

PANCREAS CANCER

By: Gil Lederman, M.D.

Pancreas cancer remains one of the most common and feared malignancies. The pancreas gland is located deep in the abdomen. There is no early screening or evaluation of this cancer.

The symptoms of pancreas cancer are often vague. Physical examination by itself is usually quite unhelpful. Sometimes patients have blockage of the biliary tree or the bile ducts and jaundice occurs. This might be an early sign. Jaundice is a yellowing of the skin due to obstruction of liver ducts. Another symptom is abdominal discomfort.

Because of the lack of screening tests, the cancer is often found when it is locally, regionally, or systemically advanced. Pancreas cancers spread locally through the adjacent tissues into the lymph nodes often into the liver and possibly beyond. Biopsy is best performed using CT-guided needle techniques or open surgery. Interventional radiologists are quite adept at placing a needle most anywhere in the body for purposes of diagnosis. Sometimes surgeons open the abdomen for other purposes and find the cancer. In certain cases, the surgeon will attempt to perform a Whipple procedure to remove the cancer.

It is known that pancreas cancer is the fourth leading cause of death in the United States and that only 20% of patients have a cancer that is respectable when diagnosed by x-ray criteria. Of this 20%, only about two-thirds have a complete resection with the surgical margins being free of malignancy. Five-year survival after resection varies from 1 to 24%. For that reason, additional or adjuvant therapy has been proposed for those with pancreas cancer.

The usual treatment beyond surgery is chemotherapy and radiation. A variety of different chemotherapy drugs have been used but most center on 5FU chemotherapy and an approximate five-week course of radiation.

A recent report by Mehta et al in the International Journal of Radiation Oncology Biology Physics evaluated treatment of 52 patients who underwent removal of the pancreas followed by chemotherapy and radiation.

Why is this an important issue? It is because often more than one-half the patient who have recurrent has local recurrence - meaning the cancer has come back in the pancreas area. I recently saw a patient who had radical resection of his pancreas at a major cancer institution only to have recurrence of the cancer in the pancreas bed within weeks (along with metastases to the liver). Also, local recurrence is quite unpleasant as it may cause further pain, nausea, loss of appetite, weight loss, blockage of intestines and even bleeding and jaundice.

In light of this, a study was proposed for patients with resected pancreas cancer to administer chemotherapy and radiation.

Between 1994 and 1999, 52 patients who underwent resection of the pancreas and duodenum (adjacent intestine) for adenocarcinoma of the pancreas, were treated on an adjuvant protocol. The protocol was started once patients had begun adequate oral ingestion, which usually occurred within six weeks after surgery.

Patients were treated with radiation on the linear accelerator with three or four fields and the volume was said to the pancreas, celiac lymph nodes and periaortic lymph nodes (lymph nodes around the aorta). Patients were given a dose of 45 Gray in 1.8 Gray fractions. This corresponds to a five-week course that would be equal to 4500 rad. If the cancer was present at the margin of resection, which suggests that cancer cells were still present, a 2cm. margin around the cancer was continued to a dose of 5400 rad, or 54 Gray. Some patients received a radiation dose as

high as 60 Gray, or 6000 rad. Ninety percent completed radiation therapy as prescribed.

Eight patients with gross or microscopic residual disease suspected, received intraoperative radiation in one dose using an orthovoltage machine before the adjuvant therapy started.

The 5FU chemotherapy was given by protracted intravenous infusion. The dose was 200 to 250 mg/m² (milligrams per meter squared), per day, seven days a week, for five weeks. The initial dose was 200mg/m² and rose 225mg/m², and later to 250mg/m² per day. If there was toxicity, the drug was discontinued and later re-started at a reduced dose.

Of the 52 patients, the age ranged from 38 to 78, with 30 men and 22 women. Of the 52 patients, 35% had surgical margins of resection involved with cancer, while 59% had cancer that had spread to the lymph nodes.

The median follow-up was 24 months with a range of 3 to 52 months for the surviving patients. The median actuarial survival was 32 months. Which patients did best? Those with uninvolved surgical margins had the best survival. If the cancer did not spread to the margins, then the median survival was 32.4 months. If the cancer spread to the margins, the median survival was 10.8 months.

Also, the two-year survival in patients with negative margins was 71% while those who had positive margins of resection, the two-year survival of 31%. Statistical analysis was performed to show this was a meaningful difference. Survival rates worsened if the lymph nodes contained cancer. Those with cancer in the lymph nodes had a 25-month median survival versus 34.8 months if there was no cancer in the lymph nodes.

Also at two years, 50% of the lymph node positive patients were alive compared to 64% of the lymph node negative patients.

The authors looked at site within the pancreas possibly predicting outcome and there was no difference seen. The benefits of intraoperative radiation also could not be determined.

Why was 5FU given by constant infusion? The reason is the half-life of 5FU is so short. When 5FU is given in the vein, the half-life is only about 20 minutes. The purpose of continuous infusion was it prolonged exposure to the chemotherapeutic agent.

Other predictive factors of survival included tumor size. Of tumors measuring less than 2cm, the median survival was 32.4 months. If the cancer was more than 3cm, the median survival was 19.2 months. There was no difference by age. For patients less than/older than 65 years, the median survival was 25.2 months. At three years, the actuarial survival for patients with tumors less than 3cm was 44%. For tumors more than 3cm, it was 29%.

At three years, the actuarial survival for positive lymph node patients was 19% and patients with negative lymph nodes, the actuarial survival was 50%. Also at three years, the actuarial survival for positive surgical margin patients was 26% and was 40% for those patients with negative margins. At the time of writing the article, 6 patients were alive at 32, 33, 36, 41, 42 and 52 months.

Also reported in the conclusion of the article was a series of 14 patients who were felt to be marginally respectable having pancreas cancer. They were treated with chemotherapy and radiation prior to surgery. Eight of the 14 patients underwent surgery and all had negative surgical margins. The median survival for that group was 23 months.

The authors concluded, "We believe that there continues to be mounting evidence from prospective trials and large single institution experience that support the role of radiation and 5FU as adjuvant therapy for surgically resected locally confined pancreatic cancer. We continue to

approach the treatment of this malignancy aggressively noting the potential for improved median survival. In this paper, we review our experience using RT with concomitant 5FU by constant infusion chemotherapy as adjuvant therapy for resected pancreatic cancer. This regimen is well tolerated by patients and results in an increase of total dose of chemotherapy, and increase in chemotherapy and RT dose intensity and a favorable raw median survival of 32 months."

"However direct comparisons of our results with other series and even our own historic controls are difficult because of small patient numbers, inadequate descriptions of favorable and unfavorable prognostic factors and the inconsistent administration of adjuvant therapy. In addition, the treatment of pancreatic cancer is evolving. The improved pre-operative imaging techniques, post-operative care and anti-emetics make our cohort different from patients referred in earlier studies. To confirm the benefit over traditional bolus administration of 5FU, a large multi-institutional randomized trial will be needed. We are hopeful that the development of improved imaging studies, serum markers, systemic agents, and further refinements in radiotherapy technique will result in greater numbers of patients."

At Radiosurgery New York we are using combined chemotherapy/radiation for patients with pancreas cancer. However, we have taken the additional major step of using stereotactic body radiosurgery for these patients. Our data using stereotactic body radiosurgery for pancreas cancer shows high control rates. (Control is defined as cessation of growth, shrinkage or disappearance of the tumors in the treated fields.) For patients with unresectable or recurrent pancreatic cancer, our success rate - or control rate - in the treated area is 90%. This is higher than even infusional radiation directly into the pancreas. Furthermore, our treatment can be used even after standard surgery, chemotherapy or radiation. We have compared our data to others and have found an improvement in cancer-free survival. Obviously patients without metastases live longer than those with metastases. We have also looked at radiosurgery and resectable cancer where the patients have declined surgery. We have found our rates of survival are better than with unresectable cancers.

We have seminars open to the public to discuss treatment options. We also have multi-disciplinary panels of physicians to review films, reports and medical history. We have a cancer hot line to answer questions: 212-CHOICES and as well have an e-mail address: gil.lederman@rsny.org.