Pancreatic cancer is one of the most lethal diseases and could be the second leading cause of cancer death in the United States by 2020.\(^1,2\) Surgical resection offers the only potential for cure; however, most patients are diagnosed in the later stages when the disease is unresectable. Systemic chemotherapy is the mainstay for the management of patients with pancreatic cancer, but it has limited efficacy. Recent advances in surgery, radiation therapy, ablative options, and endovascular therapies have brought promise and hope to these patients.

**SURGERY**

Although open pancreatic surgery has come a long way in the last century,\(^3\) minimally invasive approaches to treating the pancreas only started in the 1990s.\(^4,5\) From the onset, the results for distal pancreatectomies appeared very favorable, but surgeons remained skeptical regarding pancreatoduodenectomies due to the initial apparent increased morbidity and lack of benefit from the procedure.\(^6\) In 2007, Palanivelu et al showed the feasibility of minimally invasive pancreatoduodenectomies (MIPDs).\(^7\) The improved results compared with previous series were an indication that a steep and long learning curve was required to perform MIPDs. The learning curve is a potential reason why this procedure is still not widely accepted.

Compared with an open surgical approach, minimally invasive surgery is known to produce less inflammation\(^8\) and improved clinical outcomes across different specialties.\(^9\) These factors are especially important in pancreatic procedures to mitigate the debilitating effects of surgery when the patient’s lifespan is limited. At the same time, the minimally invasive surgical approach affords a magnified view and better access to difficult areas, which, in experienced hands, can be an asset in pancreatic procedures.\(^10\) Finally, there is faster recovery with a minimal surgical scar (Figure 1).

Several systematic reviews of laparoscopic distal pancreatectomy (ie, MIDP) have been published. All concur in showing advantages when compared with open distal pancreatectomy (ODP).\(^11-13\) The LEOPARD trial, a multi-institutional randomized controlled trial (RCT), further confirmed these benefits.\(^14\) The outcomes for MIDP were better than ODP in terms of operative blood loss, functional recovery, hospital length of stay, quality of life, and delayed gastric emptying, with similar complication rates and oncologic outcomes. The noninferior oncologic outcomes shown in the LEOPARD trial corroborate previous meta-analysis findings.\(^15\) Studies have also shown a trend in decreased overall costs, despite being a more expensive procedure.\(^16\) When performed by experienced operators, the benefits of the minimally invasive approach to ODPs have made it the preferred choice for the treatment of lesions of the body and tail of the pancreas.

Conversely, pancreatoduodenectomies are technically much more complex than left pancreatectomies for the following reasons: (1) the head and uncinate process are intimately related to major mesenteric vessels and are in a more difficult position to expose, and (2) after resection, the pancreatobiliary tract must be reconstructed. In part due to its greater complexity, MIPD
results are more controversial. Several retrospective studies and reviews have been performed, but these studies are potentially biased because they were performed in single centers or by highly experienced surgeons. Other publications from registries have not been able to consistently replicate better results for MIPD, and in some of them, the outcomes are significantly worse. Similarly, three RCTs compared open and minimally invasive approaches. Two RCTs found decreased length of stay with MIPD and similar pancreas-related complications, with one RCT reporting a better major complication profile for MIPD. Yet, one of the three trials had to be prematurely stopped because of a higher 90-day mortality rate in the MIPD group. These results should be interpreted with caution because there were concerns regarding the participating surgeons’ learning curve. This assumption is corroborated by a National Cancer Database study, which showed that low center volume is associated with higher 30- and 90-day mortality and margin positivity—trends that are especially high in laparoscopic surgery. Taken together, these findings suggest that MIPD requires a high level of skill and imply a much longer learning curve than for ODP.

Minimally invasive surgical pancreatectomy has shown a clear advantage when performed by experienced operators, particularly for left-sided pancreatectomy. Safe implementation is essential with strong consideration of the learning curve and commitment needed. As for open pancreatic resection, this procedure should be performed only in centers where a disease-focused, multispecialty group is well established.

RADIATION THERAPY

Radiation therapy for pancreatic cancer has evolved over recent decades, because the available technology has markedly improved. Previous techniques required high doses of radiation in large volumes, causing significant toxicity and thereby limiting the safe prescription dose to the tumor, which is in sharp contrast to modern conformal approaches such as stereotactic body radiation therapy (SBRT) and proton beam therapy (PBT) that achieve not only substantial normal organ sparing but also a safe delivery of higher and more effective tumor dose. SBRT is delivered within five fractions and conformally delivers a high dose to the tumor with a steep falloff to much lower doses within only a few millimeters outside of the tumor. SBRT is noninvasive and patients can perform normal activities (most do not need to take time off from work after SBRT). Originally shown to be feasible for pancreatic cancer in 2004, there is now a substantial body of literature showing that chemotherapy plus SBRT provides superior local control versus chemotherapy alone; this is especially important given that approximately one-third of pancreatic cancer patients die as a result of complications from local progression. An improvement in overall survival (OS) with SBRT has also been suggested by several studies, including one study with over 14,000 pancreatic cancer patients using the National Cancer Database. These favorable data

Figure 1. Postoperative view of port sites for a laparoscopic pancreateoduodenectomy (Whipple procedure) in a morbidly obese patient (A). Laparoscopic magnification view demonstrating vascular exposure during the uncinate process dissection of a laparoscopic pancreateoduodenectomy (B). P, divided pancreas and pancreatic duct; SMA, superior mesenteric artery; SMV, superior mesenteric vein; UP, uncinate process.
contributed to the National Comprehensive Cancer Network guidelines endorsing SBRT to treat patients with locally advanced pancreatic cancer (LAPC).  

For many years, daily pretreatment with cone-beam CT has been the standard to ensure high precision in SBRT; however, assessment was not also possible during treatment delivery until recently. Magnetic resonance–guided radiation therapy (MRgRT) technology now makes it possible to have continuous imaging of the tumor and nearby organs and automatically turns the beam on and off based on tumor positioning throughout respiration. Moreover, the treatment plan can be modified “on the fly” based on the patient’s daily stomach and bowel anatomy so that normal organ constraints are not exceeded. MRgRT can safely deliver the ablative dose, which is at least twice as high as conventional SBRT (Figure 2).  

A recently published retrospective multicenter analysis using MRgRT showed that ablative doses of about the equivalent of 100 Gy using standard fraction sizes result in improved local control and OS when compared with the use of conventional lower doses.  

PBT is a unique form of radiation therapy that was first used in the 1950s. Until recently, it had not been extensively evaluated for pancreatic cancer. The distinct advantage of PBT over x-ray therapies (eg, SBRT) is that protons stop completely within the tumor so that there is zero exit dose into the surrounding normal tissue. In contrast, an x-ray beam will not stop completely in the tumor and thus delivers some exit dose, albeit in a lower dose range compared with normal tissue. PBT can therefore result in reduced side effects and also achieve higher tumor doses than historically achievable with x-ray therapy approaches. For example, a study of PBT for localized pancreatic cancer reported no grade 3 or higher gastrointestinal toxicity or change in baseline patient-reported outcomes.  

Advances in radiation therapy have significantly increased the therapeutic index for patients with pancreatic cancer. Future studies should evaluate the role of radiation therapy compared with other localized therapies.

ABLATION: IRREVERSIBLE ELECTROPORATION

Irreversible electroporation (IRE) (utilizing NanoKnife, AngioDynamics) is an ablation technology that uses high-voltage, low-energy DC current to induce cell death (Figure 3). IRE in the pancreas was initially studied in a swine model by Charpentier et al and then used in an...
The percutaneous technique using IRE in pancreatic cancer was first described by Narayanan et al in 14 patients who underwent 15 treatments and two who were downstaged to R0 resection.\(^{38}\) A larger retrospective review of 50 patients with LAPC treated with percutaneous IRE followed,\(^ {39}\) with safety as the primary objective and OS as the secondary objective. Median OS was 27 months (95% confidence interval [CI], 22.7–32.5 months) from the time of diagnosis and 14.2 months (95% CI, 9.7–16.2 months) from the time of IRE. On multivariate analysis, OS was significantly longer in tumors ≤3 cm than those > 3 cm (33.8 vs 22.7 months from the time of diagnosis and 16.2 vs 9.9 months from IRE, respectively).

Leen et al published their results of a retrospective review of 75 patients with unresectable pancreatic carcinoma who underwent percutaneous IRE after chemotherapy between 2011 and 2016.\(^ {40}\) Postprocedural immediate and 30-day mortality rates were both zero. All-grade adverse events were 25%. Median inpatient stay was 1 day (range, 1–5 days). Median OS and progression-free survival post-IRE for LAPC were 27 and 15 months, respectively. Four patients with LAPC downstaged to surgery post-IRE ablation, with complete R0 resections in three cases.

The PANFIRE study, a prospective trial by Scheffer et al, reported a median time of 12 months to local progression after percutaneous IRE (95% CI, 8–16 months).\(^ {41}\) The median OS was 11 months from IRE (95% CI, 9–13 months) and 17 months from diagnosis (95% CI, 10–24 months). The study included patients with a median tumor size of 4 cm, and 52% underwent chemotherapy prior to IRE. A randomized controlled phase 3 trial called CROSSFIRE (NCT02791503) is currently recruiting patients in Europe, comparing the outcomes of FOLFIRINOX plus IRE with FOLFIRINOX plus MR-guided SBRT on OS for patients with LAPC. In the United States, the FDA has granted an investigational device exemption to study the role of IRE in pancreatic cancer. This step has paved the way for the first RCT in the United States to compare outcomes of chemotherapy versus chemotherapy and IRE. Patients will start with FOLFIRINOX induction chemotherapy before they are randomized. The IRE part of the study will have a surgical arm and a percutaneous arm.

IRE is one of the newest additions in the fight against pancreatic cancer. Although several retrospective studies have shown the safety and efficacy of percutaneous IRE in patients with pancreatic cancer (with a signal toward improvement in OS), the current RCTs should help standardize the role of IRE in this lethal disease.

**ENDOVASCULAR THERAPY: RENOVOCATH**

The inability of systemic chemotherapy to effectively penetrate the relatively hypovascular nature of pancreatic tumor tissue is one of the reasons why chemotherapy has limited efficacy in treating this disease. The FDA-cleared RenovoCath (RenovoRx, Inc.) is a dual-balloon catheter with proximal and distal occlusion balloons that enable effective isolation of the vascular site for targeted chemotherapy delivery to the targeted tissue/tumor (Figure 4). This catheter has the potential
to deliver much higher concentrations of drug to the tumor when delivered locally, as well as limit systemic exposure. The TAMP (Transarterial Micro-Perfusion) procedure involves arterial segment isolation with the RenovoCath to allow the generation of increased intra-arterial luminal pressure above the interstitial pressure, forcing drug across the arterial wall into the tumoral tissue.

Rosemurgy et al published the first-in-human, phase 1, multicenter safety study in patients with LAPC.42 Completed in July 2016, 20 participants were enrolled in this dose escalation study of intra-arterial, locally delivered gemcitabine with doses up to 1,000 mg/m². Of the 15 patients who completed the study with more than two treatments, 58% had a reduction of cancer antigen 19-9 tumor marker, three patients had tumor progression, one had a partial response, and 11 showed stable disease. The survival rate for this cohort was 60% at 1 year and 43% at 2 years. The benefit was greatest among those with previous chemoradiation; it is believed that radiation reduces venous outflow by decreasing microvasculature and therefore concentrating the chemotherapy in the tumor. In the patients who received chemoradiation, the median OS was 28.2 months from the time of diagnosis, and 80% of those participants were alive 24 months from the time of diagnosis.

A phase 2, multicenter, postmarket registry was designed to capture the long-term follow-up of 22 patients who underwent intra-arterial chemotherapy for pancreatic cancer with this catheter.43 As observed in the first-in-human study, the benefit was greatest in those who had previous chemoradiation, with a median OS from diagnosis of 18.8 months.

When evaluating the two previously discussed studies, the cohort of patients who had undergone previous chemoradiation and at least three treatments with intra-arterial gemcitabine had the best clinical response in terms of tumor response (CT imaging and tumor markers) and a median OS of 27.8 months.44 This finding suggests a regimen that includes induction with standard intravenous systemic chemotherapy followed by radiation therapy prior to intra-arterial gemcitabine using the RevovoCath delivers the best results and may represent a clinically significant advancement over the 12- to 15-month OS observed with currently approved therapies for LAPC.

The TIGeR-PaC is a phase 3, multicenter RCT that is currently enrolling patients and is evaluating transarterial gemcitabine versus systemic chemotherapy with gemcitabine and nab-paclitaxel following initial chemoradiation for patients with LAPC. The primary objective is OS from the time of randomization. Secondary objectives include progression-free survival, response rates, quality of life, tolerability, and safety. The outcome of this trial will help delineate the role of endovascular therapy in the management of LAPC.

CONCLUSION

There are many exciting novel and innovative therapies for pancreatic cancer that are only in their infancy. Minimally invasive surgery for pancreatic cancer allows resection for patients with anatomically resectable disease but who may have not been considered candidates for open surgery due to comorbid conditions. The ability to safely deliver very-high-dose radiation with new and improved systems, ablate the entirety of a pancreatic mass and potentially make it resectable with IRE, and deliver high-dose intra-arterial chemotherapy directly to the tumor are all promising advancements. These therapies have very encouraging initial results and there is potential to change the current treatment paradigm. Present and ongoing clinical trials will help delineate the precise role that these treatment modalities and possible combination therapy will have in the management of pancreatic cancer in the future.


