Original Article

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대한영상의학회지

A Comparative Study of Survivor Outcomes between Preoperative Evaluation Using CT Alone and Combined CT and MRI in Patients with Pancreatic Ductal Adenocarcinoma

췌장선암 환자의 수술 전 CT 단독 평가와 추가적 MRI 평가에 따른 생존 결과 비교 분석

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Purpose To compare the recurrence pattern, disease-free survival (DFS), and overall survival (OS) after curative surgery for pancreatic ductal adenocarcinoma (PDAC) in patients who underwent preoperative evaluation with CT alone or in combination with MRI, and to compare the prognosis according to the first recurrence site.

Materials and Methods We retrospectively evaluated 152 patients who underwent R0 resection of PDAC. Preoperative CT or combined CT and MRI were performed for 103 and 49 patients, respectively. Two radiologists recorded the location and date of the first recurrence in consensus. The recurrence pattern, DFS, and OS were compared between the two groups. OS was analyzed according to the first recurrence site.

Results In both groups, liver metastasis was the most common recurrence pattern. DFS (p = 0.247) or OS (p = 0.067) showed no significant difference between the two groups. OS according to the first recurrence site was the lowest for liver metastasis, followed by locoregional recurrence (p < 0.001).

Conclusion There were no significant differences in the recurrence pattern, DFS, or OS between patients evaluated with preoperative CT alone or with CT and MRI after curative resection of PDAC. Liver metastasis was the most common tumor recurrence pattern with the lowest OS.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, and remains the fourth most common cause of cancer-related deaths in the Western world (1). Surgical resection is the only known treatment for achieving a potential cure. However, most cases are detected at an advanced stage, and less than 20% of the patients present with localized, operable tumors (2, 3). The overall 5-year survival rate in patients with PDAC is less than 5% (2, 4). Even in patients with successful curative resection, tumor recurrence occurs in up to 50% to 90% of cases and the 5-year survival rate is only 20% (4, 5). Thus, early diagnosis of PDAC and precise evaluation of tumor resectability is important in treatment planning and for the avoidance of unnecessary risks associated with surgical procedures (6, 7).

Multidetector CT, using a dedicated pancreatic protocol, is primarily used for detection, staging, and resectability assessment in PDAC (8). MR imaging has also shown comparable sensitivities to CT in assessment of the tumor resectability (6, 9). However, with recent advances, including the development of a hepatobiliary MR contrast agent, and due to higher tissue contrast resolution, multiple studies have reported that MR imaging allows for the better detection of not only the primary tumor (9, 10), but also hepatic metastases (11).

The common sites of recurrence after curative resection of PDAC are the liver, locoregional areas, and the peritoneal cavity (12, 13), with the liver being the most common site for the first location of tumor recurrence (12). We hypothesized that the early tumor recurrence as liver metastasis after curative resection of PDAC may be due to the presence of tiny metastases, not detected at the time of preoperative CT imaging (14), and that with the use of MR imaging with a hepatobiliary contrast agent, tiny hepatic metastases would be better detected. This would help in the identification of good surgical candidates by excluding those who will not benefit from surgery. Hence, better survival would be expected by additionally examining patients using MR imaging with a hepatobiliary contrast agent before surgery.

In this study, we aimed to compare the recurrence pattern, disease-free survival (DFS), and overall survival (OS) after curative surgery for PDAC in patients with preoperative evaluation with CT alone or additional evaluation with MR imaging, and to compare the OS according to the first site of recurrence.

MATERIALS AND METHODS

STUDY POPULATION

This retrospective study was approved by the Institutional Review Board at our institution, and the need for informed consent was waived (IRB No. SMC202007142).

We searched our hospital's medical patient records from October 2004 through December 2015 and identified 597 consecutive patients who met the following inclusion criteria: 1) pa-

tients with pathologically proven PDAC; 2) patients who underwent contrast enhanced CT for work-up of PDAC; 3) patients with contrast-enhanced CT using a dedicated pancreatic protocol or abdominal contrast-enhanced MR imaging with a hepatobiliary contrast agent according to the routine protocol of our institution; 4) patients with potentially resectable PDAC on CT. Among these patients, 42 were excluded because they were re-categorized from potentially resectable to unresectable PDAC, due to newly noted hepatic metastasis [*n* = 34 (indeterminate hepatic lesions on CT, *n* = 25; negative-liver on CT, *n* = 9)] or major vascular invasion (*n* = 8) after MR imaging. Seven other patients also underwent MR for further evaluation of indeterminate hepatic lesions on CT, but were confirmed to be simple hepatic cysts, and were included in the study group. Afterwards, 403 patients were excluded due to following reasons: 1) patients who did not undergo surgery (*n* = 38); 2) patients with pathologically confirmed residual disease (R1 or R2) after surgery (*n* = 211); 3) patients with a history of neoadjuvant treatment before the surgery (*n* = 109); and 4) patients with less than 90 days of follow-up period after surgery, either due to follow-up loss or death (*n* = 45). The decision to undergo additional preoperative evaluation with MR imaging was made after multidisciplinary discussion, primarily when the extent of the PDAC was not clearly delineated, when there were any indeterminate hepatic lesions noted on contrast-enhanced CT, or merely by the physician's judgment.

Finally, a total of 152 consecutive patients were included in our study. Of these patients, 103 underwent preoperative imaging evaluation with CT alone (CT group), and 49 underwent additional evaluation with contrast-enhanced MR imaging (CT + MR group). The flowchart of the study population is presented in Fig. 1.

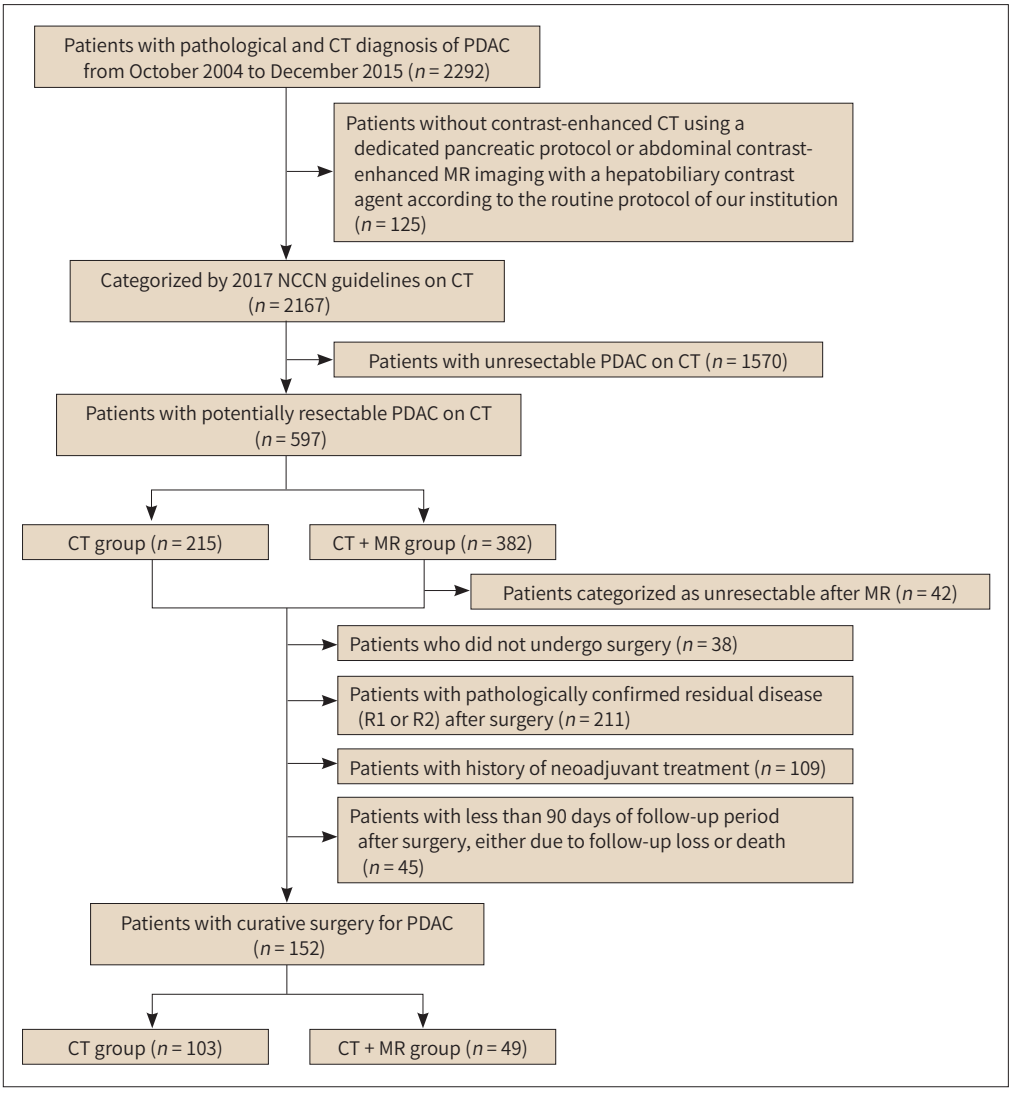
CT EXAMINATION

For preoperative and follow-up CT examination, dynamic contrast-enhanced CT imaging was performed with a 16-MDCT scanner (LightSpeed 16; GE Healthcare; Chicago, IL, USA), a 40-MDCT scanner (Brilliance 40; Philips Healthcare; Best, the Netherlands), and a 64–MDCT scanner (Aquilion 64; Toshiba Medical; Tokyo, Japan, and Lightspeed VCT 64; GE Healthcare). The scanning parameters were 120 kVp, 189–200 mAs, table speed of 18.75–26.75 mm/rotation (pitch, 0.828–1.07). After the acquisition of unenhanced images, 120 mL of nonionic contrast agent (iopamidol, Iopamiro 300; Bracco; Milano, Italy) was administered intravenously at a rate of 3–4 mL/s, using an automatic power injector. The arterial, pancreatic, and portal venous phase images were obtained at 35 s, 55 s, and 70 s after the initiation of contrast agent injection, respectively. The arterial and pancreatic phase images were reconstructed at 2.5–3-mm intervals with a slice thickness of 2.5–3 mm. The unenhanced and portal venous phase images were reconstructed at 3–5-mm intervals with a slice thickness of 3–5 mm.

MR EXAMINATION

All preoperative and follow-up MR images were obtained using a 3.0-Tesla (T) whole-body MR system (Intera Achieva 3.0-T; Philips Medical Systems) with a phased-array multicoil for the body. The MR imaging protocol included a T1-weighted turbo field-echo in-phase and out-of-phase sequence, a breath-hold multi-shot T2-weighted sequence, and a respiratory-triggered single-shot T2- and heavily T2-weighted sequence (Table 1). For preoperative MR

Fig. 1. The flow diagram shows the inclusion and exclusion criteria for our study.



NCCN = National Comprehensive Cancer Network, PDAC = pancreatic ductal adenocarcinoma

Table 1. MR Imaging Sequences and Parameters

Sequence	TR/TE (ms)	Flip Angle (Degree)	Section Thickness	Matrix Size	Bandwidth (Hz/Pixel)	Field of View (cm)	Acquisition Time (Sec)	No. of Excitations
T1W-2D dual GRE	3.5/1.15–2.3	10	6	256 × 194	434.4	32–38	14	1
BH-MS-T2WI	1623/70	90	5–7	324 × 235	235.2	32–38	55	1
RT-SS-T2WI	1342/80	90	5–7	320 × 256	506.4	32–38	-	2
RT-SS-HT2WI	1156/160	90	5–7	320 × 256	317.9	32–38	-	2
T1W-3D GRE	3.1/1.5	10	2	256 × 256	995.7	32–38	16.6	1
DWI	1600/70	90	5	112 × 112	79.5	30–38	-	2

BH-MS-T2WI = breath-hold multishot T2-weighted image, D = dimensional, DWI = diffusion-weighted imaging, GRE = gradient echo, RT-SS-HT2WI= respiration-triggered single-shot heavily T2-weighted image, RT-SS-T2WI = respiration-triggered single-shot T2-weighted image, TE = echo time, TR = repetition time, T1W = T1-weighted

imaging, nine patients used gadobenate dimeglumine (MultiHance; Bracco Imaging) and 40 patients used gadoxetic acid (Primovist; Bayer Healthcare; Berlin, Germany). Since 2008, only gadoxetic acid was used. A dose of 0.1 mL/kg (0.05 mmoL/kg gadobenate dimeglumine; 0.025 mmoL/kg gadoxetic acid) contrast agent was administered intravenously at a rate of 2 mL/s by using a power injector, followed by a 20 mL saline flush. For contrast-enhanced MR imaging, unenhanced phase, arterial phase (20–35 s), portal phase (60 s), delayed phase (3 min), and hepatobiliary phase images were obtained using a T1-weighted three-dimensional turbo-field-echo sequence (THRIVE; Philips Healthcare). After the contrast injection, hepatobiliary phase images were obtained after three hours for gadobenate dimeglumine, and after 20 minutes for gadoxetic acid.

EVALUATION OF RECURRENCE PATTERN

All patients underwent follow-up contrast-enhanced CT or MR imaging and laboratory tests including serum carbohydrate antigen (CA) 19-9 assessment every 3–6 months after surgery, and during follow-up, 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) PET/CT was occasionally used for evaluating tumor recurrence. The patients were observed for 3.2–146.3 months (mean, 31.9 months). The patients' follow-up imaging studies and medical records were reviewed, with a focus on tumor recurrence, presence or absence of adjuvant therapy, and survival. Two radiologists (J.E.L. and S.H.K.) reviewed the pre and postoperative follow-up CT and MR images on a picture archiving and communication system (PACS; Centricity, GE Healthcare), and with consensus, recorded the location and date of the first recurrence site. Tumor recurrence was defined as a newly detected lesion with typical imaging characteristics of recurrent tumor on follow-up imaging, or newly detected indeterminate lesion on CT which was confirmed as tumor recurrence on additional MR or FDG PET/CT, and/or with gradual increase in size on consecutive follow-up imaging. Recurrence patterns were classified into liver metastasis, locoregional recurrence, peritoneal dissemination, lymph node metastasis, lung metastasis, and distant metastasis other than liver or lung metastasis (15). Liver metastasis was defined as a newly developed liver lesion with either pathologic confirmation or imaging characteristics of liver metastasis. Time to liver metastasis was defined as the interval between the date of curative surgery and the date of first liver metastasis occurence on follow-up CT or MR imaging. Locoregional recurrence was defined as a newly developed enhancing soft tissue lesion at the pancreatic resection site, with a gradual increase in size over consecutive follow-up imaging studies. Lymph node metastasis was defined as a gradual increase in size of the lymph node (> 10 mm in short diameter) over consecutive follow-up imaging studies. For other types of recurrence, radiologic findings consistent with recurrent disease were considered adequate proof of recurrence, although tissue confirmation was rarely obtained.

EVALUATION OF DISEASE-FREE AND OVERALL SURVIVAL

The index date was defined as the date on which the patient underwent surgery. DFS was defined as the interval between the index date and the date of tumor recurrence or the last follow-up visit. OS was defined as the interval between the index date and the date of either death or the last follow-up visit.

Table 2. Clinicopathologic Characteristics of 152 Patients with Pancreatic Ductal Adenocarcinoma

Characteristics	Total (*n* = 152)	CT Group (*n* = 103)	CT + MR Group (*n* = 49)	*p*-Value
Age (years)*	62.2 ± 9.7 (40–82)	60.9 ± 9.1 (42–79)	64.9 ± 10.5 (40–82)	0.308
Sex				0.923
Male	86 (56.6)	58 (56.3)	28 (57.1)	
Female	66 (43.4)	45 (43.7)	21 (42.9)	
Carbohydrate antigen 19-9 (U/mL)				0.942
≤ 37	80 (52.6)	54 (52.4)	26 (53.1)	
> 37	72 (47.4)	49 (47.6)	23 (46.9)	
Location				0.646
Head/uncinate process	133 (87.5)	91 (88.3)	42 (85.7)	
Body/tail	19 (12.5)	12 (11.7)	7 (14.3)	
Mean size (cm)*	2.85 ± 1.07 (0.6–7.3)	2.98 ± 1.13 (1.3–7.3)	2.59 ± 0.86 (0.6–5.0)	0.114
T stage				0.088
T1	4 (2.6)	1 (1.0)	3 (6.1)	
T2	3 (2.0)	3 (2.9)	0 (0.0)	
T3	145 (95.4)	99 (96.1)	46 (93.9)	
T4	0 (0.0)	0 (0.0)	0 (0.0)	
N stage				0.888
N0	67 (44.1)	45 (43.7)	22 (44.9)	
N1	85 (55.9)	58 (56.3)	27 (55.1)	
TNM classification (AJCC)†				0.303
IA	4 (2.6)	1 (1.0)	3 (6.1)	
IB	2 (1.3)	2 (1.9)	0 (0.0)	
IIA	61 (40.1)	42 (40.8)	19 (38.8)	
IIB	85 (55.9)	58 (56.3)	27 (55.1)	
Histologic grade				0.394
Well differentiated	19 (12.5)	12 (11.7)	7 (14.3)	
Moderately differentiated	98 (64.5)	64 (62.1)	34 (69.4)	
Poorly differentiated	35 (23.0)	27 (26.2)	8 (16.3)	
Perineural invasion				0.002
Absent	64 (42.1)	52 (50.5)	12 (24.5)	
Present	88 (57.9)	51 (49.5)	37 (75.5)	
Lymphovascular invasion				0.473
Absent	120 (78.9)	83 (80.6)	37 (75.5)	
Present	32 (21.1)	20 (19.4)	12 (24.5)	
Type of resection				0.249
Pylorus-preserving PD	89 (58.6)	57 (55.3)	32 (65.3)	
Classic PD	41 (27.0)	33 (32.0)	8 (16.3)	
Distal pancreatectomy	6 (3.9)	4 (3.9)	2 (4.1)	
Total pancreatectomy	8 (5.3)	5 (4.9)	3 (6.1)	
Others	8 (5.3)	4 (3.9)	4 (8.2)	
Adjuvant chemotherapy				0.355
Absent	64 (42.1)	46 (44.7)	18 (36.7)	

Table 2. Clinicopathologic Characteristics of 152 Patients with Pancreatic Ductal Adenocarcinoma (Continued)

Characteristics	Total (*n* = 152)	CT Group (*n* = 103)	CT + MR Group (*n* = 49)	*p*-Value
Present	88 (57.9)	57 (55.3)	31 (63.3)	
Adjuvant radiation therapy				0.767
Absent	74 (48.7)	51 (49.5)	23 (46.9)	
Present	78 (51.3)	52 (50.5)	26 (53.1)	

Unless otherwise specified, data are presented as the number of patients, with percentage in parentheses. Percentages were calculated based on each group.
*Data are presented as mean ± standard deviation. Data in parentheses indicate the range.
†TNM staging was classified according to the sixth and seventh edition of the AJCC Staging Manual.
AJCC = American Joint Committee on Cancer, PD = pancreatoduodenectomy

CLINICAL AND HISTOPATHOLOGIC DATA COLLECTION

Clinical data, including patient age, sex, and serum CA 19-9 (normal < 37 U/mL) levels were collected from the medical records. Based on surgical pathology reports, tumor location (head/uncinate process, or body/tail), tumor size, T and N stages, TNM classification according to the sixth or seventh edition of the American Joint Committee on Cancer (AJCC), histologic grade (well, moderately, or poorly differentiated), presence or absence of perineural invasion, and lymphovascular invasion were analyzed.

STATISTICAL ANALYSIS

The characteristics of the CT and CT + MR groups were compared using a two-sample *t* test for continuous variables such as age and tumor size. Categorical variables were tested with the chi-square or Fisher's exact test. DFS and OS rates were estimated using the Kaplan-Meier method, and were compared using the log-rank test. Mann-Whitney U test was used to compare the time to liver metastases between the two groups. All statistical analyses were conducted using R 3.3.2 (Vienna, Austria; http://www.R-project.org/). The significance level was set at $p < 0.05$.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The characteristics of the study populations are shown in Table 2. There were no significant differences in most of the clinical and pathological characteristics ($p > 0.05$) between the two groups, except for the presence of perineural invasion ($p = 0.002$).

RECURRENCE PATTERN

Overall, 69.1% (105/152) of the patients showed evidence of tumor recurrence during follow up. Tumor recurrence was first detected on CT in 98.1% (103/105) of the patients. Additional information was achieved by MR in five patients with hepatic metastasis, and by FDG PET/CT in six patients with liver metastasis, 13 with locoregional recurrence, two with peritoneal dissemination, two with lymph node metastasis, seven with lung metastasis and one with distant metastasis other than liver or lung metastasis. In rest of the patients (1.9%, 2/105), tumor recurrence, specifically liver metastasis was first detected on MR. When tumor recur-

Fig. 2. A 74-year-old female with hepatic metastasis after pylorus preserving pancreaticoduodenectomy for PDAC (stage, T3N1).
A. On preoperative transverse contrast-enhanced portal-phase MR imaging, no focal lesion indicating liver metastasis is observed.
B. 95 days (3.16 months) after the curative resection of PDAC, multiple hepatic metastases are observed on a transverse contrast-enhanced portal-phase CT image. The patient died 175 days (5.83 months) after the surgery.
PDAC = pancreatic ductal adenocarcinoma

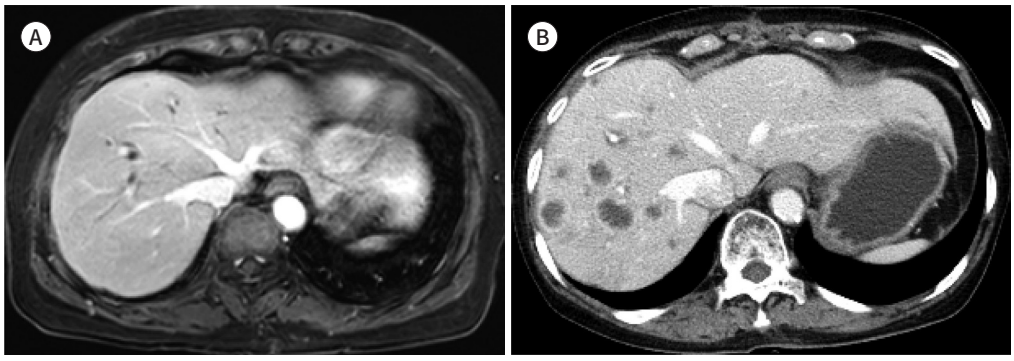
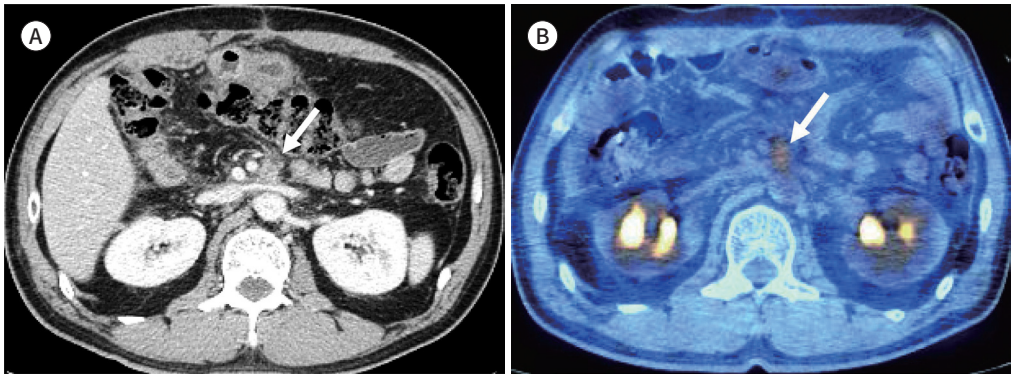


Fig. 3. A 40-year-old male with locoregional recurrence after pylorus-preserving pancreaticoduodenectomy for PDAC (stage T3N1).
A. On a transverse contrast-enhanced portal-phase CT image acquired 101 days (5.03 months) after the curative resection of PDAC, a newly developed enhancing soft tissue lesion (arrow) is observed at the pancreatic resection site.
B. On ^{18}F-FDG PET/CT, the lesion (arrow) shows increased FDG uptake. The patient died 388 days (12.93 months) after the surgery.
FDG = fluorodeoxyglucose, PDAC = pancreatic ductal adenocarcinoma



rence was first detected, the mean size of the tumor was 14.1 ± 10.4 mm (range, 3–60 mm) for liver metastasis, 16.9 ± 7.7 mm (range, 1.7–46 mm) for locoregional recurrence, 14.1 ± 4.5 mm (range, 12.1–22 mm) for lymph node metastasis, and 12.7 ± 11.1 mm (range, 1–40.3 mm) for lung metastasis. In 68.6% (72/105) of the patients with tumor recurrence, serum CA 19-9 level was elevated at the time the tumor recurrence occurred [liver metastasis (63.6%, 28/44): mean, 4214.1 ± 8621.4 U/mL; range, 44.2–39855.2 U/m], [locoregional recurrence (81.6%, 31/38): mean, 1532.45 ± 4325.7 U/mL; range, 39.3–24156.34 U/mL], [other recurrence patterns combined (56.5%, 13/23): mean, 1609.9 ± 3745.6 U/mL; range, 40.6–14341.9 U/mL]. In most patients, the first recurrence occurred in the liver (n = 44, 41.9%), followed by locoregional recurrence (n =38, 36.2%) and other recurrence patterns combined (n = 23, 21.9%)

(Figs. 2-4). Among them, 15 patients (14.3%, 15/105) were pathologically confirmed (liver metastasis, *n* = 12; lung metastasis, *n* = 3). The cumulative proportion of each recurrence in the full cohort, CT group and CT + MR group is presented in Fig. 5 and Table 3. In the complete cohort, CT group, and CT + MR group, liver metastasis occurred the most frequently, followed by locoregional recurrence and other recurrence patterns combined. Although liver

Fig. 4. A 56-year-old male with lung metastases after distal pancreatectomy for pancreatic ductal adenocarcinoma (stage N3N1).
A. On a preoperative transverse CT image, no focal lesion indicating lung metastasis is seen.
B. After 589 days (19.63 months), a newly developed nodular lesion (arrow) is observed in the right lower lobe, which gradually increased in size and was eventually identified as lung metastasis after the surgery. The patient died 1692 days (56.4 months) after the surgery.

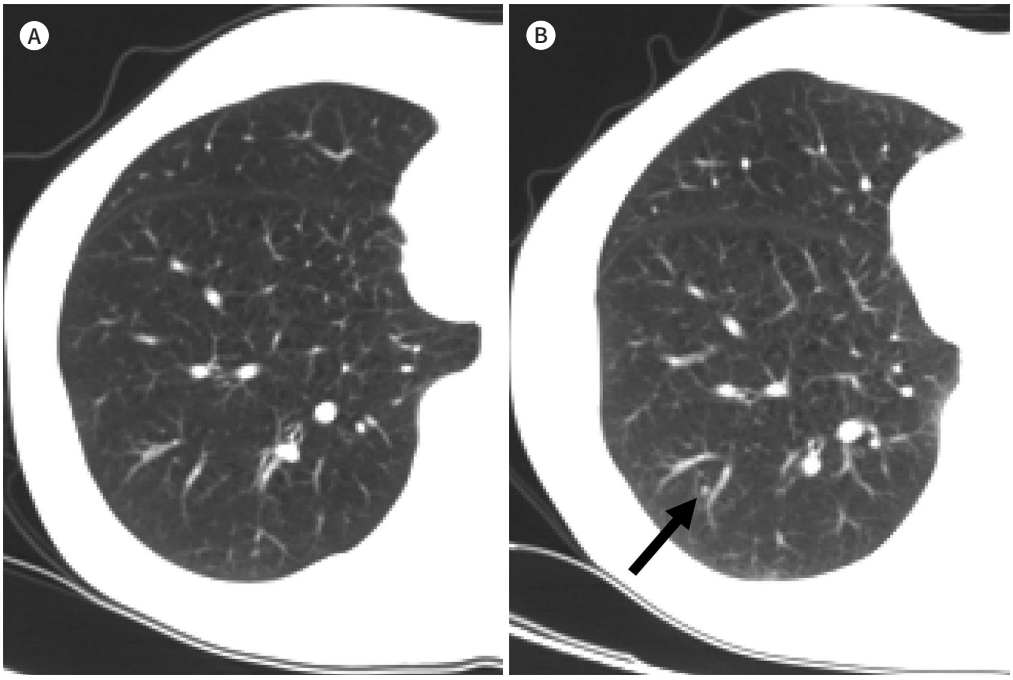


Fig. 5. Cumulative proportion of recurrences in the complete cohort (A), CT group (B), and CT + MR imaging group (C).
Liver metastasis occurred the most frequently in earlier postoperative periods, followed by locoregional recurrence and other types of recurrences.

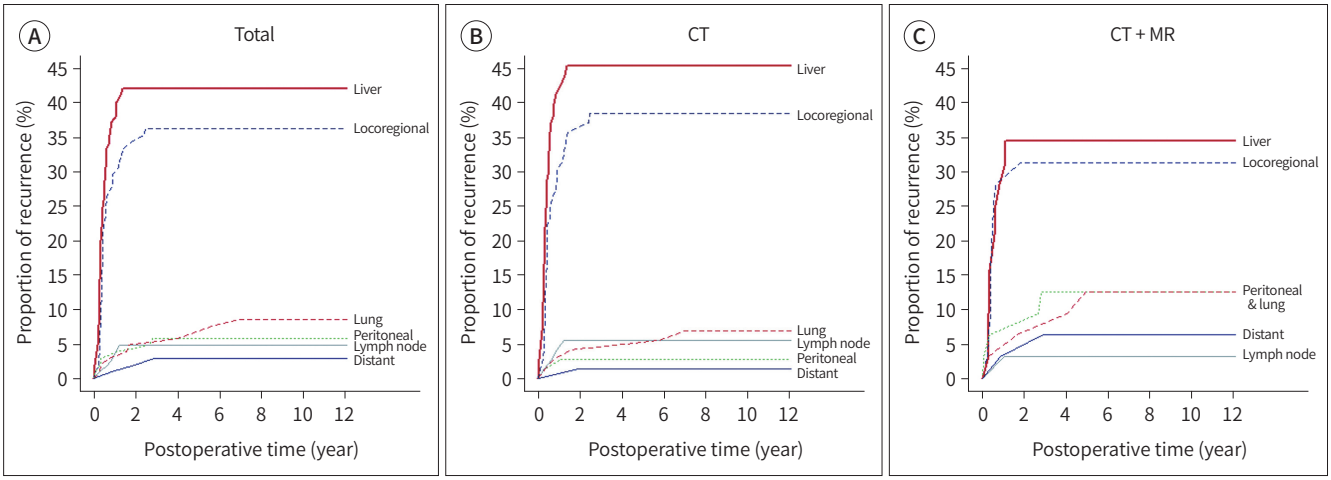


Table 3. Cumulative Proportions of Each Recurrence in the Full Cohort, CT Group and CT + MR Group

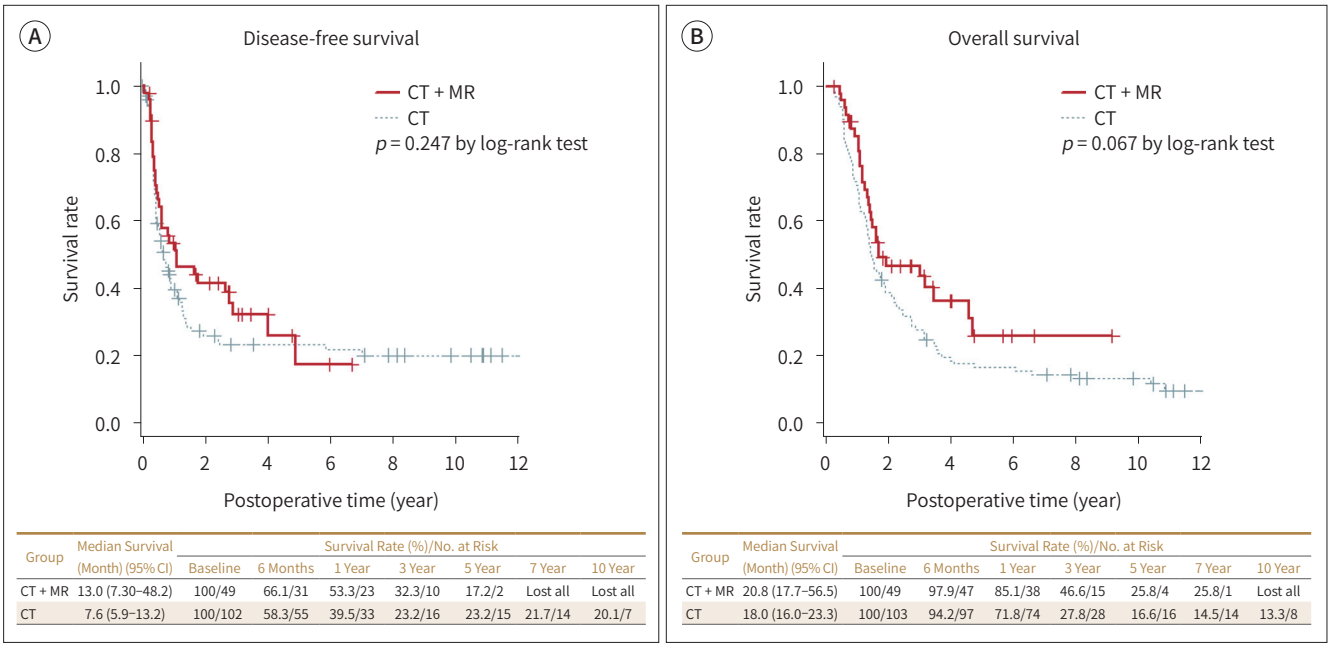
Group	Recurrence Rate (%)/No. at Risk			
	Baseline	6 Months	1 Year	3 Years
Liver metastasis				
Total	0/44	63.6/16	88.6/5	Lost all
CT	0/33	66.7/11	90.9/3	Lost all
CT + MR	0/11	54.5/5	81.8/2	Lost all
Locoregional recurrence				
Total	0/38	60.5/15	81.6/7	Lost all
CT	0/28	57.1/12	78.6/6	Lost all
CT + MR	0/10	70/3	90/1	Lost all
Peritoneal dissemination				
Total	0/6	50/3	50/3	Lost all
CT	0/2	50/1	50/1	Lost all
CT + MR	0/4	50/2	50/2	Lost all
Lymph node metastasis				
Total	0/5	20/4	60/2	Lost all
CT	0/4	25/3	75/1	Lost all
CT + MR	0/1	0/1	0/1	Lost all
Lung metastasis				
Total	0/9	22.2/7	33.3/6	55.6/4
CT	0/5	20/4	40/3	60/2
CT + MR	0/4	25/3	25/3	50/2
Distant metastasis				
Total	0/3	0/3	33.3/2	Lost all
CT	0/1	0/1	0/1	Lost all
CT + MR	0/2	0/2	50/1	Lost all

metastasis occurred more frequently in the CT group (32.0%, 33/103) than in the CT + MR group (22.4%, 11/49), there was no significant difference ($p = 0.255$). Additionally, liver metastasis and locoregional recurrence occurred earlier in the postoperative period than did other patterns of recurrences. There were no significant differences in the overall recurrence pattern ($p > 0.05$), and the median time to liver metastasis [CT group; 127 (7–488) days, CT + MR group; 175 (95–396) days] ($p = 0.271$) between the two groups.

DISEASE-FREE AND OVERALL SURVIVAL

The mean follow-up period was 31.9 months (range, 3.2–146.3 months) for the CT group, and 28.2 months (range, 3.3–109.9 months) for the CT + MR group. During follow up, 120 patients died (CT group; 91 patients, CT + MR group; 29 patients) due to disease-related causes. The 6-month and 1-, 3-, and 5-year DFS rates were 58.3%, 39.5%, 23.2%, and 23.2% for the CT group; and 66.1%, 53.3%, 32.3%, and 17.2% for the CT + MR group, respectively (Fig. 6A), with no significant difference between the two groups ($p = 0.247$). Additionally, the 6-month, and 1-, 3-, and 5-year OS rates were 94.2%, 71.8%, 27.8%, and 16.6% for the CT group and 97.9%, 85.1%, 46.6%, and 25.8% for the CT + MR group, respectively (Fig. 6B), with no significant dif-

Fig. 6. The Kaplan–Meier curves of disease-free survival (A) and overall survival (B) in the CT group and CT + MR imaging group. There are no significant differences in the disease-free survival ($p = 0.247$) or overall survival ($p = 0.067$) between the two groups.
CI = confidence interval



Group	Median Survival (Month) (95% CI)	Survival Rate (%)/No. at Risk						
		Baseline	6 Months	1 Year	3 Year	5 Year	7 Year	10 Year
CT + MR	13.0 (7.30–48.2)	100/49	66.1/31	53.3/23	32.3/10	17.2/2	Lost all	Lost all
CT	7.6 (5.9–13.2)	100/102	58.3/55	39.5/33	23.2/16	23.2/15	21.7/14	20.1/7

Group	Median Survival (Month) (95% CI)	Survival Rate (%)/No. at Risk						
		Baseline	6 Months	1 Year	3 Year	5 Year	7 Year	10 Year
CT + MR	20.8 (17.7–56.5)	100/49	97.9/47	85.1/38	46.6/15	25.8/4	25.8/1	Lost all
CT	18.0 (16.0–23.3)	100/103	94.2/97	71.8/74	27.8/28	16.6/16	14.5/14	13.3/8

ference between the two groups ($p = 0.067$).

OVERALL SURVIVAL ACCORDING TO THE FIRST SITE OF RECURRENCE

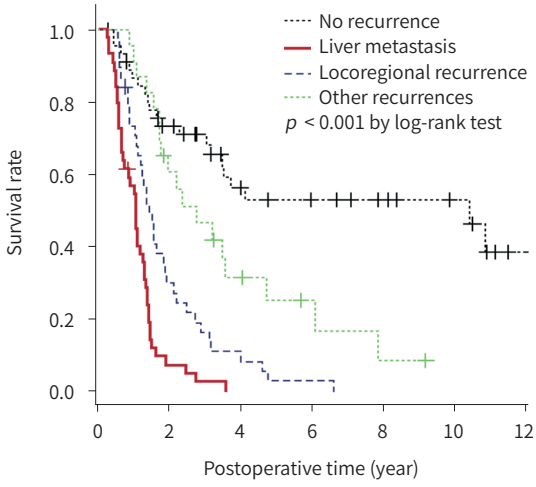
In the complete cohort, OS according to the first site of recurrence was the lowest in patients with liver metastasis [median, 12.8 (9.3–16) months], followed by locoregional recurrence [median, 17.3 (14.7–23) months] and other recurrence patterns combined [median 33.1 (21.2–94.2) months] ($p < 0.001$). Patients with no recurrence had the best survival rates [median, 124.5 (41.7–not available) months] (Fig. 7).

DISCUSSION

Our study demonstrated that after curative resection of PDAC, liver metastasis was most common tumor recurrence pattern, followed by locoregional recurrence and other recurrence patterns combined in both CT and CT + MR groups. Moreover, there were no significant differences in the DFS and OS between the two groups. OS according to the first site of recurrence was the lowest in patients with liver metastasis, followed by those with locoregional recurrence and other recurrence patterns combined.

To date, there have been several studies evaluating the patterns and timing of tumor recurrence after curative surgery for PDAC (12, 16-18). The overall recurrence rate in our study (69.1%, 105/152) was slightly lower, but generally consistent with previous studies (72.2–76.9%). The first tumor recurrence was reported to occur predominantly in the liver or locoregional areas (12, 17, 18). However, studies showed variable rates of liver metastasis (45–51.8%) and locoregional recurrence (22.5–70%). In our study, the most common site for first

Fig. 7. The Kaplan–Meier curves of overall survival according to the first site of recurrence.
The overall survival is the lowest for patients with liver metastasis, followed by those with locoregional recurrence and other recurrence patterns combined. The best overall survival occurred is observed for patients who showed no recurrence ($p < 0.001$).
CI = confidence interval, NA = not available



Group	Median Survival (Month) (95% CI)	Survival Rate (%)/No. at Risk						
		Baseline	6 Months	1 Year	3 Year	5 Year	7 Year	10 Year
No recurrenct	124.5 (41.7–NA)	100/47	95.7/44	86.9/39	71/26	52.9/15	52.9/13	52.9/8
Liver metastasis	12.8 (9.3–16)	100/44	88.6/39	56.6/24	2.4/1	Lost all	Lost all	Lost all
Locoregional recurrence	17.3 (14.7–23)	100/38	100/38	73.3/27	16.3/6	2.7/1	Lost all	Lost all
Other recurrences	33.1 (21.2–94.2)	100/23	100/23	95.7/22	46.6/10	25.2/4	16.8/2	Lost all

tumor recurrence was the liver (41.9%), followed by locoregional areas (36.2%). The variable results may be due to differences in study design, study sample sizes, or limited information on follow-up. Additionally, in previous studies, liver metastasis and locoregional recurrence occurred earlier than other types of tumor recurrences (12, 16, 19). Groot et al. (16), and Suenaga et al. (19) reported that the median DFS was 6.9 months and 6.0 months, respectively, for liver metastasis, and 14.6 months and 7.7 months, respectively, for locoregional recurrence. Our study showed that the cumulative proportion of recurrence at 1 year was 88.6% for liver metastasis and 81.6% for locoregional recurrence in the complete cohort. This was higher than other patterns of tumor recurrences, and the addition of MR imaging with a hepatobiliary agent did not change the recurrence pattern. We think that the exceptionally high tendency for PDAC to metastasize to the liver might be due to early seeding at premalignant or malignant stages of the tumor, as reported previously (3, 4, 20). In the case of locoregional recurrence, a dispersed cellular growth pattern at the periphery of the resected PDAC (21) has been reported to increase the incidence of remnant tumor cells beyond the resection margin, eventually leading to locoregional recurrence.

There is increasing evidence suggesting that MR imaging with a hepatobiliary agent shows a better sensitivity for the detection and characterization of focal hepatic lesions than does CT. This is due to the hepatocyte-specific properties of the contrast and the excellent spatial resolution achieved by the three-dimensional gradient-echo sequence (22-24). Motosugi et al. (11), Chew and O'Dwyer (25) reported that gadoxetic acid-enhanced MR imaging has a better sensitivity for detecting hepatic metastases in patients with PDAC. Based on these studies, we

hypothesized that with additional preoperative evaluation of the liver using MR imaging with a hepatobiliary agent in patients with PDAC, those with minute hepatic metastases would be excluded as surgical candidates. Consequently, we assumed that in patients who achieved R0 resection of PDAC, the DFS and OS would be better in those who underwent additional preoperative evaluation with MR imaging with hepatobiliary agent. Kim et al. (26) previously reported that there was no significant difference in the five year recurrence-free survival rates between patients who underwent preoperative evaluation with contrast-enhanced CT only or with additional contrast-enhanced MR imaging, before curative resection of PDAC. In this study, patients who used extracellular MR contrast agent and patients with R1 resection were also included. To evaluate the objective value of additional preoperative evaluation with state-of-the-art MR imaging, we applied strict enrollment criteria, only including patients who underwent contrast-enhanced CT using dedicated pancreas protocol or contrast-enhanced MR imaging with hepatobiliary agent, and those with pathologically proven R0 resection of PDAC. Also, there were no significant difference in the major variables which could affect the OS or recurrence pattern between the two groups. However, our results showed that there was no significant difference in DFS and OS between the two groups, which was in consistency with the results reported by Kim et al. (26). In contrary to the study by Kim et al. (26), there was no significant difference in the median time to liver metastasis between the two groups in our study. We speculate that this may be because only patients proven with R0 resection, with dedicated pancreas CT, and MRI with hepatobiliary contrast agent were included in our study group. Our results support the preclinical evidence that PDAC is probably a systemic disease, even in its earliest stage (3, 4, 14, 20). Therefore, even in patients with resectable PDAC, microscopic metastases—too small to be detected by state-of-the-art MR imaging—may already be disseminated within the systemic circulation at the time of surgery.

After curative surgery for PDAC, most patients die owing to metastatic disease rather than locoregional recurrence (3, 27). In particular, metastasis to the liver leads to a dismal prognosis than do other patterns of tumor recurrences (19, 28). Our results are consistent with previous studies, and patients with liver metastasis had the lowest OS [median, 12.8 (9.3–16) months]. The cause of poor survival in patients with hepatic metastasis from PDAC is thought to be the rapid growth of hepatic metastasis leading to hepatic failure. In contrast, patients with locoregional recurrence may benefit from local tumor control such as adjuvant radiation therapy. As for lung metastasis, several studies have reported a favorable prognosis in PDAC patients with lung metastasis alone (29, 30), which may be due to a less aggressive tumor biology and slower growth tendency, providing opportunities for additional treatment.

Our study has several limitations. First, there is a possibility of selection bias due to the retrospective study design. Second, the number of patients in the CT + MR group (n = 49) was smaller than that in the CT group (n = 103). This might be because CT is the most widely used imaging modality for evaluation of pancreatic cancer and also because some patients with anticipated resectable PDAC on CT did not undergo additional evaluation with MR imaging before surgery. Third, as cases were collected over an 11-year period, various types of CT scanners were used. However, our scanning parameters were uniform and met the recommended protocol parameters suggested by the Society of Abdominal Radiology and the

American Pancreatic Association (8). Fourth, this is a single center study and a validation using another set of patients was not included. Thus, further multicenter prospective studies with larger numbers of patients are warranted to confirm our results.

In conclusion, there were no significant differences in the recurrence pattern, DFS and OS between patients with preoperative CT alone and CT and MRI after curative resection of PDAC. The most common pattern of tumor recurrence was liver metastasis with the lowest OS.

Author Contributions

Conceptualization, K.S.H.; data curation, L.J.E., K.S.H., C.S.; formal analysis, L.J.E., K.S.H., L.B.R.; investigation, L.J.E., K.S.H., L.S.; methodology, L.J.E., K.S.H.; project administration, K.S.H.; resources, L.J.E., K.S.H.; supervision, K.S.H.; validation, K.S.H.; visualization, L.J.E., K.S.H.; writing—original draft, L.J.E., K.S.H.; and writing—review & editing, K.S.H., L.S.J.

Conflicts of Interest

Seong Hyun Kim has been an Editorial Board Member of Journal of the Korean Society of Radiology since 2015; however, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. Otherwise, no other potential conflicts of interest relevant to this article were reported.

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췌장선암 환자의 수술 전 CT 단독 평가와 추가적 MRI 평가에 따른 생존 결과 비교 분석

이지은[1] · 김성현[2*] · 이순진[2] · 최서연[1] · 이선영[2] · 이보라[3]

목적 췌장선암으로 완치 수술을 시행 받은 환자들 중 수술 전 CT만 시행 받은 환자군과 추가적 MRI를 시행 받은 환자군의 재발 양상 및 생존율을 비교하고, 첫 재발 위치에 따른 예후 차이를 비교하고자 한다.

대상과 방법 췌장선암으로 R0 수술을 시행 받은 152명의 환자를 대상으로 하였다. 이중 103명은 수술 전 CT만 시행 받았고, 나머지 49명은 추가적 MRI를 시행 받았다. 두 명의 영상의학과 의사가 합의하에 각 환자의 첫 재발 위치와 재발 시기를 평가하였다. 두 환자군의 재발 양상, 무병 생존율, 전체 생존율을 비교하고, 첫 재발 위치에 따른 예후를 비교하였다.

결과 두 환자군 모두 간 전이가 가장 흔한 재발 양상이었고, 무병 생존율($p = 0.247$)과 전체 생존율($p = 0.067$)은 유의한 차이가 없었다. 첫 재발 위치에 따른 예후는 간 전이가 가장 나빴고, 그다음은 국소 재발이었다($p < 0.001$).

결론 췌장선암으로 완치 수술을 시행 받은 환자에서 수술 전 CT만 시행 받은 환자군과 추가적 MRI를 시행 받은 환자군 사이에 재발 양상과 생존율은 유의한 차이가 없었다. 간 전이가 가장 흔한 재발 양상이었고, 다른 재발 양상과 비교하여 예후가 가장 나빴다.

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