Pancreatic cancer is the second most common GI malignancy and the fifth leading cause of adult cancer-related deaths in the United States. Because it is usually detected at a very advanced stage, most patients die within a year of diagnosis and fewer than 5% survive for 5 years.

The University of Chicago Hospitals has recently established one of the few formal pancreatic cancer centers in the country. This is the only center in the Chicago area devoted to this devastating disease. The center brings a multi-disciplinary approach to the diagnosis and treatment of this type of cancer, combining GI endoscopists, pathologists, and cancer geneticists with medical, surgical and radiation oncologists.

"The University of Chicago has expertise in every single field that deals with pancreatic cancer," says Irving Waxman, MD, director of endoscopy at the University of Chicago and a founder of the pancreatic cancer center. From interventional endoscopy to genetics to pathology, from radiation therapy to surgery, and from standard chemotherapies to phase I, II and III trials of investigational drugs, "we have nationally known physician-scientists at every stage," Waxman said.

"This is a very comprehensive program," confirms co-director Fabrizio Michelassi, MD, vice chairman of the department of surgery and section chief of general surgery. "We have strengths in all aspects of diagnosis and treatment of pancreatic cancer."

This depth, combined with the multi-disciplinary approach, is quite important," adds cancer surgeon Mitchell Posner, MD, because "that's what is going to make a difference. In this disease, anything we try is worthwhile, since patients do not do well with traditional therapy."
**Clinical Notes: from the Pancreatic Cancer Center June 2004**

The University of Chicago has an established reputation in the treatment of pancreatic cancer dating back to 1937 when the first pancreatico-duodenectomy was performed here. The university’s experience in this area draws a large volume of pancreatic cancer patients, nearly 50 new patients a year.

“We know that hospital volume correlates with better outcomes,” said Mitchell Posner, MD, chief of surgical oncology. “In an operation with significant morbidity and mortality, that makes a difference.” The accepted mortality from the surgery is around 2% to 3% in experienced centers and “we’re clearly at that level,” he said.

Despite the team’s skill and experience, “surgery is not the answer,” said Posner. “You may help people live a little bit longer and live a little bit better, but to think that surgery is going to make a significant impact, in and of itself, is a little naive.”

When standard therapies are ineffective, he added, “anything that is novel is the correct thing to do.” The center is testing several new therapies, including a promising new approach to gene therapy developed at the University, along with several trials not available anywhere else in the Chicago area.

**Improved diagnosis and staging with EUS**

An endoscopic ultrasound or endoscopic ultrasound-guided, fine-needle aspiration can provide very precise staging and can even detect tumors when other imaging modalities have been unable to provide a diagnosis,” said Waxman. Similar techniques can play a role in precise application of investigational therapies, such as gene therapy, and in palliative treatment.

**Surgical approaches**

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**Investigational chemotherapies**

Like surgery, chemotherapy has had disappointing results in pancreatic cancer. The standard drug for this disease is gemcitabine (Gemzar), which shrinks tumors only 5 percent of the time. It is commercially approved for this indication because it makes 25% of people feel better and it improves one-year survival from 2% to 18%.

“Those are still pretty lousy odds,” according to Hedy Kindler, MD, director of gastrointestinal oncology.

But researchers in the University of Chicago Hospitals’ program are testing promising new biological therapies. Research has shown that pancreatic tumors produce a number of different growth factors, one of which is vascular endothelial growth factor (VEGF), which enables tumor growth by stimulating the development of new blood vessels to feed the cancer.

University of Chicago researchers are testing an investigational recombinant humanized antibody to vascular endothelial cell growth factor, known as Avastin, in pancreatic cancer. The researchers are among the first to demonstrate that this angiogenesis inhibitor can affect the growth of vessels that feed pancreatic tumors.

In one study, presented by Kindler at the American Society of Clinical Oncology meeting in June, Avastin combined with gemcitabine in patients who previously received no chemotherapy, boosted one-year survival from 18% up to 53%. “That’s dramatic,” said Kindler, who devotes more than half of her GI practice to patients with pancreatic cancer. “This treatment is very well-tolerated and is getting a lot of attention.”

Kindler, who has been receiving 10 calls a day about Avastin since her ASCO presentation, said this therapy for pancreatic cancer will be studied in a randomized fashion.
Investigational chemotherapies (continued)

over the next year in a large national trial led by the University of Chicago. Patients who are on anti-coagulants are not eligible for the trial.

Another genetic approach uses an experimental drug, SDX102, which targets an abnormal pathway in pancreas cancer. Another unusual approach uses arsenic trioxide, a poison that has been used as a medicine in China for 2,000 years. "Pancreatic cancer cells respond to arsenic in the laboratory, so we're testing it in people," said Kindler. This drug is now standard therapy for one type of leukemia.

The researchers are also studying a vaccine aimed at preventing recurrence in patients who have undergone surgery. "We're trying to stimulate the immune response to find any remaining tumors that might be there. This is very early in development," said Kindler.

**TNFerade**

One experimental treatment, called TNFerade, combines gene therapy with radiation therapy. A report at ASCO showed that two patients who initially were unresectable were able to undergo surgery to remove their pancreatic tumors after this treatment. "When one specimen was opened up," said Posner, "there was no remaining tumor."

This therapy requires the collaboration of an interventional endoscopist, a radiation oncologist and a surgical oncologist. It was developed at the University of Chicago by Ralph R. Weichselbaum, MD, PhD, chairman of radiation and cellular oncology, who patented the technique and has worked with a company called GenVec to move this technology into clinical trials.

This approach uses a modified adenovirus that is delivered to a pancreatic tumor via ultrasound-guided endoscopy, with a fine needle injection. This adenovirus carries the gene for tumor necrosis factor linked to a radiation-sensitive promoter. When exposed to radiation, it induces the production of TNF-alpha. The TNF kills tumor cells, makes the cancer more radio sensitive and prevents the growth of new blood vessels.

This is "an exciting new concept," says Waxman, "to go down with a scope and be sitting in front of the pancreas under ultrasound guidance and providing gene therapy." The University of Chicago Hospitals participated in phase-I studies and is the only Midwestern center where this therapy is being tested.

In addition to new therapies, the hospital offers the latest in palliation using stents and other new experimental techniques, to deal with biliary or gastroduodenal obstructions from tumors.

Progress in radiation therapy

The pancreatic cancer center is using intensity modulated radiotherapy, or IMRT, to shape the external beam in ways that can direct a heavier dose to the tumor while sparing nearby organs.

"In the old days, we treated the tumor with beams of radiation from three or four different angles, said Ashesh Jani, MD, assistant professor of radiation oncology. With IMRT, "we can sequence the multileaf collimators to have a non-uniform beam fluence."

The radiation oncologists and medical physicists plug CT data into a computer program to design a customized treatment plan that targets the tumor but limits the dose to surrounding structures, principally the small bowel, bowel and kidney," said Dr. Jani.

IMRT, which has been approved by the U.S. Food and Drug Administration, has been shown to help in treating head-and-neck and prostate cancers, but this technology has only recently been used to treat gastrointestinal malignancies. The University of Chicago Hospitals is among the first to apply this technology to pancreatic cancer and the only center in the Chicago area currently using IMRT on pancreatic cancer.

Early results with about 15 patients over the past year have shown promise in reducing toxicity when compared with conventional therapy.

"With IMRT, radiation is given to a much broader range of patients, even certain resectable patients, who have undergone the surgery but who have risk factors that speak for needing additional measures for local control," he said. If lower toxicity is demonstrated, it will be possible to boost the radiation dose to the tumor while maintaining current toxicity. "I think IMRT probably will evolve as the standard," Jani says.
Genetics of pancreatic cancer

Physicians involved in the pancreatic cancer center also study the genes of cancer patients and their families with the goal of preventing other cancers or at least finding them before they have become incurable.

Because fewer than 20% of pancreatic cancers have a genetic link, most patients, and many physicians, are not aware of the genetic factor in the disease. As a result, patients have died without the potential impact of the genetics being shared with their kin.

“We are the only comprehensive program in Chicago that offers genetic testing and screening for pancreatic cancer,” said Funmi Olopade, MD, director of the Center for Clinical Cancer Genetics at the University of Chicago Hospitals. “Every patient who comes through,” she says, “should have a family history taken and be offered genetic testing.”

There is a strong link between the BRCA2 mutation, named for its role in breast cancer, and pancreatic cancer. “If a man has developed pancreatic cancer, we can reach out to his daughters about the risk for breast cancer,” said Olopade.

There are also links between pancreatic cancer and ovarian cancer, melanoma, and colon cancer. When such cases are found, Olopade said, the program recommends aggressive screening of relatives, aimed at early detection. For example, men from such families might be urged to begin PSA screening as young as age 40.

Olopade is working with Waxman to develop screening for early detection of pancreatic cancer by imaging the pancreas at the earliest sign before the cancer becomes invasive and incurable.