15 Novel Chemoradiation in Localized Pancreatic Cancer: Clinical Studies

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15.1 Introduction

When the use of chemoradiation for localized pancreatic cancer is considered, it is important to appreciate several disease characteristics that differ greatly from those of most other malignancies. In patients who cannot undergo curative resection the median survival is usually less than 1 year, with eventual radiographic progression of local and distant disease occurring commonly after chemoradiation or chemotherapy treatment, and very modest improvement in median survival to be expected. Even if the primary tumor is completely resected, disease-specific mortality is typically at least 80% due to the problems of local disease recurrence and distant metastases. Most pancreatic cancer patients have some combination of host-related factors, such as advanced age, poor performance status, and medical comorbidity, or tumor related factors, such as anorexia and exocrine insufficiency, that often make them relatively poor candidates for aggressive therapy. Since outcome is so poor with standard therapies in localized pancreatic cancer, these patients are appropriate for clinical trials incorporating novel chemotherapeutic agents integrated with radiotherapy as a front line treatment option. While improved local tumor control with more effective radiosensitization could have a modest impact on median survival in patients with locally advanced and resectable pancreatic cancer, significant improvement in median survival duration will require the development of more effective novel chemotherapeutic regimens that address the dominant distant failure pattern. In contrast to diseases where local disease control is the dominant problem, optimal regimens for pancreatic cancer should include a robust systemic treatment in addition to effective local treatment. The use of novel chemotherapeutic agents and molecularly targeted therapies that selectively enhance the effects of radiotherapy and chemotherapy currently seems to be the most promising avenue of clinical pancreatic cancer research. Fortunately, investigators have placed more

emphasis on pancreatic cancer in recent years than in the past, and clinical trials of novel treatments are ongoing. It is hoped that these efforts will lead to gradual improvements in outcome for patients with pancreatic cancer. In this chapter, the clinical principles of localized pancreatic cancer management are discussed with an emphasis on the role of novel radiosensitizers.

15.2 Diagnosis, Staging, and Initial Management of Pancreatic Cancer

The initial goals in the evaluation and treatment of symptomatic patients are to determine resectability, establish a histologic diagnosis, and reestablish biliary tract outflow. Pancreatic cancer is diagnosed, clinically evaluated, and managed differently from center to center in the United States, and the definition of resectability after clinical evaluation varies from surgeon to surgeon. Accurate clinical staging is critical in the clinical management of pancreatic cancer. Abdominal computed tomography (CT) is the most common diagnostic imaging technique used to reliably confirm and determine the stage of suspected pancreatic malignancies. In many centers, endoscopic ultrasonographically guided fine-needle biopsy of the pancreas is the procedure of choice for the diagnosis of pancreatic malignancies. Biliary outflow can be easily reestablished with the endoscopic placement of an endobiliary stent.

Accurate determination of resectability is the most important aspect of clinical staging. Surgical resectability is based on involvement of the superior mesenteric vessels and the celiac artery and its branches. Changes in the most recent American Joint Committee on Cancer (AJCC) staging system for exocrine pancreatic cancer reflect a clinical definition of resectability based on CT assessment. The T-stage designation classifies T1 through T3 tumors as potentially resectable and T4 tumors as locally advanced (unresectable). Tumors with any involvement of the superior mesenteric artery or celiac artery are classified as T4; however, tumors that involve the superior mesenteric, splenic, or portal veins are classified as T3 because these veins can be resected and reconstructed, provided that they are patent (American Joint Committee on Cancer 2002). Therefore, three criteria are necessary for resectability: (1) localized disease, (2) lack of involvement of the celiac axis or superior mesenteric artery, and (3) patency of the superior mesenteric/portal venous confluence. Inaccurate clinical determination of surgical resectability leads to incomplete resections which are not curative and do not prolong median survival (Neoptolemos et al. 2001). Inadequate clinical staging is a major problem in clinical practice and is reflected in the results of clinical trials of resected pancreatic cancer that have reported local tumor recurrence rates.

15.3 Chemoradiation as a Component of Multidisciplinary Management of Resectable Tumors

Chemoradiation has been shown to reduce the probability of local tumor recurrence in patients with gastrointestinal malignancies who have undergone potentially curative surgery (Anonymous 1987; Krook et al. 1991; Kapiteijn et al. 2001; Macdonald et al. 2001). Locoregional control rates of 90% or greater are achieved in virtually every tumor site where combined modality approaches are the standard (head and neck cancer, breast cancer, sarcoma, rectal cancer). Improved local tumor control with the use of postoperative chemoradiation has also been shown to improve overall survival in many gastrointestinal tumor sites, including pancreatic cancer. Chemoradiation accomplishes this by eradicating microscopic residual disease remaining in the tumor bed after complete tumor resection or through the reduction in regional lymph node recurrence. In the case of pancreatic cancer, the retroperitoneal margin is nearly always close and often positive, and isolated lymph nodal recurrences are rare. Therefore, locoregional therapy in pancreatic cancer can be optimized with complete gross tumor resection and treatment of microscopic disease at the retroperitoneal margin with chemoradiation. With appropriate patient selection, multidisciplinary teamwork, and combined modality therapy, local disease control rates of 90% or greater are achievable in pancreatic cancer (Breslin et al. 2001). Unfortunately, however, nearly all multiinstitutional trials have reported strikingly high rates of local tumor recurrence. Local tumor recurrence (or more likely) persistence was identified as a component of the first site of failure in 39% of patients enrolled on the Gastrointestinal Tumor Study Group (GITSG)