Surg Endosc (2005) 19: 638–642
DOI: 10.1007/s00464-004-8165-x

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by computed tomography

R. C. Liu, L. W. Traverso

Section of General, Vascular, and Thoracic Surgery, Virginia Mason Medical Center, 1100 Ninth Avenue, C6-GSurg, Post Office Box 900, Seattle, WA 98111, USA

Received: 6 May 2004/Accepted: 28 September 2004/Online publication: 23 March 2005

Abstract
Background: Computed tomography (CT) is insensitive to small metastatic deposits in patients with pancreatic cancer. This study aimed to evaluate additional staging information obtained by laparoscopy in the subset of patients with locally extending pancreatic cancer but no evidence of distant disease using computed tomography.
Methods: Between April 2000 and February 2004, 74 patients with locally unresectable pancreatic cancer and no evidence of metastasis detected by high-quality pancreas protocol computed tomography underwent outpatient staging laparoscopy and peritoneal lavage cytology.
Results: Occult tumor was found during staging laparoscopy in 25 of the 74 patients (34%). The results were positive for peritoneal lavage cytology in 27% (20/74), for liver lesions in 16% (12/74), and for peritoneal implants in 7% (5/74) of the patients. Body and tail tumors were twice as likely as pancreatic head tumors to have unsuspected metastasis (53% vs 28%).
Conclusions: Even the best computed tomography scan is not adequate for accurate staging of locally extended pancreatic cancer because occult distant disease will be found in half of the patients with left-sided disease and one-fourth of those with right-sided pancreatic cancer.

Key words: Neoplasm — Pancreas — Adenocarcinoma — Laparoscopy — Staging — Cytology

Despite advances in radiographic imaging, peritoneal dissemination of pancreatic adenocarcinoma often is not detected by computed axial tomography (CT). An operation is required for the most accurate staging [8]. Many occult metastases are implants on the liver or peritoneal surfaces that are too small (< 3 mm) for visualization, even with high-resolution helical (CT) scans. Because laparoscopy can detect these small deposits, it has been validated as a means of improving the assessment of tumor staging [2–4, 8]. The patient can thus avoid the inherent delay in definitive treatment and recovery imposed by an open surgical procedure. After laparoscopy, treatment can begin immediately, with the more accurate staging allowing a more appropriate management design. With knowledge of distant occult disease, the patient can be treated more appropriately with combination chemotherapy protocols. In the past, no effective treatment for distant disease existed, but recent gemcitabine-based and other combination drug treatments have resulted in increased response rates exceeding 30%, as compared with previous rates of less than 10% [10].

Laparoscopy is most often used to detect metastatic disease in patients presumed to have "resectable" pancreatic cancer. Laparoscopy is used as a means of avoiding open laparotomy in patients thought to be resectable according to CT scan. Jiminez et al. found the rate for occult metastases to be 31% in the group of patients (17% for head lesions and 36% for distal pancreatic cancer) [3, 8]. The importance of peritoneal lavage cytology (PLC) emerged in this study when 18% of the patients showed positive PLC results. Furthermore, for 10% of these patients, the only finding was a positive cytology result. Subsequent to this report, the American Joint Commission on Cancer (AJCC) designated positive intraperitoneal cytology results for patients with exocrine pancreatic cancer as indicating M1 or distant metastatic disease [1]. Any tumor with an M1 designation is identified as AJCC stage IV or distant disease.

How about the subset of patients already thought to be "unresectable" by CT scan who have no evidence of distant disease? We have considered these patients for

Presented at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) meeting, Denver, CO, USA, 26–27 March 2004
Correspondence to: L. W. Traverso

laparoscopy although they were not candidates for surgical resection. The new 2002 AJCC staging system has reclassified these locally advanced tumors from stage IVA to stage III [1]. When these cases are "clinically" deemed to be stage III by CT scan, few studies have examined the limitation of CT in determining whether they truly are stage III after pathologic staging. Are many of them actually understaged that should be stage IV? Diagnostic laparoscopy may be helpful in the staging of this latter group of patients because previous work has shown that almost one in three patients thought to be "resectable by CT" actually had occult metastatic disease [2, 4, 8]. The rate of occult (unsuspected) metastases in the patients thought to be "unresectable by CT" may be higher. This subgroup of patients thought to be "unresectable by CT" comprise the majority of patients with pancreatic cancer.

In this study, we examined our results after diagnostic laparoscopy for patients with locally advanced pancreatic cancer thought to be "unresectable by CT" who had no CT evidence of metastasis.

Materials and methods

Patients and selection

Between April 2000 and February 2004, 74 consecutive patients with a diagnosis of locally advanced, unresectable (but not metastatic) pancreatic adenocarcinoma underwent diagnostic laparoscopy. All the patients were evaluated with a double-helix, early arterial/late portal venous phase thin-cut "pancreas protocol" CT with oral water unless a high-quality CT scan had been performed at the referring hospital, as was the case for 9 of the 74 patients. No CT scan reports were used to determine clinical stage. All CT scans were interpreted during a joint meeting of the surgeon and radiologist.

The determination of local extension as "unresectable" was made by the surgeon. Tumors were considered locally advanced and unresectable when CT showed involvement of a contiguous organ or an adjacent major blood vessel (portal vein, superior mesenteric vein, superior mesenteric artery, or celiac axis). Lymph node enlargement was not an indicator of unresectability. Patients with resectable or metastatic disease determined by CT were excluded from this study. To be included, patients ultimately had to have a histologically documented adenocarcinoma of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (BUS), CT-guided or ultrasound (US)-guided biopsies were performed when appropriate for diagnosis or symptom relief. If a percutaneous biopsy was performed before diagnostic laparoscopy, then an association with PLC was sought.

Operation

Laparoscopy was performed with the patient under general anesthesia in an outpatient setting. The patient was placed in the supine position and access was obtained with a Veress needle through an infraumbilical site. Carbon dioxide pneumoperitoneum was established at 15 mmHg. A safety-shielded 5-mm port and then a 5-mm 30° laparoscope were inserted. All four quadrants were inspected. An additional 5-mm port was inserted for lavage and possible biopsy. The site of insertion depended on where potential metastatic disease was observed and was always lateral to the rectus sheath to avoid the epigastric vessels.

After inspection and before biopsy, the upper abdomen was filled with 400 ml of 0.9% saline for PLC. The fluid was distributed throughout the peritoneal cavity by external agitation of the abdominal wall and tilting of the operating table up and down. Then all possible fluid was aspirated for cytologic examination. The PLC results were considered positive if malignant cells or cells highly suspicious for malignancy were found at cytologic examination [6]. After the PLC, a biopsy of grossly suspicious liver or peritoneal lesions was performed with cold-cut scissors and biopsy forceps. Hemostasis was obtained with electrocautery. The primary purpose of the diagnostic laparoscopy was to detect metastatic disease. Therefore, the primary tumor, pancreas, and lesser sac were not examined. Laparoscopic ultrasound was not used.

Table 1. Patient and tumor characteristics (n = 74)

Age (years) mean (range)	63 (38–84)
Male gender *n* (%)	37/74 (50)
Symptoms at diagnosis *n* (%)	
Pain	52/74 (70)
Jaundice	37/74 (50)
Weight loss	45/74 (61)
Tumor size by CT (cm) mean (range)	3.8 (1.4/11)
Tumor location *n* (%)	
Head/uncinate	57/74 (77)
Body/tail	17/74 (23)
Reason for unresectability *n* (%)	
SMA/celiac involved	54/74 (73)
PV/SMV involved	20/74 (27)
CA 19-9(U/ml) median (range)	257 (3–22,289)

CT, computed tomography; SMA, superior mesentric artery; PV, portal vein; SMV, superior mesentric vein; CA, cancer antigen

Data analysis

Comparisons were made by chi-square analysis. A p value less than 0.05 indicated statistical significance.

Results

Patient and tumor characteristics are listed in Table 1. All but one patient presented with pain, jaundice, or weight loss. More than two-thirds of the tumors were located in the head of the pancreas. The preoperative workup is detailed in Table 2. Percutaneous biopsy before laparoscopy was performed in 34 (46%) patients.

Laparoscopy

Diagnostic laparoscopy was successful for all the patients. The operation demographics are shown in Table 3. The intraoperative complication rate was 4%. One patient sustained a 2-cm liver laceration, which was hemostatic at the conclusion of the operation. In another patient who had undergone multiple prior abdominal operations, a small bowel serosal tear was noted after pneumoperitoneum was established and adhesions were taken down. The tear was repaired with a minilaparotomy incision after completion of laparoscopic staging. Both patients were observed overnight without further complications. No postoperative complications were noted.

Laparoscopy found unsuspected metastases in 25 patients (34%), and the distribution is listed in Table 4. Positive PLC results, the most common unsuspected finding, occurred in 27% (20/74) of all the patients, and in 80% (20/25) of the patients with positive findings. A

Table 2. Preoperative studies ($n = 74$)

Transabdominal ultrasound	6/74 (8)
Endoscopic ultrasound (EDS)	25/74 (34)
ERCP	51/74 (79)
CT	53/53 (100)
CT-guided FNA	31/74 (42)
US-guided FNA	3/74 (4)

ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; FNA, fine-needle aspiration; US, ultrasound

Table 3. Operation demographics ($n = 74$)

Estimated blood loss (ml) mean (range)	2 (0–30)
Operative Time (min) mean (range)	47 (20–116)
Complications *n* (%)	2 (4%)
Liver biopsies *n* (%)	35/74 (47)
Peritoneal biopsies *n* (%)	5/74 (7)
Peritoneal lavage cytology (PLC) *n* (%)	74/74 (100)

Table 4. Unsuspected metastasis found at laparoscopy in 25 of 74 patients

Pattern of 25 patients with findings			Number in all 74 patients		
Liver positive by biopsy ($n = 12$)	Lavage cytology positive ($n = 20$)	Peritoneum positive by biopsy ($n = 5$)	Head/uncinate ($n = 57$)	Body tail ($n = 74$)	Total ($n = 74$)
+	+	+	0	1	1
+	+	–	5	1	6
+	–	+	0	0	0
+	–	–	5	0	5
–	+	+	1	3	4
+	–	+	0	0	0
–	+	–	5	4	9
1248%	2080%	520%	16(28%)[a]	9(53%)[a]	25 (34%)

[a] Difference not significant for head/uncinate vs body, tail, chi-square analysis

positive PLC result was the only finding for nine patients (12%).

Macrometastasis were implants smaller than 3 mm on the surface of the liver or peritoneum. The 17 patients with visible metastasis on the liver ($n = 12$) and/or peritoneum ($n = 5$) were more likely to have positive PLC results than those without evidence of intraabdominal metastasis (69% vs 16%; $p < 0.001$). All the patients with peritoneal metastasis had positive PLC results (i.e., no patient had isolated peritoneal metastasis without positive PLC results). Of the 25 patients with findings, 5 (20%) had isolated liver metastasis without positive PLC results. Eleven patients (44%) had multiple locations of metastatic deposits. The distribution of occult findings discovered by laparoscopy is best depicted by Fig. 1.

Tumors in the pancreatic body or tail were more likely to be associated with unsuspected metastasis than tumors in the head of the pancreas, although the difference did not reach statistical significance (28% vs 53%,difference not significant). The CT findings of tumor involvement of a major artery, as opposed to no arterial involvement, was not associated with a higher rate of unsuspected metastasis (31 % vs 40%, difference not significant). Interestingly, there was no difference in the prevalence of positive PLC results between the patients who underwent preoperative percutaneous biopsies and those who did not undergo this type of biopsy (31% vs 35%, difference not significant).

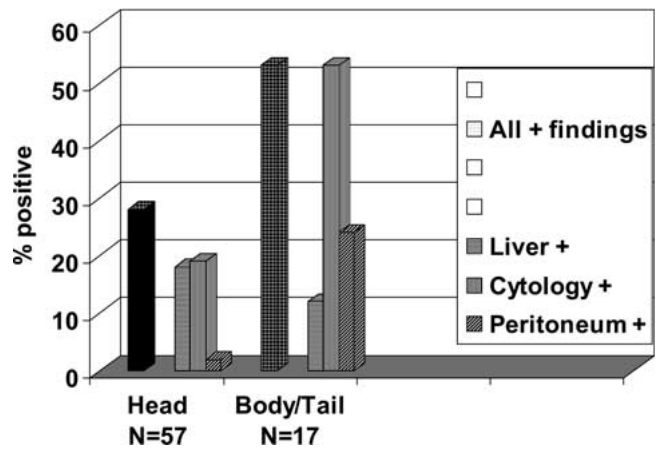

Fig. 1. The distribution of occult metastases is depicted in bar graphs to show the percentage of patients with positive results at the three distant sites where tumor was found. The incidence of positive findings (all + findings, bars with square patterns) for 57 patients with pancreatic cancer in the head (HEAD) of the gland was 28% (16/57). For 17 patients with lesions in the body/tail (Body/Tail) area it was 53% (9/17). The most common finding was positive peritoneal lavage cytology (cytology + vertical bar patterns) for both HEAD (19%, 11/57) and Body/Tail (53%, 9/17). Peritoneal metastases were not found unless cytology was positive. Surprisingly, patients with Body/Tail lesions and a poor survival reputation had less frequent liver deposits than those with HEAD lesions using the more frequent peritoneal route to disseminate, either through actual deposits on the peritoneum surfaces or free floating in the peritoneal cavity.

Discussion

Using older CT technology in the 1980s, we found that only 12% of patients with pancreatic cancer had resectable disease according to CT scan at the time of diagnosis [7]. That is, 88% of the patients with pancreatic cancer presented with unresectable disease by CT scan. Of this latter group, 50% had evidence of metastasis according to CT scan and did not require further staging workup. The remaining 50% had *locally ad-*

vanced unresectable disease without evidence of metastasis. No studies in the literature have addressed appropriate staging practices for this latter group of patients [15]. The latter group is unique for two reasons. They comprise one of the largest groups of pancreatic cancer patients, and there are new and potentially effective treatments for them. These patients are more likely to benefit from accurate staging.

Cuschieri et al. [5] described the use of laparoscopy as an adjunct to the management of pancreatic cancer in 1978. At a time when the usefulness of CT scans was still being explored, laparoscopy offered a means of directly providing accurate diagnostic information about the pancreas and intraabdominal cavity. Moreover, laparoscopy permitted a minimally invasive way to perform a biopsy of metastatic lesions under direct vision. Although this series was small (23 patients), the value of staging laparoscopy for pancreatic cancer was demonstrated.

Since Cuschieri et al.'s [5] report on laparoscopy in 1978 and our report on CT scanning in 1993, CT scanning has taken a prominent role in pancreatic cancer assessment and has become the accepted technique for diagnosis and staging [2, 8]. However, even the most modern CT scan has limitations. Diagnostic laparoscopy has a role in upstaging patients with pancreatic cancer clinically staged with CT scan. Following the lead of the Cuschieri et al. [5] pioneering manuscript, a series of papers from the Massachusetts General Hospital clearly indicated an upstaging role beyond the ability of CT scans, which is best shown in their latest report by Jimenez et al. [8]. They used simple laparoscopy with biopsy and PLC to demonstrate unsuspected metastasis in 31% of patients (39/125) with "nonmetastatic" pancreatic cancer by CT scan. Andren-Sandberg et al. [2] found the rate to be 38% in 9 of 24 patients, whereas Conlon et al. [4] observed a 31% rate of metastatic deposits (PLC not used) in 36 of 115 patients. These studies concluded that laparoscopy would significantly reduce the rate of "negative" laparotomies.

It should be considered that CT scanning would separate patients into three different categories: those with distant disease (**distant disease**), those without distant disease but with "unresectable" disease because of disease extended locally to major vessels or contiguous organs (**locally unresectable**), and those without local extension or distant disease (**resectable**). The aforementioned studies [2, 4, 8] did not focus on the large number of patients deemed "locally unresectable" by CT scan. Our study was limited to this type of patient who had no evidence of distant disease.

We observed that diagnostic laparoscopy with biopsy and PLC discovered occult metastasis in 34% of patients who had CT evidence of unresectability but no metastasis. This rate is similar to that reported by other studies [2, 4, 8] of patients with resectable disease according to CT scan. We observed a doubling of occult findings for left-sided lesions (53%) over those for head lesions (28%) for these locally advanced cases. For less extensive lesions thought to be resectable by CT, the Massachusetts General Hospital study saw a similar doubling of discovered occult lesions in cases of left-sided lesions, but with a lower incidence at 36% and 17% respectively. Of our patients with positive findings, 64% had peritoneal and/or liver implants. These lesions were smaller than 3 mm, which is well under the resolution of the best CT scans.

What about positive PLC cases in which even the human eye, much less a CT scan, would miss these metastatic lesions? Of our patients, 12% had positive PLC results but no gross metastasis, which is similar to the 9% observed in the Jiminez et al. [8] study. The latter study documented that patients with unsuspected metastasis have a significantly shorter median survival than patients who do not (9 vs 13 months $p < 0.001$). Other studies have confirmed that positive PLC results are associated with aggressive disease and dismal outcomes [9, 13]. These patients with positive PLC results would not benefit from locoregional therapy directed at the primary tumor, and they have a survival rate similar to that of patients with visible metastasis [12]. Two of our patients had "suspicious" cells (i.e., did not meet morphologic criteria for malignancy) on PLC without visible metastasis. We considered these PLC results diagnostic for metastatic disease on the basis of a prior study analyzing the reports of our cytologists. This study demonstrated that suspicious cytology was ultimately associated with malignant pancreatic cancer [6].

The distribution of metastases depicted in Fig. 1 forms an interesting pattern of anatomic sites. The most common finding for either left- or right-sided lesions was PLC. Peritoneal lesions were always associated with positive PLC results, and were more common in cases of the left-sided lesions. Left sided-lesions have a worse prognosis, which is thought to be secondary to a delay in diagnosis. This concept is supported by the higher incidence of positive PLC results, but is not supported by the lower rate of liver metastases. Why would the rate of liver deposits not also increase? A larger study is required to answer that question, but appears that the left-sided tumors may have a different tumor biology than right-sided lesions.

The high rate of unsuspected metastases observed in our study places these patients in a group of patients with a median survival of 6 months [11] and 5-year survival of less than 6% [16]. This has significant implications for the interpretation of results from studies that do not stage their patients with laparoscopy. Currently, patients with locally advanced disease are treated with radiation-based protocols aimed at locoregional control. The protocols for these studies assume that there are no metastatic deposits in their patients. The prospective study by the Gastrointestinal Tumor Study Group for locally unresectable pancreatic cancer showed that combination bolus 5-FU and external beam radiotherapy was superior to any single method and doubled median survival time [14]. Logically, patients with unsuspected metastasis would not benefit from radiation-based treatments. Would these results have been even better with accurate staging? Our study indicates that up to 34% of patients may be inappropriately considered for these protocols. Radiation treatment can result in significant morbidity and requires 5 to 6 weeks of daily time commitment. For a

group of patients with occult metastases whose survival is measured in months, elimination of radiation treatments would significantly improve the quality of life. Moreover, by appropriate upstaging of patients, suitable protocols designed for metastatic disease could be initiated in a timely manner.

Diagnostic laparoscopy also will affect patients who are considered for "down staging" protocols. Many patients are considered unresectable because of portal vein or superior mesenteric vein involvement. Several centers, including ours (unpublished data), have been able to induce tumor regression with neoadjuvant chemotherapy and to resect with negative margins [17, 18]. Our study indicates that these patients require staging with diagnostic laparoscopy to rule out metastatic disease before initiation of neoadjuvant therapy. Most of our patients with unsuspected metastasis had arterial involvement and would not have been considered "downstageable." However 7 of 25 patients (28%) with laparoscopically discovered occult distant disease had involvement only of the portal vein or superior mesentric vein, and would have been erroneously considered "candidates" by CT criteria for "downstaging."

Although all diagnostic laparoscopies were performed at a high-volume tertiary referral center with extensive experience in managing patients with pancreatic cancer, we believe that this staging method is uniquely applicable in a community setting. Patients who present with unequivocal locally unresectable disease can undergo diagnostic laparoscopy. If metastatic disease is found, the patient can immediately undergo palliative therapy without needing to receive surgical consultation at a specialized center. If metastases are not discovered, the patient may be considered for referral to a specialized center and a clinical trial of primary therapy, downstaging neoadjuvant therapy (if arterial involvement is absent), or primary radiation-based protocols. This algorithm should save the patient expense and unnecessary anxiety, while improving results based simply on better staging.

In summary, because of the inherent weakness of CT scanning, the design of chemoradiotherapy trials should include laparoscopic staging. Most protocols evaluating radiation-based treatments aim to enroll a homogeneous group of patients without occult metastatic deposits. For patients not thought to have distant disease according to CT scan, but who have locally extended "unresectable" tumors, diagnostic laparoscopy has shown that 28% with head lesions and 53% with body/tail lesions will have unsuspected metastasis. These patients would have been inappropriately enrolled in therapies directed at the primary tumor. Because these patients with distant disease are known to have shorter survival, the effect of treatment will be falsely low. Any diagnostic laparoscopic procedure should include PLC because our most common finding was positive cytology results. If CT scan alone is used for staging, then every other patient with a pancreatic body/tail lesion and one of four patients with a head lesion will be found to have occult distant disease.

References

1. American Joint Commission on Cancer (2002) Exocrine pancreas. In: Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds). AJCC cancer staging manual. 5th ed. Springer-Verlag, New York, pp 157–164
2. Andren-Sandberg A, Lindberg CG, Lundsted C, Ihse I (1998) Computed tomography and laparoscopy in the assessment of the patient with pancreatic cancer. J Am Coll Surg 186: 35–40
3. Bemelman WA, de Wit LT, van Delden OM, Smits NJ, Obertop H, Rauws EJ, Gouma DJ (1995) Diagnostic laparoscopy combined with laparoscopic ultrasonography in staging of cancer of the pancreatic head region. Br J Surg 82: 820–824
4. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF (1996) The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 223: 134–140
5. Cuschieri A, Hall AW, Clark J (1978) Value of laparoscopy in the diagnosis and management of pancreatic carcinoma. Gut 19: 672–677
6. Enayati PG, Traverso LW, Galagan K, Thirlby RC, Larson J, Hauptman EM, Kozarek RA (1996) The meaning of equivocal pancreatic cytology in patients thought to have pancreatic cancer. Am J Surg 171: 525–528
7. Freeny PC, Traverso LW, Ryan JA (1993) Diagnosis and staging of pancreatic adenocarcinoma with dynamic computed tomography. Am J Surg 165: 600–606
8. Jimenez RE, Warshaw AL, Rattner DW, Willett CG, McGrath D, Fernandez-del Castillo C (2000) Impact of laparoscopic staging in the treatment of pancreatic cancer. Arch Surg 135: 409–414
9. Leach SD, Rose JA, Lowy AM, Lee JE, Charnsangavej C, Abbruzzese JL, Katz RL, Evans DB (1995) Significance of peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreatic head. Surgery 118: 472–478
10. Louvet C, Andre T, Lledo G, Hammel P, Bleiberg H, Bouleuc C, Gameli E, Flesch M, Cvitkovic E, de Gramont A (2002) Gemcitabine combined with oxaloplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. J Clin Oncol 20: 1512–1518
11. Luque-de Leon E, Tsiotos GG, Balsiger B, Barnwell J, Burgart LJ, Sarr MG (1999) Staging laparoscopy for pancreatic cancer should be used to select the best means of palliation and not only to maximize the resectability rate. J Gastrointest Surg 3: 111–117discussion 117–118
12. Makary MA, Warshaw AL, Centeno BA, Willet CG, Rattner DW, Fernandez-del Castillo C (1998) Implications of peritoneal cytology for pancreatic cancer management. Arch Surg 133: 361–365
13. Merchant NB, Conlon KC, Saigo P, Dougherty E, Brennan MF (1999) Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg 188: 421–426
14. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW (1981) Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high-dose (6,000 rads) radiation alone, moderate dose radiation (4,000 rads + 5-fluorouracil), and high-dose radiation + S-fluorouracil. The Gastrointestinal Tumor Study Group. Cancer 48: 1705–1710
15. Pisters PW, Lee JE, Vauthey JN, Charnsangavej C, Evans DB (2001) Laparoscopy in the staging of pancreatic cancer. Br J Surg 88: 325–337
16. Senen SR, Fremgen A, Menck HR, Winchester DP (1999) Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. J Am Coll Surg 189: 1–7
17. Todd KE, Gloor B, Lane JS, Isacoff WH, Reber HA (1998) Resection of locally advanced pancreatic cancer after downstaging with continuous-infusion 5-fluorouracil, mitomycin-C, leucovorin, and dipyridamole. J Gastrointest Surg 2: 159–166
18. White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, McGrath KM, Clary BM, Pappas TN, Tyler DS (2001) Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol 8: 758–765