

## Editorial

# The Recent Past and Future of Adjuvant Therapy for Pancreatic Cancer

Charles J. Yeo, MD

There is no question that the overall prognosis for patients with pancreatic adenocarcinoma remains poor. Opportunities for improvement in outcome will likely come from improvements in early detection strategies, better identification of precursor lesions and high-risk groups, direction of patients to high-volume centers for surgical and oncologic expertise, and from ongoing trials designed to identify active agents (chemotherapeutic, immunotherapeutic, and other) and implement their use in appropriate patient groups. I applaud Dr. Chu and colleagues<sup>1</sup> for their review of some past work on adjuvant therapy for pancreatic adenocarcinoma. As the debate regarding the optimal adjuvant therapy for pancreatic cancer continues several other studies deserve mention.

First, in July 2002, the Radiation Therapy Oncology Group closed study R97-04. This phase III study of 519 patients with pancreatic cancer randomized between (1) 5-fluorouracil (5-FU) continuous infusion for 3 weeks, followed by 5-FU continuous infusion during radiotherapy, followed by two cycles of 5-FU continuous infusion, and (2) gemcitabine weekly for 3 weeks, followed by 5-FU continuous infusion during radiotherapy, followed by three cycles of gemcitabine alone.<sup>2</sup> The experimental question being asked was whether gemcitabine before and after 5-FU based chemoradiation therapy would be more efficacious than continuous infusion of 5-FU before and after the same 5-FU based chemoradiation therapy. In 1997, when this study was designed, there was inadequate knowledge regarding how to safely administer gemcitabine concurrently with irradiation to

allow for concurrent gemcitabine and radiotherapy. This now closed study is being analyzed; it serves as the first North American cooperative group trial since the Gastrointestinal Tumor Study Group trial. Although the survival results for this trial will not be known until sometime in the year 2003, a number of important observations have already resulted. These include that neither arm was observed to have unacceptable acute toxicity and that accrual could proceed rapidly, reflecting both the support of the Eastern Cooperative Oncology Group and the Southwest Oncology Group, and the current willingness of patients and their physicians to participate in adjuvant trials for pancreatic cancer in North America.

Second, recently Nukui and associates from the Virginia Mason Clinic in Seattle, Washington, have published their experience in 33 patients with resected pancreatic adenocarcinoma who received combined radiotherapy and chemotherapy, including 5-FU, weekly cisplatin, and subcutaneous interferon alpha.<sup>3</sup> After combined modality chemoradiation therapy, chemotherapy alone was administered as 5-FU continuous infusion in two 6-week courses. This single institution trial has generated a 2-year survival rate of 84% and a median survival of 45 months. These encouraging data await further confirmation, with plans to roll this protocol out under the auspices of the American College of Surgeons Oncology Group.

Third, our European colleagues are to be congratulated for following up on their European Study Group for Pancreatic Cancer (ESPAC)-1 trial. They have now commenced ESPAC-3, a trial designed to compare modern chemotherapy alone with an observation-only group in patients with resected pancreatic cancer. Although this trial will continue to accrue in multiple European centers, the results of this trial will be important in underscoring the value of postoperative adjuvant chemotherapy in the setting of resected pancreatic adenocarcinoma.

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From the Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland.

Address correspondence to: Charles J. Yeo, MD, Department of Surgery, Johns Hopkins Hospital, 600 North Wolfe St., Block 606, Baltimore, MD 21287-4606; Fax: 410-614-3539; E-mail: cyeo@jhmi.edu.

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Fourth, it is important to recognize that pancreatic cancer may require novel treatment strategies because of the late detection, solid nature of the tumor, and the impressive desmoplastic stroma seen histologically. Recently, the results of a phase I study with irradiated allogenic pancreatic tumor cell lines transfected with granulocyte macrophage colony-stimulating factor administered in sequence with adjuvant chemoradiation were reported in patients with resected adenocarcinoma of the pancreas.<sup>4</sup> Fourteen patients with stage II or III disease received an initial vaccination 8 weeks after pancreaticoduodenectomy. This was followed by a dose escalation up to a vaccine dose of  $5 \times 10^7$  granulocyte macrophage colony-stimulating factor secreting cells. Postvaccination delayed-type hypersensitivity responses to autologous tumor cells were seen at the highest vaccine doses, and patient survival exceeded those expected from surgery and chemoradiation therapy alone. The positive results from this phase I trial have led to initiation of a 60 patient phase II trial at Johns Hopkins, with recruitment nearly halfway completed.

Additionally, at many institutions, novel therapeutic approaches are being used to treat patients with disseminated, locally advanced, or resected pancreatic adenocarcinoma. As these trials progress, encouraging reports will be transformed into phase III trials.

My comments accompanying the article by Chu et al. are designed to put a more positive “spin” on their review of the previously published trials. I would urge caution in taking a nihilistic approach to the treatment of

patients with pancreatic adenocarcinoma. Tremendous strides are being made in the treatment of hematologic and solid organ cancers. I am looking forward to the day when we will look back upon the Gastrointestinal Tumor Study Group, Norwegian trial, early Johns Hopkins data, European Organization for Research and Treatment of Cancer trial, and ESPAC-1 trial as early, well-intentioned, naive efforts to impact the survival of patients with pancreatic adenocarcinoma. I anticipate that oncologists of the future (surgeons, medical oncologists, radiation oncologists, etc.) will consider our current therapeutic strategies (like pancreaticoduodenectomy, 5-FU, gemcitabine, external beam radiation therapy) in the same category that we now place the practices of blood letting and cupping frequently performed by our predecessor physicians and surgeons.

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