Treatment Decision Making in Pancreatic Adenocarcinoma

Multidisciplinary Team Discussion With Multidetector-Row Computed Tomography

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Hypothesis: Multidetector-row computed tomography reduces the frequency of use of other imaging methods in patients with pancreatic carcinoma.

Design: Validation cohort study.

Setting: Tertiary care public hospital.

Patients: Two hundred thirteen patients with pancreatic carcinoma.

Main Outcome Measure: Multidetector-row computed tomography was initially performed in patients with newly diagnosed pancreatic carcinoma.

Results: Of the 213 pancreatic carcinomas, 79 (37%) were classified as probably resectable, 127 (60%) as certainly unresectable, and 7 (3%) as probably unresectable. Of 79 tumors classified as probably resectable, 68 (86%) were found to be resectable, 7 tumors considered as probably unresectable were unresectable, and the remaining 127 tumors were treated nonsurgically. Magnetic resonance imaging was recommended in 92 patients (43%), angiography in 1 patient (0.5%), and both endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in 15 patients (7%).

Conclusions: Multidetector-row computed tomography provides reliable information for staging pancreatic carcinoma. Multidisciplinary team discussion along with use of this noninvasive technique simplifies the diagnostic strategy for pancreatic carcinoma and decreases the need for invasive staging methods.


A CCURATE TUMOR STAGING and correct prediction of resectability are primary problems in the management of pancreatic carcinoma. There is no evidence of palliative benefit for pancreatic resection in patients who have locally advanced or metastatic disease.1-3 Some advocates argue that exploratory laparotomy is the most accurate means of determining resectability4,5; however, laparotomy is associated with perioperative morbidity and requires convalescence in patients with limited expected survival.5,6

See Invited Critique at end of article

In the last 2 decades, several new imaging methods have contributed to progress in tumor staging. In a practical clinical situation, use of diagnostic examinations is often inconsistent and systematic among physicians. We are in danger of losing sight of the primary objective of staging, which is to accurately differentiate resectable tumors from unresectable tumors expeditiously and with minimal invasiveness (ie, patient discomfort), and to avert unnecessary laparotomy and cost to the patient.

Multidetector-row computed tomography (MDCT) offers the latest advancement in computed tomographic (CT) technology by combining multiple rows of detectors and faster gantry rotation speed. This technology not only enables routine examinations to be performed in a fraction of the time previously required but also can be used to develop new applications such as 3-dimensional CT angiography and multiplanar reconstruction.

The use of imaging techniques is usually evaluated by retrospective reading by radiologists blinded to the clinical information and comparison with other imaging examinations. However, this is not always practical, and many physicians believe that actual diagnostic results are different from the results reported. Moreover, most studies originating from surgical, radiologic, or medical depart-
ments tend to focus on those findings and results that they wish to argue and emphasize, and often they do not provide a full accounting of all patients seen and data collected.

The purpose of this study was to evaluate the usefulness of MDCT in selecting the appropriate treatment in patients with pancreatic carcinoma. Multidetector-row CT images were prospectively evaluated and treatment plans were decided on the basis of the MDCT findings by consensus of several physicians involved in treating pancreatic disease. We verified the use by determining whether the intended treatment based on MDCT findings was completed without major change. To assess whether MDCT decreased the frequency of use of other imaging methods for diagnosis, the incidence of diagnoses made on the basis of imaging findings other than with MDCT was also investigated. To our knowledge, this type of prospective study to evaluate the usefulness of diagnostic examination has not previously been reported.

METHODS

PATIENTS

Between September 30, 2002, and March 31, 2005, 241 consecutive patients were referred to our hospital for treatment of invasive ductal carcinoma of the pancreas. Other histologic types of pancreatic tumor such as endocrine tumor, intraductal papillary mucinous tumor, and solid and pseudopapillary tumor were excluded from this study. Twenty-eight patients who had already received surgical or medical treatment at another hospital were also excluded from the study. Thus, 213 patients (136 men and 77 women) were enrolled in the study. Their mean age was 64 years (age range, 32-82 years). Informed consent was obtained from all patients before performance of MDCT according to a protocol approved by our institutional review board.

MULTIDETECTOR-ROW CT

We used a CT scanner (Aquiline; Toshiba Medical Systems Co, Ltd, Tokyo, Japan) with 16 high-resolution central detectors. From these detectors, we selected a 1-mm section thickness and reconstructed the data at 1-mm intervals (0.5-mm overlap). The other parameters were a 0.5-second helical rotation time, 135 kV (peak), and 350 to 400 mA-s. The study protocol was a 4-phase acquisition that consisted of early arterial phase images beginning at 20 seconds, late arterial phase images beginning at 40 seconds, pancreatic phase images beginning at 70 seconds, and a delayed phase beginning at 120 seconds after the start of contrast medium injection. Early arterial images were used to reconstruct CT arteriography. Disease was primarily evaluated using late arterial and pancreatic images. Delayed phase images were used to detect the presence of fibrous tissue and for upper abdominal survey. We injected 150 mL of iopamidol (Iopamiron; Nihon Schering Co, Ltd, Tokyo, Japan) through a peripheral venous line at 4 mL/s by using a power injector (Auto Enhance A-50; Nemoto Kyorindo, Tokyo, Japan). Multiplanar reformation and CT angiographic findings were reconstructed using a freestanding workstation (Zaio Corp, Tokyo, Japan) if the diagnostic radiologists considered it necessary (Figure 1). These images were sent to a picture archiving and communication system (Synapse; Fujifilm Medical Co, Tokyo, Japan) that enables interactive analysis.

TUMOR STAGING

When each new outpatient was referred to our hospital for the treatment of pancreatic carcinoma, MDCT and laboratory tests were performed. A pancreatic disease conference consisting of surgeons (including K.U.), medical oncologists (including N.B.), endoscopists, diagnostic radiologists (including H.F.), and radiation oncologists was conducted once a week to discuss findings in new outpatients with pancreatic carcinoma, especially as seen on MDCT images. Diagnostic radiologists looked for signs of unresectability including extrapancreatic tumor spread, particularly into the celiac axis and the root of the superior mesenteric artery; para-aortic massive lymph node involvement; and the presence of distant metastases and ascites. When MDCT images showed direct contact greater than 90° between the portal vein and the tumor, the case was diagnosed as positive for portal vein invasion by the tumor.12 Lymph nodes were considered positive for disease when the short axis was greater than 1 cm in diameter or there were clusters of 3 or more smaller nodes (each <1 cm). Encasement of the portal vein and regional lymphadenopathy was not considered a surgical contraindication.

When none of these parameters were found, that is, the tumor was stage I or lower on the International Union Against Cancer TNM classification,13 the tumor was considered probably resectable (Figure 1). When any of these signs were positive, that is, the tumor was stage III or higher, the tumor was categorized as certainly unresectable. When suspect but inconclusive findings of 1 or more signs were present, the tumor was considered probably unresectable (Figure 2). When additional information was required at the conference, the recommended examination was performed and the findings were discussed again. For example, when obstruction of the pancreatic duct and mass effect were observed but the tumor was isodense on MDCTs, magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS), or both, were performed. If detailed vascular anatomy over CT angiography was reconstructed by MDCT images was needed, angiography was recommended. If the patient had jaundice and hyperbilirubinemia developed, biliary drainage was attempted. Endoscopic retrograde or percutaneous transhepatic biliary drainage was also performed if the patient had cholangitis. Such drainage procedures were not considered diagnostic imaging.

All conference members evaluated the MDCT findings and the patient’s health status. According to the consensus of the conference, the patients were divided into 2 groups. Patients with tumors considered certainly unresectable were referred to the division of gastrointestinal medical oncology and chemotherapy, and chemotherapy or radiation therapy (or best supportive care) was given. Patients with tumors considered probably resectable were admitted to a surgical ward and underwent surgery. Patients with tumors considered probably unresectable were also referred to a surgical ward, and laparotomy was performed. If no factors prohibiting resection were found at laparotomy, curative resection was attempted. A biliary or enteric bypass graft was constructed based on the surgeon’s judgment. The treatment plan decided on at the conference was presented to the patient, and informed consent was obtained.

DATA ANALYSIS

Patient classification and the intended treatment decided at the conference were recorded. We verified whether the treatment, especially surgical procedures planned based on MDCT findings, was completed. Any imaging diagnoses recommended in addition to MDCT were also recorded. The diagnostic accuracy of MDCT in detecting vascular invasion and nodal status were assessed using the histopathologic findings, and surgical
curability was also evaluated. Patient survival was calculated using the Kaplan-Meier method, and differences in survival curves were compared using the log-rank test. Statistical significance was determined at $P<.05$ in all cases.

**RESULTS**

Of 213 tumors, 79 were classified as probably resectable, 7 as probably unresectable, and 127 as certainly unresectable. Of the 79 tumors classified as probably resectable, 68 were confirmed to be resectable during surgery. In the other 11 patients, unexpected metastatic lesions were discovered at surgery, including peritoneal dissemination in 7 patients, minute liver metastases in 3, and normal-sized para-aortic lymph node involvement in 1. Thus, 7 patients underwent bypass operations and the remaining 4 underwent only laparotomy, even though the tumors were resectable insofar as local extension. The resection rate of probably resectable tumors was 86% (68 of 79) and the overall resection rate was 32% (68 of 213).

Because MDCT findings prompted suspicion of minute liver metastases in 3 patients, peritoneal dissemination in 2, and invasion to the superior mesenteric artery in 2, these 7 tumors were considered probably unresectable. These findings were confirmed at surgery. Six patients underwent bypass operations and the remaining patient underwent laparotomy only. The resection rate in 7 probably unresectable tumors was 0%. Of 127 tumors classified as certainly unresectable, MDCT images demonstrated that 31 were locally advanced and 96 had metastasized to distant sites. Chemotherapy was administered in 89 patients, chemoradiotherapy in 30, radiotherapy in 1, and best supportive care in 7.

Diagnostic examinations in addition to MDCT were performed in 92 of the 213 patients with pancreatic carcinoma. Magnetic resonance imaging was recommended to evaluate the site and extent of biliary and pancreatic duct obstruction and the equivocal liver lesions in 66 of 86 surgically treated patients (77%) and 26 of 127 medically treated patients (20%). In 9 patients, superparamagnetic...
iron oxide–enhanced MRI was performed: liver metastases were ruled out in 6 patients, and, in the remaining 3 patients, lesions were too small to determine that they were metastases. These tumors were considered probably unresectable. Endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) were simultaneously performed in 15 of the 213 patients (7%): 14 of 86 surgically treated patients (16%) and 1 of 127 medically treated patients (0.8%). In these 15 patients, pancreatic tumors were isoattenuating to normal pancreatic parenchyma and appeared as an ill-defined mass on MDCT images. Thus, the primary purpose of these diagnostic procedures was to differentiate among pancreatic diseases such as pancreatitis, not for staging. Findings of these procedures suggested that the tumors were pancreatic carcinoma. Biopsy and cytologic examination were performed at ERCP in 14 patients. In the remaining patient, the catheter could not be inserted in the pancreatic duct, and only EUS was performed. Seven tumors were confirmed as malignant lesions and 7 were not. Fine-needle aspiration with EUS guidance was not performed in this series. Angiography was performed in only 1 patient who had a probably resectable tumor (1%) to reveal the blood supply to the tumor in the early phase of the study; however, this examination provided no additional information to that obtained at MDCT and CT angiography.

The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for resectability based on MDCT findings were 100% (68 of 68), 92% (134 of 145), 86% (68 of 79), 100% (134 of 134), and 95% (202 of 213), respectively. For 68 resected tumors, these values for those tumors with portal vein invasion were 52% (13 of 25), 93% (40 of 43), 81% (13 of 16), 77% (40 of 52), and 78% (53 of 68), and for those with nodal involvement were 32% (12 of 38), 90% (27 of 30), 80% (12 of 15), 51% (27 of 53), and 57% (39 of 68), compared with histologic assessment. Resection margins were negative (R0) in 81% of tumors (55 of 68) and microscopically positive (R1) in 19% (13 of 68). No margins exhibited macroscopic residual tumor (R2).

At the time of analysis, 38 of 68 patients who underwent resection were alive at a median follow-up of 25 months. Ten of the 120 patients who received medical treatment (chemotherapy or radiation therapy or both) were alive at a median of 17 months. Figure 3 shows the overall survival curves by treatment arm. The median survival was 34.5 months in patients who underwent tumor resection; this was significantly different from the median survival of 7.6 months in patients who received medical treatment (P < .001). Survival was not different in patients who underwent palliative surgery (ie, bypass or simple laparotomy) compared with medical treatment (P = .21).

**COMMENT**

The diagnostic strategy of pancreatic carcinoma is not always systematic and consistent among physicians. Be-
fore starting this study, a series of consensus meetings was conducted and guidelines of treatment for pancreatic carcinoma were established. To avert bias based on a particular physician’s experience, the diagnostic strategy and treatment plan for each patient were decided in a multidisciplinary team conference.

Evaluating the local extension of pancreatic carcinoma is almost equivalent to diagnosing the vascular invasion by the tumor. While diagnostic accuracy of vascular invasion has been evaluated for invasion of the portal venous system, recent surgical techniques have made it possible to safely resect the superior mesenteric vein–portal vein confluence. Thus, unresectability is commonly the result of tumor extension along the superior mesenteric artery and celiac axis (ie, T4 with the International Union Against Cancer TNM staging system), and preoperative imaging diagnosis should also focus on these arteries.

Multidetector-row computed tomographic technology has further improved the capability of conventional CT to provide precise information about high-definition tumors and their vascular relationship. In this series, all 79 tumors defined as probably resectable at MDCT were thought to be resectable in terms of local extension at laparotomy, but unexpected distant metastases were associated with 11 tumors. In 2 of 7 probably unresectable tumors, obvious tumor extension to the superior mesenteric artery was confirmed at surgery. It is possible that some of the tumors considered certainly unresectable could have been resected if aggressive surgical techniques had been used. However, such an approach may be futile and provide no survival benefit or good quality of life for the patient. We believe MDCT is superior to intraoperative assessment in providing information about the local extension of pancreatic carcinoma, that is, tumor stage should be determined using MDCT.

Distant metastases are another factor in unresectability. The most common sites of distant metastasis are the liver and peritoneum. Computed tomography is a reliable technique for detection of tumor metastasis, but its sensitivity decreases with small lesions. Previous studies reported unexpected discovery of hepatic and peritoneal metastases at laparotomy or laparoscopy in more than 10% of patients with normal findings at CT. In most cases, the lesions missed are beyond the resolution of current radiologic imaging. In this series, 11 of 79 probably resectable tumors (14%) were associated with such unexpected minute distant metastases. It is impossible to achieve a perfect workup to rule out such micrometastatic disease even with MDCT. We think the incidence in this study is acceptable. In equivocal cases, it is advisable to disregard these findings so that the patient is not denied surgery, which is the only curative treatment option currently available. Staging laparoscopy can still contribute to detection of such occult metastases, although it is more invasive and time-consuming than radiologic imaging methods. We cannot use this technique as much as we would like because of limitations of the operating room and medical staff.

Sensitivity and specificity with MRI is equal to or better than with helical CT in the detection and staging of pancreatic carcinoma. However, these evaluations were done before the development of MDCT. Given the more widespread availability of CT and the familiarity of surgeons and oncologists with its interpretation, MRI is not used frequently in staging of pancreatic tumors. In recent reports, accuracy with superparamagnetic iron oxide–enhanced MRI is equal to or better than with CT during arterial portography or MDCT. Although it is not perfect, we used this technique as an adjunct to MDCT to confirm equivocal lesions.

Magnetic resonance cholangiopancreatography is non-invasive, does not require injection of contrast medium, and provides sufficient information about the presence of periampullary strictures and the site and extent of biliary and pancreatic duct obstruction, stricture, and dilatation. The technique and image quality are under development and evolving. Thus, magnetic resonance cholangiopancreatography is better than ERCP for evaluation of the biliary and pancreatic ducts. However, magnetic resonance cholangiopancreatography alone provides limited diagnostic and staging information, and additional cross-sectional imaging is required.

Endoscopic ultrasonography is a rapidly evolving method for detection, staging, and surgical assessment of pancreatic carcinoma, although the tail of the pancreas is inadequately visualized in most patients. Several studies have reported that the sensitivity, specificity, and accuracy of EUS staging were much better than with ultrasound or CT. However, a recent report concluded that EUS and dual-phase helical CT offered no difference in staging and prediction of resectability. We used EUS and ERCP in patients in whom there was strong suspicion of pancreatic carcinoma but inconclusive CT findings for differential diagnosis. The incidence of these examinations was only 7% of all patients. These techniques are also used while obtaining cytologic and histologic specimens. However, the accuracy of histologic and cytologic diagnoses is not sufficient, as shown in this study. Endoscopic ultrasound and ERCP are highly operator dependent and require an experienced biliopancreatic endoscopist for best results; in addition, they are invasive techniques. We believe routine examination using these endoscopic techniques in patients suspected of having pancreatic carcinoma is not necessary and that they should be reserved for selected patients in whom findings with other techniques are suggestive but inconclusive.

Angiography has been performed to detect congenital arterial anomalies and vascular tumor encroachment. This method is being abandoned by several hospitals. Unlike conventional angiography, CT angiography is not limited by plane or perspective, and often the optimal view is determined in retrospect. The use of a 3-dimensional display provides the vascular map in a more intuitive and esthetic fashion than classic catheter angiography. Surgeons in our hospital have accepted this imaging method.

This study is not a comparative trial, and the results were extracted from prospective work in clinical practice. We believe that sensitivity (100%) and positive predictive value (86%) of resectability, the R0 resection rate (81%), and survival in patients who underwent tumor resection demonstrate the positive effects of a preopera-
tive multidisciplinary conference with MDCT to arrive at a consensus treatment plan. To demonstrate the superiority of any method of imaging or treatment decision making, a prospective comparative study with a control group is needed, for example, MDCT vs other imaging method or multidisciplinary team vs nonmultidisciplinary team. However, such a study is not realistic. We believe that MDCT provides reliable information for resectability of pancreatic carcinoma. Multidisciplinary team discussion along with this noninvasive technique simplifies the diagnostic strategy for pancreatic carcinoma and reduces the need for other invasive staging methods.

Accepted for Publication: November 11, 2006.

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Author Contributions: Dr Furukawa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Furukawa, Uesaka, and Boku. Acquisition of data: Furukawa, Uesaka, and Boku. Analysis and interpretation of data: Furukawa, Uesaka, and Boku. Drafting of the manuscript: Furukawa. Critical revision of the manuscript for important intellectual content: Uesaka and Boku. Statistical analysis: Furukawa. Obtained funding: Furukawa. Administrative, technical, and material support: Furukawa, Uesaka, and Boku. Study supervision: Uesaka and Boku.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Foundation for Promotion of Cancer Research, Tokyo, Japan.