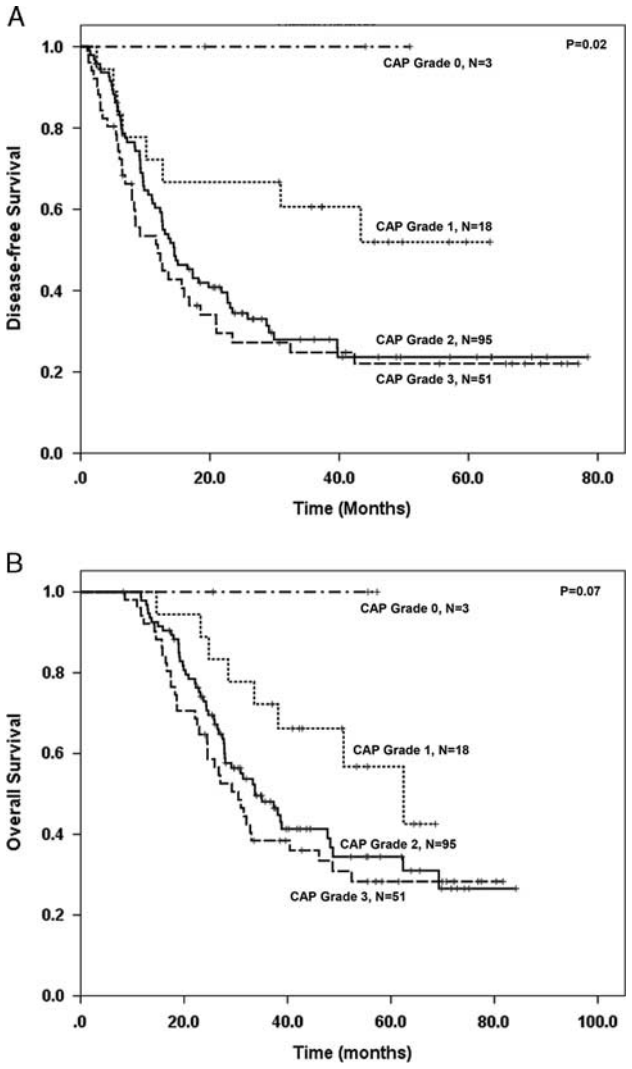

FIGURE 3. Kaplan-Meier curves of DFS (A) and OS (B) stratified by the CAP grading of tumor responses in patients with PDAC who received neoadjuvant chemoradiation followed by PD.

By univariate analysis, HTRG ($P = 0.006$), lymph node metastasis ($P < 0.001$), and AJCC stage ($P = 0.02$) correlated significantly with DFS. Tumor differentiation ($P = 0.02$), HTRG ($P = 0.02$), lymph node metastasis ($P = 0.001$), and AJCC stage ($P < 0.001$) correlated significantly with OS (Table 2). In multivariate analysis, HTRG 0 or 1 was an independent prognostic factor for better DFS ($P = 0.03$) but not OS ($P = 0.12$). The P value for OS is not significant in multivariate analysis probably because of the fact that the number of patients who had HTRG 0 or 1 response was relatively small (21/167, 12.6%). Lymph node metastasis was an independent prognosticator for both DFS ($P = 0.004$) and OS ($P = 0.002$; Table 3).

DISCUSSION

The current CAP grading scheme for tumor response in patients with PDAC who received neoadjuvant therapy is to evaluate the relative amount of residual tumor cells compared with background therapy-related fibrosis as follows: Grading 0, no viable residual tumor (pathologic complete response [pCR]); Grade 1, marked response (minimal residual cancer with single cells or small groups of cancer cells); Grade 2, partial response (residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells); and Grade 3, poor or no response (extensive residual cancer with no evident tumor regression).[21] This grading scheme for tumor response is the same as those used for carcinomas of esophagus, stomach, and rectum in the current CAP protocols. However, its prognostic significance in PDAC has not been validated. In our previous study of 223 patients with PDAC who received neoadjuvant chemoradiation therapies and PD, patients with either no residual tumor (CAP grade 0) or minimal residual tumor

TABLE 2. Univariate Cox Regression Analysis for DFS and OS in Relation to Clinicopathologic Parameters

		DFS		OS	
Variables	**No. Patients**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age at diagnosis	167	1.01 (0.99-1.03)	0.46	1.03 (1.004-1.06)	**0.02**
Sex					
Female (reference)	83	1.00	0.24	1.00	0.30
Male	84	0.89 (0.74-1.08)		0.90 (0.74-1.10)	
Tumor differentiation					
Well to moderate (reference)	104	1.00	0.11	1.00	**0.02**
Poor	63	1.36 (0.93-2.0)		1.60 (1.07-2.38)	
Margins					
Negative (reference)	5	1.00	0.39	1.00	0.28
Positive	162	1.55 (0.57-4.21)		1.75 (0.64-4.77)	
Lymph node					
Negative (ypN0, reference)	84	1.00	**< 0.001**	1.00	**0.001**
Positive (ypN1)	83	1.97 (1.35-2.88)		2.01 (1.34-3.01)	
Pathologic tumor stage					
ypT0-ypT2 (reference)	17	1.00	0.05	1.00	0.10
ypT3	150	2.05 (0.996-4.21)		1.85 (0.90-3.81)	
AJCC stage			**0.02**		**0.003**
Stage 0 and 1 (reference)	17	1.00		1.00	
Stage IIA	67	1.50 (0.70-3.20)	0.30	1.30 (0.60-2.81)	0.51
Stage IIB	83	2.73 (1.30-5.71)	0.008	2.46 (1.17-5.16)	0.02
HTRG					
HTRG 0 and 1 (reference)	21	1.00	**0.006**	1.00	**0.02**
HTRG 2	146	2.768 (1.344-5.704)		2.327 (1.13-4.81)	

Values in bold are statistically significant $P < 0.001$.
CI indicates confidence interval; HR, hazard ratio.

(< 5% of viable tumor, CAP grade 1) had better clinical outcome (mean DFS of 55.8 mo and OS of 79.2 mo) compared with those patients who had partial (CAP grade 2) or little response (CAP grade 3) with a mean DFS of 36.8 months and OS of 48.2 months.[18] However, we did not observe significant difference in either DFS or OS survival between the PDAC patients with CAP grade 2 and those with CAP grade 3 responses. The present study focused on validating our proposed 3-tier HTRG scheme, which is a potentially better method for assessing the extent of tumor response. We found that (1) HTRG 0 and 1 was associated with a lower frequency of lymph node metastasis, recurrence, lower ypT, and AJCC stage than those with HTRG 2 response, (2) patients with HTRG 0 and 1 had better DFS and OS than those with HTRG 2, and (3) HTRG 0 or 1 was an independent prognostic factor for better DFS. Similar to our previous study, there were no difference in either DFS or OS between the patients with CAP grade 2 and those with CAP grade 3 responses in the current study. Therefore the results from this study validate the proposed 3-tier HTRG scheme proposed in our previous study as follow: HTRG 0, no viable residual tumor (pCR); HTRG 1, marked response (< 5% viable tumor cells, minimal residual cancer with single cells or small groups of cancer cells); HTRG 2, moderate to poor response ($\geq$ 5% residual tumor cells). In the current study, 3 patients (1.8%) attained pCR after treatment with neoadjuvant therapy

TABLE 3. Multivariate Cox Regression Analysis for DFS and OS in Relation to Clinicopathologic Parameters

		DFS		OS	
Variables	**No. Patients**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Tumor differentiation					
Well to moderate (reference)	104	1.00	0.10	1.00	**0.01**
Poor	63	1.38 (0.94-2.02)		1.67 (1.12-2.51)	
Lymph node involvement					
Negative (ypN0, reference)	84	1.00	**0.004**	1.00	**0.002**
Positive (ypN1)	83	1.77 (1.20-2.59)		1.93 (1.27-2.92)	
Pathologic tumor stage					
ypT0-ypT2 (reference)	17	1.00	0.88	1.00	0.58
ypT3	150	0.94 (0.41-2.14)		0.78 (0.33-1.85)	
Histologic tumor response					
HTRG 0 and 1 (ref)	21	1.00	**0.03**	1.00	0.12
HTRG 2	146	2.32 (1.11-4.83)		1.80 (0.86-3.78)	

Values in bold are statistically significant $P < 0.001$.
CI indicates confidence interval; HR, hazard ratio.

and are alive with no evidence of recurrent or metastatic disease, which was similar to our previous report of 2.5% pCR from 442 patients.[17] Although the incidence of pCR is rarer in patients with potentially resectable PDAC compared with carcinomas from other gastrointestinal sites, possibly due to the aggressive nature of the disease, advanced stage of the disease at presentation, and lack of response to present chemotherapeutic regimens, we believe that it is better to separate HTRG 0 from HTRG 1 on the basis of the limited number of patients with HTRG 0 response in this study and our previous study.[18] In these 2 studies, HTRG 0 (CAP grade 0) response was observed totally in 9 patients (2.3%). None of these 9 patients had recurrence or died of PDAC during follow-up. In contrast, 8 of 18 patients with HTRG 1 (CAP grade 1) had recurrence and later died of disease in this study, and 15 of 36 patients with HTRG 1 (CAP grade 1) response died of disease in our previous study.[18] Because the number of patients with HTRG 0 response is too small to be used as a reference group in our survival analysis, we combine HTRG 0 and 1 as 1 group for statistical analysis in these 2 studies.

In treated esophageal, gastric, and rectal adenocarcinomas, the predominant histologic response to cytotoxic treatment and/or radiation is therapy-related ulceration and fibrosis. It is relatively easy to evaluate the HTRG on the basis of the extent of therapy-related fibrosis in the tumor bed of these tumors. In contrast, PDAC characteristically has abundant dense desmoplastic stroma, which is almost impossible to distinguish from therapy-related fibrosis in posttherapy PD specimens. The infiltrative growth pattern of PDAC often has widely dispersed neoplastic glands in the stroma and/or the chronic pancreatitis tissue in adjacent pancreatic parenchyma. Often, the fibrosis of chronic pancreatitis can mimic the sclerotic stroma of the carcinomas, obscuring the border of the tumor and surrounding pancreatitis. These factors make it difficult to accurately evaluate the boundary and exact size of the primary tumor bed in a treated pancreatic specimen.[22] Therefore the assessment of the percentage of viable residual tumor based on the relative amount of background therapy-related fibrosis may be highly variable among the pathologists.[23,24] In our previous and current studies, we defined HTRG 1 as minimal residual cancer with single tumor cells or small groups of tumor cells after completely embedding or extensive sampling the resected pancreas using a 5% cutoff value of residual viable PDAC cells. HTRG 0 was defined as no viable residual tumor after complete embedding of the pancreas, bile duct, and ampulla of Vater. The cases with $\geq 5\%$ residual tumor cells were classified as HTRG 2 (CAP grade 2 and 3). On the basis of this modified grading scheme, evaluation of HTRG would not be compounded by the above-mentioned factors. Thus our 3-tier HTRG scheme can be easily applied in practice and may greatly reduce the interobserver variability among the pathologists. Similar to our study, in a study for comparing TRG schemes of rectal adenocarcinoma after neoadjuvant therapy, Bateman et al[25] proposed a modified rectal cancer regression grade (RCRG) scheme with a 5% cutoff value for dividing grade 1 or 2 as follows: m-RCRG 1 had no tumor epithelium or scattered foci of malignant epithelium representing $< 5\%$ of the tumor; in m-RCRG 2 tumor cells comprise 5% to 50% of the tumor bed; and m-RCRG 3 is defined having $> 50\%$ of the tumor cells. They found that their proposed modified TRG scheme for rectal carcinoma after neoadjuvant therapy was reproducible with good interobserver variability. Our study had potential limitations, which include the retrospective nature of this study and that all patients are from a single institution. Future multi-institutional studies to examine the interobserver concordance and reproducibility of tumor regression grading schemes for treated PDAC are needed to validate our proposed HTRG scheme.

Recent studies demonstrated that patients with a partial response of esophageal and gastric carcinomas and m-RCRG 2 of rectal carcinoma were correlated with better clinical outcome and prognosis compared with those with almost no response or m-RCRG 3 in rectal carcinoma.[25–28] However, in PDAC patients who received neoadjuvant therapy and subsequent surgery, we did not observe significant difference in either DFS or OS between the patients with CAP grade 2 and those with CAP grade 3 responses ($P > 0.05$) in both studies. Therefore a partial or incomplete response of PDAC to neoadjuvant therapy is not correlated with better clinical outcome, and determination of $> 50\%$ or $< 50\%$ of viable residual tumor appears not to have any prognostic impact. The difference in prognostic significance of partial response in PDAC from those observed in esophageal or rectal carcinomas may reflect the difference in tumor biology among these tumors.

In conclusion, our study has validated our proposed 3-tier grading scheme for assessing the extent of histologic tumor response from our previous study (TRG 0, no viable tumor; TRG 1, $< 5\%$ viable tumor cells; TRG 2, $\geq 5\%$ viable tumor cells). Although our study has limitations such as data from a single institution and retrospective nature of the study, our studies represent the largest cohorts with standardized pathologic examination. Our proposed TRG grade scheme is simple and easily applicable by the pathologist with a significant prognostic relevance in evaluation of histologic response in posttherapy PD specimens. This scheme might be used as a reliable surrogate with a high reproducibility among observers and might influence important clinical decision-making and postoperative therapeutic strategies and follow-up surveillance in patients with posttherapy PDAC.

REFERENCES

1. Muniraj T, Barve P. Laparoscopic staging and surgical treatment of pancreatic cancer. *N Am J Med Sci*. 2013;5:1–9.
2. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–1210.
3. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358:1576–1585.

4. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;120:899–903.
5. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297:267–277.
6. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304:1073–1081.
7. Wang Z, Li Y, Ahmad A, et al. Pancreatic cancer: understanding and overcoming chemoresistance. *Nat Rev Gastroenterol Hepatol*. 2011;8:27–33.
8. Crane CH, Varadhachary G, Wolff RA, et al. The argument for preoperative chemoradiation for localized, radiographically resectable pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2006;20:365–382.
9. Estrella JS, Rashid A, Fleming JB, et al. Post-therapy pathologic stage and survival in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant chemoradiation. *Cancer*. 2012;118:268–277.
10. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg*. 1992;127:1335–1339.
11. Abbott DE, Tzeng CW, Merkow RP, et al. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. *Ann Surg Oncol*. 2013;20(Suppl 3):S500–S508.
12. Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. *Ann Surg Oncol*. 2009;16:836–847.
13. O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. *Ann Surg*. 2014;260:142–148.
14. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008;26:3487–3495.
15. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008;26:3496–3502.
16. Roland CL, Yang AD, Katz MH, et al. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. *Ann Surg Oncol*. 2015;22:1168–1175.
17. Zhao Q, Rashid A, Gong Y, et al. Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. *Ann Diagn Pathol*. 2012;16:29–37.
18. Chatterjee D, Katz MH, Rashid A, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer*. 2012;118:3182–3190.
19. Washington K, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with carcinoma of the exocrine pancreas. *Coll Am Pathol*. 2016. Available at: http://www.cap.org/web/home/resources/cancer-reporting-tools.
20. Edge SB. *Exocrine and Endocrine Pancreas AJCC Cancer Staging Manual*, 7th ed. New York, NY: Springer; 2010:285–296.
21. Chetty R, Gill P, Govender D, et al. International study group on rectal cancer regression grading: interobserver variability with commonly used regression grading systems. *Hum Pathol*. 2012;43:1917–1923.
22. Verbeke C, Lohr M, Severin Karlsson J, et al. Pathology reporting of pancreatic cancer following neoadjuvant therapy: Challenges and uncertainties. *Cancer Treatment Rev*. 2015;41:17–26.
23. Hruban RH, Klimstra DS. Adenocarcinoma of the pancreas. *Semin Diagn Pathol*. 2014;31:443–451.
24. Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. *Histopathology*. 2011;59:1111–1121.
25. Bateman AC, Jaynes E, Bateman AR. Rectal cancer staging post neoadjuvant therapy—how should the changes be assessed? *Histopathology*. 2009;54:713–721.
26. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer*. 2003;98:1521–1530.
27. Sannier A, Lefevre JH, Panis Y, et al. Pathological prognostic factors in locally advanced rectal carcinoma after neoadjuvant radiochemotherapy: analysis of 113 cases. *Histopathology*. 2014;65:623–630.
28. Davies AR, Gossage JA, Zylstra J, et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. *J Clin Oncol*. 2014;32:2983–2990.