

WJG 20th Anniversary Special Issues (14): Pancreatic cancer**Management of borderline and locally advanced pancreatic cancer: Where do we stand?**

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Abstract

Many patients with pancreas cancer present with locally advanced pancreatic cancer (LAPC). The principle tools used for diagnosis and staging of LAPC include endoscopic ultrasound, axial imaging with computed tomography and magnetic resonance imaging, and diagnostic laparoscopy. The definition of resectability has historically been vague, as there is considerable debate and controversy as to the definition of LAPC. For the patient with LAPC, there is some level of involvement of the surrounding vascular structures, which include the superior mesenteric artery, celiac axis, hepatic artery, superior mesenteric vein, or portal vein. When feasible, most surgeons would recommend possible surgical resection for patients with borderline LAPC, with the goal of an R0 resection. For initially unresectable LAPC, neoadjuvant should be strongly considered. Specifically, these patients should be offered neoadjuvant therapy, and the tumor should be assessed for possible response and eventual resection. The efficacy of neoadjuvant therapy with this approach as a bridge to potential curative resection is broad, ranging from 3%-79%. The different modalities of neoadjuvant therapy include sin-

gle or multi-agent chemotherapy combined with radiation, chemotherapy alone, and chemotherapy followed by chemotherapy with radiation. This review focuses on patients with LAPC and addresses recent advances and controversies in the field.

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Key words: Pancreas; Locally advanced; Chemotherapy; Radiation; Irreversible electroporation; Pancreatic cancer

Core tip: While the management of resectable patients is surgery (with or without neoadjuvant therapy), and the management of grossly metastatic patients is palliative with systemic chemotherapy with or without radiation, there is an intermediate subset of patients with locally advanced disease which is less straightforward. This review focuses on this unique population of patients with locally advanced pancreatic adenocarcinoma and addresses recent advances and controversies in this field.

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INTRODUCTION

Pancreatic adenocarcinoma is a lethal disease with a high metastatic potential. In 2012, there were an estimated 43920 patients diagnosed with pancreas cancer, and 37390 were expected to die from their disease^[1]. The only available potential cure for pancreas cancer is surgical re-

section, with only 15%-20% of patients presenting with pancreas cancer being candidates for resection. For those patients that go onto resection, the 5-year survival ranges from 15%-20%, whereas the 5-year survival for all pancreas cancer patients combined is 3%^[1,2].

The factors that lead to the overall dismal prognosis of pancreatic cancer are multiple and varied, making management a challenge. These factors include absence of nonspecific symptoms that leads to delayed diagnosis, biological aggressiveness which is resistant to chemotherapy, and surgical considerations which can be technically demanding^[3,4]. While the management of resectable patients is surgery (with or without neoadjuvant therapy), and the management of grossly metastatic patients is palliative with systemic chemotherapy with or without radiation, there is an intermediate subset of patients with locally advanced disease which is less straightforward. This review focuses on this unique population of patients with locally advanced pancreatic adenocarcinoma and addresses recent advances and controversies in this field.

DIAGNOSIS OF LOCALLY ADVANCED PANCREAS CANCER

As technology has evolved, the tools available to evaluate locally advanced pancreas cancer (LAPC) have become more accurate. The principle tools used for diagnosis and staging of LAPC include endoscopic ultrasound (EUS), axial imaging with computed tomography (CT) and magnetic resonance imaging (MRI), and diagnostic laparoscopy^[5]. Endoscopic ultrasound provides images of the pancreas and surrounding vessels, and in particular allows for tissue diagnosis with the capability to biopsy. Endoscopic retrograde cholangiopancreatography (ERCP) can be performed at the same time if there is an indication to stent the common bile duct. Therefore, EUS can diagnose the tumor with biopsy, stage the tumor by size and vascular involvement, and use ERCP to therapeutically stent the common bile duct, should it be necessary.

CT with intravenous contrast provides multiplanar, high-resolution, three-dimensional images of the pancreatic tumor, its surrounding vascular structures, and possible lymphadenopathy and liver metastases. Warshaw *et al*^[6] demonstrated that more than 90% of patients deemed unresectable by CT are actually unresectable at operation. MRI can also be used to assess extent of tumor involvement and has shown to be equivalent to CT^[7]. Difficulties with CT and MRI include measuring response to treatment, particularly in patients who have undergone treatment with radiation therapy^[8]. However, with developments in imaging technology, assessment of staging and tumor response is likely to only improve for the patient with pancreatic cancer.

Another pitfall for current axial imaging is the limitation to incompletely visualize potentially small (1-2 mm) tumor deposits^[9]. This is critical to the management of pancreas cancer, as patients with extra-pancreatic disease

have the same dismal prognosis as those with metastatic disease, and these patients should not be put at risk from a potentially morbid laparotomy or pancreatectomy. This problem can be addressed using diagnostic laparoscopy to directly visualize the intra-abdominal contents, in particular the liver and peritoneum. Patients who should be considered for diagnostic laparoscopy prior to laparotomy are those patients with possible undetectable metastatic disease, *i.e.*, primary tumors > 3 cm, marked weight loss, equivocal radiological findings, and elevated levels of carbohydrate antigen 19-9 (CA19-9)^[10].

Definition and ambiguity of LAPC

The biology of LAPC is unique in that the tumor is confined locoregionally, without evidence of distant macrometastatic disease. The precise molecular mechanisms responsible for this behavior are unclear, but involve a preservation of the epithelial cell type *vs* de-differentiating into the mesenchymal phenotype responsible for distant spread^[11]. Specific signals involved in this cell-type transformation include transforming growth factor beta (TGFβ), E-cadherin, N-cadherin, K-ras, and Snail, along with the chemokine CXCL12^[12-14]. On a macroscopic level, LAPC has an anatomic definition and is represented by two subclasses of aggressive pancreas cancer - borderline resectable LAPC and unresectable LAPC. For the patient with LAPC, there is some level of involvement of the surrounding vascular structures, which include the superior mesenteric artery (SMA), celiac axis, hepatic artery, superior mesenteric vein (SMV), or portal vein (PV). Depending on the extent of vessel involvement, and whether the associated vascular structures are amenable to reconstruction in conjunction with resection of the tumor, defines whether the LAPC is deemed borderline resectable or unresectable (Figures 1 and 2).

Unfortunately, this definition of resectability has historically been vague, as there is considerable debate and controversy as to which patients are truly deemed resectable. Factors that contribute to this confusion are multiple, and include subjective interpretation of cross-sectional imaging, technical/surgical ability, and overall institutional experience. Because of the lack of consensus of a true definition of LAPC, the literature available for LAPC is not standardized, and generalizations and conclusions about the management of LAPC have suffered^[5,8].

To address the lack of general consensus on a definition of LAPC, three guideline statements have recently been proposed. These include guideline proposals by the National Comprehensive Cancer Network (NCCN), The University of Texas M.D. Anderson Cancer Center (MDACC), and Americas Hepato-Pancreato-Biliary Association (AHPBA). All three guidelines include the aforementioned tumor relationships to vascular structures, however there is variability in the definition of the tumor-vascular involvement. Further, some guidelines have added additional subset criteria to more specifically define the population of patients with LAPC. The MDACC guidelines were supplemented with three sub-



Figure 1 Computed tomography of locally advanced pancreatic cancer. Encasement is defined as greater than 180-degree involvement of the major vessels. A: Celiac axis is encased by locally advanced pancreatic cancer (arrow); B: Superior mesenteric artery and the replaced right hepatic artery are encased by pancreatic cancer (arrow); C: The portal vein and its confluence with splenic vein are encased by pancreatic cancer (arrow).

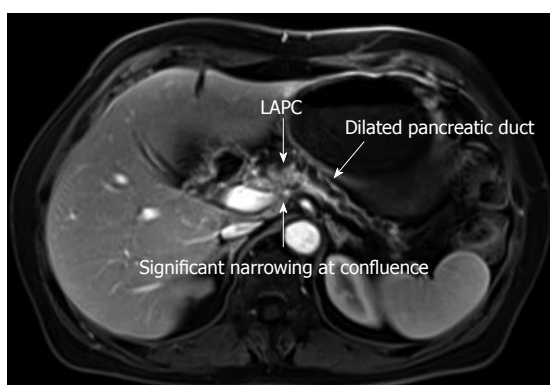


Figure 2 Magnetic resonance imaging of locally advanced pancreas cancer with vascular invasion and dilated pancreatic duct. LAPC: Locally advanced pancreatic cancer.

classifications of borderline resectable-types A, B and C. MDACC type A patients are only those patients with local, tumor-artery abutment. Type B patients are those with questionable extrapancreatic metastatic disease. Further defined, these type B patients are considered “oncologically borderline resectable” secondary to prior exploration which the original tumor was considered unresectable, a prior biopsy confirmed regional lymph node metastasis, or there is imaging concerning for liver metastases or high CA19-9. Type C patients are those defined as having a marginal pretreatment performance status^[15].

The Alliance for Clinical Trials in Oncology (Alliance) recently initiated a multi-institutional trial to examine the use of neoadjuvant for LAPC in a single arm pilot study^[16]. This study also seeks to address the lack of standardization in the definition of LAPC and to establish a research infrastructure that will create consensus around what constitutes borderline and unresectable LAPC. In the Alliance proposal, the definition of a borderline resectable pancreas cancer has an objective description of the tumor-vascular relationships, while omitting more subjective terms like abutment and encasement. These guidelines should create uniformity in how investigators define LAPC both for protocol and non-protocol based therapies^[16] (Table 1).

A multi-disciplinary approach is highly recommended

in the treatment of patients with LAPC, and can assist with arriving at a consensus recommendation for the treatment of patients with advanced disease. By bringing together medical oncologists, surgeons, radiologists, radiation oncologists, and other patient advocates, treatment plans for the patient with LAPC can be discussed and planned^[17]. The complexity of LAPC is best managed by this multidisciplinary team of physicians working in concert to deliver individualized care for each patient^[18]. The importance of a multi-modal, inter-disciplinary approach has been demonstrated in our own multidisciplinary pancreatic cancer clinic at Johns Hopkins, where we noted that 25% of patients seen in this setting had a significant change in their diagnosis or treatment^[18].

BORDERLINE LAPC

Surgical resection of LAPC

Resection of the surrounding vascular structures for LAPC has been described since the 1970s. Fortner *et al*^[19] described these “regional pancreatectomies” as type 1 (venous resection) and type 2 (arterial resection). These early reports demonstrated significant morbidity and mortality, and given the potential for likely systemic disease, combined tumor and vascular resection fell out of favor^[20]. Despite early hesitation with combined resection of tumor and surrounding vascular structures, there is now growing enthusiasm for these more aggressive surgeries. One of the most controversial topics for these patients is the role of margin status after resection. This is particularly relevant for the patient with borderline LAPC, as vascular involvement of surrounding structures, even when technically achievable, may predispose to a positive resection margin.

Multiple reports suggest that margin status after resection of pancreas cancer influences survival^[21,22]. However, other data demonstrate that margin status does not correlate with survival^[23,24]. There are a variety of factors that have led to this ambiguity. One of the strongest influences fueling this discrepancy has been the lack of standardization of pathologic technique, *i.e.*, truly defining a “positive microscopic margin.”^[25] This is evident from multiple large studies which demonstrate the rate of R1 involvement for pancreas cancer varies between

Table 1 Difference of definitions of anatomic borderline resectable pancreatic cancers from different sources

Tumor-vessel relationship on computed tomography	NCCN	MDACC	AHPBA/SSO/SSAT	Alliance
Superior mesenteric vein/portal vein	Severely narrowed or occluded with possibility of reconstruction	Occluded with possibility of reconstruction	Abutment or encasement or occlusion with possibility of reconstruction	Interface between tumor and vessel > 180°, and/or reconstructable
SMA	Abutment	Abutment	Abutment	Interface between tumor and vessel < 180°
Celiac axis	No abutment or encasement	Abutment	No abutment or encasement	Reconstructable interface
Common hepatic artery	Abutment or short segment encasement	Abutment or short segment encasement	Abutment or short segment encasement	Interface between tumor and vessel < 180°

Abutment, $\leq 180^\circ$ or $\leq 50\%$ of the vessel circumference; encasement, $\geq 180^\circ$ or $\geq 50\%$ of the vessel circumference. MDACC: Anderson Cancer Center; NCCN: National Comprehensive Cancer Network; AHPBA: Hepato-Pancreato-Biliary Association; SMA: Superior mesenteric artery.

20% and 80%, despite other clinicopathological variables being similar^[26,27]. Fortunately, there have been improvements in standardization, and consensus is growing in the pathology community regarding how to examine the pathology specimen^[28].

Other groups have also examined the effect of margin status from the surgical perspectives. Butturini *et al.*^[29] pooled hazard ratios of the effects of adjuvant therapy for resected patients, and compared the disease specific survival with their margin status. As part of their subset analysis, the authors concluded that resection margin (R0 *vs* R1) involvement was not a statistically significant prognostic factor, with a median survival of 14.1 mo for patients with an R1 resection compared with 15.9 mo for patients with R0 resections ($P = 0.24$).

From a technical standpoint, superior mesenteric vein and portal vein involvement by LAPC can be performed safely if resected and reconstructed at high-volume centers^[30]. Reconstruction of the SMV/PV can be performed in a variety of ways depending on the degree of involvement. Patch or primary closure can be done for partial involvement, with patch reconstruction often done using the greater saphenous vein. Segmental reconstruction of the SMV can be performed with an interposition vein graft using the internal jugular, renal vein or superficial femoral vein^[31,32]. Raut *et al.*^[24] examined 360 patients after pancreatectomy, of which 130 underwent SMV/PV reconstruction. Those patients who underwent vascular reconstruction had more R1 than R0 resections compared with those that did not have vascular reconstruction (HR = 2.00, $P = 0.015$). However, on multivariate analysis, there was no difference in survival between the R1 and R0 groups, leading the authors to conclude that not only was there no difference in patient survival based on R status, but venous reconstruction also did not predispose to worse disease-specific survival.

Compared with venous reconstruction, arterial involvement is probably more technically demanding. If an interposition graft is required, this can be done with polytetrafluoroethylene (PTFE) graft or saphenous vein^[33]. Bockhorn *et al.*^[34] has reported one of the largest series to examine pancreatic resection with simultaneous arterial resection and reconstruction ($n = 29$); these au-

thors found no difference in overall disease specific survival for patients who underwent arterial reconstruction *vs* those patients that had pancreatectomy alone (14.0 mo *vs* 15.8 mo respectively, $P = 0.152$). Both resection groups independently had better survival than the non-resected patients who only underwent palliative bypass (7.5 mo, $P < 0.05$ for both groups)^[34].

Therefore, if feasible, most surgeons would recommend possible surgical resection for patients with borderline LAPC, with the goal of an R0 resection for all cases. While vascular resection with reconstruction is safe, patient selection is paramount. Those patients who cannot tolerate combined pancreatectomy and vascular reconstruction would benefit more from palliative bypass or no surgery at all.

BORDERLINE LAPC AND NEOADJUVANT THERAPY

Because of the dismal prognosis of pancreatic cancer, in particular those with borderline LAPC which may have a more aggressive biology, there is a growing body of literature to suggest that there is a potential role for neoadjuvant therapy to treat micrometastatic disease with chemotherapy, as well as treat local disease with radiation^[35,36]. The rationale for neoadjuvant therapy for patients with borderline and LAPC is multifold. First, the chance of delivering full-dose chemotherapy with or without radiation is much better if given prior to surgery because of the potential delay in getting to treatment after a complex pancreatic resection. Second, neoadjuvant therapies provide insight into the biology of the disease, and can spare patients who progress or develop distant metastasis during treatment from undergoing a major surgery that would not be curative. Next, neoadjuvant therapies have the potential to downstage borderline resectable disease to the point of not requiring vascular reconstruction and/or increasing R0 resection. Lastly, preoperative therapy could be more effective than post resection therapy because the resected tumor bed may have decreased oxygenation and decreased drug delivery^[37]. While there are benefits of neoadjuvant therapy for borderline LAPC,

these benefits must be weighed against the risks, which include delaying time to potentially curative surgery and significant time and side-effects for patients with limited life expectancies.

There are only retrospective studies with subsets of borderline LAPC, and a few smaller prospective studies examining the role of neoadjuvant therapies for borderline LAPC^[15,38-40]. Patel *et al.*^[41] prospectively examined 17 patients with borderline LAPC for patients that were treated with combined chemoradiation, with 64% proceeding to surgery with 89% achieving an R0 resection. Stokes *et al.*^[40] also prospectively examined 40 borderline LAPC, also with combined chemoradiation, with 40% of patients proceeding to surgery, with 88% with an R0 resection, and median survival at 23 mo.

INITIALLY UNRESECTABLE LAPC AND NEOADJUVANT THERAPY

For initially unresectable LAPC, *i.e.*, those tumors with significant vascular involvement that involves a significant portion of the SMV or SMA, neoadjuvant therapy should be offered, and the tumor should be assessed for possible response and eventual resection. The efficacy of neoadjuvant therapy with this approach as a bridge to potential curative resection is broad, ranging from 3%-79%^[42-44]. The different modalities of neoadjuvant therapy include single or multi-agent chemotherapy combined with radiation, chemotherapy alone, and chemotherapy followed by chemotherapy with radiation.

Combined chemotherapy with radiation

5-fluorouracil (5-FU) infusion with radiation therapy has shown utility in many gastrointestinal cancers, and is used in the management of unresectable LAPC. One of the first studies to demonstrate the synergistic effects of 5-FU with radiation was the Gastrointestinal Study Group (GITSG) trial in 1981 that prospectively examined unresectable LAPC patients, randomly assigning 106 patients to three different treatments: radiation (60 Gy) alone, *vs* concurrent radiation (40 Gy) plus bolus 5-FU, *vs* higher dose concurrent radiation (60 Gy) plus bolus 5-FU^[45]. The radiation alone group demonstrated poor 1-year survival (11%) *vs* 36% in the higher dose concurrent radiation group, and 38% in the concurrent lower radiation group. Other trials have demonstrated this synergistic and radiosensitizing effect of combined 5-FU with radiation^[46-48]. Contrary to successes of these groups and the GITSG trials using combined 5-FU with radiation, a trial from the Eastern Cooperative Oncology Group (ECOG) randomized 91 patients with unresectable LAPC to either radiation (40 Gy) plus concurrent bolus 5-FU, followed by weekly maintenance 5-FU, *vs* 5-FU alone, and found no differences in survival (8.2 mo *vs* 8.3 mo)^[49,50]. Despite the conflicting success of combined 5-FU/radiation therapy, this radiosensitization treatment modality has become an established approach to management of the patient with LAPC^[51].

In an effort to capitalize on the benefits of combined 5-FU and radiation therapies, yet avoid the toxic side effects of 5-FU therapy, the oral formulation of 5-FU, capecitabine, has been introduced into many trials. To date there are multiple studies, albeit only a few prospective trials, that demonstrate that capecitabine can effectively replace infusional 5-FU in the setting of LAPC^[52-54].

As the potential utility of combined 5-FU/radiation therapies was being recognized for LAPC, gemcitabine based regimens were gaining acceptance in the management of metastatic pancreas cancer^[55]. Therefore, gemcitabine combined with radiation gained interest as a potential agent to study in the management of LAPC. Unfortunately, early phase I trials using gemcitabine with radiation were fraught with toxicities unlike the 5-FU based therapies, and required improvements in delivery of radiation^[56-58]. As the toxicities of combined gemcitabine and radiation therapy became more manageable, studies were designed to compare the established 5-FU and radiation therapy with gemcitabine combined with radiation for LAPC.

Three large prospective studies were designed with this hypothesis in mind. The Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD-SFRO) trial published in 2008 showed improved survival for those patients treated with gemcitabine alone *vs* combined radiotherapy with 5-FU (13.0 mo *vs* 8.6 mo, $P = 0.03$)^[59]. The ECOG E4201 study, published 3 years after the FFCD-SFRO study, compared gemcitabine plus radiation with gemcitabine alone, and found improved survival in the combined group (11.1 mo *vs* 9.2 mo, $P = 0.017$), although there was more toxic side effects in the combined group^[60]. The Taipei trial, which compared combined gemcitabine and radiation with combined 5-FU and radiation, concluded that combined gemcitabine and radiation therapy had improved overall survival (14.5 mo *vs* 6.7 mo, $P = 0.027$)^[48]. These large series solidified the utility of gemcitabine based chemoradiation as an acceptable option for patients with LAPC.

A recent trial has further examined 5-FU combined therapies using capecitabine, and compared efficacy with gemcitabine-based chemoradiotherapy. Mukherjee *et al.*^[61] in the Selective Chemoradiation in Advanced Localized Pancreatic Cancer (SCALOP) study, examined 74 patients with LAPC who were randomly assigned gemcitabine or capecitabine. These authors found that the capecitabine treated patients had improved survival over the gemcitabine treated patients (15.2 mo *vs* 13.4 mo, $P = 0.012$). Furthermore, the gemcitabine treated patients had more toxic non-hematologic (10 *vs* 4, $P = 0.12$) and hematologic side effects (7 *vs* 0, $P = 0.008$).

Just as the combined chemotherapy and radiation algorithm has focused on changing the chemotherapeutic agent in an attempt to maximize survival benefit and minimize toxicity, other studies have examined the different radiation delivery modalities. The earlier combined chemoradiation treatments incorporated external beam

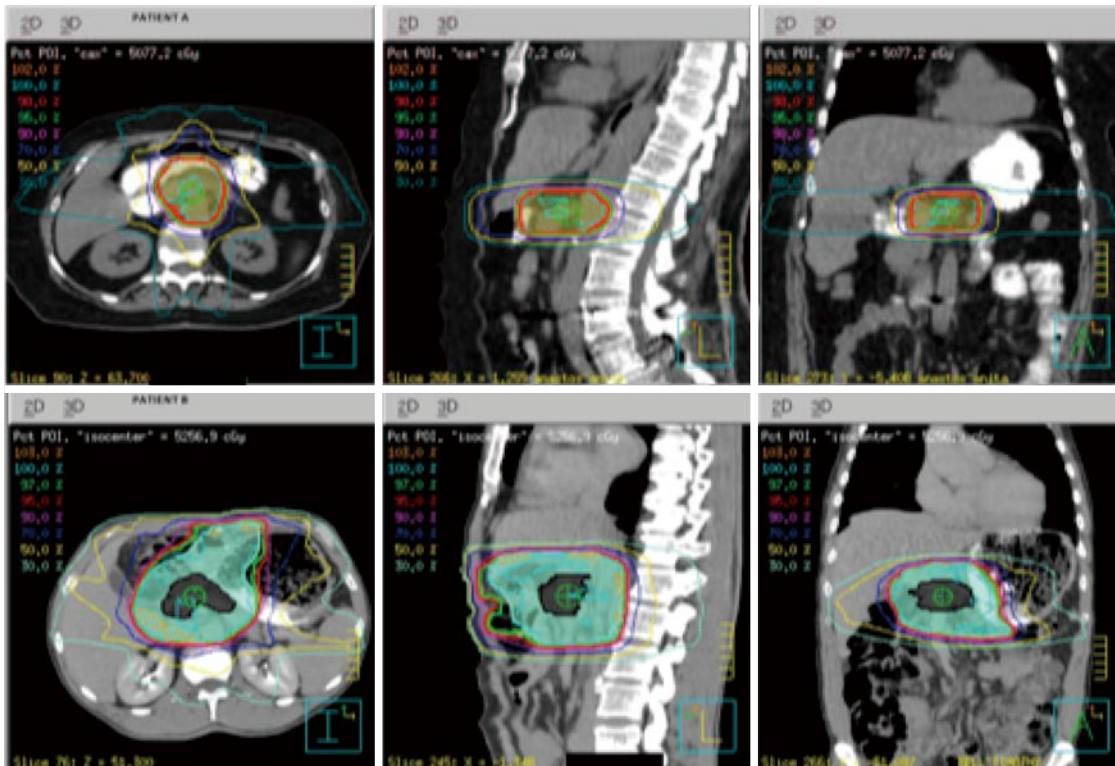


Figure 3 Depiction of stereotactic body radiation plan using computed tomography. Typically the tumor is expanded 2-3 mm to account for set up error microscopic extension and set-up error planning treatment volume. In the lower panel, (patient b) this represents a plan integrating intensity modulated radiation therapy (IMRT) where the tumor is expanded 1-3 cm to cover the tumor and peripancreatic lymph nodes. Stereotactic body radiation is often delivered over 1-5 d without chemotherapy. IMRT is delivered over 5-6 wk with concurrent chemotherapy.

radiation (EBRT). Since the 1980s, other delivery systems have developed with the integration of 3-D conformal radiation and subsequently intensity modulated radiation therapy (IMRT) and stereotactic body radiation (SBRT). Conventional EBRT has limitations in the amount of radiation that can be delivered to the pancreas tumor secondary to damage to the surrounding GI tract and other healthy tissues. In addition, EBRT also usually requires a large number of treatments given over 5-6 wk. SBRT and IMRT can deliver more focused radiation therapy to the tumor plus a margin, and thus limit dose to normal bowel resulting in less toxicity and dose escalation to the tumor. IMRT represents a further advancement from conformal EBRT. By utilizing 3-D conformations of a tumor target, radiation *via* IMRT can be delivered in smaller divisions of beams (beamlets), while both sparing healthy tissue and having the capacity to up or down regulate the intensity of the target directed beamlets^[62]. SBRT enables delivery of even more precise and large doses of radiation to the pancreas tumor plus a small margin (usually 2-3 mm) because of the rapid dose fall-off beyond the treated volumes. SBRT is also usually given in 1-5 fractions, far fewer than EBRT (10-30)^[63] (Figure 3).

Because of the toxicities which may arise during chemoradiation, combined with the overall poor survival of LAPC, it is critical in the multidisciplinary management of LAPC to identify which patients may experience worse outcomes. Rudra *et al*^[64] identified pretreatment

performance status and CA19-9 levels, along with treatment interruption as prognostic factors for patients with LAPC treated with chemoradiation. These authors proposed that patients should be identified with these poor outcome features prior to treatment, and consider other therapies such as chemotherapy alone or supportive care for patients with poor performance status.

Chemotherapy alone

Chemotherapy alone represents another management strategy for unresectable LAPC. The primary chemotherapy only regimens include gemcitabine alone; gemcitabine doublet therapy with oxaliplatin, cisplatin, erlotinib, or capecitabine; or triplet therapy with oxaliplatin and erlotinib, or oxaliplatin and bevacizumab. Other non-gemcitabine-based regimens include irinotecan with docetaxel^[65].

Multiple trials have examined patients with LAPC, comparing gemcitabine alone with various gemcitabine doublet therapies. Louvet *et al*^[66], in the GERCORD and GISCAD trials found no difference in overall survival (9.0 mo *vs* 7.1 mo, *P* = 0.13) using gemcitabine alone *vs* doublet therapies. Similar survival was also seen when gemcitabine was compared with and without tipifanib (193 d *vs* 182 d, *P* = 0.75)^[67]. Other groups have examined gemcitabine combined with irinotecan (IRINOGEN), and while time-to-progression initially showed promise for the IRINOGEN treated group *vs* gemcitabine alone

Table 2 Summary of recent chemotherapy trials for locally advanced pancreatic cancer

CHEMO trials	Component	Median survival	P value
GERCOR/GISCAD ^[66]	Gem ± oxaliplatin	9.0 mo vs 7.1 mo	0.13
Van Cutsem <i>et al</i> ^[67]	Gem ± tipifarnib	193 d vs 182 d	0.75
IRINOEM ^[68]	Gem ± irinotecan	6.3 mo vs 6.6 mo	0.79
Von Hoff <i>et al</i> ^[69]	Gem ± nab-paclitaxel	8.5 mo vs 6.7 mo	< 0.001
PRODIGE ^[70]	Gem vs FOLFIRINOX	6.8 mo vs 11.1 mo	< 0.001

CHEMO: Chemotherapy; Gem: Gemcitabine.

(median 7.7 mo vs 3.9 mo, *P* value not reported), there was no difference in overall survival (6.3 mo vs 6.6 mo, *P* = 0.789)^[68]. Von Hoff *et al*^[69] using combined gemcitabine with nab-paclitaxel vs gemcitabine monotherapy demonstrated a survival benefit in patients with metastatic pancreas cancer (8.5 mo vs 6.7 mo, *P* < 0.001). The application of this regimen for LAPC is not known. In summary for gemcitabine-based chemotherapies, in the setting of LAPC, there are no prospective data to suggest that gemcitabine doublet, or even triplet therapy improves overall survival over monotherapy using gemcitabine alone.

While multiple agent gemcitabine based chemotherapies have not shown direct promise in the management of LAPC, other non-gemcitabine based regimens are being explored. The multiple agent therapy of 5-FU/leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has recently shown promise in the management of metastatic pancreas cancer in the PRODIGE trial, and is being studied in the context of LAPC^[70]. In three retrospective reviews of FOLFIRINOX for LAPC, partial response rates ranged from 25%-40%^[71-73]. Other multiple agent therapies like oxaliplatin, 5-FU, and folinic acid (FOLF-IRI), and agents like 5-FU plus leucovorin plus irinotecan (FOLFIRI), are also being studied as potential agents to improve outcomes in unresectable LAPC^[74,75]. While some progress has been shown using chemotherapy alone regimens for LAPC, the specific treatment with best results has yet to be determined (Table 2).

Chemotherapy followed by chemoradiotherapy

An additional treatment algorithm for LAPC is the use of chemotherapy followed by chemoradiotherapy. The specific goal of this treatment is to select the patients treated with chemotherapy who will benefit from chemoradiotherapy, and also to select those who have not progressed following the initiation of chemotherapy. The earliest and one of the largest studies to examine this mode of therapy was the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR). This group retrospectively reviewed 181 patients with LAPC who had been treated with gemcitabine-based chemotherapy followed by chemoradiotherapy using 5-FU in continuous infusion^[76]. Fifty-three patients developed metastases in the first 3 mo of chemotherapy and were subsequently not eligible for chemoradiation. In the remaining 128 patients who did not progress, 56 continued with chemotherapy alone with overall survival of 11.7 mo. The other 72 patients

received chemoradiation, with overall survival of 15.0 mo (*P* < 0.01).

Another retrospective study by the University of Texas M.D. Anderson Cancer Center examined consecutive patients with LAPC who had received treatment with chemoradiation or induction chemotherapy followed by chemoradiotherapy^[77]. Of the 323 patients in this study, 76 received a median of 2.5 mo of gemcitabine prior to chemoradiation. Those who underwent chemotherapy prior to combined chemoradiation had improved median overall survival (11.9 mo vs 8.5 mo, *P* < 0.001), and also demonstrated improved progression free survival (6.4 mo vs 4.2 mo, *P* < 0.001).

While the use of chemotherapy followed by chemoradiation has shown early promise in the management of LAPC, phase II/III studies are needed. The ECOG 1200 phase II trial was initially designed to evaluate the safety of borderline resectable LAPC using the algorithm of chemotherapy followed by chemoradiation, but was closed early because of low recruitment^[44].

In summary of the treatments modalities available for unresectable LAPC, a recent retrospective review by Lloyd *et al*^[65] compared outcomes based on combined chemotherapy with radiation, chemotherapy alone, and chemotherapy followed by chemotherapy with radiation. While the sample size was small (*n* = 115), and included borderline and unresectable LAPC, the authors concluded on multivariate analysis that chemotherapy followed by chemotherapy with radiation was associated with improved overall survival over chemotherapy alone or combined chemotherapy with radiation (median survival 21.5 mo vs 13.9 mo and 12.5 mo respectively, *P* < 0.05).

Locoregional therapy with irreversible electroporation

For some patients with LAPC, irreversible electroporation (IRE) has shown promise in downstaging and prolonging survival. IRE is a non-thermal modality that uses high voltage and low energy direct current to increase cell membrane permeability and effectively create defects in cell membranes, resulting in loss of homeostasis and subsequent cell death. IRE has minimal effect on blood vessel scaffolding, which is crucial and particularly relevant for LAPC, as surrounding vascular involvement may be present^[78,79].

The NanoKnife[®] IRE system has been commercially available since 2009 and is FDA-approved to treat soft tissue tumors. The safety of IRE use in the pancreas has been shown in swine models with rapid resolution

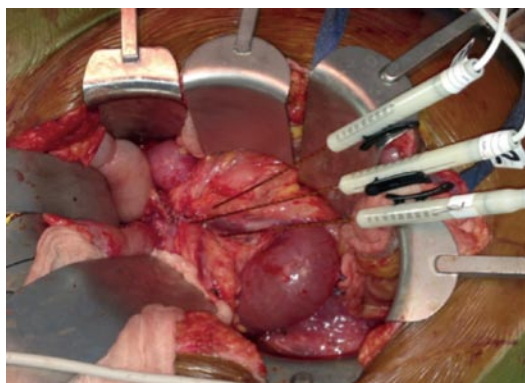


Figure 4 An intraoperative image of *in situ* irreversible electroporation being used in a patient with locally advanced pancreatic cancer. Three probes are placed around the tumor which is encasing the superior mesenteric vein causing complete occlusion plus superior mesenteric artery involvement.

of pancreatitis and preservation of vascular structures. Ablation effects can be achieved at a median size of 3 cm with 3000 volts setting of the NanoKnife® IRE system^[78]. Usually, 2-4 probes of the NanoKnife® IRE system are used to treat LAPC. The probes are placed using intraoperative ultrasound guidance. In a retrospective series of patients treated at a single institution, Martin *et al.*^[80] applied this new device and demonstrated in unresectable LAPC that IRE can improve both local (14 mo *vs* 6 mo, $P = 0.001$) and distant progression free survival (15 mo *vs* 9 mo, $P = 0.02$), compared with systemic therapy and chemoradiation. Overall survival for patients treated with IRE was also improved compared with patients treated with chemotherapy alone or chemoradiation (20 mo *vs* 13 mo, $P = 0.03$, exact chemoradiation regimens not specified) (Figures 4 and 5).

IRE can be administered percutaneously under imaging guidance, thereby avoiding the morbidity of a laparotomy. Narayanan *et al.*^[81] reported the results of 11 patients treated with IRE for LAPC. In this study, prior to IRE, all patients had received some form of chemoradiation, though the exact regimen was not specified. Patients were selected for IRE if they were not candidates for, or were intolerant of chemotherapy or radiation. The procedure was performed under general anesthesia, with CT guidance, and electrodes were placed at a maximum of 2.2 cm apart. Post treatment, all patients demonstrated patent vasculature in the treatment zone and there were no deaths related to the procedure. Two patients underwent partial responses leading to eventual resection 4 and 5 mo post IRE, with one of these patients demonstrating a complete response. Both patients remained disease free at 11 and 14 mo. At our institution, we often maximize both systemic and local therapy (radiation), then in well selected patients, we attempt surgical resection with IRE in an attempt to sterilize surgical margins or treat the tumor intra-operatively if found to be unresectable.

CONCLUSION

LAPC is a biologically aggressive cancer with unique



Figure 5 This is the representative base unit and generator for irreversible electroporation, manufactured by AngioDynamics, Latham, NY.

characteristics, prognosis, and management strategies that differentiate this pancreatic tumor from resectable cancer and metastatic disease. The only means to potentially cure LAPC is by maximizing upfront systemic and local therapy followed by a margin negative surgical resection. At Johns Hopkins Hospital, we recommend tailoring therapy to maximize the chance to offer the patient a chance at surgical resection. In general, if LAPC is pre-operatively identified as not resectable, then we proceed down a pathway of local control with radiation therapy combined with systemic control with chemotherapy. After chemoradiation, we restage and re-evaluate for possible resection, with IRE as an alternative therapy for the unresectable LAPC.

Unfortunately, surgical and chemoradiation protocols have suffered from lack of consensus on what truly defines both a resectable LAPC and a positive resection margin. But with growing adoption of consensus guidelines, and the incorporation of improved systemic therapies and local therapeutic options with decreased side effects, progress is being made in identifying which patients with LAPC can truly benefit from surgical resection.

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