High-Dose Radiation Therapy for Pancreatic Cancer

Trial tests whether radiomodulating agent GC4419 can enable higher doses of stereotactic body radiation therapy

By Angie N. Meus

Pancreatic cancer remains one of the most aggressive types of cancer, and patients with unresectable disease have a median overall survival duration of just 1 year, despite treatment with chemotherapy and radiation. Although increasing the radiation dose to the tumor might improve treatment outcomes for such patients, the adverse effects of radiation therapy have made such increases impractical. But now, researchers at The University of Texas MD Anderson Cancer Center are leading a new clinical trial to determine whether a radiomodulating agent will enable targeted radiation therapy to be delivered at high doses to unresectable pancreatic tumors without harming nearby vital structures.

“There is a lot of very important anatomic real estate right around the pancreas. There's the intestines, the liver, and major blood vessels,” said Cullen Taniguchi, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology. Even with modern modalities such as stereotactic body radiation therapy (SBRT), which allows the delivery of high doses of focused radiation to tumors while minimizing the dose to nearby organs, oncologists have not been able to deliver high enough radiation doses to substantially delay the progression of pancreatic cancer.

Dr. Taniguchi believes this situation could soon change. He is leading a randomized dose-escalation trial to see whether a bowel-protecting drug, GC4419, will enable SBRT to be delivered safely to the pancreas at higher doses than ever before.

Radiomodulating agent GC4419
The radiomodulating agent GC4419 is a superoxide dismutase mimetic. The drug removes superoxide radicals that are formed during radiation treatment and causes them to
Image-Guided Cordotomy for Cancer Pain

Computed tomography–guided cordotomy relieves cancer-related refractory pain

By Joe Munch

Cordotomy—in which open or percutaneous surgery is used to disable pain pathways in the spinal cord—has long been used to help manage severe pain. However, when performed using an open surgical technique, the procedure carried a number of risks and thus had limited clinical utility. But with the implementation of intraoperative imaging, percutaneous cordotomy for cancer patients with refractory pain is now resurgent.

“Cordotomy is a well-established procedure for pain, but it historically had a fairly high complication rate due to limitations in the surgical technique,” said Ashwin Viswanathan, M.D., a clinical associate professor in the Department of Neurosurgery at The University of Texas MD Anderson Cancer Center. “Now that we have intraoperative imaging, the procedure is much safer and more effective. For certain patients, the treatment leads to dramatic reductions in pain.”

To show definitively whether image-guided percutaneous cordotomy offers a pain management benefit over best supportive care in cancer patients with refractory pain, Dr. Viswanathan and his colleagues have undertaken the first clinical trial of its kind comparing the two pain management strategies.

Why cordotomy?

The most common approach to pain management for cancer patients is opioid therapy. However, not all patients become less damaging by converting them to hydrogen peroxide. Normal tissues contain antioxidant enzymes that neutralize hydrogen peroxide, but tumors often do not. Radiation produces superoxide radicals in a dose-dependent fashion. Because SBRT uses higher doses than do other radiation therapy modalities, scientists believe that pairing SBRT with GC4419 could help reduce the toxic effects of SBRT in normal tissues without reducing its tumoricidal benefits.

When GC4419 was tested in patients with head and neck cancer who were receiving radiation therapy, researchers reported a 40% reduction in oral mucositis, a common adverse effect of such therapy. These results led Dr. Taniguchi and colleagues to believe the radiomodulating agent could also improve outcomes for patients with pancreatic cancer.

Clinical trial

The trial (No. 2017-0606) is enrolling men and women with locally advanced, unresectable pancreatic cancer and an Eastern Cooperative Oncology Group performance status score of 2 or lower. Patients must have received 3–7 months of standard induction chemotherapy prior to beginning the trial.

Patients are randomly assigned to receive GC4419 or placebo; these are given before each of the five SBRT sessions, which take place on consecutive days. The total radiation doses are escalated using a sequentially adaptive design that accounts for efficacy and toxic effects observed in previous patients.

“The trial is designed to find the highest dose of SBRT that is safe in patients with and without GC4419,” Dr. Taniguchi said. “The underlying hypothesis is that GC4419 will let us get to a higher dose of radiation. We go through three different levels of radiation. The highest dose level will be the highest radiation dose ever given for pancreatic cancer. These are doses we think could substitute for surgery.”

So far, five patients have been enrolled; ultimately the trial will enroll 48. Each patient will be followed up over the course of 3 years, the duration of the clinical trial. The trial’s primary endpoints are toxic effects and the duration of stable disease.

“We’ll know if we’re making a difference because we’ll start seeing patients with disease progression 2 and 3 years later instead of after a year or less,” said Dr. Taniguchi. “Ultimately, we believe these treatments might lead to better outcomes in selected patients.”

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To learn more about clinical trials at MD Anderson, visit www.clinicaltrials.org and search by physician, cancer type, or treatment.
respond to opioids, even when dosages are increased; and the medications can have side effects that some patients find intolerable, including pruritus, nausea, and constipation.

Patients who do not respond to opioids or cannot tolerate the side effects may benefit from surgical interventions. These interventions include intrathecal pain pump implantation (which enables the delivery of a much smaller dose of opioids directly to the spinal fluid), myelotomy (for pain caused by abdominal cancers), and cordotomy (for one-sided pain below the shoulder level), which is usually percutaneous and increasingly performed under computed tomography (CT) guidance.

In CT-guided percutaneous cordotomy, a lumbar puncture is performed first to inject a radiocontrast agent into the spinal fluid to visualize the spinal cord. A surgeon then uses real-time CT to guide the advancement of a needle into the spinal cord at the base of the skull and then the advancement of a radiofrequency electrode through the needle to the spinothalamic tract. Once properly placed, the electrode is heated to ablate the pain pathway in the spinal cord. The procedure is performed with local anesthesia to allow communication with the patient.

“We want to be in the main pain pathway in the spinal cord, so we talk to the patient and stimulate the electrode to make sure the patient gets a sensation of where it hurts, and then we can interrupt that pain pathway,” Dr. Viswanathan said.

The procedure typically takes 1–2 hours. Possible adverse effects include leg weakness, which affects about 1% of patients; in addition, some patients may be bothered by the numbness the procedure creates.

**Randomized trial shows benefit**

To date, only retrospective or single-arm prospective studies have investigated the efficacy of cordotomy. To get some definitive answers about the extent to which cordotomy reduces otherwise unmanageable cancer pain, Dr. Viswanathan and his colleagues have undertaken a randomized controlled study.

“This is the first time we’ve had a randomized study to compare a surgical pain intervention using modern techniques with optimal supportive care,” Dr. Viswanathan said.

In the trial (No. 2014-0833), patients with advanced cancers of any type who have one-sided, refractory pain caused by tumor involvement below the shoulder level are assigned to immediately undergo CT-guided percutaneous cordotomy or to receive best supportive care for 1 week with the option to undergo CT-guided percutaneous cordotomy afterward. Before and after the procedure, cordotomy patients complete pain and symptom questionnaires and undergo quantitative sensory testing for sharpness and heat detection. Magnetic resonance imaging is performed shortly after the procedure to determine its effect on the spinal cord.

Sixteen patients have been enrolled in the study over the past 2 years. Seven patients were assigned to immediate cordotomy; of the nine patients assigned to receive best supportive care, seven ultimately also underwent cordotomy. The trial has completed its planned enrollment, and a formal comparative analysis is underway.

Although the long-term outcomes of these patients remain to be seen, so far the results are impressive. “We had 14 patients who underwent cordotomy, and of those, 13 had fairly impressive improvements in their pain,” Dr. Viswanathan said. “Compared with the supportive care, cordotomy substantially improved patients’ pain. I generally counsel patients that there’s a 70% chance of improving pain, but our study suggests a somewhat higher response rate than that.”

The trial’s early findings underscore the increasingly prominent role that CT-guided cordotomy has in combatting cancer-related pain, Dr. Viswanathan said.

“If patients have tried strong pain medications—morphine, oxycodone—and they’re still suffering from pain, I would definitely recommend this procedure,” Dr. Viswanathan said. “It’s not disruptive to their cancer care, and it can provide an immediate benefit.”

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For more information about the trial of CT-guided cordotomy, visit www.clinicaltrials.org and search for study No. 2014-0833.
Esophageal, Pharyngoesophageal Reconstruction

Advanced surgical techniques restore digestive continuity

By Bryan Tutt

In cancer patients who undergo esophagectomy or laryngopharyngectomy, restoration of digestive continuity is essential to quality of life. Although time-tested reconstructive techniques can reestablish digestive continuity in most patients, patients who undergo total or near-total esophagectomy or who undergo laryngopharyngectomy and have damaged neck tissue due to prior surgery or radiation therapy require specialized procedures. Two such procedures, supercharged jejunal flap surgery for esophageal reconstruction and chimeric free flap transfer for pharyngoesophageal reconstruction and neck resurfacing, are available at only a few centers worldwide.

Neither chimeric flap nor supercharged jejunal flap surgery is new, but these procedures are so seldom needed that very few surgeons are experienced in performing them. Surgeons at The University of Texas MD Anderson Cancer Center were among the first to perform the procedures and have reported results from relatively large patient cohorts for both operations. On the basis of this experience, the surgeons have continually refined their techniques and the selection criteria for both procedures so that digestive continuity can be restored in as many patients as possible.

Esophageal reconstruction

In patients with cancer in the thoracic esophagus or the upper part of the gastroesophageal junction, surgeons can resect a part or nearly all of the esophagus and connect the stomach directly to the remaining esophagus to restore digestive continuity. However, this procedure cannot be used in patients in whom tumor involvement has also necessitated removal of all or part of the stomach.

“We use part of the [chimeric] flap to reconstruct the esophagus and the other part to cover the neck.”

– Dr. Jesse Selber

In other situations, the stomach is not available because of previous surgery. “In these scenarios, when the stomach is not available or can’t reach far enough, we use the supercharged jejunal flap,” said Peirong Yu, M.D., a professor in the Department of Plastic Surgery. The flap is considered to be “supercharged” because it both maintains part of its original blood supply like a pedicled flap and is connected to a new blood supply like a free flap.

The supercharged jejunal flap is created by taking a long (about 30-cm) piece of the jejunum and dividing the mesentery to straighten the segment. One set of the mesentery vessels, usually the second branch of the superior mesenteric artery and vein, is divided and later anastomosed to the recipient vessels in the neck (often the left internal mammary artery and vein) to supply blood to the superior portion of the flap. The third branch is often divided to lengthen the mesentery. The blood supply from the fourth branch of the superior mesenteric artery is maintained as a pedicle for the inferior portion of the flap.

To place the flap, surgeons first remove small portions of the first rib, clavicle, and manubrium to allow access to the recipient site and the internal mammary vessels. The surgeons then attach the superior portion of the flap to the upper digestive tract and anastomose the blood vessels. Although the inferior portion of the jejunal flap can be connected to the stomach in cases in which a portion of the stomach remains viable, this can cause gastric reflux. In most cases, therefore, the remaining stomach is bypassed, and the flap is attached to the small bowel using a Roux-en-Y technique.

The supercharged jejunal flap surgery is an extremely complicated procedure that requires close coordination between the plastic surgeon and thoracic surgeon. “The surgical teamwork required to execute the supercharged jejunal flap successfully is a highly orchestrated event,” said Jesse Selber, M.D., an associate professor in the Department of Plastic Surgery. “Everyone must not only know his or her own role but also understand the roles of the other team members.”

Dr. Selber added that the procedure involves significant time pressure. “Once the bowel is disconnected in the abdomen, you have about an hour to pass...
it through the chest into the neck and reconnect the blood supply under the microscope,” he said. “If that doesn’t happen, the bowel flap may die and the result can be disastrous.”

“This is a major operation, and there are potential complications,” said Wayne Hofstetter, M.D., a professor and director of the esophageal surgery program in the Department of Thoracic and Cardiovascular Surgery. “But the vast majority of patients who undergo this procedure are able to become independent of feeding tubes.”

**Pharyngoesophageal reconstruction and neck resurfacing**

Patients who undergo laryngectomy have several options for pharyngoesophageal reconstruction. These include surgery with free tissue flaps from the anterolateral thigh, radial forearm, or jejunum and surgery with pedicled flaps from the supraclavicular region or the pectoralis major muscle. But many patients who have had prior surgery or radiation therapy to the neck have scarring and hypovascularity that make it difficult or impossible to close the neck incision primarily after pharyngoesophageal reconstruction.

“We need two flaps for these patients,” Dr. Yu said. “We need one to rebuild the esophagus so the patient can eat again, and then we need another to cover the outside. This is important because if you don’t have reliable coverage, the carotid arteries and other critical structures are at risk.”

For such reconstructions, plastic and reconstructive surgeons at MD Anderson use a chimeric flap, which is usually taken from the anterolateral thigh but can be taken from other donor sites if necessary. The chimeric flap is so named because it is composed of two (or more) semi-independent components, all of which are supplied by a common artery and vein that are anastomosed to recipient vessels in the neck.

“We use part of the flap to reconstruct the esophagus and the other part to cover the neck,” Dr. Selber said. “And they are dissected in a way that retains a common blood supply to all components.”

“In the flap used for resurfacing, we include a little bit of muscle to protect the carotid and subclavian arteries,” Dr. Yu said. “This helps prevent disastrous complications.”

Another advantage of the anterolateral thigh flap is that it facilitates the restoration of speech function. The skin flap used to reconstruct the upper esophagus is firm, which allows the vibration necessary for esophageal or tracheoesophageal speech. “The skin flap is tight, and it vibrates like the material used in a drum. The jejunal flaps are soft and produce mucus, which makes speech restoration more difficult,” Dr. Yu said. That is why the thigh or other skin flaps are preferred for upper esophageal reconstruction and the jejunum or stomach is used for lower esophageal reconstruction.

To assess the complication rate of chimeric flap surgery, Dr. Selber and colleagues recently compared the outcomes of 179 patients who received chimeric flaps for pharyngoesophageal reconstruction and neck resurfacing with those of 115 patients who underwent pharyngoesophageal reconstruction but did not require neck resurfacing. Compared with the patients who underwent pharyngoesophageal reconstruction alone, those who also underwent neck resurfacing had a significantly lower rate of pharyngocutaneous fistula formation and similar rates of other complications. The rate of fistula formation was highest in patients who had undergone prior surgery or radiation therapy but who did not receive neck resurfacing because they had adequate tissue to close the incision. Because of the impact of this work, Dr. Selber received the 2017...
Radiation therapy is curative for many head and neck cancers but can result in dysphagia that decreases patients' quality of life and puts them at risk of malnutrition and pneumonia. Although concurrent swallowing therapy during radiation therapy to the neck can help patients avoid or decrease the impact of dysphagia, the optimal approach to swallowing therapy remains unknown. To determine the appropriate timing and intensity of swallowing therapy, researchers at The University of Texas MD Anderson Cancer Center are leading a multicenter randomized trial.

“We have data from small, single-site trials and retrospective studies showing that high-intensity swallowing therapy helps patients maintain their ability to swallow during radiation therapy to the neck,” said Kate Hutcheson, Ph.D., an associate professor in the Department of Head and Neck Surgery and the associate director of research for the Section of Speech Pathology and Audiology. “However, a recent Cochrane review was unable to identify best practice in this area, citing the lack of sufficiently powered randomized clinical trials.”

Patients who are cured of their cancer appreciate the quality of life that successful reconstruction enables. Dr. Yu said, “One patient I treated 10 years ago comes back every year to say hello to me.”

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FURTHER READING
plan to undergo radiation therapy with curative intent for head and neck cancer.

Clinical trial
The PRO-ACTIVE trial is open to patients who will receive radiation therapy to both sides of the neck to a total dose of at least 60 Gy over 6–7 weeks. Patients with dysphagia at enrollment are excluded. At enrollment, each patient is randomly assigned to the reactive, low-intensity proactive, or high-intensity proactive treatment arm.

Patients in the reactive treatment arm do not initially undergo swallowing therapy. Their symptoms are monitored throughout their radiation therapy by a weekly questionnaire, and those who develop symptoms of swallowing difficulties, such as a tendency to choke on food and liquids, or who become dependent on feeding tubes begin to receive high-intensity swallowing therapy when their symptoms arise.

Patients in the low-intensity proactive treatment arm see a speech pathologist at the beginning of radiation therapy and every 2 weeks thereafter. The speech pathologist teaches the patients a mealtime routine that promotes maintenance of safe and challenging food intake during radiation therapy. This swallowing therapy regimen is based on the premise that keeping muscles active by eating can preserve their function. The speech pathologist also teaches patients to think of food as having different levels of swallowing challenges, with each of those challenges representing a step on a staircase (figure below). “The goal is to keep patients as high as possible on the staircase for as long as possible during radiation therapy,” Dr. Hutcheson said.

The effectiveness of each treatment approach will be determined by assessing patients’ duration of dependence on feeding tubes, swallowing strength as measured by videofluoroscopy, and scores on symptom and quality-of-life questionnaires. “We hypothesize that the high-intensity proactive treatment will have the best results, but it could be that we find that one of the lower-burden, lower-resource treatments offers patients a less demanding way to maintain their ability to swallow,” Dr. Hutcheson said.

Expanding access
The PRO-ACTIVE trial is enrolling patients at multiple centers in the United States and Canada. In the Houston area, the trial is open to patients at MD Anderson’s main campus in the Texas Medical Center as well as its Sugar Land, Bay Area, and Katy locations.

“In the past, patients who received radiation therapy at our other locations around Houston had to come to the main campus if they needed swallowing therapy,” Dr. Hutcheson said. “But now, in addition to providing swallowing therapy, those locations are slated to roll out additional speech pathology services for our head and neck cancer patients.”

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In swallowing therapy, speech pathologists train patients to think of food in terms of swallowing challenges, as illustrated by the staircase above. Adapted from “EAT Through Radiation,” © University Health Network in Toronto.
OncoLog Says Farewell

August marks the end of OncoLog’s 62 years of publication. The current issue will be the final one.

The University of Texas MD Anderson Cancer Center has published OncoLog continuously since 1956, when it was called simply Newsletter. The name was changed to OncoLog in 1983. OncoLog became available online in 2003.

Although the name and look of the newsletter have changed over the years, its mission has remained the same: to inform community physicians about the latest advances in cancer care and research. Over the decades, OncoLog has chronicled milestones such as using vincristine as the first successful chemotherapy in children with Wilms tumors (1960), developing limb-sparing surgery for cancers of the extremities (1966), proving that lumpectomy is as effective as radical mastectomy for some patients with breast cancer (1976), establishing the benefit of neoadjuvant chemotherapy for breast cancer (1988), demonstrating the efficacy of intensity-modulated radiation therapy for lung cancer (2010), and developing chimeric antigen receptor T cells to treat B cell malignancies (2014).

Although OncoLog will no longer be published, physicians will continue to have access to MD Anderson’s research news via the Cancer Frontline blog, available at www.mdanderson.org/publications/cancer-frontline.html.

In addition, numerous MD Anderson resources for community physicians—including clinical tools such as cancer screening and treatment algorithms—are available at www.mdanderson.org/for-physicians.html.

MD Anderson’s commitment to having open lines of communication with community physicians remains a priority. “As we look into the future, we’re going to be enhancing our strategic partnerships with community physicians, and that will be an important part of how we manage many aspects of our patients’ care,” said Peter W.T. Pisters, M.D., president of MD Anderson.