

# Adjuvant Therapy for Adenocarcinoma of the Pancreas: Analysis of Reported Trials and Recommendations for Future Progress

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The delivery of postoperative combined modality adjuvant therapy for completely resected pancreatic cancer was initially shown to be beneficial on the basis of a prospective, randomized trial published in 1985. Since then, oncologists have debated whether chemotherapy, chemoradiation, or both is optimal adjuvant therapy after pancreatectomy for ductal adenocarcinoma of the pancreas; no global consensus has emerged. Unfortunately, despite the completion of a number of subsequent randomized trials of adjuvant therapy since 1985, no further improvements in overall survival have materialized. This lack of progress is not simply the result of ineffective systemic therapies, but in part the result of poor trial design and calls for a more disciplined approach to the selection of patients for surgery, pathologic assessment of surgical resection margins, and postoperative (pretreatment) imaging. This is the only way to ensure that patients who receive adjuvant therapy are actually receiving therapy for radiographically occult possible microscopic disease, rather than therapy for incompletely resected locally advanced disease or early postoperative metastases. A critical analysis of completed adjuvant trials will be provided and a framework for the conduct of future trials of adjuvant therapy proposed.

**Key Words:** Pancreatic adenocarcinoma—Adjuvant therapy—Clinical trials—Chemotherapy—Radiation.

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In 1985, the Gastrointestinal Tumor Study Group first reported on the merits of adjuvant therapy after resection of pancreatic cancer.<sup>1</sup> However, since then, despite advances in surgical technique, chemotherapy, and radiation, no further improvements in survival have been observed among patients who received potentially curative surgery for localized disease. Unfortunately, a recent global debate on the relative contributions of radiotherapy and chemotherapy to adjuvant therapy has distracted the

oncology community from the fundamental problem: many patients who have undergone pancreatic resection are left with gross residual disease and therefore do not receive adjuvant therapy as properly defined. The “adjuvant” therapy they receive after surgery is actually serving as treatment for incompletely resected locally advanced disease. In addition, in the absence of a postoperative restaging evaluation (before the delivery of adjuvant therapy), some patients will have early distant metastases that go undetected. Most troubling, oncologists who investigate or deliver adjuvant therapy have failed to reach a consensus on standards for preoperative imaging, surgical technique for tumor resection, pathologic analysis of resection margins, and the need for post-

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operative restaging evaluation before initiation of adjuvant therapy.

This article provides a focused review of adjuvant therapy for pancreatic cancer highlighting prospective randomized trials and recent attempts to explore other strategies. A critical analysis of completed and ongoing studies is presented on the basis of the known value of high-quality computed tomography (CT) for predicting tumor resectability, the poor prognosis associated with margin-positive resections, and the frequency of early systemic relapse. The emerging recognition of borderline resectable pancreatic cancer is discussed, including the important distinction between resectable and borderline resectable tumors. Last, a strategy that is both multidisciplinary and disciplined is proposed as a means to improve the quality of adjuvant therapy and the survival of all patients with potentially resectable disease.

#### RATIONALE FOR ADJUVANT THERAPY FOR PANCREATIC CANCER

Before the advent of modern cross-sectional imaging, the anatomic relationship between a pancreatic cancer and the mesenteric vessels could not be defined preoperatively, and the surgeon estimated resectability intraoperatively by palpating the relationship of the tumor to these vessels after mobilizing the pancreatic head and duodenum (Kocher maneuver). If the tumor was thought to be grossly free of the superior mesenteric artery (SMA) on intraoperative assessment, the surgeon would usually proceed with pancreaticoduodenectomy (PD). Because the precise relationship of the tumor to the superior mesenteric vessels cannot be seen until the pancreas is divided and the surgeon is committed to resection (point of no return), if the assessment of resectability was incorrect, the patient may be left with gross tumor adjacent to the superior mesenteric vein (SMV), SMA, or celiac axis. Incomplete gross resection would predispose to local recurrence, and not surprisingly, results from clinical and autopsy series report local failure rates as high as 80% after PD.<sup>2-4</sup>

In cases where there has been a gross complete resection, the underlying molecular mechanisms responsible for the ability of pancreatic tumor cells to usurp normal tissue homeostasis and create a permissive environment for local recurrence and systemic relapse after surgery are largely unknown. In the absence of this knowledge, the two most commonly applied treatment modalities have been radiation to

prevent local failure, and cytotoxic chemotherapy to prevent or delay systemic relapse. This therapeutic rationale has proven benefit in the treatment of other gastrointestinal cancers such as rectal and gastric cancers.<sup>5-8</sup> In addition, in localized pancreatic cancer, retrospective nonrandomized studies from single institution experiences suggest that the use of combined modality therapy delivered either preoperatively or postoperatively can reduce local failure rates to approximately 25%.<sup>9-12</sup> However, even when local control is maintained after surgical resection, systemic failure predominates as the major cause of morbidity and mortality.<sup>13</sup> Improving systemic therapy for completely resected patients is a major focus of ongoing research efforts at university centers and large pharmaceutical companies.

#### ADJUVANT STUDIES USING 5-FLUOROURACIL-BASED THERAPIES

Before its use in the adjuvant setting, the delivery of 5-fluorouracil (5-FU) administered with external-beam radiotherapy (EBRT) to patients with locally advanced pancreatic cancer yielded superior results compared with EBRT alone and provided the impetus to investigate 5-FU-based chemoradiation as adjuvant therapy for resected pancreatic cancer.<sup>14</sup> Since that time, there have been several randomized and nonrandomized trials of adjuvant 5-FU-based chemoradiation.<sup>1,15-18</sup> The three prospective randomized trials most often cited were conducted by the Gastrointestinal Study Group (GITSG),<sup>1</sup> the European Organization for Research and Treatment of Cancer (EORTC),<sup>15,18</sup> and the European Study Group for Pancreatic Cancer (ESPAC).<sup>16</sup>

The first of these trials was conducted by the GITSG, and the results were published in 1985. Patients with completely resected pancreatic cancer, as defined by microscopically negative margins (R0 resection), were randomized to undergo observation or to receive bolus 5-FU (500 mg/m<sup>2</sup> daily) during the first 3 days of each period of split course EBRT (20 Gy in 10 fractions, 2-week break, and resumption of radiation to a total dose of 40 Gy), followed by up to 2 years of weekly bolus 5-FU. The study was designed to enroll a minimum of 100 patients, but an early analysis performed after only 43 patients had completed treatment demonstrated that the overall survival advantage for patients receiving combined modality therapy was so great compared with patients who underwent surgery alone (median 21.0 months vs. 10.9 months, respectively,  $P = .03$ )

that the investigators considered it unethical to continue enrollment.

In contrast were the findings from a subsequent EORTC trial.<sup>15,18</sup> In a prospective, randomized study (EORTC-40891) that enrolled 218 patients from 1987 to 1995, patients with curatively resected cancers of the head of the pancreas or periampullary region (defined as tumors of the distal common bile duct, papilla of Vater, or duodenum) were randomized to undergo observation or to receive infusional 5-FU (25 mg/kg/d to a maximum dose of 1500 mg/d) provided concurrently during the first week of two split courses of EBRT (total dose 40 Gy).<sup>15</sup> A subgroup analysis of the 114 patients with cancer of the pancreatic head showed a trend toward improved overall survival for those who received adjuvant therapy compared with those in the observation group (median 17.1 months vs. 12.6 months, respectively), but the difference was not statistically significant ( $P = .099$ ), and when the long-term follow-up results were reported, the median survivals were 1.3 years and 1.0 years, respectively.<sup>18</sup> The authors concluded that postoperative chemoradiation provided no benefit for patients with resected pancreatic cancer.

The ESPAC launched a more robust effort to determine the contributions of chemotherapy and chemoradiation to patient survival after surgery for pancreatic cancer.<sup>16</sup> ESPAC-1 enrolled 289 patients from 53 hospitals across Europe. After pancreatic resection, patients were randomized to one of four arms: observation; chemotherapy with bolus 5-FU (425 mg/m<sup>2</sup>) and leucovorin (20 mg/m<sup>2</sup>) both provided daily for 5 days every 28 days for 6 months; chemoradiation with bolus 5-FU, 500 mg/m<sup>2</sup>, provided during the first 3 days of split-course EBRT (as in the GITSG trial); or chemoradiation followed by 6 months of chemotherapy with bolus 5-FU and leucovorin. Importantly, the study analyzed the survival outcomes using a 2 × 2 factorial design, pooling survival data on the basis of randomization to chemotherapy (yes or no), or chemoradiation (yes or no). When overall survival durations of the four arms were compared, there was no statistically significant survival difference among them. However, when the results were pooled using the 2 × 2 factorial design, patients who received chemoradiation did worse (median survival of 15.9 months; hazard ratio for death 1.28; 95% confidence interval [95% CI], .99–1.66) than those not receiving chemoradiation (median survival of 17.9 months,  $P = .05$ ). Conversely, patients who received chemotherapy had a median survival of 20.6 months (hazard ratio for death .71; 95% CI, .55–.92) versus 15.5 months for those who

did not receive chemotherapy, a statistically significant result ( $P = .009$ ). The investigators concluded that adjuvant chemotherapy improved survival, and that chemoradiation not only failed to benefit patients, but also reduced survival when provided before chemotherapy.

## GEMCITABINE-BASED ADJUVANT THERAPY

Because gemcitabine is modestly superior to bolus 5-FU for the treatment of advanced pancreatic cancer, its integration into adjuvant therapy trials for patients with resected disease was a logical next step. Two large studies have recently been completed. One evaluated gemcitabine as systemic therapy alone; the other investigated gemcitabine as a component of adjuvant therapy that also included 5-FU-based chemoradiation.

Oettle and colleagues<sup>19</sup> from Charite Onkologie (CONKO) have recently published results from CONKO-001. The objective of this trial was to determine whether gemcitabine prolonged disease-free survival (DFS) after pancreatectomy with curative intent compared with observation alone. Eligibility criteria were somewhat more stringent compared with prior adjuvant trials. Patients were required to have levels of carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) less than 2.5 times the upper limit of normal. In their trial, 368 patients who underwent a complete resection for pancreatic adenocarcinoma were randomly assigned to undergo observation, or to receive six cycles of standard-dose gemcitabine (1000 mg/m<sup>2</sup> over 30 minutes) on days 1, 8, and 15 every 28 days. Patients randomized to receive gemcitabine had a median DFS of 13.9 months (95% CI, 11.4–15.3), and those who underwent surgery alone had a median DFS of only 6.9 months (95% CI, 6.1–7.8,  $P < .001$ ). Importantly, there was no statistically significant difference in overall survival between those assigned to receive adjuvant gemcitabine and those assigned to observation (median 22.1 months vs. 20.2 months, respectively,  $P = .06$ ), but there were differences in estimated 3-year and 5-year survival rates. The authors reported that almost all patients in the observation arm received gemcitabine at relapse, perhaps explaining the lack of overall survival advantage for adjuvant gemcitabine.

The Radiation Therapy Oncology Group (RTOG) has performed a prospective randomized trial (RTOG 9704) comparing gemcitabine with infusional 5-FU as the systemic component of therapy with all

patients also receiving 5-FU–based chemoradiation.<sup>20</sup> The eligibility criteria allowed for the enrollment of patients with resected adenocarcinoma of the pancreatic head, body, or tail. A total of 538 patients were enrolled onto the study, with most patients having tumors of the pancreatic head. Eighty-seven patients (16%) were ineligible, and of the remaining 451 patients, 230 were randomly assigned to 5-FU and 221 to gemcitabine. There was no difference in overall survival for all patients in the two groups. For patients with pancreatic head tumors ( $n = 388$ ), the addition of gemcitabine to adjuvant 5-FU–based chemoradiation was associated with a survival benefit that approached statistical significance after adjusting for protocol-specified stratification variables (20.5 months vs. 16.9 months,  $P = .05$ ).

### CRITICAL ANALYSIS OF LARGE RANDOMIZED ADJUVANT TRIALS

Others have already described apparent flaws in the design and conduct of some of the completed adjuvant therapy trials.<sup>21–23</sup> Most of these concerns relate to sample size, methodology, and to a lesser degree statistical analysis. For example, the very small sample size of the initial GITSG trial (49 enrolled patients with 43 actually treated) has been considered to be insufficient to endorse chemoradiation as the standard of care for adjuvant therapy. Importantly, the investigators originally planned to enroll 100 patients, but the doubling of survival with the use of adjuvant therapy led to early closure of the trial. In an effort to increase confidence in their results, the researchers registered 32 additional patients (2 of whom were deemed ineligible on the basis of positive resection margins) who were subsequently treated with the same postoperative adjuvant chemoradiation regimen.<sup>24</sup> The median overall survival of these 30 patients was 18 months, similar to that reported in the experimental arm of the GITSG trial.

EORTC 40891 has also been criticized predominantly on the basis of sample size. Of the 218 patients enrolled in the trial, 110 were randomized to adjuvant chemoradiation and 108 to observation, 11 were deemed ineligible, reducing the sample sizes to 104 in the treatment arm and 103 in the observation arm.<sup>15,18</sup> Of the 104 patients in the treatment arm, 10 refused therapy, 11 could not receive treatment after randomization, and 2 were found ineligible after pathology review, leaving 81 (74%) of the original 110 patients able to be evaluated. EBRT (40 Gy) was

received by 75 of the 81 patients, or 68% of the original 110. Of the 75 patients who received intended therapy, the number who had pancreatic cancer was not provided; 63 (57%) of the 110 patients initially randomized to the treatment arm had ductal adenocarcinoma of the pancreas. Therefore, if 57% of the 75 treated patients had pancreatic cancer, this would represent only 38 (34%) of the 110 patients randomized to the treatment arm. These relatively small numbers led to an initial result that seemed clinically significant (overall median survival, 17.1 months for chemoradiation vs. 12.6 months for observation), but this was not statistically significant and did not become so on longer-term follow-up ( $P = .165$ ).<sup>18</sup> Some researchers, however, noting similarities in survival between the GITSG trial and the EORTC study, suggested that EORTC 40891 was an underpowered positive trial and have argued that the results support the integration of chemoradiation into adjuvant therapy.<sup>25–27</sup>

Similarly, the results of the ESPAC-1 trial have come under some criticism, in particular for the lack of standardized trial methodology, the large number of patients who did not receive the intended therapy (46 [31%] of 147 randomized to receive chemotherapy and 28 [19%] of 145 randomized to receive chemoradiation), and the reported high rates of local failure.<sup>16,27</sup> The eligibility criteria allowed for enrollment of patients with positive surgical margins and used the R designation to describe the completeness of tumor resection. Surgical resections were described as being R0 if there was no gross or microscopic evidence of tumor at the surgical margins, R1, if there were microscopically positive margins, or R2 if there was a grossly positive surgical margin (tumor left in situ). In ESPAC-1, patients who underwent a pancreatic resection classified as R2 were excluded, and the proportion of patients who underwent an R1 resection was only 18%, a proportion lower than that reported for both EORTC 40891 (in which 21% of patients had positive margins) or RTOG 9704 (in which 33% to 35% of enrolled patients had a known positive margin). Although >80% of enrolled patients were reported to have undergone an R0 resection, among patients with a known recurrence, >60% had local recurrence as a component of failure. This very high rate of local recurrence implies a high rate of grossly incomplete (R2) resections and is inconsistent with the author's reported rates for R0 and R1 resections. These concerns are supported by the absence of protocol-defined criteria for local tumor resectability and a lack of surgery, pathology, and radiation quality control.

Another troubling result from ESPAC-1 involved the detrimental effect of chemoradiation in the adjuvant therapy setting, a stark contrast to the findings of the GITSG and EORTC studies as well as an analysis of prospectively collected data from the Johns Hopkins Medical Institutes (JHMI).<sup>17,28</sup> These other reports have not demonstrated chemoradiation as harmful.<sup>1,15,17,28</sup> The lack of quality control for radiation portals has been implicated as a possible explanation for the poor outcomes of ESPAC-1 patients assigned to chemoradiation. A central review of radiation dosimetry was not required, allowing for the possibility of poor quality control given the number of participating sites. This concern is not unreasonable when viewed in the context of the U.S. Intergroup trial of adjuvant therapy for resected gastric cancer. In that study, mandated central review of planned radiation portals led to modification of >30% of portals before initiation of therapy.<sup>7</sup>

The ESPAC-1 trial results were also notable for the outcome of the 72 patients who received chemoradiation and then received further chemotherapy; their overall survival as a group was not statistically significantly different from that of patients who received chemotherapy alone (median, 19.9 months vs. 21.6 months, respectively). This result seems to demonstrate that treatment with chemoradiation alone may be toxic (median survival for these patients was a dismal 13.9 months), but subsequent chemotherapy negates any deleterious effects of chemoradiation. There is no obvious explanation for these findings on the basis of current knowledge of combined modality therapy in oncology. Surprisingly, the ESPAC-1 results are often considered level I evidence for the benefit of bolus 5-FU and leucovorin as adjuvant therapy for patients with resected pancreatic cancer (and the lack of benefit of chemoradiation).

Results from the CONKO-001 trial are just beginning to be critically evaluated.<sup>19</sup> Importantly, the primary end point of this study was DFS, and the investigators designed the trial to determine whether gemcitabine as adjuvant therapy would prolong DFS by at least 6 months compared with surgery alone. Previous trials of adjuvant therapy have not used DFS as the primary endpoint, and although it was reasonable to assume that a 6-month prolongation of DFS would lead to improved overall survival for patients receiving adjuvant gemcitabine, an overall survival benefit was not observed. Of note, similar to the findings of ESPAC-1, local failure as a component of failure was common in CONKO-001, occurring in 35% of patients randomized to receive

gemcitabine and 41% of patients who underwent observation after surgery. Importantly, local failure was not defined, and abdominal follow-up was largely based on transabdominal ultrasound (repeated every 8 weeks) with one CT scan performed 6 months after study entry. Therefore, one would assume that local recurrence may have been underestimated.

Last, the recently reported results from RTOG 9704 also need close examination.<sup>20</sup> One concern with trial design is the lack of a chemotherapy-only treatment arm, yet randomization for and against EBRT may have negatively influenced accrual. Another criticism is with surgery and pathology quality control—namely, the apparent inability to confirm that all study patients underwent a gross complete resection. Surgical margin status was a stratification factor at the time of randomization, but margin status was unknown in approximately 25% of patients in each treatment arm as a result of the absence of margin assessment in the final pathology reports. The proportion of patients with documented positive resection margins was 33% for those randomized to infusional 5-FU and 35% for patients receiving gemcitabine. With >50% of patients enrolled in this trial having a positive margin or unknown margin status, assessment of the completeness of surgical resection was an obvious concern, specifically the number of patients who may have had a grossly incomplete resection (R2). However, CT imaging was required within 3 weeks of randomization to exclude those patients with persistent local or newly developed metastatic disease. Interestingly, only 17 (3%) of the 538 patients were listed as being ineligible because of incomplete or ineligible staging.

Thus, the three most recently completed trials, ESPAC-1, CONKO-001, and RTOG 9704, all seem to reflect problems with quality control—problems that resulted in an inability to determine the presence or absence of a gross complete resection at the time of surgery. There was no attempt in any study to review pretreatment imaging for the presence of a resectable tumor (which should have been objectively defined on the basis of CT), and central review of operative reports and pathology assessment of the resected specimen (when performed) failed to accurately differentiate R2 from R1 resections. In the RTOG 9704 study, resection margin status was unknown for approximately 25% of patients. Although RTOG 9704 required post-operative (pre-treatment) CT imaging, the absence of central review by experienced radiologists probably limited the value of this important aspect of trial design. These issues, when

**TABLE 1.** Overall survival data from completed randomized trials of adjuvant therapy for patients with resected pancreatic cancer

Study (year)	Number of patients	Treatment assignment	Median survival (months)	P value
GITSG <sup>1</sup> (1985)	49	Chemoradiation vs. Observation	21.0 vs. 10.9	.035
ESPAC-1 <sup>16</sup> (2004)	289	Chemotherapy vs. No chemotherapy	20 vs. 15.5	.009
		Chemoradiation vs. No chemoradiation	15.9 vs. 17.9	.05
EORTC <sup>18</sup> (2007)	120	Chemoradiation vs. Observation	15.6 vs. 12.0	.165
CONKO <sup>19</sup> (2007)	368	Gemcitabine vs. Observation	22.1 vs. 20.1	.06
RTOG <sup>20</sup> (2008)	380 <sup>a</sup>	Gemcitabine with 5-FU/EBRT vs. 5-FU with 5-FU/EBRT	20.5 vs. 16.9	.05

5-FU, 5-fluorouracil; EBRT, external-beam radiation.

<sup>a</sup> Head tumors.

taken together with the high local failure rates observed in ESPAC-1 and CONKO-001, lead to concern over the adequacy of patient selection for surgery, the failure of participating surgeons to document whether a gross complete resection was performed, and the system (or lack thereof) for determination of margin status on both sides of the Atlantic.

### MUCH CONTROVERSY, NO PROGRESS

Reviewing the available data from completed adjuvant therapy studies leads to the conclusion that some form of adjuvant therapy is probably better than no therapy, particularly because many of the study patients were likely receiving therapy for persistent local disease (incompletely resected locally advanced disease) or early metastatic disease that was not detected as a result of the absence of high-quality postoperative/pretreatment imaging or the accurate interpretation of such studies if performed. Moreover, if the results are reviewed objectively, no single postoperative approach can claim conclusive superiority to others. Currently, however, because of the results of the ESPAC-1 and the EORTC trials, including a meta-analysis of adjuvant therapy studies completed before 2006, many physicians worldwide do not support the role of radiation as a necessary component of adjuvant therapy.<sup>29</sup> Nevertheless, regardless of the biases of the investigators or readers, or the drawbacks of the trials conducted to date, it is clear from the survival data (GITSG to CONKO-001, Table 1) that no meaningful progress is being made in adjuvant therapy for patients with resected pancreatic cancer.

Nihilists may argue that until systemic therapy (to include molecular therapy and or immunotherapy) is greatly improved, no meaningful advances in survival can be expected for pancreatic cancer patients with

localized disease. This is debatable, but to date, the flaws in the design and conduct of clinical trials have prevented an accurate analysis of the potential benefit of adjuvant therapy (therapy for presumed microscopic local and/or metastatic disease). One can provide a more uniform framework in which to conduct clinical trials in adjuvant therapy by incorporating what is already known about preoperative imaging, surgical technique, assessment of surgical margins, tumor biology and the natural history of pancreatic cancer, and nonsurgical therapies. This is an obligation that the oncology community cannot ignore, and recognition of the challenges involved is a necessary first step.

### Positive Surgical Margins Are Frequent

There is a large body of evidence showing that incomplete surgical resection of the primary tumor leads to median survival durations comparable to those reported for patients with inoperable, locally advanced (stage III) disease treated with chemotherapy and radiation.<sup>17,30–35</sup> Even in academic centers around the world, recent data suggest that positive surgical margins occur frequently and portend poor survival (Table 2).<sup>28,30,34,35</sup> The frequency of positive surgical margins observed worldwide suggests that improvements are needed in patient selection (preoperative imaging), surgical technique, or both. Importantly, as a result of the failure of surgeons to document the presence or absence of a complete resection at the time of surgery and the inability of pathologists to differentiate a microscopically positive (R1) from a grossly positive (R2) margin of resection, many of the reported margin positive resections had gross tumor left in the pancreatic bed or root of mesentery. Although surgeon experience and surgical technique may be partly responsible for a grossly positive margin of resection, patient selection is possibly even more important. At present,

**TABLE 2.** Selected reports of margin positive resections and the overall median survival of patients with positive margins after surgical resection for pancreatic cancer

Study	Country	No. of patients	% Positive margin resections	Median survival (months)	Independent prognostic factor for survival
Winter et al. <sup>28</sup>	United States	1175	42	14	Yes
Richter et al. <sup>35</sup>	Germany	194	37	12	Yes
Kuhlmann et al. <sup>30</sup>	Netherlands	160	50	NS	Yes
Takai et al. <sup>34</sup>	Japan	89	47	8	Yes

NS, not stated.

resectability can be determined with great accuracy when dynamic-phase multidetector CT imaging or magnetic resonance imaging (MRI) is obtained before surgery.<sup>36–39</sup> None of the completed adjuvant trials required preoperative imaging to define a potentially resectable tumor by means of widely accepted objective imaging criteria.<sup>40</sup> Importantly, even when an operative report contains information regarding the completeness of resection, without adequate preoperative imaging, it represents a subjective, nonreproducible assessment. Assessment of preoperative imaging (the relationship of the tumor to adjacent vascular structures) can add an objective measure of tumor extent to the information reported from the time of surgery.

Surprisingly, the frequency of positive surgical margins among patients enrolled in adjuvant trials has varied considerably. In the ESPAC-1 trial, 18% of patients were reported to have had a positive surgical margin, 14% in CONKO-001, and 33% in the RTOG 9704 trial (in addition to the approximately 25% of patients for whom the margin status was unknown). Of note, none of these three trials incorporated a standardized pathologic evaluation of the PD specimen to ensure accurate assessment of the soft tissue margin adjacent to the SMA. Further, although the proportion of patients with positive surgical margins in both ESPAC-1 and CONKO-001 was low, the actual rate of positive margin resections must have been higher because local failure developed in 35% to 60% of patients.

Specific recommendations for the assessment of margins in surgical specimens, especially the SMA margin, also known as the retroperitoneal or uncinate margin, have been published by the American Joint Committee on Cancer (AJCC) in the AJCC Cancer Staging Manual (6th edition) and are present in guidelines of the College of American Pathologists (CAP).<sup>40,41</sup> If these recommendations were used consistently, margin positive rates would likely be higher than those previously reported. Nevertheless, on the bases of the data shown in Table 2 and the reported local failure rates from completed adjuvant trials, it

can be conservatively estimated that up to a third of patients who undergo surgery for pancreatic cancer may be left with a grossly positive margin of resection.<sup>28,30,34,35</sup> This subset of patients can be expected to have a median survival equivalent to patients with locally advanced, unresectable (stage III) pancreatic cancer. Therein lies the importance of accurate preoperative assessment of resectability, both for the conduct of clinical trials and for the proper management of patients with pancreatic cancer.

#### Metastatic Disease May Be Radiographically Apparent Within Weeks of Surgery

Although preoperative therapy for resectable pancreatic cancer has not been widely investigated, single-institution and cooperative group studies do provide some insight into the natural history of stage I/II pancreatic cancer relevant to the delivery of postoperative adjuvant therapy. Reported studies of preoperative (neoadjuvant) therapy in patients with radiographically resectable disease demonstrate that a subset of patients may develop radiographic evidence of metastatic disease at the time of posttreatment (preoperative) restaging. Table 3 illustrates data from the University of Texas M. D. Anderson Cancer Center, Duke University, and the Eastern Cooperative Oncology Group showing that 77 (18%) of 427 patients who underwent preoperative therapy had radiographic evidence of metastatic disease within 2 to 4 months of beginning preoperative treatment—metastatic disease that was not radiographically apparent at the time of study entry.<sup>42–48</sup> Of note, some of these patients underwent staging laparoscopy, or laparotomy with an unsuccessful attempt at tumor resection, before initiation of preoperative therapy and were considered to have been surgically staged. Translating the preoperative experience into the adjuvant setting would suggest that at least 15% of patients who receive up-front surgery will have evidence of overt metastatic disease in the early recovery period. This is probably an underestimate because the physiologic response to surgery (e.g.,

**TABLE 3.** Frequency of developing metastatic disease at the time of posttreatment (preoperative) restaging or at surgery in patients with potentially resectable pancreatic cancer treated with preoperative (neoadjuvant) therapy

Study	Year	Number of eligible patients	Duration of preoperative therapy (wk)	Approximate time from study entry to restaging/surgery (wk)	No. patients with metastatic disease at restaging/surgery (%)
Evans et al. <sup>42</sup>	1992	28	5.5	9–11	5 (18)
Pisters et al. <sup>43</sup>	1998	35	2	6–8	5 (14)
Hoffman et al. <sup>44</sup>	1998	53	5.5	9–11	6 (11)
White and Tyler <sup>45</sup>	2001	111	5–5.5	8–10	19 (20)
Pisters et al. <sup>46</sup>	2002	35	2	6–8	7 (20)
Evans et al. <sup>47</sup>	2008	86	6	10–12	17 (20)
Varadhachary et al. <sup>48</sup>	2008	79	12	16–18	18 (23)
Total		427			77 (18)

immunosuppression, cytokine and growth factor surge) may promote the growth of existing micrometastases. Therefore, when oncologists deliver adjuvant therapy to resected patients without obtaining postoperative/pre-treatment restaging studies, as is commonly practiced, the risk of treating metastatic disease is at least 15%. Only the RTOG trial required post-operative CT imaging prior to study entry.

#### Adjuvant Therapy Is Being Delivered to Heterogeneous Patient Populations

The third problem with adjuvant therapy trials is a result of the two issues discussed above: patients who undergo adjuvant therapy represent a heterogeneous population comprised of those with completely resected disease, others with persistent local disease, and some with metastatic disease. To describe post-operative therapy as adjuvant therapy is therefore incorrect for a substantial subset of operated patients, and it ignores the obvious deficiencies in clinical trial design that have been discussed. Unfortunately, efforts to improve trial design in pancreatic cancer have lagged behind other solid tumor sites.

#### ONGOING ADJUVANT TRIALS IN PANCREATIC CANCER

Current randomized trials of adjuvant therapy are continuing to test gemcitabine in the adjuvant setting. The ESPAC investigators, having dismissed radiation as a component of adjuvant therapy, are currently enrolling patients onto ESPAC-3, a multicenter trial with a planned accrual of 900 patients. ESPAC-3 randomizes patients after pancreatectomy and adequate recovery, to receive gemcitabine (1000 mg/m<sup>2</sup> over 30 minutes, weekly for 3 weeks, every 28 days) for 6 months, or bolus 5-FU and leucovorin (as administered in ESPAC-1) for 6 months.<sup>16</sup>

The EORTC continues to investigate the role of adjuvant chemoradiation in EORTC 40013. This is a phase II/III trial of gemcitabine followed by gemcitabine-based chemoradiation versus 6 months of systemic gemcitabine alone. Currently, there is limited experience with adjuvant gemcitabine-based chemoradiation after PD. In a phase II trial conducted by Blackstock and colleagues,<sup>49</sup> gemcitabine-based chemoradiation was delivered to 46 patients who had undergone a potentially curative pancreatic cancer resection. Gemcitabine was provided twice weekly at a dose of 40 mg/m<sup>2</sup> concurrently with EBRT to a total dose of 50.4 Gy provided over 5.5 weeks. Although toxicities were acceptable, median survival was only 18 months, unfortunately no better than that reported with 5-FU-based chemoradiation.

Other exploratory trials of adjuvant therapy are being conducted by the American College of Surgeons Oncology Group (ACoSOG) and researchers at JHMI. ACoSOG-Z05031 has been designed on the basis of encouraging results from a multiagent chemoradiation regimen originally described by investigators at Virginia Mason University.<sup>50</sup> The regimen consists of infusional 5-FU (200 mg/m<sup>2</sup>/d for 5 weeks), weekly cisplatin (30 mg/m<sup>2</sup>), and subcutaneous interferon alfa (3 million international units provided subcutaneously three times a week) combined with EBRT to a total dose of 50 Gy followed by two cycles of infusional 5-FU (200 mg/m<sup>2</sup>/d) on days 64 to 105 and 120 to 161. The original trial enrolled 43 patients over 7 years, with 84% of patients having node-positive tumors. Despite this high-risk population, the 3-year and 5-year survival rates were 64% and 55%, respectively, and at a mean follow-up of 32 months, median survival has not been reached. Although this regimen has been associated with marked toxicity, there were no treatment-related deaths. The ACoSOG trial has now enrolled 89 patients and is closed to accrual. Preliminary

**TABLE 4.** Eligibility criteria for an optimal trial of adjuvant therapy and criteria used in completed or ongoing clinical trials of adjuvant therapy in patients with resected pancreatic cancer

Optimal trial design vs. reported adjuvant therapy trials <sup>a</sup>	Pretreatment high-quality CT or MRI	Defined radiographic criteria for resectability	Standardized system for assessment of surgical margins	Postoperative imaging before enrollment
Optimal Trial Design	Yes	Yes	Yes	Yes
GITSG	No	No	No	No
EORTC 40891	No	No	No	No
ESPAC-1	No	No	No	No
EORTC 40013	Yes	No	No	No
ESPAC-3	Yes	No	Yes	No
RTOG 9704	No	No	No	Yes
ACoSOG ZQ5201	No	No	No	Yes
JHMI	No	No	Yes	Yes

CT, computed tomography; MRI, magnetic resonance imaging.

<sup>a</sup> Refer to text for full name of trials and further details.

analysis has shown fairly high toxicity, with 96% of patients able to be evaluated having grade 3+ toxicity; survival results have been somewhat encouraging, with a median survival of 27 months.<sup>51</sup>

At JHMI, research in adjuvant therapy has focused on the potential benefits of tumor vaccination after conventional surgery and 5-FU-based chemoradiation. These investigators have developed an allogeneic pancreatic tumor cell vaccine genetically manipulated to express granulocyte-macrophage colony-stimulating factor to enhance T cell responsiveness. In a pilot study of 14 patients who underwent PD for pancreatic cancer, allogeneic pancreatic tumor cells engineered to secrete granulocyte-macrophage colony-stimulating factor were injected subcutaneously at various doses 8 weeks after surgery.<sup>52</sup> Chemoradiation was subsequently delivered, and for those patients without relapse at completion of therapy, further vaccinations were delivered monthly for up to 3 additional months. Of note, three patients who received the highest number of allogeneic tumor cells ( $>10 \times 10^7$ ) had increased delayed hypersensitivity responses and were reported to have had the best survival. A phase II trial that used vaccination as a component of adjuvant therapy has been completed with 60 patients enrolled; 30% of these had an R1 resection.<sup>53</sup> One vaccine was administered 8 to 10 weeks after surgery, followed by 5-FU-based chemoradiation. Patients who were disease-free 1 month after completion of chemoradiation received vaccines 2 through 4 (1 month apart), and the fifth and final booster dose was administered 6 months after the fourth vaccine. The reported overall survival was 26 months.<sup>53</sup>

Although the current approaches outlined above may provide small incremental improvements in adjuvant therapy, some of the flaws of previously completed trials are being repeated. For example,

major drawbacks of the ongoing ESPAC-3 and EORTC 40013 trials involve eligibility criteria and patient selection. Although both studies mandate acquisition of preoperative high-quality cross-sectional imaging, neither study uses radiographic criteria to define a resectable tumor. In addition, postoperative imaging before the initiation of adjuvant therapy is not required. Predictably, a substantial subset of patients on these two trials will not be getting adjuvant therapy as properly defined; some will be receiving therapy for locally advanced disease (which was incompletely resected), and 15% to 20% will be receiving therapy for overt metastatic disease (which would be apparent after surgical recovery if postoperative imaging was obtained). Under these circumstances, the task of assessing the added benefit of various components of adjuvant therapy will be challenging, if not impossible (Table 4).

## APPROACHES TO CONSIDER FOR THE FUTURE

### The Emerging Recognition of Borderline Resectable Disease

Amazingly, especially for nonsurgeons, there is not general consensus on the definition of a resectable tumor in the pancreatic head. Most agree that a patient with CT evidence of tumor extension to adjacent arterial structures (SMA, celiac axis, common hepatic artery) would not be resectable with up-front surgery because of the concern for a positive margin of resection (microscopically positive if not grossly positive). There is less consensus on the surgical implications of tumor extension to the SMV, portal vein (PV), or SMV-PV confluence.<sup>54</sup> Because long-term

**TABLE 5.** Clinical/radiographic staging system used at University of Texas M. D. Anderson Cancer Center for adenocarcinoma of the pancreatic head and uncinate process

Clinical stage of disease	AJCC stage	Tumor-vessel relationship on computed tomography			
		SMA	Celiac axis	CHA <sup>a</sup>	SMV-PV
Resectable (all four required to be resectable) <sup>b</sup>	I/II	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Patent (may include tumor abutment or encasement)
Borderline Resectable (only one of the four required)	III	Abutment	Abutment	Abutment or short segment encasement	May have short segment occlusion if reconstruction possible
Locally advanced (only one of the four required)	III	Encasement	Encasement	Extensive encasement with no technical option for reconstruction	Occluded with no technical option for reconstruction

AJCC, American Joint Committee on Cancer; SMA, superior mesenteric artery; CHA, common hepatic artery; SMV, superior mesenteric vein; PV, portal vein confluence; abutment,  $\leq 180^\circ$  or  $\leq 50\%$  of the vessel circumference; encasement,  $> 180^\circ$  or  $> 50\%$  of the vessel circumference.

<sup>a</sup> Assumes normal vascular anatomy; for example, encasement of the CHA is not a limitation in performing PD when there is an uninvolved replaced right hepatic artery arising from the SMA.

<sup>b</sup> Assumes the technical ability to resect and reconstruct the SMV, PV, or SMV-PV confluence when necessary. Others would consider tumor-vein abutment/encasement which results in deformity of the vein as borderline resectable.

survival is unlikely in the absence of surgical resection of the primary pancreatic cancer, traditional training has prompted surgeons to attempt resection whenever a pancreatic tumor is not clearly unresectable, rather than attempting resection only when it is clearly resectable. Although noble, this philosophy may be misguided because trying to resect a tumor that extends to one or more of the adjacent arteries puts the patient at high risk for an incomplete resection, which then jeopardizes any meaningful chance of long-term survival.

Fortunately, as high-quality cross-sectional imaging is increasingly used and the implications of positive surgical margins more fully appreciated, important tumor-vessel relationships are more commonly recognized before surgery. In a series of publications, our group has defined borderline resectable pancreatic cancer as a distinct clinical/radiographic entity (Table 5).<sup>55-57</sup> Borderline resectable tumors are defined by tumor abutment ( $\leq 180^\circ$  or  $\leq 50\%$  of the vessel circumference) of the SMA or celiac axis, short segment abutment or encasement ( $> 180^\circ$  or  $> 50\%$  of the vessel circumference) of the common hepatic artery (typically at the gastroduodenal artery origin) that is amenable to segmental resection and primary repair, or segmental venous occlusion with an adequate SMV below, and PV above, the area of tumor-induced occlusion to allow for interposition grafting. The most common borderline resectable tumors are those with arterial abutment, which, if successfully treated in a neoadjuvant fashion, may allow for a complete tumor resection.<sup>55-57</sup> Tumors that involve the adjacent artery for  $> 180^\circ$  (encasement) would

require the surgeon to cut through tumor to access the artery; these therefore are defined as locally advanced and surgically unresectable. Given the frequency of positive margins in RTOG 9704 and the high local recurrence rates reported in other recently completed adjuvant trials, it is likely that a substantial subset of patients on these trials underwent resection for borderline resectable tumors (or even locally advanced cancer).

If high-quality imaging is obtained before surgical intervention, and if strict definitions of resectability are applied to these CT images (Table 5), more tumors will likely be recognized as borderline for resection. This is especially true if the borderline category is expanded to include any CT evidence of tumor-vein abutment (which in the author's classification [Table 5] is resectable). Furthermore, if borderline resectable tumors are broadly accepted as high risk for a positive margin with up-front surgery, improved survival may ultimately be observed for both groups of patients—those with resectable disease and those with borderline resectable tumors. That is, if a pancreatic cancer is determined to meet strict radiographic criteria for resectability by high-quality CT imaging, margin-positive resection rates should be low and chances for long term survival improved, particularly when followed by adjuvant therapy. Conversely, when high-quality CT imaging demonstrates a tumor to be equivocal for a margin-negative resection (borderline resectable due to arterial abutment), preoperative combined modality therapy should be considered (with the goal of sterilizing tumor at the periphery that may be in direct

contact with arterial structures) and a decision on surgical resection deferred.<sup>55,57,58</sup> When a neoadjuvant strategy is used in patients with borderline resectable tumors, objective evidence of tumor downstaging (decline in serum level of CA 19-9, radiographic evidence of stable or responding disease) may be demonstrated for at least a subset of patients providing a greater chance of an R0 resection. In addition, a neoadjuvant approach provides sufficient time to observe the tumor's biology and reevaluate for interval development of metastatic disease, which would obviate the need for, and the benefit of, surgical intervention. In a recent report from our institution, 160 patients with borderline resectable pancreatic cancer received neoadjuvant therapy.<sup>57</sup> The median survival of all 160 patients was 18 months, but was 40 months for the 66 patients who completed all therapy including surgery, and only 13 months for the 94 patients who did not undergo resection of the primary tumor due to disease progression or a decline in performance status. The data, although retrospective, are encouraging, and we believe that this strategy accurately discriminates those who would benefit from surgery from those who would not.

### **Preoperative Therapy: An Alternative Approach to Resectable Disease**

Although most groups have continued to focus on postoperative therapy for patients with resectable pancreatic cancer, investigation of preoperative (neoadjuvant) therapy, typically with chemoradiation, has continued. Preoperative therapy has sound rationale to include initiation of local and systemic therapy shortly after diagnosis rather than weeks after surgery, treatment of a relatively well-perfused tumor bed, and provision of a time interval to assess for onset of overt metastatic disease before surgical intervention. Thus far, preoperative strategies for pancreatic cancer have not been widely adopted among academic medical centers despite growing evidence of the potential benefits of a neoadjuvant approach for other gastrointestinal tumors, including rectal cancer, gastric cancer, and esophageal cancer.<sup>23,59-62</sup> A common reason for rejecting preoperative therapy centers on the potential for local tumor progression, which may preclude surgical intervention and a chance for cure. However, none of the preoperative studies published to date suggests that this risk is substantial.<sup>42-46</sup> Moreover, when such strategies are used, isolated local recurrence rates have been low (<10%), even when detected radio-

graphically in asymptomatic patients.<sup>47,48,63-65</sup> In addition, emerging data suggest that R0 resection rates are somewhat higher when preoperative chemoradiation is used compared with up-front surgical resection.<sup>40,66</sup>

### **WHERE TO GO FROM HERE?**

Presently, for patients with potentially resectable and borderline resectable pancreatic cancer, surgery is necessary (but probably not sufficient in most patients) for a meaningful chance of cure. Unfortunately, potential for cure has been equated with immediate surgery, an intervention endorsed by most physicians and patients but often performed without adequate preoperative imaging. For too many patients, the psychological relief of having a large abdominal incision and knowledge that the cancer has been removed may be quickly replaced by despair when fully informed of the findings and implications of an incomplete resection. Such events must be minimized. In addition to improved preoperative assessment, a disciplined multidisciplinary approach to adjuvant or neoadjuvant therapy must be adopted if meaningful improvements in patient survival are to occur.

### **Quality Improvement Meets Clinical Research**

Quality improvement focuses on decreasing variability and delivering high-quality care more consistently by using pathways and algorithms. Adjuvant therapy trials need quality improvement to provide a framework for reliable comparisons between various studies as well as to improve patient outcomes. Such comparisons are currently not possible, as demonstrated in Table 4.

What follows should be considered minimal requirements for the conduct of clinical trials and the delivery of adjuvant therapy.

All patients being considered for surgery should be evaluated by a multidisciplinary team to include, at a minimum, an experienced surgeon and a dedicated radiologist with expertise in contrast-enhanced multidetector CT or MRI. Resectability of the primary tumor should be determined preoperatively by using strict radiographic criteria. Too often, multidisciplinary input is obtained after an incomplete surgical resection, and at that point in time, adjuvant therapy cannot compensate for inadequate (or ill-advised) surgery.

Patients defined as having borderline resectable tumors are best treated with neoadjuvant therapy

before any attempt at surgical intervention. Failure to do so will confound results and impede progress in the study of adjuvant therapy.

Strict assessment of surgical margins should be mandated in all future adjuvant therapy trials. Specific recommendations for margin assessment, both gross (operative findings with comment on the presence or absence of a gross complete resection) and microscopic (especially the SMA margin), should be described in the protocol. The AJCC or CAP guidelines/recommendations are easy to follow, and they represent a good first step in the application of a standardized pathologic system for analysis of surgical specimens.

Adjuvant therapy should be offered only to patients with adequate recovery from surgery, particularly for enrollment in a clinical trial.

Postoperative imaging should be required before the delivery of adjuvant therapy to exclude patients who have radiographic evidence of locally persistent or distant metastatic disease. Although there is growing interest in the use of postoperative CA19-9 levels for prognosis<sup>67</sup> or as an entry criterion (such as in CONKO-001), no prospective data have clearly defined the usefulness of this serum tumor marker.

Importantly, the objective of treating patients with localized pancreatic cancer is to improve the survival of all patients to include stages I, II, and III; this is often confused with the goal of improving *adjuvant therapy* for patients who have undergone surgical resection (complete or incomplete) of the primary tumor. Accurate radiographic staging will facilitate the delivery of stage-specific therapy, thereby allowing patients with resectable disease to undergo a gross complete resection of the tumor, and for patients with borderline resectable and locally advanced disease to receive initial systemic therapy; those with stable or responding disease may then receive locoregional chemoradiation with or without surgery. The ongoing debate over the value of radiation as part of a postoperative adjuvant therapy strategy has been a further distraction from the understanding of how to maximize survival in all patients with localized pancreatic cancer. Given the high rates of margin-positive resections and the associated high rates of local recurrence (despite the use of adjuvant therapy), strategies that integrate radiation as a component of preoperative therapy to reduce margin positive resection rates should be more broadly investigated (in both phase II and phase III trials), as they have been in rectal cancer and esophageal cancer. This pertains particularly to patients with borderline resectable tumors.

## CONCLUSION

There have been no improvements in the published survival results achieved with adjuvant therapy for patients with resected pancreatic cancer in more than 20 years. The reasons for failure include poor patient selection preoperatively, frequent incomplete surgical resections intraoperatively (often not confirmed by the surgeon or the pathologist), and the failure to include restaging studies postoperatively. Too many patients undergo pancreatic resection with presumed curative intent but have no real chance of cure as a result of a grossly incomplete resection or the early development of distant metastatic disease; many of these patients receive what is inappropriately termed adjuvant therapy, either off protocol or as part of a clinical trial. A more disciplined approach needs to be taken to define tumor resectability preoperatively and to ensure that patients who undergo surgery have a far higher chance of achieving a complete resection of all gross disease than has historically been reported. This may decrease the number of patients eligible for up-front surgery and subsequent adjuvant therapy. However, if preoperative (neoadjuvant) therapy is carefully designed and delivered, especially to patients with tumors objectively classified as borderline for immediate resection, more patients may ultimately benefit from surgery and enjoy long-term survival.

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