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Treatment of Locally Unresectable Carcinoma of the Pancreas

Woo Yoon Park, M.D., Moon June Cho, M.D., Sung Whan Ha, M.D.
Charn Il Park, M.D., Kuk Jin Choe, M.D. *
Kuhn Uk Lee, M.D.* Noe Kyung Kim, M.D.**

Department of Therapeutic Radiology, Department of Surgery, Department of Internal Medicine,** College of Medicine, Seoul National University*

From January, 1981 to December, 1985, 22 patients with locally unresectable carcinoma of the pancreas were treated in the Department of Therapeutic Radiology, Seoul National University Hospital. Radiation was given in two split courses; each consisting of 2000 cGy over two weeks sepatated by two-week rest period. 5-FU was administered on the first three days of each radiation therapy course. FAM (5-fluorouracil, adriamycin, mitomycin) was administered for maintenance chemotherapy. For pain control, complete relief was obtained in 22% (4/18) of patients and partial relief in 39% (7/18). Median survival was 31 weeks.

Pretreatment performance status was the only statistically significant prognostic factor.

Key Words: Carcinoma of the pancreas, Radiation therapy, Chemotherapy.

INTRODUCTION

Carcinoma of the pancreas is an insidiously developing, relentlessly progressive, and nearly universally fatal malignancy arising in the epigastric retroperitoneum. Carcinoma of the pancreas diagnosed at an early stage and localized to the pancreatic parenchyma is the only clinical circumstance in which the disease is amenable to potential cure. Unfortunately, more than 85% of patients have surgically incurable disease at the time of diagnosis. The reported 5-year survival rate for surgically resectable pancreatic carcinoma is less than 5%; this has not been improved by superradical surgical removal of the tumor[1,2]. Palliative treatment for metastatic disease has been particularly frustrating since there is no evidence that single or multi-drug chemotherapy contributes to prolongation of survival.

Although seldom diagnosed at a stage suitable for potentially curative surgery, pancreatic carcinoma will appear in about 30% of patients as locally unresectable disease without evidence of distant metastasis[3]. Such a presentation would raise the hope of possible utility of regional treatment such as radiation therapy.

A recent study by the Gastrointestinal Tumor Study Group (GITSG) demonstrated prolonged survival when surgery was followed by radiation therapy and 5-fluorouracil (5-FU) administation[4]. Our study evaluates the treatment results of radiation therapy combined with 5-fluorouracil for locally unresectalbe pancreatic carcinoma at the Department of Therapeutic Radiology, Seoul National University Hospital from January, 1981 through December, 1985.

PATIENT SELECTION AND METHODS

Between January, 1981 and December, 1985, 27 patients with carcinoma of the pancreas were seen at the Department of Therapeutic Radiology, Seoul National University Hospital. Of these, 5 patients, who received palliative radiation therapy only without chemotherapy, were excluded from this study. 6 patients were dignosed by only clinical grounds without histologic confirmation. Diagnostic and metastatic work up was performed by physical examination, blood chemistries, computerized tomography (CT), ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), radionuclide studies and/or tumor markers.

Radiation was delivered by 6 or 10MV linear accelerator and was given in two split courses; each consisting of 2000 cGy given over 2 weeks

Table 1. Patient Characteristics

Characteristic	No. of patients (%)
Sex	
Male	13 (59)
Female	9 (41)
Age (years)	
Median	53
Range	40 – 66
Initial performance status	
ECOG 0	1 (5)
1	8 (36)
2	10 (45)
3	3 (14)
4	0
Prior surgery	
Bypass surgery	13 (59)
Exploration only	2 (9)
Other	1 (5)
None	6 (27)
Primary site	
Head	15 (68)
Body or Tail	7 (32)
Symptoms	
Abdominal pain	16 (73)
Weight loss	15 (68)
Anorexia	10 (45)
Weakness	10 (45)
Jaundice	9 (41)
Back pain	8 (36)
Indigestion	5 (23)
Diabetes	
Yes	6 (27)
No	16 (73)
CEA at the time of study entry	
Under 5.0ng/ml	8 (36)
5.0 –10.0ng/ml	3 (14)
Over 10.0ng/ml	1 (5)
Unknown	10 (45)

(200 cGy/day 5 days/week) separated by two-week rest period. Treatment fields were AP and PA covering the tumor bed and the entire pancreas as defined by computed tomography.

5-FU was administered by intravenous bolus at a dose of 500 mg/M²/day on the first three days of each 2000 cGy radiation therapy course.

Maintenance FAM chemotherapy was initiated four weeks after completion of the last course of radiation until tumor progression was evident or for 2 years if not.

Table 2. FAM Chemotherapy Regimen Drug Schedule

Drug	Weekly schedule	
	Dose	Days
5-Fluorouracil	600mg/m² IV	1, 8, 26, 36
Doxorubicin	30mg/m² IV	1, 29
Mitomycin-C	10mg/m² IV	1
	Cycle repeated every 56 days	

Table 3. Treatment Completion Status

	No. of patients (%)
Began treatment	22 (100)
Completed course 1	19 (86)
Completed course 2	12 (55)
Began maintenance therapy	8 (36)

RESULTS

In many patients therapy was prematurely discontinued or maintenance chemotherapy was not given, in the main, because of the appearance of distant metastasis or severe general deterioration of the patient (Table 3).

Toxicity (Table 4)

Nausea and vomiting were frequent complications. These problems, however, were seldom severe not to be controlled by antiemetics. Hematologic depression was observed in some patients. But no treatment was interrupted due to these problems.

Pain control

Complete relief was obtained in 22% (4/18) of patients and partial relief in 39% (7/18). Thus, it was possible to reduce the dosage or alter the class of analgesics in 62% (11/18) of patients who used medication to control pain (narcotic analgesics, or nonnarcotics).

Survival

Survival period was measured from the day at which locally unresectable disease was confirmed surgically or from the day of initiation of irradiation in patients who were not operated on. Survival ranged from 2 to 143 weeks with a median survival of 31 weeks. Survival curve were calculated by the life-table method of Kaplan-Meier (Fig. 1).

The Log-Rank test was used to study the prog-

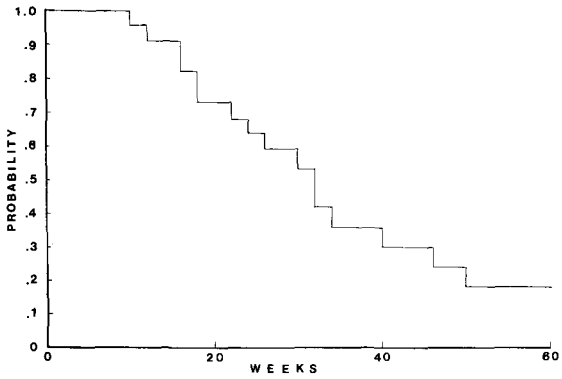

Fig. 1. Acturial overall survival of patients with locally unresectable carcinoma of the pancreas (N=22).

Table 4. Toxicities Related to Treatment

Degree	No. of patients (%)
Nausea	13 (59)
Vomiting	6 (27)
Diarrhea	2 (9)
Anemia	
9.5 – 11.0g%	4 (18)
Under 9.5g%	4 (18)
Leukopenia	
2,000 – 4,000/mm^3	5 (23)
Under 2,000/mm^3	0
Thrombocytopenia	
50,000 – 90,000/mm^3	1 (5)
Under 50,000/mm^3	0

Table 5. Prognostic Factors

Factors	P – value
Performance status	
ECOG 0 – 1	< 0.05
2 – 3	
Bypass surgery	
Performed	NS
None	
Primary site	
Head	NS
Body or Tail	
Diabetes	
Yes	NS
No	
CEA level	
0.5ng/ml	NS
> 0.5ng/ml	

* NS : Not significant

nostic influence of pretreatment variables on survival. Bypass surgery, primary site, diabetes, and pretreatment CEA level did not have significant survival influences. Pretreatment performance status (ECOG 0 & 1 vs. 2 & 3) was the only statistically significant prognostic variable in this study ($p<0.05$).

DISCUSSION

In 1922, Richards[5] reported the use of external beam radiation therapy for pancreatic carcinoma, describing excellent pain relief in two of the three treated patients. There were anecdotal case reports of effective palliation of pain with external irradiation in the 1920s and 1930s. However, the deep location of the pancreas and its intimate anatomic association with the bowel, liver, kidneys, stomach, and spinal cord largely precluded the delivery of definitive doses of external beam irradiation prior to the megavoltag era[6,7,8,9].

Hence, cancer of the pancreas acquired a reputation of being radioresistant. The development of megavoltage X-rays (over 1MV) facilitated the use of high doses of radiation to treat deep-seated tumors including pancreatic carcinoma, with relative sparing of adjacent normal tissues. The first megavoltage serises by Philips reported effective palliation of symptoms in 25% of patients with doses of 4400 to 5000 roentgens over 4 weeks[10]. A dose-response relationship for unresectable pancreatic carcinoma to megavoltage radiation therapy may be suggested by comparing the various radiation treatment series of patients using palliation of symptoms and overall survival as the end points of treatment[11,12]. The relatively low doses of external beam irradiation (4000-5000 rad) that may be safely delivered to the pancreas can achieve some degree of palliation (20-40%) but fail to affect survival[13,14,15].

Chemotherapy combined with radiation therapy has been used in carcinoma of the pancreas with some success in prolonging survival and providing palliation of symptoms in locally advanced unresectable disease. In 1958 Heidelberger et al[15] demonstrated that regression of certain transplanted animal tumors was enhanced by the addition of 5-fluorouracil (5-FU) to radiation therapy. In a prospective trial at the Mayo Clinic, 64 patients

with locally advanced unresectable pancreatic carcinoma were given 3500 to 4000 rad external beam irradiation and were allocated randomly to receive 5-FU or placebo.

The patients treated 5-FU in combination with radiotherapy had a mean survival of 10.4 months, significantly superior to the survival time of 6.3 months in the radiotherapy alone group[16].

In 1973, Haslam et al[8] reported 23 patients who had regional pancreatic adenocarcinoma and were treated with curative intent. Radiation therapy was administered in three series of 2000 rad in ten fractions spaced by intervals of 2 weeks and the total dose ranged from 5040 to 6680rad. In three of these patients treatment could not be completed. Thirteen of the patients received 5-fluorouracil during irradiation. Six additional patients with widespread disease were treated as well. Median survival of the 23 patients with localized disease was 7.5 months, with 6 patients alive at 30 months.

To determine whether a therapeutic advantage actually exists for high dose radiation compared to lower doses of radiotherapy, the Gastrointestinal tumor study group performed a prospective study in which 84 patients with locally unresectable pancreatic adenocarcinoma were allocated randomly to receive high-dose radiation therapy (6000rad) alone, high-dose radiation (6000rad) and 5-FU, or low-dose radiation (4000rad) and 5-FU[4]. The median time to disease progression for patients with 6000rad radiotherapy alone was 13 weeks, compared to 33 weeks with 6000rad and 5-FU and 30 weeks with 4000 rad radiotherapy alone was 23 weeks, however, the median survival time was 40 weeks for patients given 6000rad and 5-FU, 42 weeks for patients given 4000rad and 5-FU.

The optimal chemotherapy regimen to be used in combination with radiation therapy has yet to be determined. The addition of semustine to 5-FU and 6000rad of external beam irradiation by the Southwest Oncology Group[17] in an uncontrolled series failed to improve the results obtained by the GITSG for 5-FU with irradiation. An attempt to exploit the potential radiosensitizing effects of doxorubicin was proved to be unsuccessful when the drug was given with 4000rad of external beam radiation in a trial by the GITSG[18]. The doxorubicin-radiotherapy treatment regimen was associated with a median survival of 33 weeks and severe toxicities. It is of considerable interest to observe whether such results will improve if radiation therapy is combined with more potent drug combinations, such as the SMF (streptozotocin, mitomycin, 5-fluorouracil) or FAM (5-fluorouracil, adriamycin, mitomycin) regimens.

Our study utilized FAM as maintenance chemotherapy. But our results are inferior to those of GITSG. In our study, comparing the results of GITSG, premature discontinuation of radiation therapy was more frequent because of the appearance of distant metastases, severe general deteoration or poor economic status. In GITSG the strict criteria of locally unresectable disease based on laparotomy eliminated patients with small hepatic or peritoneal metastasis that might not have been detected by noninvasive studies. The GITSG protocol evaluated on group of patients with more favorable prognosis than would have been the case had selection of nonresectable tumors been made solely on clinical grounds.

In our study, some of the patients without histologic diagnosis might have had already regional or distant metastasis.

There is at present no standard treatment regimen for patients with advanced carcinoma of the pancreas. Improved means of delivering ionizing radiation and new chemotherapeutic agents need to be developed and evaluated in patients with good performance status. Careful delineation of tumor margins, precision treatment planning, and precision dose delivery can minimize damage to adjacent normal tissues. Interstitial implantation and intraoperative electron beam therapy are being studied as methods of accurate dose delivery. Improvement in radiotherapy through hyperfractionation and high linear energy transfer (LET) radiation to minimize the oxygen enhancement ratio (OER) could be used for enhancing the therapeutic ratio. Combined modality regimens may have much to offer in terms of improved palliation and survival for patients with locally advanced adenccarcinoma of the pancreas.

REFERENCES

1. **Zimmerman SE, Smith FP, Schein PS:** Chemotherapy of pancreatic carcinoma. Cancer 47:1724-1728, 1981.
2. **Morrow AR, Hilaris B, Brenna ME:** Comparison of convention surgical resection, radioactive implantation, and bypass procedures for exocrine carcinoma of the pancreas 1975-1980. Ann Surg 199:1-5, 1984.
3. **Howard JM, Jordan GL:** Cancer of the pancreas.

Curr Probl Cancer 2:1-52, 1977.
4. **The Gastrointastinal Tumor Study Group:** Therapy of Rocally unresectable pancreatic carcinoma: A randomized comparison of high dose (6,000rads) radiation alone, moderate dose radiation (4,000rads+5-Fluorouracil), and high dose radiation+5-Fluorouracil. Cancer 48:1705-1710, 1981.
5. **Richards GE:** *Possibilities of roentgen-ray treatment in cancer of the pancreas. Am J Roentgenol 9:150-152, 1922.*
6. **Dobelbower RR Jr, Strubler KA, Kutcher G, et al:** Precision radiotherapy for cancer of the pancreas: Techniques and results. Int J Radiat Oncol Biol Phys 6:1127-1133, 1981.
7. **Merritt EA, Rathbone RR:** The diagnosis and roentgen treatment of carcinoma of the head of the pancreas. Radiology 26:459-464, 1936.
8. **Haslam JB, Cavanaugh PJ, Stroup SL:** Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. Cancer 32:1341-1345, 1973.
9. **Komaki R, Wilson JF, Cox JD, et al:** Carcinoma of the pancreas: Results of irradiation for unresectable lesions. Int J Radiat Oncol Biol Phys 6:209-212, 1980.
10. **Philips R:** Principles and results of palliative radiotherapy in nonresectable cancer. Med Clin North Am 40:807-820, 1956.
11. **Billingsley JS, Bartholomew LG, Childs DS:** A study of radiation therapy in carcinoma of the pancreas. Proc Staff Meet Mayo Clin 33:426-430, 1958.
12. **Dobelbower RR, Borgelt BB, Strubler KA, et al:** Precision radiotherapy for cancer of the pancreas: Technique and results. Int J Radiat Oncol Biol Phys 6:1127-1133, 1980.
13. **Miller TR, Fuller LM:** Radiation therapy of carcinoma of the pancreas. Am J Roentgenol 80:787-792, 1958.
14. **Dobelbower RR, Jr.:** The radiotherapy of pancreatic cancer. Sem Oncol 6:378-389, 1979.
15. **Heidelberger C, Griesbach L, Montg BJ, et al:** Studies on fluorinated pyrimidines. Cancer Res: 18:305-317, 1958.
16. **Moertel CG, childs DS, Reitemeier RJ, et al:** Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 2:865-867, 1969.
17. **McCracken JD, Ray P, Heilbrun LK, et al:** 5-Fluorouracil, methyl CCNU, and radiotherapy with or without testolactone for localized adenocarcinoma of the exocrine pancreas. A Southwest Oncology Group study. Cancer 46:1518-1522, 1980.
18. **Gastrointestinal Tumor Study Group:** Radiation therapy combined with adriamycin or 5-fluorouacil for the treatment of locally unresectable pancreatic carcinoma. Cancer 56:2563-2568, 1985.

= 국문초록 =

국소적으로 절제불가능한 췌장암의 치료

서울대학교 의과대학 치료방사선과학교실*

박우윤 • 조문준 • 하성환 • 박찬일

외과학교실**

최 국 진 • 이 건 욱

내과학교실

김 노 경

1981년 1월부터 1985년 12월까지 서울대학교병원 치료방사선과에서 22명의 국소적으로 절제불가능한 췌장암 환자를 방사선과 약물요법으로 치료하였다. 방사선은 2주의 간격을 두고 2000 cGy씩 총 4000 cGy를 조사하였으며 5-FU (5-fluorouracil)는 방사선 조사의 각 course의 첫 3일에 걸쳐 주입하였다. 방사선치료 종료 4주후 부터 FAM (5-FU, Adriamycin, Mitomycin)을 지속요법으로 사용하였다. 통증 완화는 22%(4/18)에서 완전관해를, 39%(7/18)에서 부분관해를 보였다. 생존기간의 중앙치는 31주 였으며 치료전 Performance status가 중요한 예후인자였다. 국소적으로 절제불가능한 췌장암의 치료에 있어서 방사선과 FAM regimen의 병용은 통증완화 및 생존기간의 연장에 기여할 수 있는 바 이에 대한 보다 많은 연구와 고찰이 있어야 하겠다.