Current Status of Adjuvant Therapy for Pancreatic Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the rationale for the use of adjuvant and neoadjuvant chemoradiation and/or chemotherapy in the treatment of patients with potentially resectable pancreatic cancer.
2. Describe the limitations of prior prospective, randomized trials of adjuvant therapy strategies and the clinical implications of these limitations.
3. Compare modern strategies for the multidisciplinary management of potentially resectable and borderline resectable pancreatic cancer.

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ABSTRACT

In this article, we review the rationale for and outcomes associated with the use of adjuvant and neoadjuvant therapy for resectable and borderline resectable cancer

of the pancreatic head and uncinate process. Localized pancreatic cancer is a systemic disease that requires nonoperative therapies to minimize the local and sys-

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temic recurrences that almost invariably occur in the absence of such therapy, even following complete surgical resection. A well-defined role exists for the systemic administration of gemcitabine or 5-fluorouracil in the postoperative setting. Although the survival benefit associated with adjuvant chemoradiation has not been as rigorously defined, its use is supported by extensive historic experience; chemoradiation should be considered particularly for patients at high risk for local recurrence. Delivery of chemotherapy and/or chemoradiation prior to surgery has multiple potential advantages, although the superiority of neoadju-

vant therapy over standard postoperative therapy has yet to be demonstrated. Neoadjuvant therapy may be particularly beneficial among patients with borderline resectable cancers. Although the existing literature is confusing, and indeed controversial, available evidence suggests that systemic chemotherapy and/or chemoradiation should be offered to all patients with pancreatic cancer who undergo potentially curative resection. Well-designed prospective trials are needed to define the optimal adjuvant or neoadjuvant therapy strategy for these patients. *The Oncologist* 2010;15:1205–1213

INTRODUCTION

For patients with potentially resectable adenocarcinoma of the pancreatic head and uncinate process (PC), surgical resection of the primary tumor and regional lymph nodes has long been characterized as the only potentially curative therapy. However, with surgery alone, the median overall survival time is only 11–20 months as a result of high rates of local and distant cancer recurrence [1–4]. Thus, although surgery is necessary for the long-term survival of patients with localized PC, it is clearly insufficient. For patients with potentially resectable PC, research has therefore increasingly focused on multidisciplinary strategies, which have provided 5-year actual overall survival rates as high as 27% in major PC treatment centers [5, 6]. Nevertheless, almost all patients—including those who undergo macroscopically and microscopically complete (R0) resection and have negative lymph nodes—develop postoperative recurrence as late as 7 years after diagnosis [5]. These data support the concept that “localized” PC is in fact a systemic disease and underscore the need to develop more effective adjuvant therapy strategies that inhibit both locoregional and distant failure. In this article, we review the use of adjuvant therapy for patients with potentially resectable PC.

ADJUVANT CHEMORADIATION FOR RESECTABLE PC

Although controversial, the postoperative administration of combined chemotherapy and radiation (chemoradiation) for patients with resectable PC is supported both by local recurrence rates as high as 60% without such therapy and by the proven efficacy of adjuvant chemoradiation against other malignancies at significant risk for locoregional recurrence [7, 8].

Three major randomized trials have compared the overall survival of patients with resectable PC who received postoperative chemoradiation with that of patients who did

not. In the first, the Gastrointestinal Tumor Study Group randomized 43 patients to receive 5-fluorouracil (5-FU)-based chemoradiation followed by maintenance 5-FU or observation following resection [1]. Although the trial was prematurely terminated because of low patient accrual, it demonstrated a statistically significant difference in median overall survival between the two treatment arms (21 months versus 11 months; $p = .03$).

A subsequent trial conducted by the European Organisation for Research and Treatment of Cancer (40891) randomized 218 patients with periampullary cancers (114 with pancreatic head cancers) to receive bolus 5-FU-based chemoradiation or observation after resection [2]. Patients with cancers of the pancreatic head who received chemoradiation had a longer median overall survival time (17.1 months, versus 12.6 months in the observation arm), but the difference was not statistically significant ($p = .09$). Long-term follow-up of these patients confirmed the absence of a significant difference in overall survival between the two groups [4].

The third trial, by the European Study Group for Pancreatic Cancer (ESPAC-1), enrolled 541 patients with resected PC [9, 10] into a complicated trial design comparing postoperative observation, chemoradiation, chemotherapy, and chemoradiation followed by chemotherapy. The initial analysis revealed a significant survival benefit from chemotherapy versus no chemotherapy (median overall survival time, 19.7 months versus 14 months; $p = .0005$), but not from chemoradiation (median overall survival time, 15.5 months versus 16.1 months; $p = .24$) [9]. Moreover, data from a follow-up analysis suggested that chemoradiation might actually be detrimental: patients who received chemoradiation had a median overall survival duration of only 15.9 months, versus 17.9 months in the group who did not ($p = .05$) [10].

The confusing and inconsistent results of the published randomized trials do not provide clear evidence to

Table 1. Published randomized trials of adjuvant chemoradiation and/or chemotherapy after resection of pancreatic cancer

Trial	Year	n	Treatment arm	Control arm	Median OS, mos (treatment versus control)	p
GITSG [1]	1985	43	5-FU–based chemoradiation followed by maintenance 5-FU	Observation	21.0 versus 10.9	.03
EORTC [2, 4] ^a	1999	114	5-FU–based chemoradiation	Observation	17.1 versus 12.6	.09
ESPAC-1 [9, 10]	2001	541	Chemotherapy	No chemotherapy	19.7 versus 14.0	.0005
			Chemoradiation	No chemoradiation	15.5 versus 16.1	.24
ESPAC-1 [9, 10]	2004	289	Chemotherapy	No chemotherapy	20.1 versus 15.5	<.01
			Chemoradiation	No chemoradiation	15.9 versus 17.9	.05
CONKO-001 [3, 16] ^b	2008	368	Gemcitabine	Observation	22.8 versus 20.2	.005
RTOG 97–04 [17] ^c	2008	388	Gemcitabine, 5-FU–based chemoradiation, gemcitabine	5-FU, 5-FU–based chemoradiation, 5-FU	20.5 versus 16.9	.05
ESPAC-3 [18]	2009	1,088	Gemcitabine	5-FU	23.6 versus 23.0	.39

^a218 patients total; 114 with pancreatic head cancers.

^bResults from 2008 update presented in abstract form.

^cPatients with pancreatic head cancers.

Abbreviations: 5-FU, 5-fluorouracil; CONKO, Charité Onkologie; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumor Study Group; OS, overall survival; RTOG, Radiation Therapy Oncology Group.

support the use of chemoradiation as adjuvant therapy after PC resection. Criticisms of these trials, however, have led to considerable controversy in this regard [11]. Furthermore, a large, primarily American experience attests to the potential therapeutic benefit of adjuvant chemoradiation [12–14], but recent evidence suggests that this benefit may be greatest in subpopulations of patients at high risk for local failure, such as those with involved lymph nodes [15]. Given the toxicity of chemoradiation and the considerable investment of time and expense it requires, further well-designed clinical studies are essential to elucidate the subgroups of patients with resectable PC who will benefit most from adjuvant chemoradiation.

ADJUVANT CHEMOTHERAPY FOR RESECTABLE PC

The high distant recurrence rates among patients with resected PC and data from the ESPAC-1 trial have stimulated study of adjuvant systemic chemotherapy. Among the relatively recent studies of adjuvant chemotherapy is the CONKO-001 (Charité Onkologie) trial, which randomized 368 patients with resectable PC and serum carcinoembryonic antigen and cancer antigen (CA) 19–9 levels $<2.5\times$ the upper limits of normal to receive adjuvant systemic gemcitabine or observation after resection. The initial analysis of that study showed a statistically significant difference in the median disease-free survival interval between the gemcitabine arm and the observa-

tion arm (13.4 months versus 6.9 months; $p < .001$) [3]. Furthermore, final results of the study, reported at the 2008 American Society of Clinical Oncology annual meeting, also demonstrated a significantly longer median overall survival time with gemcitabine (22.8 months versus 20.2 months; $p = .005$), and the 5-year overall survival rate was 21% for patients who received gemcitabine, versus 9% for patients who were observed [16].

Two modern studies compared systemic gemcitabine and 5-FU after PC resection. The recently reported Radiation Therapy Oncology Group (RTOG) 97–04 study compared systemic gemcitabine with 5-FU given before and after 5-FU–based chemoradiation in 388 patients with resected pancreatic head tumors [17]. The median overall survival time for the subset of patients who received gemcitabine before and after chemoradiation was 20.5 months; that of patients who received 5-FU before and after chemoradiation was 16.9 months—a difference significant on multivariate ($p = .05$) but not univariate ($p = .09$) analysis.

In the ESPAC-3 trial [18], 1,088 patients were randomized following resection to receive 6 months of infusional gemcitabine or bolus 5-FU plus folinic acid. The median overall survival time of patients treated with gemcitabine did not differ from that of patients treated with 5-FU (23.6 months versus 23.0 months; $p = .39$).

Table 2. Trials of neoadjuvant chemoradiation regimens in patients with potentially resectable pancreatic adenocarcinoma conducted by The University of Texas MD Anderson Cancer Center

Characteristic	5-FU/50.4 Gy [30]	5-FU/30 Gy [31]	Paclitaxel/30 Gy [32]	Gem/30 Gy [33]	Gem/Cis followed by Gem/30 Gy [34]
Patients, <i>n</i>	28	35	37	86	90
Overall survival, mos	NA	NA	12	23	17
Completed all treatment including PD, <i>n</i> (%)	17 (61)	20 (57)	20 (54)	64 (74)	52 (58)
SMA margin positive, <i>n</i> (%)	3 (18)	2 (10)	6/19 (32)	4 (6)	1 (2)
Median overall survival of patients who completed all treatment, mos	NA	25	19	34	31
Median survival of patients who did not complete all treatment, mos	NA	7	10	7.1	10.5
Local recurrence, <i>n</i> (%) ^a	NA	1 (5)	0	7 (11)	13 (25)
Isolated local recurrence, <i>n</i> (%) ^a	NA	1 (5)	0	2 (3)	3 (6)

^aOf patients who completed all therapy, including PD.

Abbreviations: 5-FU, 5-fluorouracil; Cis, cisplatin; Gem, gemcitabine; NA, not applicable; PD, pancreaticoduodenectomy; SMA, superior mesenteric artery.

Modified from 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;26:3487–3495.

CURRENT RECOMMENDATIONS FOR ADJUVANT THERAPY FOR RESECTABLE PC

Although inconsistent, the results of the prospective, randomized studies surveyed above suggest a benefit from the use of adjuvant therapy after resection in patients with resectable PC (Table 1). Nonetheless, further study is needed to elucidate the optimum adjuvant therapy approach. Reflecting current ambiguity, the National Comprehensive Cancer Network (NCCN) guidelines recommend either systemic gemcitabine chemotherapy followed by 5-FU–based chemoradiation (45–54 Gy) or systemic chemotherapy alone with gemcitabine, 5-FU, or capecitabine after potentially curative resection in patients with resectable PC [19]. Furthermore, a recent consensus statement acknowledged that chemoradiation remains controversial but recommended its use as part of a multimodality regimen including systemic chemotherapy, particularly for patients in whom the likelihood of local recurrence is substantial [20]. To help to clearly establish the role of chemoradiation in this context, the RTOG recently opened RTOG 0848, a large, phase III trial in which the outcome of patients with resected PC randomized to receive six cycles of adjuvant gemcitabine-based chemotherapy will be compared with that of patients randomized to receive five cycles of gemcitabine-based chemotherapy followed by 5-FU–based chemoradiation [unpublished protocol].

Regardless of which adjuvant therapy is used, its administration should be immediately preceded by a complete restaging evaluation to ensure the absence of residual cancer and to exclude the possibility of early

disease progression. Although the optimum interval between surgery and initiation of adjuvant therapy is unknown, we generally recommend that treatment begin within 8 weeks of resection. Although up to one third of patients who undergo surgery with the intent of receiving postoperative adjuvant therapy have historically had their adjuvant therapy delayed or failed to receive it entirely, a delay in the recovery of performance status necessitating postponement of adjuvant therapy should be rare in patients with an initially acceptable performance status who undergo a nonemergent operation [1, 2, 21].

NEOADJUVANT THERAPY FOR RESECTABLE PC

Although NCCN guidelines currently recommend the administration of postoperative adjuvant therapy to all patients with resectable PC except those who are being treated as part of a clinical trial [19], evidence is accumulating to support the administration of chemotherapy and/or chemoradiation in the preoperative period. Preoperative adjuvant (neoadjuvant) therapy has several potential advantages [22]. Preoperative therapy allows for the delivery of chemotherapy and/or ionizing radiation to an intact, well-vascularized primary tumor; provides early treatment of micrometastatic disease; provides a time interval within which to identify patients with unfavorable (i.e., highly aggressive) tumor biology in whom surgery would not be of benefit; and facilitates the evaluation of biomarkers and surrogate measures of treatment response that may be exploited in the postoperative period. The use of preoperative chemoradiation may also reduce the risk for pancreatic leak

Table 3. The University of Texas MD Anderson Cancer Center (MDACC) classification of borderline resectable pancreatic cancer

MDACC type	Definition of borderline type	Radiographic and clinical criteria
A	Anatomically borderline resectable	Absence of extrapancreatic disease and one or more of the following on high-resolution CT: 1) Tumor abutment of the superior mesenteric artery or celiac axis 2) Tumor abutment or encasement of a short segment of the common hepatic artery 3) Short-segment occlusion of the SMV, PV, or SMV-PV confluence amenable to vascular resection and reconstruction
B	Possible extrapancreatic disease	One or more of the following: 1) CT findings suspicious for, but not diagnostic of, metastatic disease 2) N1 disease verified by prereferral laparotomy or EUS-guided FNA
C	Pre-existing comorbidity or reversible depression in performance status	One or more of the following: 1) Marginal, but reversible performance status 2) Insufficiently evaluated medical comorbidity felt to preclude immediate surgery

Abbreviations: Abutment, tumor involvement of $\leq 180^\circ$ of the vessel circumference; encasement, tumor involvement of $> 180^\circ$ of the vessel circumference; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; N1, node positive; PV, portal vein; SMV, superior mesenteric vein.

after pancreatic reconstruction [23]. Furthermore, preoperative administration of cytotoxic therapy has been associated with high rates of tumor fibrosis and low rates of involved surgical margins at resection [24–27]. In fact, the high rate of negative-margin (R0) resections may be one factor contributing to the low rates of local recurrence ($<10\%$) reported following neoadjuvant chemoradiation and surgery [28, 29].

The University of Texas MD Anderson Cancer Center evaluated neoadjuvant chemoradiation strategies for resectable PC in a series of nonrandomized phase II trials (Table 2) [30–34]. The 276 patients enrolled in these trials met identical eligibility criteria, which included objective, computed tomography (CT)-based determination of resectability and histologic confirmation of PC, and the patients underwent resection (when appropriate) with a uniform surgical technique. In addition, all pancreaticoduodenectomy specimens were analyzed using a standardized system. Median overall survival durations as long as 34 months were observed among the 54%–74% of enrolled patients who completed all therapy, including surgery; in contrast, patients who did not complete treatment had median overall survival times of only 7–11 months. Similarly favorable results have been reported in other single-center [24, 35, 36] and multicenter [37–39] studies of neoadjuvant chemoradiation for resectable PC, as well as in a recent review of the Surveillance, Epidemiology, and End Results database [40].

Critics of preoperative therapy for patients with resect-

able PC cite the poor cytotoxic efficacy of existing agents against PC and contrast this with the relatively favorable treatment response elicited by nonsurgical therapies against other cancers for which neoadjuvant therapy is favored, such as those of the breast and rectum. These critics express concern that neoadjuvant treatment with the relatively ineffective agents available today may allow local primary tumor growth sufficient to convert resectable into unresectable cancers. Indeed, approximately 30% of patients enrolled in preoperative therapy trials develop disease progression during treatment that precludes surgery. However, such progression typically occurs at distant sites; isolated local progression during neoadjuvant therapy rarely leads to unresectability [33, 36]. Thus, it seems likely that disease progression during neoadjuvant therapy is most often a result of micrometastases that were present at the time of diagnosis and would have likely led to early recurrence regardless of whether aggressive local surgery had been the initial treatment. Nonetheless, the optimal length of treatment required to maximize the cytotoxic and selective effects of preoperative therapy is as yet unknown.

NEOADJUVANT THERAPY FOR BORDERLINE RESECTABLE PC

Recently, a subset of patients with American Joint Committee on Cancer (AJCC) stage III, locally advanced PC have been recognized to have “borderline resectable” disease [41–43]. This substage of PC has not been defined by the

AJCC, and controversy continues regarding the definition and treatment of patients with this clinical substage.

Regardless of how the substage is anatomically defined, patients with borderline resectable PC are those at particularly high risk for undergoing resection with microscopically positive margins (R1). According to the NCCN, borderline resectable tumors are those that cause severe unilateral superior mesenteric vein–portal vein impingement, abut the superior mesenteric artery, abut or encase the hepatic artery, or occlude the superior mesenteric vein but with unoccluded superior mesenteric vein segments proximally and distally sufficient to allow reconstruction [19]. A similar definition was proposed by the American Hepatopancreaticobiliary Association [41]. These definitions were based largely on work from the MD Anderson Cancer Center that established an anatomic classification of borderline resectable disease based on rigorous CT criteria [42, 43].

Recognizing the profound influence on clinical staging of pretreatment performance status and the limitations of CT in fully characterizing subcentimeter lesions, the M. D. Anderson classification system for borderline resectable disease broadly categorizes patients into three types [42]: type A, patients with borderline resectable local tumor anatomy as previously described [43]; type B, patients with findings on initial staging suspicious for but not diagnostic of extrapancreatic disease; and type C, patients with a marginal performance status who have the potential for improvement and patients with extensive comorbidities that require a prolonged evaluation that precludes immediate major abdominal surgery (Table 3). Whereas patients with extensive arterial involvement, definite metastatic disease, or a poor performance status that is not expected to improve would not benefit from resection, patients with types A, B, and C borderline resectable PC may all have a relatively favorable outcome when a multidisciplinary approach that includes surgery is used.

The ideal multidisciplinary treatment strategy for patients with borderline resectable PC is evolving. Currently, these patients are often treated by exploiting the theoretic advantages of neoadjuvant therapy over a prolonged period. In the largest series of borderline resectable PC patients reported to date, patients were typically treated first with systemic therapy followed by consolidating chemoradiation and finally surgery [42]. Restaging prior to the initiation of each therapeutic modality selected patients for the subsequent modality; only patients with an acceptable performance status and no evidence of disease progression after the entire 4- to 6-month course of neoadjuvant therapy ultimately underwent resection. Among the 160 patients who began treatment, 41% of patients completed all therapy, including surgery; 56% of resected specimens exhib-

ited a level of tumor necrosis consistent with a >50% pathologic response to neoadjuvant therapy; and 94% of resections resulted in microscopically negative (R0) margins. The group who underwent resection had a median overall survival time of 40 months; the median overall survival time was 13 months among the 59% of patients who were not selected for surgery because of disease progression or an irreversible decline in performance status during neoadjuvant therapy ($p = .001$).

Prospective studies of patients with borderline resectable PC are essential to elucidate the optimum treatment algorithm. Of course, such studies will be meaningful only once a uniform definition of this substage of disease has become well accepted.

NOVEL BIOLOGIC AND TARGETED AGENTS

In an effort to improve upon the modest results observed with systemic cytotoxic chemotherapy alone, new biologic agents have been evaluated against PC in patients with advanced disease. In a recent phase III study, 569 patients with locally advanced or metastatic PC were randomly assigned to receive gemcitabine or gemcitabine plus the epidermal growth factor receptor inhibitor erlotinib. Treatment with gemcitabine plus erlotinib was associated with a significantly longer median overall survival time (6.2 months versus 5.9 months; $p = .038$) and progression-free survival interval (3.75 months versus 3.55 months; $p = .004$) than treatment with gemcitabine alone [44]. Treatment was well tolerated in both arms, although a higher rate of complications (typically grade 1 or 2 adverse effects) was observed in the gemcitabine plus erlotinib arm. Interestingly, patients who received erlotinib and developed a skin rash survived significantly longer than those who did not ($p = .037$).

Building on the findings with erlotinib, a recent phase III study added the vascular endothelial growth factor–targeted agent bevacizumab to gemcitabine and erlotinib in patients with metastatic PC; however, the three-agent combination did not significantly improve overall survival over that seen with gemcitabine and erlotinib alone [45]. Results of other phase III studies comparing gemcitabine alone with gemcitabine plus the biologic agents cetuximab [46], bevacizumab [47], axitinib [48], and marimastat [49] for metastatic PC have also been disappointing. It is possible that these targeted agents would have greater activity in the adjuvant therapy setting, when the disease burden is smaller. To this end, a phase II study of perioperative gemcitabine and erlotinib for patients with resectable PC has been activated by the American College of Surgeons Oncology Group [unpublished protocol], and the RTOG is exploring the efficacy of combination therapy

with gemcitabine and erlotinib as part of the RTOG 0848 trial [unpublished protocol].

LIMITATIONS OF ADJUVANT THERAPY TRIALS AND IMPLICATIONS FOR FUTURE STUDIES

Knowledge of the limitations of adjuvant and neoadjuvant therapy trials performed to date for patients with resectable PC is critical both to understand and compare the results of these trials and to improve the design of future clinical studies.

To provide clear data upon which clinical recommendations can be made and to facilitate comparisons between clinical trials, trials of adjuvant and neoadjuvant treatments for resectable PC must examine homogeneous patient populations. Accurate, objective disease staging is essential in achieving this goal [50]. Unfortunately, although a CT-based definition of “resectable” PC has been well established and accepted by the NCCN, none of the major trials previously reported relied on state-of-the-art imaging to objectively define resectability [19]. Moreover, patient stratification within trials based on cancer-associated prognostic factors such as tumor size or the presence of lymphatic involvement has been largely neglected. Although recent attempts have been made to improve the homogeneity of PC patient populations enrolled in adjuvant therapy trials by using tumor marker levels as an inclusion criterion [3], the effectiveness of levels of serum CA 19–9 in defining subgroups of patients with a similar stage of disease remains unclear. Indeed, recent evidence suggests that pretreatment serum biomarker levels have little role in the initial staging evaluation of PC patients who will be treated with a neoadjuvant therapy approach [51]. Future studies must therefore emphasize accurate staging with objective, CT-based criteria for resectability as approved by the NCCN, and such staging must be performed both before and after surgery or, in the case of neoadjuvant treatment sequencing, before and after neoadjuvant therapy [19].

The method of pathologic assessment of surgical margins in trials must also be standardized. Local failure rates as high as 60% in previously reported adjuvant therapy trials despite low rates of margin positivity suggest that a significant proportion of patients with “negative” surgical margins actually had positive margins that were incompletely or improperly evaluated. Many patients reported to have received “adjuvant” therapy therefore very likely actually received palliative postoperative therapy for persistent disease. To prevent the inclusion of similar patients in future adjuvant therapy trials, the strict margin assessment protocol described by the AJCC must be used [50, 52].

Similarly, standardization of the PC resection method with strict quality control must be emphasized in future trials, particularly with regard to the technique of the oncologically important retroperitoneal dissection. All these important issues are currently under close scrutiny by the American College of Surgeons Oncology Group [52].

CONCLUSION

Although the existing literature is difficult to interpret, available evidence suggests that systemic chemotherapy and/or chemoradiation should be used in all patients with potentially resectable PC who undergo pancreatic resection. Well-designed prospective trials are necessary to define the optimal adjuvant or neoadjuvant therapy strategy for these patients.

AUTHOR CONTRIBUTIONS

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Provision of study material or patients: Peter W.T. Pisters

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