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Predicting Unresectability in Pancreatic Cancer Patients: The Additive Effects of CT and Endoscopic Ultrasound

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Abstract
Background A standardized method for predicting unresectability in pancreatic cancer has not been defined. We propose a system using CT and endoscopic ultrasound (EUS) to assess patients for unresectable pancreatic cancers.
Methods Radiologic and surgical data from 101 patients who underwent exploration/resection for pancreatic cancer were reviewed. Chi-squares were used to identify five factors significantly correlated with unresectability, which were incorporated into a scoring system (one point for each factor).
Results The resectability rates were 84, 56, and 10% for patients with scores of 0, 1, and 2, respectively. All four patients with three risk factors for unresectability had unresectable tumors. The most accurate results were achieved in patients evaluated with both CT and EUS.
Discussion This scoring system stratifies pancreatic cancer patients into three groups: (1) patients with a score of zero (likely to undergo successful resection), (2) patients with a score of one (likely to benefit from laparoscopic staging prior to attempting resection), and (3) patients with a score of two or higher (low probability of successful resection, who may be better served by neoadjuvant therapy).

Keywords Pancreatic cancer · CT scan · Endoscopic ultrasound

Introduction

Pancreatic cancer represents one of the greatest challenges in oncology. In 2004, more than 30,000 new cases were diagnosed, with a dismal overall survival rate of only 4%.[1] Surgery remains the cornerstone of curative treatment. Among patients with resectable disease, 5-year survival is approximately 20% with multimodality treatment.[2] However, in unresectable patients (even those who receive

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aggressive multimodality treatment), 2-year survival is only 10% and long-term survival is rare.[3,4,5,6] Consequently, many pancreatic cancer patients are referred for surgery in the hope of achieving a successful resection, even when imaging is concerning for unresectable disease. A systematic and accurate method of predicting unresectable disease could spare these patients the morbidity and mortality associated with nontherapeutic surgery. Further, by accurately predicting resectable disease, such a method could maximize the number of patients who are able to undergo a potentially curative procedure.

The major contraindications to surgical resection of pancreatic adenocarcinoma include proven metastatic disease and definitive evidence on imaging of superior mesenteric artery/vein, portal vein, or celiac axis involvement by tumor. Traditionally, angiography, computed tomography (CT) scans, and open laparotomy were the primary methods of evaluating patients for resectability. Newer diagnostic tools such as thin section high-resolution multislice spiral CT, magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), and laparoscopy allow increasingly accurate diagnosis and preoperative staging of pancreatic cancer. However, the optimal use of these tests in selecting unresectable patients has not been definitively established. There remains a clinically significant subset of patients who appear on imaging studies to have resectable tumors, yet have locally unresectable or metastatic disease at exploratory laparotomy.

There are a number of benefits to increasing the accuracy of preoperative staging in pancreatic cancer patients. Identifying patients with unresectable tumors would reduce the morbidity and mortality associated with a nontherapeutic laparotomy. In such patients, symptoms such as duodenal obstruction, pain, and jaundice can often be palliated with nonsurgical procedures.[7,8,9,10] By avoiding a laparotomy, one can also eliminate the delays in starting palliative chemotherapy that are associated with the postlaparotomy recovery period. Additionally, patients who are accurately classified as high risk for unresectability would be more appropriate for laparoscopic staging than open surgical exploration. Effective preoperative staging methods would also help select the most appropriate candidates for aggressive neoadjuvant radiation and chemotherapy. Finally, more accurate preoperative staging would allow better comparison of outcomes among different institutions. In the absence of a systematic method of predicting resectability, the selection of operable patients is inherently subjective and highly variable from one institution to another. This variability among different institutions complicates comparisons of the accuracy of diagnostic testing, as well as of the effectiveness of multidisciplinary interventions in the treatment of pancreatic cancer.

The goals of this investigation were to identify characteristics common to patients who were found to have unresectable pancreatic adenocarcinoma without definitive evidence on imaging of unresectability, and to compare these characteristics with those of patients at the same institution who underwent successful resection. We looked carefully for CT and EUS findings that were predictive for patients who were ultimately found to have unresectable pancreatic cancer but whose preoperative imaging did not demonstrate obvious unresectability (i.e., metastatic disease or vessel encasement/thrombosis).

Materials and Methods

Patient Selection

One hundred and one consecutive patients of a single surgeon, who underwent exploration and either resection or palliation for pancreatic adenocarcinoma, were identified. All surgeries were performed between September 2000 and October 2005. Patients with tumors of the endocrine pancreas, cholangiocarcinoma, or nonpancreatic periampullary tumors were excluded from the analysis.

Data Analysis

Data on tumor size, vascular abutment, distant metastases, and pathologically enlarged lymph nodes (defined as larger than 1 cm in the short axis) were collected by reviewing reports of EUS procedures and CT scans. For purposes of this study, abdominal CT scans both from this institution and from outside facilities were reviewed by one of our institution's radiologists specializing in the interpretation of abdominal imaging. The EUS procedures were performed by gastroenterologists at one institution with specific experience in pancreatic ultrasonography. EUS features considered suspicious for vascular invasion (but not encasement/thrombosis) include loss of interface between the mass and adjacent vessels without tumor in the lumen and/or irregular appearance of the wall of the vessel (but the vessel still has flow by Doppler examination). CT features considered suspicious for unresectability include the presence of liver lesions too small to characterize or biopsy percutaneously, as well as compression, abutment, or deformation of the superior mesenteric artery/vein. All patients with definite evidence on CT scan of thrombosis or encasement of a significant length of the superior mesenteric artery/vein were determined to be unresectable preoperatively, as were those with liver lesions large enough to confirm malignancy on biopsy percutaneously. These patients were not included in this study. Symptoms present at the time of surgery were determined from

previously documented preoperative history and physical examinations. Preoperative hemoglobin, bilirubin, alkaline phosphatase, and CA19-9 levels were also documented. Operative notes were reviewed for information about surgery performed, as well as reasons for aborting an attempted resection. Tumor size, histology, pathologic staging, and nodal status were obtained from surgical pathology reports.

The chi-square method was used to identify five radiologic factors that were significantly correlated with unresectability. The scoring system incorporates these five individual factors; patients were assigned one point for each of the factors associated with unresectability, so that a higher score was associated with a greater chance of unresectability. Chi-square analysis was then repeated based on total point scores of one, two, and three (no patient who underwent exploration received a score higher than three of a potential five). Sensitivity, specificity, and accuracy were also calculated for each identified factor, as well as each total score level.

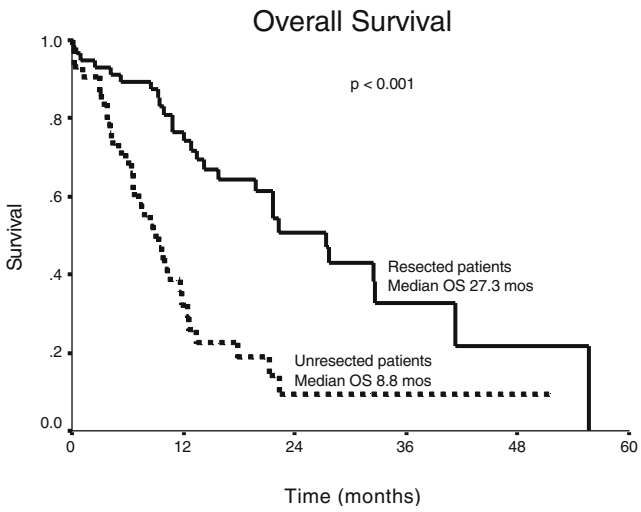

Figure 1 Kaplan–Meier survival curve, overall survival.

Table 1 Patient Characteristics

Characteristic	Number	Percent
Sex		
Female	48	48
Male	53	52
Presenting symptom		
Jaundice	72	71
Pain	16	16
Incidental finding	4	4
Weight loss	3	3
Pancreatitis	3	3
Nausea/vomiting	2	2
Duodenal obstruction	1	1
AJCC stage group		
IA	4	4
IB	10	10
IIA	7	7
IIB	36	36
III	16	16
IV	27	27
Pathologic CR	1	1
Resected		
Yes	58	58
No	43	42
Reason unresectable		
Metastases	27	63
Locally unresectable	16	37
Site of metastasis		
Liver	17	63
Peritoneum	9	33
Bowel	1	4
Surgery performed		
Pylorus-sparing Whipple	41	40
Classic Whipple	10	11
Distal pancreatectomy	7	8
Exploratory laparotomy (+/− bypass)	37	37
Laparoscopic biopsy	3	3
Angiogram	1	1

Survival was calculated from the date of surgery in all patients. Follow-up was conducted by review of medical records, interviews with patients/families, and searches of the Social Security Death Index, and was available in 100/101 patients (99%). Actuarial survival analysis was performed using the Kaplan–Meier method, with the log-rank test used to compare survival curves. All statistical analyses were performed with SPSS (version 10.0 for

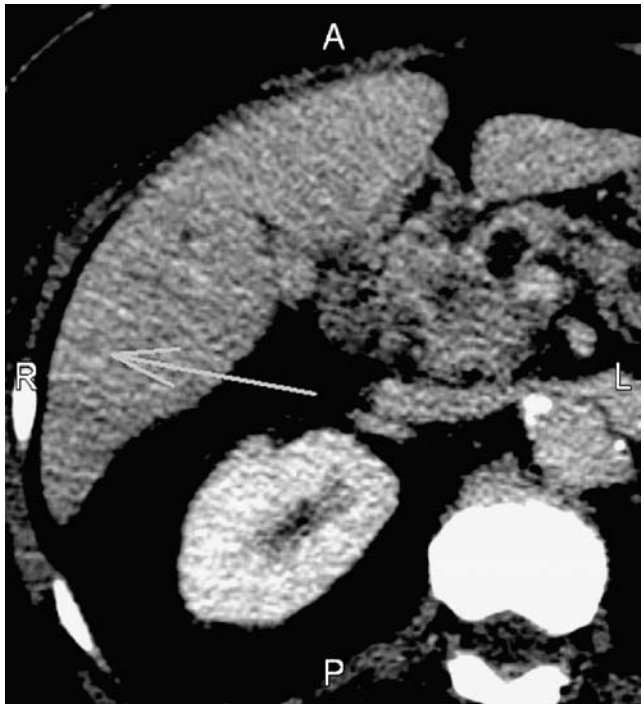

Figure 2 Abdominal CT scan with indeterminate but suspicious lesion in the liver (*arrow*).

Figure 3 CT scan of the abdomen with a pathologically enlarged lymph node in the celiac region (*arrow*).

Windows®). Statistical significance was defined as $p<0.05$. The collection and reporting of these data were approved by the institutional review board at the University of Maryland.

Results

Patient Data

A total of 101 patients were analyzed in this study. Median age was 64 years (range 36–86 years), and 48% of the patients were women. Detailed demographic and clinical patient characteristics are presented in Table 1. The most common presenting symptom was obstructive jaundice (71%), followed by pain (16%). A majority of patients (58%) underwent curative-intent resection, with the remainder undergoing exploratory laparotomy or laparoscopic biopsy. Six of the Whipple resections included a partial superior mesenteric vein (SMV) resection. In every case, these were resections of a "knuckle" of SMV, i.e., a small piece and not a circumferential resection. In none of these cases was SMV reconstruction necessary. One patient proved to be unresectable by angiography and was therefore never explored. Among the 58 patients who ultimately underwent resection, the most common (70%) surgery was a pylorus-preserving Whipple procedure (pancreatico-duodenectomy), followed by a classic Whipple procedure (17%), and a distal pancreatectomy with splenectomy (14%). Of the 43 patients found to be unresectable, 27 (63%) were unresectable because of distant

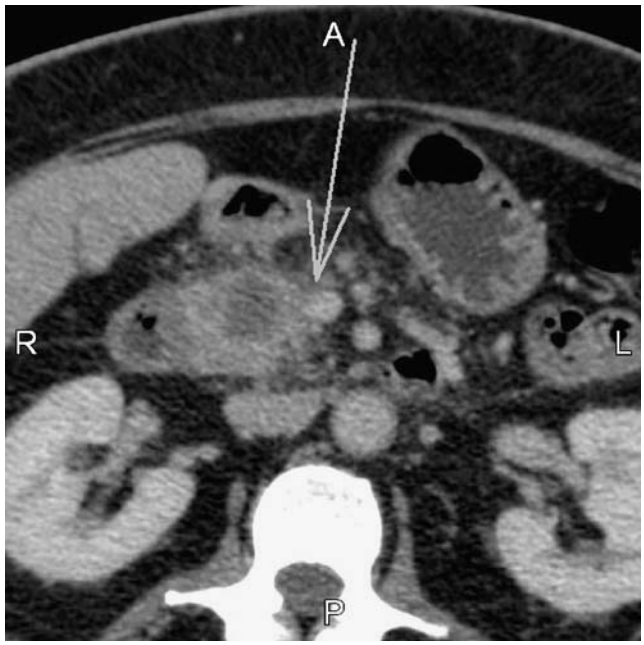

Figure 4 Abdominal CT scan showing tumor in the pancreas abutting and deforming the SMV (*arrow*).

Figure 5 EUS image with pathologically enlarged lymph node (marked by *dashed lines*).

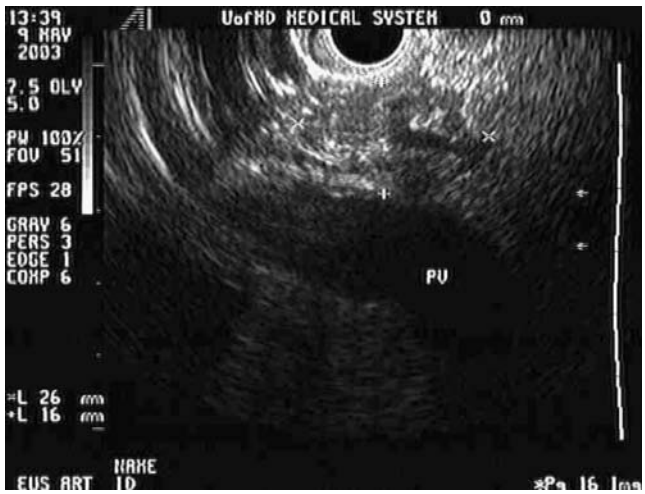

Figure 6 EUS image with tumor abutment of the portal vein (*plus sign*).

Table 2 Criteria Which Individually Predicted Unresectability

Criterion	*n*	*p*[a]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	RR[b]
Vascular abutment, CT	16	<0.001	94	74	44	98	3.16 (2.12–4.70)
Adenopathy >1 cm, CT	29	<0.001	76	74	69	80	2.88 (1.63–5.10)
Liver lesion, CT	10	0.06	70	60	18	94	1.77 (1.09–2.88)
Vascular abutment, EUS	18	0.004	72	67	42	88	2.17 (1.35–3.48)
Adenopathy >1 cm, EUS	13	0.03	69	64	30	90	1.91 (1.16–3.15)

PPV = positive predictive value, NPV = negative predictive value, RR = relative risk
[a] *p* vs resectable patients
[b] 95% CI are in parentheses

metastases. The most common site of metastasis was the liver. The remainder of inoperable patients had locally unresectable disease secondary to vascular involvement. Three patients had received neoadjuvant chemotherapy.

Survival

Median survival for the entire group was 13.5 months. As expected, patients who underwent a resection had significant improvement in median survival when compared with unresectable patients: 27.3 vs 8.8 months, $p<0.001$ (see Fig. 1).

Imaging

Ninety-three of the 101 patients had a preoperative CT scan report available for evaluation. Forty-seven (51%) of these patients did not have a discrete mass seen on CT. Among these patients (i.e., those who did not have a discrete mass on CT), 35 underwent further evaluation with EUS, which demonstrated a mass in 33 patients. This yielded a sensitivity of 94% for EUS detection of a pancreatic mass in the setting of a CT that was negative for a focal mass. Overall, EUS identified a mass in 65/71 (92%) patients who underwent the test.

Predicting Unresectability

Through univariate analysis, we identified five criteria that were associated with a higher risk of unresectability: (1) suspicious liver lesions that were too small to characterize or biopsy percutaneously, (2) intra-abdominal adenopathy (>1 cm in short axis) identified by CT, (3) vascular abutment or deformation on CT, (4) intra-abdominal adenopathy (>1 cm) identified by EUS, and (5) vascular abutment or deformation on EUS. These findings are depicted in Figs. 2, 3, 4, 5, and 6; statistical analyses of these five criteria are summarized in Table 2.

A number of other variables were analyzed but did not significantly predict unresectability in univariate analysis. Notably, these factors included tumor size, CA19-9 levels, and the presence of pain preoperatively; all of which have been suggested as possible markers for unresectable disease by other investigators.

As described in the "Materials and Methods" section, each patient was assigned a score of 0–5 based on the number of criteria that they fulfilled. Eighty four percent (41/49) of the patients with a score of "0" had a resectable tumor, but only 56% (15/27) of the patients with a score of "1" had a resectable tumor (see Tables 3, 4, and 5). In the group of 52 patients who had a score of "≥1," 35 (67%) were unresectable, yielding a relative risk for unresectability in this group of patients (when compared with patients with a score of "0") of 2.7 [95% confidence interval (CI) 1.3–5.8]. Accuracy in predicting unresectability improved further with a score of "≥2" (see Table 6). That is, 56/58, or 97%, of the resectable patients had a score of "0" or "1," whereas 23/25, or 92%, of patients with a score "≥2" were unresectable (see Table 4). Of the four patients who had three risk factors for unresectability, none were found to have a resectable tumor. None of the patients

Table 3 Resectability Rates by Total Score

Score	# Resectable	# Unresectable
0	41/49 (84%)	8/49 (16%)
1	15/27 (56%)	12/27 (44%)
≥1	17/52 (33%)	35/52 (67%)
2	2/21 (10%)	19/21 (90%)
≥2	2/25 (8%)	23/25 (92%)
3	0/4 (0%)	4/4 (100%)

Table 4 Resectability Rates by Total Score (Among Patients Who Had Preoperative CT and EUS)

Score	# Resectable	# Unresectable
0	27/29 (93%)	2/29 (7%)
1	9/21 (43%)	12/21 (57%)
≥1	17/46 (37%)	29/46 (63%)
2	2/18 (11%)	16/18 (89%)
≥2	2/22 (9%)	20/22 (91%)
3	0/4 (0%)	4/4 (100%)

Table 5 Resectability by Score of 0 vs 1

	Score=1	Score=0	Total
Unresectable	12	8	20
Resectable	15	41	56
	27	49	76

Relative risk for unresectability, score of 1 vs score of 0=2.7 (1.3–5.8). $p \leq 0.01$

had a score greater than three. The most accurate results were achieved in the group of 72 patients who were evaluated with both CT and EUS, as shown in Tables 4 and 7; in this group of patients, 29/31 (94%) of the unresectable patients had a score ≥1, with a relative risk for unresectability (when compared with patients with a score of "0") of 9.8 (95% CI 2.5–37.8). These radiographic features were also statistically significant in tumors of the pancreatic body and tail (n=11).

Discussion

A number of recent studies have evaluated the ability of CT and EUS to diagnose and stage pancreatic cancers. DeWitt et al. described 104 patients who underwent preoperative EUS and CT. In this study, EUS and CT correctly predicted for unresectability in 68 and 64% of cases, respectively.[11] Ahmad et al. reported on 89 patients evaluated for resectability with EUS.[12] This study found no significant difference in resectability rates between patients whose tumors were staged by EUS as T4 (locally unresectable) vs those who were staged as T3, suggesting that EUS alone is not a satisfactory modality for predicting local resectability. Contemporary CT techniques are better able to predict resectability than unresectability; recent studies have reported that thin-slice helical CT scan correctly predicted resectability in 74[13] to 88%[14] of patients. However, one bias that should be considered when evaluating these studies is that patients who are determined to be "unresectable" by radiographic criteria generally do not undergo surgical exploration. Because of this, radiographic findings cannot be confirmed at surgery, and thus, institutional variation in what is deemed "resectable" and "unresectable" invariably

Table 6 Resectability by Score ≥2

	Score≥2	Score≤1	Total
Unresectable	23	20	47
Resectable	2	56	58
	29	76	101

Relative risk for unresectability, score of ≥2 vs score of ≤1=3.5 (2.4–5.2). $p \leq 0.001$

Table 7 Resectability by Score ≥1, Patients Who Had CT and EUS

	Score≥1	Score=0	Total
Unresectable	29	2	31
Resectable	14	27	41
	43	29	72

Relative risk for unresectability, score of ≥1 vs score of 0=9.8 (2.5–37.8). $p \leq 0.001$

influences results. Presumably, studies from centers that use stricter radiographic criteria will report a relatively high success rate for CT in predicting resectability.

We would like to emphasize that the unexpected finding of unresectability in those patients with adenopathy described on CT was not secondary to pathologic nodal involvement. In fact, CT was not sensitive for the diagnosis of pathologically positive lymph nodes (18.2% sensitivity, 71.4% specificity). Among the 22 unresectable patients with adenopathy >1 cm (in short axis) on CT scan, eight patients had locally unresectable disease, and 14 had metastatic disease. A possible explanation for this correlation is that locally advanced/metastatic disease may worsen low-grade cholangitis (from obstruction) or low-grade pancreatitis (from atrophy/inflammation of the gland involved by tumor).

Other studies have identified nonradiographic factors that predict for unresectability, including carbohydrate antigen 19-9 (CA19-9) levels above 150 units/ml,[15] positive peritoneal cytology,[16] and the presence of pain before surgery.[17] We were unable to replicate the results of Schlieman et al., who reported on CA19-9 as a significant predictor of unresectability. This is most likely due to the relatively small proportion of patients (30%) that had preoperative CA19-9 levels available for review. At our institution, peritoneal cytology is not routinely used in the preoperative evaluation of pancreatic cancer.

We believe that the scoring system described in this paper provides an effective method of stratifying pancreatic cancer patients into three groups. The first group would include patients with a score of zero and a high probability of undergoing successful resection. The second group includes patients with a score of one who are likely to benefit from laparoscopy to look for metastatic disease. In the absence of metastatic disease, the majority of patients in this group would still be resectable. The third group is comprised of patients with a score of two or higher who have a low probability of undergoing successful resection and are therefore more likely to benefit from expedited chemotherapy and radiation therapy. Patients who had no risk factors (i.e., a score of zero) had an 84% chance of resectability. In the presence of only one risk factor (i.e., a score of one), resectability rates dropped to 56%. That is, of the 27 patients with only one risk factor present, 12 were

unresectable (eight due to metastatic disease). We feel that this subgroup of patients—with only one risk factor for unresectability—would be ideal candidates for laparoscopic staging before laparotomy. In fact, in this series, after the patients in this group with metastatic disease are excluded, 18 of 23 (78%) patients were resectable. In our study, laparoscopic staging could have prevented eight unnecessary laparotomies by detecting metastatic disease. Patients with more than two risk factors (i.e., a score of two) are ideal patients for whom to consider neoadjuvant therapy protocols with the intent to downstage the tumor because greater than 85% of this group of patients had unresectable tumors. Even if attempts to downstage the primary tumor are unsuccessful, these patients would still benefit from nonsurgical methods of palliation, including endoscopic stent placement for biliary decompression, percutaneous or endoscopic celiac plexus block for pain control, and palliative chemotherapy/radiotherapy to decrease tumor burden.

Conclusion

In this paper, we propose a scoring system derived from both CT and EUS imaging data for predicting resectability and unresectability in patients with pancreatic cancer. We also present a previously unreported radiologic risk factor for unresectability, namely, the presence of intra-abdominal adenopathy >1 cm (in short axis) on CT scan and/or EUS. Our results suggest that by combining data from both CT and EUS, a clinically relevant scoring system can be utilized to help select appropriate interventions and therapy for patients with pancreatic cancer.

References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995;221(6):721–731.
3. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the Gastrointestinal Tumor Study Group. Cancer 1981;48(8):1705–1710.
4. Gastrointestinal Tumor Study Group. Radiation therapy combined with adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Cancer 1985;56(11):2563–2568.
5. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. J Clin Oncol 1985;3(3):373–378.
6. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 1988;80(10):751–755.
7. Mittal A, Windsor J, Casey P, et al. Matched study of three methods of palliation for malignant pyloroduodenal obstruction. Br J Surg 2004 Feb;91(2):205–209.
8. Maetani I, Tada T, Ukita T, et al. Comparison of duodenal stent placement with surgical gastrojejunostomy for palliation in patients with duodenal obstructions caused by pancreaticobiliary malignancies. Endoscopy 2004 Jan;36(1):73–78.
9. Levy M, Wiersema M. EUS-guided celiac plexus neurolysis and celiac plexus block. Gastrointest Endosc 2003;57(7):923–930.
10. Espat N, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. J Am Coll Surg 1999 Jun;188(6):649–655.
11. Dewitt J, Devereaux B, Chriswell M. et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for diagnosis and staging of pancreatic cancer. Ann Intern Med 2004 Nov 16;141(10):753–763.
12. Ahmad N, Lewis J, Ginsberg G. EUS in preoperative staging of pancreatic cancer. Gastrointest Endosc 2000 Oct;52(4):463–468.
13. Valls C, Andia E, Sanchez A. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. AJR Am J Roentgenol 2002 Apr;178(4):821–826.
14. Fuhrman GM, Charnsangavej C, Abbruzzese JL. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. Am J Surg 1994 Jan;167(1):104–111; discussion 111–113.
15. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in predicting resectability of pancreatic cancer. Arch Surg 2003 Sep;138(9):951–955.
16. Merchant NB, Conlon KC, Saigo P, et al. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg 1999;188(4):421–426.
17. Kelsen DP, Portenoy R, Thaler H, et al. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. Surgery 1997 Jul;122(1):53–59.