Despite attempted curative resection of localized adenocarcinoma of the pancreas, most patients experience a recurrence and die of their disease. The Gastrointestinal Tumor Study Group, European Organisation for Research and Treatment of Cancer, and European Study Group for Pancreatic Cancer trials have suggested the benefit of adjuvant therapy. However, the relatively few randomized trials available have not established a definite standard of care due to study limitations. Although these trials, and the recently published Charité Onkologie (CONKO)-001 trial, have shown a definite advantage of adjuvant chemotherapy, the most effective chemotherapy and the role of radiation therapy remain unclear. This review will discuss the data available from reported trials of adjuvant and neoadjuvant therapy in pancreatic cancer, address the issues leading to the ongoing controversies, and consider future directions for clinical trials.

Surgical resection remains the only curative therapy for localized pancreatic cancer. Unfortunately, less than 20% of patients present with potentially resectable disease.[1] Even among patients who undergo successful resection, the rate of recurrence is around 90%, and local recurrence occurs in 50% to 80%, with a 5-year overall survival of only 10% to 15%. Due to the high recurrence rate and poor survival of resected patients, adjuvant therapy is a logical treatment option.

Historical Perspective

GITSG Trial

The first randomized trial providing evidence in favor of adjuvant therapy was conducted by the Gastrointestinal Tumor Study Group (GITSG). In this trial, Kalser et al compared observation to bolus fluorouracil (5-FU) plus split-course radiation followed by 2 years of 5-FU.[2] The study was closed early due to slow accrual with a total of 43 evaluable patients, and an interim analysis showed a statistically significant improvement in survival. An improvement in median survival of 20 vs 11 months \( (P = .035) \), and in 2-year survival of 42% vs 15%, was shown for the adjuvant chemoradiation group. This trial was the first to show a survival advantage, but the study population was small, and it used a radiation regimen that is now felt to be inferior. Additionally, since all patients received both chemoradiation and chemotherapy, the relative contribution of each modality could not be assessed. Nonetheless, as the first such report, this study started the use of combined chemoradiation as an American standard for adjuvant therapy.

EORTC Trial

The European Organisation for Research and Treatment of Cancer (EORTC) compared observation to adjuvant infusional 5-FU and split-course radiation in a larger group of 218 patients.[3] This trial included patients with periampullary cancers, and only 114 of the 207 evaluable patients had pancreatic head cancers, but the two groups were stratified before randomization. Among all patients, the investigators found a non-statistically significant difference in 2-year survival between the treatment and control groups—51% (95% CI = 41%-61%) vs 41% (95% CI = 31%-51%), respectively—and a relative risk of death of 0.8 (95% CI = 0.6-1.1). In the analysis of pancreatic head cancer patients, 2-year survival was 37% (CI = 24%-50%) for the treatment arm vs 23% (CI = 11%-35%) for the control arm. Although there appears to be a trend favoring the treatment arm, no conclusion about the benefit of adjuvant chemoradiation in pancreatic cancer can be made from this trial.

ESPAC-1

While the EORTC trial studied only combined chemoradiation, the GITSG trial included both chemoradiation and subsequent chemotherapy but could not differentiate the effect of these two modalities. The European Study Group for Pancreatic Cancer (ESPAC) group attempted to address adjuvant therapy with chemotherapy, radiation, and chemoradiation. In the ESPAC-1 trial the investigators began with a 2X2 factorial design with one randomization to chemoradiation or no
chemoradiation and the other to chemotherapy vs no chemotherapy.\[4\] This resulted in four treatment groups: observation, concurrent chemoradiation, chemotherapy alone, and chemoradiation followed by chemotherapy (Figure 1). The study was powered to compare chemoradiation vs no chemoradiation and chemotherapy vs no chemotherapy.

In addition to this 2X2 factorial design, an additional 256 patients were allocated to one of two randomizations, chemoradiation vs observation, or chemotherapy vs observation. According to the authors, this option was allowed because some study centers may not have had access to both modalities. The treating physician was allowed to choose the randomization for each patient, although it was not intended for these patients to be part of the planned primary analysis.

In the first ESPAC-1 report, all three randomization methods were combined in the data analysis. The 175 patients receiving chemoradiation in the 2X2 factorial and the chemoradiation randomization were compared to the 178 patients who did not receive chemoradiation (ie, the observation and chemotherapy-only groups). There was no difference in 2-year survival between the two groups—15.5 vs 16.1 months, respectively. Similarly, in the 2X2 design and the chemotherapy randomization groups, the 238 patients who received chemotherapy alone were compared to the 235 patients who did not receive chemotherapy (observation and chemoradiation). This comparison did show a statistically significant improvement in 2-year survival—19.7 months (95% CI = 16.4-22.4) vs 14 months (95% CI = 11.9-6.5).[5]

After a median follow-up of 47 months, data were reported for the 289 patients from the primary analysis group involved in the 2X2 randomization design. The 2-year survival for patients who received "chemotherapy alone" (both the chemotherapy and chemoradiation-followed-by-chemotherapy groups) was 40%, whereas the survival for those who did not receive chemotherapy alone (observation and chemoradiation groups) was 30%.[6] Five-year survival also improved at 21% vs 8%, respectively (no P value given). Conversely, chemoradiation appeared to be detrimental, as the 2-year survival in those patients who received chemoradiation was 29% compared to 41% in those who did not receive any radiation, with a hazard ratio for death...
of 1.28 (CI = 0.99-1.66, P = .05). The authors of the ESPAC-1 trial concluded that all patients should receive adjuvant chemotherapy. However, several issues must be considered in interpreting these results. The statistical design was written originally to evaluate a primary endpoint of 2-year survival for margin-negative patients.[4] The final results for this endpoint were never reported. Appropriately, no comparison was made for each of the four individual treatment groups, as ESPAC-1 was not powered for this. Although the addition of the other randomizations adds complexity to the interpretation of the results, the data from the single randomization groups were appropriately not included in the final analysis and paper. The ESPAC-1 authors also suggested that chemoradiation is ineffective. However, these results are relevant to the split-course radiation used in this trial and cannot be extrapolated to more modern chemoradiation regimens. Use of infusional 5-FU regimens and single-course radiation without breaks may provide benefit, and these strategies have not yet been compared to non-radiation-containing arms in prospective, randomized trials. Additional concerns for the chemoradiation question in ESPAC-1 have been raised. First, the doses of radiation varied between sites despite a recommendation for 40 Gy. Second, the lack of central review for radiation ports is of significant importance.[7]

**Meta-analysis**

Recently, investigators (including the authors of ESPAC-1) performed a meta-analysis to address the issues of adjuvant chemoradiation and adjuvant chemotherapy for pancreatic cancer separately.[8] This analysis showed a benefit for chemotherapy with a pooled hazard ratio of 0.75 (CI = 0.64-0.90), and no effect for chemoradiation (HR = 1.09, CI = 0.89-1.32). Analysis of prognostic subgroups showed a potential benefit for chemoradiation in patients with positive margins, with a hazard ratio of 0.62 (but the confidence interval was wide).

The majority of patients in the meta-analysis were from the ESPAC-1 trial, including those randomized in the 2X2 design as well as those in the separate randomization groups. In addition, subgroups of three other trials were used in this analysis. ESPAC-1 weighed significantly in determining the results, and the use of subgroups may not be valid for meta-analysis. A meta-analysis is designed only as a tool for hypothesis generation, and based on the limitations of this report, the results should be interpreted with caution.

**Recent Trials**

Since the publication of the meta-analysis, other randomized trials have been reported (Table 1). Based on data showing the benefit of gemcitabine (Gemzar) in the metastatic setting, the Radiation Therapy Oncology Group (RTOG) opted to test its use in the adjuvant setting.
In the RTOG R9704 trial, Regine et al randomized patients with potentially resectable pancreatic cancer to either pre- and postchemoradiation 5-FU or pre- and postchemoradiation gemcitabine, with both groups receiving concurrent chemoradiation using infusional 5-FU.[9] Tumors of the pancreatic body and tail were included, but because of rapid accrual, an additional primary endpoint of survival in patients with pancreatic head tumors was added. Patients were also stratified by nodal status, tumor size, and surgical margin status.

For the group with tumors of the head of the pancreas, a statistically significant improvement in 3-year survival was seen in the arm that received gemcitabine compared to the arm that received 5-FU—32% vs 21% respectively ($P = .033$), with a hazard ratio of 0.76 ($CI = 0.61-0.97$). When all tumor locations were analyzed, no significant improvement in survival was revealed. Although more hematologic toxicity was seen, neutropenic fever and infection rates were similar, and more than
85% of patients completed therapy in both arms.

CONKO-001

More recently, the Charité Onkologie (CONKO)-001 trial published promising data regarding disease-free and overall survival for patients receiving adjuvant gemcitabine vs observation.[10] This was a large multicenter trial that randomly assigned 368 patients with pancreatic cancer to adjuvant gemcitabine, 1,000 mg/m² weekly for 3 weeks of a 4-week cycle, or to observation. Margin-positive and node-positive patients were included. The primary endpoint of disease-free survival was reached with a median follow-up of 53 months.

Disease-free survival in the gemcitabine arm was 13.4 months (CI = 11.4-15.3) vs 6.9 months (CI = 6.1-7.8) in the control arm (P < .001), and this benefit was maintained in both the margin-negative and margin-positive subgroups. Overall survival in this intent-to-treat analysis was not statistically significant, but the data demonstrated a trend in favor of the gemcitabine arm. Median survival was 22.1 months for the gemcitabine arm (CI = 18.4-25.8) and 20.2 months in the control arm (CI = 17-23.4), with a P value of .06.

In addition to an intent-to-treat analysis, the investigators also performed a preplanned "qualified" analysis excluding patients in the treatment arm who did not receive at least one cycle of treatment, patients in the control arm who received adjuvant radiation or chemotherapy, or patients with protocol violations in either arm. Improvement in disease-free survival was also seen in this qualified analysis—13.7 vs 6.9 months for the control group (P < .001). Overall survival was statistically significant in this analysis, with a median survival of 24.2 months in the gemcitabine group vs 20.5 months in the control group (P = .02). The benefit in overall survival seen in the qualified analysis was small, but the authors concluded that this is likely due to most of the patients in the control arm receiving gemcitabine-based therapy at relapse.

Thus, this well-designed study showed a significant benefit for adjuvant gemcitabine for both margin-negative and -positive resections, and this will likely become a standard of care for treatment of resected pancreatic cancer.[10]

Combination Chemotherapy

Despite the improvement in progression-free and median survival shown in the ESPAC-1 and CONKO-001 trials, most patients with resected pancreatic cancer still recur and die of their disease. Therefore investigations of other adjuvant treatment regimens need to be investigated.

A trial from the Norwegian group compared no adjuvant therapy to adjuvant chemotherapy alone.[11] This study used AMF (doxorubicin, mitomycin, and 5-FU) for six cycles after surgery. In 61 patients, median survival was 23 months in the AMF arm vs 11 months in the control arm (P = .02), and 2-year survival was 43% vs 32%, respectively (P = .04). This study did include carcinoma of the ampulla of Vater and cancer of the body and tail (in a total of 18 patients). This was the first major trial to suggest a potential survival advantage of adjuvant chemotherapy without the addition of radiation. However, this survival advantage was not maintained after 3 years.

The American College of Surgeons Oncology Group (ACOSOG) recently stopped accrual on a multi-institutional trial (Z05031) using radiation combined with an aggressive chemotherapy regimen after surgical resection. This trial used a protocol combining radiation with continuous infusion 5-FU, cisplatin, and interferon-alpha, followed by 4 months of infusional 5-FU. This regimen showed promising survival data when it was first evaluated at the Virginia Mason Cancer Center in a 43-patient, single-institution trial. In this study, Piccotti et al demonstrated 2- and 5-year survival rates of 64% and 55% respectively, but this was associated with significant morbidity.[12] As there were no treatment-related deaths and the survival data were encouraging, ACOSOG went on to perform the larger Z05031 trial to better clarify the efficacy and toxicity of this aggressive regimen, and results are currently pending.

Another small, single-institution trial using interferon-based therapy was recently reported. Based on the data showing gemcitabine's superiority over 5-FU, this trial used a similar interferon-and-chemoradiation induction regimen, albeit with smaller doses, but followed by two cycles of consolidative gemcitabine rather than 5-FU. Like the Piccotti trial, toxicity was high, with 35% of patients requiring hospitalization. Nonetheless, survival data were promising, with actuarial survival rates of 53% at 2 years and 44% at 4 years.[13]

Ongoing Trials

Multiple studies have suggested the benefit of adjuvant therapy in resected pancreatic cancer, both with and without positive margins. The most beneficial regimen remains uncertain. Many studies have used 5-FU therapy, but evidence suggests that gemcitabine is superior in the metastatic setting. More recent studies have used gemcitabine therapy, but with the exception of R9704, gemcitabine has not been directly compared to 5-FU. ESPAC-3 is attempting to answer this question.
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by comparing adjuvant 5-FU to adjuvant gemcitabine. This trial has completed accrual, and results are currently pending.

Significant controversy surrounds the role of radiation in the adjuvant setting, as many argue that local recurrence rates suggest the need for this modality. However, no randomized phase III trial directly addresses the effect of chemoradiation vs chemotherapy alone, and regardless of the issues addressed, the only trial that studied the value of chemoradiation, ESPAC-1, suggested that chemoradiation may be detrimental in this setting. A randomized phase II trial, EORTC 40013-22012, hopes to address this issue by comparing adjuvant gemcitabine vs gemcitabine followed by chemoradiation. Accrual is complete, but there are plans to expand this important trial to a phase III study.

Future Directions in Adjuvant Therapy
As the poor prognosis of pancreatic cancer is due to the systemic nature of the disease, further improvements on local control, surgery, and radiation may have only a modest impact. Significant improvements in prognosis will likely rely upon improvements in systemic therapies and multimodality therapy. The role of newer chemotherapy agents such as oxaliplatin (Eloxatin) and irinotecan (Camptosar) is currently being evaluated in the metastatic setting. However, results of phase III trials have not suggested a significant benefit when these agents are combined with gemcitabine.[14,15]

The combination of targeted therapies with gemcitabine has shown more promising results in the metastatic setting. In a large randomized, controlled trial, erlotinib (Tarceva) combined with gemcitabine showed an improved hazard ratio for death compared to gemcitabine alone.[16] Phase II trials had shown promising data combining cetuximab (Erbitux) and bevacizumab (Avastin) with gemcitabine.[17,18] Phase III trials are now complete for these regimens, and while bevacizumab did not add significantly to the effects of gemcitabine in the metastatic setting, the cetuximab trial has not yet reported results.[19]

Given the therapeutic action of these targeted agents, tolerability in the metastatic setting may not correlate with safety postoperatively. To address this issue, an ongoing intergroup trial, Eastern Cooperative Oncology Group (ECOG) 2204, is evaluating the safety of both bevacizumab and cetuximab in combination with gemcitabine in the adjuvant setting. This randomized phase II trial will evaluate bevacizumab compared to cetuximab when given with both adjuvant chemotherapy (gemcitabine) and chemoradiation (capecitabine [Xeloda]). This study will also provide safety data for the use of capecitabine, rather than infusional 5-FU, in combination with concurrent radiation. As the adjuvant setting is much different from metastatic disease, the bevacizumab arm remains part of the study despite the results reported for the phase III metastatic trial.

Neoadjuvant Treatment
While adjuvant therapy has been the most widely studied approach to pancreatic cancer, neoadjuvant treatment has multiple theoretical benefits. First, as many as 20% to 30% of patients do not receive their planned adjuvant chemotherapy and/or radiation due to factors such as delayed recovery from surgery.[3,20] Neoadjuvant treatment may allow all eligible patients to receive the entire planned treatment course, and thus benefit from the full effect of combined-modality treatment.

Second, patients who develop early metastases are unlikely to benefit from surgical resection, and identifying this population prior to surgery would be ideal. Delaying surgery while administering chemoradiation may spare these patients from a complicated surgery. Finally, incomplete resections are common, and the incidence of positive margins can be as high as 51%.[21,22] Moutardie et al demonstrated improved margin-negative resections (91% vs 65%) in patients treated with neoadjuvant chemoradiation, and other centers have also found improved fibrosis, increased negative margins, and decreased lymph node involvement.[22,23]

Most studies addressing neoadjuvant therapy are small, use a variety of regimens, and use different criteria to define resectability. Most include either bolus or infusional 5-FU, and radiation doses vary from 30 to 50 Gy with continuous irradiation or up to 60 Gy for split-course therapy. Moutardier et al conducted a review of patients with localized pancreatic head carcinomas, comparing patients who received neoadjuvant 5-FU and cisplatin with radiation to those who went directly to surgery. This was not a randomized trial, and the reasons for patients going directly to surgery included inability to obtain a biopsy, inability to endoscopically drain the biliary system, and patient refusal of chemoradiation. In patients who went on to resection, they found improvements in median survival from 13.7 to 26.6 months and in 2-year survival from 31% to 51% in the no neoadjuvant therapy and neoadjuvant therapy groups, respectively. Of the 39 patients thought to be initially resectable who received neoadjuvant therapy, 15 developed unresectable disease and did not go on to resection. In
addition, there were more margin-negative resections in the neoadjuvant group.[22] Nakamori et al recently reported data from a randomized phase II trial using gemcitabine and radiation. Patients who went directly to surgery and achieved negative margins did not receive adjuvant therapy. Of 19 patients receiving neoadjuvant chemoradiation, 83% went on to resection. The rate of margin-negative resections in this group was 70% in the treatment group vs 89% in the control group (no \( P \) value given). Despite the apparent adverse effect on margin status, among those patients who did achieve negative margins, 1-year survival was 81.2% in the treatment group vs 70.6% in the control group; however, this difference was not statistically significant. As gemcitabine has been shown to be effective in metastatic pancreatic cancer, it will be important to follow the results of further trials using this agent.[24]

Whether neoadjuvant therapy can downstage a tumor from unresectable to resectable status is even less clear. The Moutardier study showed no downstaging of the initially unresectable tumors after concurrent chemoradiation. Other studies have shown 0% to 40% downstaging to resectable disease.[25-27] The wide disparity in benefit between studies is likely due to small population size, selection bias, treatment regimen, and variation in the definition of resectability. Although there is good rationale for neoadjuvant approaches and some promising preliminary data, randomized controlled trials with standardization of inclusion criteria, resectability, radiation modality, and surgical technique are necessary to better understand this option. Ideally, trials comparing neoadjuvant therapy to adjuvant therapy will be required to truly define the role of neoadjuvant therapy in the treatment of pancreatic cancer.

Conclusions

Pancreatic cancer, even when resectable, remains a deadly disease. Older small, randomized trials did not definitively establish adjuvant therapy with either chemotherapy or chemoradiation. While two recent trials (CONKO-01 and ESPAC-1) demonstrated benefit for adjuvant chemotherapy with either gemcitabine or 5-FU, respectively, the majority of patients still have recurrences with either of these regimens. Therefore, more active agents and/or combinations need to be found and evaluated in the adjuvant setting. Retrospective analyses and the GITSG study have been used in the United States to justify the establishment of chemoradiation as a standard of care. However, with regard to chemoradiation, the only study that ESPAC-1 fully refutes is the GITSG study. While no data have proven that modern chemoradiation is ineffective as part of adjuvant therapy for pancreatic cancer, lack of proof against a regimen does not justify its routine use. Without an adequately powered randomized trial proving the benefit of adjuvant chemoradiation in pancreatic cancer, its role should appropriately be limited to clinical trials. One intriguing area of investigation for chemoradiation is the neoadjuvant setting.

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The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:


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