

PRELIMINARY REPORT OF THE FERMILAB EXPERIENCE
USING NEUTRON IRRADIATION FOR THE TREATMENT OF
PANCREATIC CANCER *

JoAnne Mansell, R.N., P.A., Lionel Cohen, M.D.,
Frank Hendrickson, M.D., Raman Kaul, M.D.

INTRODUCTION.

Forty cases of pancreatic carcinoma have been treated at Fermilab between November, 1976 and July, 1979. Follow-up ranges from 6 to 25 months. All patients had histopathologically confirmed adenocarcinomas with the exception of one case, in which the pathology indicated a possible APUD tumor. Minimum tumor dose delivered to the 90% isodose line was 19.5 neutron Gy (equivalent to 60 photon Gy) in most cases. Fractions were delivered 2 to 3 times per week over 6 to 7 weeks, without planned interruption.

PILOT CASES.

The first 10 patients were treated as pilot cases with various doses ranging from 6 to 23 neutron Gy. Many of these patients had either confirmed or suspected metastases prior to treatment as well as low Karnofsky scores. The purpose of treatment was to establish dose and tolerance to neutron irradiation. All but one of these 10 patients completed

* This investigation was supported by National Cancer Institute Grant #5P01 CA18081.

treatment without interruption. The degree of anorexia, lethargy, nausea, and diarrhea was negligible in 2 cases, tolerable with no medication required in 3 cases, and tolerable with medication in 5 cases.

Patient #77-129 received the highest dose in this series, 23 neutron Gy, which is approximately equivalent to 69 photon Gy to the tumor volume. This particular patient continued to work throughout therapy and came for treatment on his lunch hour. He received Torecan for use on a PRN bases and gained 7.5 lbs from the initiation of therapy to his first follow-up one month after completion. This patient developed nausea and epigastric pain 6 months after therapy. A large duodenal ulcer was found and a vagotomy and gastro-jejunosomy were performed. At the time of this surgery, a visual inspection and multiple biopsies of the pancreas were done. These revealed no tumor. The patient healed without problems. Twelve months later, a second surgery was performed due to bowel adhesions. At this time, the pancreatic tumor had recurred and the patient had an atonic stomach. He subsequently expired 21 months after diagnosis, with no evidence of distant metastases. The other 9 patients in the pilot series survived an average of 5.9 months from the time of diagnosis.

Two of the 9 had autopsies which revealed a persistent primary tumor. The remaining 7 patients gave a clinical impression of persistent primary tumors. Three of the 9 had distant metastases confirmed radiographically. (See summary table attached.)

PHASE II CASES.

Thirty patients were treated according to a local, non-randomized, Phase II protocol. These patients were generally in better functional condition. They had no evidence of distant metastases, no previous chemotherapy or abdominal radiotherapy and adequate marrow function. All were 10 days or more past major abdominal surgery. Most had surgical clips marking the gross tumor and many had CAT scans and standing IVPs for kidney localization prior to therapy. Adjuvant chemotherapy was permitted, but only 2 patients received it.

This group of patients all received 19.5 neutron Gy delivered to the 90% isodose line. They were treated twice a week for 13 fractions in 6 weeks. In general, the target volume was treated by means of 3 converging fields. These included an anterior portal covering the anatomical projection of the pancreas and the entire tumor as outlined by the surgical clips, with a 2 cm margin extending beyond all known disease where possible. Two lateral wedged portals were matched to the anterior to encompass the antero-posterior extension of the tumor. The posterior margins of the lateral fields were tangential to the anterior surface of the kidneys and intersected the bodies of the adjacent lumbar vertebrae. The spinal cord dose did not exceed 12 neutron Gy. Volume treated ranged from 800 cm³ to 1350 cm³. (See typical isodose plan attached.)

Twenty-seven of these 30 Phase II patients completed treatment without interruption. Two patients completed with less than a 7-day break, and one did not complete the prescribed course due to general deterioration. Eight

patients had minimal or no anorexia, lethargy, nausea, or diarrhea. Fifteen patients had tolerable symptoms that required no medication. Seven patients required medication for one or all of the above symptoms. No patient had reactions of sufficient magnitude to necessitate discontinuing treatment.

Five of the Phase II patients suffered complications of treatment. These occurred at 3, 4, 6, 7, and 9 months after completion. One of these complications, a gastric hemorrhage, was lethal. Two duodenal ulcers occurred. One ulcer was found just prior to death and was confirmed at autopsy. The other patient who developed a duodenal ulcer is undergoing conservative management currently. A fourth patient has an atonic stomach and will probably have a surgical removal. A fifth patient developed an obstruction at the gastric outlet as a result of local edema. A bypass surgery was performed 2 months ago. The patient has since gained 20 lbs, and remains alive and well. Biopsies performed at the time of the bypass reveal no tumor. (See attached table.)

Ten patients had CAT scans performed to measure the response of the tumor to therapy. These were done 3 to 6 months following treatment. Eight of these scans revealed the primary tumor the same as, or larger than, the extent prior to treatment. One scan revealed no tumor, and one was inconclusive.

Twelve patients who did not have radiographic investigations to determine tumor response had persistent, or progressive, tumors clinically. Two other such patients have no evidence of tumor at 25 and 13 months. Six patients had persistent, or progressive, primary tumors at autopsy.

Fifteen patients developed evidence of distant metastases. Six patients had metastases at autopsy. Six had confirmation of metastases radiographically, and 3 had clinical evidence of metastases, but no confirmation. Ten patients had no evidence of distant metastases. Four of the 10 had negative radiographic work-ups. However, 6 of this group were evaluated only clinically, and certainly may have had subclinical metastases, or may have developed it had they survived longer. Three patients had inconclusive evaluation for distant metastases.

The medial survival for the Phase II patients is 8 months. There are presently 6 patients alive, 5 of whom appear to be free of disease at present. (See survival graph, attached.)

Good palliation of symptoms occurred in most of the patients treated. Almost all patients complained of pain requiring the use of narcotic analgesics at the initiation of therapy. Pain was relieved sufficiently to discontinue these analgesics by one month following treatment in 70% of such cases. Others were able to decrease the amount or strength of the analgesic used. Functional status, as measured by the Karnofsky scale, remained stable or improved in 75% of patients at the time of their 3 month follow-up. Skin reactions were uniformly mild. Nausea and diarrhea related to treatment resolved as expected. About 15% of these patients required pancreatic enzymes as a result of symptoms of insufficiency. Ten per cent required the use of antacids due to irritation of the stomach wall.

SUBSEQUENT THERAPY REVISIONS.

As a result of our analysis of these two groups of patients, several changes have been implemented in our

treatment of pancreatic carcinomas. A CAT scan is now required prior to treatment planning, as well as an IVP taken in the upright position. Since our neutron beam is fixed horizontally, patients are treated in the upright position and the standing IVP is required to localize the kidneys as they move to a more anterior, caudal position. The placement of surgical clips is strongly recommended. A functional status adequate for out-patient visits and immobilization is required, as well as a complete metastatic work-up.

A majority of the pilot and Phase II patients had persistent tumor leading to their death. The treatment complication rate did not seem unacceptable in light of the disease. We have therefore increased our minimum tumor dose to 22.5 neutron Gy delivered to the 90% isodose line. The maximum target volume considered acceptable has been increased to 1700 cm³ (e.g. 13 x 13 x 10 cm). Pancreas patients referred in the past 6 months have been treated according to this revised plan.

The Radiation Therapy Oncology Group has recently activated a Phase III study for pancreatic carcinoma, 79-21. This protocol randomized eligible patients to one of three arms: photons only, mixed - photons and neutrons, and neutrons only. Chemotherapy is not included as part of this study. Fermilab's accrual to this protocol began March 1, 1980.

SUMMARY TABLE - PILOT CASES

CTF#	DATE OF DIAGNOSIS	DOSE DELIVERED TO 90% ISODOSE LINE		TREATMENT TOLERANCE a/b	COMPLICATIONS AND TIME OF OCCURENCE	SURVIVAL IN MONTHS, ALIVE OR DEAD	DISEASE STATUS (c) METHOD OF DETERMINATION (d)		
							T	N	M
76-015	9/30/76	22	Gy	1/3	acute dehydration 2 mo. post therapy.	6D	+4	+4	-4
77-001	7/15/76	20	Gy	1/1	none	8D	+1	?1	?1
77-018	10/30/76	16	Gy	1/3	none	8D	+1	?1	?1
77-128	10/31/77	6	Gy	4/1	none	4D	+4	-4	-4
77-129	11/30/77	23	Gy	1/3	duodenal ulcer, atonic stomach 6 mo. post therapy.	21D	+4	-1	-1
78-029	1/25/78	19.5	Gy	1/3	none	6D	+1	?1	?1
78-038	4/11/78	20	Gy	1/2	none	2D	+1	+1	-1
78-046	4/5/78	19.5	Gy	1/3	none	4D	+1	+4	+3
78-062	5/5/78	20	Gy	1/2	none	6D	+1	?1	+3
78-070	5/15/78	20	Gy	1/2	none	9D	+1	?1	+3

(a) 1 = completed according to plan;
 2 = completed, interruption less than 1 week;
 3 = completed, interruption more than 1 week;
 4 = incomplete.

(b) Degree of anorexia, lethargy, nausea, diarrhea:
 1 = none;
 2 = tolerable, no medication required;
 3 = tolerable, medication required;
 4 = treatment interrupted or discontinued.

(c) + = tumor present;
 - = no tumor;
 ? = unable to determine if tumor is present.

(d) 1 = clinical impression;
 2 = CAT scan;
 3 = other radiographic;
 4 = biopsy or autopsy.

SUMMARY TABLE - PHASE II CASES

CTF #	DATE OF DIAGNOSIS	DOSE DELIVERED TO 90% ISODOSE LINE	TREATMENT TOLERANCE a/b	COMPLICATIONS AND TIME OF OCCURENCE	SURVIVAL IN MONTHS, ALIVE OR DEAD	DISEASE STATUS (c) METHOD OF DETERMINATION (d)		
						T	N	M
78-073	1/10/77 Chemotherapy pre-neutrons. Possibly APUD	19.5 Gy	1/2	none	25A	-1	-1	-1
78-093	5/22/78	19.5 Gy	1/3	none	6D	+1	?1	-3
78-100	6/19/78	19.5 Gy	1/2	none	7D	+2	?1	+3
78-115	6/13/78	19.5 Gy	1/3	none	6D	+1	?1	?1
78-138	8/4/78	19.5 Gy	1/2	none	17D	+1	?1	+3
78-179	9/13/78	19.5 Gy	1/2	none	5D	+1	+1	+1
78-181	9/12/78	19.5 Gy	1/2	none	10D	+2	-2	-2
78-183	8/17/78	19.5 Gy	1/2	none	8D	+1	?1	+3
78-184	7/3/78	8.25n/58.5p mixed beam	1/1	none	13D	+2	?1	-1

(a) 1 = completed according to plan;
 2 = completed, interruption less than 1 week;
 3 = completed, interruption more than 1 week;
 4 = incomplete.

(b) Degree of anorexia, lethargy, nausea, diarrhea:
 1 = none;
 2 = tolerable, no medication required;
 3 = tolerable, medication required;
 4 = treatment interrupted or discontinued.

(c) + = tumor present;
 - = no tumor;
 ? = unable to determine if tumor is present.

(d) 1 = clinical impression;
 2 = CAT scan;
 3 = other radiographic;
 4 = biopsy or autopsy.

SUMMARY TABLE - PHASE II CASES

CTF #	DATE OF DIAGNOSIS	DOSE DELIVERED TO 90% ISODOSE LINE	TREATMENT TOLERANCE a/b	COMPLICATIONS AND TIME OF OCCURENCE	SURVIVAL IN MONTHS, ALIVE OR DEAD	DISEASE STATUS (c) METHOD OF DETERMINATION (d)		
						T	N	M
78-185	9/11/78	19.5 Gy	1/2	none	4D	+1	?1	+1
78-191	5/11/78	19.5 Gy	1/2	duodenal ulcer 4 mo. post-treatment.	11D	+4	+3	+3
78-211	8/30/78	19.5 Gy	1/1	none	12D	+2	+3	-1
78-224	10/12/78	19.5 Gy	2/3	none	6D	+4	+4	+4
78-234	10/26/78	19.5 Gy	1/1	none	6D	+4	?2	+4
78-238	10/13/78	19.63Gy	1/2	none	7D	+4	+4	+4
78-242	11/22/78	16.5 Gy	4/3	none	4D	+1	?1	-1
78-249	11/30/78	19.5 Gy	1/1	gastric hemor- rhage 7 mo. post-treatment.	7D	+2	-1	-1
79-016	11/21/78	19.5 Gy	1/8	none	12D	+2	+1	+4
79-028	1/31/79	19.5 Gy	1/1	none	13A	-1	-1	-1

(a) 1 = completed according to plan;
 2 = completed, interruption less than 1 week;
 3 = completed, interruption more than 1 week;
 4 = incomplete.

(b) Degree of anorexia, lethargy, nausea, diarrhea:
 1 = none;
 2 = tolerable, no medication required;
 3 = tolerable, medication required;
 4 = treatment interrupted or discontinued.

(c) + = tumor present;
 - = no tumor;
 ? = unable to determine if tumor is present.

d) 1 = clinical impression;
 2 = CAT scan;
 3 = other radiographic;
 4 = biopsy or autopsy.

SUMMARY TABLE - PHASE II CASES

CTF #	DATE OF DIAGNOSIS	DOSE DELIVERED TO 90% ISODOSE LINE	TREATMENT TOLERANCE a/b	COMPLICATIONS AND TIME OF OCCURENCE	SURVIVAL IN MONTHS, ALIVE OR DEAD	DISEASE STATUS (c) METHOD OF DETERMINATION (d)		
						T	N	M
79-030	1/29/79	19.5 Gy	1/1	none	7D	+1	?1	+2
79-082	3/30/79	19.5 Gy	1/2	none	6D	+2	?1	?1
79-083	2/7/79	19.5 Gy	1/3	none	11D	+4	+4	+4
79-086	4/9/79	19.5 Gy	1/2	none	7D	+1	?1	+1
79-089	4/23/79	19.5 Gy	1/2	none	10D	+1	?1	+3
79-092	3/23/79	19.5 Gy	1/2	none	6D	+1	?1	+3
79-094	3/22/79	19.5 Gy	1/2	duodenal ulcer at 6 mo. post-treatment.	11A	-2	-1	-3
79-099	3/14/78 chemother- apy pre- neutrons.	19.5 Gy	1/2	gastric outlet obstruction 2 ^o to edema at 4 mo. post-neutrons.	23A	-4	-4	?3

(a) 1 = completed according to plan;
 2 = completed, interruption less than 1 week;
 3 = completed, interruption more than 1 week;
 4 = incomplete.

(b) Degree of anorexia, lethargy, nausea, diarrhea:
 1 = none;
 2 = tolerable, no medication required;
 3 = tolerable, medication required;
 4 = treatment interrupted or discontinued.

(c) + = tumor present;
 - = no tumor;
 ? = unable to determine if tumor is present.

(d) 1 = clinical impression;
 2 = CAT scan;
 3 = other radiographic;
 4 = biopsy or autopsy.

SUMMARY TABLE - PHASE II CASES

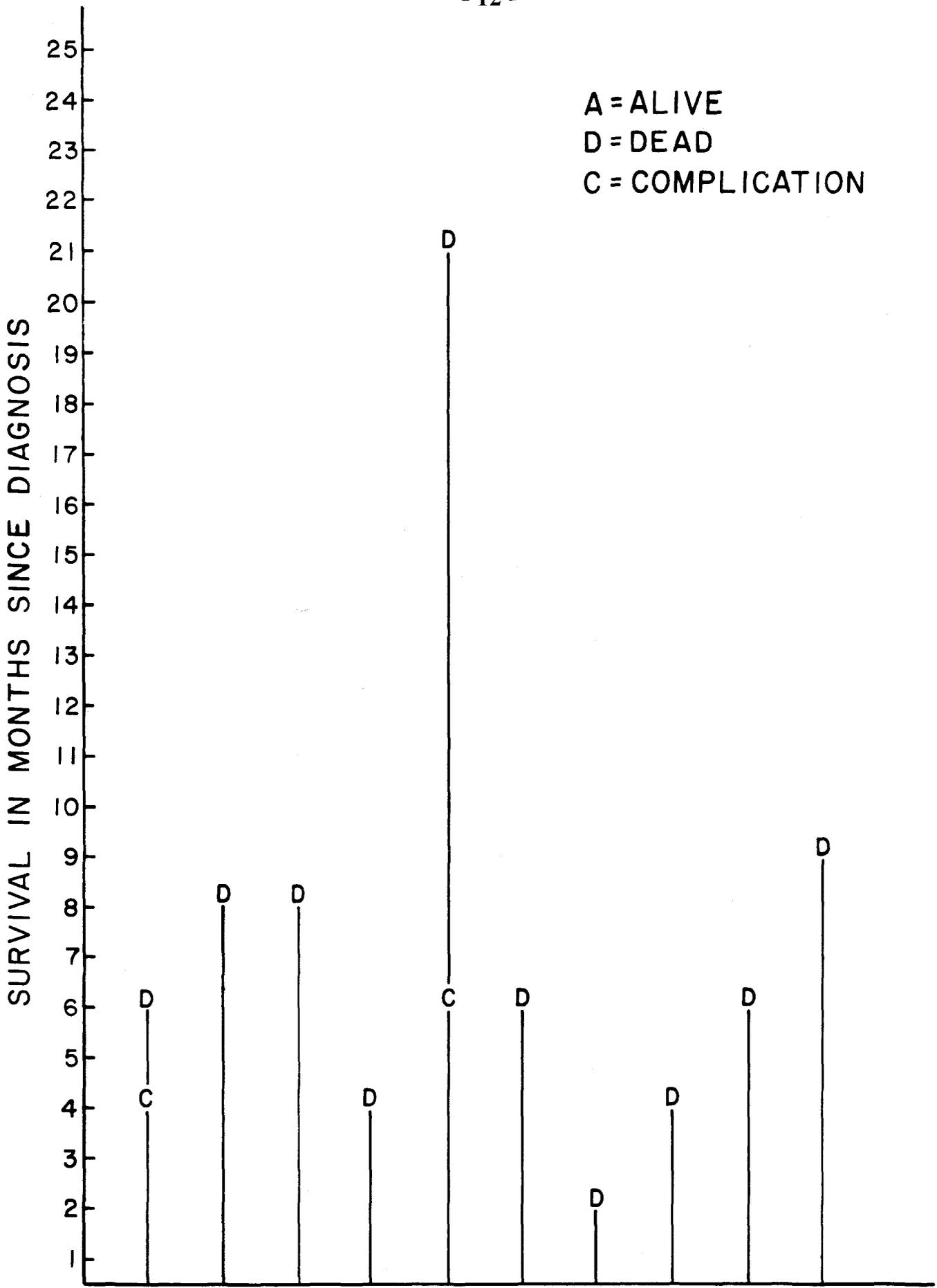
CTF #	DATE OF DIAGNOSIS	DOSE DELIVERED TO 90% ISODOSE LINE	TREATMENT TOLERANCE a/b	COMPLICATIONS AND TIME OF OCCURENCE	SURVIVAL IN MONTHS, ALIVE OR DEAD	DISEASE STATUS (c) METHOD OF DETERMINATION (d)		
						T	N	M
79-104	4/27/79	19.5 Gy	1/1	none	10A	?2	?2	-3
79-119	5/31/79	19.5 Gy	1/1	possible atonic stomach at 8 mos.	9A	+3	?3	+3
79-127	6/19/79	19.5 Gy	2/3	none	6D	+4	+4	+4

(a) 1 = completed according to plan;
 2 = completed, interruption less than 1 week;
 3 = completed, interruption more than 1 week;
 4 = incomplete.

(b) Degree of anorexia, lethargy, nausea, diarrhea:
 1 = none;
 2 = tolerable, no medication required;
 3 = tolerable, medication required;
 4 = treatment interrupted or discontinued.

(c) + = tumor present;
 - = no tumor;
 ? = unable to determine if tumor is present.

(d) 1 = clinical impression;
 2 = CAT scan;
 3 = other radiographic;
 4 = biopsy or autopsy.



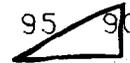
PILOT STUDY PANCREAS CASES TREATED WITH NEUTRONS, NOVEMBER, 1976 TO MAY, 1978

SCHW. R. (PANCREAS)

CASE 80018 PLAN 3 80/01/25.

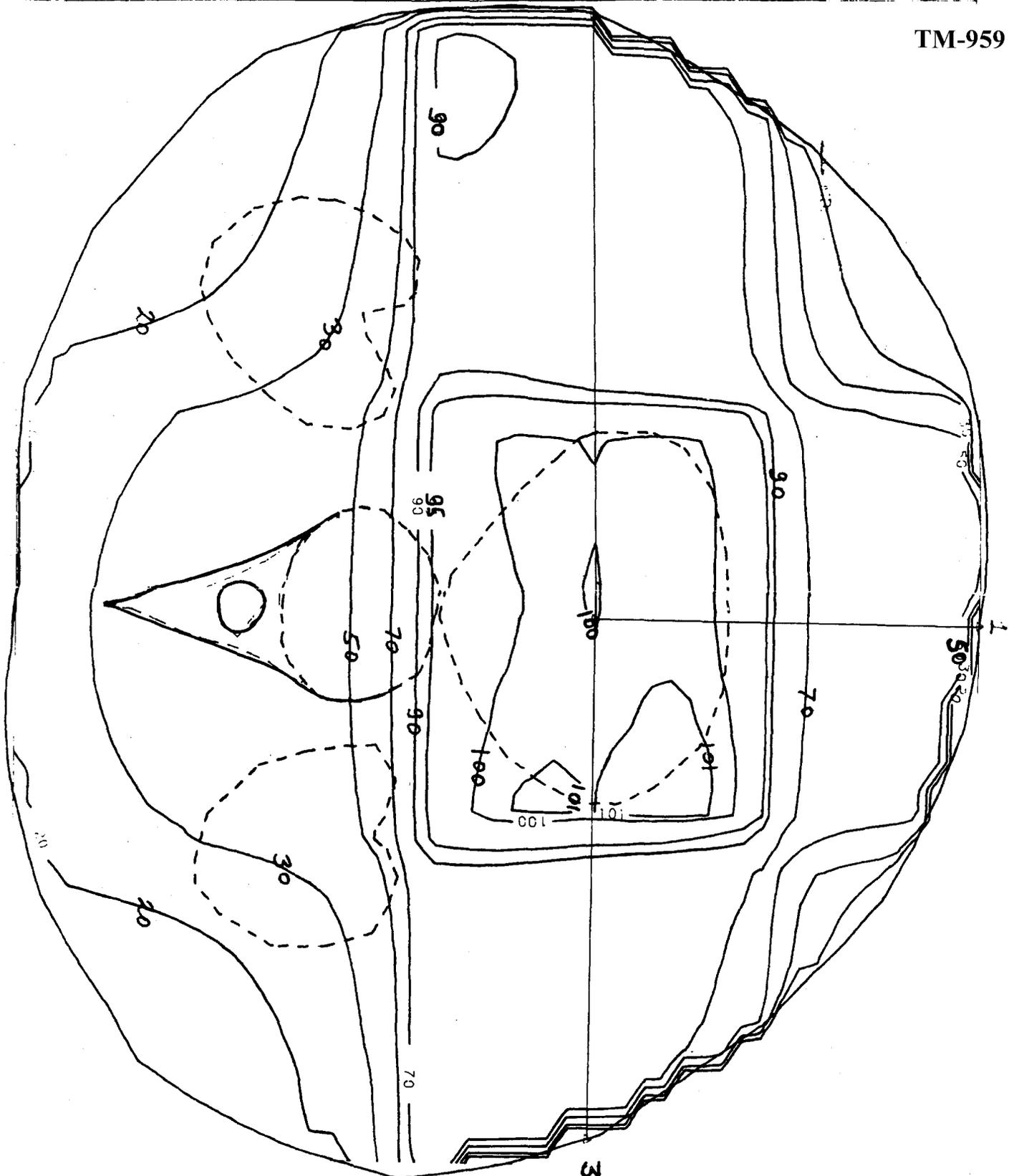
FL	MCHV	SSD	DPTH	WIDTH	LENG	TILT	WEDGE	WTG	ENTRY	X,Y	ANG
1	NE	180.0	10.0	12.0 X	14.0	0	0	1000	0.0,	10.0	0
2	NE	174.3	15.7	10.0 X	14.0	0	45N	1000	-15.7,	0.0	269
3	NE	176.7	13.3	10.0 X	14.0	0	45S	1000	13.3,	0.0	90

DNCP= 3000 DMAX= 3050 DOSES 101 100 95 90 70 50 30 20



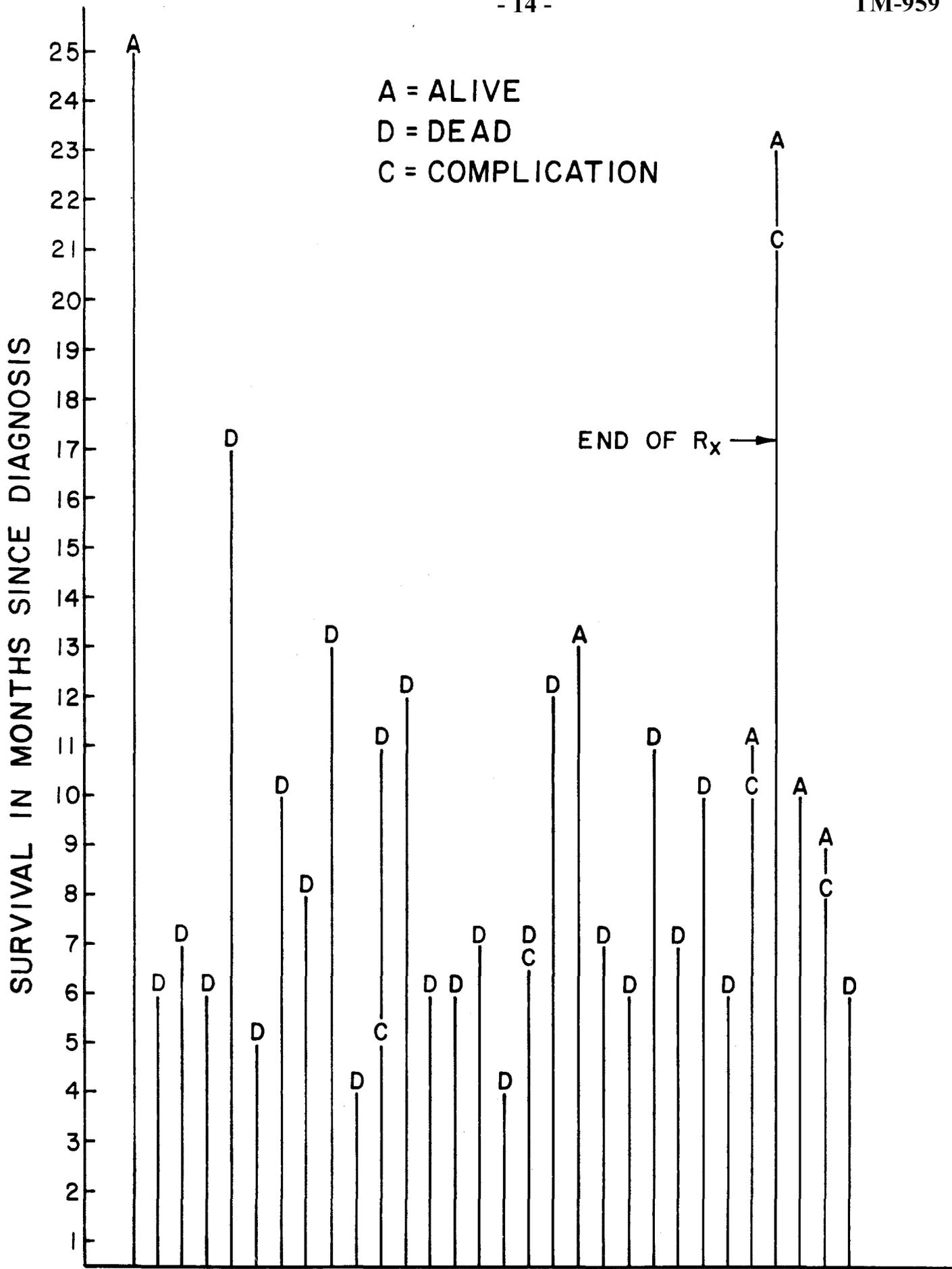
2

TM-959



3





PHASE II STUDY PANCREAS CASES TREATED WITH NEUTRONS, MAY, 1978 TO JULY, 1979

PANCREATIC CARCINOMA
NO. OF PATIENTS = 30
p(66 MeV) Be(47 MeV) NEUTRONS
PHASE II STUDY

