Pancreatic Cancer-Clinical Analysis of 122 Cases from 1975 to 1982

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=Abstract=The clinical course of 122 patients with pancreatic cancer seen at Seoul National University Hospital were analysed dividing into two periods: 1975-78 and 1979-82.

In respect to the more imporved diagnostic tools such as ultrasonography(US) and computed tomography(CT), the sensitivity of US behind CT, as 65% for US and 90% for CT.

We didn't find any significant change of survival between two periods.

For the resectable cases we prefer Whipple's operation rather than total pancreatectomy, because the latter produces more morbidity and no significant prologation of survival. We did not routinely perform dual bypass procedure when doing bypass surgery in patients with non-resectable tumor.

As for the prognostic factors, tumor size below 2 cm, negative capsular and major vessels invasion showed a trend toward a good prognosis.

Key words: **Pancreatic cancer, Adequate operation, Prognostic factors**

INTRODUCTION

Pancreatic cancer has been increased slightly in incidence but still ranks high in death rate. It is also difficult to diagnose early enough to resect and, what is more, the prognosis is usually guarded in spite of the development of various modalities. On the other hand, operation for pancreatic cancer produces high morbidity and mortality because of anatomical reasons.

Some surgeons have insisted on palliative surgery even for resectable cases (Crile 1970); other surgeons have a more aggressive attitude, i.e. wider excision of lesions, including major vessels around the pancreas when they are involed by tumor (Fortner et al. 1984). Most surgeons agree that resection provides the only chance for cure and longer survival than pallia-

tive surgery for the resectable tumors (Levin et al. 1978; Longmire and Traverso 1981; Morrow et al.1984). For the unresectable cancers, chemotherapy and radiation treatment have been used with slight increased survival (GITSG 1979).

We reviewed 122 cases of pancreatic cancer operated upon at Seoul National University Hospital and analysed to see if improved diagnostic techniques would increased the survival of patients, and which operation would appropriate for the pancreatic cancer according to each stage. Finally, we tried to suggest several prognostic factors for the adequate surgical management.

MATERIALS AND METHODS

This is a retrospective review of 122 cases with exocrine carcinoma of the pancreas admitted and operated upon at Seoul National University Hospital from 1975 to 1982. We divided the cases into two groups, because we have used ultrasonography and computed tomography since 1979. Group A included 53 cases in the period of 1975-78, and group B 69 cases in the
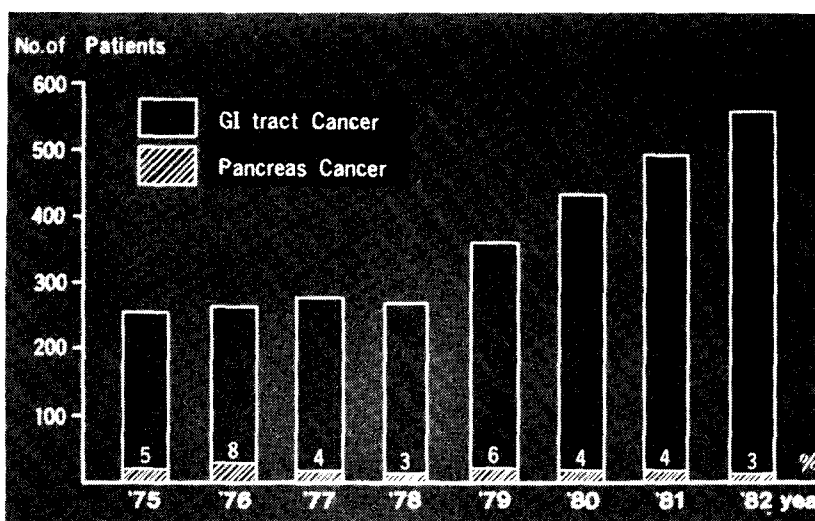
Fig. 1. The relative incidence of pancreatic cancer among all gastrointestinal malignancies between 1975 and 1982.

Table 1. Comparison of age & sex distribution between two periods in patients with pancreatic cancer

Age	A (1975-78)			B (1979-82)		
	Male	Female	Total(%)	Male	Female	Total(%)
20-29				1		1(2)
30-39	3	2	5(9)	3	2	5(7)
40-49	5	2	7(13)	12	2	14(20)
50-59	18	6	24(45)	13	8	21(31)
60-69	9	4	13(25)	15	8	23(33)
70 <	3	1	4(8)	2	3	5(7)
Total	38	15	53	46	23	69

period of 1979-82.

We used the 80-L compound scanner for US and the GE 7860 CT scanner.

In the diagnosis of pancreatic cancer, we first used non-invasive diagnostic modalities. As initial diagnostic tools, upper GI series and hypotonic duodenography were used in group A, whereas US and CT in group B.

These groups were compared in terms of incidence, diagnosis, staging and operations, survival, and prognostic factors.

In the statistical analysis, survival was calculated by Kaplan-Meier method. Comparison of two groups was performed with chi square test and paired t-test.

RESULTS

Incidence

Fig. 1 shows the relative incidence of pancrea-tic cancer among all gastrointestinal malignancies treated in our department. The incidence of 1st-half period was 5.0%, while that of 2nd was 4.3%. But the total number of pancreatic cancer were increased annually.

Distribution by age or sex was similar in both groups. 6th and 7th decades were most prevalent, as 71% in group A, 66% in group B. Male to female ratio was 2 to 1 in both groups (Table 1).

Symptoms, physical findings, and laboratory data

The most frequent symptoms and signs were pain, weight loss and jaundice as 85%, 62% and 53% in group A, 71%, 58%, and 56% in group B respectively. Mass was palpable in 17% of group A and 38% of group B. Fever and chill occurred in 13% of group A and 23% of group B. Both groups had similar symptoms and signs

Table 2. Comparison of symptoms between two periods (1975-78, 1979-82) in patients with pancreatic cancer

Symptoms	Number of patients (%)	
	A (1975-78)	B (1979-82)
Pain	46(85)	49(71)
Weight loss	33(62)	40(58)
Jaundice	28(53)	39(56)
Nausea & Vomiting	23(43)	15(22)
Mass	9(17)	26(38)
Fever & Chill	7(13)	16(23)

Table 3. Comparison of laboratory findings between two periods in patients with pancreatic cancer

Lab. findings	Number of patients (%)	
	A(1975-78)	B(1979-82)
Total bilirubin (1.5 mg/dl <)	31(58)	42(61)
Alk. P'tase (5 u*, 120 u**<)	33(62)	49(71)
SGOT/PT (40 u <)	31(58)	32(46)
Amylase (180 Su <)	6(11)	13(19)
Glucose (FBS/PP2, 100/140mg/dl<)	12(23)	38(55)
Urine sugar (1+ <)	7(13)	6(9)

*Bodansky unit
**International unit

(Table 2).

The incidence of hyperbilirubinemia was similar in both groups 58% and 61%. Hyperglycemia was more frequent in group B, 56% compared to 23% for group A (Table 3).

The diagnostic accuracy of UGI and HTD were 66% and 72% respectively, and these detected only the cases in the late phase, so we seldom recommended such tests in the latter period. The sensitivity of US was less than that of CT: 65% for US and 90% for CT. As for the invasive techniques used selectively in the latter period, the sensitivities of PTC and ERCP were around 80% (Table 4).

Histopathology

The carcinoma of duct cell origin were predominant, 85 out of 86 cases (Table 5). Among

Table 5. Pathologic type & survival

Pathologic type	Number of patients (%)
Duct cell origin	85(98.8)
Duct cell ca	75(87.2)
Papillary-cystic tumor	4
Adenosquamous ca	2
Mucinous (colloid) ca	2
Giant cell ca	1
Cystadenocarcinoma	1
Acinar cell origin	1(1.2)
Acinar cell ca	1

Table 4. Comparison of sensitivities of radiologic imaging procedures inpatients with pancreatic cancer

Procedures	A (1975-78)			B (1979-82)		
	Number of cases	Diagnosis	Sensit. (%)	Number of cases	Diagnosis	Sensit. (%)
UGI	33	19	50	19	13	68
HTD	22	14	64	18	14	77
PTC	15	11	68	14	11	68
ERCP	9	7	78	15	12	80
US				52	34	65
CT				11	10	90

Table 6. Comparison of clinical stagings between two periods in patients with pancreatic cancer

Stage	Number of patients (%)	
	A (1975-78)	B (1979-82)
I	1(2)	6(9)
II	7(16)	7(10)
III	16(31)	14(20)
IV	29(51)	42(61)

*the clinical staging was bases on the classification of Hermreck, Thomas and Friesen (1974).

them, 75 cases (87.2%) were duct cell carcinoma, whereas papillary-cystic tumor and cystadenocarcinoma known as rare pancreatic cancers with good prognosis were 4 cases and 1 case each. Acinar cell carcinoma was 1 case only.

Stagings and operations

We classified the pancreatic cancer by the classification of Hermreck, Thomas and Friesen (1974). In our pateints, stage I and II were less than 20% of all cases. More than 80% were stage III and IV. Although US and CT were available in the latter period, advanced lesions still predominated (Table 6).

The resectability of our pancreatic cancer patients was 17% in both groups, so it was not improved by using more sophisticated diagnostic

tools such as US and CT. Bypass procedures were performed in 50-60% of cases. Simple exploration (open and close) was done in 26% of group A, 22% of group B (Table 7). While pancreatico-duodenectomy was most frequently performed in the resected cases, total pancreatectomy was only selectively perfomed in one case each in both groups. Through both periods we did bypass procedures in 53 cases (56%), i.e. biliary bypass in 9 cases, enteric bypass in 9 cases, and dual bypass in 14 cases. So we didn't routinely perform dual bypass.

Survival

Overall median survivals by stage were as follows: stage I 10.4 months, stage II 6.7 months, stage III 5.4 months, stage IV 3.3 months. Between stage I, statistically significant difference was not found (p = 0.56), but showed significance (p < .01) between stage I and III or stage I and IV. 2-year survival in stage I and II were 22.9% and 12.4% repsectively (Fig. 2). One year survival between the resected and bypass or simple exploration group in stage II showed 47.3% in the resected and 31.9% in the latter, but statistically insignificant (Fig. 3).

Prognostic factors

Three characteristics in the stage I & II showed a trend toward significance with a good prognosis: size of tumor below 2 cm, negative capsular and major vessels invasion (Table 8).

Table 7. Comparison of Operations between two periods in patients with pancreatic cancer

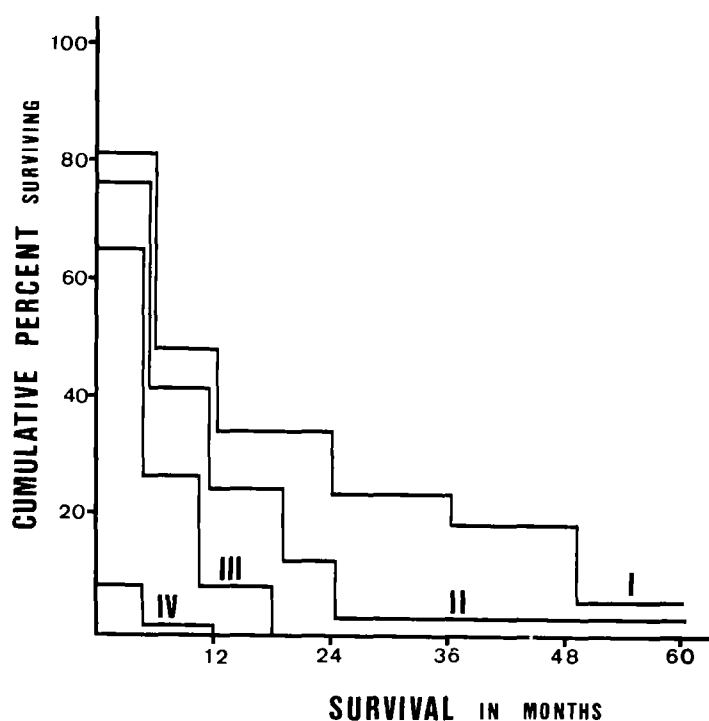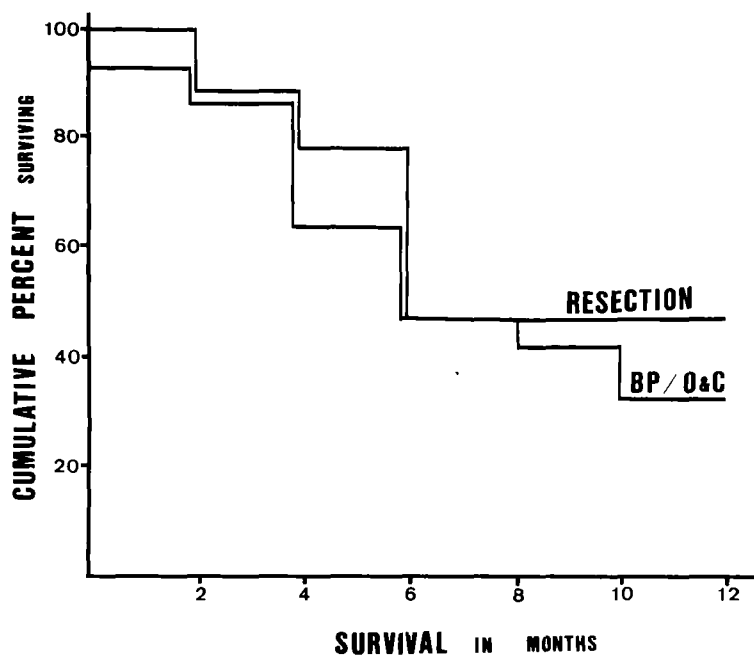| Operations	Number of patients (%)	
	A (1975-78)	B (1979-82)
Resection	9(17)	12(17)
Pancreaticoduodenectomy	7	8
Total pancreatectomy	1	1
Distal Pancreatectomy	1	3
Bypass	30(57)	42(61)
Biliary	21	23
Enteric	6	5
Dual	3	14
Simple laparotomy (Open & close)	14(26)	15(22)

Fig. 2. Overall cumulative survival by stage.

Fig. 3. Difference of survival between resection and by pass or O & C in stage II.

DISCUSSION

In Korea, the incidence of pancreatic cancer has slowly increased during last several years. Malignant tumor was 9.5% of all patients admitted to Seoul National University Hospital (Annual report of SNUH 1975-79), and pancreatic cancer was 2.4% of the malignant tumor (Lee and Kim 1980). Brooks et al.(1976) reported that pancreatic cancer consisted of 5.2% of gastrointestinal tract cancer in USA.

As for the role of glucose metabolism in the carcinogenesis of pancreatic cancer, as Karmody and Kyle (1969) insisted, glucose intolerance was usually a result of pancreatic cancer and not a causative factor (Moossa 1982). In our cases, glucose intolerance was found in half of the cases. We could not determine the hyperglycemia to be the cause or the result of pancreatic cancer, but this finding helped us to differntiate this cancer from other periampullary cancers.

Early symptoms such as anorexia, indigestion, and abdominal discomfort were not helpful in diagnosing the pancreatic cancer in our study, and only 14% of the patients with pancreatic cancer were admitted to the hospital within one month after the onset of symptoms (Moossa 1982). Most patients consulted doctors with symptoms of obstructive jaundice or duodenal obstruction caused by direct invasion of tumor into the distal common bile duct or duodenum. Our study also has a high rate of jaundice (57%), weight loss (69%), and abdominal pain (70%). These findings have continued through both periods without improvement, so patient-side delay of consulting doctor hindered early diagnosis of pancreatic cancer.

Serologic diagnosis of pancreatic cancer with CEA and POA failed in detection of early stage (Favero et al. 1986; Moossa 1982). Studies on the value of CA 19-9 or DU-PAN 2 for diagnosis and monitoring of pancreatic cancer are ongoing with some hopeful results (Lan et al, 1985; Metzgar et al. 1982; Safi et al. 1986).

As imaging modalities in the diagnosis of pancreatic cancer, UGI and HTD were commonly used until the early 70s'. With the introduction of more convenient and accurate tools such as US, CT and NMR, they have been seldom used for their diagnostic limitations. Ultrasonography is safe and accurate, and used first in the diagnosis of pancreatic cancer (Barkin et al. 1977; Go et al. 1981), but our early data showed poor results because of unskillful handling and mechanical limitations of old model. In contrast to US, CT gave us the most precise information about the pancreatic cancer, i.e. diagnosis, resectability, and prognosis (Go et al. 1981). Its sensitivity

in our study was 90%. Sometimes, US had diffi-culty in differentiating cancer of pancreas tail from retroperitoneal tumor, but CT could diffe-rentiate these (Moossa 1982).

In the severely jaundiced patient, PTC has been performed as a preliminary step to percu-taneous transhepatic biliary drainage (Bernardino and Barnes 1982). Fine needle aspiration biopsy can be done under guidance of US for the pa-tients with suspected pancreatic cancer especial-ly in advanced cases or high risk groups, includ-ing old patients without any obstruction of bile duct or gastrointestinal tract (Bernardino and Barnes 1982; Go et al. 1981), thus unnecessary laparotomy was avoided in those patients (Gud-jonsson and Spiro 1978; Moossa 1982).

Tissue diagnosis is essential before doing some kind of procedure during operation for pan-creatic cancer, but it is difficuclt to get an accu-rate diagnosis due to the location of tumor and surrounding pancreatitis (Beazley 1981). Most surgeons get tumor tissue through transduoden-al needle biopsy during operation (Levin et al. 1978). If there is no positive result even after several trials with this technique, then clinical symptoms and signs, operative findings, and the surgeon's experience may determine whether to perform extensive resection or not. As a rule, extensive resection should be abandoned when tumor cells are found in the excised lymph node (Brooks and Culebras 1976; Levin 1978).

The most common type of pancreatic cancer found in our study was an adenocarcinoma aris-ing from the cells of the duct (or ductular) sys-tem, composing 87.2% of all malignancies of the exocrine pancreas.

The resectability of pancreatic cancer is very low: 15-20% (Morrow et al. 1984; Levin 1978). We got 17% of resectability in both periods, in other words, we did not improve the resectabil-ity even by using more sophisticated diagnostic instruments such as US and CT.

There has been controversy in the extent of resection for the resectable pancreatic cancer (Brooks 1976; Collins et al. 1966; Crile 1979; Fortner 1984; Levin et al. 1978). We did partial pancreaticoduodenectomy in alomst all cases. We performed total pancreatectomy in patients with tumor which could not completely removed by Whipple's procedure, and with overt diabetes mellitus. Regional pancreatectomy should be considered selectively in patients with tumor which is adherent to, but not invaded into the surrounding major vessels. Partial pancreatec-tomy has been preferred because total pan-createctomy produces brittle diabetes mellitus. malabsorption, and no significant improvement of survival. If cancer cells were found on the frozen section at the resection margin of the pancreas at the time of partial pancreatectomy, then the toal pancreatectomy should be consi-dered (Moossa 1982).

For the non-resectable cancer, the most com-mon problem is obstructive jaundice. In some terminal patients, we preferred the percutaneous transhepatic biliary drainge rather than operative intervention. When the patients are expected to survive more than one month, we performed op-erative biliary bypass, marking tumor margins with metal clips in locally advanced cases for the purpose of later radiation. We do not routinely perform enteric bypass because duodenal ob-structon would develop in one quarter of pa-tients only. Postoperatively, split-course radia-tion combining 5-FU somewhat prolong the me-dian survival up to 30-40 weeks (Park et al. 1986; GITSG 1982).

Operative mortality of resection cases is acceptable in these days, at less than 5% (Mor-row et al. 1984; Levin et al. 1978). We got more prolonged survival in the resection group of the patients with stage I and II than palliative surgery, but not so much with stage III.

We recommended surgical resection for cases with stage I and II, and surgical bypass proce-dures for cases with stage III and IV with good operative risk. We have to avoid needless opera-tion in cases of stage IV with poor operative risk. However sophisticated diagnostic tools such as US and CT could not increase the survival of patients with pancreatic cancer.

Mannell et al reported following factors with a poor prognosis: malignant infiltration of pancrea-tic capsule, proximity of tumor to lymphatics and blood vessels, round-cell infiltration at the tumor margin, atypia of the pancreatic ductal epithe-lium, and Broder's grade 3 and 4 (Mannell et al. 1986). Among them, lost three items were con-firmed from multivariate analysis. In our study, tumor size (< 2cm), negative capsular and major vessels invasion showed some significant trend toward a good prognosis.

In conclusion, long-term survival can be expected only by early detection and curative resection for patients with stage I and II. For the early detection, new diagnostic tools might be necessary.

REFERENCES

Barkin J. Vining D. Miale A Jr. Gottlieb S, Redhammer DE, Kalser MH. Computerized tomography, diagnostic ultrasound, and radionuclide scanning. J.A.M.A. 1977, 238:2040-2042

Brooks JB, Culebras JM. Cancer of the pancreas. Palliative operation, Whipple procedure or total pancreatectomy? Am. J. Surg. 1976, 131:516-520

Bernardino ME, Barnes PA. Imaging the pancreatic neoplasm. Cancer 1982, 50:2681-2688

Beazley RM. Needle biopsy diagnosis of pancreatic cancer. Cancer 1981, 47:1985-1987

Collins JJ JR, Craighead JE, Brooks JR. Rationale for total pancreatectomy for carcinoma of the pancreatic head. New England J. of Medicine 1966, 274:15-18

Cooperman AM, Herter FP, Marboe CA, Helmreich ZV, Perzin KH. Pancreato-duodenal resection and total pancreatectomy-an institutional review. Surgery 1981, 90:707-712

Crile G. The advantages of bypass procedures over radical pancreatoduodenectomy in the treatment of pancreatic cancer. S.G.O. 1970, 130:1049-1053

Favero GD, Fabris C, Plebani M, Panucci A, Piccoli A, Perobelli L, Pedrazzoli S, Baccagliri U, Burlina A, Naccarato R. CA 19-9 and carcinoembryonic antigen in pancreatic cancer diagnosis. Cancer 1986, 57:1576-1579

Fortner JG, Kim DK, Cubilla A. Turnbull A, Phanke LD, Shils ME. Regional pancreatectomy. Ann. Surg. 1977, 186:42-50

Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Ann. Surg. 1984, 199:418-425

Go VL, Talor WH, Dimagno EP. Efforts at early diagnosis of pancreatic cancer. Cancer 1981, 47: 1698-1703

Gudjonsson B, Spiro HM. Biopsy techniques in the diagnosis of pancreatic cancer. Gastroenterology 1978, 75:726-728

Hermereck AS, Thomas CY, Friesen SR. Importance of pathologic staging in the surgical management of adenocarcinoma of the exocrine pancreas. Am. J. Surg. 1974, 127:653-657

Karmody AJ, Kyle J. The association between carcinoma and diabetes mellitus. Br. J. Surg. 1969, 56:362-364

Lan MS, Finn OJ, Fernsten PD, Metjgar RS. Isolation and properties of adenocarcinoma-associated antigen, Du-Pan-2. Cancer Research 1985, 45:305-310

Lee KU, Kim JP. Surgical management of the pancreatic cancer. J. Korean Cancer Asso. 1980, 12:91-99

Levin B, ReMine WH, Herman RE, Schein PS, Cohn I. Pannel; Cancer of the pancreas. Ann. Surg. 1978, 135:181-191

Longmire WP, Traverso LW. The Whipple procedure and other standard operative approaches to pancreatic cancer. Cancer 1981, 47:1706-1711

Mannell A, Weiland L, Heerden JA, Ilstrup DM. Factors influencing survival after resection for ductal adenocarcinoma of the pancreas. Ann. Surg. 1986, 203:403-407

Metjgar RS, Gaillard MT, Levine SJ, Tuck FL, Bossen EH, Borowitz MJ. Antigens of human pancreatic adenocarcinoma cells defined by Murine monoclonal antibodies. Cancer Research 1982, 42:601-608

Moosa AR. Pancreatic cancer. Cancer 1982, 50: 2689-2698

Morrow M, Hilaris B, Brennan MF. Comparison of conventional surgical resection, radioactive implantation, and bypass procedures for exocrine carcinoma of the pancreas. Ann. Surg. 1984, 199:1-5

Park WY, Cho MJ, Ha SH, Park CI, Choe KJ, Lee KU, Kim NK. Treatment of locally unresectable carcinoma of the pancreas. J. Korean Soc. Ther. Radiol. 1986, 4:141-145

Safi F, Beger HG, Bittner R, Buchler M, Krautjberger W. CA 19-9 and pancreatic adenocarcinoma. Cancer 1986, 57:779-783

Schantz SP, Schickler W, Evans TK, Coffey RJ. Palliative gastroenterostomy for pancreatic cancer. Am. J. Surg. 1980, 147:793-796

The Annual report of Seoul National University Hospital, 1975-1979

The gastrointestinal tumor study group. A multi-institutional comparative trial of radiation therapy alone & in combination with 5-FU for locally unresectable pancreatic cancer. Ann. Surg. 1979, 189:205-208

＝ 국문초록 ＝

췌 장 암
－1975년부터 1982년까지 122예의 임상적 분석—

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　췌장암 환자에서 초음파 조영술 및 전산화 단층 조영술과 같은 향상된 진단방법이 그 예후에 미치는영향과 췌장암에서 어떤 수술이 적합한지를 연구하였다. 췌장암 환자를 두 그룹으로 나누었는데 A그룹은 1975—78년 사이의 53예와, B그룹은 1979—82년 사이의 69예를 대상으로 하였는데, 이는 초음파 조영술과 전산화 단층 조영술이 1979년 이후부터 실시되었기 때문이다.

　초음파 조영술의 진단정확도는 65%로서 전산화 단층조영술의 90%보다 낮았다. 고식적 수술에서 보다 절제예에서 생존기간이 좀더 길었으나, 두 그룹 사이에서의 생존율의 의미있는 변화는 없었다.

　절제예에서 췌두십이지장 절제술이 전췌절제술보다 선호되었는데 이는 전췌절제술에서 수술 합병증이 보다 많이 발생되고, 생존기간이 연장되지 못하기 때문이다.

　절제 불가능한 예에서 회로술을 시행시 통상적으로 담도 및 위장의 2중 회로술을 시행치 않았다. 한편 예후에 좋은 영향을 미치는 인자로는 종양크기 (＜2cm), 췌장피막 및 주혈관 침윤이 없는 경우이며 이들은 통계적 유의성 경향을 보였다.

　결론적으로 췌장암의 진단방법으로서 초음파 조영술과 전산화 단층 조영술을 생존기간을 의미있게 증가시키지 못하였으며, 장기 생존은 제 I, II병기예의 조기 발견과 근치적 절제술로서만 이루어 질수 있기 때문에 좀더 새로운 진단방법이 췌장암의 조기진단에 필요할 것으로 사료된다.