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Intraoperative Irradiation Combined with Radical Resection for Cancer of the Head of the Pancreas

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Since December, 1976, intraoperative irradiation combined with resection for cancer of the head of the pancreas has been used in our clinic to prevent local recurrence. Thirty Gy of the electron beam from a linear accelerator were administered to the operative field including the celiac axis and mesenteric artery following pancreaticoduodenectomy. Results of the combined therapy in 12 patients were compared to results in 12 patients who underwent pancreaticoduodenectomy alone. The combined therapy group compared to pancreaticoduodenectomy alone showed improvement in the 1-year survival rate, but not in the 2-year survival rate. Autopsy of 3 paients who underwent the combined therapy did not reveal any involvement of the lymph nodes in the irradiation field. However, there was involvement of the lymph nodes around the aorta from the diaphragm above to the inferior mesenteric artery below (except in the irradiation field). Additionally, there were metastases to the liver in all autopsied patients and recurrence in the pancreatic remnant in 1 patient. In spite of the local effect of irradiation therapy, there was no prolongation of survival. These results suggest that treatment for carcinoma of the head of the pancreas should be intensified toward liver metastases and the lymph nodes around the aorta from the diaphragm above to the inferior mesenteric artery below.

Despite recent advances in diagnostic and surgical techniques, the results of treatment of carcinoma of the pancreas continue to be discouraging. Even if radical resection for pancreatic carcinoma is performed, local recurrence is very often found at autopsy. Especially in pancreatic cancer, elimination of malignant cells may not be possible by surgical resection. Since 1976, we have applied intraoperative irradiation for resectable pancreatic cancer. The results of this combined therapy, especially for carcinoma of the head of the pancreas, are presented.

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Methods and Materials

From January, 1966, to June, 1983, there were 144 patients with cancer of the periampullary region seen at our clinic and resection was performed on 88 patients (61%). Seventy-nine of the 144 patients had cancer of the head of the pancreas, 34 of whom underwent resection: pancreaticoduodenectomy for 28 patients and total pancreatectomy for 6 patients. Twelve of the 28 patients who underwent pancreaticoduodenectomy were treated with intraoperative irradiation therapy. In 47 patients with carcinoma of the distal common bile duct and papilla of Vater, combined therapy was perfomed on 11. The effect of intraoperative irradiation therapy on treatment of pancreatic cancer was evaluated by comparing the group with combined pancreaticoduodenectomy and intraoperative irradiation to the group with pancreaticoduodenectomy alone (control group) and to the group with carcinoma of the distal common bile duct and papilla of Vater.

Pancreatic cancer was classified from stage I to III, according to the Vermont Tumor Registry: stage I, tumor apparently localized in the pancreas; stage II, local extension of tumor to regional lymph nodes; and stage III, distant metastases [1].

The method of intraoperative irradiation therapy was as follows: After resection of the pancreatic le-

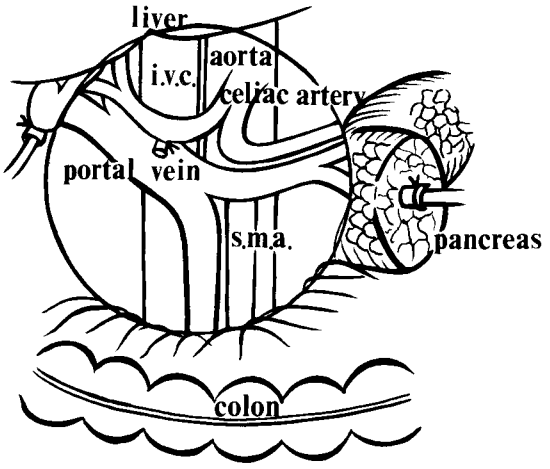

Fig. 1. The circle indicates the range of the irradiation field.

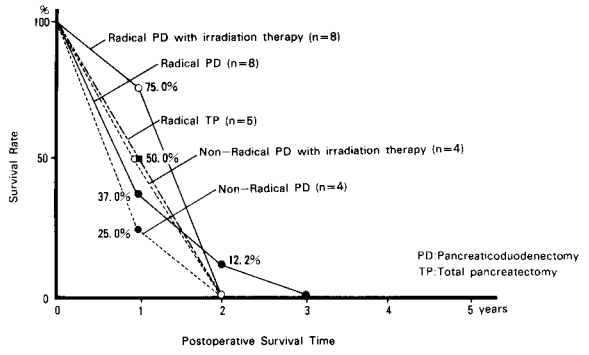

Fig. 2. Cumulative survival rate of patients with radical or non-radical resection for cancer of the head of the pancreas.

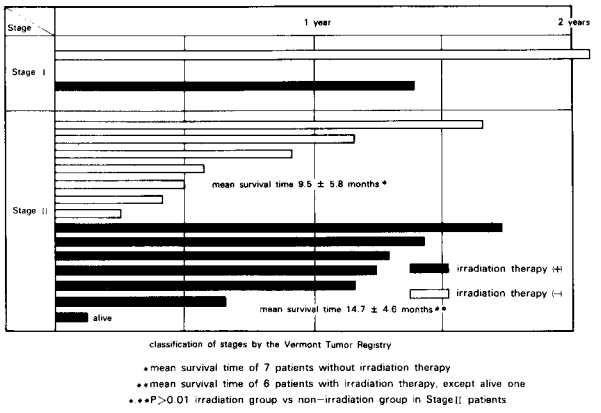

Fig. 3. Survival time according to cancer stage in patients with cancer of the head of the pancreas who have undergone radical pancreaticoduodenectomy.

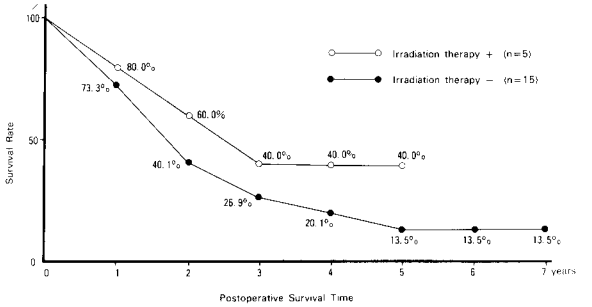

Fig. 4. Cumulative survival rate in patients who have undergone radical resection for cancer of the periampullary region, excluding pancreatic cancer. All patients have lymph node involvement.

sion, 30 Gy of electron beam with 8 MeV from a linear accelerator was administered to the operative field including the celiac axis and superior mesenteric artery. The pancreatic remnant and the bile duct were kept outside of the irradiation field (Fig. 1). The treatment cone was a 6–8-cm diameter circle. The electron beam can be sharply focused and concentrated within a depth of approximately 5 cm from the surface, thus minimizing unnecessary exposure to adjacent normal tissue. A sterilizing, cancericidal dose can be administered to the target mass with a sharp limitation. All patients were anesthetized by epidural anesthesia and endotracheal anesthesia with dinitrogen monoxide and oxygen.

Results

Survivors

Of the 28 patients with pancreaticoduodenectomy, there were 4 operative deaths for a 14% mortality rate; none were in the combined therapy group. There were no postoperative complications in the combined therapy group. As shown in Fig. 2, the cumulative survival rate of 8 patients who were treated by radical pancreaticoduodenectomy with intraoperative irradiation is compared to that of 8 patients with radical pancreaticoduodenectomy alone. It showed a markedly higher survival rate, 75% in the combined therapy group, at 1 year, but did not show any difference between the 2 groups at 2 years. Additionally, in Fig. 2 is shown the cumulative survival rate of 4 patients with, and 4 patients without irradiation therapy after palliative pancreaticoduodenectomy. There was no difference between the 2 groups. Figure 3 shows survival time related to therapy and stage of disease in 16 patients. In the stage II group, a significant ($p < 0.01$) prolongation of survival time was found in the combined therapy group. In Fig. 4, cumulative survival rate of patients after radical pancreaticoduodenectomy with or without radiotherapy for cancer of the distal common bile duct and papilla of Vater with involvement of lymph nodes is compared. The

survival rate of the combined therapy group was higher than that of the control group, but the numbers of the patients evaluated was too small for statistical comparison.

Autopsy Finding

Autopsy of 4 patients who underwent pancreaticoduodenectomy alone showed recurrence in the pancreatic remnant in 1 patient, metastasis to the liver in 3 patients and, in spite of dissection of the lymph nodes, involvement of lymph nodes at the mesenteric artery and celiac axis and around the aorta in all 4 patients. Autopsy of 3 patients who underwent combined therapy showed recurrence in the pancreatic remnant in 1, metastasis to the liver in all 3 patients, and involvement of lymph nodes around the aorta outside the irradiation field in all 3 and at the mesentery of the jejunum in 2 patients. Involvement of the lymph nodes and local recurrence were seldom found in the irradiation field for 5.2 to 21 months after combined therapy, but recurrences were found outside the irradiation field. As expected, this shows a therapeutic effect of intraoperative irradiation on the prevention of local recurrence in the irradiation field.

Discussion

The prognosis for patients with pancreatic cancer is extremely poor and there is not much agreement among surgeons as to the proper therapeutic approach to this type of cancer. Total pancreatectomy [2, 3] and regional pancreatectomy including resection and reconstruction of the portal vein and/or superior mesenteric artery [4] were suggested recently, but there still remain many problems in evaluating the results of these operations [4, 5].

The results of pancreaticoduodenectomy for pancreatic cancer have been unsatisfactory. One of the reasons for these disappointing results, we have noticed from autopsy findings, is local recurrence at the celiac axis and mesenteric radix. In this area, involvement of lymph nodes and single cancer cells or cancer cell clumps cannot always be removed by the surgical procedure alone. Therefore, as the first step, we have applied intraoperative irradiation to the celiac axis and mesenteric radix following pancreaticoduodenectomy. However, prolongation of survival in patients with pancreatic cancer did not result from this combined therapy, in spite of the local effects of irradiation therapy. At present, we are performing subtotal pancreatectomy followed by intraoperative irradiation with a more expansive irradiation field, including the lymph nodes around the aorta from the diaphragm above to the inferior mesenteric artery below. On the other hand, a beneficial therapeutic effect of the combined therapy was suggested in patients with carcinoma of the distal common bile duct or papilla of Vater.

No side effects were noticed postoperatively in patients who underwent the combined therapy. However, when irradiation is given over a more expansive field, some consideration should be given to the low tolerance of the ureter to a dose of 30 Gy as indicated by Sindelar et al. [7].

Regarding a suitable dose of intraoperative irradiation, our clinical experiences and experimental studies showed that at least 30 Gy was necessary as a cancericidal dose. Further, there were no serious pathological changes in major vessels with an irradiation dose of 30–40 Gy.

For prevention of recurrence in the pancreatic remnant, intraoperative irradiation toward the remnant may also be possible. However, our experimental study with dogs showed that an irradiation of 30 Gy of 8 MeV electron beams seriously damaged the exocrine gland of the pancreas, although the endocrine gland was relatively preserved. Further studies will be needed concerning this. At present, it would appear that subtotal pancreatectomy should be carried out whenever possible, because multicentricity of origin of the cancer appears to be rare except in areas immediately around the primary pancreatic cancer, and management of the diabetic state is difficult in most totally pancreatectomized patients. However, anticancer treatment toward metastases of the liver will remain to the last as a most important key point for the cure of pancreatic cancer.

Résumé

Depuis 1976, les auteurs ont associé l'irradiation per-opératoire à la duodéno-pancréatectomie céphalique pour tenter de prévenir la récidive locale du cancer de la tête du pancréas. Trente Gy provenant d'un accélérateur linéaire furent concentrés sur le champ opératoire, l'axe coeliaque, l'artère mésentérique après l'exérèse. Les résultats de ce traitement mixte pratiqué chez 12 malades ont été comparés à ceux d'une série de 12 malades qui avaient subi une simple exérèse. Le traitement mixte s'est soldé par une amélioration du taux de survie à un an alors que le taux de survie à deux ans n'a pas été modifié. L'autopsie de 3 malades qui avaient été traités par la méthode combinée a montré l'absence d'adénopathies malignes au niveau du champ opératoire alors que les ganglions juxta-aortiques au dessus du diaphragme et au dessous de l'artère mésentérique inférieure

étaient le siège de métastases associées dans les 3 cas à des métastases hépatiques et à une récidive au niveau de pancréas restant. La survie de ces malades n'avait pas été prolongée.

Ces résultats selon les auteurs invitent à étendre le traitement du cancer de la tête du pancréas aux ganglions péri-aortiques situés au dessus du diaphragme et au dessous de l'artère mésentérique inférieure.

Resumen

La irradiación intraoperatoria combinada con resección para cáncer de la cabeza del páncreas ha sido utilizada en neustra clínica desde diciembre de 1976, con el proposito de prevenir recurrencia local. Treinta Gy del haz de electrones de un acelerador linear fueron administrados al campo operatorio, incluyendo el tronco celíaco y la arteria mesentérica, a continuación de la pancreatoduodenectomía. Los resultados de la terapia combinada en 12 pacientes fueron comparados con los resultados en 12 pacientes sometidos a pancreatoduodenectomía solamente. El grupo de tratamiento combinado demostró mejor supervivencia a un año sobre el grupo con pancreatoduodenectomía solamente, pero no en la tasa de supervivencia a dos años. La autopsia de 3 casos que recibieron la terapia combinada demostró que no había invasión tumoral de los ganglios linfáticos en el campo irradiado. Sinembargo, había invasión de los ganglios alrededor de la aorta, desde el diafragma hasta la arteria mesentérica inferior, excepto en el campo irradiado. Además, se demostraron metástasis hepáticas en todos los casos y recurrencia en el remanente pancreático en un caso. A pesar del efecto local de la terapia de irradiación, no se observó prolongación de la supervivencia.

Estos resultados sugieren que el tratamiento del carcinoma de la cabeza del páncreas debe ser intensificado hacia el control de las metástasis hepáticas y de los ganglios periaórticos ubicados entre el diafragma y la arteria mesentérica inferior.

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Invited Commentary

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It is generally acknowledged that the treatment of pancreatic cancer is difficult and largely unsuccessful. The results of treatment utilizing standard techniques of surgery, radiotherapy, and chemotherapy have consistently been poor, offering at best only the expectations of modest prolongation of survival or temporary palliation of symptoms. The overall discouraging clinical outcome of the treatment of pancreatic cancer has led many practitioners to adopt a nihilistic attitude about the disease and consequently to avoid aggressive treatment. It is, therefore, encouraging to see attempts at the application of new therapeutic modalities in pancreatic cancer in hopes of adding to what is admittedly a very limited therapeutic armamentarium.

Interoperative radiotherapy (IORT) has engendered considerable recent enthusiasm as a potentially valuable innovation in cancer treatment [1, 2]. IORT allows direct appositional irradiation of intact neoplasms or resected tumor beds while allowing surgical shielding or displacement from the treatment volume of normal tissues or organs that potentially could be damaged by radiation therapy. Conventional irradiation of large abdominal fields is poorly tolerated because of gastrointestinal toxicity. IORT theoretically can allow the delivery of tumoricidal doses to the adbomen or retroperitoneum while minimizing the risk of radiation toxicity to normal organs or tissues [3]. However, it is unknown at present whether IORT does lead to an