Gut and Liver
https://doi.org/10.5009/gnl20312
pISSN 1976-2283 eISSN 2005-1212

Original Article

Four-Tier Pathologic Tumor Regression Grading System Predicts the Clinical Outcome in Patients Who Undergo Surgical Resection for Locally Advanced Pancreatic Cancer after Neoadjuvant Chemotherapy

Soomin Ahn[1]*, Jong-chan Lee[2], Jaihwan Kim[2], Young Hoon Kim[3], Yoo-Seok Yoon[4], Ho-Seong Han[4], Haeryoung Kim[5], and Jin-Hyeok Hwang[2]

Departments of [1]Pathology, [2]Internal Medicine, [3]Radiology, and [4]Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, and [5]Department of Pathology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Article Info

Received October 13, 2020
Revised January 11, 2021
Accepted January 25, 2021
Published online April 23, 2021

Corresponding Author

Jin-Hyeok Hwang
ORCID https://orcid.org/0000-0002-5643-8461
E-mail woltoong@snu.ac.kr

*Current affiliation: Department of Pathology and Translational Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Background/Aims: Neoadjuvant chemotherapy is increasingly utilized in patients with borderline or locally advanced pancreatic cancer (LAPC). However, the pathologic evaluation of tumor regression is not routinely performed or well established. We aimed to evaluate the prognostic value of three tumor regression grading systems frequently used in LAPC and to determine the correlation between pathologic and clinical response.

Methods: We included a total of 38 patients with LAPC who were treated with neoadjuvant chemotherapy and subsequent resection. Pathologic tumor regression was graded based on the College of American Pathologists (CAP), Evans, and MD Anderson grading systems.

Results: One out of 38 patients (2.6%) achieved a pathologic complete response. Unlike other grading systems (Evans, p=0.063; MD Anderson, p=0.110), the CAP grading system was a significant prognostic factor for overall survival (p=0.043). Pathologic N stage (p=0.023), margin status (p=0.044), and radiologic response (p=0.016) correlated with overall survival. In the multivariate analysis, CAP 3 was an independent predictor of shorter overall survival (p=0.026). The CAP grading system correlated with the radiologic response (p=0.007) but not the carbohydrate antigen 19-9 level (p=0.333).

Conclusions: The four-tier CAP pathologic tumor regression grading system predicted the clinical outcome in LAPC patients who underwent resection after neoadjuvant chemotherapy. Therefore, a more comprehensive pathologic evaluation is warranted in these patients. **(Gut Liver 2022;16:129-137)**

Key Words: Pancreatic neoplasms; Neoadjuvant therapy; Tumor regression grading

INTRODUCTION

Pancreatic cancer (PC) is a highly aggressive tumor with increasing incidence.[1] Surgical resection is the only known curative option for PC. However, only 15% to 20% of patients are diagnosed with resectable PC.[2] In the era of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel, there is growing evidence supporting the use of neoadjuvant chemotherapy in borderline resectable/locally advanced PC (LAPC) patients; this strategy has become widely accepted in the clinical setting.[3,4] Neoadjuvant chemotherapy is considered to provide better patient selection for surgery, offer much higher R0 resection rate, and improve survival rates for patients with borderline PC or LAPC.[5,6]

While recent advances in neoadjuvant chemotherapy in patients with LAPC have been remarkable, the pathologic evaluation of tumor regression in resection specimen has not made much progress. Pathologic evaluation in post-chemotherapy specimens is widely used and provides prog-

nostic information in colon and breast cancers. However, it is yet to be established in PC. In a recent meta-analysis of 5,520 PC patients treated with neoadjuvant chemotherapy, only 37.5% of studies included tumor regression data.[7] In addition, data regarding the prognostic value of tumor regression score in PC are still limited.[8-12] One of significant limitations of the application of tumor regression grading system in the clinical setting is the lack of standardization.[8] Currently, there are several pathologic tumor regression grading systems; the three most frequently used grading systems are: three-tier MD Anderson, four-tier College of American Pathologists (CAP), and five-tier Evans grading system.[11,13,14] The main aim of our study is to evaluate the prognostic value of three frequently used tumor regression grading systems in PC and to determine a correlation between pathologic response and clinical response based on the radiology and carbohydrate antigen 19-9 (CA19-9) level.

MATERIALS AND METHODS

1. Patient cohort

This retrospective study included LAPC patients who underwent neoadjuvant chemotherapy and subsequent surgical resection at Seoul National University Bundang Hospital, Korea, between June 2005 and June 2017. We excluded histologic variants other than ductal adenocarcinomas and intraductal papillary mucinous neoplasm-associated carcinomas. Patients who had distant metastasis at the time of operation were excluded. Finally, a total of 38 patients were selected in this study. Clinical data, including age, sex, tumor location, operation, chemotherapy, concurrent radiotherapy, CA19-9, and survival, were retrieved from the medical records. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number: B-2001-586-106); the requirement for informed consent was waived due to the retrospective nature of the study.

2. Pathologic evaluation

The pathologic staging was determined according to the American Joint Committee on Cancer 8th edition. Our institution applied the standardized gross examinations of pancreatic specimen using the axial cutting and entire tissue sampling since 2014, and reported detailed margin status, including posterior surface, superior mesenteric artery, and superior mesenteric vein (SMV)/portal vein (PV) groove for pancreaticoduodenectomy/pylorus-preserving pancreaticoduodenectomy specimens. For head/uncinate process cancers, the margin status was comprehensively evaluated, including SMV/PV groove margin and superior mesenteric artery margin. In the case of pancreatic tail cancers, posterior margin was comprehensively evaluated, and anterior surface involvement was not considered as margin positive. Pathological findings on the full sections of the resected specimen were evaluated in 28 of 38 cases (73.7%). The margin status was classified into three groups: (1) safety distance of 0 mm; (2) safety distance 0–1 mm; and (3) safety distance >1 mm. Data on tumor size, nodal status, and margin status were extracted from original pathology reports. For the evaluation of pathologic tumor regression grading system, the hematoxylin and eosin-stained slides of all patients were reviewed by a single pathologist who specialized in pancreatobiliary pathology (S.A.), blinded to all clinical information. The pathologic tumor regression grading systems was graded according to three grading systems (Table 1, Fig. 1).[11,13,14]

3. Radiologic response

Computed tomography images were reviewed by a radiologist who specializes in abdominal imaging (Y.H.K.),

Table 1. Tumor Regression Grading Systems for Pancreatic Ductal Adenocarcinoma after Neoadjuvant Chemotherapy

Tumor regression grading system	Score	Criteria
College of American Pathologist[13]	0	No viable cancer cells (complete response)
	1	Single cells or rare groups of cancer cells (near complete response)
	2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells (partial response)
	3	Extensive residual cancer with no evident tumor regression (poor or no response)
Evans[14]	I	<10% or no tumor cell destruction
	IIa	Destruction of 10%–50% of tumor cells
	IIb	Destruction of 51%–90% of tumor cells
	III	Few (<10%) tumor cells present
	IV	No viable tumor cells present
MD Anderson[11]	0	No residual carcinoma (complete response)
	1	Minimal residual carcinoma (single cells or rare groups of cancer cells, <5% residual carcinoma)
	2	>5% residual carcinoma

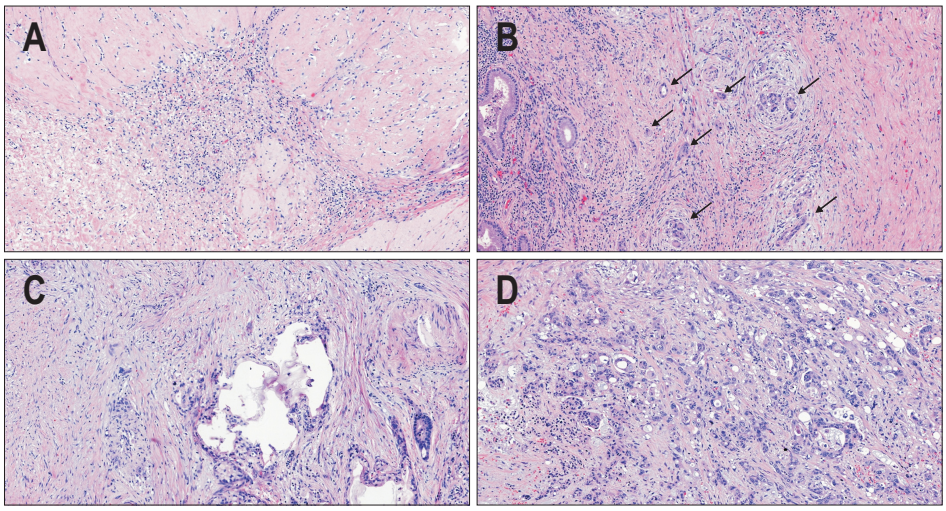

Fig. 1. Representative images of College of American Pathologists (CAP) tumor regression grading system in pancreatic cancer. (A) CAP score 0: no viable cancer cells (complete response) (H&E, ×10). (B) CAP score 1: single cells or rare groups of cancer cells (near complete response) (arrows: cancer cells, H&E, ×10). (C) CAP score 2: residual cancer with evident tumor regression but more than single cells or rare groups of cancer cells (partial response) (H&E, ×10). (D) CAP score 3: extensive residual cancer with no evidence of tumor regression (poor or no response) (H&E, ×10).

blinded to all clinicopathologic information. The maximum diameter of pancreatic mass at the time of initial diagnosis and after completion of neoadjuvant chemotherapy was measured. The radiologic response was evaluated following the response evaluation criteria in solid tumors (RECIST) criteria version 1.1,[15] and determined among progressive disease, stable disease, partial response, and complete response.

4. Statistical analyses

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Survival analysis was performed using the Kaplan-Meier method and was compared using the log-rank test. Univariate and multivariate analysis with the calculation of hazard ratios and 95% confidence interval (CI) for overall survival (OS) was performed using the Cox proportional hazard model. Contingency tables and the Mantel-Haenszel chi-square tests were used to correlate the radiologic and CA19-9 response and pathologic response score. The correlation between radiologic tumor size and pathologic tumor size was evaluated using the Spearman rank correlation assay. A p-value <0.05 was considered to be significant.

RESULTS

1. Patient demographics and their associations with OS

The patient demographics are presented in Table 2. The age of patients at diagnosis ranged from 30 to 73 years (median, 59 years). Among all patients, 50% were male. The location of tumor was head/uncinate process in 47.4%, and body/tail in 52.6%. For neoadjuvant regimen, gemcitabine-based chemotherapy was administered in 60.5% and FOLFIRINOX was administered in 39.5%. Radiotherapy was performed in 28.9%. Radiologically, 29 patients (76.3%) achieved partial response, and the remainder (23.7%) had stable disease. The type of surgery was total pancreatectomy in 5.3%, pancreaticoduodenectomy/pylorus-preserving pancreaticoduodenectomy in 44.7%, and distal pancreatectomy in 50.0%. Major vessel resection (SMV, PV, or celiac axis) was accompanied in 42.1%.

During the median follow-up period of 37 months, median OS was 32.75 months (95% CI, 30.53 to 43.58). Cumulative survival rate at 2 and 5 years was 76.3% and 31.8%, respectively. Among clinical factors, stable disease of RECIST criteria was significantly associated with OS in univariate analysis (hazard ratio, 2.86; 95% CI, 1.17 to 6.99; p=0.021).

2. Pathologic findings and their associations with OS

The pathologic findings are summarized in Table 3. Of 38 patients, one patient (2.6%) revealed no residual tumor in the resection specimen. Of the 38 patients, the pathologic T stage, based on the American Joint Committee on Cancer 8th criteria, was ypT0 in one patient (2.6%), ypT1c in five patients (13.2%), ypT2 in 24 patients (63.2%), and ypT3 in eight patients (21.1%). Of these 38 patients, the pN stage, according to the American Joint Committee on Cancer 8th criteria, was ypN0 in 19 patients (50.0%), ypN1 in 17 patients (44.7%), and ypN2 in two patients (5.3%). While the pT stage was not associated with OS (p=0.310), pN stage correlated with OS (p=0.005) (Fig. 2A).

R1 status (safety margin=0 mm) was observed in seven out of 38 patients (18.4%), and was revealed as an unfavorable prognostic factor in the Kaplan-Meier curve (p=0.034) (Fig. 2B). In detail, of the 38 patients, safety distance >1 mm, safety distance 0–1 mm, and safety distance of 0 mm were observed in 21 (55.3%), 10 (26.3%), and seven patients (18.4%), respectively. When 1 mm clearance rule was

Table 2. Patient Cohort Demographics and Univariate Cox Regression Analysis of Clinical

Variable	No. of patient (%)	Overall survival		
		HR	95% CI	p-value
Age, yr				0.265
≤65	21 (55.3)	Reference		
>65	17 (44.7)	1.66	0.68–4.06	
Sex				0.603
Male	19 (50.0)	Reference		
Female	19 (50.0)	0.80	0.34–1.88	
Tumor location				0.262
Head/uncinate process	18 (47.4)	Reference		
Body/tail	20 (52.6)	1.68	0.68–4.18	
Operation type				0.260
Total pancreatectomy	2 (5.3)	Reference		
Pancreaticoduodenectomy/PPPD	17 (44.7)	0.29	0.06–1.47	
Distal pancreatectomy	19 (50.0)	0.52	0.11–2.42	
Major vessel excision				0.921
Not performed	22 (57.9)	Reference		
SMV/PV resection	14 (36.8)	0.88	0.35–2.22	
Celiac axis resection	2 (5.3)	0.70	0.09–5.38	
Chemotherapy				0.810
Gemcitabine-based	23 (60.5)	Reference		
FOLFIRINOX	15 (39.5)	0.89	0.36–2.23	
Radiotherapy				0.085
Not performed	27 (71.1)	Reference		
Performed	11 (28.9)	0.40	0.14–1.14	
RECIST 1.1				0.021
Complete response	0			
Partial response	29 (76.3)	Reference		
Stable disease	9 (23.7)	2.86	1.17–6.99	
Progressive disease	0			

HR, hazard ratio; CI, confidence interval; PPPD, pylorus-preserving pancreaticoduodenectomy; SMV, superior mesenteric vein; PV, portal vein; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; RECIST, response evaluation criteria in solid tumors.

applied (safety margin >1 mm vs ≤1 mm), however, it was not statistically significant for predicting OS (p=0.185). Of the 17 patients with safety distance ≤1 mm, the involved margin site was pancreatic neck (n=3), SMV/PV grove margin (n=3), SMV margin (n=1), superior mesenteric artery margin (n=2), posterior margin (n=10) and splenic artery margin (n=1). Some cases showed involvement of multiple margins.

Resection of the major vessel (SMV, PV, or celiac axis) was performed in 16 of 38 patients, of which vascular invasion was pathologically confirmed in six patients. Vascular resection and pathologically confirmed vascular involvement were not associated with OS (vascular resection, p=0.921; vascular tumor involvement, p=0.537) (Tables 2, 3).

When CAP grading system was applied, the number of patients with a CAP score of 0 (complete response), score of 1 (near complete response), score of 2 (partial response), and score of 3 (poor response) was one (2.6%), one (2.6%), 14 (36.8%), and 22 (57.9%), respectively, out of the 38 patients (Fig. 1). Based on the Evans grading system, the number of I, IIa, IIb, III, and IV was four (10.5%), 25 (65.8%), six (15.8%), two (5.3%), and one (2.6%), respectively. Based on the MD Anderson grading system, the number of patients with a score of 0, 1, and 2 was one (2.6%), one (2.6%), and 36 (94.7%), respectively, out of the 38 patients. The Kaplan-Meier survival curves indicated that only the CAP grading system was a significant prognostic factor (p=0.043) predicting OS (Fig. 3A). Meanwhile, the Evans grading and MD Anderson grading systems had no statistical significance in predicting OS, based on the Kaplan-Meier survival curves (Evans, p=0.063; MD Anderson, p=0.110) (Fig. 3B and C). In univariate analysis, CAP 3 was associated with unfavorable outcome, compared with CAP 0-2 (hazard ratio, 2.97; 95% CI, 1.14 to 7.72; p=0.026). In multivariate analysis, CAP 3 was an independent predictor of shorter OS (p=0.026) (Table 4).

3. Correlation between radiologic and biochemical response and pathologic response

The correlation between tumor size measured in preoperative computed tomography and pathologic tumor size

Table 3. Pathologic Findings and Univariate Cox Regression Analysis of Pathologic Factors

Variable	No. of patient (%)	Overall survival		
		HR	95% CI	p-value
T stage				0.490
ypT0	1 (2.6)	Reference		
ypT1c	5 (13.2)	1.60	0.07–39.36	
ypT2	24 (63.2)	2.40	0.12–47.57	
ypT3	8 (21.1)	4.24	0.20–88.88	
N stage				0.023
ypN0	19 (50.0)	Reference		
ypN1	17 (44.7)	1.39	0.56–3.45	
ypN2	2 (5.3)	10.11	1.94–52.66	
Margin status				0.044
Negative	31 (81.6)	Reference		
Positive (safety distance=0 mm)	7 (18.4)	3.03	1.03–8.86	
Vessel invasion (SMV, PV, celiac axis)				0.537
Absent	32 (84.2)	Reference		
Present	6 (15.8)	1.48	0.43–5.18	
CAP tumor regression grading				0.026
0	1 (2.6)			
1	1 (2.6)			
2	14 (36.8)	Reference (0, 1, 2)		
3	22 (57.9)	2.97	1.14–7.72	
Evans tumor regression grading				0.118
I	4 (10.5)	Reference (IIb, III, IV) vs I, IIa		
IIa	25 (65.8)	2.68	0.78–9,196.00	
IIb	6 (15.8)			
III	2 (5.3)			
IV	1 (2.6)			
MD Anderson tumor regression grading				0.306
0	1 (2.6)	Reference (0, 1) vs 2		
1	1 (2.6)	25.19	0.05–12,078.27	
2	36 (94.7)			

HR, hazard ratio; CI, confidence interval; SMV, superior mesenteric vein; PV, portal vein; CAP, College of American Pathologists.

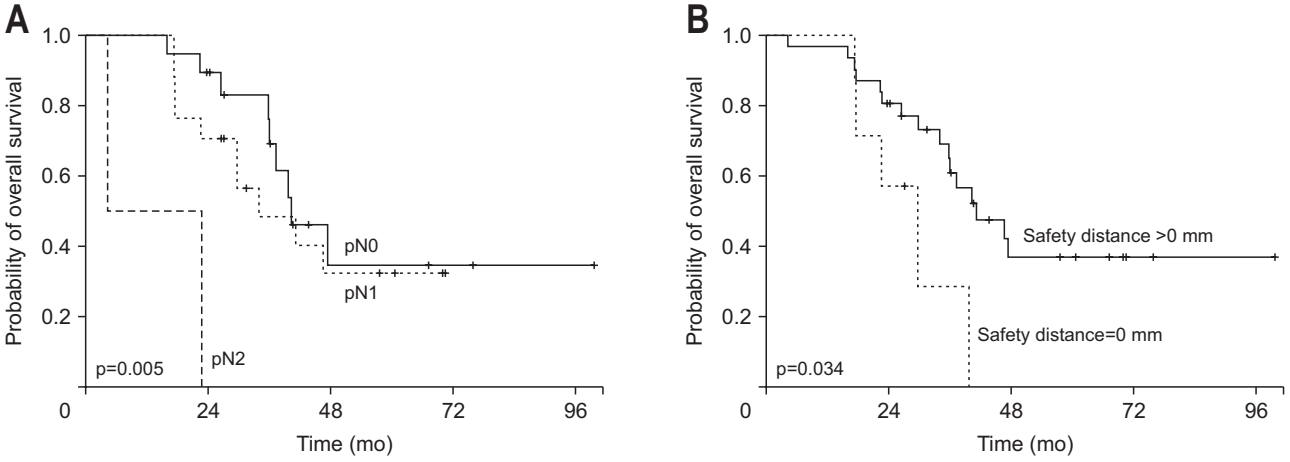

Fig. 2. Correlations of nodal status and margin status with overall survival. (A) Kaplan-Meier curves indicate that the pathologic nodal status is a significant prognostic factor predicting overall survival. (B) Kaplan-Meier curves indicate that conventional resection margin status is a significant prognostic factor predicting overall survival (R0 vs R1).

is depicted in Fig. 4. As expected, there was a correlation between the radiologic and pathologic tumor size (Spearman correlation value=0.551, p<0.001). Notably, the pathologic tumor size was larger than radiologic tumor size in 29 of 38 cases (76.3%). As only the CAP grading system showed a prognostic significance, its correlation with the radiologic

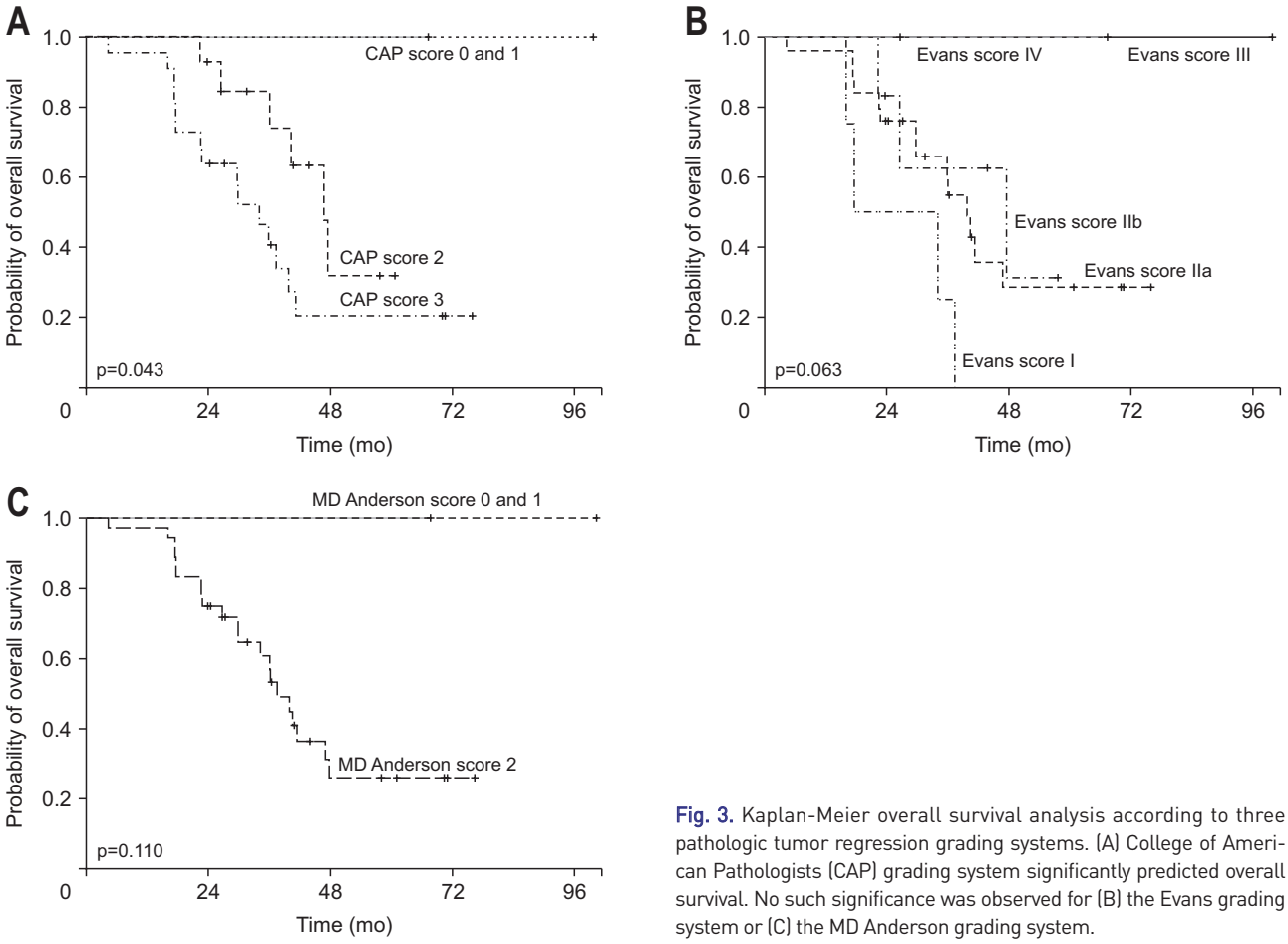

Fig. 3. Kaplan-Meier overall survival analysis according to three pathologic tumor regression grading systems. (A) College of American Pathologists (CAP) grading system significantly predicted overall survival. No such significance was observed for (B) the Evans grading system or (C) the MD Anderson grading system.

Table 4. Multivariate Cox Regression Analysis for Overall Survival

Variable	No. of patient (%)	Multivariate analysis		
		HR	95% CI	p-value
RECIST 1.1				
Complete response	0			0.246
Partial response	29 (76.3)	Reference		
Stable disease	9 (23.7)	1.829	0.659–5.074	
Progressive disease	0			
N stage				0.716
ypN0	19 (50.0)	Reference (ypN0) vs ypN1 and 2		
ypN1	17 (44.7)	1.182	0.482–2.899	
ypN2	2 (5.3)			
Margin status				0.313
Negative	31 (81.6)	Reference		
Positive (safety distance=0 mm)	7 (18.4)	1.794	0.577–5.574	
CAP tumor regression grading				0.026
0	1 (2.6)			
1	1 (2.6)			
2	14 (36.8)	Reference (0, 1, 2)		
3	22 (57.9)	2.970	1.140–7.720	

HR, hazard ratio; CI, confidence interval; RECIST, response evaluation criteria in solid tumors; CAP, College of American Pathologists.

and CA19-9 response was evaluated. The radiologic response was significantly correlated with the CAP pathologic tumor regression grading system (p=0.007) (Table 5). While 44.8% of partial response cases were classified as the worst group (CAP 3) in the CAP criteria, all cases that had a radiologically stable disease were classified as the worst group (CAP 3).

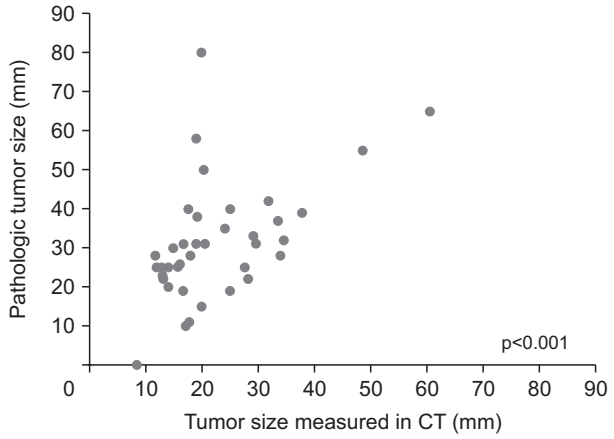

Fig. 4. Correlation between radiologic tumor size measured on preoperative computed tomography (CT) and pathologic tumor size. There was a correlation between radiologic and pathologic tumor sizes (Spearman correlation value=0.551).

Patients with an initial elevated CA19-9 (n=24) were divided into two groups: the elevated then normalized (n=10) and elevated then still elevated (n=14) groups. There was no significant correlation between the change of CA19-9 response and the pathologic regression score (p=0.333). In addition, any decrease of CA19-9 was not correlated with pathologic regression score (p=1.000) (data not shown).

DISCUSSION

Although the standard of care for resectable PC remains to be "complete resection" followed by adjuvant chemotherapy, more than 80% of PC patients do not have the opportunity to receive surgery at diagnosis due to local invasion or distant metastasis.[16] Since the introduction of FOLFIRINOX, the role of neoadjuvant chemotherapy (FOLFIRINOX or gemcitabine plus nab-paclitaxel) has been expanded in borderline resectable PC as well as LAPC, considering higher RO resection rate and its favorable outcomes.[5] In the era of changing strategy (from upfront surgery to neoadjuvant therapy followed by surgery) for borderline resectable PC, even for resectable PC, we aimed to evaluate the prognostic significance of three different pathologic tumor regression grading systems in LAPC; CAP, Evans, and MD Anderson criteria, because the tumor regression grading in PC has not been standardized and regarding data are limited.[17,18] In the current study, only the four-tier CAP grading system revealed a good correlation with the long-term prognosis as well as with radiologic response.

Among the various grading systems, the Evans tumor regression grading system is known to be widely used in clinical studies.[14,17] However, in a previous study of 223 PC patients, the CAP grading system was more prognostic for OS than the Evans grading system.[11] Recently, Kim *et al.*[8] examined the tumor regression grading of the residual tumor in 32 homogeneous group of PC patients (FOLFIRINOX only without radiation), and showed that both the Evans and CAP grading systems were prognostic for OS. Meanwhile, the MD Anderson grading system is a three-tier grading system; Lee *et al.*[9] validated its prognostic significance in 167 PC patients and suggested that it is a simple and easy-to-apply method in daily practice. Each system has its own advantages and disadvantages, and utilization depends largely on the preference of the institution. Although the number of patients was not large in the current study, the CAP grading system was the only grading system that provided prognostic information on OS. Unlike other cancers, no or minimally residual tumor was observed only in a few cases even after intensive neoadjuvant chemotherapy because PC is well known to be chemoresistant. Therefore, when the three-tier MD Anderson criteria was applied, most cases were classified into the worst group (score 2: >5% residual carcinoma). The four-tier CAP grading system seems to be more applicable in real practice, due to its relative simplicity when compared with the Evans grading system, while providing the benefit of distinguishing between partial and poor response groups. However, a large prospective cohort study is warranted to validate these results for the standardization of tumor regression grading.

Recently, margin assessment based on 1 mm clearance has been widely used in resected PC,[19] and it has been reported that patients with a resection margin of 0–1 mm had better outcome than those with 0 mm margin, but worse outcome than those with >1 mm margin.[20] Although we failed to demonstrate statistical significance of three categories of margin status, this margin classification tended to show different trend of OS (data not shown). On the other hand, conventional margin assessment by 0 mm showed prediction of OS in our study. In colorectal

Table 5. Correlation between Radiologic Response (RECIST 1.1) and Pathologic Response Score (CAP)

Pathologic response	Radiologic response				p-value
	CR	PR	SD	PD	
CAP score					0.007
0&1	0	2 (6.90)	0	0	
2	0	14 (48.28)	0	0	
3	0	13 (44.83)	9 (100)	0	

RECIST, response evaluation criteria in solid tumors; CAP, College of American Pathologists; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

cancers, a specimen with tumor ≤1 mm from the inked margin was considered as a positive circumferential margin, regardless of neoadjuvant treatment.[21,22] However, in PC, data on margin comparing 0 mm versus 1 mm clearance are lacking in neoadjuvant setting. Studies evaluating the margin comparing neoadjuvant setting versus upfront surgery setting in PC are needed.

Next, we correlated the pathologic response with clinical response based on RECIST 1.1. While data on radiologic-pathologic correlation in neoadjuvant setting are still limited,[23,24] radiologic response has been reported to correlate with pathologic response.[24] We also observed the correlation between the radiologic and pathologic tumor sizes. Notably, pathologic tumor size measured in specimens was larger than radiologic tumor size in 76.3% of cases. Radiologic response evaluation has certain limitations due to its difficulty in radiologically distinguishing between fibrosis and tumor involvement. In terms of prognosis, there have been controversies on prognostic significance of radiologic response.[25] In the present study, RECIST itself revealed a prognostic significance for OS. The RECIST partial response group showed more favorable OS than the RECIST stable disease group.

CA19-9 is used as a prognostic biomarker for PC, especially with regard to predicting prognosis following treatment.[26] However, its prognostic value remains controversial in neoadjuvant setting.[25,27] It has been reported that CA19-9 response was an independent prognostic factor which could allow a better selection of patients who would benefit from resection after neoadjuvant chemotherapy.[27] However, Xia *et al.*[23] reported that 15.4% of patients with pathologic response and 20% of patients with a poor pathologic response had normalization of CA19-9, and the majority of patients with a pathologic response demonstrated a survival benefit despite lack of CA19-9 normalization. Similarly, four-fifths of CA19-9 normalization revealed a poor pathologic response and CA19-9 response did not correlate with pathologic response in the present study. However, large-scale studies are needed to determine the prognostic significance of CA19-9 response in neoadjuvant setting.

Our study had several other limitations in addition to having a small number of patients. First, this is a retrospective study in a single institution. Second, the enrolled population was heterogeneous, including various chemotherapy regimens and radiation therapies. Lastly, the issue of interobserver variability on tumor regression grading can be raised.[18,28] Despite these limitations, our study may add valuable information in pathological evaluation from the perspective of a pathologist, showing which system best correlates with long-term outcomes in resected LAPC after neoadjuvant treatment. Although several studies have reported the prognostic value of tumor regression grading systems in PC, each used a different grading system which is not standardized and applied a simple classification such as complete response versus the rest. However, our results cannot be generalized due to the limitation of this study being a retrospective analysis in a small number of patients.

In conclusion, we applied three pathologic tumor regression grading systems in PC specimens after neoadjuvant chemotherapy and found that the four-tier CAP tumor regression grading system was prognostic for OS. Nonetheless, a further larger prospective cohort study is warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception: J.H.H. Data collection: S.A., J.L., J.K., Y.H.K., Y.S.Y., H.S.H., H.K. Data analysis: S.A., J.L. Writing: S.A. Review and editing: J.H.H. Approval of final manuscript: all authors.

ORCID

Soomin Ahn https://orcid.org/0000-0001-8243-2445
Jong-chan Lee https://orcid.org/0000-0001-6590-2353
Jaihwan Kim https://orcid.org/0000-0003-0693-1415
Young Hoon Kim https://orcid.org/0000-0001-5554-3828
Yoo-Seok Yoon https://orcid.org/0000-0001-7621-8557
Ho-Seong Han https://orcid.org/0000-0001-9659-1260
Haeryoung Kim https://orcid.org/0000-0002-4205-9081
Jin-Hyeok Hwang https://orcid.org/0000-0002-5643-8461

REFERENCES

1. Saad AM, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. BMC Cancer 2018;18:688.
2. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. Br J Surg 2004;91:1410-1427.

3. Balaban EP, Mangu PB, Yee NS. Locally advanced unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline summary. J Oncol Pract 2017;13:265-269.
4. Heinrich S, Lang H. Neoadjuvant therapy of pancreatic cancer: definitions and benefits. Int J Mol Sci 2017;18:1622.
5. Russo S, Saif MW. Neoadjuvant therapy for pancreatic cancer: an ongoing debate. Therap Adv Gastroenterol 2016;9:429-436.
6. 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.
7. Dhir M, Malhotra GK, Sohal DPS, et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. World J Surg Oncol 2017;15:183.
8. Kim SS, Ko AH, Nakakura EK, et al. Comparison of tumor regression grading of residual pancreatic ductal adenocarcinoma following neoadjuvant chemotherapy without radiation: would fewer tier-stratification be favorable toward standardization? Am J Surg Pathol 2019;43:334-340.
9. Lee SM, Katz MH, Liu L, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. Am J Surg Pathol 2016;40:1653-1660.
10. 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.
11. 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.
12. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. Ann Surg 2021;273:341-349.
13. Shi C, Adsay V, Bergsland EK, et al. Protocol for the examination of specimens from patients with tumors of the endocrine pancreas. Version PancreasExocrine 4.0.0.1. Northfield: College of American Pathologists, 2017.
14. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335-1339.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.
16. Lambert A, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol 2019;11:1758835919875568.
17. Pai RK, Pai RK. Pathologic assessment of gastrointestinal tract and pancreatic carcinoma after neoadjuvant therapy. Mod Pathol 2018;31:4-23.
18. Cacciato Insilla A, Vivaldi C, Giordano M, et al. Tumor regression grading assessment in locally advanced pancreatic cancer after neoadjuvant FOLFIRINOX: interobserver agreement and prognostic implications. Front Oncol 2020;10:64.
19. Verbeke C, Löhr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev 2015;41:17-26.
20. Kim KS, Kwon J, Kim K, Chie EK. Impact of resection margin distance on survival of pancreatic cancer: a systematic review and meta-analysis. Cancer Res Treat 2017;49:824-833.
21. Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133:1539-1551.
22. Gosens MJ, Klaassen RA, Tan-Go I, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. Clin Cancer Res 2007;13:6617-6623.
23. Xia BT, Fu B, Wang J, et al. Does radiologic response correlate to pathologic response in patients undergoing neoadjuvant therapy for borderline resectable pancreatic malignancy? J Surg Oncol 2017;115:376-383.
24. Cassinotto C, Mouries A, Lafourcade JP, et al. Locally advanced pancreatic adenocarcinoma: reassessment of response with CT after neoadjuvant chemotherapy and radiation therapy. Radiology 2014;273:108-116.
25. Sherman WH, Hecht E, Leung D, Chu K. Predictors of response and survival in locally advanced adenocarcinoma of the pancreas following neoadjuvant GTX with or without radiation therapy. Oncologist 2018;23:4-e10.
26. Poruk KE, Gay DZ, Brown K, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med 2013;13:340-351.
27. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol 2017;28:2786-2792.
28. Kalimuthu SN, Serra S, Dhani N, et al. Regression grading in neoadjuvant treated pancreatic cancer: an interobserver study. J Clin Pathol 2017;70:237-243.