

The case for adjuvant chemoradiation for pancreatic cancer

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Despite the best current therapies, treatment outcomes in pancreatic cancer continue to be poor. Surgery remains the single most important curative modality for the minority of patients who present with resectable disease and continues to be the cornerstone of curative-intent therapy in such patients. The value of adjuvant treatment in these patients has been the subject of much debate and has led to several phase III randomized clinical trials in both the United States and Europe. Inconsistent trial results as well as trial design critiques have led to differing conclusions with regard to the value of adjuvant chemoradiotherapy. This chapter will critically review the randomized trials that have led to this controversy and establish a rationale for the use of adjuvant chemoradiation in patients with resectable pancreatic cancer. Modern radiotherapy delivery techniques will also be discussed and future trial designs suggested.

Key words: pancreas cancer; radiation; radiation therapy; chemotherapy; chemoradiotherapy.

Abbreviations CRT, chemoradiation; 5-FU, 5-fluorouracil; GEM, gemcitabine.

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Despite continuing research, effective treatments for adenocarcinoma of the pancreas continue to remain elusive. Pancreatic cancer affects roughly 32 000 patients per year and is the fourth leading cause of cancer-related deaths in the United States. Virtually all patients diagnosed with the disease ultimately die, and there are estimated to be approximately 30 000 deaths per year in the United States and 40 000 per year in Europe.¹ Thus, continued efforts to improve treatment outcomes for these patients are vital. Pancreatic cancer is often unresectable at presentation due to local invasion or distant metastases. It is estimated that only 10–20% of patients are able to undergo a curative surgical resection.² Surgery continues to be the single most important curative modality. Surgical techniques and post-operative care have reduced surgical morbidity and mortality through the years, while advances in radiology have improved the ability to distinguish between potentially resectable and unresectable patients.^{3,4} Although important, the survival rates after surgical resection alone remain poor, with less than 20% of patients surviving 5 years.^{5–7}

Postoperative chemoradiotherapy and chemotherapy have been shown to improve overall survival in some multi-center randomized trials in the United States and Europe, however, inconsistent results and differing outcome interpretations of these phase III trials has led to a controversy with respect to optimal adjuvant therapy. While researchers in the United States have generally concluded that there is a benefit to radiation in addition to chemotherapy in the adjuvant setting, this conclusion have not been shared by our European colleagues. Modern trial design in the United States (US) and in Europe is reflective of the differing opinions with respect to the value of adjuvant chemoradiotherapy. The most recent US randomized trial included chemoradiotherapy in both arms. Conversely, modern European trials have eliminated radiation therapy from any treatment arm and are evaluating the benefit of different adjuvant systemic therapies. Consequently, the ideal adjuvant therapy is debated at the present time. The landmark US trial, GITSG #9173, was the first to demonstrate a survival advantage for the addition of postoperative chemoradiotherapy. This trial established the standard of care for the postoperative treatment of pancreatic cancer patients in the United States and led to the development of more aggressive, continuous-course chemoradiotherapy regimens in the adjuvant setting. Randomized trials from collaborative European groups have not demonstrated the same advantage to postoperative chemoradiotherapy, however, they do suggest a benefit to adjuvant chemotherapy. Consequently, chemotherapy alone is presently recommended after surgical resection at most European centers. Reviewing the patterns of failure in these studies indicates that both local and distant failures are common. The relapse patterns and poor overall survival indicate the need to develop new treatment paradigms for the future.

- Pancreatic cancer affects approximately 32 000 people per year in the United States and has a 5-year overall survival of <10%.
- Surgical resection is a potentially curative modality, but most patients present with unresectable disease.
- Postoperative treatment with chemotherapy or chemoradiotherapy has led to improved outcomes, but the results of multicenter randomized trials have been inconsistent and based on differing interpretations, have led to different standards of care between US and Europe.

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