Pancreatic Cancer: Neoadjuvant Chemo-RT Can Increase the Chance for Life-Extending Surgery

BY ED SUSMAN

SAN FRANCISCO—Neoadjuvant chemotherapy plus radiation appears to allow a high percentage of pancreatic cancer patients deemed borderline resectable to safely undergo surgery—which leads to significantly extended overall survival—researchers reported here at the Gastrointestinal Cancers Symposium (***Abstract 360***).

The three-day meeting, which is co-sponsored by the American Gastrointestinal Association Institute, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology, had approximately 3,400 attendees this year.

Even a few patients who are diagnosed with locally advanced pancreatic cancer—usually not considered eligible for surgical resection—can undergo successful resection, said Eric Mellon, MD, PhD, a resident in radiation oncology at H. Lee Moffitt Cancer Center and Research Institute.

"In our experience, whether a patient has borderline resectable pancreatic cancer or locally advanced pancreatic cancer status entering the treatment protocol, it is unimportant compared with whether patients undergo complete resection," he said in an interview at his poster presentation. "Patients who undergo resection after treatment have the best prognosis."

Among patients who were resectable after chemotherapy and stereotactic body radiation, about 50 percent were alive at 36 months compared with only about five percent who did not undergo surgery, he reported.

"About 10 to 20 years ago, all of the patients in this series would not have had surgery—they would have been doomed to die. The only way to cure someone with pancreas cancer is to get them to surgery. Our goal here is to treat these patients who are borderline resectable or even some of those who are locally advanced and get them to surgery.

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"Some of those patients with locally advanced pancreatic cancer who were never going to get surgery before can be resected, probably because of treatment with FOLFIRINOX [fluorouracil, leucovorin, irinotecan, and oxaliplatin]," Mellon continued, adding that none of the patients with locally advanced pancreatic cancer who received gemcitabine-based chemotherapy responded sufficiently to undergo resection.

Goal: To Shrink the Tumor Enough to Get It Off the Superior Mesenteric Artery

In addition to the chemotherapy regimen, stereotactic body radiation is also used to further shrink the tumor, he explained. "The goal is to shrink the tumor enough to get it off the vessel—the superior mesenteric artery. If you have to clip the blood vessel and take out part of the artery to remove the tumor, it is considered unresectable."

He said that attempts to perform surgery that would take out the tumor and then re-attach the artery segments generally have not been successful.

Mellon said that in the few cases in which locally advanced tumors have been reduced enough to permit surgery, the outcomes are encouraging: Of the 49 patients initially diagnosed with locally advanced pancreatic cancer, five of the patients or 10 percent had complete resection of their tumor. The small number of patients kept the results from achieving statistical significance, he noted.

"After six months of follow-up, none of those patients have died. None of them have even had cancer recurrence." Two other patients went to surgery but could not be resected. The remaining 86 percent of these locally advanced pancreatic adenocarcinoma patients did not undergo surgery.

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The Real Issue...

"The point we are trying to make here is that it is not important whether you come in with borderline resectable or locally advanced disease, the real issue is whether you got to surgery," Mellon said. "If you get to surgery, you do so much better."

Of the borderline resectable patients, about 50 percent got to surgery, and while the median survival is three years for the group who underwent the neoadjuvant chemoradiation, historically, the survival is better than that seen with upfront surgery, he said.

Two Schedules

Mellon said he is currently working on a study that compares the two schedules—i.e., upfront surgery versus surgery following neoadjuvant therapy.

He said that prospective, randomized data are necessary to change treatment guidelines. Moffitt is a member of the National Comprehensive Cancer Network (NCCN), which writes guidelines for treatment of cancer that are accepted worldwide. Mellon said that current NCCN guidelines suggest that neoadjuvant treatment be given to patients with borderline resectable pancreatic adenocarcinoma before surgery is attempted in these patients, but there are no data about which regimen is preferred for neoadjuvant therapy—"This may be one option."

He said that the use of stereotactic body radiation therapy is emerging for use in pancreatic cancer in hopes of increasing the radiation dose to the

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cancer without causing radiation toxicity to nearby organs such as the duodenum and stomach.

And even if the neoadjuvant therapy fails to reduce the tumor enough to permit safe surgery, there are still benefits: "Local disease control is good after stereotactic body radiation therapy even if the cancer is never amenable to surgery," Mellon said. "In patients who were not surgically resected, our one-year local control was 78 percent. However, the patients still die of metastatic disease."

Study Details

He and his colleagues reviewed all cases of non-metastatic borderline resectable or locally advanced pancreatic cancer patients who were treated by stereotactic body radiation therapy from 2009 to 2013 at Moffitt. Median follow-up from the start of chemotherapy was 14 months, and patients underwent induction therapy with gemcitabine, docetaxel, and capecitabine (GTX), FOLFIRINOX, or other gemcitabine-based regimens.

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One week after chemotherapy ended, the patients underwent stereotactic body radiation therapy. Patients were prescribed stereotactic body radiation therapy in five equal fractions. Dose-painting techniques were used to increase the dose to areas of tumor-vessel abutment—a median of 40 Gy. Gross disease received a minimum dose of 30 Gy.

A median of seven weeks after radiation therapy—up to three months after radiation—patients were reassessed for resectability. Of the 110 borderline resectable pancreatic cancer patients, 51 percent underwent resection with a three percent positive margin rate.

A total of 21 percent of patients did not go on to surgery due to

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Study Finds Breast Cancer Survivors More Unfit than Expected

BY SARAH DIGIULIO

SAN ANTONIO—Previous data has shown that breast cancer survivors who are overweight and inactive have higher rates of breast cancer recurrence and overall mortality. So a group of researchers set out to design an exercise intervention for this population of patients to reduce the effect. But, finding insufficient data on the baseline fitness of this population of patients—and how breast cancer therapies affected their fitness—the researchers instead designed their study to provide that observational data as a starting point to design future interventions. Kathy D. Miller, MD, Professor of Medicine and the Ballvé-Lantero Scholar at Indiana University Melvin and Bren Simon Cancer Center, was the lead author of the resulting study, which was presented in a poster presentation at the San Antonio Breast Cancer Symposium.

"Bottom line—many of our patients are much more debilitated than we ever expected," she said. "Our treatments have a profound impact, with further decline in muscle mass and muscle function. Most exercise recommendations suggest 150 minutes a week of aerobic exercise, plus strength training. Our patients are starting already so debilitated that starting there would likely result in injury, pain, and early discontinuation of the program."

She and her colleagues evaluated 43 patients who were newly diagnosed with stages 0 to III breast cancer who had not yet started therapy and who

KATHY D. MILLER, MD: "We envision an oncology version of cardiac rehab."

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progression to unresectable status on imaging; seven percent were unresectable at surgery; metastases were found in 14 percent of patients at surgery; and seven percent of patients were deemed medically inoperable due to performance decline during neoadjuvant therapy,

Mild acute radiation-induced toxicities, including Grade 1 and Grade 2 fatigue, pain, nausea, and diarrhea, were common but no toxicity prevented surgical resection.

Possible Selection Bias

Asked for his perceptive for this article, Tony Philip, MD, an attending physician in hematology/oncology at North Shore-Long Island Jewish Cancer Institute, said: "We need a randomized clinical trial to determine if neoadjuvant chemotherapy is really changing outcomes in pancreatic disease for patients who have borderline resectable pancreatic cancer—It may be that the patients who are selected for neoadjuvant therapy are simply better candidates for surgery and so these outcomes look better because of that selection bias."

Related Study

In a related study also performed by researchers at Moffitt, Omar Rashid, MD, JD, a complex general oncology surgery fellow, suggested that by following a multidisciplinary treatment pathway, more than half of patients with borderline resectable pancreatic cancer can undergo potentially curable surgery (***Abstract 374***).

"We looked at the clinical pathway that is used to assess these patients,"

Ed Susman

OMAR RASHID, MD, JD: "It shouldn't be that the treatment you get depends on where you end up. It should be based on data. The only way we will get that is if the Pancreatic Cancer Intergroup comes together and says, 'Look, we are going to do this.'"

Rashid noted at his poster presentation "Right now how borderline resectable pancreatic cancer is treated in different parts of the country depends upon where the patients are, in terms of how they are staged and to what regimen is used.

"Some things are unique to Moffitt. We use a CT-scan, PET-scan and also endoscopy with ultrasound to image the patient," he said. "Then everyone comes together—different surgeons, gastroenterologists, and the tumor board—and they decide if the patients are indeed borderline resectable. If they are, then we give them GTX and stereotactic body radiation therapy, and then re-stage the patient. If there is a chance of resection, we then take patients to surgery."

The study showed that from 2006 to 2013, borderline resectable pancreatic cancer was diagnosed in 121 patients presenting at Moffitt. Of that group, 101 were entered into the study of the multidisciplinary clinical pathway assessment.

Rashid reported that about 93 percent of these patients were able to complete adjuvant therapy. The panel of doctors then determined that 55 (54.5%) of the patients were suitable for and underwent surgery. Of those who went to surgery, 53 (96%) had a complete resection of the tumor—an R0 resection; and two patients had an R1 resection.

"One of the reasons we did so well, maybe," Rashid speculated, "was that we were so selective at the beginning. Another might be the chemotherapy regimen—81 percent of patients had a partial response, and 14.5 percent had a complete pathological response."

Patients who were not resectable after therapy achieved a median 14-month overall survival compared with 33 months for patients who were able to have surgery. "We are not curing these people with surgery, but we are moving the curve more in that direction," Rashid said.

He said that a prospective study needs to be performed to test the various regimens: "It shouldn't be that the treatment you get depends on where you end up. It should be based on data. The only way we will get that is if the Pancreatic Cancer Intergroup comes together and says, 'Look, we are going to do this.'"