ACR Appropriateness Criteria® Borderline and Unresectable Pancreas Cancer


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These guidelines review the use of radiation, chemotherapy, and surgery in borderline and unresectable pancreas cancer. Radiation technique, dose, and targets were evaluated, as was the recommended chemotherapy, administered either alone or concurrently with radiation. This report will aid clinicians in determining guidelines for the optimal treatment of borderline and unresectable pancreatic cancer.

Summary of Literature Review

Introduction/Background

Pancreatic cancer diagnosis and treatment remain among the most challenging areas of oncology. The American Cancer Society estimates that there will be approximately 49,000 cases of pancreatic cancer diagnosed in 2015, with an essentially equal distribution between men and women. This incidence will be associated with approximately 40,500 deaths, again about equal in men and women, and representing 3% of all cancers and 7% of cancer deaths.[1] Even for cases of early-stage disease, the 5-year survival rate between 1999 and 2006 was only 23%. Once the disease involves lymph node metastases, the 5-year survival rate drops to 9%; the 5-year survival rate among patients with metastatic disease is approximately 2%.[2] Given these results, and with no effective screening techniques yet identified, the challenge to develop effective therapy remains daunting.

Treatment recommendations are clearly defined for patients with resectable or distantly metastatic pancreatic cancer. Surgical resection of localized disease remains the only proven curative treatment, and even then, rates of 5-year survival are only 18% to 24%. Widely metastatic disease is treated with chemotherapy.[3] Questions remain regarding the optimal treatment for locally advanced and borderline resectable disease, and the purpose of these appropriateness criteria is to assess the merits of these options for different patient groups (see Variants 1–5).

Diagnosis and Definition of Locally Advanced and Borderline Pancreas Cancer

The clinical evaluation of the patient suspected of having pancreas cancer begins with appropriate imaging studies, ideally through a multidisciplinary clinic or tumor board.[4] Based on these results, surgery at a high-volume institution should be considered[5] in patients with a high likelihood of resection based on current guidelines,[6] with others being spared exploration as a means of defining the extent of their disease.

The most common choice of imaging for visualization of the pancreatic tumor is the multiphase or triphasic computed tomography (CT) scan. Triphasic CT imaging (rapid, small-increment arterial-phase, portal-venous-phase, and parenchymal contrast data sets) allows assessment of the pancreas and adjacent vasculature as compared to standard CT techniques. These images are best obtained prior to interventions such as biopsy or stent placement, as these can limit the accuracy of interpretation. Endoscopic ultrasound can provide information regarding the extent of disease and it can be used to obtain tissue for diagnosis with fine-needle aspiration.[7] Magnetic resonance imaging and magnetic resonance cholangiopancreatography can also be used and may provide more...
refined assessment of point of pancreatic duct obstruction, peritoneal carcinomatosis, vascular involvement, and small liver lesions.[8,9]

With these tools, the resectability of pancreatic cancer can be determined preoperatively in the great majority of cases. Per the guidelines of the National Comprehensive Cancer Network (NCCN), resectable tumors are those with no arterial tumor contact (ie, no contact with the celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]), no tumor contact with the superior mesenteric vein (SMV) or portal vein (PV), or ≤ 180° contact without vein contour irregularity.[10]

NCCN defines unresectable disease, in lesions of the pancreatic head/uncinate process, as including solid tumor contact with the SMA > 180°, solid tumor contact with the CA > 180°, solid tumor contact with the first jejunal SMA branch, an unreconstructible SMV/PV due to tumor involvement or occlusion, or contact with the most proximal draining jejunal branch into the SMV. In the body and tail of the pancreas, this includes solid tumor contact of > 180° with the SMA or CA, solid tumor contact with the CA and aortic involvement, or unreconstructible SMV/PV due to tumor involvement or occlusion.[10]

Borderline resectable tumors in the pancreatic head/uncinate process are classified as having solid tumor contact with the CHA without extension to the CA, hepatic artery bifurcation allowing for safe and complete resection and reconstruction, or solid tumor contact with the SMA of ≤ 180°. In the pancreatic body/tail, borderline resectable tumors include solid tumor contact with the CA of ≤ 180° and solid tumor contact with the CA of > 180° without involvement of the aorta and with an intact and uninvolved gastroduodenal artery. Borderline unresectable (venous) disease includes solid tumor contact with the SMV or PV of > 180°; contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with a suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction; or solid tumor contact with the inferior vena cava.[10]

The ideal definition of borderline resectable tumor should be free of subjective terminology, can be applied using routine axial pancreatic-protocol CT images, and should be reproducible. According to Katz et al,[6] borderline resectable pancreatic cancer is defined radiographically as localized tumors with 1 or more of the following: (1) interface between the primary tumor and SMV/PV measuring ≥ 180° of the circumference of the vein wall; (2) short-segment occlusion of the SMV/PV, with normal vein above and below the level of obstruction amenable to resection and venous reconstruction; (3) short-segment interface (of any degree) between tumor and hepatic artery, with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction; and/or (4) an interface between the tumor and SMA or celiac trunk measuring < 180° of the circumference of the artery wall.

**Treatment of Locally Advanced Disease**

Although it is understood that locally advanced, nonmetastatic pancreatic cancer (LAPC) carries a high rate of distant recurrence, a significant percentage of LAPC patients may succumb to their primary disease. In an autopsy study, approximately 30% of patients died of isolated failure, suggesting the importance of isolated local failure in patients with pancreas cancer.[11] Especially before the advent of more effective systemic therapy, treatment of locoregional disease has been shown to provide improved survival and palliative benefits.

Present treatment approaches incorporating local treatment (radiation therapy [RT]) trace their rationale to a study by Moertel et al for the Gastrointestinal Tumor Study Group (GITSG) that was first published over 30 years ago.[12] This randomized study sought to improve the prognosis of patients treated with RT alone—estimated to have median survival times of 5 to 7 months[12-14]—by adding concurrent 5-fluorouracil (5-FU) chemotherapy. Patients were randomized to RT alone to 60 Gy or two separate doses of either 40 Gy or 60 Gy with concurrent 5-FU (500 mg/m²/d by rapid intravenous injection). The techniques of both forms of treatment are antiquated by today's standards (eg, the RT was a split course with 2-week breaks after each 20-Gy increment and was given with supervoltage equipment). Also, because it was closed early, the RT-alone arm had fewer than one-third the number of patients as the RT-plus-chemotherapy arm. Nevertheless, the results remain historically important, since chemoradiation led to an improved median survival from just over 5 months in patients treated with chemotherapy alone to approximately 8 to 11 months in patients treated with chemoradiation. The 1- and 2-year survival rates both increased significantly (with the 1-year survival rate increasing from 11% to 36%-38% at RT doses of 40 Gy and 60 Gy, respectively). A follow-up GITSG trial[15] added weekly adriamycin to 40-Gy split-course
RT with maintenance doxorubicin and 5-FU and compared it to a 60-Gy RT arm with concurrent and maintenance 5-FU, similar to the previous study. However, this approach failed to yield further improvement. The median survival rate was approximately 8 months in both arms, and there was increased toxicity in patients who received concurrent doxorubicin. The Eastern Cooperative Oncology Group (ECOG) evaluated RT alone compared to chemoradiation and found no benefit to combined-modality treatment. For trial E8282,[13] a total of 114 patients received 59.4 Gy of external-beam radiation therapy (EBRT) with and without concurrent 5-FU and mitomycin-C delivered at two different time points. There was no advantage to the addition of chemotherapy to EBRT, and increased toxicity resulted.

The ECOG and GITSG groups again came to different conclusions in small randomized trials that compared chemotherapy alone to chemoradiation followed by maintenance chemotherapy. The GITSG[16] study compared patients with surgically confirmed unresectable, nonmetastatic adenocarcinoma of the pancreas who received either streptozocin, mitomycin-C, and 5-FU (n = 21) or RT at 54 Gy with concurrent-bolus 5-FU followed by maintenance treatment with streptozocin, mitomycin-C, and 5-FU (n = 22). The patients who received RT had an improved median survival time (9.7 vs 7.4 months) and a significantly better 1-year survival rate of 41% compared to 19% for patients treated with chemotherapy alone. The ECOG study[17] looked at both adenocarcinoma of the pancreas and stomach and compared 5-FU to 40 Gy of EBRT with concurrent-bolus 5-FU at the beginning of EBRT. Eligible patients included those with locally advanced disease as well as partially resected or locally recurrent disease. For the 91 patients with pancreatic cancer, there was no advantage to adding RT to chemotherapy; the median survival time was just over 8 months in either arm. However, given the potentially different prognoses represented by including patients with partially resected and recurrent disease, comparisons with this study are limited.

As mentioned, all of these trials are outdated by modern technology standards. Currently, the delivery of RT is dramatically more conformal and homogeneous, and concurrent 5-FU has been shown to be more effective and equally tolerated when administered with continuous-infusion 5-FU.[18,19] Due to improved imaging with thin-sliced pancreas-protocol CT imaging, surgical exploration is only offered to patients for whom a margin-negative resection (R0) is likely, or following preoperative therapy.

ECOG tried to acquire more contemporary treatment results with study E4201.[20] This phase III trial compared gemcitabine-based chemoradiation (RT to 54 Gy limited to involved fields, along with gemcitabine at 600 mg/m²/wk) to gemcitabine alone (at 1,000 mg/m²/wk for 6 weeks). Both groups were given consolidation gemcitabine. Unfortunately, accrual was poor and only 74 patients were entered. Median survival favored the combined-modality group (11.1 vs 9.2 months with gemcitabine alone; \( P = .044 \)), as did the 1-year survival rate (50% vs 32%, respectively). However, due to the limited number of patients, the confidence intervals overlapped. Additionally, the addition of RT to chemotherapy resulted in more severe toxicity than gemcitabine alone (grade 4 toxicities were 41% vs 6%).

In another attempt to compare gemcitabine with combined-modality treatment including up-to-date technology, the Fédération Francophone de Cancérologie Digestive and the Société Française de Radiothérapie Oncologique produced a phase III trial that accrued patients from 2000 to 2005.[21] A total of 119 patients were randomized to either single-agent gemcitabine (1,000 mg/m² weekly for 7 weeks) or 60-Gy (2 Gy/d) conformal RT directed to the primary and draining regional lymphatics, along with continuous-infusion 5-FU (300 mg/m²/d, days 1–5 and weekly) and cisplatin (20 mg/m²/d, days 1–5 and weeks 1 and 5). Patients in both arms received maintenance gemcitabine (1,000 mg/m² every 3 out of 4 weeks). In this trial, better results were seen with single-agent gemcitabine; median survival was 13 months compared to 8.3 months in the combined-modality arm \( ( P = .03) \), and the 1-year survival rate was 53% vs 32%. The toxicity profile also favored gemcitabine alone. However, reasonable criticism of the trial included the use of cisplatin in addition to 5-FU, which increased toxicity in the combined-modality arm. Also, there was a higher-than-standard dose of RT (60 Gy) and inclusion of uninvolved lymph nodes in the radiation-planning volume; both of these factors might have contributed to delays reported in administering chemotherapy (grade 3/4 toxicities were 22% vs 36% during induction and 18% vs 32% during maintenance).

In a systematic review of available studies, Sultana et al.[22] in 2007 searched the literature seeking support for a superior treatment approach in terms of survival outcomes for patients with LAPC treated with RT alone, chemoradiation with or without adjuvant chemotherapy, and chemotherapy alone. They looked at 11 trials with 794 patients, and concluded there was evidence that chemoradiation improved survival over RT alone, although chemotherapy following chemoradiation was not superior to chemotherapy alone. Importantly, the authors recognized the difficulties in
drawing conclusions based on wide confidence intervals. The LAP-07 trial is a recently reported multicenter randomized trial comparing chemoradiation to chemotherapy alone. The study compared gemcitabine alone to gemcitabine plus erlotinib, and after 4 months, to either chemoradiation (54 Gy with concurrent capecitabine at 1,600 mg/m²/d) or 2 more months of chemotherapy. A total of 269 patients were randomized between chemoradiation and chemotherapy (the second randomization). With a median follow-up of 36 months, there was no difference in overall survival (16.5 vs 15.3 months), and therefore, no survival benefit was shown for adding RT to gemcitabine-based chemotherapy for LAPC. However, in the chemoradiation therapy arm, patients had significantly less local tumor progression compared to the chemotherapy arm (34% vs 65%; \( P < .0001 \)) and median time without treatment (ie, reintroduction of chemotherapy) was longer in the chemoradiation therapy arm compared to the chemotherapy arm (159 vs 96 days, respectively; \( P = .05 \)). It is important to note that this has been reported in abstract form only and we are awaiting publication of the final article.[23,24]

Continued efforts to improve outcomes have included: (1) improving local control that remains suboptimal and (2) reducing systemic failure rates. Attempts to improve local control have included dose escalation and improving the delivery of RT in various ways. Intraoperative radiation therapy (IORT) offers the opportunity to add dose at the time of surgery without increasing normal tissue exposure. Multiple studies have shown IORT to be feasible with increased local control. However, few studies have demonstrated a clear survival benefit.[25,26]

The use of smaller radiation volumes can improve the therapeutic profile of radiation by simultaneously reducing the dose to adjacent critical organs while increasing the dose to the target volume (tumor). The combination of the two requires more limited treatment volumes (ie, a target of the gross disease without extension to adjacent areas [nodes] at risk for harboring subclinical metastases). With this approach, it has been shown that both hypofractionated RT[27-29] and standard fractionation RT[30] can result in survival outcomes comparable to, if not slightly better than, other regimens. Continued attempts to increase the therapeutic ratio (ie, maximize dose while minimizing normal tissue exposure/risk) have included particle-beam therapy such as protons. There is early evidence that this type of treatment is feasible; however, the data are limited in number and maturity.[31-33]

Another form of RT used to increase the biologically effective dose is stereotactic body radiation therapy (SBRT). SBRT incorporates real-time image guidance to deliver high doses of radiation per fraction (5-25 Gy) delivered over 1–5 days. It is hypothesized that SBRT results in improved biological effectiveness, leading to improved local tumor control and/or response. As reported by Schellenberg et al,[34] investigators at Stanford University initially used SBRT (25 Gy × 1 fraction) in a phase II trial to treat patients with LAPC as well as those with various stages of pancreas cancer. The authors reported an excellent 1-year local control rate of 94%. The median overall survival time was 11.8 months, but the incidence of late grade 2 or higher toxicity was 20% in this single-institution study. In an attempt to decrease late toxicity associated with SBRT, Herman et al[35] conducted a multi-institutional study that incorporated fractionated SBRT (6.6 Gy × 5 fractions) with gemcitabine (before and after SBRT). They reported minimal acute and late gastrointestinal toxicity, with a median overall survival of 13.9 months (95% CI, 10.2–16.7 months) and a freedom from local disease progression at 1 year of 78%. Single-institution studies by Mellon et al[36] and Moningi et al[37] support surgery after chemotherapy and SBRT, although data are preliminary (see Variant 1, Variant 2, and Variant 4).

**Treatment of Borderline Resectable Disease**

It is recognized that the resectability of pancreatic cancer varies with the skill, experience, and attitude of different surgeons and that surgical decision making likewise depends on the skill and expertise of diagnosticians in radiology and gastroenterology. Although LAPC has been estimated to include 30% to 40% of newly diagnosed cases, it remains difficult to determine what percentage of these are borderline resectable, owing to differences in the definition of borderline resectable pancreatic cancer, in clinical acumen, and in policies of various institutions.[38]

In an attempt to evaluate the benefits of preoperative therapy for pancreas cancer patients, Ishikawa et al[39] reported a retrospective evaluation of preoperative radiation (50 Gy) compared to immediate surgery in patients who were all deemed operable. Twenty-three patients who received radiation before resection were compared to 31 patients who had upfront surgery. The resection rates were similar (74% vs 61%); however, the patients given preoperative RT had a better 1-year survival rate (75% vs 61%), and 3- and 5-year survival rates were not improved. The authors
attributed the improvement in the first year to better locoregional control.

Summary of Recommendations

- In good-performance-status LAPC, the use of initial chemotherapy, followed by chemoradiation in patients with response or stable disease, is a preferred treatment.
- In poor-performance-status LAPC, aggressive therapy may not be warranted and palliative therapy is prioritized.
- In good-performance-status borderline resectable patients, neoadjuvant chemotherapy followed by chemoradiation in patients with response or stable disease is a preferred treatment. The goal is then to perform a margin-negative resection.
- The target for radiation is the GTV ± immediately adjacent lymph node regions.
- Radiation techniques should include motion management.
- The use of SBRT is an emerging form of therapy.
- Chemotherapy-alone regimens include FOLFIRINOX, gemcitabine, and gemcitabine + nab-paclitaxel. The use of FOLFIRINOX is limited to good-performance-status patients.
- Concurrent chemotherapy regimens include infusional 5-fluorouracil, capecitabine, and gemcitabine.

This study illustrated the feasibility of preoperative treatment and the difficulty obtaining long-term control even with better locoregional control, due to the high rates of distant metastases. In a series of phase II studies from the University of Texas MD Anderson Cancer Center, preoperative chemoradiation was explored in a total of 276 patients. RT included EBRT treatments with and without IORT. The studies included (1) a regimen of 5-FU, paclitaxel, and gemcitabine with irradiation, along with adjuvant gemcitabine; and (2) induction cisplatin and gemcitabine with combined-modality treatment with gemcitabine.[40-43] The resection rate ranged from 35%[40] to 74%,[41] with vascular resection/reconstructions performed in 20% to 50% of the cases and R0 resections in 68% to 96%. Local recurrence after resection was reported to be between 5% and 25%. Distant metastases occurred in 59% to 84% of cases. Median survival among resected patients ranged from 29 to 34 months, and unresected cases survived a median of 7 to 10.5 months.

Numerous other smaller neoadjuvant trials have been performed, with similar results reported.[44-46] Gillen et al.[47] conducted a systematic review of the literature and meta-analysis of response and resection percentages of reported trials of preoperative therapy for pancreas cancer, reviewing studies from 1966 to 2009. Their analysis looked at patients with initially resectable tumors separately from those with initially unresectable disease. The authors found no advantage to neoadjuvant therapy for initially resectable disease. About one-third of initially unresectable tumors were converted to resectable, and in this group, survival outcomes were thought to be equivalent to those of patients with initially resectable tumors. As in unresectable disease, early data are beginning to accumulate regarding proton-beam therapy as part of a neoadjuvant approach. As with primary treatment, the literature is limited, but a regimen of neoadjuvant 5 Gy × 5 fractions with concurrent capcitabine followed by surgery appears to be safe[48] (see Variant 3).

Neoadjuvant Systemic Therapy Followed by Local Treatment

Because of the high rates of distant metastases in LAPC, the Groupe Coopérateur Multidisciplinaire en Oncologie has published data on initial treatment with systemic therapy followed by re-evaluation, to select patients for local treatment with chemoradiation. Local treatment was not mandated; if patients did not show evidence of systemic failure, they could continue to receive systemic treatment alone or be directed to chemoradiation. This retrospective analysis of 181 patients with LAPC showed a distant failure rate of 29% after 3 months of chemotherapy. The remaining patients were deemed to be comparable groups who received either chemoradiation or chemotherapy alone. The progression-free survival rate was increased by approximately 3 months with the addition of RT (10.8 vs 7.4 months; \( P = .005 \)), and the median overall survival rate increased from 11.7 to 15.0 months (\( P = .009 \)) with the addition of RT.[49] Krishnan et al.[50] from MD Anderson reviewed 323 patients treated with chemoradiation vs induction chemotherapy followed by chemoradiation. The patients who received neoadjuvant induction chemotherapy had improved overall survival (11.9 vs 8.5 months) and progression-free survival (6.4 vs 4.2 months). The authors suggest that neoadjuvant chemotherapy can exclude patients with rapid distant progression and enrich the population of patients receiving locoregional treatment. As noted
previously, the LAP-07 trial did report improvements in local control and time-without-treatment outcomes in patients who were randomized to chemoradiation therapy after 4 months of chemotherapy and stable disease.[25,26]

**Chemotherapy**

The choice of systemic therapy in LAPC and patients with borderline resectable pancreatic cancer is often extrapolated from the metastatic setting. As noted above, gemcitabine has been the agent most frequently utilized. Multiple attempts at combination therapy with or without gemcitabine have been attempted, most commonly in the metastatic setting. Louvet et al[51] randomized 313 patients with metastatic or locally advanced pancreatic cancer to gemcitabine alone or gemcitabine and oxaliplatin. The combination therapy improved clinical benefit but failed to demonstrate a statistical benefit in terms of survival. FOLFIRINOX (5-FU, oxaliplatin, leucovorin, and irinotecan) was compared to gemcitabine in the metastatic setting. FOLFIRINOX was noted to improve median overall survival as compared to gemcitabine alone (11.1 months vs 6.8 months, respectively). However, this improved survival was associated with increased toxicity.[3] Von Hoff et al[52] showed that the addition of nab-paclitaxel to gemcitabine monotherapy provided a survival benefit in patients with metastatic pancreatic cancer. Therefore, in good-performance-status patients with LAPC or borderline resectable pancreatic cancer when initial systemic therapy is planned, the use of FOLFIRINOX or gemcitabine/nab-paclitaxel is a reasonable option, given the favorable results reported in the metastatic setting. A recent study by Ferrone et al[53] concluded that after neoadjuvant FOLFIRINOX and RT (in most patients), imaging no longer accurately predicted for resectability. Among 40 patients undergoing resection, 19 were deemed radiographically unresectable, and yet there was a 92% R0 resection rate. These data are intriguing and will need further validation (see Variant 5).

*The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria® through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.*

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Variant 1. 65-year-old woman with no comorbidities presents with jaundice...
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