Ablation for Pancreatic Carcinoma

Changing the paradigm of treatment options for one of the most lethal cancers.

BY GOVINDARAJAN NARAYANAN, MD, AND MEHUL H. DOSHI, MD

According to the Surveillance, Epidemiology, and End Result program of the National Cancer Institute, 48,960 new cases of pancreatic cancer are expected in United States in 2015.[1] Pancreatic cancer has a peak incidence in the sixth and seventh decade of a person's life, affecting men more commonly than women. Even though it is only the twelfth most common cancer by incidence (accounting for only 3% of all new cancers diagnosed), it is one of the most lethal cancers, with a 7.2% expected 5-year survival and 40,560 attributed deaths in 2015.[1] One of the contributing factors leading to high mortality is delayed diagnosis due to vague early symptoms.

OPTIONS FOR TREATMENT

Surgical Option

At the time of diagnosis, fewer than 20% tumors are resectable, approximately 40% are locally advanced, and 40% have distant metastasis. Surgical resection (pancreaticoduodenectomy) imparts improved survival of 23 months when a tumor-free margin of 1 mm (R0 resection) can be achieved. Survival is increased to 35 months when a greater than 1-mm tumor-free margin (R0 wide) can be achieved. The survival advantage of the resection is mostly lost when tumor is detected within 1 mm of the resection margin. Of the approximately 15% of patients who undergo surgical resection, 5-year survival is 12% to 18%.[2,3] Although its applicability is limited due to late-stage presentation in the majority of cases, surgery remains the most effective treatment modality in improving survival. Data have shown effectiveness of chemotherapy, radiotherapy, or combination therapy in downstaging some locally advanced tumors to allow successful subsequent resection.

Chemotherapy

Systemic chemotherapy has been used in a neoadjuvant or palliative form, with or without combination radiation therapy, depending on the cancer stage and objective. Chemotherapy is successful in downstaging locally advanced pancreatic cancer (LAPC) in one-third of patients, with comparable survival after resection as those with primarily resectable disease.[4,5] Since 2010, a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) has been the first-line therapy for LAPC and metastatic pancreatic cancer (mPC) patients with relatively preserved performance status (ie, Eastern Cooperative Oncology Group performance status score of 0 or 1).[5] Its applicability and successful completion rate is limited by a much worse toxicity profile compared to gemcitabine. A modified FOLFIRINOX regimen omitting 5-FU bolus and routinely using growth factor stimulator has been evaluated to improve tolerability, but the data are limited.[5] Gemcitabine continues to be a first-line therapy for patients with poor performance status, because it is tolerated well compared to FOLFIRINOX and has a relatively low incidence of hematologic complications. Various combination therapies involving gemcitabine and molecu-

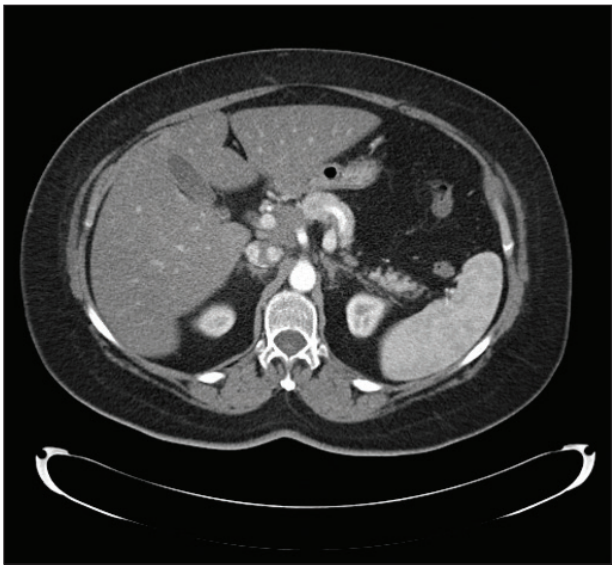

Figure 1. A CT scan showing pancreatic adenocarcinoma.

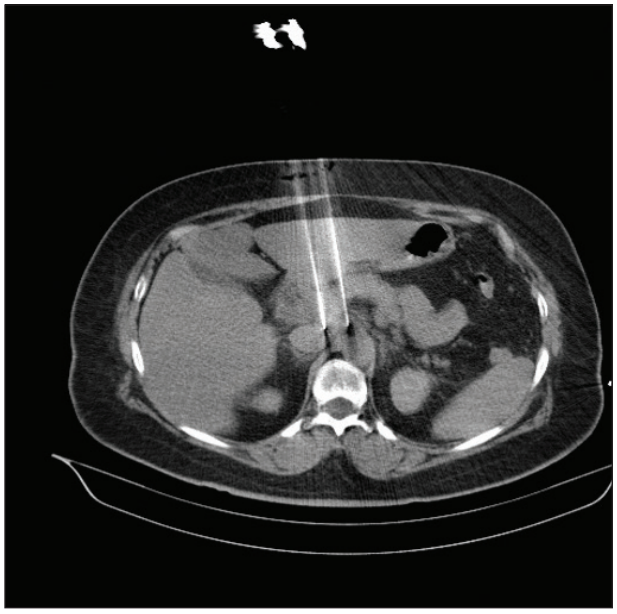

Figure 2. A CT scan showing IRE of the pancreas.

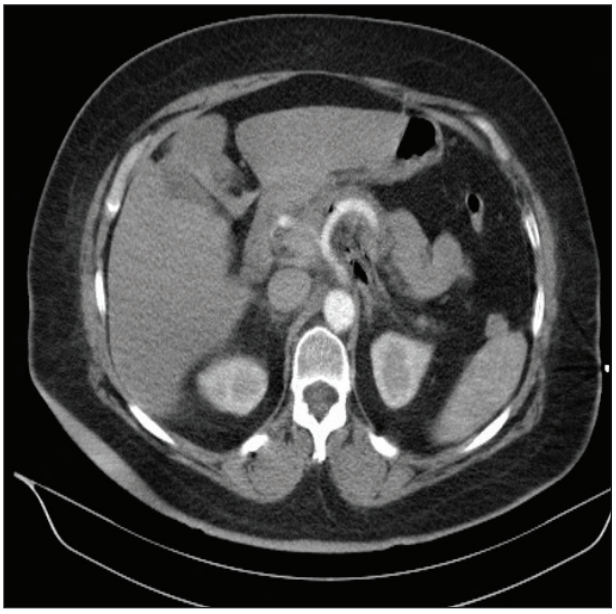

Figure 3. A CT scan taken immediately after IRE.

lar target agents have been tested, with the intention of improving the efficacy of gemcitabine in patients with mPC. Most of these combined therapies have shown equivocal results, with the notable exception of gemcitabine with nab-paclitaxel.[6] After initial results from the MPACT trial in 2013 and subsequent publication of long-term results, combination therapy of gemcitabine and nab-paclitaxel has emerged as a standard therapy for mPC.[6-8]

Ablative Treatment for Locally Advanced Pancreatic Cancer

Ablative therapy for pancreatic cancer presents a unique set of challenges. Unlike other solid organ tumors, pancreatic tumors either involve, or are surrounded by, medium- to large-sized blood vessels (such as portal vein, superior mesenteric vessels, celiac and hepatic arteries, and splenic vessels) (Figure 1). The blood vessels pose a three-fold problem. First, they undermine the efficacy of radiofrequency ablation due to the heat sink effect. Second, they are prone to heat damage themselves, with consequences such as thrombosis. Last, they are at risk of direct damage from the electrode when close to the planned trajectory, with a resultant risk of bleeding complications (Figure 2). The result of all three effects can be devastating in the pancreatic application, due to the size and physiologic importance of these vessels. In addition, vital ductal structures (such as the main pancreatic duct and common bile duct) are also often involved and subjected to potential collateral damage. These challenges are reflected in the high morbidity and mortality previously demonstrated with thermal ablative technique.[9-11]

Mechanism of Irreversible Electroporation

Irreversible electroporation (IRE) is an ablative technique in which high-voltage, low-energy DC current is delivered to the targeted tissue to cause irreversible nanoscale defects in the phospholipid bilayer of the cellular membrane, resulting in cellular apoptosis. Once the theoretic and mathematical models were put to test on large animals, it was evident that the technology could be exploited to achieve non-thermal destruction of tumors with sharp transition zones, and spare vascular, ductal, and connective tissue structures (which are often exposed to collateral damage with thermal ablative technologies) (Figures 3 and 4). In addition, because IRE is primarily nonthermal, it is not vulnerable to the heat sink effect that often compromises the efficacy of radiofrequency ablation and limits its applicability in tumors close to blood vessels. This held a huge promise for tumors in difficult anatomic locations, such as the pancreas and prostate.[12-14] IRE in the pancreas was initially studied in a swine model by Charpentier et al and was concluded to be a safe method for pancreatic tissue ablation.[15]

Surgical Data on IRE. Martin et al presented results of a multicenter study involving 107 patients and 117 IRE procedures involving pancreatic cancer (n = 84), liver lesions (n = 17), and tumors of lung, kidney, mediastinum, pelvis, and prostate (n = 16). Out of 84 pancreatic cancers, 75 were treated via open laparotomy, with or without concomitant other surgical procedures. Eighty-four total complications were noted in 43 of 107 (40%) patients, with high-grade complications in 21 (17.9%) patients. Diabetes, pancreatic cancer, open laparotomy approach, and concomitant surgical procedures were associated with significantly higher

complication rates, whereas percutaneous approach and colorectal hepatic metastasis were associated with lower complication rates.[16]

A prospective study of 10 patients who underwent IRE for LAPC utilizing a laparoscopic approach with intraoperative ultrasound guidance was published by Paiella et al. All patients who underwent IRE had previously undergone chemotherapy or chemoradiation therapy. The average length of hospital stay was 9.5 days, with one patient (10%) developing a postoperative abscess. One patient (10%) died of septic shock, which was attributed to an ulcerative colitis complication. The average time from diagnosis to treatment was 9.2 months. Three of the 10 (30%) patients received postprocedural chemotherapy. The average overall survival was 7.5 months after the procedure, with diagnosis-to-death time averaging 16.8 months.[17]

Most recently, Martin et al published results from a cohort of 200 patients with radiographic stage 3 LAPC who were treated with IRE between July 2010 to October 2014 and monitored under a multicenter, prospective institutional review board–approved registry.[18] Of the 200 patients with LAPC, 150 underwent IRE alone, and 50 had pancreatic resection plus IRE for margin enhancement. All patients underwent induction chemotherapy, and 52% received chemoradiation therapy as well for a median of 6 months (range, 5–13 months) before IRE. IRE was successfully performed in all patients. Thirty-seven percent of patients sustained complications, with a median grade of 2 (range, 1–5). Median length of stay was 6 days (range, 4–36 days). With a median follow-up of 29 months, 6 patients (3%) had experienced local recurrence. Median overall survival was 24.9 months (range, 4.9–85 months). This study concluded that for patients with LAPC (stage 3), the addition of IRE to conventional chemotherapy and radiation therapy resulted in substantially prolonged survival compared with historical controls. These results suggest that ablative control of the primary tumor may prolong survival.[18]

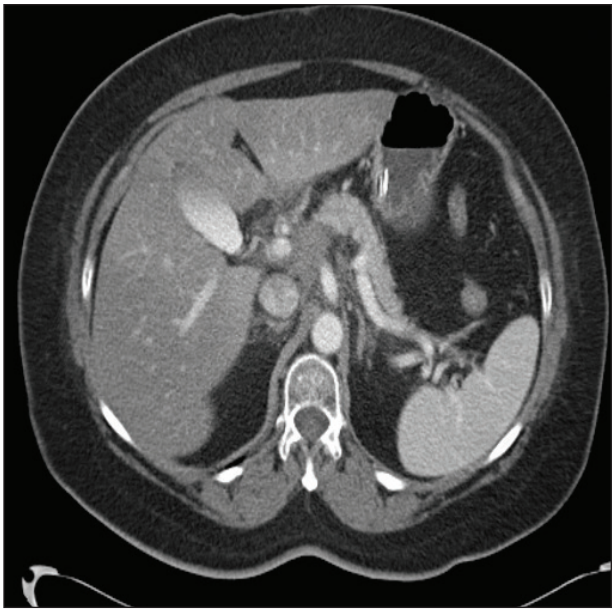

Figure 4. A CT scan taken 24 hours after IRE.

Percutaneous IRE of the Pancreas. Narayanan et al reported the first human series of percutaneous IRE of pancreatic cancer, which included data on 14 patients. Fifteen IRE procedures were performed in 14 patients (one was treated twice). Three patients had metastatic disease and 11 had LAPC. All patients had received chemotherapy previously, and 11 had received radiation. The median tumor size was 3.3 cm (range, 2.5–7 cm). Immediate and 24-hour post-procedural scans demonstrated patent vasculature in the treatment zone in all patients. Two patients underwent surgery 4 and 5 months after IRE, respectively. Both had margin-negative resections, and one had a pathologic complete response. Complications in this cohort included spontaneous pneumothorax during anesthesia (n = 1) and pancreatitis (n = 1), and both patients recovered completely. There were no deaths directly related to the procedure. In this series, two patients were successfully downstaged to surgery.[19] This study established the feasibility of treating pancreatic cancer percutaneously and paved the way for further studies that have since been published using the percutaneous technique.

A retrospective review by Narayanan et al of 43 patients who underwent 50 IRE procedures using a percutaneous approach between November 2010 and January 2014 demonstrated an overall survival of 14.5 months (95% confidence interval [CI], 10.4–18.6) from the date of IRE. In the 30 patients with LAPC, overall survival was 16.2 months (95% CI, 10.1–22.3 months) as opposed 8.6 months (95% CI, 3.1–14.1 months) for the 13 patients with mPC.[20] While 41 patients (95%) had undergone previous chemotherapy, only 18 had undergone previous radiation therapy. Nineteen patients received chemotherapy after IRE (44%).[20] Two patients were able to undergo surgery 4 and 5 months after IRE, respectively. Both had R0 (margin-negative) resections. One patient had recurrence after 34 months and was retreated with IRE. The second remained disease free at 34.5 months, which was the last follow-up.

Complications included abdominal pain (n = 10), pancreatitis (n = 7), hematoma (n = 7), spontaneous pneumothorax (n = 1), duodenal stent (n = 1), main portal vein thrombus found at 1 month on follow-up CT (n = 1), and sepsis 48 hours after IRE (n = 1.) To date, 20 patients have died. None of the deaths were directly related to the procedure.[20] This series demonstrated the potential for prolonged survival in these

highly selected patients with localized or mPC using the percutaneous IRE technique.

DISCUSSION

Given the limitations of thermal ablative techniques and complex vascular anatomy in close proximity to the pancreas, diagnosis or management of pancreatic cancer was not an area of involvement for interventional oncologists before 2010. IRE caused this paradigm shift, because it is different from thermal ablative techniques. IRE triggers cell death by creating nanopores in the cell membrane. The extracellular matrix is preserved, allowing ablation adjacent to critical structures.

Patient selection starts with cases being reviewed in a multidisciplinary tumor board with interventional radiologists, medical oncologists, radiation oncologists, and surgeons to determine eligibility. Although most data on IRE of the pancreas have shown a benefit in stage 3 LAPC patients, IRE has been used in carefully selected stage 4 patients with stable oligometastatic disease on chemotherapy.

Candidates for percutaneous IRE of the pancreas are then evaluated in the interventional oncology clinic to complete the preprocedure workup. All patients are informed that this is an off-label use of the technology. All patients should have biopsy-proven disease. Performance status is documented using the Eastern Cooperative Oncology Group criteria. Patients with a performance status greater than two have a life expectancy of less than 3 months, and these patients are excluded. A detailed cardiac history is obtained, as cardiac arrhythmias prevent the ability to synchronize pulse delivery with the R wave and can result in ventricular arrhythmias. Coagulation tests, renal function, metabolic panel, and blood count are evaluated. Preprocedure imaging includes cross-sectional imaging and positron emission tomography (PET)/CT, which should be obtained within 1 month of the date of consultation. The PET/CT helps define foci of active disease, especially in cases with previous radiation. Clearance to undergo general anesthesia is also required.

CONCLUSION

Percutaneous IRE for pancreatic cancer is a minimally invasive option, but it does have a learning curve and patient selection is crucial. IRE can be safe near vasculature, but the actual placement of the needles does carry the risk of bleeding and other forms of vascular injury.[14,21,22] Colonic interposition in the access path can also present a problem. Some of these limitations of a percutaneous approach can be averted by an open approach. Both techniques have their advantages and disadvantages, and choosing between the open and the percutaneous approach is another important decision that needs to be made by a multidisciplinary tumor board.

The early data for both surgical and percutaneous management of pancreatic cancer using IRE are promising. Prospective studies looking at safety, like the PANFIRE trial, will move IRE into the next step of a randomized controlled trial where its utility and effectiveness will be tested against the current standard of care. Combined with data from registries and retrospective series, these data will help establish the role of IRE in the management of pancreatic cancer with IRE. ■

Govindarajan Narayanan, MD, is with the University of Miami Miller School of Medicine, Jackson Memorial Hospital, Department of Radiology/Vascular Interventional Radiology Section in Miami, Florida. He has disclosed that he is a consultant and speaker for AngioDynamics, Biocompatibles UK Ltd, and Boston Scientific Corporation. Dr. Narayanan may be reached at gnarayanan@med.miami.edu.

Mehul H. Doshi, MD, is with the University of Miami Miller School of Medicine, Jackson Memorial Hospital, Department of Radiology/Vascular Interventional Radiology Section in Miami, Florida. He has stated that he has no financial interests related to this article.

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