**Gemcitabine based Chemoradiation in Pancreatic Cancer**

Long term results of the U.S. Intergroup/RTOG 9704 Phase III study demonstrate that previously observed improvement in median and 3-year OS with the addition of gemcitabine to adjuvant fluorouracil-based CRT for patients with resected pancreatic head adenocarcinoma (at $P = 0.05$ on multivariate analysis), is no longer seen at 5 years. In this study, after resection of pancreatic adenocarcinoma, patients were randomized to pre- and post-CRT 5-FU versus pre- and post-CRT gemcitabine. 5-FU was administered continuously at 250 mg/m2/day, and gemcitabine at 1000 mg/m2 weekly. Both were administered for 3 weeks before and 12 weeks after CRT. CRT was administered at 50.4 Gy. The primary end point was overall survival.

Results of 5 years analysis:

451 patients eligible.

Univariate analysis: No difference in OS. Pancreatic head tumor patients ($n = 388$) had a median survival and 5-year OS of 20.5 months and 22% respectively with gemcitabine versus 17.1 months and 18% with 5-FU.

Multivariate analysis: patients on the gemcitabine arm with pancreatic head tumors experienced a trend toward improved OS ($P = 0.08$).

First site of relapse local recurrence in 28% of patients versus distant relapse in 73%.

Some points to ponder in regards to the conduct and design of this trial.

41% of patients on 5-FU arm received salvage chemotherapy after any recurrence, of which 81% of patients received gemcitabine. This crossover-like occurrence may have diluted differences in survival between the two study arms.

A greater proportion of patients on the gemcitabine arm had T3/T4 disease (81% vs. 70%, $P = 0.013$).

Given the known exponential rate of tumor recurrence associated with this disease, the prolonged interruption of gemcitabine therapy between the first cycle of gemcitabine and resumption of the final 3 cycles of gemcitabine (between 9.5 to 12.5 weeks) may well have been a contributing factor.

The 5-year results from this study must also be reviewed in the context of the recently updated phase III CONKO- 001 trial and recently reported phase III ESPAC-3 trial. When viewed in total, the findings would suggest the following:

1. survival benefit associated with gemcitabine is observed with use of 6 cycles;
2. survival benefit seen with gemcitabine in comparison to 5-FU appears to be temporary/marginal at best and seen only with the inclusion of CRT;
3. Although the local recurrence rate of 28% seen in RTOG 9704, which made use of central RT QA, is the lowest reported to date and is approximately half of that reported in previous phase III adjuvant CRT trials, distant disease relapse remains the primary mode of failure, occurring in 70%.


**Commentary by:**
Dr. Sudeep Gupta, Medical Oncologist