# The Evolving Role of Radiation in Pancreatic Cancer

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**KEYWORDS**

• Pancreatic cancer • Radiation • Chemoradiation therapy • SBRT • SABR • IMRT

**KEY POINTS**

- The role of radiation in pancreatic cancer is still evolving.
- The data supporting this modality are mixed and likely reflect the systemic nature of this disease.
- Using the correct patient selection, in combination with the newer radiation technology, a role for radiation likely still exists.

Pancreatic cancer is an aggressive malignancy with a poor long-term survival and only mild improvement in outcomes over the past 30 years. Local failure remains a problem and radiation can help improve control. The role of radiation therapy in pancreatic cancer has been controversial and is still evolving. This article reviews the trials of pancreatic cancer and radiation in adjuvant, neoadjuvant, and unresectable lesions. The article reviews the impact and outcomes of evolving radiation technology.

## ADJUVANT CHEMORADIATION

The benefit of chemoradiation therapy (CRT) following a pancreatic resection is unclear. There have been 3 randomized trials with conflicting outcomes. The first randomized trial performed by Gastrointestinal Tumor Study Group (GITSG) showed a survival benefit with split-course radiation and 5-fluorouracil (5FU) chemotherapy.[1] A confirmatory trial showed no survival benefit for CRT compared with observation.[2] The most recent data are from a phase 3 randomized trial performed by the European Study Group for Pancreatic Cancer (ESPAC) using a complex 2 by 2 factorial design trial that randomized postresection subjects to 4 arms: observation, 5FU, 5FU plus

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split-course radiation, and 5FU plus split-course radiation therapy followed by 5FU. The trial found that chemotherapy improved projected 5-year survival to 21% versus 8% in the non-chemotherapy arm ($P = .009$). The CRT arm was inferior to the non-CRT arm with a 5-year survival of 10% versus 20% ($P = .05$), respectively.[3] Attempts to combine radiation with gemcitabine using modern radiation techniques have not shown a survival benefit for radiation.[4] Only a single randomized trial from the 1980s showed a survival benefit to CRT, with recent data showing either no benefit or a detriment.

These trials have been criticized for multiple reasons. All 5FU trials used a now antiquated split-course of radiation with a planned 2 week hiatus, which may be inferior in to the current sequential treatment. In addition, the ESPAC trial, had a complex 2 by 2 factorial design, no quality assurance of radiation therapy planning, and field size and technique were not standardized, which may explain the poor CRT outcomes. A subsequent (Radiation Therapy Oncology Group [RTOG] 97–04) report confirmed that the radiation quality affects survival.[5] Finally, current treatment differ vastly from the randomized trials designed in the 1980–1990. All of these phase 3 trials utilized two dimensional x-ray based targeting with limited motion management, poor image guidance and antiquated radiation planning, and as such raises questions of applicability to modern treatment.

As multiple critiques have been raised, some have pointed to retrospectives series as support for adjuvant CRT. A John Hopkins series of 908 subjects status postpancreatectomy showed a nearly 7-month median survival benefit in CRT (21.2 vs 14.4 months, $P=<.001$).[6] In addition, similar findings were shown in a cohort of 472 subjects, with a 25.5-month versus 19.2-month median survival benefit ($P = .001$).[7] These conflicting data have influenced current guidelines. The National Comprehensive Cancer Network favors chemotherapy alone or induction chemotherapy followed by CRT. The European Society for Radiotherapy and Oncology guidelines do not recommend adjuvant CRT.[8] The RTOG 08-48 is currently accruing subjects for a trial testing 6 months of adjuvant induction chemotherapy and randomization to CRT versus observation in stable subjects. This trial uses modern techniques and has a computed tomography (CT)-based atlas to ensure appropriate target delineation (available at https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0848).

### *Unresectable Pancreatic Cancer*

Thirty percent of patients have locally unresectable pancreatic cancer at diagnosis[9] and overall mean survival is limited to 13.6 months.[10] The best management is controversial.

#### *Concurrent chemotherapy and radiation*

The benefit of concurrent CRT is controversial because of conflicting trial outcomes. Two initial trails compared antiquated concurrent chemotherapy and radiation versus chemotherapy alone. The GITSG trial of 43 subjects with locally advanced pancreatic cancer (LAPC) showed the combination 5FU and 54 Gy of radiation showed an improved 10-week survival but toxicity in the CRT was “severe” in 50% of patients.[11] In 1985, a study of LAPC patients of 5FU versus 5FU and 40 Gy radiation, and showed no benefit of CRT with nearly identical median survival.[12]

After the acceptance of gemcitabine as standard chemotherapy, 2 CRT versus chemotherapy trials were published, again with different outcomes. The Federation Francophone de Cancerologie Digestive (FFCD) group randomized LAPC subjects to a high dose of radiation of 60 Gy with infusional 5FU and intermittent cisplatin