Chapter 31
Adjuvant Chemoradiation for Pancreatic Cancer: Past, Present and Future

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1 Introduction

Adjuvant chemoradiation began to be investigated for pancreatic cancer over three decades ago. During the intervening years we have achieved a better understanding of the molecular and genetic basis of pancreatic cancer; however the survival of patients treated with the best modern therapies has changed very little. According to data from the American Cancer Society, the 5-year survival for pancreatic cancer patients remains a dismal 5%, up from a historical 3% three decades ago (1). In 2007, an estimated 37,170 newly diagnosed cases of pancreatic cancer in the United States will be nearly equaled by an estimated 33,170 pancreatic cancer deaths (1). This underscores the continued need to develop novel multimodality treatment approaches to this disease. Surgery remains the cornerstone to any hope for long-term survival, however only approximately 10–20% of newly diagnosed patients present with non-metastatic and potentially resectable disease (2). Pancreatic cancer is considered uniformly fatal in patients unable to undergo a resection. With respect to the minority of patients with resectable disease, cooperative groups both in the United States (US) and Europe have conducted randomized clinical trials in recent decades that have sought to define the potential benefit of adjuvant chemotherapy or adjuvant chemoradiotherapy versus surgery alone for patients with resectable disease. The results of these trials have been conflicting and as a consequence, no current standard exists with respect to adjuvant therapy. Gemcitabine appears to be the most promising agent based on recent phase III trials and may provide a foundation on which to build future trial designs (3, 4). Refinements in delivery techniques for continuous-course modern radiation therapy (RT) as well as promising targeted therapies may also improve upon historical outcomes when added to a gemcitabine backbone. The ideal time sequence of combined adjuvant therapies is also an area of active deliberation. Though there is no current standard for adjuvant therapy in pancreatic cancer, continued investigations into combinations of chemotherapy, radiation therapy, and biologic therapy are warranted. This chapter reviews the historical trials that have defined the potential benefits for adjuvant chemoradiation and examine ongoing and future trial concepts for adjuvant chemoradiation.
2 Rationale for Adjuvant Therapy in Pancreatic Cancer

For the select few who present with resectable nonmetastatic disease, surgery is vital toward a curative-intent treatment approach. Unfortunately, even after pathologically complete (R0) resections, most patients eventually fail and ultimately die of disease progression (5, 6). It has been estimated that up to approximately 75% of patients with recurrent disease have a component of local-regional failure following surgery, and that approximately 25% of patients have local only failures. The high rate of both locoregional and distant disease recurrence in pancreatic cancer following surgery provides a strong rationale for developing novel combinations of adjuvant therapies toward improved clinical outcomes for these patients (5, 7–12). The retroperitoneal location of the pancreas and its proximity to major vascular structures make resections with widely negative margins challenging, which often results in close or microscopically positive surgical margins. Residual microscopic locoregional disease can be eradicated by adjuvant chemoradiation. Considering other gastrointestinal malignancies, the locoregional control benefits conveyed by adjuvant chemoradiation have been proven in phase III trials to translate into improved overall survival (13, 14). The historical “split-course” adjuvant chemoradiation trials performed by the Gastrointestinal Tumor Study Group (GITSG) and European Organization for Research and Treatment of Cancer (EORTC) groups suggested a benefit to adjuvant chemoradiation in pancreatic cancer patients whereas the recent ESPAC-1 trial conducted by the European Study Group for Pancreatic Cancer (ESPAC) suggested a detriment to adjuvant radiation therapy (15–21). These important historical trials and the recently reported results of the Radiation Therapy Oncology Group (RTOG) 97-04 trial provide the foundation on which future adjuvant chemoradiation trials will be built (4).

3 Historical “Split-Course” Chemoradiation Trials

Investigations into the potential benefit of adjuvant chemoradiation for patients with resected pancreatic cancers were borne out of the positive results of chemoradiation in patients with locally advanced, inoperable pancreatic cancers (22, 23). The benefits of combining 5-fluorouracil (5-FU) with radiation therapy in the locally advanced population prompted the GITSG to initiate the first prospective phase III randomized trial designed to evaluate the potential benefit of adjuvant chemoradiation in patients with resected disease. Two European phase III trials, the EORTC trial and the ESPAC-1 trial, followed the GITSG trial and the conflicting results of these trials have set the stage for the ongoing controversy surrounding adjuvant therapy in pancreatic cancer. These three trials have in common “split-course” radiation therapy delivery and 5-FU. Modern trial designs have moved away from split-course radiation therapy delivery to continuous-course and have incorporated the more active agent gemcitabine (4).