American College of Radiology
ACR Appropriateness Criteria®

BORDERLINE AND UNRESECTABLE PANCREAS CANCER

Expert Panel on Radiation Oncology–Gastrointestinal: William Small Jr, MD[1]; John P. Hayes, MD[2]; W. Warren Suh, MD, MPH[3]; May Abdel-Wahab, MD, PhD[4]; Ross A. Abrams, MD[5]; Nilofer Azad, MD[6]; Prajnan Das, MD[7]; Jadranka Dragovic, MD[8]; Karyn A. Goodman, MD[9]; Salma K. Jabbour, MD[10]; William E. Jones III, MD[11]; Andre A. Konski, MD, MBA, MA[12]; Albert C. Koong, MD, PhD[13]; Rachit Kumar, MD[14]; Percy Lee, MD[15]; Timothy M. Pawlik, MD[16]; Joseph M. Herman, MD, MSc.[17]

Summary of Literature Review

Introduction/Background

Pancreatic cancer diagnosis and treatment remains one of the most challenging areas of oncology. The American Cancer Society estimates that there will be approximately 49,000 cases 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. These numbers amount to 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 in metastatic disease is approximately 2% [2]. Given these results, with no effective screening techniques having been 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%–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.

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, resectable tumors are those with no

[1]Principal Author, Stritch School of Medicine Loyola University Chicago, Maywood, Illinois. [2]Research Author, Stritch School of Medicine Loyola University Chicago, Maywood, Illinois. [3]Panel Vice-chair, Cancer Center of Santa Barbara, Santa Barbara, California. [4]Cleveland Clinic, Cleveland, Ohio. [5]Rush University Medical Center, Chicago, Illinois. [6]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland, American Society of Clinical Oncology. [7]University of Texas MD Anderson Cancer Center, Houston, Texas. [8]Henry Ford Hospital, Detroit, Michigan. [9]University of Colorado School of Medicine Anschutz Medical Campus, Aurora, Colorado. [10]Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey. [11]University of Texas Health Science Center at San Antonio, San Antonio, Texas. [12]University of Pennsylvania, The Chester County Hospital, West Chester, Pennsylvania. [13]Stanford Cancer Institute, Stanford, California. [14]Banner MD Anderson Cancer Center, Gilbert, Arizona. [15]University of California Los Angeles, Los Angeles, California. [16]Johns Hopkins University, Baltimore, Maryland, American College of Surgeons. [17]Panel Chair, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland.

Reprint requests to: publications@acr.org

arterial tumor contact (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].

For unresectable disease, in lesions of the head/uncinate process, this includes solid tumor contact with the SMA >180°, solid tumor contact with the CA >180°, solid tumor contact with the first jejunal SMA branch, 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, 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) 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 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 for borderline resectable 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 cancers 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 pancreas 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) 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 radiation therapy (RT) alone—estimated to have median survival rates 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 2 separate doses of either 40 Gy or 60 Gy with concurrent 5-FU (500 mg/m^2/day 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), and the RT-alone arm had less than one-third as many patients because it was closed early. Yet the results remain historically important as chemoradiation led to an improved median survival from just over 5 months in chemotherapy alone to approximately 8 to 11 months in patients receiving chemoradiation. One- and 2-year survival rates both increased significantly (1-year survival rate increased from 11% to 36%–38% with doses of 40 Gy and 60 Gy RT, 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 failed to show 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], 114 patients received 59.4 Gy of external-beam

radiation therapy (EBRT) with and without concurrent 5-FU and mitomycin-C delivered at 2 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 streptozosin, mitomycin-C, and 5-FU (n=21) or 54-Gy RT with concurrent-bolus 5-FU with maintenance treatment with streptozosin, mitomycin-C, and 5-FU (n=22). The patients who received RT had an improved median survival (9.7 versus 7.4 months) and a significantly better 1-year survival rate of 41% compared to 19%. 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 pancreatic cancer patients, there was no advantage to adding RT to chemotherapy as the median survival was just over 8 months in either arm. However, given the potentially different prognosis 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 in patients where 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 600 mg/m^2/wk gemcitabine) to gemcitabine alone (1000 mg/m^2/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 versus 9.2 months, P=0.044), as did the 1-year survival rate (50% versus 32%). 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% versus 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 (1000 mg/m^2 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/m^2/d, days 1–5 and weekly) and cisplatin (20 mg/m^2/d, days 1–5 and weeks 1 and 5). Patients in both arms received maintenance gemcitabine (1000 mg/m^2 every 3 out of 4 weeks). In this trial, better results were seen with single-agent gemcitabine as median survival was 13 months compared to 8.3 months in the combined-modality arm (P=0.03), and the 1-year survival rate was 53% versus 32%. The toxicity profile also favored gemcitabine alone. However, reasonable criticism of the trial included the use of cisplatin in addition to 5-FU, increasing 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 which might have contributed to delays reported in administering chemotherapy (grade 3-4 toxicities were 22% versus 36% during induction and 18% versus 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 regarding survival for LAPC patients 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 1600 mg/m^2/d) or 2 more months of chemotherapy. Two hundred sixty-nine 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 versus

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% versus 65%, $P<0.0001$) and median time without treatment (ie, reintroduction of chemotherapy) was longer in the chemoradiation therapy arm compared to the chemotherapy arm (159 versus 96 days, respectively, $P=0.05$). It is important to note that this has been reported in abstract form only and we are awaiting the final manuscript [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 2 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 survivals 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. Investigators at Stanford University [34] initially used SBRT (25 Gy × 1) to treat patients as well as those with various stages of pancreas cancer. In a phase II single-institution study of SBRT in patients with LAPC, Schellenberg et al [34] reported an excellent 1-year local control rate of 94%. The median overall survival was 11.8 months, but the incidence of late G2 or higher toxicity was 20%. In an attempt to decrease late toxicity associated with SBRT, Herman et al conducted a multi-institutional study [35] that incorporated fractionated SBRT (6.6 Gy × 5) with gemcitabine (before and after SBRT). The study reported minimal acute and late gastrointestinal toxicity, with a median overall survival of 13.9 months (95% confidence interval, 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%–40% of newly diagnosed cases, it remains difficult to define the percentage of these that are borderline resectable because of differences in the definition of borderline resectable pancreatic cancer, in clinical acumen, and in policy 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% versus 61%); however, the patients given preoperative RT had a better 1-year survival rate (75% versus 61%), and 3- and 5-year survival rates were not improved. The authors attributed the improvement in the first year to better locoregional control.

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 MD Anderson Cancer Center, preoperative chemoradiation was explored in 276 total patients. RT included EBRT treatments with and without IORT. The studies included 1) 5-FU, paclitaxel, 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% [40-43]. Local

recurrence after resection was reported to be between 5% and 25% [40-43]. Distant metastases occurred in 59% to 84%. 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] performed 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 initially unresectable disease. In summary, they found no advantage to neoadjuvant therapy for initially resectable disease. About a third of initially unresectable tumors were converted to resectable, and in this group, survival was thought to be equivalent to 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 with concurrent capecitabine 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, 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. Progression-free survival rate was increased by approximately 3 months with the addition of RT (10.8 versus 7.4 months; P=0.005), and median overall survival rate went from 11.7 to 15.0 months (P=0.009) with the addition of RT [49]. Krishnan et al [50] from MD Anderson reviewed 323 patients treated with chemoradiation versus induction chemotherapy followed by chemoradiation. The patients that received neoadjuvant chemotherapy had improved overall survival (11.9 versus 8.5 months) and progression-free survival (6.4 versus 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 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 borderline resectable pancreatic patients 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 metastatic or locally advanced pancreatic cancer patients 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, irinotecan) was compared to gemcitabine in the metastatic setting. FOLFIRINOX was noted to have improved median overall survival as compared to gemcitabine alone (11.1 months versus 6.8 months). This improved survival was, however, 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 metastatic pancreatic cancer patients. 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 these favorable results 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. Of 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).

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 gross tumor volume +/- 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-florouracil, capecitabine, and gemcitabine.

Summary of Evidence

Of the 53 references cited in the *ACR Appropriateness Criteria® Borderline and Unresectable Pancreas Cancer* document, 48 are categorized as therapeutic references including 19 well designed studies and 23 good quality study/studies. There are 9 references that may not be useful as primary evidence. There are 2 references that are meta-analysis studies.

The 53 references cited in the *ACR Appropriateness Criteria® Borderline and Unresectable Pancreas Cancer* document were published from 1969-2015.

Most of the references are well designed or good quality studies and provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.
2. Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. *CA Cancer J Clin.* 2013;63(5):318-348.
3. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817-1825.
4. Pawlik TM, Laheru D, Hruban RH, et al. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. *Ann Surg Oncol.* 2008;15(8):2081-2088.
5. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. *Ann Surg.* 2005;242(4):540-544; discussion 544-547.
6. Katz MH, Marsh R, Herman JM, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol.* 2013;20(8):2787-2795.
7. Tummala P, Junaidi O, Agarwal B. Imaging of pancreatic cancer: An overview. *J Gastrointest Oncol.* 2011;2(3):168-174.
8. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging.* 2007;18(6):421-429.
9. Vachiranubhap B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging.* 2009;20(1):3-9.
10. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 2.2015. 2015; Available at: http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf.
11. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol.* 2009;27(11):1806-1813.
12. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer.* 1981;48(8):1705-1710.
13. Cohen SJ, Dobelbower R, Jr., Lipsitz S, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1345-1350.

14. Moertel CG, Childs DS, Jr., Reitemeier RJ, Colby MY, Jr., Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet.* 1969;2(7626):865-867.
15. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. *Cancer.* 1985;56(11):2563-2568.
16. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst.* 1988;80(10):751-755.
17. Klaassen DJ, MacIntyre JM, Catton GE, Engstrom PF, Moertel CG. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 1985;3(3):373-378.
18. Boz G, De Paoli A, Innocente R, et al. Radiotherapy and continuous infusion 5-fluorouracil in patients with nonresectable pancreatic carcinoma. *Int J Radiat Oncol Biol Phys.* 2001;51(3):736-740.
19. Whittington R, Neuberg D, Tester WJ, Benson AB, 3rd, Haller DG. Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a phase I Eastern Cooperative Oncology Group Trial. *J Clin Oncol.* 1995;13(1):227-232.
20. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol.* 2011;29(31):4105-4112.
21. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol.* 2008;19(9):1592-1599.
22. Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer.* 2007;96(8):1183-1190.
23. Hammel P, Huguet F, Van Laethem J-L, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *ASCO Meeting Abstracts.* 2013;31(15_suppl):LBA4003.
24. Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study. *J Clin Oncol.* 2014;32(5s):(suppl; abstr 4001^).
25. Mohiuddin M, Regine WF, Stevens J, et al. Combined intraoperative radiation and perioperative chemotherapy for unresectable cancers of the pancreas. *J Clin Oncol.* 1995;13(11):2764-2768.
26. Willett CG, Del Castillo CF, Shih HA, et al. Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg.* 2005;241(2):295-299.
27. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer.* 2013;119(15):2692-2700.
28. Small W, Jr., Berlin J, Freedman GM, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. *J Clin Oncol.* 2008;26(6):942-947.
29. Small W, Jr., Mulcahy MF, Rademaker A, et al. Phase II trial of full-dose gemcitabine and bevacizumab in combination with attenuated three-dimensional conformal radiotherapy in patients with localized pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2011;80(2):476-482.
30. Ben-Josef E, Schipper M, Francis IR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1166-1171.
31. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I/II study of Proton-based Short Course Chemoradiation and Early Surgery for Adenocarcinoma of the Pancreas. *International Journal of Radiation Oncology*Biology*Physics.* 2010;78(3, Supplement):S99-S100.
32. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2014;89(4):830-838.
33. Kozak KR, Kachnic LA, Adams J, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. *Int J Radiat Oncol Biol Phys.* 2007;68(5):1557-1566.

34. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2011;81(1):181-188.
35. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer.* 2015;121(7):1128-1137.
36. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol.* 2015;54(7):979-985.
37. Moningi S, Dholakia AS, Raman SP, et al. The Role of Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Single-Institution Experience. *Ann Surg Oncol.* 2015;22(7):2352-2358.
38. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. *Ann Surg.* 2007;246(2):173-180.
39. Ishikawa O, Ohigashi H, Imaoka S, et al. Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? *Arch Surg.* 1994;129(10):1075-1080.
40. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg.* 1992;127(11):1335-1339.
41. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3496-3502.
42. Pisters PW, Abbruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol.* 1998;16(12):3843-3850.
43. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol.* 2002;20(10):2537-2544.
44. Talamonti MS, Small W, Jr., Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol.* 2006;13(2):150-158.
45. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3487-3495.
46. White RR, Tyler DS. Neoadjuvant therapy for pancreatic cancer: the Duke experience. *Surg Oncol Clin N Am.* 2004;13(4):675-684, ix-x.
47. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med.* 2010;7(4):e1000267.
48. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. *Int J Radiat Oncol Biol Phys.* 2011;79(1):151-157.
49. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol.* 2007;25(3):326-331.
50. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer.* 2007;110(1):47-55.
51. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005;23(15):3509-3516.
52. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.
53. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg.* 2015;261(1):12-17.

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition: **Borderline and Unresectable Pancreas Cancer**

Variant 1: **65-year-old woman with no comorbidities presents with jaundice and an ECOG performance status of 1. Pancreas-protocol CT scan reveals a 2.5-cm mass in the pancreatic head with encasement of the celiac artery without evidence for nodal or distant metastasis. Biopsy at the time of metal stent placement revealed adenocarcinoma. Stent normalized the bilirubin and the CA 19-9 was 150. She has no pain.**

Treatment	Rating	Comments
Supportive care only	2	
Upfront surgery	1	
Systemic chemotherapy only	6	
Systemic therapy and if response or stable disease consider standard RT with concurrent chemotherapy	8	
Upfront RT with concurrent chemotherapy	5	Consider this option if pain is refractory to pain block or opioids.
Systemic therapy and if response or stable disease consider standard RT with concurrent chemotherapy +/- surgery if technically resectable	6	
Systemic chemotherapy and if response or stable disease consider SBRT +/- surgery if technically resectable	6	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **80-year-old man presents with severe abdominal pain and an ECOG performance status of 2. CT scan reveals a mass in the body of the pancreas with 360° encasement of the celiac axis and SMA, with evidence of regional lymph node metastasis without other distant metastasis; CA 19-9 is 1000.**

Treatment	Rating	Comments
Supportive care only	5	
Upfront surgery	1	
Systemic chemotherapy only	7	
Palliative RT alone	6	Consider using a short course (10–15 fractions).
Systemic therapy and if response or stable disease consider standard course RT with concurrent chemotherapy	6	
Upfront palliative RT with concurrent chemotherapy	5	Consider using a short course (10–15 fractions).
Systemic therapy and if response or stable disease consider standard RT with concurrent chemotherapy +/- surgery if technically resectable	2	
Systemic chemotherapy and if response or stable disease consider SBRT +/- surgery if technically resectable	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Borderline and Unresectable Pancreas Cancer**

Variant 3: **54-year-old healthy woman with an ECOG performance status of 0 presents with vague abdominal pain. CT scan notes a pancreatic head mass with no evidence for metastasis. The tumor abuts the celiac axis, although <180°.**

Treatment	Rating	Comments
Immediate surgery +/- adjuvant therapy	3	
Supportive care only	1	
Systemic therapy only with gemcitabine then consideration for surgery	4	
Systemic therapy only with FOLFIRINOX then consideration for surgery	6	
Planned combined 5-FU and standard fractionation RT to 45–50.4 Gy to gross tumor volume and regional nodes followed by surgery	5	
Planned combined full dose gemcitabine and hypofractionated RT to 30–40 Gy to gross tumor volume then consideration for surgery	6	
FOLFIRINOX chemotherapy and if there is a response or stable disease RT + chemotherapy followed by surgery	7	
Gemcitabine chemotherapy and if there is a response or stable disease, RT + chemotherapy followed by surgery	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Chemotherapy and if response or stable disease consider SBRT with consideration for surgery	5	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Variant 4: **Standard RT details in treating a locally advanced pancreatic cancer.**

Treatment	Rating	Comments
Tumor Volume		
Treat the gross tumor volume only plus small margins (no expansion for prophylactic lymph nodes)	7	
Treat the gross tumor volume and limited prophylactic lymph nodes (ie, only immediately adjacent nodal regions to the GTV)	8	
Treat the gross tumor volume and full prophylactic lymph node coverage	5	
Technique		
3-D technique	7	
IMRT	7	
IMRT only if needed for normal tissue constraints	8	
Respiratory gating	6	
4-D CT with the utilization of a MIP	8	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Borderline and Unresectable Pancreas Cancer**

Variant 5: **Chemotherapy details in treating a locally advanced pancreatic cancer.**

Treatment	Rating	Comments
FOLFIRINOX	7	
Gemcitabine	8	
Gemcitabine and Nab-paclitaxel	7	
Concurrent with RT		
Infusional 5-FU	8	
Capecitabine	8	
FOLFIRINOX	3	
Gemcitabine	7	
Gemcitabine and Nab-paclitaxel	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		