Randomized Clinical Trials in Pancreatic Cancer

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KEYWORDS

• Randomized trials • Pancreatic cancer • Chemotherapy • Chemoradiation
• Randomized control trails

KEY POINTS

- To gain a thorough understanding of the evolution of pancreatic cancer management.
- To discuss the most recent level 1a evidence for management of pancreatic cancer.
- To discuss the future of pancreatic cancer management and ongoing clinical trials.

REVIEW OF OLDER ADJUVANT TRIALS

Adjuvant Chemotherapy

The CONKO-001 (Charite Onkologie 001) trial was designed to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete curative resection for pancreatic cancer.[1] Three-hundred and sixty-eight patients without prior chemotherapy or radiation were randomized to 6 cycles of standard-dose gemcitabine or observation, following complete resection. More than 80% of patients had an R0 resection. During median follow-up of 53 months, 133 patients (74%) in the gemcitabine group and 161 patients (92%) in the control group developed recurrent disease. Median disease-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group ($P<.001$). Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group and the control group (median, 22.1 months and 20.2 months, respectively; $P = .06$). However, there were differences in estimated 3-year and 5-year survival. In the gemcitabine group, the estimated survivals were 34% at 3 years and 22.5% at 5 years compared with the control group, in which estimated survivals were 20.5% at 3 years and 11.5% at 5 years. This study has been criticized for its high local failure rate (92% in

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observation arm). Nevertheless, this study further strengthened the efficacy of gemcitabine-based chemotherapy for patients in the adjuvant setting.

Long-term outcomes analyzing whether the previously reported improvement in disease-free survival with adjuvant gemcitabine therapy translated into improved overall survival were published in *JAMA* in 2013. With a median follow-up of 136 months, long-term follow-up of the CONKO-001 study showed a significant improvement in overall survival that favors gemcitabine (median survival, 22.8 months vs 20.2 months; $P = .01$). The median disease-free survival was 13.4 months in the treatment group compared with 6.7 months in the observation group ($P<.001$). Gemcitabine compared with observation alone yielded improved survival rates at 5 years of 20.7% for the gemcitabine arm versus 10.4% for the observation-alone arm, and at 10 years the survival rates were 12.2% for the gemcitabine arm versus 7.7% for the observation-alone arm. Thus, among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 months compared with observation alone resulted in increased overall survival as well as disease-free survival. These findings provide strong support for the use of gemcitabine in this setting.[2]

Adjuvant Chemoradiation

The Gastrointestinal Tumor Study Group (GITSG) trial published in 1985 was one of the first phase III trials exploring the role of adjuvant therapy in pancreas adenocarcinoma. The GITSG trial reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold with adjuvant chemoradiation.[3] Patients were randomly assigned to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) postresection. A standard split course of 4000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2000-cGy segment of RT. The 5-FU regimen was then continued weekly for 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group. Criticisms of this study include having a small patient population and inadequate quality assurance of RT. Furthermore, although patients in this study derived a survival benefit with adjuvant treatment, it is unclear whether the benefit was from the systemic chemotherapy or the chemoradiation or both. Although the GITSG study has been used by some as a basis for 5-FU–based chemoradiation in the adjuvant setting, other studies have challenged the value of chemoradiation.[4]

The European Organisation for Research and Treatment of Cancer (EORTC) 40891 trial was a large multicenter phase III study of patients with resected pancreatic head cancer and periampullary tumors performed to investigate the results of the GITSG trial from 1985, and reported their 5-year and 10-year follow-up. Two-hundred and eighty patients with resected cancers of the pancreatic head or periampullary region were randomized to surgery alone or surgery and chemoradiation (5-FU and 40 Gy). Subgroup analysis of 114 patients with pancreatic head cancers revealed a trend toward improved overall survival for those who received adjuvant therapy compared with the surgery-only arm (median, 17.1 months vs 12.6 months), but this difference was not statistically significant ($P = .99$). Long-term results in the patients with pancreatic head cancer over a greater than 10-year follow-up period reported median survivals of 1.3 and 1 year, which were not statistically significant. Overall, unlike the previous, much smaller 43-patient GITSG trial, EORTC-40891 did not support the benefit of 5-FU-based chemoradiation.[5]

The European Study Group of Pancreatic Cancer (ESPAC)-1 trial further investigated the impact of chemoradiation and suggested that chemotherapy alone