Chemotherapy Alone and Chemotherapy Plus Concurrent Chemoradiotherapy in Unresectable Locally Advanced Pancreatic Cancer

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Abstract

Background: Background: Locally advanced pancreatic cancer (LAPC) remains a formidable therapeutic challenge, with most patients presenting at an unresectable stage. The optimal management strategy for LAPC continues to be debated, particularly the role of chemoradiotherapy (CRT) following induction chemotherapy. While systemic chemotherapy remains the mainstay of initial treatment, the addition of concurrent chemoradiotherapy has been proposed to enhance local tumor control and potentially improve survival. However, the comparative benefits and risks of chemotherapy alone versus sequential chemoradiotherapy remain unclear. This review aims to compare outcomes between chemotherapy alone and chemotherapy followed by concurrent chemoradiotherapy in patients with unresectable LAPC, focusing on overall survival, progression-free survival, local control, toxicity, and quality of life. Multiple randomized controlled trials and retrospective studies have explored the role of consolidative CRT following chemotherapy. Some evidence, including the LAP07 trial, suggests no significant improvement in overall survival with the addition of CRT, although benefits in local control and disease stabilization were noted. In contrast, other studies have reported modest survival advantages in selected patient subgroups, particularly those with good performance status and disease control after initial chemotherapy. Concurrent CRT using modern radiation techniques (e.g., IMRT or SBRT) combined with radiosensitizing agents such as gemcitabine or fluoropyrimidines has shown acceptable toxicity profiles, with manageable gastrointestinal and hematologic adverse events. Nonetheless, patient selection and timing of CRT initiation remain crucial considerations.

Conclusion: While chemotherapy remains the cornerstone in managing unresectable LAPC, the incorporation of chemoradiotherapy following chemotherapy may offer additional local disease control and potential survival benefit in carefully selected patients. The heterogeneity of patient populations, treatment regimens, and study designs makes it challenging to draw definitive conclusions. Personalized approaches based on molecular profiling, response to initial therapy, and improved radiotherapy techniques are likely to refine treatment strategies. Further large-scale, prospective studies are needed to identify which patients derive the greatest benefit from this combined-modality approach.

Keywords: *Chemotherapy, Advanced Pancreatic Cancer, Chemoradiotherapy*

Introduction

Pancreatic cancer remains one of the most aggressive and lethal malignancies worldwide, primarily due to its late presentation and resistance to conventional therapies. It represents the seventh leading cause of cancer-related deaths globally, with a five-year survival rate lingering below 10% [1]. Despite comprising only 2–3% of all cancer diagnoses, pancreatic cancer accounts for a disproportionately high mortality burden, particularly in developed nations where aging populations contribute to rising incidence rates [2].

The pancreas plays essential exocrine and endocrine roles, and neoplasms can arise from both compartments. However, more than 90% of pancreatic malignancies are of ductal origin, with pancreatic ductal adenocarcinoma (PDAC) being the predominant histological subtype [3]. The disease's clinical presentation is typically nonspecific—often involving abdominal pain, weight loss, or jaundice—resulting in a significant proportion of patients being diagnosed at an advanced or metastatic stage [4].

Understanding the anatomical complexity of the pancreas, its lymphatic drainage, and its proximity to vital vascular structures is crucial for accurate staging and surgical planning. Imaging modalities such as CT, MRI, and endoscopic ultrasound (EUS) have enhanced diagnostic accuracy but still face limitations in detecting early-stage tumors [5]. Moreover, despite advancements in systemic chemotherapy and radiation therapy, surgical resection remains the only potentially curative treatment, though it is feasible in less than 20% of cases at diagnosis [6].

Ongoing research is now exploring biomarkers for early detection, molecular subtyping for individualized therapy, and novel therapeutic approaches including immunotherapy and targeted agents [7]. This review aims to comprehensively explore the anatomy, epidemiology, clinical and pathological features, diagnostic strategies, staging systems, and therapeutic options in pancreatic cancer, with a particular focus on locally advanced and unresectable cases.

The pancreas is a retroperitoneal organ extending obliquely across the posterior abdominal wall, spanning from the duodenum on the right to the splenic hilum on the left. Anatomically, it is divided into four parts: the head, neck, body, and tail. The pancreatic head lies nestled within the duodenal curve and is traversed posteriorly by the common bile duct, which joins the main pancreatic duct at the ampulla of Vater [8]. The neck lies anterior to the superior mesenteric vessels and connects the head with the body, which continues toward the tail—located in close proximity to the spleen and left kidney.

Vascular supply to the pancreas is rich and derived mainly from branches of the celiac trunk and superior mesenteric artery (SMA). The pancreatic head is primarily supplied by the superior and inferior pancreaticoduodenal arteries, whereas the body and tail receive blood from branches of the splenic artery [9]. Venous drainage follows a similar path, ultimately draining into the portal vein system. Importantly, the anatomic relationship between the pancreas and major vessels—including the SMA, celiac axis, portal vein, and superior mesenteric vein (SMV)—has critical implications for tumor staging and surgical resectability [10].

The lymphatic drainage of the pancreas is complex, contributing to early regional nodal involvement in malignancy. Lymphatic vessels follow the vascular structures and drain into peripancreatic, celiac, and superior mesenteric lymph nodes [11]. This widespread lymphatic network partially explains the aggressive nature and early dissemination of pancreatic cancers.

Functionally, the pancreas has both exocrine and endocrine components. The exocrine part, comprising acinar and ductal cells, produces digestive enzymes, whereas the endocrine component consists of islets of Langerhans that secrete hormones such as insulin and glucagon [12]. Most pancreatic cancers arise from the exocrine portion, particularly the ductal epithelium, which forms the basis of pancreatic ductal adenocarcinoma (PDAC), the most prevalent and deadly subtype.

Epidemiology of Pancreatic Cancer

Pancreatic cancer is one of the most lethal malignancies worldwide, with an overall 5-year survival rate of less than 10% despite advancements in diagnostic and therapeutic strategies [13]. Globally, it ranks as the seventh

leading cause of cancer-related mortality, accounting for over 466,000 deaths annually [14]. In high-income countries, it often ranks among the top five causes of cancer deaths, reflecting both its aggressive biology and late presentation.

The incidence of pancreatic cancer varies geographically, with the highest rates reported in North America, Western Europe, and Australia, and lower rates in Africa and South-Central Asia [15]. According to GLOBOCAN 2020 data, the global incidence was estimated at 495,773 new cases annually, with a slightly higher burden in men than in women [16]. The incidence rises significantly with age, peaking between the sixth and eighth decades of life, and is rare before the age of 40.

Several risk factors have been consistently associated with pancreatic cancer, including smoking, which is the most well-established modifiable risk factor and accounts for nearly 25% of cases [17]. Other major contributors include chronic pancreatitis, long-standing diabetes mellitus, obesity, physical inactivity, and diets high in red or processed meats [18]. A family history of pancreatic cancer and certain genetic syndromes such as Peutz-Jeghers syndrome, Lynch syndrome, and BRCA2 mutations also markedly increase risk [19].

Recent trends suggest a gradual increase in the incidence of pancreatic cancer globally, particularly in countries undergoing rapid urbanization and lifestyle changes. This rise may be attributed to aging populations, improved cancer registration systems, and the growing prevalence of risk factors like obesity and type 2 diabetes [20].

Given its increasing global burden and poor prognosis, early detection strategies, improved public awareness, and targeted prevention approaches are vital to altering the epidemiologic landscape of pancreatic cancer.

Clinical Presentation of Pancreatic Cancer

Pancreatic cancer is often referred to as a "silent killer" due to its insidious onset and vague symptoms, which frequently lead to delayed diagnosis. Most patients present with non-specific complaints that overlap with benign gastrointestinal conditions, contributing to the advanced stage at diagnosis in nearly 80% of cases [21].

The most common presenting symptom is **abdominal pain**, often described as a dull ache in the epigastric region that may radiate to the back and worsen with eating or lying supine. **Weight loss** and **anorexia** are also prevalent and may be profound, resulting from malabsorption, catabolic effects of the tumor, or early satiety due to duodenal compression [22]. **Jaundice**, particularly painless jaundice, is a hallmark of tumors located in the pancreatic head due to biliary obstruction. It is often accompanied by **dark urine**, **pruritus**, and **clay-colored stools** [23].

Less commonly, patients may present with **new-onset diabetes mellitus**, which can be both a risk factor and a paraneoplastic manifestation. In fact, new-onset diabetes in individuals over 50 years of age may be a red flag for underlying pancreatic malignancy [24]. Other symptoms include **nausea**, **vomiting**, and **steatorrhea**, particularly in cases involving exocrine insufficiency. A subset of patients may develop **depression**, which has been reported to precede the diagnosis of pancreatic cancer in some cases [25].

On physical examination, findings may include **hepatomegaly**, **palpable gallbladder** (Courvoisier's sign), or a **palpable abdominal mass**, although these are late manifestations. **Thrombophlebitis migrans** (Trousseau's syndrome), a hypercoagulable state associated with malignancy, may also be observed.

Because symptoms often appear late and are non-specific, heightened clinical suspicion and prompt investigation of atypical or persistent gastrointestinal symptoms are critical, especially in high-risk individuals.

Histopathology of Pancreatic Cancer

Pancreatic cancer encompasses a spectrum of histologic subtypes, with pancreatic ductal adenocarcinoma (PDAC) being the most common, accounting for over 90% of all cases. PDAC arises from the exocrine component of the pancreas and is characterized histologically by irregular glandular structures infiltrating a dense, desmoplastic stroma. Tumor glands are often angulated, haphazardly arranged, and exhibit cellular atypia, mitotic activity, and frequent perineural and lymphovascular invasion [26].

The tumor grade is based on the degree of gland formation, nuclear pleomorphism, and mitotic rate, and ranges from well-differentiated (G1) to poorly differentiated (G3). Well-differentiated tumors display relatively

uniform glandular structures, while poorly differentiated variants may lose glandular architecture altogether and exhibit marked cellular atypia [27].

Several histologic variants of PDAC exist, including mucinous (colloid) carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, and signet ring cell carcinoma. These variants differ in their biological behavior and prognosis. For example, adenosquamous carcinoma typically exhibits more aggressive behavior, while mucinous carcinoma may have a relatively better prognosis when resected early [28].

Immunohistochemistry aids in confirming pancreatic origin, particularly in small biopsies. PDAC typically expresses cytokeratin 7 (CK7) and cytokeratin 19 (CK19), and may show loss of DPC4/SMAD4 expression—a tumor suppressor gene inactivated in approximately 55% of PDACs [29,30]. Additional markers such as MUC1 and CA19-9 may support the diagnosis.

Diagnosis and Staging of Pancreatic Cancer

The diagnosis of pancreatic cancer relies on a combination of clinical evaluation, imaging modalities, and histopathological confirmation. Patients often present with non-specific symptoms such as abdominal pain, weight loss, jaundice, and new-onset diabetes, which usually indicate advanced disease [31].

Imaging plays a central role in both diagnosis and staging. Multidetector computed tomography (MDCT) with a pancreatic protocol is the first-line imaging modality for detecting pancreatic masses, assessing vascular invasion, and evaluating for distant metastasis [32]. Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP) provide complementary information, particularly in delineating the biliary tree and liver lesions [33].

Endoscopic ultrasound (EUS) offers high-resolution images and allows for fine-needle aspiration (FNA) of pancreatic lesions for cytological confirmation. EUS-guided FNA is considered the gold standard for obtaining tissue diagnosis in cases of suspected pancreatic neoplasms [34]. Positron emission tomography (PET) combined with CT (PET/CT) may aid in detecting occult metastases and evaluating treatment response but is not routinely used for initial diagnosis [35].

Staging is based on the TNM classification system by the American Joint Committee on Cancer (AJCC), which incorporates tumor size (T), lymph node involvement (N), and presence of metastasis (M). Accurate staging is essential for determining resectability, which is categorized as resectable, borderline resectable, locally advanced unresectable, or metastatic disease [36].

Treatment Modalities in Pancreatic Cancer

The management of pancreatic cancer is dictated by tumor stage at diagnosis. Surgical resection remains the only potentially curative treatment, but only 15–20% of patients present with resectable disease [37]. For these patients, pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy, or total pancreatectomy are standard surgical approaches depending on tumor location. Margin-negative (R0) resection is the goal, as positive margins (R1 or R2) are associated with significantly poorer outcomes [38].

Adjuvant chemotherapy is critical to improving survival after resection. The modified FOLFIRINOX regimen (leucovorin, fluorouracil, irinotecan, oxaliplatin) has become the preferred option for patients with good performance status due to its superior efficacy over gemcitabine monotherapy, as demonstrated in the PRODIGE 24 trial [39]. In patients with borderline resectable or locally advanced tumors, neoadjuvant therapy using FOLFIRINOX or gemcitabine-based regimens may increase resectability and downstage the disease [40].

For patients with unresectable or metastatic pancreatic cancer, systemic chemotherapy remains the mainstay of treatment. FOLFIRINOX or gemcitabine with nab-paclitaxel are first-line regimens, selected based on patient performance status and comorbidities [41]. Targeted therapies have shown limited success, although a small subset of patients with BRCA mutations may benefit from PARP inhibitors such as olaparib [42].

Radiotherapy may be used in select cases, especially for local control in unresectable disease or as part of chemoradiation in borderline resectable tumors. However, its impact on overall survival remains debated [43]. Palliative care, including biliary stenting, pain control, and nutritional support, plays a vital role in improving

quality of life in advanced stages [44-48].

Locally Advanced Pancreatic Cancer (LAPC): Multimodal Therapeutic Strategies

Locally advanced pancreatic cancer (LAPC) represents a challenging subgroup within pancreatic malignancies, defined by the National Comprehensive Cancer Network (NCCN) guidelines (version 3.2024) as tumors involving >180° of the celiac or superior mesenteric artery, unreconstructable portal or superior mesenteric vein involvement, or celiac artery invasion extending to the aorta, rendering surgical resection initially unfeasible [49-52].

Neoadjuvant Chemotherapy and Chemoradiation

Initial management often relies on systemic therapy, primarily with FOLFIRINOX or gemcitabine/nab-paclitaxel, depending on performance status. This induction phase typically lasts 2–4 months, after which restaging imaging is performed. Patients with stable or responsive tumors may then be candidates for chemoradiation with capecitabine or 5-fluorouracil as radiosensitizers, using total radiation doses of 50.4–54 Gy over several weeks [52,53]. Surgical re-evaluation follows for possible resection in selected cases [54].

Surgical Considerations and Techniques

Surgery in LAPC requires meticulous preoperative planning and multidisciplinary expertise. Pancreaticoduodenectomy (PD) or pylorus-preserving variants are performed depending on tumor location, with reconstruction through multiple anastomoses [55]. For tumors of the body or tail, distal pancreatectomy with splenectomy is standard [56]. However, preoperative biliary drainage has shown increased infectious risks postoperatively [57]. Standard lymphadenectomy targets specific nodal stations, though extended dissections are more common in Japanese centers [58].

Systemic Chemotherapy and Response Assessment

Preoperative multi-agent chemotherapy has become standard, allowing for systemic control and downstaging. Biological markers like CA19-9 are crucial in assessing treatment response, although conventional imaging remains insufficient for definitive evaluation [59–61]. The selection of regimens, including FOLFIRINOX and gemcitabine combinations, is detailed in NCCN-aligned algorithms for all stages of pancreatic cancer [52].

Targeted Therapy and Immunotherapy

Emerging targeted agents include KRASG12C inhibitors (e.g., sotorasib) and PARP inhibitors like olaparib for BRCA-mutated cases [62,63]. Immunotherapy holds promise for the rare subset of microsatellite instability-high (MSI-H) or mismatch repair-deficient tumors, with pembrolizumab approved for this indication [64,65]. T-cell therapies remain investigational in solid tumors [66].

Combination Therapies and Experimental Approaches

Innovative strategies combining chemotherapy, immunotherapy, and virotherapy (e.g., pelareorep with atezolizumab) have shown encouraging results in early-phase trials, achieving objective response rates over 50% and 6-month survival above 80% in advanced disease [67,68].

Concurrent Chemoradiotherapy (CRT)

CRT remains controversial but is considered in select patients without metastatic progression post-chemotherapy. Meta-analyses reveal no survival advantage over chemotherapy alone but suggest improved local control at the cost of increased toxicity [69–71]. Both fluoropyrimidine- and gemcitabine-based CRT regimens are used, each with specific toxicity profiles [72–74]. Platinum-based agents like cisplatin and carboplatin are also used with caution due to nephrotoxicity and myelosuppression [75].

Radiotherapy Techniques

Modern radiation techniques for LAPC include 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT), and hypofractionated ablative radiation therapy (HART). IMRT offers enhanced normal tissue sparing, while SBRT delivers high-dose, short-course treatment with promising local control rates [76–80]. HART further escalates the dose in a fractionated

scheme, improving outcomes without increasing toxicity [81,82].

Particle Therapy and Ablative Modalities

Proton and carbon ion therapy provide conformal dose delivery with minimal exit dose, reducing toxicity while maintaining efficacy. Clinical data remain limited but are expanding [83]. Other ablative approaches like cryoablation, high-intensity focused ultrasound (HIFU), and iodine-125 seed implantation show modest palliative benefit but are not standard of care [84–86].

Total Neoadjuvant Therapy (TNT) and Future Directions

TNT, involving both chemotherapy and (chemo)radiotherapy prior to resection, is gaining traction for LAPC. It may improve treatment adherence and downstaging, facilitating potentially curative surgery. ART in the neoadjuvant setting appears safe and effective but should be limited to specialized centers [87–90]. Intraoperative radiation therapy (IORT) and ongoing trials continue to refine TNT protocols [91,92].

Conclusion

Locally advanced pancreatic cancer (LAPC) remains a formidable clinical challenge due to its complex anatomical constraints, limited resectability, and propensity for early systemic dissemination. The treatment landscape has evolved significantly, shifting from isolated chemoradiotherapy to a multimodal strategy integrating systemic therapy, radiation, and—where feasible—surgical intervention. Contemporary guidelines, such as those by the NCCN, now favor neoadjuvant chemotherapy with regimens like FOLFIRINOX or gemcitabine/nab-paclitaxel, followed by restaging and consideration of chemoradiation and surgery in suitable candidates. The development of advanced radiotherapy techniques, including stereotactic body radiation therapy (SBRT), hypofractionated ablative radiation therapy (HART), and intensity-modulated radiation therapy (IMRT), offers the potential to escalate tumoricidal doses while minimizing toxicity to surrounding tissues.

Moreover, targeted therapies, such as KRAS and PARP inhibitors, and immune checkpoint inhibitors have opened new therapeutic avenues, particularly in biomarker-selected subgroups. Although still limited, these approaches underscore the growing importance of precision medicine in LAPC. Emerging concepts like total neoadjuvant therapy (TNT) and intraoperative radiation therapy (IORT) also reflect a trend toward intensified and personalized care strategies aimed at improving resectability and long-term outcomes.

Despite these advances, LAPC continues to carry a poor prognosis. Future research should focus on optimizing patient selection for surgery after neoadjuvant therapy, refining radiographic and serologic response assessments, and validating multimodal regimens through prospective trials. Collaborative, high-volume centers remain essential for the delivery of complex care, ensuring patients receive the most effective therapies based on evolving evidence.

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