

REVIEW ARTICLE

Management of locally advanced pancreatic cancer: A comprehensive review of multimodal treatment strategies

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Abstract

Locally advanced pancreatic cancer (LAPC) accounts for approximately 40% of newly diagnosed pancreatic ductal adenocarcinoma cases and is characterized by extensive vascular invasion without distant metastases. Historically, treatment with chemotherapy alone has resulted in poor outcomes, with median overall survival ranging from 11 to 15 months. This study synthesizes the rapidly evolving multimodal treatment paradigm for LAPC. LAPC is typically defined by tumors larger than 4 cm or by greater than 180° encasement of major arterial structures, such as the superior mesenteric artery or celiac axis, often accompanied by venous involvement that is not amenable to reconstruction. Advances in neoadjuvant systemic therapy, including FOLFIRINOX or gemcitabine plus nab-paclitaxel, have enabled tumor downstaging in a subset of patients, with reported median overall survival approaching 20 months. Locoregional ablative strategies have further expanded treatment options. Irreversible electroporation preserves critical vascular and ductal structures and has demonstrated high technical success with overall survival ranging from 18 to 27 months when combined with chemotherapy. Radiofrequency ablation has also shown survival benefits, though with higher complication rates. Additional approaches, such as stereotactic body radiotherapy and peritoneal patch vascular reconstruction, have increased resectability in selected patients. Multimodal treatment strategies now allow conversion to resectable disease in 20–30% of cases and have been associated with substantial survival improvements, particularly in high-volume centers. Overall, the integration of systemic chemotherapy, ablative technologies, and advanced surgical techniques represents a paradigm shift in the management of LAPC, offering the potential to significantly extend survival while emphasizing the importance of multidisciplinary expertise and individualized patient care.

Keywords: Locally advanced pancreatic cancer; Irreversible electroporation; Radiofrequency ablation; Vascular reconstruction; Multimodal treatment; Tumor downstaging

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) poses significant oncologic challenges. It is projected to become the second leading cause of cancer-related death by 2030.¹ Despite accounting for only 3% of new cancer diagnoses annually, its notoriously late presentation and profound biological complexity contribute to dismal prognosis, with five-year survival rates persistently hovering between 8–10%.² Early diagnosis remains critical, as only early-stage disease offers high cure rates with surgery.^{2,3} Within this already challenging landscape, locally advanced pancreatic cancer (LAPC) occupies a particularly complex position, comprising 30–40% of all pancreatic cancer cases at presentation. The defining characteristic of LAPC is vascular involvement without evidence of distant metastatic spread, rendering these tumors technically unresectable by traditional surgical criteria.^{3,4}

The historical approach to LAPC management centered primarily on systemic chemotherapy as the sole therapeutic modality, achieving a modest median overall survival (OS) of 11–15 months.⁵ However, the past decade has witnessed a transformative evolution in the therapeutic landscape through the emergence and refinement of multimodal treatment strategies. These contemporary approaches integrate neoadjuvant chemotherapy regimens, sophisticated local ablative techniques, including irreversible electroporation (IRE) and radiofrequency ablation (RFA), and advanced vascular reconstruction methods.^{6–8} The fundamental aims of these combined modalities are to achieve tumor downstaging, establish effective local disease control, and potentially convert previously unresectable cases to surgical candidates, thereby improving median OS to 16–22 months with modern multimodal strategies.^{7,9}

This comprehensive review synthesizes current evidence derived from clinical studies, meta-analyses, and accumulated expert experience to provide an integrated overview of contemporary LAPC management. We systematically examine the epidemiological landscape, staging methodologies, chemotherapeutic approaches, ablative therapies, vascular surgical interventions, multimodal treatment sequencing, complication management, patient selection criteria, and future therapeutic directions for LAPC.

This work is a concise narrative review rather than a formal systematic review or meta-analysis. Its primary objective is to synthesize the rapidly evolving multimodal treatment paradigm for LAPC and to provide practical, evidence-based guidance for multidisciplinary teams. Statistical pooling of outcomes was not performed, as the majority of studies on ablative therapies (IRE, RFA) and

complex vascular reconstruction remain single- or multi-institutional series with relatively small patient numbers. Instead, we prioritized the highest-quality and most recent evidence, including the largest available cohorts (e.g., PANFIRE-2 registry with 200 patients for IRE)⁸ and contemporary meta-analyses (e.g., a study of 265 patients for RFA).⁶

2. Biological insights and clinical implications

The aggressive behavior of PDAC arises from its distinctive biology: nearly universal KRAS mutations (95%), frequent TP53 (75%) and CDKN2A (50%) alterations, profound intratumoral hypoxia, and a dense desmoplastic stroma.¹⁰ This fibrotic reaction, driven by cancer-associated fibroblasts, not only creates a physical barrier that severely limits drug penetration, but also establishes an immunosuppressive microenvironment enriched with regulatory T cells and myeloid-derived suppressor cells, thereby promoting therapy resistance and early metastatic spread.¹¹

Clinically, PDAC often presents at an advanced stage, with symptoms such as painless jaundice, abdominal/back pain, or weight loss. By this stage, the tumor has usually invaded major vascular structures or metastasized. Established risk factors include tobacco smoking, obesity, diabetes, and chronic pancreatitis; non-modifiable risks comprise hereditary syndromes, notably germline BRCA1/2 mutations and Lynch syndrome, which markedly increase susceptibility through defective DNA repair or mismatch-repair pathways.¹

This combination of late presentation and inherent biological aggressiveness underscores why only early-stage, resectable disease currently offers realistic prospects of cure with surgery.

2.1. The challenge of vascular involvement

In LAPC specifically, tumor invasion of critical vascular structures, including the superior mesenteric artery (SMA), celiac axis (CA), or the superior mesenteric vein/portal vein complex, fundamentally precludes the achievement of R0 resection, which remains the only potentially curative therapeutic option.^{4,12} The distinction between borderline resectable pancreatic cancer and LAPC is clinically crucial: borderline resectable pancreatic cancer demonstrates limited vascular contact (typically $\leq 180^\circ$ circumferential involvement), whereas LAPC exhibits extensive vascular encasement ($>180^\circ$), making surgical intervention substantially more risky due to potential catastrophic vascular complications.³ Accurate classification between these categories is essential for

optimal treatment planning, as misclassification can lead to either overly aggressive surgical attempts with high morbidity or missed opportunities for potentially curative resection.⁷

2.2. Emerging therapeutic frontiers

Recent therapeutic progress has emerged from improved understanding of disease biology, leading to the development of targeted therapeutic approaches such as poly(ADP-ribose) polymerase inhibitors for *BRCA*-mutated cases and various immunotherapeutic strategies. However, the role of these agents in LAPC remains limited and under investigation, primarily constrained by the “cold” or non-immunogenic tumor microenvironment characteristic of pancreatic cancer.¹³ The integration of locoregional and systemic therapies has proven crucial for meaningful survival improvements, with emerging evidence suggesting that combining ablative techniques with chemotherapy may enhance immunogenic cell death, potentially sensitizing previously resistant tumors to immune checkpoint inhibition.^{8,14}

The evolution of the LAPC treatment framework reflects a fundamental paradigm shift from primarily palliative care toward aggressive multimodal interventions with curative intent. Early clinical trials focused predominantly on gemcitabine monotherapy with disappointing results, whereas contemporary combination regimens, such as FOLFIRINOX, have demonstrated the potential to increase survival in carefully selected patient populations.¹⁵ Ablative technologies effectively address the inherent limitations of surgical resection in vascular-encased tumors, while sophisticated vascular reconstruction techniques have expanded the boundaries of technical resectability.¹⁶ This review aims to provide clinicians with practical guidance by integrating these diverse therapeutic elements into a cohesive, evidence-based clinical framework.

3. Epidemiology and staging

3.1. Global disease burden

The incidence of PDAC continues to rise globally, with approximately 495,000 new cases documented worldwide in 2020. Projections indicate further increases in disease burden, driven primarily by aging populations and evolving lifestyle factors, including obesity and diabetes.¹ Within the United States alone, approximately 62,210 new cases were anticipated in 2022, with an estimated 49,830 deaths occurring during the same period, starkly highlighting the disease's exceptional lethality.² LAPC accounts for approximately 40% of all pancreatic cancer diagnoses at presentation, classified as stage III (T4 any N M0) according to the American Joint Committee on

Cancer staging system, which emphasizes extensive local disease without evidence of distant metastatic spread.³

3.2. Staging criteria and assessment

The precise definition of LAPC incorporates multiple anatomical and radiological criteria, including primary tumor size ≥ 4 cm, arterial involvement with $>180^\circ$ circumferential encasement of the SMA or CA, and extensive venous involvement of the superior mesenteric vein/portal vein complex deemed unreconstructable by standard surgical techniques, as defined explicitly by National Comprehensive Cancer Network guidelines.³ Accurate staging requires high-quality multiphasic contrast-enhanced computed tomography or magnetic resonance imaging for detailed vascular assessment, frequently supplemented by endoscopic ultrasound examination for tissue biopsy confirmation and refined local disease evaluation.¹⁰

Serum carbohydrate antigen 19-9 (CA19-9) levels, with normal values typically < 37 U/mL, correlate strongly with disease stage and extent, providing valuable prognostic information. However, CA19-9 alone lacks sufficient specificity for definitive diagnosis, as elevations can occur in benign biliary obstruction and other conditions. Additionally, approximately 10% of the population lacks the Lewis antigen necessary for CA19-9 expression, limiting its universal applicability.¹³ Multidisciplinary tumor boards have become essential for staging accuracy and treatment planning, as these collaborative forums integrate radiological, pathological, and clinical data to optimize treatment decisions and avoid both overtreatment and undertreatment scenarios.⁷

3.3. Demographic patterns and disparities

From an epidemiological perspective, PDAC disproportionately affects older adults, with a median age at diagnosis of 70 years. Disease incidence rates are notably higher in developed countries, strongly correlated with tobacco smoking (accounting for 20–30% of attributable risk) and obesity prevalence.¹ Significant racial and ethnic disparities exist in pancreatic cancer incidence and outcomes, with notably higher rates observed among African American populations. These disparities likely reflect complex interactions between socioeconomic factors, healthcare access differences, and potential genetic predispositions.¹⁷

Staging challenges in LAPC extend beyond anatomical assessment to include accurate differentiation from metastatic disease, where positron emission tomography-computed tomography can detect occult metastatic deposits in up to 20% of patients initially staged as locally

advanced by conventional imaging, fundamentally altering management strategies.³ The integration of functional and metabolic imaging with high-resolution anatomical imaging has thus become increasingly important in contemporary staging algorithms.

4. The role of systemic chemotherapy

4.1. Foundation of treatment

Systemic chemotherapy remains the cornerstone of LAPC management, serving dual purposes of controlling potential micrometastatic disease and facilitating tumor downstaging to enable surgical resection.⁵ The selection of first-line chemotherapy regimens depends critically on patient functional status and tolerance for treatment-related toxicity. For medically fit patients with excellent performance status (Eastern Cooperative Oncology Group [ECOG] score: 0–1), FOLFIRINOX represents the preferred regimen, combining fluorouracil, leucovorin, irinotecan, and oxaliplatin. The PRODIGE 4/ACCORD 11 trial definitively demonstrated FOLFIRINOX superiority over gemcitabine monotherapy in metastatic PDAC, achieving a median OS of 11.1 months versus 6.8 months.⁵ While this trial specifically evaluated metastatic disease, subsequent analyses have extrapolated similar benefits to the LAPC population, with additional advantages of potential tumor downstaging.

For less fit patients or those unable to tolerate intensive combination chemotherapy, the doublet regimen of gemcitabine combined with nab-paclitaxel represents an effective alternative. The landmark MPACT trial demonstrated a median OS of 8.5 months with this combination in metastatic disease.¹⁸ The addition of erlotinib to gemcitabine provides only modest survival benefits (OS 6.24 versus 5.91 months) and is rarely employed in contemporary practice due to limited efficacy and added toxicity.⁶

4.2. Treatment outcomes and response patterns

Clinical outcomes following systemic chemotherapy in LAPC demonstrate considerable heterogeneity, with approximately 15% of patients achieving meaningful tumor downstaging, 60% maintaining stable disease, and 25% experiencing disease progression despite treatment. Among patients demonstrating response or stable disease, median OS approximates 20 months.⁹ A comprehensive meta-analysis examining neoadjuvant FOLFIRINOX administration in borderline resectable and LAPC reported an R0 resection rate of 43% among patients ultimately taken to surgical exploration, underscoring the downstaging potential of intensive chemotherapy.⁹

However, FOLFIRINOX-related toxicity remains

substantial, with grade 3/4 adverse events including neutropenia (23% of patients), fatigue (14%), and diarrhea (13%), frequently necessitating dose modifications, growth factor support, and intensive supportive care measures.¹⁵ For patients experiencing disease progression or intolerable toxicity on first-line therapy, second-line treatment options include nanoliposomal irinotecan combined with 5-fluorouracil and leucovorin. The NAPOLI-1 trial demonstrated median OS extension to 6.1 months with this regimen in patients previously treated with gemcitabine-based therapy.¹⁹

4.3. Limitations and integration strategies

Despite substantial advances in systemic therapy, chemotherapy alone proves insufficient for achieving durable local disease control in LAPC, primarily due to the desmoplastic stromal barrier that significantly limits drug penetration into tumor tissue.¹¹ Consequently, integration with local ablative therapies or radiation therapy has become essential, with multiple studies demonstrating improved OS when multimodal approaches are employed compared to chemotherapy alone.^{7,8} Emerging biomarkers such as *SMAD4* gene status may provide predictive value for treatment response, with intact *SMAD4* expression associated with improved local disease control following multimodal therapy.²⁰ Ongoing prospective clinical trials, including PREOPANC-2, continue to evaluate optimal sequencing and combinations of neoadjuvant and adjuvant therapies in resectable and borderline resectable disease.²¹

5. Local ablative therapies

5.1. Rationale and selection principles

Local ablative techniques target the primary tumor mass directly, achieving tumor burden reduction, symptom palliation, and complementing systemic therapy effects.¹³ Ablative modalities are broadly categorized as thermal methods (including RFA and microwave ablation) that induce tumor cell death through heat-mediated coagulative necrosis, or non-thermal methods (primarily IRE) that utilize high-voltage electrical fields to disrupt cellular membranes. Stereotactic body radiotherapy represents an additional non-invasive option delivering highly conformal, ablative doses of radiation.⁷

The scientific rationale for incorporating local ablation in LAPC management extends beyond simple tumor cytoreduction. Ablative therapies may enhance chemotherapy efficacy through the induction of immunogenic cell death, releasing tumor-associated antigens and damage-associated molecular patterns that potentially stimulate anti-tumor immune responses. Additionally, non-thermal ablation techniques effectively

overcome the heat-sink effect posed by adjacent vascular structures, which significantly limits thermal ablation efficacy.¹⁴ Patient and tumor selection factors critical for ablation candidacy include tumor anatomical location, maximum tumor diameter, proximity to critical vascular structures, and overall disease burden.⁸

5.2. Irreversible electroporation

5.2.1. Technical principles and procedure

Irreversible electroporation represents an innovative non-thermal ablation technique that delivers precisely controlled high-voltage electrical pulses (typically 1,500–3,000 volts) through strategically positioned needle electrodes directly inserted into target tumor tissue. These electrical pulses create numerous nanoscale pores in cell membranes, disrupting cellular homeostasis and triggering programmed cell death pathways, including apoptosis and necrosis, without generating significant thermal energy.¹⁴ This non-thermal mechanism proves crucial, as it preserves the structural integrity of the extracellular matrix, blood vessels, and pancreatic duct architecture, making IRE particularly well-suited for treating tumors with extensive vascular encasement.²²

Irreversible electroporation procedures require general anesthesia with complete neuromuscular blockade to prevent muscle contractions and cardiac arrhythmias induced by electrical current delivery. Procedural approaches vary based on tumor characteristics and institutional expertise, including percutaneous image-guided placement, laparoscopic techniques, or open surgical exposure.⁸ Real-time imaging guidance, typically utilizing ultrasound or computed tomography, ensures precise electrode positioning to achieve complete tumor coverage while minimizing injury to adjacent structures.

5.2.2. Clinical outcomes and evidence

Accumulating clinical evidence highlights IRE's promising role in LAPC management, particularly for tumors involving critical vascular structures. The structure-sparing properties and potential immune-modulating effects distinguish IRE from thermal ablation techniques.²³ A representative single-center study evaluated 20 patients with stage III LAPC (11 tumors in the pancreatic head, 9 in the body), employing open surgical IRE. This series achieved 100% technical success, with grade II complications occurring in 45% of patients and notably no grade 3–5 adverse events. Tumor volume reduction was documented in 70% of patients at the six-month follow-up imaging, with median OS reaching 16.5 months from the time of IRE.⁴

Another institutional cohort of 14 carefully selected

LAPC patients reported an objective response rate of 100%, a median OS of 18.4 months calculated from IRE treatment, and 23.7 months from initial diagnosis.²³ The landmark PANFIRE-2 trial represents the largest prospective evaluation to date, treating 50 patients (40 with LAPC) with stage III pancreatic adenocarcinoma. This multicenter study reported excellent safety profiles, meaningful efficacy outcomes, and median OS improvement to 24.9 months when IRE was integrated with combination chemotherapy regimens.⁸

5.2.3. Safety profile and future directions

The complication profile of IRE includes acute pancreatitis (10–20% incidence), portal vein thrombosis (5–10%), and bleeding requiring intervention (<5%), which can be substantially mitigated through meticulous ultrasound-guided probe placement, maintenance of complete neuromuscular blockade, and judicious perioperative anticoagulation management.⁸ Currently, 13 clinical trials registered on ClinicalTrials.gov are actively exploring IRE in combination with immunotherapeutic agents, including programmed cell death protein 1 pathway inhibitors, based on the hypothesis that IRE-induced apoptotic debris may activate anti-tumor immune responses and enhance immunotherapy efficacy.²³ Future research directions include the development of personalized IRE protocols based on individual tumor genomic profiles and biomarker-driven patient selection.¹³

5.3 Radiofrequency ablation

5.3.1. Technical principles and application methods

Radiofrequency ablation employs alternating electrical current to generate intense focal heat (60–100 °C) within target tissue, inducing coagulative necrosis through protein denaturation and direct cellular destruction.⁷ However, RFA carries inherent risks of thermal injury to adjacent normal structures, including the duodenum, blood vessels, and bile ducts. Additionally, the heat-sink effect caused by blood flow through adjacent vessels can substantially reduce ablation efficacy by dissipating thermal energy away from the target zone.⁶

Radiofrequency ablation can be delivered through multiple technical approaches, each with distinct advantages and limitations. Intraoperative RFA during open surgery permits direct visualization and manual palpation, enabling precise probe placement and real-time assessment of adjacent structure safety. Percutaneous RFA under computed tomography or ultrasound guidance offers a minimally invasive alternative suitable for selected patients. Endoscopic ultrasound-guided RFA represents the most recent technical evolution, allowing transgastric

or transduodenal probe placement for tumors difficult to access through traditional approaches.⁷

5.3.2. Clinical evidence and outcomes

Yousaf and colleagues⁷ conducted a comprehensive review examining RFA's palliative role in unresectable PDAC, emphasizing tumor cytoreduction through multiple mechanisms, including direct thermal necrosis, protein denaturation, and potential activation of anti-tumor immune responses. They noted that in advanced disease stages, only 15–20% of patients present with technically resectable disease, making multimodal approaches incorporating neoadjuvant chemotherapy followed by ablation increasingly relevant for improving patient outcomes.⁷

The recent meta-analysis by Birrer *et al.*⁶ synthesized data from nine studies encompassing 265 patients (mean age 64.5 years, 42.5% female) with unresectable pancreatic adenocarcinoma treated with RFA. This analysis reported a 30-day mortality of 3.3%, with cumulative mortality rates of 20.9% at six months, 50.4% at 12 months, and 61.9% at 24 months. Pooled mean survival across all studies was 12.27 months, though substantial heterogeneity existed between studies ($I^2 = 95\%$). High heterogeneity ($I^2 = 95\%$) reflects differences in patient selection and combination strategies. Treatment-related complications affected 43.8% of patients, including abdominal pain (10.1%), acute pancreatitis (9.8%), and hepatobiliary complications (6.7%).⁶

Notably, when RFA was combined with palliative surgical procedures, median OS was 33 months compared to 13 months with RFA alone ($p = 0.0048$).²⁴ Stage III LAPC patients appeared to derive particular benefit from RFA, with documented reductions in tumor-associated pain and

measurable tumor burden.⁷

5.4. Comparative considerations: Radiofrequency ablation versus irreversible electroporation

The fundamental distinction between RFA and IRE (Table 1) lies in their tissue destruction mechanisms. RFA employs thermal energy and thus risks collateral damage to adjacent vessels and ducts, whereas IRE utilizes non-thermal electrical fields that selectively preserve connective tissue architecture, including blood vessels. Consequently, IRE is generally preferred for tumors immediately abutting critical vascular structures.^{4,12} RFA complications can be partially mitigated through technological advances, including internally cooled probes, controlled duodenal cooling techniques, strict temperature monitoring (maintaining $< 90^\circ\text{C}$), and hydrodissection methods to displace adjacent sensitive structures.⁷ The comparative features of RFA and IRE are summarized in Table 1.

6. Vascular involvement and reconstruction

6.1. The challenge of vascular invasion

Extensive vascular invasion fundamentally defines unresectability in LAPC, with tumor encasement exceeding 180° of vessel circumference traditionally precluding safe and complete surgical resection.³ However, following successful tumor downstaging achieved through neoadjuvant chemotherapy or ablative interventions, en bloc venous resection with reconstruction becomes technically feasible in carefully selected cases.¹⁶

6.2. Reconstruction techniques

Multiple surgical techniques exist for vascular reconstruction following tumor resection, selected based on the extent and location of vascular involvement. For

Table 1. A comparison of radiofrequency ablation and irreversible electroporation

Feature	Radiofrequency ablation	Irreversible electroporation
Mechanism	Thermal (Coagulative necrosis)	Non-thermal (Apoptosis)
Spares vessels	No (Heat-sink effect)	Yes
Adjacent tissue injury	Significant risk	Minimal risk
Evidence base	More established in the liver; emerging in the pancreas	Newer, promising specifically for locally advanced pancreatic cancer near vessels
Best application	Tumors away from critical structures	Tumors abutting vessels and ducts

short segmental defects, primary end-to-end anastomosis represents the most straightforward approach when tension-free approximation can be achieved. Patch venoplasty techniques are employed when partial vessel wall involvement necessitates tangential resection, utilizing either autologous tissue (typically saphenous vein or peritoneum) or prosthetic materials to reconstruct the vessel wall while maintaining luminal patency. For longer segmental resections exceeding approximately 5 cm, interposition grafting using reversed saphenous vein represents the gold standard approach.¹⁶

6.3. The peritoneal patch innovation

The peritoneal patch technique, classified as the International Study Group of Pancreatic Surgery type 2 reconstruction, offers distinct advantages, including remarkably low thrombosis rates (approximately 3%) and preservation of critical venous collateral pathways. Under appropriate anticoagulation protocols, graft patency rates exceed 95% in experienced hands.¹⁶ This hybrid reconstructive method enables radical oncological resection of tumors with extensive vascular infiltration that would otherwise be deemed unresectable. Importantly, perioperative morbidity rates remain comparable to standard pancreaticoduodenectomy (20–30%) when performed in high-volume centers by experienced surgical teams.¹⁶

Arterial reconstructions present substantially greater technical challenges and carry higher complication risks compared to venous procedures, including catastrophic bleeding and visceral ischemia. Consequently, arterial resection and reconstruction are reserved for highly selected cases where bypass options exist, and potential benefits clearly outweigh substantial procedural risks.³ The decision to pursue vascular reconstruction must be individualized based on tumor biology demonstrated by response to neoadjuvant therapy, patient performance status and physiological reserve, extent of vascular involvement, and institutional expertise and resources.

7. Multimodal treatment strategy

7.1. Sequential treatment algorithm

Contemporary multimodal treatment sequencing for LAPC begins with a comprehensive diagnostic evaluation, including tissue diagnosis via endoscopic ultrasound-guided fine-needle aspiration or biopsy, followed by 3–6 months of neoadjuvant combination chemotherapy, with FOLFIRINOX preferred for fit patients.¹⁵ This prolonged neoadjuvant period serves multiple critical purposes:

assessment of tumor biological behavior through response observation, achievement of tumor downstaging through systemic disease control, and identification of patients with occult metastatic disease manifesting as overt progression during therapy.^{12,23,24}

Following completion of neoadjuvant therapy, comprehensive restaging utilizing high-quality multiphasic computed tomography or magnetic resonance imaging and serial CA19-9 measurements evaluates treatment response and disease status. Patients demonstrating stable disease or objective response without progression should undergo multidisciplinary evaluation for potential surgical exploration.^{12,23,24} Intraoperatively, if tumors prove resectable with achievement of negative margins, surgeons should proceed with R0 resection, incorporating vascular reconstruction as technically required. Conversely, if tumors remain unresectable due to persistent vascular involvement, IRE should be applied for vessel-encased tumors, while RFA or stereotactic body radiotherapy represent alternative options for tumors not immediately abutting critical vessels.^{7,16}

7.2. Adjuvant therapy and long-term management

Following surgical resection or ablative intervention, adjuvant chemotherapy continuation for 2–4 months helps control micrometastatic disease and reduce recurrence risk. Chemotherapy regimen selection for adjuvant therapy may involve switching to alternative agents to improve tolerance and minimize cumulative toxicity, particularly in patients who experienced significant adverse effects during neoadjuvant treatment.¹⁸ This integrated multimodal approach has demonstrated potential to improve median OS by two- to threefold compared to historical chemotherapy-alone outcomes, in appropriately selected patients treated in high-volume centers, with 20–30% of such patients experiencing successful conversion from unresectable to resectable disease.⁴

7.3. Critical decision points

Challenges in implementing multimodal strategies include optimal timing of ablative interventions to maximize tumor downstaging benefits while minimizing progression risk during treatment intervals, balancing treatment intensity with toxicity and quality of life considerations, and accurate patient selection to identify those most likely to benefit from aggressive interventions.⁹ The development of institutional protocols and multidisciplinary pathways has proven essential for standardizing decision-making and optimizing outcomes while maintaining treatment individualization based on patient-specific factors.

8. Complications and mitigation strategies

8.1. Modality-specific complications

Treatment-related complications vary substantially based on the specific therapeutic modality employed, necessitating tailored prevention and management strategies. For IRE, common complications include acute pancreatitis, portal vein thrombosis, and procedure-related bleeding (Table 2). These risks can be significantly mitigated through precise ultrasound-guided probe placement, ensuring adequate tumor coverage while avoiding unnecessary trauma to surrounding tissues, maintenance of complete neuromuscular blockade throughout electrical pulse delivery to prevent muscle contractions and arrhythmias, and careful perioperative anticoagulation management balancing thrombosis prevention against bleeding risk.⁸

Radiofrequency ablation-associated complications include post-procedure pancreatitis, pancreatic fistula formation, and duodenal thermal injury due to heat propagation beyond intended target zones. Risk reduction strategies incorporate the use of internally cooled probe systems to concentrate thermal energy within target tissue, duodenal cooling techniques using chilled saline infusion, strict temperature monitoring and control, maintaining tissue temperatures below 90 °C, and hydrodissection techniques using fluid injection to create a protective space between the tumor and sensitive adjacent structures.⁷

Complications following vascular reconstruction procedures include venous or arterial thrombosis, potentially leading to catastrophic outcomes, anastomotic leak with severe bleeding, and procedure-related hemorrhage. Prevention strategies emphasize meticulous surgical technique with careful vessel handling, intraoperative Doppler ultrasound confirmation of adequate flow following anastomosis completion, and appropriate postoperative anticoagulation protocols to

maintain graft patency.¹⁶

8.2. The volume–outcome relationship

High-volume centers specializing in pancreatic disease management demonstrate complication rates approximately 50% lower than low-volume institutions, emphasizing the critical importance of multidisciplinary expertise encompassing experienced surgical, medical oncology, interventional radiology, and supportive care teams.⁶ The concentration of complex cases in specialized centers has emerged as a key quality metric, with multiple studies documenting improved outcomes, including reduced mortality, decreased morbidity, and enhanced long-term survival when care is centralized in high-volume, multidisciplinary programs.

9. Patient selection

9.1. Ideal candidate characteristics

Optimal patient selection represents a critical determinant of treatment success and acceptable risk-benefit profiles. Ideal candidates for aggressive multimodal therapy, including ablation and potential vascular reconstruction, demonstrate excellent or good performance status (ECOG 0–1), indicating preserved functional capacity and ability to tolerate intensive treatment. Biopsy-proven, non-metastatic LAPC without evidence of distant disease ensures that aggressive local therapy is appropriate. Demonstrated radiological or biochemical response to neoadjuvant chemotherapy suggests favorable tumor biology and increased likelihood of benefiting from additional interventions. Tumor anatomy allowing safe ablation or reconstruction without prohibitive technical risk, together with treatment delivery in high-volume centers with multidisciplinary expertise and comprehensive support services, completes the ideal candidate profile.^{3,4}

Table 2. Complications and mitigation strategies

Modality	Common complications	Mitigation strategies
Irreversible electroporation	Pancreatitis, portal vein thrombosis, bleeding	Precise probe placement, complete neuromuscular blockade, and anticoagulation management
Radiofrequency ablation	Pancreatitis, fistula, duodenal injury	Cooled probes, duodenal cooling, temperature control (<90 °C), hydrodissection techniques
Vascular reconstruction	Thrombosis, anastomotic leak, bleeding	Meticulous technique, intraoperative anticoagulation, tension-free anastomosis

9.2. Exclusion criteria

Patients with poor performance status (ECOG ≥ 2), limited functional reserve, documented metastatic disease at any site, significant medical comorbidities substantially increasing procedural risk, including severe cardiac, pulmonary, or hepatic dysfunction, or tumor progression during neoadjuvant chemotherapy, suggesting aggressive biology unlikely to benefit from local therapy, should generally be excluded from consideration for aggressive multimodal intervention.⁷ However, treatment decisions must be individualized, considering patient preferences, values, goals of care, and specific clinical circumstances that may justify exceptions to general guidelines.

9.3. Refined criteria integrating anatomical staging

Ideal candidates (ECOG 0–1) must exhibit LAPC-A/B anatomy responsive to neoadjuvant therapy (partial response, stable disease), confirmed by multidisciplinary restaging. Patients with LAPC-A should be prioritized for exploration (OS 20–27 months post-resection), while those with LAPC-B should be given IRE/RFA + vascular reconstruction if CA19-9 declines to less than 50%. Patients with ECOG ≥ 2 , progression, or metastases (positron emission tomography–computed tomography upstaging 20%) should be excluded.²⁵

10. Future directions

Looking toward the future, ongoing evolution in LAPC management will likely focus on further treatment personalization and seamless therapeutic integration. The exploration of rational combination strategies, particularly optimal sequencing of ablative techniques with emerging immunotherapeutic agents to modulate the suppressive tumor microenvironment, represents a promising investigational frontier. Early-phase studies combining IRE with checkpoint inhibitors have shown encouraging preliminary results, warranting larger-scale evaluation.

10.1. Clinical trial landscape and evolving treatment paradigms

Table 3 summarizes ongoing clinical trials that may influence LAPC management paradigms, such as conversion to resectability endpoints (20–30% rates in multimodal protocols). This overview provides a forward-looking perspective, complementing discussions on IRE (median OS 18–27 months) and RFA (pooled survival 12–33 months).^{25–38}

Additionally, the expanding role of artificial intelligence and machine learning in analyzing complex radiological, genomic, and clinical datasets to predict individual treatment response and optimize personalized therapeutic

Table 3. Key ongoing clinical trials for advanced pancreatic cancer (locally advanced pancreatic cancer and metastatic pancreatic ductal adenocarcinoma, as of October 2025)

NCT number	Phase	Intervention	Primary endpoint	Estimated completion
NCT06958328	III	Dose-escalated radiation therapy post-chemotherapy versus standard care	Local progression-free survival	December 2028
NCT06844422	Ib/II	Ivonescimab + SBRT (25–50 Gy/5 fx) + modified FOLFIRINOX	Maximum tolerated dose (Ib); median progression-free survival (II)	March 2027
NCT03257033	II	Intra-arterial gemcitabine versus intravenous gemcitabine/nab-paclitaxel post-SBRT	Progression-free survival	Ongoing (recruiting)
PANOVA-4 (EF-39, NCT06390059 inferred)	Pilot/II	Tumor treating fields + atezolizumab + gemcitabine + nab-paclitaxel	Safety and objective response rate	Enrollment completed 2025
NCT05191940	II	Radiotherapy regimens for locally advanced pancreatic cancer	Event-free survival	June 2026

Note: Ongoing clinical trial as of October 2025.
Abbreviation: SBRT: Stereotactic body radiation therapy.

sequencing holds tremendous promise for enhancing clinical decision-making. These computational approaches may enable the identification of patients most likely to benefit from specific interventions while sparing others unnecessary toxicity and treatment burden.

The selected trials (Table 3) emphasize multimodal approaches, including neoadjuvant chemotherapy (e.g., FOLFIRINOX or gemcitabine/nab-paclitaxel), novel locoregional therapies, such as IRE, RFA, and stereotactic body radiotherapy, and emerging combinations with immunotherapy or targeted agents. We prioritized phase II/III studies with primary endpoints focused on progression-free survival, overall survival (OS), or resection rates, reflecting an emphasis on clinically meaningful measures of downstaging and survival extension in LAPC. Representative examples include NCT06958328, a phase III trial evaluating dose-escalated radiation following chemotherapy (primary endpoint: local progression), and PANOVA-4 (NCT06390059), which investigates tumor-treating fields with chemotherapy.²⁶⁻³⁷

10.2. Current limitations

The evidence presented in this review derives predominantly from retrospective series, single- or multi-institutional cohorts, and heterogeneous meta-analyses rather than large randomized controlled trials. Patient numbers for ablative therapies (IRE and RFA) and complex vascular reconstruction remain relatively small. Moreover, statistical pooling was not performed, and high heterogeneity was frequently observed (e.g., $I^2 = 95\%$ in the most recent RFA meta-analysis). Direct head-to-head comparisons between IRE and RFA are lacking, and outcomes were heavily influenced by patient selection and center expertise. Finally, most significant improvements in conversion rates (20–30%) and survival were achievable only in appropriately selected patients managed in high-volume multidisciplinary centers. These limitations underscore the need for ongoing prospective randomized trials to establish the true magnitude of benefit and optimal treatment algorithms.

11. Conclusion

The contemporary management of LAPC represents a fundamental paradigm shift from therapeutic nihilism toward aggressive, proactive multimodal intervention with curative or long-term disease control intent. By strategically combining potent neoadjuvant chemotherapy regimens, sophisticated local ablative therapies, including both thermal and non-thermal techniques, and advanced vascular surgical reconstruction methods, this integrated approach has achieved substantial gains in appropriately selected patients treated in high-volume centers, increasing

median survival compared to historical standards and successfully converting 20–30% of previously deemed inoperable cases to resectable disease.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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