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Diagnostic Accuracy of CT for Evaluating Circumferential Resection Margin Status in Resectable or Borderline Resectable Pancreatic Head Cancer: A Prospective Study Using Axially Sliced Surgical Pathologic Correlation

Ji Hoon Park[1, 2, 3], Yoo-Seok Yoon[4], Seungjae Lee[3], Hae Young Kim[1], Ho-Seong Han[4], Jun Suh Lee[4], Won Chang[1], Haeryoung Kim[5], Hee Young Na[6], Seungyeob Han[7], Kyoung Ho Lee[1, 2, 3, 8]

[1]Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea; Departments of [2]Radiology, [4]Surgery, and [6]Pathology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea; [3]Department of Applied Bioengineering, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea; [5]Department of Pathology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [7]Department of Medicine, Seoul National University College of Medicine, Seoul, Korea; [8]Interdisciplinary Program in Bioengineering, Seoul National University, Seoul, Korea

Objective: CT plays a central role in determining the resectability of pancreatic cancer, which directs the use of neoadjuvant therapy. This study aimed to assess the diagnostic accuracy of CT in predicting circumferential resection margin (CRM) involvement in patients with resectable or borderline resectable pancreatic head cancer.

Materials and Methods: Seventy-seven patients who were scheduled for upfront surgery for resectable or borderline resectable pancreatic head cancer were prospectively enrolled, and 75 patients (38 male and 37 female; mean age ± standard deviation, 68 ± 11 years) were finally analyzed. The CRM status was evaluated separately for the superior mesenteric artery (SMA) and posterior and superior mesenteric vein/portal vein (SMV/PV) margins. Three independent radiologists reviewed the preoperative CT images and evaluated the resection margin status. The reference standard for CRM status was pathologic examination of pancreaticoduodenectomy specimens in an axial plane perpendicular to the axis of the second portion of the duodenum. The diagnostic accuracy of CT was assessed for overall CRM involvement, defined as involvement of the SMA or posterior margins (per-patient analysis), and involvement of each of the three resection margins (per-margin analysis). The data were pooled using a crossed random effects model.

Results: Forty patients had pathologically confirmed overall CRM involvement in pancreatic cancer, while CRM involvement was not seen in 35 patients. For overall CRM involvement, the pooled sensitivity and specificity were 15% (95% confidence interval: 7%–49%) and 99% (96%–100%), respectively. For each of the resection margins, the pooled sensitivity and specificity were 14% (9%–54%) and 99% (38%–100%) for the SMA margin, 12% (8%–46%) and 99% (97%–100%) for the posterior margin; and 37% (29%–53%) and 96% (31%–100%) for the SMV/PV margin, respectively.

Conclusion: CT showed very high specificity but low sensitivity in predicting pathological CRM involvement in pancreatic cancer.

Keywords: *Carcinoma, pancreatic ductal; Margins of excision; Multidetector computed tomography; Neoadjuvant therapy; Sensitivity and specificity*

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Corresponding author: Yoo-Seok Yoon, MD, PhD, Department of Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
• E-mail: yoonys@snubh.org

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INTRODUCTION

Surgical resection is the only curative treatment for pancreatic cancer. Margin-negative resection rates have remained low over the past decades, resulting in poor survival rates. In an effort to improve survival outcomes, neoadjuvant therapy has been introduced for borderline resectable pancreatic cancer, showing promising results, such as improved survival and margin-negative resection rates [1-3]. The National Comprehensive Cancer Network (NCCN) guidelines now recommend neoadjuvant therapy over upfront surgery for patients with borderline resectable pancreatic cancer [4]. There have been attempts to adopt neoadjuvant therapy for patients with resectable pancreatic cancer [5,6]. However, upfront surgery followed by adjuvant chemotherapy remains the standard treatment for resectable pancreatic cancer.

CT plays a central role in determining the resectability of pancreatic cancer, particularly in the preoperative prediction of surgical margin status, which is an important factor affecting patient prognosis [4,7]. However, few studies have directly measured the diagnostic accuracy of CT in predicting the surgical margin status. Such a dearth of research would be partly attributable to the complexity of resection planes involved in pancreatic surgery, making correlation of CT and pathologic findings very difficult. Among several pathologic specimen preparation techniques used for pancreatic head cancer, the axial slicing method proposed by the Royal College of Pathologists allows direct correlation between CT and pathologic specimens, as well as accurate pathologic evaluation of the resection margin status [8,9].

In general, surgical margins of pancreatic head cancer are categorized as transection and circumferential resection margins (CRMs). While the transection margin can be extended according to intraoperative frozen-section results, the extension of the CRM is limited when major vessels such as the superior mesenteric artery (SMA) and inferior vena cava (IVC) are involved. Thus, in practice, most cases of margin-positive resection occur at the CRMs [10-13], which should be the focus of preoperative tumor evaluation using CT.

This prospective study aimed to assess the diagnostic accuracy of CT for CRM involvement in patients with resectable or borderline resectable pancreatic head cancer. We used pathologic examination of pancreaticoduodenectomy specimens using the axial slicing method as the reference standard, and made direct correlations between CT and surgical pathologic findings.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted in a tertiary teaching hospital in South Korea between October 2014 and January 2018. The protocol was approved by the Institutional Review Board (IRB No. B-1407-257-004), and informed consent was obtained from each patient. We included patients with pancreatic head cancer preoperatively judged to be resectable or borderline resectable (see Patients section for details). Three readers independently evaluated the preoperative CT images of eligible patients. The readers' individual and pooled diagnostic accuracies using CT in predicting CRM status were assessed. This report was made in line with the guidelines of the Standards for Reporting of Diagnostic Accuracy [14].

Patients

Eligible patients were adults (> 18 years) who were regarded to have resectable or borderline resectable pancreatic head cancer according to clinical assessment, and were scheduled for upfront surgery without neoadjuvant therapy. One of the four board-certified abdominal radiologists in service initially assessed the resectability of pancreatic head cancer using dynamic contrast-enhanced CT. The resectability was further discussed and determined at a multidisciplinary conference comprising hepatobiliary surgeons, abdominal radiologists, gastroenterologists, oncologists, radiation oncologists, and pathologists, according to the NCCN guidelines [4]. During the earlier part of the study period, upfront surgery was the treatment of choice for both resectable and borderline resectable pancreatic head cancer at our institution. However, later in the study period, there was a gradual shift towards neoadjuvant therapy for borderline resectable cancer; hence, there was a reduction in the number of enrolled patients with borderline resectable cancer. A history of severe adverse reaction to iodinated intravenous contrast material or renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) were additional exclusion criteria (Fig. 1).

CT Imaging

Multiphase scans comprising precontrast, pancreatic

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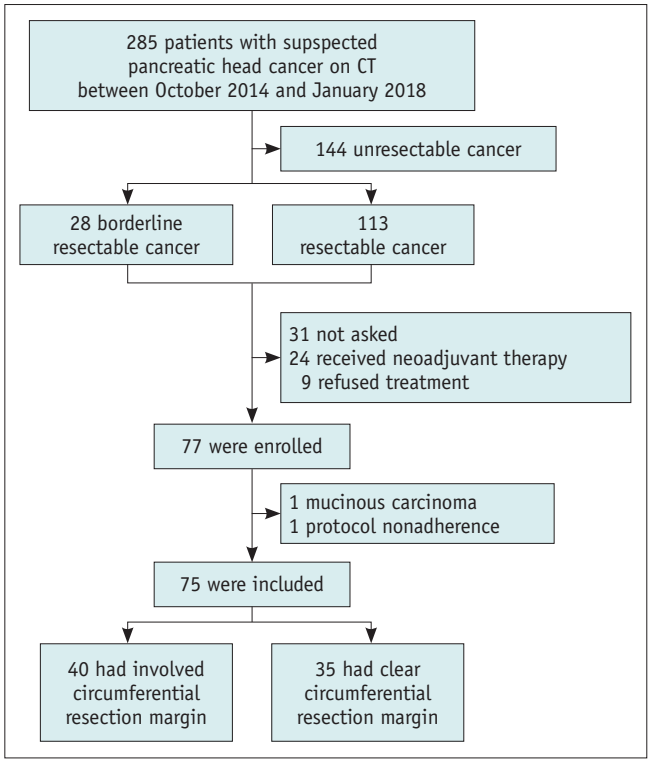

Fig. 1. Patient flow diagram.

parenchymal, and portal venous phases were acquired using 64- (Briliance 64, Philips Healthcare) or 256-detector row (iCT 256, Philips Healthcare) machines in a supine position in the craniocaudal direction. All patients received nonionic iodinated contrast material (iomeprol 350; 2 mL/kg) at a rate of 3 mL/s. Detailed scan parameters are listed in Supplementary Table 1.

Image Interpretation

We invited three readers other than the four radiologists involved in the initial CT interpretation and treatment decisions. They were fellowship-trained abdominal radiologists with 6, 8 and 8 years of experience after board certification, respectively. They were informed of the patient inclusion criteria but blinded to the original CT reports and final pathologic results. The readers independently reviewed the 3-mm-thick axial and coronal images of the multiphase scans. The choice of contrast-enhancement phase to be evaluated was left to the discretion of the readers. For a more detailed evaluation of the local extent of pancreatic cancer, they optionally reviewed 2-mm-thick images using multiplanar reformation and three-dimensional volume-rendering techniques using a dedicated workstation (Aquarius, Terarecon).

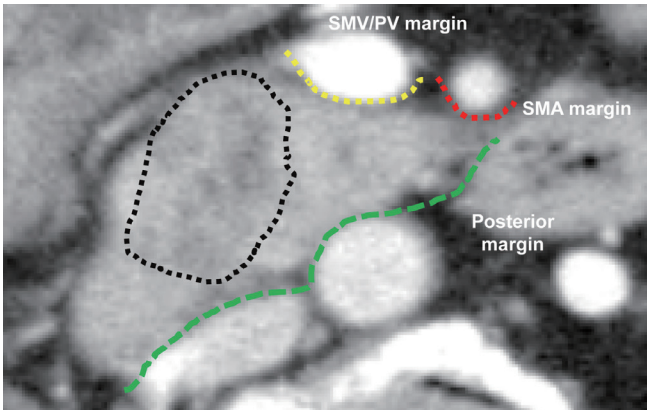

Fig. 2. Schematic illustration of image analysis. Black dotted line, the extent of the tumor; red dotted line, SMA margin; green dotted line, posterior margin; and yellow dotted line, SMV/PV margin. SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

For the analysis, CRM status was evaluated separately for the SMA and posterior and superior mesenteric vein/portal vein (SMV/PV) margins. We did not consider the anterior resection margin because controversy exists as to whether it should be included as part of the CRM. As surgeons do not transect any tissue at the anterior margin, it is not a true resection margin but is rather a surface of the pancreatic head [11,15]. On CT, the outermost surface of the SMA was regarded as a presumptive SMA resection margin. Similarly, the outermost surface of the IVC (or the aorta) and SMV/PV were regarded as presumptive posterior and SMV/PV resection margins, respectively (Fig. 2). The readers rated the CT resection margin on a 3-point scale: score 0, not involved (tumor-to-presumptive-resection-margin distance > 1 mm); score 1, very close (0 mm < the distance ≤ 1 mm); and score 2, involved (distance = 0 mm). The overall (per-patient) CRM status was regarded as being involved if either the SMA or posterior margin was rated as being involved by the tumor. As surgical resection and reconstruction of the SMV/PV are often feasible, we assumed that tumor involvement of the SMV/PV margin would not affect the surgical outcome if successfully resected. Therefore, the SMV/PV margin was not considered when determining the overall CRM status in our study. The readers were instructed that both the solid-looking portion and features of perineural invasion (coarse reticulation or over 2-mm strand-shaped soft tissue density connecting to the cancer mass) should be regarded as a tumor in rating the CT resection margin. Peritumoral fine lines or reticulation were not regarded as tumors, because they are known to be features of micro-vessels/lymph nodes and fibrosis [16].

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Reference Standard Procedure

The patients underwent pancreaticoduodenectomy. For pathologic examination of surgical specimens, we used the axial slicing method proposed by the Royal College of Pathologists [8]. Each resection margin was marked on the surgical specimen by an operating surgeon immediately after pancreaticoduodenectomy. The surgeon packed three or four 4 x 4-inch gauzes into the duodenal lumen of the pancreaticoduodenectomy specimen to preserve the *in vivo* anatomical configuration of the surgical specimen during fixation as much as possible. The specimens were then sent to the pathology department, where the surgical margins were stained according to the predetermined color code (SMA margin, red; posterior margin, green; SMV/PV margin, yellow; and anterior surface, white) (Fig. 3A, B).

After fixation in 10% buffered formalin for over 12 hours, all the transection margins (stomach/proximal duodenum, pancreas neck, bile duct, distal duodenum) and CRMs were identified and completely embedded. The specimens were prepared in 3- to 5-mm-thick slices in an axial plane

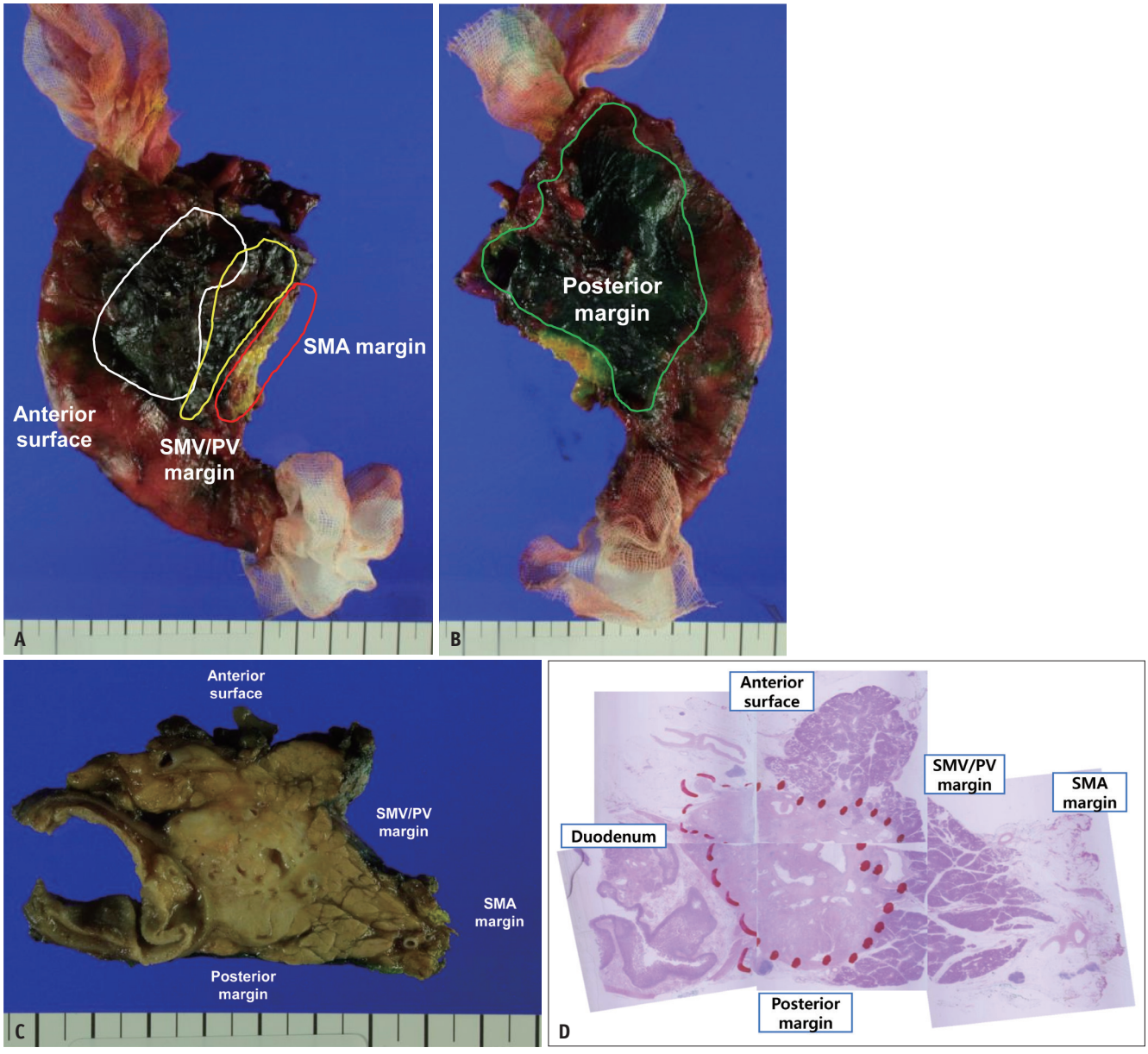

Fig. 3. Preparation of pathologic specimen.
A-D. After inking the surgical margins according to the predetermined color codes **(A, B)**, the specimen was sliced in 3- to 5-mm thick slices following an axial plane perpendicular to the duodenal axis **(C)**. The circumferential resection status was evaluated microscopically. Hematoxylin and eosin staining (x 4) **(D)**. SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

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perpendicular to the axis of the second portion of the duodenum. The CRM status was macro- and microscopically evaluated by one of two dedicated hepatobiliary pathologists, who had access to clinical information, including CT results and surgical reports (Fig. 3C, D). A positive resection margin was defined as the presence of tumor cells within 1 mm of the resection margins [17]. Even when there was no definite macroscopic tumor invasion of the resection margins, the pathologists evaluated the margin status microscopically on at least two slices for each surgical margin.

Statistical Analysis

All analyses were planned before data collection, except for a subgroup analysis using the patient enrollment period. The sample size was determined by the number of eligible patients during the study period. We measured the pooled sensitivity and specificity of the three readers in predicting CRM status. The diagnostic accuracy was measured for the overall CRM status (per-patient analysis) and for each SMA, posterior, and SMV/PV margin (per-margin analysis). For the primary analysis, the diagnostic accuracy was calculated by considering a CT resection margin score of 2 as positive.

Subgroup analyses were performed by the patient enrollment period, sex, body mass index, and preoperative assessment results regarding resectability, which were assumed to be pertinent to the diagnostic accuracy. The between-group heterogeneity of diagnostic accuracy was assessed using a likelihood ratio test in a crossed random-effects model. Sensitivity analyses were performed by modifying the positivity threshold of the index test or the reference standard. We modified the index test positivity threshold as a CT resection margin score of ≥ 1. We modified the reference standard positivity threshold as the presence of tumor cells at the resection margins, unlike in the primary analysis, where we considered the presence of tumor cells at or within 1 mm of the resection margin as a positive resection margin.

We pooled the sensitivity and specificity across the readers using a crossed random effects model to adjust for clustering (or heterogeneity) within readers as well as within patients. Based on the fitted crossed random effects model, we obtained 95% confidence intervals (CIs) of the pooled sensitivity or specificity from 1000 Monte Carlo simulations. Fleiss κ was used to measure interobserver agreement across the three readers in predicting the CRM status, and Cohen's κ was used for agreement between any two readers. Statistical analyses were performed using R software version 4.0.3 (the R Foundation for Statistical Computing).

RESULTS

Patients

Among 285 consecutive patients with suspected pancreatic head cancer on CT between October 2014 and January 2018, 141 patients were determined to have resectable (n = 113) or borderline resectable (n = 28) pancreatic head cancer. Among those patients, 77 patients who were being considered for upfront surgery without neoadjuvant therapy agreed to participate in the study. Two patients were later excluded from the analysis due to pancreatic neoplasms other than pancreatic ductal adenocarcinoma on the final pathology, and protocol nonadherence regarding patient eligibility. Finally, 75 patients with pathologically proven pancreatic ductal adenocarcinoma were included in the study. The patients' baseline characteristics, including T and N stages according to the American Joint Committee on Cancer (AJCC) 8th edition [18] and time interval between CT and operation, are detailed in Table 1 and Supplementary Table 2. The study included 37 female and 38 male with a mean age of 68 ± 11 years (interquartile range, 65–75 years). Fifty-one patients (68%) were preoperatively regarded as having resectable cancer and 24 patients (32%) as having borderline cancer. SMV/PV was resected in 28 patients (38%). In 27 of these 28 patients, the distance between the tumor and SMV/PV was less than or equal to 1 mm on pathologic examination. Among 46 patients who did not undergo SMV/PV resection, 27 patients were confirmed with a positive SMV/PV margin. Positive overall CRM was pathologically confirmed in 40 patients (53%). Among the resection margins, the SMV/PV margin (54 patients, 73%) was the most frequently involved, followed by the posterior margin (26 patients, 35%), and the SMA margin (23 patients, 31%).

Diagnostic Accuracy of CT

The pooled sensitivity and specificity of the three readers for overall CRM involvement was 15% (95% CI: 7%–49%) and 99% (96%–100%), respectively. In per-margin analysis, the pooled sensitivity and specificity of the SMA margin status of the three readers were 14% (9%–54%) and 99% (38%–100%) (Figs. 4, 5); for the posterior margin status, 12% (8%–46%) and 99% (97%–100%); and for the SMV/

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Table 1. Patient Characteristics

Characteristic	Value
Total number of patients	75
Age, years	71 (65–75)
Sex	
Male	38 (51)
Female	37 (49)
Body mass index, kg/m²*†	23.3 (21.0–24.8)
< 18.5 (underweight)	5 (7)
18.5–24.9 (normal)	53 (71)
≥ 25.0 (overweight)	17 (23)
Carbohydrate antigen 19-9	183.0 (55.5–375.0)
Total bilirubin	2.3 (0.7–9.7)
Time interval between CT and operation, day	8.5 (5.4–13.4)
Preoperative assessment for resectability	
Resectable	51 (68)
Borderline resectable	24 (32)
Operative procedure	
Operation method	
Pylorus preserving pancreatoduodenectomy	59 (79)
Whipple's operation	15 (20)
Futile surgery	1 (1)
Resection of SMV/PV‡	
Yes	28 (38)
No	46 (62)
Pathologic stage‡	
T stage†	
T1	5 (7)
T2	56 (76)
T3	13 (18)
N stage	
N0	20 (27)
N1	26 (35)
N2	28 (38)
Pathologic overall CRM status§	
Involved	40 (53)
Not involved	35 (47)
Pathologic each resection margin status‡§	
SMA resection margin	
Involved	23 (31)
Not involved	51 (69)
Posterior resection margin	
Involved	26 (35)
Not involved	48 (65)
SMV/PV resection margin	
Involved	54 (73)
Not involved	20 (27)

Data are n (%) or median (interquartile range). *Weight in kilograms divided by the square of the height in meters, †Because of rounding, percentages may not total 100, ‡One patient who turned out to have unresectable cancer during surgery was excluded, §Pathologic resection margin status by preoperative assessment for resectability is detailed in Supplementary Table 2. CRM = circumferential resection margin, SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

PV margin status, 37% (29%–53%) and 96% (31%–100%), respectively. The individual readers' sensitivity and specificity for per-participant and per-margin status are summarized in Figure 6.

In the subgroup analyses, a trend of high specificity and low sensitivity was observed without substantial heterogeneity ($p > 0.2$). The results of subgroup analyses for overall and each resection margin status are summarized in Table 2 (per-patient analyses) and Supplementary Table 3 (per-margin analyses). In the sensitivity analysis, where the index test positivity threshold was modified as the CT resection margin score ≥ 1 (very close or involved: tumor-to-presumptive- resection-margin distance < 1 mm), the sensitivity was increased to 30% (12%–62%), and the specificity was slightly lowered to 93% (73%–94%). The results of the sensitivity analyses by varying the index test and reference standard positivity thresholds are shown in Table 3.

Interobserver Agreement

Fleiss κ in predicting the overall CRM status across the three readers was 0.37 (95% CI: 0.24–0.50). In the per-margin analysis, Fleiss κ was 0.47 (0.34–0.60) for the SMA margin; 0.48 (0.35–0.61) for the posterior margin; and 0.48 (0.35–0.61) for the SMV/PV margin. Cohen's κ values between the two readers are shown in Table 4.

DISCUSSION

In this prospective study, we measured the diagnostic accuracy of CT for CRM status in patients with resectable or borderline resectable pancreatic head cancer. Both per-patient and per-margin analyses showed very high specificity but low sensitivity of CT in predicting CRM status. The readers showed low interobserver agreements in predicting the CRM status, which corroborates the results of a previous interobserver agreement study on resectability [19]. However, a trend of high specificity and low sensitivity was consistently observed across the readers and surgical margins. The subgroup and sensitivity analyses that modified the patient enrollment period or the criteria for positive resection margins (0 mm vs. < 1 mm) also showed no substantial heterogeneity. These findings suggest that CT shows excellent performance in selecting surgical candidates who would have negative pathologic CRMs after upfront surgery (pooled specificity, 99%). Meanwhile, the performance of CT was very limited in selecting patients

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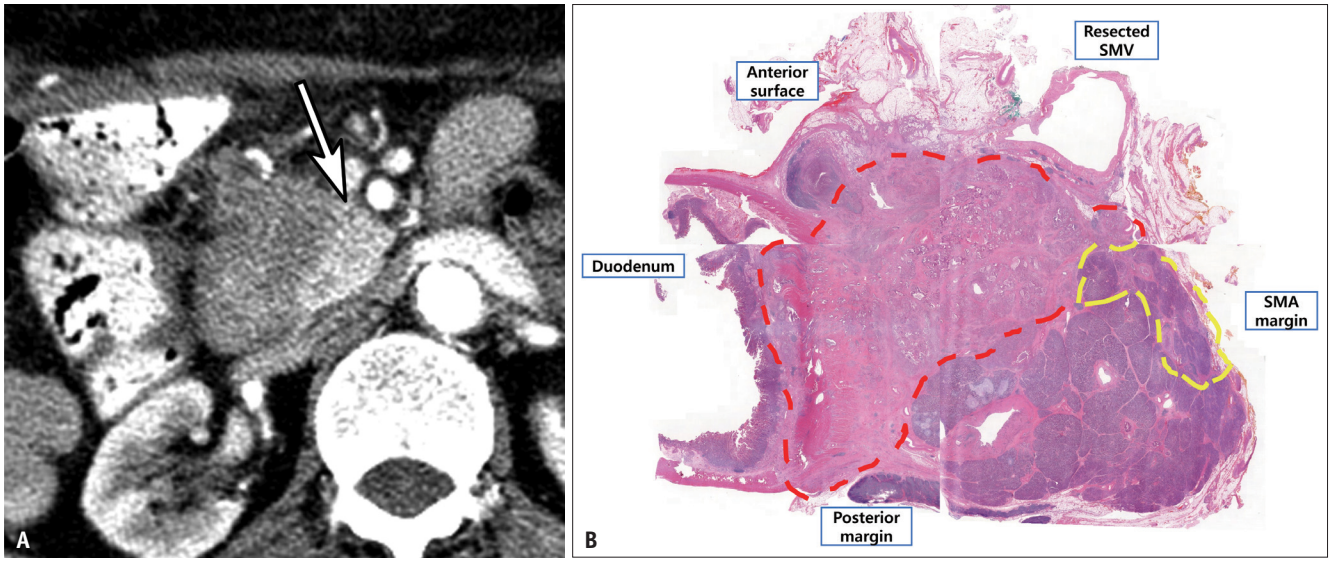

Fig. 4. A contrast-enhancement 4-mm-thick transverse image in the pancreatic phase and pathologic slides of a 70-year-old female.

A. On CT, normal pancreatic parenchyma was noted between the cancer and the SMA (arrow). **B.** On pathologic specimen, most tumor glands were accompanied by fibrosis (red dotted line), while some were noted in the relatively preserved pancreatic parenchyma (yellow dotted line). All three readers predicted the SMA margin to be negative, while it was positive (< 400 μm) on pathologic examination. Hematoxylin and eosin staining (x 4). SMA = superior mesenteric artery, SMV = superior mesenteric vein

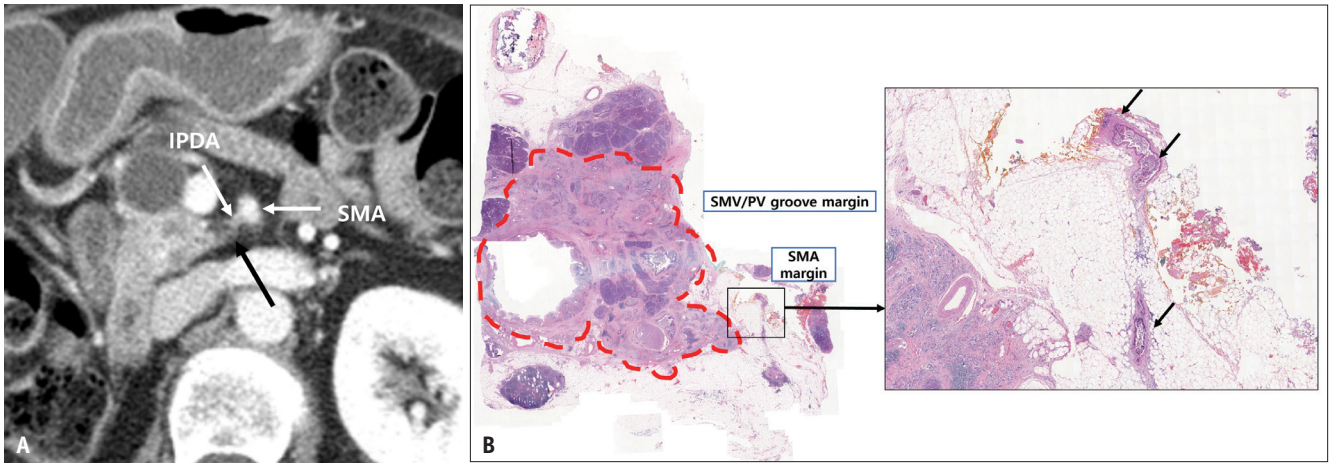

Fig. 5. A contrast-enhancement 4-mm-thick transverse image in the portal venous phase and pathologic slides of a 78-year-old female.

A. On CT, subtle fatty infiltration (black arrow) was noted near the SMA. **B.** On pathologic specimen, cancer glands were seen within adipose tissue (arrows in the high-power field of view) apart from the main mass (red dotted line). All three readers predicted SMA margin to be negative, while it was positive (< 100 μm) on pathologic examination. Hematoxylin and eosin staining (x 4, x 100). IPDA = inferior pancreaticoduodenal artery, SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

who would have positive pathologic CRMs after upfront surgery and therefore could benefit from neoadjuvant therapy (pooled sensitivity, 15%).

Although we did not formally assess the cause of the low sensitivity of CT, there are several possible explanations. First, unlike previous studies investigating resectability evaluation using CT [19,20], we excluded patients with unresectable cancer. Excluding cancers with overt vascular involvement might have made the diagnostic task more challenging. Second, the characteristics of pancreatic cancer might hinder accurate delineation of the tumor extent on CT. Tumor spread along the lymphatic or perineural network is a well-known characteristic of pancreatic cancer. Such microscopic spread is observed as fuzzy reticular infiltration on CT [21,22], which frequently mimics normal micro-vessels, lymph nodes, or benign fibrosis. In addition, the

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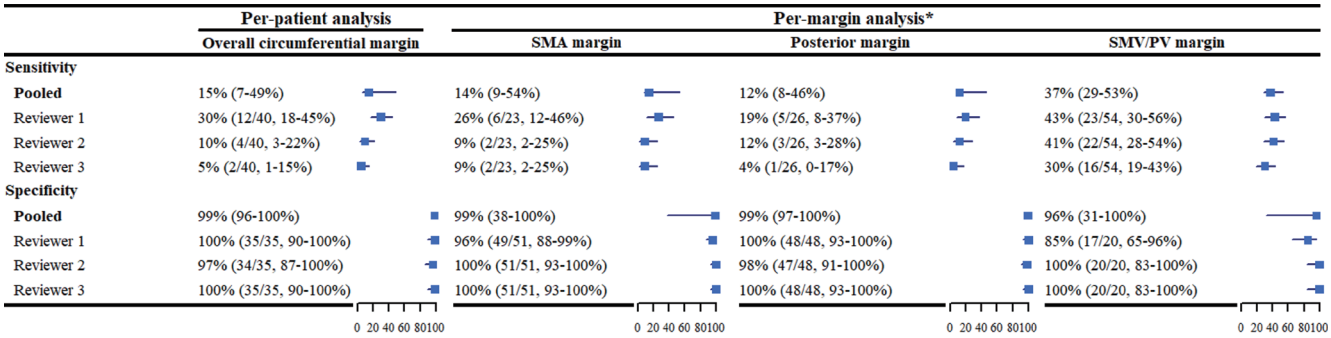

Fig. 6. Diagnostic accuracy of overall CRM status (per-patient analysis) and for each of the SMA, posterior, and SMV/PV margin (per-margin analysis). Data for pooled estimate are percentages (95% confidence intervals). Data for each reviewer are percentages (numerators/denominators, 95% confidence intervals). *One patient who turned out to have unresectable cancer during surgery was excluded in per-margin analysis. CRM = circumferential resection margin, SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

Table 2. Accuracy of CT for Overall Circumferential Resection Margin Status (Per-Patient Analysis)

Groups	Sensitivity	$P^{\dagger}$	Specificity	$P^{\dagger}$
Total (n = 75)	15 (7–49)		99 (96–100)	
Varying patient enrollment period		0.90		0.41
Patients who enrolled in earlier period (n = 50)	17 (8–55)		99 (95–100)	
Patients who enrolled in latter period (n = 25)	11 (0–58)		100 (NC)	
Sex		0.85		0.23
Male (n = 38)	12 (7–47)		100 (NC)	
Female (n = 37)	18 (7–60)		98 (92–100)	
Body mass index, kg/m^2*		0.91		0.47
< 24.9 (underweight or normal) (n = 58)	17 (9–52)		99 (95–100)	
≥ 25.0 (overweight) (n = 17)	6 (0–85)		100 (NC)	
Preoperative assessment for resectability		0.83		0.41
Resectable (n = 51)	12 (1–58)		99 (95–100)	
Borderline resectable (n = 24)	21 (12–67)		100 (NC)	

Data are pooled percentages (95% confidence intervals) across the readers. *Weight in kilograms divided by the square of the height in meters, $^{\dagger}P$ values were calculated by a likelihood ratio test in a crossed random effects model. NC = not calculated

Table 3. Sensitivity Analyses

Criteria	Parameter	Per-Patient Analysis	Per-Margin Analysis*		
		Overall Circumferential Margin	SMA Margin	Posterior Margin	SMV/PV Margin
Test positivity CT resection margin score ≥ 1†	Sensitivity	30 (12–62)	25 (13–58)	18 (10–47)	61 (36–79)
Reference standard positivity Tumor-to-resection-margin distance ≤ 1 mm	Specificity	93 (73–94)	92 (67–97)	94 (72–95)	82 (45–90)
Test positivity CT resection margin score = 2†	Sensitivity	25 (10–65)	33 (11–78)	18 (7–67)	51 (35–67)
Reference standard positivity Tumor-to-resection-margin distance = 0 mm	Specificity	97 (76–99)	99 (33–100)	97 (78–98)	87 (67–90)
Test positivity CT resection margin score ≥ 1†	Sensitivity	35 (18–69)	48 (19–81)	18 (7–67)	67 (37–86)
Reference standard positivity Tumor-to-resection-margin distance = 0 mm	Specificity	86 (56–95)	92 (67–97)	91 (68–93)	62 (41–75)

Data are pooled percentages (95% confidence intervals) across the readers. *One patient who turned out to have unresectable cancer during surgery was excluded in per-margin analysis, †3-point scale: score 0, not involved (tumor-to-presumptive-resection-margin distance > 1 mm); score 1, very close (0 mm < the distance ≤ 1 mm); and score 2, involved (the distance = 0 mm). SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

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Table 4. Interobserver Agreement

Diagnostic Task	Three Readers	Reader 1 vs. 2	Reader 1 vs. 3	Reader 2 vs. 3
Overall (SMA or posterior margins)	0.37 (0.24–0.50)	0.42 (0.12–0.72)	0.25 (-0.03–0.54)	0.55 (0.11–1.00)
SMA margin	0.47 (0.34–0.60)	0.37 (-0.00–0.75)	0.37 (-0.00–0.75)	1.00 (1.00–1.00)
Posterior margin	0.48 (0.35–0.61)	0.65 (0.27–1.00)	0.32 (-0.16–0.79)	0.39 (-0.15–0.92)
SMV/PV margin	0.48 (0.35–0.61)	0.31 (0.08–0.53)	0.52 (0.32–0.72)	0.65 (0.46–0.85)

Data are κ values (95% confidence interval). SMA = superior mesenteric artery, SMV/PV = superior mesenteric vein/portal vein

growth pattern in pancreatic cancer is known to be more dispersed than in other cancers, particularly in the tumor periphery [23], and this characteristic might have led to the underestimation of tumor extent on CT [24,25]. Third, even if a thin fat plane was correctly identified to be preserved on CT, CRM may be involved during surgery, resulting in a false-negative diagnosis. In real practice, various factors affect the extent of surgical dissection, such as the individual surgeon's strategy/skill and the anatomical relationship between the tumor and the major vessels [26], which makes R0 resection technically demanding.

The oncologic benefits of neoadjuvant therapy for borderline resectable pancreatic cancer are well established. However, its role in patients with resectable cancer is debatable. Several studies on neoadjuvant therapy for resectable pancreatic cancer have reported promising results, showing high R0 resection rates of over 95% [27,28]. However, those studies lacked comparison with patients who underwent upfront surgery in a parallel-group setting. More importantly, as those studies were conducted based on data from surgical databases, patients who could not undergo surgery after neoadjuvant therapy were not included [6].

Nonetheless, our findings may favor the treatment strategy of applying neoadjuvant therapy for resectable cancers. The low sensitivity of CT for positive CRM indicates the limitation of CT in identifying patients at a high risk of positive resection margins after upfront surgery. Thus, most patients who would benefit from neoadjuvant therapy could be assigned to upfront surgery. However, there is a concern that such indiscriminate use of neoadjuvant therapy may increase the risk of cancer progression during neoadjuvant therapy, thereby losing the chance for curative resection. There have been no formal studies showing whether the benefit of neoadjuvant therapy in patients with positive pathologic CRM after upfront surgery (patients with a false-negative prediction on CT) outweighs the potential harm of cancer progression in patients who can have negative pathologic CRM after upfront surgery (patients with a true-negative prediction on CT). Trials investigating the effectiveness of neoadjuvant therapy for resectable pancreatic cancer are currently ongoing [29-31]. Based on the results of these trials, the limited sensitivity of CT should be considered when establishing future guidelines.

Our study had several strengths. First, to our knowledge, this is the first study to directly measure the diagnostic accuracy of CT in predicting individual and overall CRM status. Second, we prospectively included patients with resectable or borderline resectable pancreatic head cancer using a predetermined study protocol. Third, with careful preparation of pathologic specimens by operating surgeons and pathologists, we could create robust reference standards for CRM status.

Our study had several limitations. First, due to the constraints of time and resources, the number of patients included in our study was too small to obtain precise estimates of diagnostic accuracy. Second, the generalizability of our results is unclear because our study was conducted in a single institution involving a limited number of surgeons, pathologists, and radiologists. There might have been inter-institutional variation in our eligibility criteria that excluded patients with unresectable cancer. Third, as mentioned earlier, we could not include all patients with borderline resectable pancreatic head cancer in our study due to the transition of treatment strategy towards neoadjuvant therapy. Therefore, selection bias may have affected our results. Fourth, we conducted a retrospective image analysis instead of prospective CT reports. It was logistically not feasible for multiple radiologists to read the same CT of a single patient in daily practice, and to uniformly use a standard reporting format that could be applied for both research and practice purposes. Fifth, we included only patients with pancreatic head cancer. Pancreatic body or tail cancer requires different techniques in surgery and pathologic specimen preparation.

In conclusion, CT showed very high specificity but low sensitivity in predicting pathologic CRM involvement in patients with resectable or borderline resectable pancreatic

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head cancer according to clinical assessment. The limited sensitivity of CT should be considered when establishing future guidelines as well as in designing clinical trials for patients with pancreatic head cancer.

Supplement

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Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Ji Hoon Park, Yoo-Seok Yoon. Data curation: all authors. Formal analysis: Seungjae Lee. Funding acquisition: Yoo-Seok Yoon. Investigation: all authors. Methodology: Ji Hoon Park, Yoo-Seok Yoon. Project administration: Ji Hoon Park, Yoo-Seok Yoon. Resources: all authors. Supervision: Ji Hoon Park, Yoo-Seok Yoon. Writing—original draft: all authors. Writing—review & editing: all authors.

ORCID iDs

Ji Hoon Park
https://orcid.org/0000-0002-6794-4909
Yoo-Seok Yoon
https://orcid.org/0000-0001-7621-8557
Seungjae Lee
https://orcid.org/0000-0001-5508-8634
Hae Young Kim
https://orcid.org/0000-0002-9508-4280
Ho-Seong Han
https://orcid.org/0000-0001-9659-1260
Jun Suh Lee
https://orcid.org/0000-0001-9487-9826
Won Chang
https://orcid.org/0000-0001-7367-9841
Haeryoung Kim
https://orcid.org/0000-0002-4205-9081
Hee Young Na
https://orcid.org/0000-0002-2464-0665
Seungyeob Han
https://orcid.org/0000-0001-9046-2062
Kyoung Ho Lee
https://orcid.org/0000-0001-6045-765X

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