

Preoperative Chemoradiation and Pancreaticoduodenectomy with Portal Vein Resection for Localized Advanced Pancreatic Cancer

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Pancreatic adenocarcinoma is a common disease that is rarely cured. Surgical resection remains the only treatment modality that has a curative potential, although the majority of patients are unsuitable for resection at the time of diagnosis. Chemoradiation therapy prior to a pancreaticoduodenectomy ensures that a patient who undergoes a complete resection multimodality therapy, avoids a resection in patients who have a rapidly progressive disease, and allows radiation therapy to be given to well oxygenated cells before, surgical devascularization. This permits the chance of resection of an unresectable pancreatic cancer by downstaging.

A patient with cytologic proof of localized adenocarcinoma of the pancreatic head received an intravenously chemoradiation (Taxol, 50 mg/m² intravenously for 3 hours week on 5 cycles, of Gemcytabine 1000 mg/m²/day intravenously for 3 days week on 2 cycles, of 4500 cGy) with the intention of proceeding to a resection operation, restaging was performed by computed tomography, magnetic resonance imaging from 5 weeks every months due to ongoing decreasing of tumor size after the chemoradiation. At laparotomy, the patient didn't have suspected metastatic disease, the tumor size was 2 × 3 cm on the pancreas head and was infiltrating into the portal vein for about 3 cm length on right side. A pancreaticoduodenectomy along with a portal vein and superior mesenteric vein resection was done and then reconstruction of a vascular anastomosis by using the right side of the internal jugular vein. Perioperative complications didn't occur. In conclusion, preoperative chemoradiation of a localized advanced pancreatic tumor has no added risk to the operative complications and the prospects for resectability are enhanced.

Key Words: Chemoradiation therapy, pancreatic cancer

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INTRODUCTION

Pancreatic adenocarcinoma is a common disease that is rarely cured. It represents the 12th most frequent malignancy and the fourth leading cause of cancer death in the United States.¹ In patients that were reported to the National Cancer Data Base (NCDB), the overall 5-year survival was 4% in 1995.² Surgical resection remains the only treatment modality that has a curative potential, although the majority of patients are unsuitable for resection at the time of diagnosis. Among 15,120 cases that were reviewed by the NCDB, only 14.2% underwent a surgical resection. Our preoperative use of chemoradiation before a Whipple's operation for the pancreatic cancer was supported by the following considerations: (1) radiation therapy is more effective on well oxygenated cells that have not been devascularized by surgery; (2) radiation therapy before surgery may prevent implantation and dissemination of tumor cells at the time of laparotomy, thereby decreasing the chance of a subsequent peritoneal tumor recurrence; (3) potentially unresectable tumors may be downstaged to enables a surgical resection; (4) patients who have a disseminated disease that is evident in restaging studies after chemoradiation will not be subjected to a laparotomy; and (5) because radiation therapy and chemotherapy is given first, which delays the postoperative modality therapy, which is a frequent problem that is encountered in adjuvant therapy studies.³ Preoperative and postoperative chemoradiation studies have also an improved

survival and a reduced local recurrence rate.^{4,5}

Criteria for resectability as seen on computerized tomography are the absence of extrapancreatic disease, no tumor encasement of the superior mesenteric artery (SMA) or the celiac axis and a patent superior mesenteric portal vein (SMPV) confluence. But in the case of a superior mesenteric artery encasement, although resection and reconstruction is done, it usually includes an extensive involvement of the mesenteric neural plexus, making it impossible to achieve a negative retroperitoneal resection at the margin of the excision even after a radical resection. In contrast to an arterial resection, a segmental resection of the SMV or SMPV confluence can be performed safely with no increase in the perioperative morbidity or mortality rate compared with a standard pancreaticoduodenectomy. Tumor involvement at the SMPV confluence in the absence of a tumor extension to the proximal SMA or celiac axis is not associated with histopathological signs that are predictive of a poor prognosis; Tumor invasion of the SMV or SMPV confluence appears to be a function of the tumor location rather than being an indicator of biological aggressiveness.⁶

We performed pancreaticoduodenectomy with an internal jugular vein graft for a portal vein invasion after a down staging that was produced by preoperative chemoradiation. Presently report a case with a review of the literature.

CASE REPORT

A 60-year old male patient was admitted for further evaluation and operation of a mass at the head of his pancreas. He had been treated for diabetes mellitus since January 1999 by an oral hypoglycemic agent, but the glucose level was not controlled by this. Therefore he underwent more evaluations and a 2.5 × 3.5 cm mass was found at the head portion of the pancreas on abdominal computerized tomography (CT) scan. A physical examination at the time of admission showed no significant findings. The blood pressure was 110/60 mmHg, the pulse rate was 76 beats/min, the body temperature was 36.7°C and the respiratory rate was 20/min. There were no signs of cervical lymphadenopathy and no mass was pal-

pable in the abdomen. There were no significant findings on a rectal examination. Laboratory findings were as follows; WBC count 5400/mm³, Hgb 11.6g/dl on CBC, and biochemical analysis was normal. CA19-9 was 38.6 U/ml, Lewis phenotype a/b(-/+), CEA: 10.28 ng/ml in his tumor marker analysis. The magnetic resonance cholangiopancreatography (MRCP) findings before taking concomitant chemoradiation therapy (CCRT) showed that a 2.5 × 3.5 cm of mass which totally replaced the pancreatic head portion and partially extended into the body. The distal pancreatic duct (6.7 mm) and common bile duct (CBD) were dilated. This can be the evidence for a mass invasion to the ampulla of Vater. The SMV was surrounded by the mass more than 3/4 of its circumference which was also suspicious of mass invasion. The SMV was narrowed at the proximal 1 cm level of the confluence of the splenic vein and the portal vein. But narrowing of the celiac axis origin was separate from the mass and the result of the atherosclerotic change in the aorta, not to tumor involvement. A 1 × 1.5 cm lymph node in the portocaval space was noted (Fig. 1). The CT findings after CCRT show that, the size of irregular margin mass at the pancreatic head portion had decreased to 2 × 3 cm compared with the magnetic resonance image (MRI) findings of May 1999. The mass abutted to part of duodenum and to the confluent level of the splenic vein and portal vein at an angle of 180°. Because the part of splenic vein showed beak appearance toward the mass, a possible mass invasion into the vessels couldn't be completely excluded. No metastatic nodule were found in the liver. No lymph node metastasis was found in the peripancreatic, periaortic or aortocaval spaces. The pancreatic duct was dilated slightly. A CBD invasion could not be visualized by computed tomography. There were no signs of CBD dilatation and there were no abnormalities on both sides of intrahepatic bile duct (Fig. 2). Ultrasound guide fine needle aspiration biopsy was done. Pathologic report was adenocarcinoma of pancreas. A pre-operative CCRT was done on the patient. Taxol was injected for 3 hours, at a dose of 50 mg/m²/day, every other week total 5th cycle to function as the radiosensitizer. Simultaneously, the patient underwent 10 MeV photon radiotherapy by the 4 field

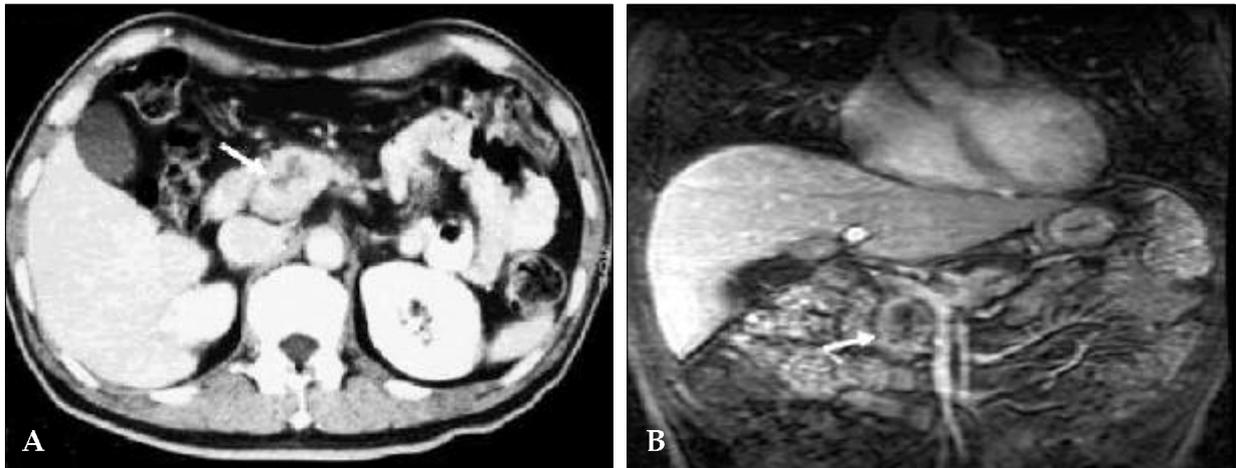


Fig. 1. A low density mass on pancreatic head portion that is 2.5×3.5 cm in size. There is portocaval lymph node involvement, the superior mesenteric vein is narrowed due to invasion by the tumor (white arrow).



Fig. 2. Compared to the previous MRI, the pancreatic head mass was decreased to a 2×3 cm size (white arrow). Abutting the duodenum and the SMV, at the portal vein confluent level, there is a possible short segment vessel invasion. There is no lymph node metastasis.

method, 180 cGy/d, 5 days/week for 5 weeks (total 4500 cGy). After completion of the Taxol chemotherapy, he was placed on Furtulon 600 mg/day oral medication for 30 days. After that, he took 2 cycles of Gemcytabine medication. 1 cycle was 1000 mg/m²/day intravenously for 3 days. Xeloda 1000 mg/day per oral was taken continually for 2 weeks. The operation findings were as follows; There was 2×3 cm size mass at the head portion of pancreas. The mass invaded the portal vein about 3 cm, but didn't invade the inner layer of the vessel. A radical pyloric preserving pancreaticoduodenectomy was done in-

cluding of 4 cm length of portal vein which included 3 cm of the SMV was resected. The inferior mesenteric vein was ligated. Reconstruction was done with using internal carotid vein.

The pathologic findings were as follows; The gross findings were the mass of pancreas was 2×3 cm of a whitish gray, hard and solid mass that had an irregular margin. The pancreatic duct was narrowed by the mass. The mass was separated from the distal resection margin of pancreas. The CBD and duodenal mucosa were normal. All resection margins were non-cancerous. The mass was microscopically diagnosed as a moderately

differentiated adenocarcinoma which was invading the peripancreatic soft tissue.

DISCUSSION

Pilepich, Miller and Kopelson^{7,8} first reported treatment using preoperative radiation therapy without chemotherapy in the early 1980s. This therapy resulted in 5-year survivals of 3 of the 10 patients who underwent a Whipple resection between 1972 and 1981. None of the other 7 patients survived beyond 17 months, although their median survival time was not reported. No chemotherapy was given in addition to the 4000-5000 cGy delivered by a 2-field technique using 200-cGy fractions. Ishikawa, et al.⁹ also reported a series of patients who had a preoperative radiation therapy without chemotherapy. A more recent analysis of 23 patients who were receiving preoperative radiation therapy revealed a 74% resectability rate and a significantly lower local recurrence rate than in patients undergoing surgery alone. However, the 3, 5-year survival rates were no different from those for surgery alone (28% vs. 32% and 22% vs. 26%, respectively). According to another report, the median survival was 20 months in those patients who were treated by pancreaticoduodenectomy and adjuvant therapy compared with 11 to 12 months in those who were treated by a pancreaticoduodenectomy alone.^{10,11} These differences resulted from a decrease of a local recurrence.¹²⁻¹⁵

Pancreatic adenocarcinoma is known to be notoriously resistant to chemotherapy. The best available strategies for an unresectable disease state includes a combination therapy using both chemotherapy and radiotherapy. Single-agent chemotherapy studies have shown that 5-fluorouracil seems to have the greatest effect on adenocarcinomas of the pancreas. The use of mitomycin-C or ifosfamide alone has shown only a modest effect. A combination of streptozotocin, mitomycin, and 5-FU (SMF) has been widely used. However this has failed to show a survival advantage over that using 5-FU alone or other 5-FU-containing regimens.¹⁶⁻¹⁹ A gastrointestinal Tumor Study Group trial using a combined modality approach using SMF and radiotherapy has

shown an improved survival rate over that using either chemotherapy or radiotherapy alone in the case of locally advanced unresectable adenocarcinomas of the pancreas.²⁰ In our case, we used Paclitaxel (Taxol) as a the radiosensitizer. Paclitaxel was discovered as part of a National Cancer Institute program in which the extracts of thousands of plants were screened for their anticancer activity. In 1963, a crude extract from the bark of the Pacific yew *Taxus brevifolia*, which is a scarce and slow-growing evergreen found in the old-growth forests of the Pacific Northwest, was found in preclinical studies to have a cytotoxic activity against many tumors.²¹

Paclitaxel enhanced microtubule assembly and inhibited the depolymerization of Tubulin, which can lead to bundles of microtubules in the cell. The cell becomes blocked during the G₂ and M phases of the cell cycle and cannot form a normal mitotic spindle and is unable to divide. Microtubules are essential cellular components and are required for the maintenance of cell shape, motility, transport between organelles, and cell division. The G₂ and M phases of the cell cycle, which are affected by the taxoids, are also extremely sensitive to radiation.^{22,23} Paclitaxel has recently been shown to act as a radiosensitizer in clinical studies involving patients who had non small cell lung cancer or primary brain tumors. In addition to its effect during radiation therapy by means of reoxygenation of hypoxic tumor cells. Tumor cell loss that is due to Paclitaxel-induced apoptosis results in improved oxygenation of the remaining neoplastic cells within a tumor probably because of an improved blood flow to the remaining cells.

In clinical trials, patients who had a variety of solid tumors including ovary, breast, and metastatic pancreatic adenocarcinomas have demonstrated objective responses to conventional therapy. Safran and colleagues²⁴ from the Brown University Oncology Group performed a Phase I study using Paclitaxel and concurrent radiation therapy in patients who had locally advanced pancreatic and gastric adenocarcinomas. The dose limiting toxicity level that caused abdominal pain, nausea and anorexia occurred at a dose of 60 mg/m²/week. Four objective partial responses which were determined radiologically were observed in

13 patients who had pancreatic cancer. Standard-fractionation preoperative radiation therapy was given over a 5.5 week period by 18-MeV photons using a four-field technique at a total dose of 50.4 Gy, which is the 95% isodose, at 1.8 Gy per fraction (28 fractions), 5 days/week. They underwent the operation for a planned pancreaticoduodenectomy after 5 weeks. Rapid fraction chemoradiation therapy was given over a 2 week period by 18-MeV photons using a four-field technique to a total dose of 30 Gy, which is the prescribed 95% isodose, at 3 Gy per fraction (10 fractions), 5 days/week.

Francis, et al.²⁵ discussed the advantages of preoperative chemoradiation: (1) All patients who had a resection received all of the components of multimodality therapy, and surgery was not delayed in any patient because of chemoradiation toxicity. The surgery that was performed after chemoradiation was well tolerated. (2) The overall treatment duration of the rapid-fraction program was significantly shorter than in the other two programs, and the toxicity was minimal despite the lack of supplemental enteral feeding in the these patients. (3) Twenty-four of 91 patients (26%) were found to have a progressive disease at restaging after the chemoradiation. These patients were spared an unnecessary laparotomy with its attendant morbidity, definable mortality, and frequently prolonged recovery. (4) There was a trend to see a decreased positive rate at the microscopic retroperitoneal margin positivity in the preoperative chemoradiation group, despite data that suggested a more locally advanced disease in these patients. Consistent with the low rate of a positive microscopic retroperitoneal resection margin, no patient in the preoperative chemoradiation group developed a local tumor recurrence.

The advantages of undertaking surgery first, followed by the selective use of postoperative chemoradiation in this group of 51 patients, include the following: (1) Of the nine patients who were found to have an unresectable disease, seven had extrapancreatic disease. These seven patients were not treated by local-regional therapy and were spared the potential toxicity of this therapy. (2) Seventeen of the 42 patients who had resections had a periampullary adenocarcinoma of nonpancreatic origin. Adjuvant chemoradiation is

of unproven value in patients who have such tumors. (3) In the 19 patients who received the standard-fraction postoperative chemoradiation, the toxicity level was acceptable and was no different from that when a similar regimen was given preoperatively. Because surgery was performed first, all patients had a jejunostomy tube and received enteral feeding during adjuvant therapy.

We administered preoperative chemoradiation for 5 weeks and a pancreaticoduodenectomy & superior mesenteric vein and portal vein resection was performed 4 months after diagnosis. A duodenum and common hepatic duct resection margin were diagnosed as being negative in frozen sections. The retroperitoneal resection margin and pancreatic resection margins also showed negative. We followed up the patient for 13 months without there being a recurrence.

In conclusion, preoperative chemoradiation is down staging, and improves the respectability.

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