1066936

710001

FS-87
SFS(.001)

Am J Clin Oncol (CCT) 5: 579-587, 1982

# Clinical problems in radiotherapy of carcinoma of the pancreas*

Joseph R. Castro, M.D.
William M. Saunders, Ph.D., M.D.
Jeanne M. Quivey, M.D.
George T. Chen, Ph.D.
J. Michael Collier, Ph.D.
Kay H. Woodruff, M.D.
John T. Lyman, Ph.D.
Patrick Twomey, M.D.
Charles Frey, M.D.
Theodore L. Phillips, M.D.

SINCE 1975, 84 PATIENTS WITH LOCALLY-ADVANCED unresectable carcinoma of the pancreas have been irradiated using helium and heavier particles at the University of California Lawrence Berkeley Laboratory. Despite surgical exploration and an extensive diagnostic workup including radiological, nuclear medicine, and computer-assisted tomographic studies, many patients proved to have occult liver metastases manifested within 9 months post treatment. In addition, local and regional control of the primary neoplasm (~20%) has been difficult to obtain even with doses of 6000 equivalent rad in 7½ weeks. Gastric and biliary obstruction have required surgical bypass procedures since irradiation has not been successful in relieving obstructive symptoms.

Evidence of gastrointestinal injury has been present in postradiation therapy in approximately 10% of patients, a figure which might be higher if more patients had a longer survival (average 10 months). Some patients require pancreatic enzyme supplementation because of pancreatic deficiency either secondary to tumor or treatment.

Further improvement in local control and survival requires better diagnostic methods for evaluation of local and metastatic spread, improved therapy for local and regional disease, as well as therapy directed at occult liver metastases that are frequently present.

From the University of California Lawrence Berkeley Laboratory Division of Biology and Medicine; University of California School of Medicine, San Francisco, California; Department of Radiation Oncology, Veterans Administration Hospital, Martinez, California, Veterans Administration Surgical Oncology Group

* Presented at the 64th Annual Meeting of the American Radium Society.

Pancreatic cancer continues to increase in frequency in the United States with approximately 20,000 deaths per year now attributable to this disease. Rarely can these cancers be successfully managed by surgical means to permit radical extirpation, except in tumors limited to the pancreas or with minimal extension to neighboring structures. Only about 15–20% of patients present with tumors localized to the pancreas; the remainder have either extension to surrounding tissues and/or regional lymph nodes or liver. The frequency of liver metastases is high, various investigators[4,8] estimating the incidence from 65–80%.

While radiotherapy has been utilized in this disease for many years[1,9,12] only recently has progress been made in increasing local and regional control and prolonging survival. The results to date are still unsatisfactory and continued efforts are needed to find better methods of local and systemic therapy.[9,15,16]

Pancreatic cancer appears suited to multimodality treatment since surgery, chemotherapy, and radiotherapy can each offer potential treatment benefits and no single therapy is likely to be successful alone.

Radiotherapy can provide local and regional control if sufficient dose can be delivered to the tumor and adjacent lymph nodes without causing injury to nearby vital organs such as gut, spinal cord, kidneys, or liver.

Single-agent chemotherapy (5-fluorouracil) has improved survival modestly in controlled clinical trials[10] and ideally could be used as an adjuvant to diminish the incidence of distant metastases and to assist in local and regional control.



DOE/HQ

1066931



Surgical intervention is required to establish the histologic diagnosis, perform required bypass procedures for both the biliary and gastrointestinal tracts, and to assist in demarcating the pattern and extent of spread of the tumor. For truly limited disease, radical resection can be performed, although most tumors will have spread too far for complete resection. Interstitial implant of Iodine-125 seeds performed at surgery may be helpful in improving local control by allowing increased local dose to the tumor bulk. Combination with external irradiation is needed to deliver adequate doses to areas of direct extension and nodal spread.

Radiotherapy alone is unlikely to relieve the biliary or gastric obstruction common in these tumors; therefore percutaneous needle biopsy for histologic confirmation is only rarely useful in small tumors, usually in the head of the pancreas, when it is certain that no obstruction of the biliary or intestinal tract exists.

High-energy photon beams, alone or with electrons, have been combined to create advantageous dose distributions to the pancreatic region.[14] Interstitial implants of the tumor mass, usually with Iodine-125 seeds, have the apparent advantage of delivering a higher local dose, albeit over a prolonged period of time.[10,11]

High LET charged particles have also been used to deliver high effective doses to a limited volume and offer the promise of improved dose localization with less damage to adjacent normal structures, and enhanced biological potential because of their high deposition of energy at the end of their path in tissue.[7,9,15,16]

While some patients have been cured of their disease with current techniques, the overall level of tumor control within the irradiated volume still remains low, somewhere in the range of 15–30%. Similarly, survival has been low, with the median survival ranging from 8–10 months. In part this reflects failure to control the tumor locally, but survival is also markedly affected by the high rate of occult liver metastases (60–80%) in these patients. A continued search for improved management methods is needed therefore, and the radiation oncologist should be an important part of this effort.

## Material and methods

Between July 1, 1975 and December 31, 1981, we definitively irradiated 94 patients with locally advanced carcinoma of the pancreas as part of a systematic study of heavy charged particle radiotherapy at the University of California Lawrence Berkeley Laboratory. These patients were referred from a variety of cooperating institutions and physicians in the region, including members of the Northern California Oncology Group. Some patients were referred from other areas through the Veterans Administration Surgical Oncology Group and the Radiation Therapy Oncology Group.

All patients had histologic proof of adenocarcinoma of the pancreas; various types of surgical procedures had been performed to bypass the biliary and gastric obstruction present in the majority of patients, although not all were in need of such procedures. Although some surgeons were concerned early in the study about possible complications of biopsy of the pancreas tumor, we did not see any problems arise from this procedure in our patients.

For the most part these patients had Karnofsky ratings of greater than 70 and were ambulatory. Epigastric distress, anorexia, and weight loss were frequent and often debilitating features of the disease however, and appeared to be independent of the radiotherapy administered to the upper abdomen with particles. Dietary supplements including pancreatic enzymes appeared to be of value only occasionally in improving the nutritional status. Generally, patients with back or abdominal pain were palliated, although severe pain remained a bad prognostic sign.

Usually, radiotherapy was administered with patients in the standing or seated position using helium or heavier particle (carbon, neon) beams available from accelerators at the Lawrence Berkeley Laboratory. Multiple diagnostic studies were utilized to localize the tumor and plan the particle radiation treatment, including CT scanning, contrast radiographs, surgical demarcation, and clipping in some patients. Occasionally, other procedures such as ultrasound were used. Multi-beam-directed therapy was given, generally consisting of anterior plus opposed lateral portals, although often a right or left lateral and anterior port was utilized. Doses ranged from 41 Gray-equivalents, to 70 GyE in 7–9 weeks with the most frequent dose being 60 GyE in 7–8 weeks. Patients were ordinarily treated 4 times per week with daily doses of 2.0 GyE. Portal films were obtained daily to assure correct positioning of the patient and



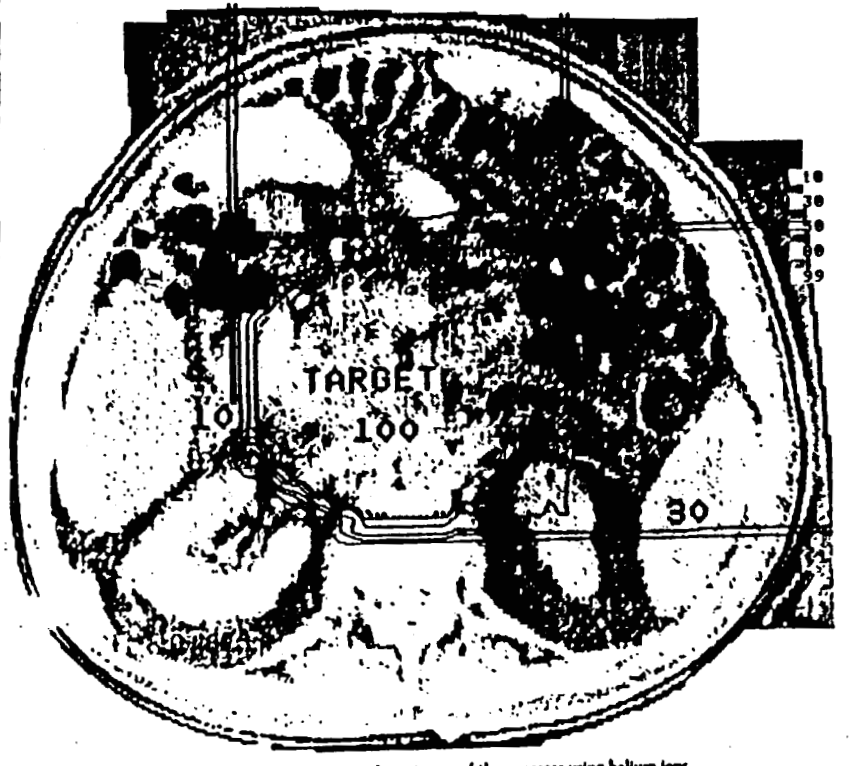


FIGURE 1. Isoeffect curve for two-field treatment of carcinoma of the pancreas using helium ions.

multi-beam delivery. A typical isodose distribution, and portal films for particle irradiation of pancreatic tumors, is shown in Figures 1, 2a, and 2b.

These patients were followed both at the Lawrence Berkeley Laboratory and by their referring physicians except for a small group of patients referred through the Veterans Administration Surgical Oncology Group from different parts of the United States, who were followed closer to home, with follow-up information forwarded to Lawrence Berkeley Laboratory. Wherever possible, serial CT scans were obtained as part of the follow-up. Analysis of serial changes in the pancreatic tumor mass were made wherever possible and have been found useful in assessing results of therapy.[17]

An effort was made to obtain histologic evidence of local control or failure, either in the occasional patient undergoing a second laparotomy, usually for intestinal bypass, or by means of autopsy examination in patients who had expired. As many patients entered the terminal portion of their illness at some distance from the laboratory, autopsies were difficult to obtain in some instances. The addition of a study pathologist assisted in increasing the autopsy rate in recent years through closer communication with referring physicians and hospital pathologists.

The patients irradiated in this study are grouped into four series (Tables 1 and 2): 1) pilot (phase I and II) irradiations with helium ions; 2) a phase III prospective randomized trial in which patients were assigned either to helium ion irradiation at

DOE/HQ

FIGURE 2a. Port film of anterior treatment volume in a patient with carcinoma of the pancreas being treated with helium ions.

Lawrence Berkeley Laboratory or photon irradiation at one of the collaborating facilities, both arms also receiving 5-fluorouracil chemotherapy; 3) a group referred from the Veterans Administration Surgical Oncology Group for a nonrandomized phase I–II trial of heavy particle irradiation; and 4) a group consisting of patients with tumors too advanced for the randomized helium study who were assigned to a phase I study of heavy particle irradiation.

In addition to the 94 patients who completed treatment, an additional 13 patients are excluded from analysis. One patient did not have histologic confirmation of his disease; 12 patients had progressive disease with distant metastases during therapy and were unable to complete treatment.

The most common dose prescription utilized was 60 GyE (6000 rad equivalents) given at 2.0 GyE per fraction; four fractions per week over a time course of 7.5–9 weeks. With better selection of patients and more complete pretherapeutic evaluation, and as experience was gained in treatment techniques,



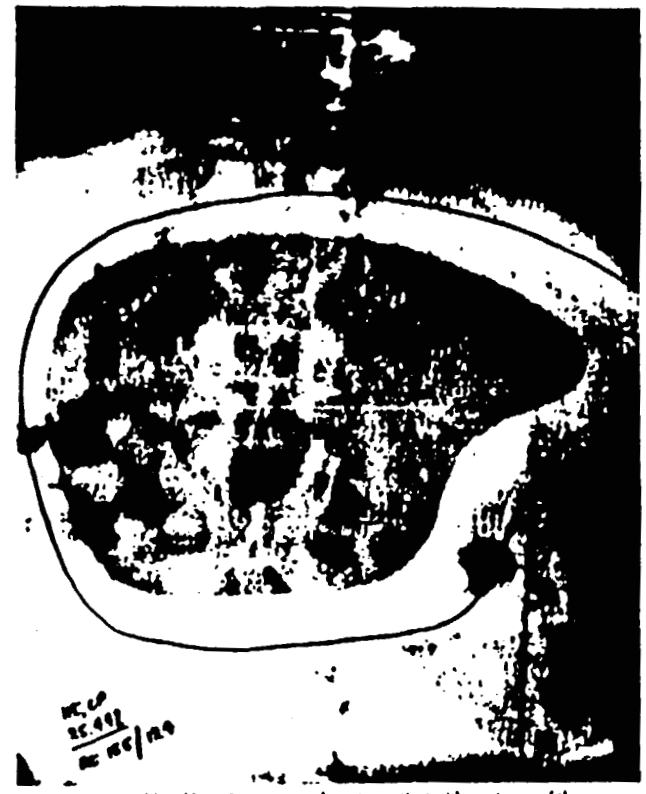

FIGURE 2b. Port film of lateral treatment volume in a patient with carcinoma of the pancreas being treated with helium ions.

the number of patients failing to complete treatment fell to very low levels. The total dose was gradually escalated, reaching a level of 66 GyE in 8 weeks.

Most of these patients were treated with helium ion irradiation. A small group of patients received heavy particle irradiation consisting of either carbon ion or neon ion irradiation most commonly given as a boost form of therapy. Only a few patients, mostly with quite large tumors, and often with metastases to liver or regional and paraaortic lymph nodes, received all of their therapy with heavy particle irradiation.

A sizeable number of patients received 5-fluorouracil chemotherapy as a part of the overall management. Most of these patients received concomitant 5-fluorouracil chemotherapy given as part of the phase III randomized clinical trial. For this group, the dosage was 500 mg/m² given daily for 3 days at the beginning of radiotherapy and repeated monthly until completion of irradiation. Maintenance therapy consisted of weekly doses of 5-Fu in the amount of 500 mg/m². In other patients, the dosage schedules varied widely according to the referring physician and/or the associated medical oncologist.

1066938

DOE/HQ

1066939



TABLE 1

Helium and Heavy Particle Irradiation of Locally Advanced Adenocarcinoma of Pancreas—Lawrence Berkeley Laboratory 1975–1981

| | Time Period | No. of Pts. Entered | No. of Pts. Excluded | No. of Pts. Evaluable |
|---|---|---|---|---|
| Pilot group Helium | 1975–1979 | 47 | 7—Inc. Rx, Progression<br>1—No Rx | 39 |
| Prospective, randomized Helium arm | 1978–1981 | 28 | 1—Inc Rx, Progression | 27 |
| Veterans Surgical Oncology Group Helium, heavy | 1980–1981 | 14 | 2—Inc Rx, Progression | 12 |
| Advanced tumors Helium, heavy | 1979–1981 | 18 | 2—Inc Rx, Progression | 16 |
| Totals | | 107 | 13 | 94 |

TABLE 2

Locally Advanced Carcinoma of Pancreas—Lawrence Berkeley Laboratory 1975–1981 Evaluable Patients

| | Dose Range | TDF Range | Dose Per Fraction | Average Tumor Dose |
|---|---|---|---|---|
| Pilot group Helium | 50–64 GyE* | 81–102 | 2.0 GyE* | 60 GyE* |
| Prospective randomized Helium arm | 50–66 GyE* | 79–104 | 2.0 GyE* | 60 GyE* |
| VASOG (nonrandomized) Helium and heavy | 56–66 GyE* | 95–105 | 2.0–2.5 GyE* | 61 GyE* |
| Advanced tumors pilot (nonrandomized) Helium and heavy | 41–70 GyE* | 77–105 | 2.0–3.0 GyE* | 60 GyE* |

* GyE = Gray Equivalent = Particle dose equivalent to 100 Rad Low LET X-ray

## Results

Control within the irradiated volume ranged from 15–25% (Table 3) with an overall rate of 18%. Only 10% of patients remain alive and well for periods ranging from 4–42 months, although several other individuals survived more than 2 years only to succumb to intercurrent disease. The longest survivor lived 73 months from first day of therapy before developing a second primary lung tumor with metastatic disease. At autopsy, there was no evidence of tumor within the pancreas. The average survival ranged from 7 months in patients with more advanced tumors to 12 months in the initial pilot series irradiated with helium ions. The average survival in all patients completing therapy was 10 months.

There was a trend to longer survival in the patients receiving 5-Fu chemotherapy. The average survival was 10 months in those receiving chemotherapy but only 8 months in those not receiving chemotherapy. An absolute conclusion cannot be drawn as these groups were not comparable in all respects.

A sizable number of patients were shown to have distant metastases, most often in the liver, despite careful pretherapeutic workup including isotope and CT scans of the liver as well as liver function studies. About 65% of our patients demonstrated metastatic disease within 1–10 months post treatment.

Although most patients had mild signs of anorexia, nausea, and epigastric distress secondary to the irradiation, the acute side effects clinically appeared less than one would expect with photon irradiation of the upper abdomen to these dose levels. Some patients who received photon irradiation followed by heavy particle boost therapy



TABLE 3

Locally Advanced Carcinoma of Pancreas—Lawrence Berkeley Laboratory 1975–1981

| | No. of Pts. Evaluable | LFU | Average Survival | Loc. Cont. | Alive and Well | Difference LC, A & W | Pts with DM |
|---|---|---|---|---|---|---|---|
| Pilot group Helium | 39 | — | 12 Mos. | 6/39 (15%) | 2/39 (2–24 Mos.) | 3—ID<br>1—DC | 27/39 |
| Prospective Randomized Helium | 27 | — | 10 Mos. | 5/27 (19%) | 3/27 (4–10 Mos.) | 1—DM<br>1—DC | 16/27 |
| VASOG (Nonrandomized) Helium and heavy | 12 | 3 | 7.5 Mos. | 3/12 (25%) | 3/12 (6–12 Mos.) | | 5/12 |
| Advanced tumors Pilot (nonrandomized) Helium and heavy | 16 | — | 7 Mos. | 3/16 (19%) | 2/16 (4–10 Mos.) | 1—DM | 13/16 |
| Total | 94 | | 10 Mos. | 17/94 (18%) | 10/94 (10%) | | 61/94 (65%) |

remarked at the improved tolerance they noted when transferring to the particle irradiation.

Nevertheless, a portion of the distal stomach and proximal duodenum was unavoidably included in the high dose irradiation zone. Seven patients who did not have persistent tumor developed evidence of gastrointestinal injury, most often manifested by upper gastrointestinal bleeding and/or fibrosis of distal stomach and duodenum with partial bowel obstruction. Several patients required surgery to bypass obstruction, while those with bleeding had need of prolonged medical care and/or hospitalization with frequent transfusions. Two additional patients had fatal complications secondary to chemotherapy and irradiation with resultant cytopenia, hemorrhage, and infection.

No patients encountered renal toxicity, spinal cord injury, or liver damage secondary to the irradiation. Thus 9/94 patients (Table 4) or 10% incurred severe complications secondary to the therapy. Of 17 patients with control within the irradiated area who survived from 6–73 months post therapy, however, seven incurred severe gastrointestinal injury. Thus a note of caution is indicated, since a higher severe complication rate might have been encountered if more patients had survived for long periods of time.

An additional source of potential confusion regarding true rates of therapeutic complication is 13/77 patients with persistent tumor who developed signs of gastrointestinal bleeding, ulceration, or obstruction secondary to persistent disease. Careful autopsy examination is the only way to exclude these tumor-caused effects from those ascribed to therapy.

## Discussion

Our experience with patients having locally advanced, unresectable adenocarcinoma of the pancreas mirrors that of other investigators. These tumors are often silent until obstruction of the biliary tract causes painless jaundice. Other routes of spread may give rise to symptoms of pain, nausea, vomiting, or signs of gastric outlet obstruction. Most patients note anorexia, epigastric distress of some

TABLE 4

Lawrence Berkeley Laboratory 1975–1981—Severe Complications of Therapy

| | No. of Pts. | Complications |
|---|---|---|
| Pilot group Helium | 39 | 3—GI bleeding, fibrosis<br>1—Cytopenia* |
| Prospective randomized Helium arm | 27 | 1—GI bleeding, fibrosis<br>1—Cytopenia* |
| VASOG (nonrandomized) Helium and heavy | 12 | 1—GI bleeding, fibrosis |
| Advanced tumors pilot (nonrandomized) Helium and heavy | 16 | 2—Fibrosis, obstruction |
| Total | 94 | 9 |

* Two fatal—bleeding following chemotherapy.

DOE/HQ

type, and significant weight loss before the diagnosis is made. Computer-assisted tomographic scanning of the upper abdomen has revolutionized the diagnosis of this disease and greatly aids in accurate radiation treatment planning. Since this disease is becoming more frequent in the United States and other industrialized societies, a high index of suspicion with appropriate diagnostic workup is indicated for any patients presenting these symptoms or signs.

The etiology of this disease is unclear, although environmental agents have been suggested.[5] Whether environmental exposure to carcinogens, smoking, or western dietary habits may ultimately be shown to have a role in the causation of this disease awaits further study.

Improved delivery of higher doses to the tumor through use of charged particle radiotherapy, combinations of high-energy photons and/or electrons, and interstitial implants, combined with external therapy, offers techniques for improving local and regional control. Recent reported results with Iodine-125 seed implants[10,11] suggest an improved local control rate although care must be taken in interpreting these results since patients with small tumors in the head of the pancreas have long been known to have a better chance of cure than those with large tumors extending to adjacent structures or arising in the body and/or tail of the pancreas. When utilized, interstitial seed implant should be combined with external photon therapy so that adjacent routes of spread can be adequately irradiated. The high incidence of liver metastases makes a search for irradiation techniques designed to treat the entire liver worthwhile. Combinations of low-dose whole liver irradiation plus multidrug chemotherapy could offer an improved chance of control of occult metastases within the liver. Such studies are being piloted within our own facility but only in a small group of patients as yet. A continued search for better chemotherapeutic agents should be undertaken in view of the prevalence of this disease and its rising incidence.

Radiotherapists should not attempt to utilize radiation to relieve gastrointestinal or biliary tract obstruction. Attempts to accomplish this in a small group of patients treated early in our series met with complete failure. Surgical bypass should be insisted on for obstruction of either biliary tract or gastrointestinal tract. This should be accomplished before irradiation is begun and should be adequate so as not to interfere with therapy. If incomplete or inadequate, surgical revision should be requested before therapy is undertaken. Histologic confirmation should always be obtained; the feared risk of biopsying pancreatic tumor appears groundless as no complications have been incurred to date from this biopsy.

As these patients have significant anorexia and weight loss, every attempt should be made to sustain their nutritional competence. Hyperalimentation should be considered for those patients who steadily continue to lose weight despite aggressive dietary measures. Pancreatic enzymes may be of some value although not as much as was hoped. The possibility of diabetes mellitus should also be considered, although it has been rare in our series.

Careful pretherapeutic evaluation of the liver should be obtained, including liver function tests, isotope scans, and CT scans. Needle or wedge biopsy of the liver at the time of exploratory laparotomy was not accomplished in our series, although in view of the high rate of occult metastases, it may be of merit in patient selection and management. A high index of suspicion for liver metastasis should be maintained throughout the therapy and follow-up, and appropriate tests undertaken to establish it if it is suspected.

A minimum tumor dose of 60 GyE should be delivered to the tumor bulk, and a higher dose if possible, through the use of reduced field techniques or intestitial implant. Multifield beam-directed therapy appears the best technique for pancreatic irradiation. By use of lateral fields, the kidneys can virtually be avoided, since in most instances they lie posterior to the pancreas and adjacent lymph nodes.

Careful CT scanning should be utilized to plan the irradiation treatment. Modern diagnostic CT scans offer the best information relative to tumor location, size, and routes of spread. In our experience this has proven more valuable than surgical demarcation and clipping given the limitations of surgical exploration that are present in most patients undergoing laparotomy for this tumor.

Whole liver irradiation of 2500 rads in 2.5–3 weeks appears well tolerated in a small group of patients, and is consistent with past experience in liver irradiation. If whole liver low-dose irradiation is undertaken, however, care should be taken not to overirradiate a significant portion of the liver through the pancreatic target volume portals.



The possibility of intestinal tract injury can be minimized by careful treatment planning with exclusion of as much gut as possible. Some risk will have to be taken in terms of distal stomach and proximal duodenum which often lie in immediate apposition to the tumor. Careful follow-up examinations are needed for early diagnosis of injury to the stomach and/or duodenum. Endoscopy appears to be of the greatest value in excluding persistent tumor as a cause of gastrointestinal bleeding although serial CT scanning is also of value.

Although the tumor bulk may be seen to regress in serial CT scans in patients with local and regional control the scan does not appear to return to normal, as some residual, presumably fibrotic, mass is evident for many months and even years. An enlarging mass on serial CT scans almost invariably means persistent, growing tumor.

Consideration of combination chemotherapy including 5-Fu, adriamycin and mitomycin-C is under way. This will increase the risk of gastrointestinal injury and therefore must be approached cautiously.

Earlier diagnosis, better treatment planning, and multidisciplinary management offer improved chances of control of this disease. Radiotherapists, surgeons, and chemotherapists should work together to improve therapeutic management. The long-held, pessimistic outlook regarding this disease should be replaced with the cautious observation that some patients can be successfully treated and continued efforts can be made to improve on current results.


## ACKNOWLEDGMENT

This work was supported in part by NIH/NCI CA19138, CA15184, CA21744, and DOE W7405ENG-48.


## References


1. Pack, G. T. and McNeer, G.: Radiation treatment of pancreatic cancer. Vol. 40, No. 5, November 1968.
2. Pilipech, M. V. and Miller, H. H.: Preoperative irradiation in carcinoma of the pancreas. *Cancer 46: 1945-1949, 1980.*
3. Abe, M., Takahashi, M., Yokumoto, E., Adachi, H., Yoshii, M., and Mori, K.: Clinical experiences with intraoperative radiotherapy of locally advanced cancers. *Cancer 45: 40–48, 1980.*
4. Wendruff, K. H., Castro, J. R., Quivey, J. M., Saunders, W. M., Chen, G. T. Y., Lyman, J. T., Tobias, C. A., Walton, R. E., and Peters, T. G.: Postmortem examination of twenty pancreatic carcinoma patients treated with helium ion irradiation. Presented in part at the National Pancreatic Association, Chicago, Illinois, November, 1981.
5. Lin, R. S., Kessler, I. I.: A multifactorial model for pancreatic cancer in man. *JAMA Vol. 245, No. 2, 147-152, 1981.*
6. Fortner, J. G.: Surgical principles for pancreatic cancer. *Cancer 47: 1712-1718, 1981.*
7. Kaul, R., Cohen, L., Hendrickson, F., Awschalom, M., Hrejsa, A. F., and Rosenberg, I.: Pancreatic carcinoma I. Results with fast neutron therapy. *Int J Radiat Oncol Biol Phys 7: 173-178, 1981.*
8. Al-Abdulla, A. S. M., Hussey, D. H., Olson, M. H., and Wright, A. E.: Experience with fast neutron therapy for unresectable carcinoma of the pancreas. *Int J Radiat Oncol Biol Phys 7: 165-172, 1981.*
9. Dobelbower, Jr., R. R.: Current radiotherapeutic approaches to pancreatic cancer. *Cancer 47: 1729-1734, 1981.*
10. Shipley, W. U., Nardi, G. L., Cohen, A. M., and Ling, C. C.: Iodine-125 implant and external beam irradiation in patients with localized pancreatic carcinoma. *Cancer 45: 709-714, 1980.*
11. Tepper, J., Nardi, G., and Suit, H.: Carcinoma of the pancreas. Review of MGH experience from 1963-1973. *Cancer 37: 1519-1524, 1976.*
12. Cavanaugh, P. J.: Considerations appropriate to a clinical trial of definitive radiation therapy in adenocarcinoma of the pancreas. *J Surg Oncol 7: 135-137, 1975.*
13. Whittington, R., Dobelbower, R. R., Mohiuddin, M., Rosato, F. E., and Weiss, S. M.: Radiotherapy of unresectable pancreatic carcinoma. A 6-year experience with 104 patients. *Int J Radiat Oncol Biol Phys 7: 1639-1644, 1981.*
14. Dobelbower, R. R., Strubler, K. A., and Suntharalingam, N.: Treatment of cancer of the pancreas with high-energy photons and electrons. *Int J Radiat Oncol Biol Phys 1: 141-146, 1977.*
15. Castro, J. R., Quivey, J. M., Lyman, J. T., Chen, G. T. Y., Phillips, T. L., Tobias, C. A.: Radiotherapy with heavy charged particles at Lawrence Berkeley Laboratory. *J Can Assoc Radiol 31: 30-34, 1980.*
16. Castro, J. R., Quivey, J. M., Lyman, J. T., Chen, G. T. Y., Phillips, T. L., Tobias, C. A., and Alpen, E. L.: Current status of clinical particle radiotherapy at Lawrence Berkeley Laboratory. *Cancer, 46: 633-641, 1980.*
17. Quivey, J. M., Castro, J. R., Chen, G. T. Y., Moss, A. A., and Marks, W. M.: Computerized tomography in the quantitative assessment of tumor response. *Br J Cancer 41: Suppl IV, 30, pp. 31-34, 1980.*
18. Moertel, C. G., Lokich, J. J., Childs, D. S., Schein, P. S., and Lavin, P. T.: An evaluation of high-dose radiation and combined radiation and 5-fluorouracil therapy for locally unresectable pancreatic cancer (Abstract). *Proc Am Soc Clin Oncol 17: 244.*


*Write for reprints to:* Joseph R. Castro, M.D., Building 55, Room 105, Lawrence Berkeley Laboratory, Berkeley, California 94720.

DOE/HQ