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RESECTABLE PANCREATIC CANCER

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

Summary of Literature Review

Introduction/Background

The American Cancer Society estimates there will be 48,960 new cases of pancreatic cancer in 2015 (evenly divided by gender), with approximately 40,560 deaths, declaring this malignancy one of the most lethal and the fourth leading cause of cancer death in the United States [1]. Despite the research and advances in cancer treatment over the past 40 years, the 5-year overall survival (OS) rate for patients diagnosed with pancreatic adenocarcinoma has barely improved, from 2% in 1975–1977 to 6% in 2003–2009 [1]. Surgery remains the mainstay of treatment; however, only approximately 15% of patients diagnosed with this devastating disease are eligible for surgical resection—the vast majority present with either metastatic or locally advanced disease precluding surgery [2]. Nonetheless, patients who are able to undergo resection with curative intent still suffer from high rates of both local and distant recurrence. This highlights the importance of high-quality adjuvant therapy. The body of literature for pancreatic cancer suffers from a dearth of well-designed randomized clinical trials, with little consensus regarding recommendations for adjuvant treatment. Herein, we will review the literature associated with resectable pancreatic cancer and discuss future investigations.

Biomarkers

Carbohydrate antigen 19-9 (CA19-9), a serum carbohydrate antigen directed against Lewis antigens, is one of the best-characterized biomarkers for pancreatic adenocarcinoma. However, 5%–10% of the population possesses a defect in the gene for Lewis antigen, resulting in a false-negative test for CA19-9 and limiting clinical utility [3]. Furthermore, CA19-9 may be elevated as a result of poorly controlled diabetes or gastrointestinal complications, including biliary obstruction [4,5]. The overall sensitivity of CA19-9 for detecting pancreatic adenocarcinoma is approximately 80% and its specificity is 90%; however, a Korean study investigating its utility as a screening marker in an asymptomatic population found that the positive predictive value is only 0.9% [6,7]. Furthermore, both preoperative and postoperative levels of CA19-9 have been shown to be prognostic. Preoperative increases in CA19-9 correlate with increasing stage as well as resectability, and very high levels are associated with increasing risk of peritoneal dissemination [4,8-10]. Following surgery, persistently elevated CA19-9 suggests a poor prognosis and early appearance of metastatic disease [5]. Although CA19-9 is the only biomarker currently approved by the Food and Drug Administration for use in pancreatic adenocarcinoma, its limitations underscore the importance of further investigations into additional biomarkers that may be useful for screening [11].

SMAD4 (DPC4) is a key tumor suppressor for pancreatic adenocarcinoma impeding progression of KRAS-initiated malignancies that is inactivated in >50% of pancreatic ductal adenocarcinomas [12]. Loss of the *SMAD4* gene in pancreatic cancer is prognostic for a decrease in OS [13]. Clinically, inactivation of the *SMAD4* gene is associated with increasing tumor aggression, including higher incidence of lymph node metastases and tumor size

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

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[14]. Researchers at Johns Hopkins performed an autopsy study and compared patterns of failure to molecular markers for the *KRAS2*, *TP53,* and *SMAD4 (DPC4)* genes [15]. The findings revealed that 30% of patients die of locally invasive disease, as opposed to distant metastases. Importantly, no clinicopathologic features were found to correlate with the locally invasive versus distant metastatic recurrence pattern. However, evaluation of *DPC4* protein expression, a surrogate for *DPC4* gene status, correlates significantly with widespread metastases [15]. Identification of patients at greater risk for local progression may have utility in selecting patients who may maximally benefit from aggressive local therapy, including radiation therapy (RT).

Prognostic Factors

In addition to CA19-9, resection margin status and lymph node involvement are major prognostic factors for survival in patients who have undergone surgical resection. Additional minor factors have been reported, including age, tumor size, and tumor grade. High-quality surgery is essential in the curative management of pancreatic adenocarcinoma, with multiple studies confirming worse outcomes in patients who have undergone a margin-positive resection regardless of adjuvant therapy [5,16-18]. The presence of even a microscopically positive margin (R1), defined as a tumor within ≤1 mm of the surgical margin, after surgical resection is associated with decreased OS and disease-free survival (DFS) on par with those not undergoing resection [5]. The presence of lymph node metastases is a strong negative risk factor for recurrence, and the extent of lymph node involvement expressed as the ratio of positive lymph nodes to the total number of lymph nodes dissected is prognostic for OS [19-21]. Proper assessment of the lymph nodes at the time of surgery requires evaluation of at least 12 lymph nodes [22]. Tumors in the pancreatic head are typically detected earlier than those found in the body or tail of the pancreas, especially in patients presenting with early-onset jaundice. As a result, body and tail tumors are often less likely to be resectable [23].

Adjuvant Therapy

Several significant randomized studies investigating adjuvant therapy after curative resection for pancreatic adenocarcinoma are included in the literature from the past 4 decades; however, much of the research utilized outdated methods or was methodologically flawed. The first of the adjuvant studies is the Gastrointestinal Tumor Study Group (GITSG) 9173 study, which accrued patients with resected adenocarcinoma of the pancreas and negative margins (R0) from 1974–1982. In this era, patients were treated with conventional split-course 40-Gy radiation delivered using anterior-posterior/posterior-anterior (AP/PA) fields concomitantly with 5-fluorouracil (5-FU)–based chemotherapy, followed by maintenance 5-FU for a total of 2 years. The study was terminated early due to poor accrual, yet despite only randomizing 42 patients after surgical resection to either observation or chemoradiation, a survival benefit was evident in the chemoradiation arm; median OS was 20 months in the treatment arm versus 11 months with observation alone [24]. An additional 30 patients were subsequently enrolled into the adjuvant arm as a confirmatory study, with 2- and 5-year OS of 46% and 17%, respectively [25]. Although criticisms of the study include antiquated techniques and poor accrual, the GITSG 9173 study established the foundation for adjuvant chemoradiation after curative resection for pancreatic adenocarcinoma that remains a standard of care in the United States.

A subsequent European Organisation for Research and Treatment of Cancer (EORTC) study attempted to confirm the results of the GITSG study by enrolling more patients to increase the study power. Eligibility differed from the GITSG study by including periampullary tumors and patients with positive resection margins. Treatment was similar to the GITSG study, randomizing patients with curative-intent surgery to either observation or concurrent 5-FU–based chemoradiation utilizing RT to a total dose of 40 Gy in split-course fashion with a 2-week treatment break after the first 20 Gy, but without maintenance 5-FU [26]. The broader eligibility of the EORTC study successfully enrolled more patients; however, periampullary tumors are often associated with a better prognosis, with both increased DFS and OS compared with pancreatic tumors, thus decreasing the probability of detecting a survival difference. Additionally, 20% of patients in the experimental arm did not receive adjuvant chemoradiation as intended, and 44% did not receive chemotherapy per protocol (PP). The study concluded there is no benefit to adjuvant chemoradiation even after subgroup analysis of pancreatic head cancers resulting in a 2-year OS rate of 26% in the observation group and 34% in the treatment group utilizing a 2-sided log-rank test (P=0.099). It has been argued that the low toxicity in the original GITSG trial demonstrated the safety of the experimental arm, and because there was no reason to suspect harm associated with excessive toxicity in the adjuvant chemoradiation arm, a 1-sided log-rank test would have been more appropriate. Reanalysis of the EORTC data investigating pancreatic head adenocarcinoma utilizing a 1-sided log-rank test results in a benefit

with the addition of concurrent chemoradiation, even without maintenance chemotherapy, at the 0.05 level of significance [27].

The European Study Group for Pancreatic Cancer (ESPAC) conducted a prospective randomized phase III study investigating adjuvant therapy in pancreatic adenocarcinoma, the ESPAC-1 study, which is the largest of the adjuvant studies, enrolling a total of 541 patients [28]. Randomization after surgery was either to a 2×2 factorial design or physicians could choose to enroll patients directly into 2 randomized arms: chemotherapy versus observation or chemoradiation versus observation. The 2×2 factorial design randomized patients to observation, 6 cycles of 5-FU chemotherapy, RT alone, or chemoradiation with 6 additional cycles of maintenance chemotherapy. Prescribed RT was very heterogeneous, with a recommended dose of 40 Gy in a split-course fashion, but, at the discretion of the physician, allowed up to 60 Gy with no quality assurance. RT to doses well above standards in previous trials suggests a number of less-than-R0 resections. The initial publication in 2001, with a median of 10 months of follow-up for all surviving patients, revealed no significant survival difference between patients assigned to chemoradiation therapy or observation (median survival, 15.5 versus 16.1 months; *P*=0.24) but a highly significant improvement in median survival for patients randomized to chemotherapy versus no chemotherapy (19.7 versus 14.0 months, *P*=0.0005) [29]. With further follow-up, the authors report a 5-year OS benefit with the addition of chemotherapy, 21% versus 8% (*P*=0.009); however, it was concluded that the addition of adjuvant concurrent chemoradiation is detrimental when compared to observation alone, with 5-year OS being 10% versus 20% (*P*=0.05) [28]. Given the methodological flaws in the study, there have been many challenges to the data, and the question regarding the optimal adjuvant therapy for resected pancreatic cancer remains unanswered [30,31].

The German Study Group for Pancreatic Cancer completed the Charité Onkologie (CONKO)-001 study investigating the use of adjuvant gemcitabine without RT in the postoperative setting for pancreatic adenocarcinoma [32]. This high-quality, well-designed phase III trial randomized 354 highly selected patients with postoperative carcinoembryonic antigen/CA19-9 ≤2.5 times the upper limit of normal and either a R0 or R1 resection to observation versus 6 cycles of adjuvant gemcitabine alone. Over 80% of patients in this trial underwent R0 surgical resection. At a median follow-up of 136 months, 5-year OS favored the adjuvant gemcitabine arm at 20.7% versus 10.4%, with a median survival of 22.8 months compared with 20.2 months in the observation arm (*P*=0.01) [33]. Improvement in median DFS was also statistically significant, reported as 13.4 months compared to 6.7 months in the observation-alone arm (see Variant 1).

An Intergroup trial conducted in the United States, Radiation Therapy Oncology Group® (RTOG) 97-04, is the first study to incorporate modern RT techniques combined with rigorous radiation quality assurance. The study investigates the use of gemcitabine with RT in patients undergoing high-quality surgery with curative intent and an adequate lymph node dissection [34]. Following surgical resection, patients were randomized to either 3 weeks of continuous-infusion 5-FU chemotherapy or gemcitabine, during which time a central review of proposed RT plans was performed. All patients were then treated with concurrent 5-FU–based chemoradiation therapy to a total dose of 50.4 Gy followed by 3 months of maintenance chemotherapy. Patients enrolled on RTOG 97-04 were higher risk than those in the CONKO-001 study, with only 40% of postoperative patients achieving R0 resection status versus >80% in the German study [35]. A total of 451 patients were enrolled, and in a planned subgroup analysis of 388 patients with pancreatic head malignancies, the median survival at 3 years was 20.5 months in patients receiving gemcitabine compared to 16.9 months in patients receiving 5-FU [34]. OS at 3 years was 31% with gemcitabine compared to 22% with 5-FU–based chemotherapy.

Perhaps the most important lesson from RTOG 97-04 comes from a secondary analysis of adherence to protocol therapy and illustrates the importance of quality control in delivery of RT. Adherence to protocol specifications was scored for all patients in both arms as either PP or less than PP. In multivariate analysis, adherence to therapy correlated more strongly to survival than did treatment arm [36]. For all patients, including the subgroup of pancreatic head patients, treatment PP resulted in statistically significant benefits. Additionally, in the gemcitabine arm, RT delivery <PP was potentially detrimental, with a trend towards increased toxicity for both hematologic grade 4 and nonhematologic toxicity. Based on the inclusion criteria for the CONKO-001 trial requiring a postoperative CA19-9 ≤2.5 times the upper limit of normal, the clinical importance of postoperative CA19-9 was prospectively validated [37]. A 5-year update of RTOG 97-04 underscores the prognostic significance of postoperative CA19-9 levels, with patients having serum levels ≥90 U/mL suffering a decrease in median survival [35]. The improved survival seen at 3 years with the addition of gemcitabine was only a trend towards increased OS at 5 years (*P*=0.08) [38]. An improvement in survival for the select group of patients with

pancreatic head tumors, CA19-9 levels <90 U/mL, and receiving RT PP was maintained at 5 years, with a median survival of 24 months and a 5-year survival of 34% [35].

Following the suggestion of a detriment to patients receiving adjuvant RT, the ESPAC has initiated another 3 trials investigating adjuvant chemotherapy alone. The ESPAC-3 version 2 study is a multicenter, phase III, randomized controlled trial initially designed as a 3-arm study for patients undergoing curative resection for pancreatic adenocarcinoma [39]. Patients were randomized to observation or 6 cycles of adjuvant chemotherapy consisting of either 5-FU or gemcitabine. Following the final results from the ESPAC-1 study confirming a benefit to the addition of adjuvant chemotherapy, the observation arm was closed to accrual, and a total of 1088 patients were randomized between the 2 chemotherapy arms. There was no difference in progression-free survival or median survival for either 5-FU or gemcitabine, 23.0 compared to 23.6 months, respectively (P=0.39). However, there was a statistically significant increase in serious adverse events in the 5-FU arm compared to gemcitabine, with no decrease in global quality-of-life scores. Further analysis of this study suggests completion of all therapy is more important to patient outcome than a delay in delivery of adjuvant therapy, with no decrement in outcome associated with delayed chemotherapy up to 12 weeks [40]. These findings may explain why no benefit was seen in either the EORTC 40891 study, in which approximately 20% of patients in the chemoradiation arm did not receive the assigned therapy, or the ESPAC-1 study, in which 30% of patients in the chemoradiation arm received either no RT or nonstandard radiation. CONKO-005, investigating the addition of erlotinib to gemcitabine in the adjuvant setting, was recently published in abstract form [41]. The study randomized patients after surgical resection with negative margins to either gemcitabine alone or in combination with erlotinib. Unfortunately, no improvement in either median DFS or median OS was detected with the addition of erlotinib to gemcitabine.

Although these studies investigating adjuvant therapy for resectable pancreatic adenocarcinoma leave many questions unanswered, taken together they emphasize the importance of enrolling patients in clinical trials. They also demonstrate the need for adjuvant therapy after surgical resection. These studies suggest either postoperative chemotherapy alone or high-quality chemoradiation are acceptable therapies and support the delivery of adjuvant therapy over observation following resection. The median OS in all of these studies is quite similar at approximately 20 months, and yet the RTOG 97-04 study included higher-risk patients, with 66% having positive lymph nodes, 59% with tumor size ≥3 cm, 58% with either positive or unknown surgical margin status, and only 15% with well-differentiated tumors.

Adjuvant therapy inclusive of RT may be even more important as the number of risk factors increase and as systemic chemotherapy becomes more effective. Local failure continues to constitute a significant failure pattern after surgical resection, suggesting a role for improved local control via RT. Autopsy studies reveal an insidious infiltrating retroperitoneal recurrence pattern not readily detected on conventional imaging, with local recurrence rates as high as 75% [42]. Several large single-institution studies support the addition of RT to chemotherapy for local control. Analysis of a prospective database from Johns Hopkins Hospital from 1993 to 2005 reveals the addition of 5-FU–based chemoradiation therapy to a population of 81.9% node-positive and 48% margin-positive high-risk patients resulted in improved survival versus surgery alone [43]. A similar retrospective review from Mayo spanning 3 decades from 1975–2005 analyzed only patients with negative surgical margins, confirming improved OS with the addition of chemoradiation [44]. Despite the presence of higher-grade tumors, more positive lymph nodes, and higher T-stage, patients receiving adjuvant chemoradiation therapy experienced a median OS of 25.2 months versus 19.2 months with observation alone. The Johns Hopkins Hospital–Mayo Clinic Collaborative Study retrospectively evaluated the outcomes of 1092 patients between the 2 institutions, treating resectable pancreatic cancer with either concurrent 5-FU–based chemoradiation or observation [45]. Matched-pair analysis confirms improved OS (median survival, 21.9 versus 14.3 months) with the addition of concurrent chemoradiation despite approximately 67% having positive lymph nodes, 60% ≥T3, and a third having positive surgical margins (see Variant 2 and Variant 3).

Neoadjuvant Therapy

In the setting of resectable pancreatic adenocarcinoma, a surgery-first approach is still the standard of care; however, consideration of novel approaches is necessary as little progress has been made over the past 4 decades with conventional approaches. Neoadjuvant chemoradiation is preferred in many tumor sites for theoretical as well as practical benefits and may have a role in pancreatic adenocarcinoma. An intact blood supply improves delivery of chemoradiation to the target, and delivery of adjuvant therapy prior to surgery improves the probability of delivery of all planned therapy. Delivery of therapy prior to surgical resection may downstage

tumor, resulting in a higher probability of high-quality surgery and/or a decrease in lymph node metastases. Analysis of 5414 patients treated with resection and RT either preoperatively or postoperatively reveals a higher rate of negative surgical margins in the patients receiving neoadjuvant therapy (82% versus 72%) as well as decreased probability of lymph node involvement (41% versus 65%) [46]. Additionally, early treatment may benefit those with micrometastases, and the time to surgery may allow those with blossoming metastatic disease to present. Identifying patients with early metastatic disease may spare them undergoing an unnecessary morbid surgical procedure and allows selection of those patients who may most benefit from surgical resection.

Several small studies have investigated the role of neoadjuvant therapy in resectable pancreatic cancer, with the most extensive experience at MD Anderson Cancer Center [47-53]. The MD Anderson experience suggests that administering neoadjuvant gemcitabine-based therapy is not inferior to historical data and is associated with significant treatment effect, with high rates of both negative margins and local control. A comparison of the various neoadjuvant strategies from MD Anderson reveals an increase in survival for patients completing both induction with the gemcitabine-based regimen and pancreaticoduodenectomy as compared to prior strategies utilizing either neoadjuvant 5-FU or paclitaxel (median survival, 34 months; 5-year OS, 36%) [48]. Proof of feasibility is supported by other studies, including a multi-institutional phase II investigation of neoadjuvant full-dose gemcitabine with concurrent RT [54]. Participating institutions enrolled 41 patients with potentially resectable pancreatic adenocarcinoma, treating with full-dose gemcitabine (1000 mg/m^2) for 3 cycles and delivering concurrent 3-D conformal RT to the tumor with the second cycle to a total dose of 36 Gy in 15 fractions. Consistent with the MD Anderson experience, the 20 patients taken to surgery experienced a high rate of surgical completion, with 16 of the 17 obtaining negative surgical margins and 11 of 17 specimens with negative lymph nodes. The regimen was adequately tolerated, with 2 patients experiencing grade 4 toxicity, including 1 hematologic and 1 gastric outlet obstruction [55]. Grade 3 neutropenia (12.8%), grade 3 nausea (10.3%), and grade 3 vomiting (10.3%) were the most common adverse effects experienced by patients. Only 1 randomized study investigating neoadjuvant chemoradiation in resectable pancreatic cancer has been reported after failing to adequately accrue patients and closing early [49]. This phase II study randomized patients to either surgery followed by adjuvant gemcitabine chemotherapy per the CONKO-001 trial or to neoadjuvant chemoradiation utilizing 3-D conformal RT to a dose of 55.8 Gy to the tumor and 50.4 Gy to the regional lymph nodes with concurrent gemcitabine and cisplatin followed by maintenance gemcitabine. Only 29 patients were treated with neoadjuvant chemoradiation, and although there was no statistical difference between the 2 arms, the median OS in patients undergoing surgical resection was 18.9 months with chemotherapy alone and 25.0 months in patients receiving neoadjuvant therapy. There was no difference in postoperative complication rates. A retrospective study from the Medical College of Wisconsin treating both borderline and resectable disease suggests an increased rate of R0 resection with neoadjuvant chemoradiation, and patients completing all treatment experience a median survival of 26 months [51]. Neoadjuvant hypofractionated proton RT (25 Gy in 5 fractions) given concurrently with oral capecitabine 1–2 weeks prior to surgery has been evaluated at a single institution and it appears to be safe with reasonable local control, although additional data are needed to determine long-term efficacy [50]. Although neoadjuvant chemoradiation may have a role in the treatment of patients deemed to have resectable disease, its role is still unproven at this time, and such patients should be ideally enrolled on clinical trials (see Variant 4).

Radiation Therapy

Technological advances in radiation oncology, including imaging, treatment planning, and treatment delivery, pose increasing challenges for the radiation oncologist. Quality assurance analysis conducted as part of RTOG 97-04 demonstrated that 48% of RT quality assurance scores were less than PP, and this poor-quality treatment was associated with inferior survival [36]. Historically, 2-D treatment planning relied on visualizing vertebral bodies on x-rays to identify nodal targets. However, access to modern 3-D imaging confirms variability among the lymphatics relative to bony anatomy, emphasizing the importance of a comprehensive understanding of anatomy [56]. The use of conformal intensity-modulated RT (IMRT) potentially decreases the dose to surrounding organs at risk, including the kidney, stomach, liver, and small bowel [57], and has the potential to decrease symptoms associated with treatment of the small bowel, including a decrease in grade 3–4 nausea, vomiting, and diarrhea [58,59].

Increasing conformality associated with IMRT treatment planning increases the probability of a geographic miss without properly understanding and accounting for motion. The pancreas is susceptible to both intrafraction motion, primarily respiration, and interfraction motion, primarily due to gastric filling [60-62]. The combined

intra- and interfraction motion necessitates either substantial planning target volume expansion to account for uncertainties in motion or daily image-guided RT (IGRT) to visualize anatomic shifts. The American-French Consensus Recommendations on treatment of locally advanced pancreatic cancer recommend "expansion of 1.5 to 2 cm anteriorly, posteriorly, and laterally, and 2 to 3 cm craniocaudally to generate the planning target volume" when not utilizing IGRT [63]. The use of daily IGRT, especially with the addition of abdominal compression to minimize respiratory motion, can dramatically reduce the required planning target volume expansion [60,62]. Contouring guidelines have been published to aid in accurately targeting areas at greatest risk for local recurrence [64]. Contouring aids should be used for target volume delineation, and the RTOG has published an atlas with stepwise instructions for IMRT field design based on patterns of recurrence [65]. High-quality IMRT utilizing evidence-based contouring guides and motion management can be delivered without an increase in local recurrence associated with marginal misses [66].

The use of increasingly conformal treatments such as IMRT allows dose escalation in the treatment of pancreatic cancer. The dose to the pancreas has increased since the era of the GITSG study, with most studies utilizing 50–54 Gy in 1.8- to 2.0-Gy daily fractions in the adjuvant setting. Notably, the ESPAC-1 study permitted a wide range of dose from 40–60 Gy. Although no single trial has established the optimum dose, analysis of data from the National Cancer Data Base for all patients treated with adjuvant radiation from 1998–2002 utilizing multivariate survival analysis and Kaplan-Meier finds the optimum dose to be in the range of 50 Gy to <55 Gy [67]. Both higher and lower doses are associated with lower survival in this analysis. Although unclear, the inferior survival with higher doses of RT delivered utilizing older radiation techniques is likely due to increased treatment-related toxicities.

Future Directions

There is a paucity of high-quality data regarding treatment of resectable pancreatic adenocarcinoma, with discrepancies between similar studies performed by various clinical trial groups. Ideally, clinicians will increase enrollment in clinical trials to answer existing questions and validate future therapies. Patients frequently remain asymptomatic until disease is advanced and rarely resectable. The discovery of a reliable biomarker could provide the opportunity for early detection, rendering surgery a curative option for many patients. A recent publication identifies glypican-1 as a reliable novel marker of exosomes from pancreatic adenocarcinoma, which may identify early pancreatic cancer [68]. Further research and validation of this potential biomarker is necessary for clinical utility. Conventional therapies have failed to significantly improve survival in this population over the past 4 decades, demonstrating the need for novel therapies. Current studies are investigating newer chemotherapeutic and biologic agents with or without the addition of local RT. The current RTOG 0848 study for resected pancreatic cancer investigates the addition of erlotinib to gemcitabine and subsequently randomizes patients to either continued chemotherapy or chemoradiation therapy. Although this study is currently open, the erlotinib arm closed on April 2, 2014 [69]. Multiagent chemotherapy such as FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) and gemcitabine with nab-paclitaxel (Abraxane) has been shown to be superior to gemcitabine in the metastatic setting. However, it has not been prospectively evaluated in the neoadjuvant or adjuvant setting, although it will be tested in a future cooperative group trial. Other combination chemotherapy regimens such as gemcitabine and capecitabine as well as gemcitabine with cisplatin or oxaliplatin have been evaluated in the neoadjuvant and adjuvant settings with or without RT, with mixed results [70,71].

Newer systemic agents are under investigation, including studies combined with immunotherapy to stimulate the innate immune system to recognize cancer as foreign. Vaccine therapy may be promising, and a recent publication demonstrates efficacy and safety with an incremental improvement in OS in patients with metastatic pancreatic adenocarcinoma [72]. The GVAX vaccine stimulates T cells to recognize various antigens associated with pancreatic adenocarcinoma, and published phase II data in resected pancreatic adenocarcinoma treated with adjuvant fluorouracil-based chemoradiation followed by the vaccine enjoyed a DFS of 17.3 months and median survival of 24.8 months [73]. Recognition that the tumor stromal environment plays a critical role in the behavior of the tumor identifies the tumor microenvironment as a novel and important target [74]. The use of immune checkpoint inhibitors may also have value in the treatment of pancreatic cancer and are an area of active investigation [75]. Finally, in the neoadjuvant setting a combination of multiagent chemotherapy and stereotactic body RT with photons or protons may result in improved pathologic tumor response and outcomes; however, more studies are needed [50,76-78].

Summary of Recommendations

- Patients with no or few risk factors for local recurrence after surgical resection of their pancreatic cancer may benefit from adjuvant chemotherapy alone as suggested by the high-quality CONKO-001 study. Adjuvant chemotherapy alone may especially be useful when performance status is compromised and patients may not be able to tolerate concurrent chemoradiation.
- Patients undergoing surgical resection of pancreatic adenocarcinoma benefit from adjuvant therapy to include either chemotherapy or combinations of chemotherapy and concurrent chemoradiation. Appropriate selection of therapy includes patient ability to tolerate multimodality therapy and evaluation of risk factors for distant and local recurrence.
- Patients with positive surgical margins are at increasing risk for local recurrence and may benefit from adjuvant therapy to include chemoradiation.
- Although upfront surgery remains the standard of care in patients with resectable pancreatic cancer, multiple trials demonstrate the feasibility and good outcomes with neoadjuvant chemoradiation. Benefits of this approach include appropriate selection of patients for surgical resection and ability to deliver all intended therapy for maximum tumor treatment.

Summary of Evidence

Of the 78 references cited in the *ACR Appropriateness Criteria® Resectable Pancreatic Cancer* document, 69 are categorized as therapeutic references including 21 well designed studies and 34 good quality studies. Additionally, 9 references are categorized as diagnostic references including 1 well designed study and 4 quality studies that may have design limitations. There are 18 references that may not be useful as primary evidence.

The 78 references cited in the *ACR Appropriateness Criteria® Resectable Pancreatic Cancer* document were published from 1985-2015.

While there are references that report on studies with design limitations, 56 well designed or good quality studies provide good evidence.

Supporting Documents

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

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Clinical Condition: **Resectable Pancreatic Cancer**

Variant 1: **78-year-old man with resected well-differentiated adenocarcinoma of the pancreatic head, pT1N0M0 with negative margin of resection, and no evidence of perineural invasion. Postoperative CA19-9=80. Karnofsky performance status (KPS) of 80.**

Treatment	Rating	Comments
Observation	4	
Chemotherapy Alone		
5-FU	6	Gemcitabine may have less toxicity.
Gemcitabine	8	
Multiagent chemotherapy	4	
Chemoradiation therapy followed by adjuvant chemotherapy	4	
Chemotherapy followed by chemoradiation therapy followed by chemotherapy	6	
Chemotherapy × 4–6 months followed by chemoradiation therapy	6	
Dose to Tumor Bed		
45 Gy/1.8 Gy	5	
50.4 Gy/1.8 Gy	8	
54 Gy/1.8 Gy	5	
59.4 Gy/1.8 Gy	3	
RT Technique		
AP/PA photons	2	
4–5 field photon 3-D conformal plan	8	
IMRT	8	Using atlas and daily image guidance is recommended.
RT Volume		
Tumor bed alone	5	
Tumor bed + nodal basin	8	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Resectable Pancreatic Cancer**

Variant 2: **65-year-old woman with resected moderately-differentiated adenocarcinoma of the pancreatic head, pT2N1M0 with negative margin of resection, 1 of 15 lymph nodes involved, and no evidence of perineural invasion. Postoperative CA19-9=120. KPS 80.**

Treatment	Rating	Comments
Observation	2	
Chemotherapy Alone		
5-FU	7	
Gemcitabine	8	
Multiagent chemotherapy	4	
Chemoradiation therapy followed by adjuvant chemotherapy	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 followed by chemoradiation therapy followed by chemotherapy	7	
Chemotherapy × 4–6 months followed by chemoradiation therapy	7	
Dose to Tumor Bed		
45 Gy/1.8 Gy	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.
50.4 Gy/1.8 Gy	8	
54 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	3	
RT Technique		
AP/PA photons	3	
4–5 field photon 3-D conformal plan	8	
IMRT	8	
RT Volume		
Tumor alone	3	
Tumor + nodal basin	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Resectable Pancreatic Cancer**

Variant 3: **70-year-old man with resected poorly-differentiated adenocarcinoma of the pancreatic head, pT3N0M0 with a positive uncinate margin of resection, and postoperative CA19-9=140. KPS 80.**

Treatment	Rating	Comments
Observation	1	
Chemotherapy Alone		
5-FU	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.
Gemcitabine	7	
Multiagent chemotherapy	5	
Chemoradiation therapy followed by adjuvant chemotherapy	6	
Chemotherapy followed by chemoradiation therapy followed by chemotherapy	8	
Chemotherapy × 4–6 months followed by chemoradiation therapy	8	
Dose to Tumor Bed		
45 Gy/1.8 Gy	3	
50.4 Gy/1.8 Gy	7	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	5	This option is performed with the use of breathing motion management, close attention to bowel dose, and no small bowel in the field.
RT Technique		
AP/PA photons	2	
4–5 field photon 3-D conformal plan	7	
IMRT	8	
RT Volume		
Tumor bed alone	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.
Tumor bed + nodal basin	8	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Resectable Pancreatic Cancer**

Variant 4: **65-year-old woman with resectable moderately-differentiated adenocarcinoma of the pancreatic head, cT2N0M0, and preoperative CA19-9=140. KPS 90.**

Treatment	Rating	Comments
Upfront Surgery	8	
Neoadjuvant chemoradiation therapy followed by surgery	6	
Neoadjuvant chemotherapy followed by surgery	6	
Neoadjuvant chemotherapy followed by chemoradiation therapy followed by surgery	6	
Neoadjuvant Dose to Tumor		
Standard fractionation 45–50 Gy/1.8 Gy fx	8	
Hypofractionation 2.4–3 Gy/fx 30–36 Gy	7	
RT Technique		
AP/PA photons	2	
4–5 field photon 3-D conformal plan	7	
IMRT	8	
RT Volume Needed		
Tumor alone	6	
Tumor + nodal basin	8	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		