



# Computed Tomography Prediction of Resectability of Pancreatic Adenocarcinoma Using National Comprehensive Cancer Network Criteria

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## Abstract

**Introduction:** We evaluated the diagnostic accuracy of computed tomography (CT) in determining resectability of pancreatic adenocarcinoma using National Comprehensive Cancer Network (NCCN) Criteria.

**Methods:** Two radiologists retrospectively reviewed abdominal CT images from 36 patients with non-metastatic pancreatic adenocarcinoma who were operated on between 2018 and 20120. Based on CT findings six patients were reported as resectable, seven patients as borderline resectable, and 23 patients as unresectable using NCCN criteria for resectability. Positive predictive values for negative resection margin (R0) were assessed for CT using post-operative histopathological reports as reference standards.

**Results:** In 36 patients who preceded to surgery R0 resection rates were 83% (5 of 6), 71% (5 of 7), and 60% (14 of 23) for resectable, borderline resectable, and unresectable disease, respectively ( $p < 0.001$ ).

**Discussion and Conclusion:** CT can be used to identify patients with pancreatic cancer who can benefit from surgery with the possibility of R0 resection. Our study results showed that using NCCN guidelines the diagnostic accuracy of CT to predict R0 resection can be improved.

**Keywords:** Computed tomography; pancreas cancer; resectability.

Pancreatic adenocarcinoma is the most common form of pancreatic cancer and the fourth leading cause of cancer death in the Western world, accounting for approximately 22% of the deaths from malignant gastrointestinal neoplasms. In 2018, 458.918 new cases of pancreatic can-

cer were registered worldwide, representing 2.5% of all cancers<sup>[1]</sup>. The high mortality rate is due to the aggressive nature of the disease and due to the delayed diagnosis as the symptoms are usually vague and appear only after the disease reaches an advanced stage.

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**Submitted Date (Başvuru Tarihi):** 15.01.2021 **Accepted Date (Kabul Tarihi):** 22.01.2021

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Surgical resection of pancreatic adenocarcinoma is the only option for potential cure. However, it is estimated that only 15–20% of patients have resectable disease at presentation and even after resection the overall 5-year survival rate remains at 15–27%<sup>[2-4]</sup>. Treatment with neoadjuvant chemotherapy may enable achieve a negative margin resection (R0) and improve survival for patients diagnosed with early-stage pancreatic adenocarcinoma. Surgical resection should be avoided in patients who will likely not benefit from surgery<sup>[5,6]</sup>. Tumor detection and staging by assessment of resectability with diagnostic imaging are important in planning treatment. Imaging is also critical for monitoring treatment response. Although several imaging techniques, such as ultrasound (transabdominal or endoscopic ultrasound), multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography can be used, MDCT is the most preferred modality for the initial diagnosis and staging of pancreatic adenocarcinoma thanks to its widespread availability, superior spatial resolution, and ultra-fast coverage of a wide anatomical area that is needed for assessing of the pancreatic tumor<sup>[5-7]</sup>. In this study, we aimed to evaluate the resectability and staging of pancreatic adenocarcinoma with MDCT.

## Materials and Methods

Our institutional review board approved this study. Informed patient consent was not obtained due to the retrospective nature of the study.

## Study Patients

We reviewed the MDCT examinations of patients with pathologically confirmed pancreatic ductal adenocarcinoma who met the following inclusion criteria between October 2018 and October 2020: (1) Patients who had a multi-phasic CT with a pancreas protocol before surgery, (2) a time interval of less than 4 weeks between the CT scan and surgery. Among 55 eligible patients, we excluded nine patients who received neoadjuvant therapy before pancreatic surgery and ten patients who did not undergo surgery because of poor performance status, overt locally advanced or metastatic disease on imaging leaving 36 patients as our study group (33 men, three women; mean age, 63 years  $\pm$  10 [standard deviation]; age range, 34–85 years). The data of 36 patients who underwent surgery (33 men [mean age, 62 years  $\pm$  9; age range, 40–85 years] and three women [mean age, 64 years  $\pm$  10; age range, 35–81 years]) were retrospectively analyzed to evaluate the completeness of the tumor resection.

## Imaging Techniques

Multiphasic CT was performed by following a pancreas protocol and using a 64-channel multidetector row CT scanner (Optima 660, GE Medical Systems, Milwaukee, USA). The scanning protocol included unenhanced and contrast material-enhanced biphasic imaging in the arterial and portal venous phases after intravenous administration of 150 mL of ioversol (Optiray 320; Guerbet, Villepinte, France) at a rate of 3 mL/s using an automated power injector. Images were reconstructed at 5.0-mm thickness in the axial plane for unenhanced images and at 2.5–3.0-mm thickness in the axial and coronal planes for arterial and portal venous phase images obtained at 20 s and 65 s, respectively, following onset of contrast injection. Volume-rendered (3D) and maximal intensity projection reconstructed images for the evaluation of invasion of arterial and venous structures were generated and sent to the picture archiving and communication system for review by radiologists.

## Image Analysis

Two radiologists with 17 and 4 years of experience in abdominal radiology evaluated the images. In alignment with the pancreatic cancer staging according to the National Comprehensive Cancer Network (NCCN) guidelines, version 1.2021 (Table 1) the degree of tumor–vascular contact was classified as no contact, abutment, encasement, occlusion, or tumor thrombosis<sup>[8]</sup>. Abutment was defined as tumor contact with no more than 180° of the vessel circumference. Encasement was defined as tumor involvement with more than 180° of the vessel circumference or vascular deformity suggesting invasion<sup>[8]</sup>. Hazy attenuation–vascular contact was not considered tumor–vascular contact. Lymph nodes larger than 1 cm in the short-axis diameter and necrotic lymph nodes were regarded as metastatic lymph nodes. Regional lymph nodes included (a) lymph nodes along the common bile duct, common hepatic artery, portomesenteric vein, and pancreaticoduodenal arcades for pancreas head cancer and (b) lymph nodes along the common hepatic artery, celiac axis, splenic artery, and splenic hilum for pancreas body or tail cancer<sup>[9]</sup>. Variant arterial anatomy, including accessory or replaced right hepatic artery and replaced common hepatic artery, and degree of tumor contact with variant arteries also were evaluated.

After determining the tumor location and size, the tumor–vascular contact, adjacent organ invasion or metastatic spread were assessed and the tumor was classified as resectable, borderline resectable, or unresectable based on NCCN resectability criteria (Table 1)<sup>[8]</sup>. Resectable disease

**Table 1.** Criteria defining resectability status at diagnosis<sup>a</sup>

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact (CA, SMA, or CHA)	No tumor contact with the SMV or PV or *180° contact without vein contour irregularity
Borderline resectable <sup>b</sup>	Pancreatic head/uncinate process: <ul style="list-style-type: none"> <li>•Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction</li> <li>•Solid tumor contact with the SMA of <math>\leq 180^\circ</math></li> <li>•Solid tumor contact with variant arterial anatomy (e.g., accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning</li> </ul> Pancreatic body/tail: <ul style="list-style-type: none"> <li>•Solid tumor contact with the CA of <math>\leq 180^\circ</math></li> <li>•Solid tumor contact with the CA of <math>&gt; 180^\circ</math> without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category)</li> <li>•Solid tumor contact with the IVC</li> </ul>	<ul style="list-style-type: none"> <li>•Solid tumor contact with the SMV or PV of <math>&gt; 180^\circ</math>, contact of <math>*180^\circ</math> with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction</li> </ul>
Locally advanced <sup>b,c</sup>	Head/uncinate process: <ul style="list-style-type: none"> <li>•Solid tumor contact with SMA <math>&gt; 180^\circ</math></li> <li>•Solid tumor contact with the CA <math>&gt; 180^\circ</math></li> </ul> Pancreatic body/tail: <ul style="list-style-type: none"> <li>•Solid tumor contact of <math>&gt; 180^\circ</math> with the SMA or CA</li> <li>•Solid tumor contact with the CA and aortic involvement</li> </ul>	<ul style="list-style-type: none"> <li>•Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)</li> </ul>

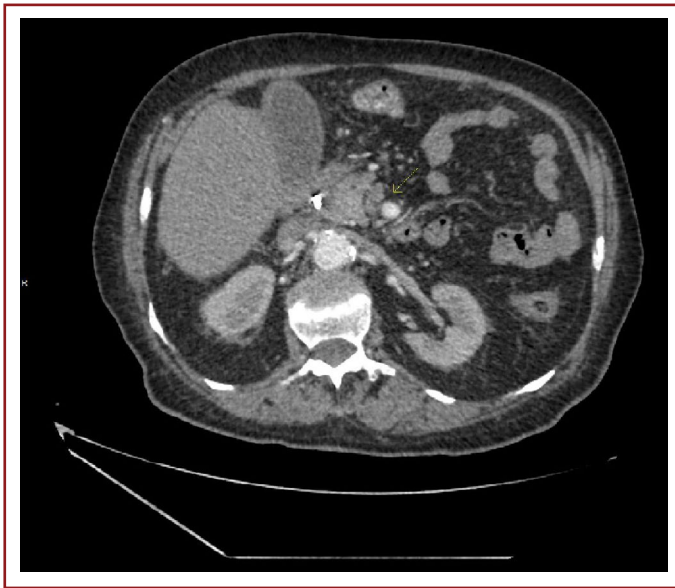
<sup>a</sup>El Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Radiology* 2014; 270:248-260. <sup>b</sup>Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. <sup>c</sup>Distant metastasis (including non-regional lymph node metastasis), regardless of anatomic resectability, implies disease that should not be treated with upfront resection. CA: Celiac axis, SMA: Superior mesenteric artery, CHA: Common hepatic artery, SMV: Superior mesenteric vein, PV: Portal vein, IVC: Inferior vena cava.

is defined as no contact with celiac axis, SMA, CHA, SMV, or portal vein (Fig. 1). Tumor contact  $\leq 180^\circ$  without vein contour irregularity is also considered resectable (Fig. 2a, b). Unresectable disease was further subdivided as locally advanced disease (pancreatic cancer without distant metastasis but with vascular invasion) (Figs. 3, 4) or M1 pancreatic cancer<sup>[8]</sup>. Radiological evaluation and assessment were done by consensus of both readers.

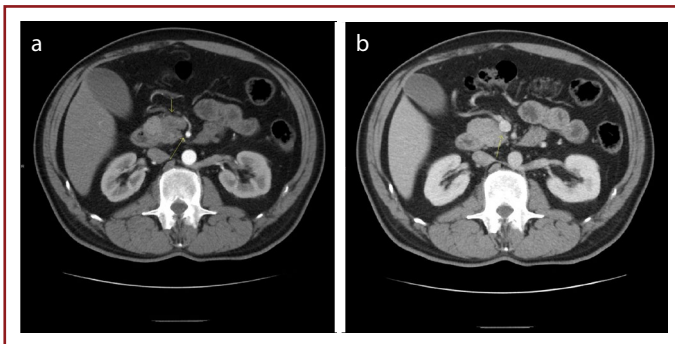
### Clinical, Surgical, Pathologic, and Follow-up Data Collection

Therapeutic decisions were made after multidisciplinary discussion between radiologists, oncologists, and surgeons and were based on the general condition and

comorbidity of patients, CT resectability, and additional imaging examinations (abdominal MRI, n=24; combined PET/CT, n=11). At our hospital, upfront Whipple resection without neoadjuvant therapy is the primary treatment opted in patients who are considered resectable on imaging as long as patient's general condition allows surgical intervention. The treatment for borderline resectable or locally advanced pancreatic cancer is tailored on a patient-based policy. Neoadjuvant therapy is generally saved for some borderline resectable cases and is only scarcely used at our institution. For most cases of non-metastatic borderline resectable disease, for all cases of non-metastatic locally advanced disease involving the portomesenteric veins and for selected tumors with short-segment arterial



**Figure 1.** Adenocarcinoma in pancreatic neck with clear fat plane around superior mesenteric artery (arrow) suggesting a resectable tumor.



**Figure 2. (a)** Pancreatic head adenocarcinoma seen as hypodense area compared to lateral pancreatic parenchyma (short arrow) with a clear fat plane around celiac trunk and arising common hepatic artery (long arrow). **(b)** There is (<180° abutment of the tumor with superior mesenteric vein suggesting a borderline resectable tumor (arrow).

involvement, which can be surgically re-moved with arterial decortication or short-segment arterial resection an ex-tended pancreatic surgery including the Whipple procedure and vascular reconstruction of resected vascular structures is performed. Adjuvant chemotherapy is given for these patients and for patients with metastatic pancreatic tumor at our institution.

At our hospital, surgery was performed by surgeons who have specialized at hepatobiliary and surgery. Following pancreatic resection, the pancreatic resection margin and the circumferential resection margins were marked with ink. The circumferential resection margin included the anterior and posterior surfaces of all pancreatic resec-



**Figure 3.** Circumferential encasement of common hepatic artery by pancreatic head adenocarcinoma suggesting a locally advanced unresectable tumor (arrows).



**Figure 4.** Pancreatic adenocarcinoma (long arrow) with abutment of superior mesenteric artery (short arrow) >180° suggesting an unresectable tumor.

tions and the common bile duct margin, uncinate process margin, superior mesenteric artery surface, and superior mesenteric vein surface for pancreaticoduodenectomy (Whipple procedure). Intraoperative pathologic examination was performed on the resected pancreas specimen. Based on British Royal College of Pathology guidelines, R0 resection was defined as complete tumor resection with a negative resection margin, R1 a positive resection margin with presence of tumor cells at the resection margin or within 1 mm of the circumferential re-section mar-

gins, and R2 as the presence of gross residual tumor at surgery<sup>[10]</sup>.

All patient medical, surgical and pathology reports, as well as data including: Pre-operative serum cancer antigen 19–9 level; history of adjuvant chemotherapy; surgical resection method, including the presence of artery, vein, or additional organ resection; and status of resection margin (R0, R1 or R2) were retrieved. Surgical resection was classified as standard surgery (i.e., Whipple procedure or distal pancreatectomy) or extended surgery (i.e., pancreaticoduodenectomy with portomesenteric vein/artery resection for head tumors and distal pancreatectomy with splenectomy for tail tumors) according to the consensus definition of the international study group for pancreatic surgery<sup>[11]</sup>.

## Statistical Analysis

$\chi^2$  tests were used for proportions and one-way analysis of variance tests or the Kruskal–Wallis test for continuous variables. All statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY).

## Results

### Patient Characteristics

Information about our study population characteristics is summarized in Table 2. The study population consisted of 36 patients (33 men and three women) with a mean age of 60 years  $\pm$  10 (range, 31–77 years). The mean interval between the CT examination and surgery was 11 days  $\pm$  6.3

**Table 2.** Characteristics of the study population

Characteristic	Total	CT resectability according to NCCN criteria			p
		Resectable	Borderline resectable	Unresectable	
All patients					
No. of patients	55	8	16	31	NA
Age (y)*	60 $\pm$ 10	63 $\pm$ 10	61 $\pm$ 10	65 $\pm$ 10	0.20
Sex (M/F)	40/15	7/1	12/4	21/10	0.17
Patients who underwent surgery					
No. of patients	36	6	7	23	<0.001
Age (y)*	60 $\pm$ 10	62 $\pm$ 9	61 $\pm$ 10	65 $\pm$ 10	0.19
Sex (M/F)	33/3	4/2	6/1	23/0	0.50
Tumor location in pancreas					<0.001
Head	25 (70)	4 (60)	6 (82)	15 (65)	
Body or tail	11 (30)	2 (40)	1 (18)	8 (35)	
Surgery					<0.001
Standard pancreaticoduodenectomy	11 (30)	3 (50)	1 (14)	7 (30)	
Standard distal pancreatectomy	8 (22)	2 (33)	1 (14)	5 (22)	
Extended pancreaticoduodenectomy	13 (36)	1 (17)	2 (28)	10 (43)	
Extended distal pancreatectomy	3 (8)	-	2 (28)	1 (4)	
Exploration or palliative surgery	1 (3)	-	1 (14)	-	
Resection margin status					<0.001
R0	23 (63)	5 (83)	5 (71)	14 (61)	
R1 or R2	13 (36)	1 (17)	2 (29)	10 (39)	
Pathologic tumor differentiation					0.48
Well differentiated	3 (8)	1 (17)	1 (14)	-	
Moderately differentiated	29 (81)	5 (83)	5 (71)	19 (82)	
Poorly differentiated	4 (11)	-	1 (14)	4 (18)	
Pathological perineural invasion	32 (88)	5 (88)	6 (86)	21 (91)	0.40
Serum CA 19-9 level (U/ml)‡	95 (0.5,24 100.0)	97.0 (0.5,24 100.0)	105.2 (0.5,24 100.0)	91 (0.5,24 100.0)	0.55
Adjuvant chemotherapy	35 (97)	6 (100)	6 (86)	23 (100)	

\*Data are mean  $\pm$  6 standard deviation, \*\*Categorized as negative margin (R0), microscopically positive margin (R1), or grossly residual tumor (R2), \*\*\*Data are the median, and data in parentheses are the range. Unless otherwise indicated, data are number of patients and data in parentheses are percentages. NCCN: National comprehensive cancer network, CA: Cancer antigen, NA: Not applicable.

(range, 1–28 days). According to NCCN criteria, six (17%) of 36 patients had resectable disease, seven (19%) had borderline resectable disease, and 23 (64%) had unresectable locally advanced disease. Surgical resection was attempted in all 36 patients. The surgical procedure included standard pancreaticoduodenectomy [n=20 (56%)]; standard distal pancreatectomy [n=4 (11%)]; extended pancreaticoduodenectomy [n=11 (31%)] involving portomesenteric vein resection (n=13), artery resection (n=1), and additional organ resection (n=5) alone or in combination; and extended distal pancreatectomy [n=1 (3%)] involving portomesenteric vein and artery resection with splenectomy. In five patients, pancreatic resection was aborted due to unresectable arterial invasion (n=4) or unexpected metastases in the liver and peritoneum (n=1) which were detected intraoperatively.

### R0 Resection Rate According to CT Resectability

Of the 36 patients who underwent surgery, R0 resection was achieved in 23 (63%). The R0 resection rate (positive predictive value) differed significantly according to resectability status as reported by CT ( $p < 0.001$ ): It was 83% [5 of 6; 95% confidence interval (CI): 67%, 78%] in patients with resectable disease, 71% (5 of 7; 95% CI: 45%, 65%) in patients with borderline resectable disease, and 60% (14 of 23; 95% CI: 5%, 33%) in patients with locally advanced disease. R0 resection was achieved with standard surgery in 4 (66%) of six patients with resectable disease and with extended surgery in six (84%) of seven patients with borderline resectable, and 18 (80%) of 23 patients with locally advanced disease. Of the 36 patients with non-metastatic pancreatic cancer, R0 resection was achieved in 63% (5 of 8) of patients with resectable disease, 31% (5 of 16) of those with borderline resectable disease, and 45% (14 of 31) of those with locally advanced disease ( $p < 0.001$ ) (Table 2).

### Discussion

CT is a modality of choice to identify patients with a higher likelihood of margin-negative (R0) resection in pancreatic adenocarcinoma who may be candidates for upfront pancreatic resection. In these patients, neoadjuvant therapy is being increasingly used before surgery in an attempt to ensure an R0 resection. In locally advanced cases neoadjuvant therapy can also be used to downstage tumors to enable surgery<sup>[12,13]</sup>. According to the NCCN criteria to predict R0 resection, our results indicate that CT can be used to identify patients with pancreatic cancer with a likelihood of R0 resection; in our study group, the positive predictive values of CT for R0 resection were 83%, 71%, and 60% of patients

who underwent surgery for resectable, borderline resectable, and locally advanced pancreatic cancer, respectively.

We compared some previous studies in the literature that evaluated the positive predictive value of CT in the prediction of resectability of pancreatic cancer. Zamboni et al.<sup>[14]</sup>, Kaneko et al.<sup>[15]</sup>, and Lee et al.<sup>[16]</sup> conducted studies that ignored the pathological status of the resection margin and reported positive predictive values in the range of 85%–89%. Other studies such as those by Cassinotto et al.<sup>[17]</sup> and Fujii et al.<sup>[18]</sup> included the resection margin parameter and focused on the predictability of margin-negative R0 resection. Similar to the results of our study they reported slightly lower predictive values compared to studies that ignored the R0 parameter<sup>[17,18]</sup>. However, we believe that prediction of R0 resection rather than the resectability of the tumor should be the ultimate goal for imaging techniques as the prognostic role of the margin status is important<sup>[19,20]</sup>.

It has been suggested that some tumor parameters other than the vascular invasion findings provided by CT imaging may improve the prediction of R0 resection. Chiang et al. and Hong et al. reported that pancreatic cancers larger than 4 cm in diameter had significantly higher odds of margin-positive resection than smaller tumors thereby aiding in the prediction of unresectability<sup>[21,22]</sup>. In these studies, tumor abutment to the portomesenteric vein was significantly associated with margin-positive resection in patients with resectable pancreatic cancer suggesting that absence of these findings may be associated with higher possibility of R0 resection. The clinical implication of this could be the identification of patients who appear to have a high risk of margin-positive resection on surgery. These patients may be considered to benefit from neoadjuvant therapy in an attempt to downstage the tumor<sup>[23,24]</sup>. Due to the relatively small number of resectable patients in our study group, we could not calculate appropriate statistics to evaluate these parameters.

Our study had some limitations. First, our study group consisted only of patients who proceeded directly to surgery after imaging so patients who received neoadjuvant therapy before surgery were not included because assessment of CT resectability after neoadjuvant therapy is more complicated owing to post-treatment structural changes<sup>[25-27]</sup>. Second, in patients with vascular involvement pancreatic resection was performed only when venous structures were invaded. Overt signs of arterial invasion on CT precluded upfront surgery so these patients were not included. Third, abdominal MRI, PET/CT, or both were also used

when making therapeutic decisions in most patients and this has probably prevented abortion of surgery due to unexpected detection of intraoperative metastasis. Therefore, the calculated PPV for R0 resection in our study, especially in patients with borderline resectable and locally advanced diseases, may have been overestimated. Fourth, our study may have the same limitations as all retrospective studies leading to potential weaknesses concerning the inter-reader variability and decreased consistency of study findings compared to prospective studies.

## Conclusion

CT can be used to identify patients with pancreatic cancer who can benefit from surgery with the possibility of R0 resection. Our study results showed that CT can predict R0 resection with a positive predictive value of 75%.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: L.S.; Design: L.S., M.T.; Data Collection or Processing: M.T., C.K.D., T.Ö., K.C.; Analysis or Interpretation: L.S., C.K.D., T.Ö., K.C., U.K., İ.E.S.; Literature Search: U.K., K.C., İ.E.S.; Writing: L.S., M.T.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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