PERSPECTIVES

Pancreatic Cancer Interventions: The End of the Beginning?

Experts weigh in on the current roles of various therapeutic options for pancreatic cancer.

Current Evidence for IRE and Other Minimally Invasive Options

BY GOVINDARAJAN NARAYANAN, MD; THOMAS SCAGNELLI, MD; AND MEHUL DOSHI, MD

The diagnosis of pancreatic cancer carries a dismal prognosis with an 8% overall 5-year survival rate, and there is a desperate need for viable treatment options to improve the survival and quality of life for these patients. Due to the vague nature of the symptoms, nearly 80% of patients present with stage III locally advanced pancreatic cancer (LAPC) or stage IV metastatic pancreatic cancer (MPC) at the time of diagnosis. In patients who have undergone potentially curative resection, the 5-year survival is only 20%.[1]

The combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil (5-FU), and leucovorin (FOLFIRINOX) is first-line therapy for LAPC and MPC patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 and a median overall survival (OS) of 11.1 months.[2] In patients with MPC, combination therapy of gemcitabine and nanoparticle albumin-bound (nab)-paclitaxel is considered a standard therapy based on the results of the MPACT trial.[3]

The lack of significant improvement in the OS in pancreatic cancer poses a challenge in identifying additional treatment options. Over the years, several minimally invasive options such as radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation, as well as noninvasive options including high-intensity–focused ultrasound, stereotactic body radiation therapy

(SBRT), magnetic resonance (MR)–guided linear accelerator, and photodynamic therapy have been added to the list of treatment options. Irreversible electroporation (IRE) is the newest ablation technology that has been used in the treatment of pancreatic cancer with promising results. Although surgery and chemotherapy continue to be the current standard of care depending on the presentation of the disease, the following sections present a brief review of IRE and a few other minimally invasive treatment options for pancreatic cancer.

RADIATION TREATMENT

The role of radiation for both resectable pancreatic cancer and LAPC remains controversial. Two randomized European studies (EORTC[4] and ESPAC[5]) concluded that radiation therapy offers no benefit after pancreatic cancer surgery. Currently, a trial sponsored by the National Cancer Institute (NCT01013649) is studying the role of adjuvant radiotherapy in addition to gemcitabine versus gemcitabine alone after resection. For LAPC, the LAP07 trial did not show a survival advantage when radiotherapy was added after a 4-month chemotherapy induction period.[6]

The benefit of chemotherapy versus chemoradiotherapy was also addressed in the phase 3 FFCD-SFRO study from France, in which patients with LAPC were randomly assigned to receive either gemcitabine alone

or an intensive induction regimen of chemoradiotherapy with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[7] In this study, gemcitabine alone was associated with a significantly increased OS rate at 1 year compared with chemoradiotherapy (53% vs 32%; hazard ratio, 0.54; 95% confidence interval [CI], 0.31–0.96; *P* = .006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiotherapy arm had a lower survival rate.

Thus, the role of upfront chemoradiotherapy in the setting LAPC is still undefined. The role of SBRT following gemcitabine monotherapy in patients with LAPC has been examined in phase 2 trials.[8] This regimen was associated with low toxicity and favorable rates of freedom from local disease progression.

ABLATION THERAPIES

RF ablation in pancreatic cancer has been mostly used in an open surgical approach. Early clinical applications in the pancreas were associated with unacceptably high rates of morbidity (0%–40%) and mortality (0%–25%). One of the largest prospective series of 100 patients with pancreatic cancer treated by RF ablation was reported by Girelli et al.[9] The median OS from the date of diagnosis was 20 months. In this study, half of the patients were first treated with RF ablation and then with chemoradiotherapy, systemic or intra-arterial chemotherapy, or a combination of these. In the other half of the patients, RF ablation was performed after other primary treatments, leading to possible selection bias.

Data on cryoablation and MW ablation are limited. Lygidakis et al reported on the feasibility, safety, and efficacy of MW ablation in 15 patients with LAPC.[10] Partial necrosis was achieved in all patients, with no major procedure-related morbidity or mortality.

PERCUTANEOUS IRE OF THE PANCREAS

IRE is a predominantly nonthermal ablative technique that uses high-voltage DC current to cause irreversible nanoscale defects in the cell membrane, disrupting homeostasis and leading to cellular apoptosis. The role of 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.[11]

Narayanan et al established the feasibility of treating pancreatic cancer percutaneously in the first human series, which included data on 14 patients treated with IRE using a percutaneous technique.[12] This was followed by a retrospective review of 50 patients with LAPC treated with percutaneous IRE.[13] The primary objective was safety and the secondary objective

was OS. All 50 patients had previous chemotherapy and 30 (60%) had previous radiation therapy. There were no treatment-related deaths and no 30-day mortality. Median OS was 27 months from the time of diagnosis (95% CI, 22.7–32.5 months) and 14.2 months from the time of IRE (95% CI, 9.7–16.2 months). Patients with tumors < 3 cm had a significantly longer OS than those with tumors > 3 cm (33.8 vs 22.7 months from the time of diagnosis and 16.2 vs 9.9 months from IRE). The study concluded that percutaneous IRE was safe in the treatment of pancreatic cancer.

The survival results of this study are similar to surgical data on IRE from Martin et al.[14] This study reported results from a cohort of 200 patients with stage III LAPC treated with IRE. In this cohort, 150 patients 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. Median OS was 24.9 months (range, 4.9–85 months). This study concluded that for patients with LAPC (stage III), the addition of IRE to conventional chemotherapy and radiation therapy results in substantially prolonged survival compared with historical controls. These results suggest that ablative control of the primary tumor may prolong survival.

The prospective PANFIRE study reported a 12-month median time to local progression after percutaneous IRE (95% CI, 8–16 months).[15] 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. Leen et al published their experience with the use of IRE for LAPC in 75 patients.[16] Median OS and progression-free survival after IRE were 27 and 15 months, respectively, and 30 months from the time of diagnosis.

DISCUSSION

Percutaneous IRE of the pancreas is minimally invasive and usually only requires a single treatment with a short hospital stay compared to other local treatment options. It is not limited by the heat sink effect of thermal ablation and its nonthermal nature makes it safe for use near vasculature.[17] Although IRE is a relatively new ablation modality, it has been shown to be safe and effective in the treatment of pancreatic cancer, and the similarity of the results from several studies from different centers seem to suggest a survival benefit. Although many of these studies are single-center retrospective studies, this is a positive signal that requires

attention. The ongoing CROSSFIRE trial (NCT02791503) is a randomized controlled phase 3 trial comparing the outcome of FOLFIRINOX plus IRE with FOLFIRINOX plus MR-guided SBRT on OS for patients with LAPC. Given the dearth of treatment choices in pancreatic cancer, this randomized controlled trial (RCT) and future multicenter registries will help further define the impact of IRE in the management of pancreatic cancer.

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STEREOTACTIC BODY RADIATION THERAPY FOR LOCAL CONTROL AND TREATMENT

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Pancreatic carcinoma is one of the most lethal cancers in the United States and is currently the fourth leading cause of cancer death in both men and women. Although the only curative option is complete surgical resection, only selected patients are eligible at the time of presentation, leading to a 5-year survival rate of < 10%.

Recent advances in technology have led to multiple therapeutic options with improved clinical outcomes. Given the natural history of the disease, the best management for patients with pancreatic cancer occurs at the multidisciplinary level with collaboration between gastroenterologists, oncologists, pathologists, surgeons, radiologists, radiation oncologists, dieticians, palliative care experts, and social workers.[1]

RADIOTHERAPY

A recent autopsy series showed that approximately 30% of patients with pancreatic cancer die from local disease, emphasizing the importance of local treatment, such as radiotherapy, for these patients.[2] Radiotherapy has his-

torically been part of the multimodality treatment, along with chemotherapy and possible surgical resection for patients with pancreatic cancer. The goal of radiotherapy is to improve local control of disease, delay progression to distant metastatic disease, and alleviate symptoms secondary to obstruction from the tumor (eg, pain).

External beam radiotherapy has been traditionally delivered to the tumor and surrounding lymph nodes at risk in a long-course fashion over 5 to 6 weeks at doses ranging from 50 to 54 Gy. Recent advances in imaging and radiotherapy have allowed for improved treatment planning and dose escalation techniques. This has led to the development of SBRT, which allows for more precise delivery of radiation to the target tumor. SBRT has become the standard of care in several malignancies such as lung, brain, spine, and liver cancer[3] and has shown promise in treating intra-abdominal tumors, including pancreatic cancer.[4]

ADVANTAGES OF SBRT

SBRT has multiple advantages and is becoming widely adopted in the United States for patients with pancreatic cancer. This type of treatment allows for dose-escalated radiation to be aimed precisely at the tumor while minimizing dose to surrounding, radiosensitive organs at risk (eg, the duodenum).

SBRT allows for shorter treatment times (3–5 days vs 25–30 days) with standard radiotherapy techniques. These allow for quicker implementation of systemic treatment options, milder side effects, and deposition of higher biologically effective doses within the tumor that result in improved tumor control.[5] Additionally, it has been shown to improve pain while preserving quality of life and increasing the likelihood of a margin-negative resection due to the ability to escalate dose near the tumor vessel interface.[6] SBRT also result in less lymphopenia than conventional radiotherapy and can be more easily combined with systemic therapy and immunotherapy.[7-9]

The delivery of SBRT requires close monitoring and advanced technologic measures to properly and safely deliver an escalated dose to pancreatic tumors. Image guidance for treatment typically includes the placement of gold fiducial markers prior to treatment and a four-dimensional CT simulation scan with management of respiratory motion for treatment planning and imaging, along with cone-beam CT scans during treatment delivery. Advanced treatment planning allows for some heterogeneity in plans and modification of dose to successfully minimize dose to surrounding organs such as the duodenum and stomach.

OTHER LOCAL THERAPIES

Due to the importance of local control, other types of therapies have emerged recently for patient with local-

ized pancreatic cancer. Recent studies have investigated endoscopy-driven therapeutic options for treatment of pancreatic cancer such as endoscopic ultrasound-guided RF ablation, cryo/thermal ablation, photodynamic therapy, ethanol ablation, high-intensity focused ultrasound, and brachytherapy.[10] As in the case of fiducial placement for SBRT, the endoscopist can deliver brachytherapy or ablate the tumor directly under endoscopic guidance. Although a number of studies have demonstrated the potential of this technique,[11] RCTs are still needed to establish treatment benefit and survival. There is current pilot study evaluating the safety and tolerability, along with efficacy as secondary endpoint, of an implantable radioactive phosphorus source that locally deposits dose to the tumor.[12]

CONCLUSION

SBRT and techniques that allow for enhanced local dose deposition show potential for treatment and local control of pancreatic tumors. Due to their localized nature, these techniques allow for additional treatment modalities to control systemic disease without added toxicity usually encountered with chemoradiation. SBRT can be used to palliate pain and allow for treatment breaks from systemic chemotherapy, leading to improvements in quality of life for patients with localized and oligometastatic disease.[13,14] ∎

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Advances in Surgical Treatment

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Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related mortality in the United States, with only 9% of patients alive 5 years after diagnosis.[1] A major reason for this dismal prognosis is that the vast majority of patients are diagnosed with metastatic disease and median survival at this stage is typically < 1 year. Clearly, earlier diagnosis and advances in systemic therapies are needed to improve the outcomes of these patients. However, even patients with localized PDAC who are able to undergo curative-intent therapies will likely experience local or distant relapse and ultimately die of cancer-related recurrence.[2]

The poor outcomes of these patients suggest that surgery is necessary (the long-term survival rate of patients with PDAC who do not undergo resection is negligible) but not sufficient for curative-intent treatment. Indeed, several large RCTs have confirmed that patients who undergo systemic chemotherapy[3-5] and possibly chemoradiotherapy[6] after resection of PDAC experience improved OS compared to those who do not. These observations have led to a renewed focus on multimodality therapy as part of a multidisciplinary treatment strategy for PDAC. As innovations in systemic treatments, radiation protocols, and interventional techniques continue to occur, these therapies will likely be complementary to, not in lieu of, surgical resection. Given the recent advances that have occurred in the surgical care of patients with PDAC, surgery will continue to play an important role in its multidisciplinary management.

PERIOPERATIVE OUTCOMES

One of the most important advances in the surgical care of patients with PDAC has been significant improvements in perioperative outcomes. Indeed, although morbidity rates have remained high, largely due to postoperative pancreatic fistula and delayed gastric emptying, rates of 30- and 90-day mortality have significantly decreased over the past several decades.[7,8] The reasons for these marked improvements are likely multifactorial and include better patient selection and preoperative optimization, advances in biliary stenting and nutritional intervention, centralization of patients to high-volume institutions, improvements in surgical technique and minimization of intraoperative blood loss, as well as advances in perioperative care and enhanced recovery after surgery protocols. However, one of the most important developments in the perioperative care of patients undergoing pancreatectomy has been the ability to "rescue" patients who experience major complications. Advances in endoscopic, interventional, and medical therapies have enabled the safe resolution of complex postoperative complications at experienced centers. The rates of "failure to rescue" have declined in recent years, which has been considered a major contributor to improved postpancreatectomy outcomes.[9]

MINIMALLY INVASIVE APPROACHES

Over the past 2 decades, improvements in technology, training, and surgeon experience have facilitated the expansion of minimally invasive approaches to pan-

creatic surgery. In general, this has allowed for the traditional benefits of minimally invasive surgery, including the use of smaller incisions, reduced postoperative pain, and shortened recovery time, to be extended to patients with pancreatic neoplasms. Minimally invasive approaches (ie, laparoscopic or robotic) for left-sided pancreatic tumors (ie, distal pancreatectomy) have become well accepted.[10] Given the equivalence in short-term[11] (ie, margin status, lymph node yield) and long-term[12] oncologic outcomes between open and minimally invasive approaches, there are no absolute contraindications to minimally invasive distal pancreatectomy, including its use for PDAC.[13]

The recently published LEOPARD trial was the first RCT to compare minimally invasive versus open distal pancreatectomy (21.3% had PDAC) in a patient-blinded fashion and found less blood loss, increased operative time, reduced length of hospital stay, and faster functional recovery among patients who underwent minimally invasive surgery.[14]

Minimally invasive pancreatoduodenectomy (MIPD) for tumors in the head of the pancreas are more challenging, and a significantly greater learning curve exists. In fact, early nationwide analyses demonstrated a significantly higher postoperative mortality rate among patients undergoing MIPD, although this difference seemed to be driven by low-volume hospitals performing MIPD early in their experience.[15] More recent studies limited to high-volume centers suggest similar perioperative and short-term oncologic outcomes.[16] Nevertheless, as the currently available literature is limited to highly selected retrospective series, more research is needed, especially on long-term outcomes. Importantly, the LEOPARD-2 trial will randomize patients with pancreatic tumors requiring pancreatoduodenectomy to either a minimally invasive or open approach.[17]

NEOADJUVANT THERAPY

Because multimodality therapy is known to benefit all patients with PDAC and yet the rate of receipt of adjuvant chemotherapy following pancreatectomy is relatively low, an alternative approach is to administer nonsurgical therapies prior to pancreatectomy. Theoretical benefits of this approach include the early treatment of micrometastatic disease presumed present in nearly all patients, facilitation of a margin-negative resection, selection of a physiologically robust population of patients with biologically favorable tumors, and assurance that all patients who undergo surgery will receive all intended components of therapy. On the other hand, some worry about local progression occurring during neoadjuvant therapy, which may preclude an opportunity to resect the primary tumor. Other disadvantages include the potential for toxicity and deconditioning prior to pancreatectomy and the logistical challenges of obtaining durable biliary decompression, confirming a tissue diagnosis, and coordinating multidisciplinary care.

Regardless of the advantages and disadvantages, neoadjuvant therapy is increasingly utilized[18] and is now established in practice guidelines for both borderline-resectable[19] and resectable cancers.[20] Multiple studies have confirmed that neoadjuvant chemotherapy or radiation therapy does not worsen postoperative outcomes, and in fact, preoperative chemoradiation may actually lead to a lower rate of postoperative pancreatic fistula.[21] Although RCT data supporting the use of neoadjuvant therapy are still lacking, a recent intention-to-treat meta-analysis found that neoadjuvant therapy was associated with improved OS compared to upfront surgery for patients with resectable and borderline-resectable PDAC.[22] In addition, a 25-year review of outcomes from a single institution that routinely administers preoperative therapy prior to pancreatectomy has demonstrated consistently improved long-term outcomes over time.[23]

LOCALLY ADVANCED PDAC

Perhaps one of the most important advances in the surgical treatment of patients with PDAC has been the ability to offer surgical resection to more patients. Because the pancreas has an intimate relationship with retroperitoneal structures, locally advanced cancers often abut or even invade critically important vasculature such as the superior mesenteric vein, superior mesenteric artery, or branches of the celiac axis. Historically, vascular involvement, whether diagnosed radiographically prior to surgery or at the time of laparotomy, was considered a contraindication to surgical resection; these patients were then treated solely with chemotherapy and radiation. However, over the past several decades, developments in cross-sectional imaging, preoperative staging, and vascular surgical techniques have led investigators to again consider the merits of vascular resection at the time of pancreatectomy. In fact, pancreatectomy with venous resection now comprises a substantial proportion of operations for PDAC at high-volume centers, and a large series suggests no worse survival in patients who underwent margin-negative resection.[24]

Equally important has been the observation that with the increased use of neoadjuvant chemotherapy and radiation therapy, margin-negative resections are

attainable in a significant proportion of patients with locally advanced cancers that were previously deemed to be unresectable.[25] This is important because a large series suggests that arterial resections in the setting of pancreatectomy for PDAC are associated with poor short- and long-term outcomes.[26] Therefore, utilizing nonsurgical therapies in a neoadjuvant fashion in order to sterilize the surgical margins has been an important breakthrough in increasing the number of patients who are surgical candidates.

The management of patients with locally advanced and truly unresectable PDAC remains controversial, especially following an extended period of systemic chemotherapy that has ensured the absence of progressive metastatic disease. The LAP07 trial randomized such patients to ongoing systemic chemotherapy versus chemoradiation and found no difference in OS but improved local control in those who underwent radiation. An alternative surgical option is IRE, which is a form of nonthermal ablation typically delivered at the time of surgery for unresectable tumors, although it can also be utilized for margin accentuation as well. Although the evidence for IRE remains limited, results from select centers suggest acceptable morbidity rates and the potential for improved local control and possibly OS compared to nonoperative treatments.[27]

CONCLUSION

The incidence of PDAC is increasing in the United States while improvements in the survival durations of patients diagnosed with PDAC are occurring slowly. Future improvements in patient outcomes will likely require disruptive advances in systemic therapies based on an enhanced understanding of tumor biology. Technologic developments enabling earlier detection and improved delivery of novel therapies will likely be required. Nonetheless, for patients with localized cancers, the delivery of safe and timely surgical resection will remain a critical component of multimodality cancer care. Further improvements in patient selection, surgical technique, and perioperative care should only increase the number of patients who are candidates for curative-intent resection as well as enable their expedited return to intended oncologic therapies following surgery. Ongoing advances in minimally invasive approaches, vascular reconstruction techniques, and ablative strategies will expand the surgical options for patients with PDAC.

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Literature Review of Current Novel and Combination Therapies

BY MOHAMMAD ALASKER, MD, AND DAVID K. IMAGAWA, MD, PhD, FACS

Pancreatic cancer remains a very challenging disease to treat. It is the second most common gastrointestinal malignancy and fourth most common cause of cancer deaths in the United States.[1] Surgical resection offers the only chance for cure. Unfortunately, fewer than one-fifth of patients have resectable disease at the time of diagnosis[2,3]; as many as 30% present with stage III LAPC. By definition, these tumors are unresectable if they involve the celiac trunk, the superior mesenteric artery, or both. With the difficulty in surgical resection of these tumors, novel techniques such as RF ablation, MW ablation, cryoablation, and IRE have been developed in an attempt to reduce tumor burden and increase survival as well as quality of life. Historically, LAPC patients are expected to survive 6 to 11 months from the time of diagnosis with standard chemotherapy and/or radiotherapy treatment.[3] Recent trials have demonstrated improvement in survival using ablative techniques.

RF ABLATION

RF ablation has been used in multiple organs with a successful track record with solid tumors such as the liver, kidney, and bone.[4] However, the soft, friable nature of the pancreas discouraged many physicians from attempting the procedure for pancreatic tumors. Elias et al treated two patients with metastatic kidney tumors of the pancreas.[5] Both patients died of necrotizing pancreatitis after RF ablation. Hadjicostas et al successfully performed the procedure in four LAPC patients; all four patients were alive at the 12-month follow-up, suggesting an improvement in survival.[6] Additionally, one patient who was on long-term morphine for intractable pain reported significant pain relief postprocedure.

MW ABLATION

MW ablation is a technique that induces excitation of water molecules with electromagnetic waves of frequencies between infrared and radio waves to produce coagulative necrosis. Compared to RF ablation, MW ablation can produce larger areas of ablation more quickly and with fewer applications.[7,8] Vogl et al demonstrated the therapy's feasibility in a study on 20 patients in which they achieved a mean ablation volume of 7.8 cm^3 with only two cases of mild complications involving postablation pain.[9] Carrafiello et al evaluated the procedure in 10 patients, and although they observed both improved quality of life and a 1-year

survival of 80%, minor complications included one case of mild pancreatitis, one case of pancreatic pseudocyst, and one gastroduodenal pseudoaneurysm.[10]

CRYOABLATION

Cryoablation has a few advantages over the other ablation techniques including visibility of the ice ball on ultrasound, allowing precise control of the ablation zone both intraoperatively and percutaneously, as well as its ability to preserve cellular architecture.[7] Xu et al treated 49 patients with LAPC using combined cryotherapy and I^{125} seed implantation. Six patients suffered acute pancreatitis, although all cases were controlled with medical management.[11] Twenty patients underwent repeat procedures; however, the authors concluded that because the procedure was minimally invasive and median survival was 16.2 months, cryotherapy with I^{125} seed implantation should be the recommended therapy of choice for LAPC.

NEOADJUVANT AND INTRAOPERATIVE THERAPY

Massachusetts General Hospital completed two prospective studies exploring the possibility of aggressive neoadjuvant therapy in borderline-resectable pancreatic cancer and LAPC. In the borderline-resectable setting, patients received a combination of the FOLFIRINOX regimen for eight cycles followed by chemoradiation and surgery. At the time of resection, those with close or positive margins received 10 Gy of radiation; patients who remained unresectable received 15 Gy. At 2 years, 72% of patients who underwent resection were still alive; 56% of patients across both groups were alive at 2 years posttreatment, suggesting favorable survival.

In the second trial, losartan was added to FOLFIRINOX in the hopes of improving chemotherapy delivery and improving resectability of otherwise unresectable LAPC. After neoadjuvant therapy, 52% of patients underwent R0 resection and 91% of those patients were alive at 2 years; across all patients, 2-year survival was 65%. The results of these two trials suggest that early, intensive, neoadjuvant therapy can improve resectability in LAPC, and intraoperative radiotherapy is a feasible option to prolong survival in patients whose tumors remain unresectable. The University of California, Irvine Medical Center will soon be conducting a phase 3 trial for intraoperative radiotherapy in pancreatic cancer.

IRREVERSIBLE ELECTROPORATION

IRE is the newest technique in the treatment of LAPC and unresectable pancreatic tumors. It is a nonthermal technique that uses high-voltage DC energy to permanently destabilize cell membranes and induce apoptosis of cells adjacent to an electrode. Although some heat is generated by the pulse of electrical energy, it is not enough to destroy surrounding structures such as ducts and blood vessels.[12,13] From 2009 to 2011, Martin et al performed a pilot evaluation of the use of IRE in the treatment of LAPC.[3] Twenty-six patients were treated with IRE by an open approach and one was treated percutaneously. At 90 days, there was one mortality from complications related to portal vein thrombosis on postprocedure day 25, and no patient showed signs of pancreatitis or fistula formation. Nine patients experienced mild complications associated with the surgical approach. No patients developed local recurrence.

Additional multiple large-scale trials of IRE-based treatment of LAPC combined with the current standards of care have succeeded in demonstrating the procedure's survival benefit. Huang et al combined gemcitabine or titanium-silicate-1–based chemotherapy with laparoscopic IRE in 70 patients, achieving a median OS of 22.6 months.[14] In an even larger trial, Martin et al treated 200 patients with chemotherapy and IRE with or without pancreatic resection with a median OS of 24.9 months.[15]

Because the procedure is still in its infancy, standardized protocols have not been developed. Martin et al point out that there is considerable variance in procedure parameters such as voltage, electrode spacing, and number of pulses in the existing literature.[16] Further studies and meta-analyses have the potential to maximize benefit and minimize risk as the procedure becomes more commonplace.

IRE may have yet undiscovered synergy with other methods of cancer treatment. The process is derived from reversible electroporation, a process using less intense currents to create temporary pores in the cell membranes of target cells, through which plasmids can be taken up. Gene therapy can potentially be combined with IRE for enhanced eradication of tumor cells. Au et al performed IRE in animal liver models and administered plasmids expressing fluorescent proteins.[17] Of the 36 livers treated, 31 demonstrated strong fluorescence postablation. As apoptotic tumor cells are likely to leak tumor antigens into surrounding tissue, this suggests promising future potential of combining IRE with immunomodulatory gene therapy for enhanced tumor eradication and even greater survival benefit than has already been demonstrated.

INTRAOPERATIVE RADIATION AND OTHER NOVEL SURGICAL TECHNIQUES

Novel ablative and neoadjuvant techniques have only just begun to see widespread adoption in the treatment of LAPC. IRE in particular has already demonstrated promise, perhaps beyond that of other techniques in only its first decade of study. As the technology progresses and these techniques become more integrated into the standard current medical management, as well as other novel therapies such as gene therapy, there is great potential for prolonged survival and positive outcomes for patients suffering from pancreatic cancer. ∎

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