

Treatment of Locally Advanced Pancreatic Cancer

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From January 1981 to December 1991, forty patients with localized advanced carcinoma of the pancreas were treated at the Department of Therapeutic Radiology, Seoul National University Hospital. The treatment protocol consisted of two split course external radiation therapy with each 2000 cGy over two weeks separated by two week rest period. Intravenous 5-fluorouracil (5-FU) was administered on the first three days of each radiotherapy course. Twenty three of these patients were treated by maintenance 5-FU or FAM (5-FU, adriamycin, mitomycin) chemotherapy. Median survival was 9 months and the 2-year survival rate was 10.0%. Good prognostic indicators were good performance status, palliative bypass surgery and tumor located in the head of pancreas.

Key Words: Carcinoma of the pancreas, Radiotherapy, Chemotherapy

INTRODUCTION

Pancreatic cancer is a highly malignant disease because it is technically unresectable due to local extension of disease and spreads frequently through blood stream or peritoneum. Furthermore, most patients have no specific symptoms or signs, which makes early detection of lesion difficult. Therefore resectability with curative intent varies from 10% to 25% of initially presented patients with operative mortality rates of 10% to 30%¹⁾. The main surgical options of locally advanced tumor are palliative biliary bypass surgery alone or in combination with elective gastroenterostomy.

Given the clinical limitations of variable individual modalities (surgery, radiation therapy, and chemotherapy), increasing attention has been paid to combination therapies. Among the many chemotherapeutic agents, 5-FU is the only one proven to be effective when combined with radiotherapy. Combined chemoradiotherapy using 5-FU was performed as a standard treatment in advanced pancreas cancer for over 10 years in this hospital and the treatment results were analyzed.

MATERIALS AND METHODS

From January 1981 to December 1991, 79 patients with localized unresectable pancreatic cancer were treated at the Department of Therapeutic Radiology, Seoul National University Hospital. Among them, 39 patients who received incomplete radiotherapy or palliative radiotherapy without concur-

rent chemotherapy were excluded from this study. This study is based on the remaining 40 patients.

Thirty patients of them were diagnosed with pathologic examination. Most of these patients were proven as adenocarcinoma except two; mucinous adenocarcinoma in one and papillary adenocarcinoma in the other. Ten patients were diagnosed on only clinical ground without histologic confirmation. Diagnostic work-up was performed by physical examination, blood chemistries, upper gastrointestinal study, ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP), computerized tomography (CT), magnetic resonance imaging (MRI), and tumor markers.

The patient characteristics are shown in Table 1. The age ranged from 27 to 72 years and peak incidence occurred in sixth decade. The follow-up period ranged from 1 to 33 months and median follow-up was 8 months. Palliative bypass surgery, including procedures such as Roux-en Y cholecystojejunostomy, cholecystoduodenostomy, choledochoduodenostomy, choledochojejunostomy and gastroenterostomy was done in 23 patients, and 4 patients had taken the exploration laparotomy only. No surgical option was performed in 13 patients.

The forty patients were treated according to a protocol consisting of 40 Gy external irradiation by split course concomitant with intravenous 5-fluorouracil (5-FU) 500 mg/m² given in a bolus injection 4 hours before irradiation on each of the first 3 days of each treatment course. The daily irradiation fraction size was 2 Gy. The interval

Table 1. Patient Characteristics (n=40)

Characteristic	No of patients (%)
Age (year)	
range	27~72
median	56
Sex	
male	29(72.5)
female	11(27.5)
ECOG status	
0~1	16(40.0)
2~3	24(60.0)
CEA (ng/ml)	
≤2.5	6(15.0)
>2.5	17(42.5)
not checked	17(42.5)
Surgery	
none	13(32.5)
exploration	4(10.0)
bypass	23(57.5)
Tumor size (cm)*	
≤5	11(27.5)
>5	23(57.5)
unknown	6(15.0)
Site	
head	33(82.5)
body	5(12.5)
tail	2(5.0)

*maximum diameter

between the 2 courses was 2 weeks.

Radiation was delivered by 6 or 10 MV linear accelerator. The majority of number of treatment ports were three, but occasionally two or four ports were used. The target volume that received 40 Gy was planned to include the primary tumor mass and regional lymph nodes as shown on CT with an adequate margin. Maintenance single 5-FU (n=14) or FAM (5-FU, adriamycin, mitomycin) (n=9) chemotherapy was initiated four weeks after completion of the last course of radiation and continued for two years or until tumor progression was evident. In general, during the early years of this study, FAM chemotherapy was used for chemotherapy and in the later years it was replaced by 5-FU chemotherapy. Maintenance chemotherapy could not be performed in 17 patients because of poor performance status or prolonged leukopenia.

The survival periods were measured from the day of initiation of irradiation and survival rate was calculated by Kaplan-Meier method²⁾. The log-rank test³⁾ was used to evaluate the prognostic influence of pretreatment variables on survival.

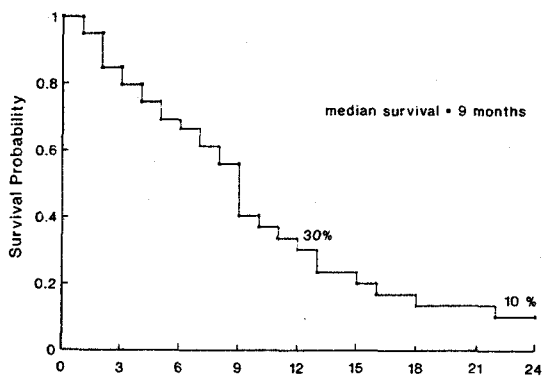


Fig. 1. Overall survival (N=40).

RESULTS

The data of 40 patients who had completed external radiotherapy concomitant with 5-FU chemotherapy were reviewed. During the follow-up period five patients were lost and three are alive. In eight patients maintenance chemotherapy was prematurely discontinued because of severe deterioration of general condition. Mild complications such as nausea, vomiting or diarrhea were reported in 21 patients at some time during treatment.

Complete and partial relief of pain were obtained in 30% (n=12) and 40% (n=16) of the patients, respectively, and it was possible to reduce the dosage of or change to the less potent analgesics in patients who used medication for pain control.

Overall survival ranged from 1 to 33 months with a median of 9 months. Survival rate is displayed in the Fig 1. Actuarial 1-year and 2-year survival rates were 30% and 10%, respectively.

The prognostic influence of pretreatment variables on survival was evaluated (Table 2). Patients in good performance status (ECOG 0 & 1) had better prognosis than those in poor performance status (ECOG 2 & 3) (Fig. 2). Two-year survival rate was 16.1% in 16 patients with ECOG 0 & 1 and 6.9% in 24 patients with ECOG 2 & 3 (p=0.04). Bypass surgery and tumor located in the head had favorable influence on the survival (Fig. 3 & 4). Two year survival was 17.5% in 23 patients with bypass surgery, and none of 17 patients who were not treated by bypass surgery survived 2 years (p=0.01). Two-year survival of 33 patients whose tumor located in the head of pancreas was 12.1%, and none of 7

Table 2. Prognostic Factors

Factor	No of pts	2-yr survival(%)	p-value
Sex			
male	29	7.7	NS*
female	11	17.9	
ECOG status			
0~1	16	16.1	0.04
2~3	24	6.9	
CEA (ng/ml)			
≤2.5	6	20.0	NS
>2.5	17	7.3	
Surgery			
none or exploration	17	5.9	0.01
bypass	23	17.5	
Tumor size (cm)**			
≤5	11	14.0	NS
>5	23	10.9	
Tumor site			
head	33	12.1	0.01
body or tail	7	0	

*NS: Not significant

**maximum diameter

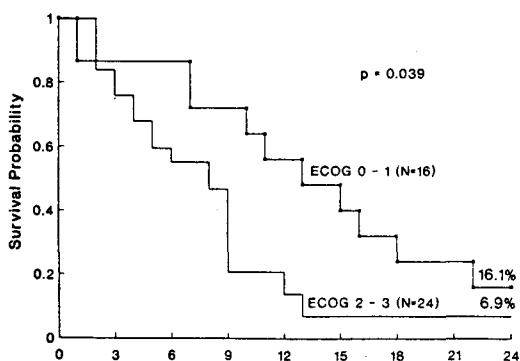


Fig. 2. Survival by ECOG status.

patients whose tumor located in the body or tail of pancreas survived 2 years ($p=0.01$). No significant difference was shown between the subgroups classified by sex, pretreatment CEA level and tumor size.

Survival of patients treated with maintenance chemotherapy was not different comparing with patients who were not treated with it. Among patients who received maintenance chemotherapy, there was no significant difference in survival between the patients treated with FAM and those treated with 5-FU.

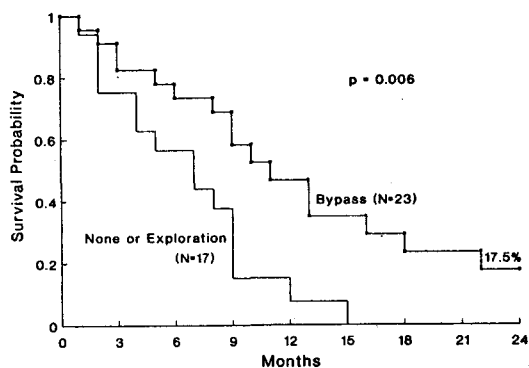


Fig. 3. Survival by surgery.

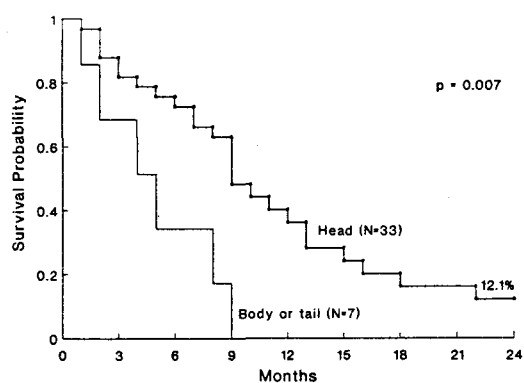


Fig. 4. Survival by tumor site.

DISCUSSION

The incidence of pancreatic cancer is currently increasing and ranks tenth in Korea as a cause of cancer death⁴). Although diagnostic methods have improved, early diagnosis of pancreatic cancer in a early stage is still uncommon due to a lack of specific symptoms and the rapid course of the disease. In spite of advances in surgery, radiation therapy, and chemotherapy, less than 2% of patients survive five years after diagnosis^{5,6}). Most patients survive less than one year. In a limited number of patients, surgical resection in early stage offers a potentially curative treatment option.

A combination of radiotherapy and chemotherapy was reported to result in a better median survival than radiotherapy alone by Moertel⁷) in 1969 and by Haslam⁸) in 1973. The treatment for locally advanced, unresectable pancreatic carcinoma remains radiation therapy in combination

with 5-FU, first described at Mayo clinic in 1969. It has been reported that combined external beam radiation with 5-FU resulted in median survival of 10.4 months compared with 6.3 months in external beam radiation therapy only.

In 1981 the Gastrointestinal Tumor Study Group (GITSG) published the results of a randomized study⁹⁾ which compared high dose radiation alone (60 Gy), high dose radiation therapy (60 Gy) plus concomitant and subsequent 5-FU, and moderate dose radiation therapy (40 Gy) plus concomitant and subsequent 5-FU. The two combined modality arms of the study involving 194 patients showed a median survival of 10 months, whereas in the radiation alone group median survival was 5.5 months.

An Eastern Cooperative Oncology Group (ECOG) randomized study¹⁰⁾ on 91 patients, however, showed that combined modality treatment was no better than 5-FU alone (median survival 8.3 months vs 8.2 months).

In 1988 randomized trial of the GITSG¹¹⁾ compared the survival of patients treated with multidrug chemotherapy, SMF (streptozotocin, mitomycin, and 5-FU) versus radiation combined with 5-FU followed by the same three drug SMF combination. In 43 patients, an improved median survival for the combined modality therapy (42 weeks) compared with chemotherapy alone (32 weeks) was demonstrated. Overall survival following combined modality treatment (41% at 1 year) was significantly superior to SMF chemotherapy alone (19% at 1 year) by a two-tailed log-rank test ($p < 0.02$). Thereafter, many series^{12,13,14)} have confirmed that survival rate for combined radiation and chemotherapy for locally unresectable pancreatic cancer is better than that of radiation therapy alone or chemotherapy alone.

The aim of our study is to confirm the results of combined modalities and find out prognostic factors. In our study, median survival is 9 months which is comparable to 9.6 months with 4000 cGy and 5-FU and 9.2 months with 6000 cGy and 5-FU in GITSG. 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 and the patients was followed up from the day of laparotomy. Whereas, in this study, only the patients who had completed the combined radiation therapy with concomitant chemotherapy were included and follow-up was based on the initial day of external radiation therapy.

Among the three patients who survived more than 2 years, two were dead at 28 and 33 months and the other one patients is alive for 28 months, whose pathologic type is papillary adenocarcinoma, well differentiated. It is likely that pancreatic cancer other than ductal adenocarcinoma, such as papillary cystic adenocarcinoma, often show a more indolent course and may remain in local area for many years¹⁵⁾. Analysis for prognostic factor shows that patients with tumors located at the head of pancreas have significantly better survival ($p < 0.007$), and it is probably caused by the fact that generalized peritoneal involvement is more common with carcinoma of the body and tail than with carcinoma of the head and by the fact that carcinoma of the head of pancreas raise the obstructive hepatobiliary symptoms earlier than in carcinoma of other sites¹⁶⁾.

From the above poor results, it is clear that current approaches to the treatment of pancreatic cancer are inadequate. Surgery offers a small chance of cure for localized tumors, but the probabilities of distant metastasis and locoregional recurrence remain unacceptably high. At this time, treatment with radiation therapy and chemotherapy does not promise cure, but only offers palliation, slight prologation of survival, and less morbidity. There is evidence that a combination of surgery and intraoperative and external beam radiation therapies may be required to achieve better local control. In the Massachusetts General Hospital^{17,18)} and Mayo clinic¹⁹⁾ studies combining external beam and intraoperative irradiation, local tumor control has been improved and median survival is approximately 12 months, and the 2-year survival rate varies from 12% to 55%. Unfortunately, the lack of effective systemic treatment to prevent or control distant metastatic disease has blunted the clinical effect of these therapeutic advances. Future prospects must grow out of continued trials of systemic treatment in conjunction with appropriate local modalities.

REFERENCES

1. Brennan MF, Kinsella TJ, Casper ES: Cancer of the pancreas. "In" Cancer, 4th, DeVita VT, Hellman S, Rosenberg SA, Philadelphia, JB Lippincott, 1993, 849-877
2. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 58:457-481, 1958
3. Peto R, Pike MC, Armitage P, et al: Design and

- analysis of randomized clinical trial requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 35:1-39, 1977
4. 보건사회부: 한국인 암등록 조사자료 분석보고서, 1991
 5. Gudjonsson B: Cancer of the pancreas: 50 years of surgery. *Cancer* 60:2284-2303, 1987
 6. Connoily MM, Dawson PJ, Michelassi F, et al: Survival in 1001 patients with carcinoma of the pancreas. *Ann Surg* 206:366-373, 1987
 7. Moertel CT, Childs DS, Reiteir RJ, et al: Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* 2:865-867, 1969
 8. Halsam GB, Cavanaugh PJ, Stroup SL: Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. *Cancer* 32:1341-1345, 1973
 9. Gastrointestinal Tumor Study Group: Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads+5-fluorouracil), and high dose radiation+5-fluorouracil. *Cancer* 48:1705-1710, 1981
 10. Klaassen DJ, MacIntyre JM, Catton GE, et al: Treatment of locally unresectable cancer of the stomach and pancreas: A randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 3: 373-378, 1985
 11. Gastrointestinal Tumor Study Group: Treatment of locally unresectable carcinoma of the pancreas: Comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *JNCI* 80:751-755, 1988
 12. Park WY, Cho MJ, Ha SW, et al: Treatment of locally unresectable carcinoma of the pancreas. *J Korean Soc Ther Radiol* 4:141-145, 1986
 13. Treurniet Ad, Mierlo MJM: Localized unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 18: 59-62, 1990
 14. Gastrointestinal Tumor Study Group: Radiation therapy combined with adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreas carcinoma. *Cancer* 56:2563-2568, 1985
 15. Sclafani LM, Reuter VE, Coit DG, et al: The malignant nature of papillary and cystic neoplasms of the pancreas. *Cancer* 68:153-158, 1991
 16. Gunderson LL, Willett CG: *Pancreas and hepatobiliary tract. "In" Principles and practices of radiation oncology*, 2ed, Perez CA, Brady LU, Philadelphia, JB Lippincott, 1992, 985-999
 17. Roldan GE, Gunderson LL, Nagorney DM, et al: External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer* 61:1110-1116, 1988
 18. Tepper JE, Nardi GL, Suit HD: Carcinoma of the pancreas. *Cancer* 37:1519-1524, 1976
 19. Pilepich MV, Miller HH: Preoperative irradiation in carcinoma of the pancreas. *Cancer* 46:1945-1950, 1980

＝국문초록＝

국소적으로 진행된 췌장암의 치료

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김 대 응 · 하 성 환

1981년 1월부터 1991년 12월까지 서울대학교병원 치료방사선과에서 방사선치료를 받은 40명의 국소적으로 절제불가능한 췌장암 환자를 대상으로 후향적 분석을 실시하였다. 방사선치료를 2주의 간격을 두고 2000 cGy씩 총 4000 cGy를 조사하고 5-FU (5-fluorouracil)를 방사선조사의 각 course의 첫 3일에 걸쳐 투여한 40명의 모든 환자에 대해 분석을 하였으며 그중 23명의 환자는 방사선치료 4주 후부터 5-FU 단독 혹은 FAM (5-FU, Adriamycin, Mitomycin)을 유지요법으로 시행하였다. 생존의 중앙치는 9개월이며, 2년 생존율은 10.0%이었다. 통증완화는 70.0%에서 완전 혹은 부분관해를 보였다. 치료전 performance status가 중요한 예후 인자였으며 치료전 고식적 수술을 시행한 군 및 종양이 두부에 위치한 군이 의미있게 생존율이 높았다.