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Combined Modality Treatment of Resectable and Borderline Resectable Pancreas Cancer: Expert Consensus Statement

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This year approximately 5000 patients in the United States will undergo resection of pancreatic cancer with curative intent. Despite concerted international efforts, especially over the past 20 years, survival statistics for such patients have changed little and remain disappointing. Reported 2- and-5 year overall survival rates for patient with resected pancreas cancer are 40–50% and 15–20%, respectively, and rates of local and systemic recurrence also remain high—35–60% and 80–90%, respectively.[1–7] Considerable debate surrounds the best therapeutic approach for such patients.

Efforts to increase the number of long-term survivors after curative-intent pancreas cancer resection have to date centered on one of four areas: (1) neoadjuvant therapy before surgery, (2) adjuvant chemotherapy, (3) whether or not to include radiation treatment, and (4) the extension of potentially curative treatment to patients with borderline resectable disease. While we acknowledge the controversies and complexities associated with each of these four areas, as well as the limitations of available data, our goal here is to articulate working consensus statements that provide focus for future study and express present levels of agreement.

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PREOPERATIVE THERAPY FOR LOCALIZED OPERABLE PANCREAS CANCER

Over the past 2 decades, four randomized trials of adjuvant therapy have been completed in patients undergoing potentially curative surgery for pancreas surgery.[2–5] These trials used different eligibility criteria, various regimens of chemoradiation and/or chemotherapy, and different control arms, making comparison across studies challenging. Nevertheless, the median overall survival of patients randomized to the "best" arms of these four trials ranged from 17 to 22 months. Local recurrences were observed in 35–60% of cases, similar to results reported with surgery only.[2–5] The limitations of these results created interest in an exploration of neoadjuvant therapy as well as further exploration and study aimed at improving "classically sequenced" adjuvant therapy.

Rationale for Neoadjuvant Therapy in Resectable Pancreas Cancer

A neoadjuvant paradigm allows for early treatment of micrometastatic disease in all patients; delivers chemotherapy and/or ionizing radiation to an intact, well-

vascularized primary tumor (potentially improving negative-margin [R0] resection rates); and provides a time interval in which to identify patients with aggressive tumor biology. Patients who develop radiographic evidence of metastatic disease during such therapy are spared a surgical procedure that offers no meaningful survival benefit. Furthermore, preoperative anticancer therapy places a significant physiologic stress on the patient, potentially assisting in the identification of patients with poor physiologic reserve not evident on initial evaluation.

Since the early 1990s, a handful of centers, most notably The University of Texas M.D. Anderson Cancer Center's Pancreatic Tumor Study Group, have studied preoperative chemoradiation regimens in patients with potentially resectable pancreas cancer.[8–11] These studies have been uniform in the application of consistent definitions of resectability, surgical technique, margin assessment, and grading of treatment effect and therefore have allowed for internal comparisons among the various regimens—5FU, paclitaxel, and more recently, gemcitabine over time. The preoperative gemcitabine-based regimens have been associated with very low rates of microscopically positive margins on resection (R1), greater treatment effect, low rates of postoperative local recurrence, and most importantly, improved overall survival in those undergoing resection compared with earlier 5FU- or paclitaxel-based regimens. The survival results also compare favorably with those reported in large adjuvant therapy trials.

Importantly, preoperative therapy can be delivered only when patients with established histologic diagnosis and adequate and durable biliary decompression. This approach requires a fully committed team of multidisciplinary subspecialists, potentially limiting the investigation of neoadjuvant therapy to tertiary-care referral centers. The American College of Surgeons Oncology Group (www.ACOSOG.org) is planning a multicenter, single-arm phase II trial of preoperative and postoperative gemcitabine and erlotinib for patients with localized pancreas cancer (ACOSOG Z5051). This trial will help to determine whether preoperative treatment is feasible and worthy of further exploration on a larger scale in the cooperative group context.

Consensus Statement

1. Preoperative adjuvant (neoadjuvant) therapy provides a rational alternative to a "surgery-first" approach to resectable pancreas cancer.
2. Neoadjuvant therapy can be initiated for all eligible patients and successfully identifies a subset of patients for whom resection will not offer a survival benefit.
3. Neoadjuvant therapy may improve negative-margin resection rates and decrease local failure rates.
4. Neoadjuvant therapy should be considered investigational for patients with potentially resectable pancreas cancer, but merits broader study by centers with multidisciplinary expertise in pancreatic cancer treatment.
5. With accepted definitions of resectability, standardized surgical technique, strict criteria for assessment of margin status, and a standardized system for grading treatment effects, the relative contributions of chemotherapy, radiation, and molecular therapeutics in neoadjuvant therapy will become better defined. Moreover, in the longer term, as more prognostic biomarkers are identified, individualized preoperative therapy programs can be designed.

ROLE OF RADIATION THERAPY FOR LOCALIZED OPERABLE PANCREAS CANCER

After 5FU plus radiotherapy was shown to be superior to radiotherapy alone for locoregionally unresectable pancreas cancers, this combination was brought into use as adjuvant therapy by the Gastrointestinal Tumor Study Group (GITSG) in the 1970s. The GITSG's findings, published in 1985, demonstrated that adjuvant 5FU plus radiotherapy (40 Gy in a split course) followed by maintenance 5FU weekly for 2 years was superior to surgery alone,[1] but were regarded with considerable reservation because of the small number of patients involved and the protracted interval required to accrue them. The concept of adjuvant chemoradiation issue lay mostly dormant in North America until the early 1990s, by which time the morbidity and mortality associated with pancreaticoduodenectomy were sufficiently reduced to allow more meaningful exploration of postoperative adjuvant therapy.

The combined-modality approach was used for RTOG 97-04, which opened in 1998 and was the first multicenter adjuvant therapy trial for resected pancreas cancer in North America since the GITSG trial.[5] Concurrently, in Western Europe, chemotherapy alone approaches to adjuvant therapy have become dominant based on the outcomes of the EORTC and ESPAC trials performed in the mid and late 1990s, and, more recently, the results of the CONKO 001 trial using gemcitabine with radiotherapy.[2–4,12,13]

The rationale for continuing to use combined chemotherapy and radiotherapy approaches includes both conceptual factors (radiation sensitization and spatial synergy), high local recurrence rates (up to 50%) following surgery alone, and the proven efficacy of chemoradiotherapy approaches in multiple phase III studies of gastrointestinal and nongastrointestinal malignancies where there is a well-established risk of both local-regional recurrence and more distant dissemination.[6,7,14] Three

5FU-radiotherapy experiences are especially worthy of mention. Two of these reflect large retrospective compilations of 5FU chemoradiation results from Johns Hopkins and the Mayo Clinic, respectively, each showing significant advantage for patients receiving 5FU based chemoradiotherapy.[15,16] The third represents preliminary results from the American College of Surgeons Oncology Group Z5031 trial using cisplatin, 5FU, and alpha interferon with radiation therapy.[17] This latter trial is important because it illustrates the potential for chemotherapeutic intensification with modified radiotherapy planning to provide manageable, although significant, toxicity with encouraging disease-related outcomes.

Consensus Statement

1. Patients who have undergone surgical resection for localized pancreas cancer should receive adjuvant therapy, provided adequate recovery from surgery has occurred.
2. There is no single adjuvant regimen of chemotherapy or chemoradiation that can claim unequivocal superiority to others, although the administration of gemcitabine as systemic therapy should be considered.
3. The role of radiation as a component of adjuvant therapy remains controversial, but radiotherapy might especially benefit distinct subsets of patients (for example those undergoing an R1 resection or those who are otherwise considered at increased risk for locoregional recurrence).
4. Postoperative computed tomography (CT) imaging is strongly recommended prior to embarking on adjuvant therapy and should definitely be obtained prior to the delivery of radiation.

ROLE OF ADJUVANT CHEMOTHERAPY FOR LOCALIZED OPERABLE PANCREAS CANCER

Early clinical trials of adjuvant therapy for resected pancreas adenocarcinoma were limited by their small size and lack of standardization of patient entry criteria and quality controls for therapy. Over the past decade, several larger, more standardized adjuvant therapy studies were completed and have shed a clearer light on what constitutes optimal adjuvant therapy for resected pancreas cancer.

Rationale for Adjuvant Chemotherapy in Resected Pancreas Cancer

The rationale for systemic chemotherapy with or without radiotherapy in the management of resected pancreas cancer is given by the high risk of systemic and locoregional recurrence following surgery alone.[6,7] Bakkevold et al. suggested an early benefit to multiagent chemotherapy, although this benefit was not sustained at the 5-year mark.[18] The initial GITSG trial, though criticized for its design and sample size, provided the foundation for adjuvant chemotherapy with the conclusion that the 5FU in adjuvant chemoradiation contributed to the improved outcome for that treatment compared with no adjuvant treatment after pancreatectomy [1]. A subsequent study by the EORTC did not confirm the original GITSG findings.[3,12] However, the EORTC trial was limited by inadequate study power and a short duration of systemic therapy. The ESPAC-1 study, while criticized for its enrollment criteria, analytical design, and radiation therapy techniques, concluded that adjuvant chemotherapy with 5FU administered for 6 months offered an overall survival advantage, whereas adjuvant chemoradiotherapy did not and might be detrimental to survival.[2,13] Building on the results of ESPAC-1, ESPAC-3 is exploring the concept of adjuvant systemic therapy without radiation. This study directly compares the value of gemcitabine to bolus "Mayo Clinic"-style 5FU. A third arm, observation alone, closed early because an interim analysis revealed inferior outcomes compared with the chemotherapy arms. Accrual has been completed for pancreas adenocarcinoma, and results are awaited.

An important modern adjuvant therapy study, noteworthy for its rigorous trial design, is the CONKO-001 trial, which compared gemcitabine to observation alone (control) after surgery in 368 patients.[4] The patients in the gemcitabine arm had a median disease-free survival of 13.4 months (95% confidence interval [CI] 11.4–15.3 months) compared with 6.9 months (95% CI 6.1–7.8 months, $P < .001$) in the control arm. The median overall survivals were 22.1 months (95% CI 18.4–25.8 months) and 20.2 months (95% CI 17–23.4 months), respectively. The lack of a clear ($P = 06$) overall survival advantage in the gemcitabine arm may have been related to the relatively low study power and the fact that gemcitabine could be used as salvage therapy after recurrence in the control arm.

The Radiation Therapy Oncology Group (RTOG) 97-04 study reported by Regine et al. provides more recent support for adjuvant gemcitabine.[5] This trial is notable for the incorporation of contemporary principles of chemoradiotherapy and for its radiotherapy quality assurance analysis. The major finding was that gemcitabine administered before and after 5FU-based chemoradiation resulted in a median overall survival of 20.5 months, versus 16.9 months in the control (5FU) arm for patients with cancer of the pancreas head (hazard ratio for overall survival 0.50, 95% CI 0.63–1.00, $P = .05$),in a multivariate model). Other important findings in this study were the adverse prognostic value of a postoperative baseline CA19-

9 level >180 U/mL and the importance of radiation therapy quality control.[19,20]

Planned Adjuvant Chemotherapy Studies

Clinical trials in late development/final planning stages in 2008 include ESPAC-4, which is based on the assumption that gemcitabine is superior to 5FU in the adjuvant therapy setting and will directly compare gemcitabine to a gemcitabine-capecitabine combination after resection of localized pancreas cancer. Enrollment of more than 1000 patients is planned. In addition, the EORTC has completed a phase II trial for toxicity assessment of the gemcitabine followed by gemcitabine with irradiation.[21]

Consensus Statement

1. Six months of adjuvant chemotherapy with 5FU or gemcitabine is the standard adjuvant therapy for patients with resected pancreas cancer.
2. Six months of adjuvant therapy consisting of 5FU-based chemoradiation preceded and followed by maintenance chemotherapy is an acceptable alternative.
3. Chemoradiation without additional systemic therapy is not an acceptable adjuvant treatment choice.
4. Randomized data comparing adjuvant chemotherapy and chemoradiation to chemotherapy alone are awaited.

APPROACHES TO BORDERLINE RESECTABLE PANCREAS CANCER

In addition to identifying tumors with a high likelihood of being resectable with negative margins, CT imaging has facilitated the identification of tumors that, while perhaps technically resectable in some centers, are more likely to be removed with positive surgical margins. This group of tumors, termed "borderline resectable" or "marginally resectable," represents a distinct set whose management needs to be considered separately from those that meet criteria for resectability and those that are locally advanced.

Currently, there is no consensus definition of borderline resectable pancreas cancer. The National Comprehensive Cancer Network classifies a tumor as borderline resectable if one of the following conditions is met: (1) tumor abutment of the superior mesenteric artery (SMA), (2) severe unilateral superior mesenteric vein (SMV) or portal vein (PV) impingement, (3) gastroduodenal artery encasement to its origin, or (4) invasion of the transverse mesocolon.[22] Among the problems associated with this definition are the inability to objectively quantify "severe" impingement and the fact that transverse mesocolon involvement is not clearly associated with an increased risk of a positive-margin resection, nor is it always identifiable by CT.[23–25]

On the basis of this consensus conference, a potentially useful definition of borderline resectable pancreas cancer combining multiple criteria has been developed:

- Tumor-associated deformity of the SMV or PV
- Abutment of the SMV or PV $\geq 180°$
- Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
- Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction
- Abutment of the SMA ($<180°$)

To allow for clinical trial design and to permit comparison between retrospective reports, it is imperative that a consensus definition of borderline resectable be adopted and consistently applied.

Importance of Identifying Borderline Resectable Pancreas Cancer

The underlying premise for identifying borderline resectable pancreas cancer is that tumor downstaging is required to enhance the chance of an R0 resection. This appears important because several reports have suggested decreased resectability or a high likelihood of R1 or R2 resections (microscopically or grossly positive margins) for these types of borderline cases, particularly when neoadjuvant therapy is not administered.[23–25] Thus, there is considerable rationale to a neoadjuvant approach for patients with borderline resectable disease.

Ideally, patients with borderline resectable pancreas cancer should be enrolled in clinical trials. When this is not possible, induction systemic therapy followed by chemoradiation and CT reassessment of resectability is the preferred approach.[26,27] The arguments for induction systemic therapy followed by chemoradiation in borderline resectable pancreas cancer patients are many. First, >80% of these patients will have occult metastatic disease at presentation; systemic therapy addresses this disease as early as possible. Second, neoadjuvant chemotherapy allows for in vivo assessment of drug activity. Third, patients whose tumors rapidly progress during systemic therapy are spared the toxicity of chemoradiation and morbidity of surgery. Finally, this approach separates the patient population into a responding group that may benefit from high-risk, technically difficult surgery and a nonresponding group that cannot and should not be subjected to this type of surgery.

Patients with borderline resectable pancreas cancer should be studied separately from those with resectable and

clearly unresectable disease. In the largest report of patients with borderline respectable disease published to date, the M.D. Anderson Group described three types of borderline patients: Type A—borderline resectable by objective anatomic criteria, Type B—borderline resectable because of findings suggestive but not diagnostic of metastatic disease, and Type C—borderline operable because of marginal performance status or extensive comorbidity. A total of 160 patients (84 Type A, 44 Type B, and 32 Type C) were classified as borderline resectable and were treated with a program of induction chemotherapy, chemoradiation, or both. Patients of sufficient performance status who completed preoperative therapy without disease progression were considered for surgery. There were 125 patients (78%) who completed preoperative therapy and restaging and 66 (41%) who underwent pancreatectomy. Median survival was 40 months for the 66 borderline patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy ($P < 0.001$).[27] This neoadjuvant approach allowed for identification of the significant subset of borderline patients that was most likely to benefit from resection as evidenced by the favorable median survival in this group.

Consensus Statement

1. To facilitate comparison of future clinical trials, a standard definition of borderline resectable pancreas cancer that uses objective CT criteria should be adopted.
2. Patients with borderline resectable pancreas cancer should be studied separately from those whose tumors meet objective CT criteria for resectability or unresectability.
3. Patients with borderline resectable pancreas cancer should be treated with neoadjuvant therapy, ideally in the context of a clinical trial.

ISSUES FOR CONSIDERATION IN THE DESIGN OF CLINICAL TRIALS

Outcomes in pancreas cancer are influenced by myriad nontherapeutic variables including surgical experience, margin status, tumor differentiation, and extent of lymph node involvement. Furthermore, there is emerging evidence that postoperative CA 19-9 levels have prognostic significance.[19] Unfortunately, these variables have not been adequately considered in trial design and execution. Moreover, recent data from the RTOG suggest that the extent to which defined radiotherapy guidelines are followed successfully may also be a predictor of outcome in trials incorporating radiotherapy.[20]

The factors that need to be considered in the design, execution, and analysis of future trials include limiting enrollment to patients with pancreatic adenocarcinoma and excluding nonpancreatic, periampullary adenocarcinomas; tumor size; margin status (especially the SMA margin); extent of tumor differentiation; presence and extent of peripancreatic lymph node involvement; CA19-9 levels; and the experience of the surgeon and institution in which the surgical management occurs. The role of radiotherapy as a component of adjuvant therapy should be further investigated with separate arms randomizing patients to regimens with and without radiation treatment. However, such trials need to emphasize facility certification and qualifying criteria for cooperative group participation; detailed, specific treatment planning and administration guidelines; and reducing the tissue volume irradiated through the use of CT-based simulation to account for the increased radiosensitization and risk of gastrointestinal toxicity especially with gemcitabine-based regimens. Chemotherapy should also be given in a standardized way, including detailed approaches to toxicity management.

The ideal adjuvant treatment trial for patients with localized pancreatic cancer should include these considerations along with: (1) state-of-the-art pretreatment staging and mandate radiographic criteria to define resectability, (2) standardized, quality-controlled surgery and pathology, and (3) restaging CT scans done prior to and during adjuvant treatment. Postoperative CA19-9 determinations could be used to exclude patients with persistent elevations, or alternatively, stratify patients (normal versus elevated) at the time of protocol entry.

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