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Pancreatic cancer and SBRT: A new potential option?

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ABSTRACT

Local control remains a major issue for patients with unresectable, locally advanced pancreatic cancer (LAPC). The role of radiation therapy in the management of LAPC represents an area of some controversy. Stereotactic body radiotherapy is an emerging treatment option for LAPC as it can provide a therapeutic benefit with significant advantages for patients' quality of life over standard conventional chemoradiation. The objective of this review is to present the rationale for stereotactic body radiotherapy in LAPC, as well as to discuss the potential limitations and caveats of the currently available studies.

1. Introduction

Pancreatic cancer remains a highly lethal disease with 5-year survival rates of approximately 6%.[1,2] It is the second most common gastrointestinal malignancy and the fourth leading cause of cancer related deaths in men and women of all age groups in developed countries. Despite advances in multimodality treatments, the incidence rate of pancreatic cancer still approximates its mortality rate. In 2014, the incidence of pancreatic cancer was estimated at 46,420 with over 38,000 deaths.[1] Surgical resection is the only potentially curative option for managing pancreatic cancer. Unfortunately, fewer than 20% are eligible and of those, 30–50% are found to be unresectable intra-operatively.[3] Patients with locally advanced, unresectable pancreatic cancer comprises a group of patients with intermediate prognosis between resectable and metastatic disease. They require non-surgical treatment and are committed to non-curative options with chemotherapy and conventional fractionated radiotherapy over 2–6 weeks. Local failure remains a major component of disease progression, which often can lead to symptoms of pain, obstruction, and other morbidities that can considerably decrease quality of life. In a recent autopsy series, it was shown that 30% of patient with pancreatic cancer died with locally destructive disease and only minimal systemic disease.[4] Improved methods of controlling the primary cancer are warranted.

2. Criteria for resection and staging of pancreatic tumors

The National Comprehensive Cancer Network (NCCN) guidelines define clear criteria to describe tumor resectability so as to improve patient selection for surgery and improve the

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likelihood of attaining negative surgical margins.[5] Following staging by CT or MRI (and EUS/ERCP in some cases), liver function tests, and chest imaging, disease is classified as: (1) resectable; (2) borderline resectable (i.e., tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable); (3) locally advanced unresectable (i.e., tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); or (4) disseminated (i.e., distant metastases or metastases to lymph nodes beyond the field of resection). The distinction between borderline and locally advanced designations is based on the likelihood of attaining a margin negative (R0) resection; however, this may vary depending on surgical technique and institutional practices. In fact, recent advances in surgical techniques now allow for resection of selected patients with tumors involving the superior mesenteric vein and performing venous reconstructions, thus, making what might be called a borderline tumor at one institution a resectable one in the hands of a surgeon who performs vein grafts.[6] Locally advanced tumors considered to be truly unresectable demonstrate the following: greater than 180° superior mesenteric artery encasement, celiac or inferior vena cava abutment, unreconstructible superior mesenteric vein or portal vein, or aortic invasion or occlusion. In this chapter, we will focus on the use of stereotactic body radiotherapy in the setting of locally advanced pancreatic cancer (LAPC).

3. Role of radiotherapy for locally advanced pancreatic cancer

Clinical trials have demonstrated conflicting results regarding the role of radiotherapy in the treatment of LAPC (Table 1). Nonetheless, the rationale for chemoradiation treatment (CRT) for patients with LAPC is based on the role it plays as the only option for local therapy in the setting of unresectable disease. Serial studies of the Gastrointestinal Tumor Study Group (GITSG) with patients with LAPC have shown that combined-modality therapy is superior to either optimal radiotherapy or chemotherapy alone. In 1981, GITSG randomized 194 patients with histologically confirmed locally unresectable adenocarcinoma of the pancreas to therapy 60 Gy alone, to 40 Gy+ 5-fluorouracil (5-FU), and to 60 Gy plus 5-FU. Radiotherapy was delivered as a split-course of 2 weeks on 1 week off. Both 5-FU-containing treatment regimens produced a highly significant survival improvement when compared with radiation alone. The 1-year overall survival was 40% in the combined regimens group compared with 10% in the radiation-only group. Survival differences between 40 Gy plus 5-FU and 60 Gy plus 5-FU were not significant with an overall median survival of 10 months. Twenty-six percent of patients in each of the combined modality treatment arm experienced local failure plus distant metastases at first progression. Although this study is criticized for using split-course radiotherapy and for having small numbers, it had nevertheless established a role for combined modality therapy in the management of locally advanced pancreatic cancer.[7]

This study was followed by another GITSG prospective trial that compared the survival of patients treated with multidrug chemotherapy [streptozocin, mitomycin, and 5-fluorouracil (SMF)] versus radiation combined with 5-fluorouracil followed by the same three-drug SMF combination. This study showed an improvement in overall survival following the combined-modality treatment program (41% at 1 year) compared with SMF chemotherapy alone (19% at 1 year). The first site of progression was local in 10 patients in each arm.[8]

Likewise, the Eastern Cooperative Oncology Group (ECOG) 4201 study revealed an increase in overall survival with CRT. This study evaluated the role of radiation therapy with concurrent gemcitabine (arm B) compared with gemcitabine alone (arm A) in patients with LAPC. Overall survival was 9.2 months and 11.1 months in the gemcitabine-alone group and the CRT group, respectively. Overall grades 3 and 4 toxicities were common in both arms (77% versus 79%), but as expected, grades 4 and 5 toxicities were greater in arm B (41%) versus arm A (9%). One grade 5 toxicity occurred in each arm (arm A, cardiac; arm B, acute respiratory distress syndrome). Local recurrences were at the documented first site of metastasis in 11 and 4 patients in arms A and B, respectively (not statistically significant).[9]

A combined analysis of the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trials also confirmed an increase in overall survival with CRT versus chemotherapy alone with a median overall survival of 15.0 and 11.7 months, respectively. Treatment-related toxicities and local control in the CRT arm were not assessed.[10]

Conversely, the Fédération Francophone de Cancérologie Digestive and Société Francophone de Radiothérapie Oncologique (FFCD-SFRO) study reported diminished overall survival and increased toxicity with CRT. In this study, patients were randomly assigned to either chemotherapy and high-dose radiotherapy group (60 Gy, 2 Gy/fraction; concomitant 5-fluorouracil infusion and cisplatin) or gemcitabine alone. Maintenance gemcitabine was given in both arms until disease progression or toxicity. This intensive combined CRT was more toxic and less effective than gemcitabine alone. Overall survival was shorter in the CRT than in the gemcitabine arm (median survival 8.6 and 13 months, respectively), likely related to the inability to deliver adequate systemic therapy in the high-dose radiotherapy group due to increased toxicity with this regimen. Local control was not assessed in this study.[11]

Recently, the phase III GERCOR LAP 07 study reported no significant improvement in overall survival with the addition of CRT. In this study, LAPC patients were first randomized to gemcitabine or gemcitabine plus erlotinib. Patients with controlled disease after 4 months of chemotherapy were then randomized to two additional months of chemotherapy or CRT with 54 Gy and concurrent capecitabine. The overall survival was not significantly different between the two arms (15.2 versus 16.5 months).[12]

A total of 238 patients were found to have progression of disease, in 96 patients (50.5%) first site of progression was locoregional and in 97 patients (49.5%) it was distant metastatic disease. In the CRT arm, patients had significantly less local tumor progression compared to the chemotherapy arm (34% versus 65%, $p < 0.0001$). Median time without treatment (i.e., reintroduction of chemotherapy) was longer in the CRT arm compared to the chemotherapy arm (159 versus 96 days, respectively, $p = 0.05$). Therefore, the conclusion was