

Neoadjuvant radiotherapy for pancreatic cancer: rationale and outcomes

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Abstract: Pancreatic cancer is an aggressive disease with median survival in localized resectable cases measured by months. Surgery is necessary for cure, but remains only part of the treatment paradigm; the ideal treatment is multimodal. After undergoing surgery alone for pancreatic cancer, most patients will recur and the use of neoadjuvant chemoradiation therapy is an attractive, more novel treatment approach for several reasons: to facilitate down staging in borderline or locally advanced patients so that surgical resection is feasible; to increase the rate of R0 resections while sterilizing there section field; to expedite the delivery of adjuvant therapy, which may be delayed or infeasible postoperatively because of complications in therapy; to allow time preoperatively for the natural process of the disease to present itself while undergoing therapy for prognostic value; and to decrease toxicity owing to smaller radiation fields and less radiation to the small bowel. Although there have been no phase III multicenter randomized controlled trials for this patient population, there have been multiple single-institution reports published, and clinical trials are on the horizon.

Keywords: Pancreatic cancer; neoadjuvant therapy; radiation therapy; chemoradiation

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Introduction

Pancreatic cancer is an aggressive disease with grim survival statistics for which even small improvements in treatment require further study. Pancreatic cancer represents the 10th most common cancer in the United States, yet it is the 4th most common cause of cancer-related death (1). In 2015 there will be an estimated 48,960 new cases of pancreatic cancer with 40,560 estimated deaths, representing 3% of all new cancer cases and 6.9% of all cancer deaths (1). Surgery, either pancreaticoduodenectomy or distal pancreatectomy, is the only curative treatment approach.

Between 10% and 20% of patients with pancreatic cancer will present with resectable disease. For these patients, the

cure rate at 5 years reaches only 20%, as disease will recur in 80% to 85% of these patients (2). Distant metastases develop after resection in roughly 50% to 60% of patients who present with localized disease (3). Because pancreatic cancer acts as a systemic disease, any attempt at cure must be multimodal and include both adjuvant systemic chemotherapy and localized radiation therapy. Adjuvant chemoradiation therapy has been the historical approach to the treatment of resectable pancreatic cancer; however, recent literature and medical practice has elucidated the benefits to neoadjuvant chemoradiation. This manuscript will review the rationale for neoadjuvant chemoradiation and the available data to support this treatment approach.

Rationale for neoadjuvant chemoradiation

The use of neoadjuvant therapy in the treatment of pancreatic cancer is rationalized throughout much of the literature as well as in the 6th edition of Perez and Brady's *The Principles and Practice of Radiation Oncology* (2-6):

- (I) A large percentage of patients experience a significant delay in therapy or do not receive adjuvant therapy following surgical resection partly because of postoperative complications and concerns with healing, which can lead to an unacceptable performance status that precludes further treatment;
- (II) Twenty percent to 40% of patients will be spared the morbidity of resection as their metastatic disease becomes clinically apparent during the course of neoadjuvant therapy allowing physicians and patients to avoid unnecessary invasive therapies in an incurable medical situation;
- (III) Preoperative radiation therapy allows for decreased toxicity and lower small bowel radiation doses since the treatment fields for neoadjuvant radiation therapy are smaller. In addition, the decreased oxygenation of the resection bed postoperatively decreases the radiobiological effectiveness of the radiation therapy and the delivery of the systemic therapy to the targeted tissues in the resection bed;
- (IV) Like the use of neoadjuvant chemotherapy in breast cancer in the approach to downsize and facilitate the resectability of the gross tumor, neoadjuvant chemoradiation therapy in pancreatic cancer aids in converting a borderline or unresectable tumor into a resectable case while sterilizing the resection bed and improving the ability to achieve an R0 resection.

Disadvantages of neoadjuvant therapy

The disadvantages to neoadjuvant therapy in the treatment of pancreatic cancer are as follows: (I) potential complications from pretreatment endoscopic procedures (such as biopsy or biliary stent placement) that may not be needed in the upfront surgical resection setting; (II) biliary stent-related morbidity or stent occlusion during neoadjuvant therapy; (III) disease progression obviating resectability; and loss of a "window" of resectability which may occur (rarely) in the borderline resectable patient;

(IV) physicians must work together during the preoperative phase; discrete handoff from the surgeon to the medical oncologist to the radiation oncologist is not possible in the neoadjuvant setting (as occurs with adjuvant therapy). A surgeon may need to assess the patient during neoadjuvant treatment to decide if and when surgical resection is recommended (4).

Definitions and criteria of resectability status

The definition of resectability varies by institution. The most accepted radiographic imaging modality for determining anatomical involvement and local tumor resectability is the multidetector computed tomography (CT) scan with a pancreatic protocol generated by the institution (7-13). In general practice, pancreatic tumors can be classified as resectable (stage I or II), unresectable (stage III), and metastatic (stage IV). Criteria for defining resectability have been outlined by Sunni Hosemann of the M.D. Anderson Cancer Center (Houston, TX, USA) as well as by the National Comprehensive Cancer Network in their clinical practice guidelines for pancreatic adenocarcinoma (9,14). The NCCN criteria for "resectable" is (I) no arterial tumor contact (celiac axis, superior mesenteric artery or common hepatic artery) and (II) no tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤ 180 -degree contact without vein contour irregularity. The MD Anderson criteria for "resectable" is (I) no extension to SMA; normal fat plane; (II) no extension to the celiac axis/hepatic artery; and (III) SMV/PV patent (14).

Neoadjuvant chemoradiation for pancreatic cancer: clinical evidence

It is well known that omitting surgical resection in the treatment of pancreatic cancer significantly compromises survival. One of the greatest benefits of neoadjuvant therapy is that it converts inoperable patients to operable ones. Habermehl *et al.* reported on a single-institution experience treating 215 patients neoadjuvantly with locally advanced pancreatic cancer with a median of 52.5 Gy over 1.8 Gy fractions (15). Patients undergoing complete resection demonstrated a median overall survival of 22.1 months compared to 11.9 months in non-resected patients. The median overall survival and disease-free survival times were 12.3 and 8.1 months. In most cases, the first site of disease

progression was systemic with hepatic (52%) and peritoneal (36%) metastases (15). Thus, in the case of borderline resectable patients, allowing for the most curative treatment is highly desirable. Christians *et al.* reported on 18 borderline resectable patients treated with neoadjuvant FOLFIRINOX followed by chemoradiation (16). Six patients experienced disease progression, which precluded them from surgical resection. The median survival time for this group of patients was 12.5 months. The remaining 12 patients underwent R0 resections and had a median survival of 22 months. Ashman *et al.* reported on 48 patients with locally advanced pancreatic ductal adenocarcinoma who received preoperative chemoradiation and intraoperative electron irradiation (IOERT) (17). Of these patients, 65% were able to proceed to curative-intent surgical resection. Prior to preoperative chemoradiation, 20 patients were deemed locally unresectable and 11 patients were borderline resectable. Radiation therapy was delivered to a dose of 45 to 50.4 Gy over 25 to 38 fractions concurrently with 5-fluorouracil (5FU) or gemcitabine-based regimens. A gross total resection was achieved in 16 patients (R0, 11 patients; R1, 5 patients). IOERT was delivered in 28 patients at a dose of 10-20 Gy. In addition, 16 patients received adjuvant postoperative systemic chemotherapy. The investigators found that resection status was predictive for both survival and patterns of relapse. Patients with at least a gross total resection after preoperative chemoradiation therapy (R0/R1; n=16) when compared to patients with no resection (n=15) experienced an improvement in median survival of 23 months versus 10 months, respectively. The overall survival rate also improved at 2 years (40% vs. 17%) and 3 years (40% vs. 0%; P=0.002) (17).

A recent prospective study by Sherman *et al.* was undertaken in patients with pancreatic adenocarcinoma presenting with locally advanced, unresectable disease treated with neoadjuvant chemoradiation therapy. The investigators analyzed 45 patients with unresectable disease due to arterial and/or venous involvement who were treated with neoadjuvant gemcitabine, docetaxel, and capecitabine; those with arterial involvement received additional gemcitabine and capecitabine plus radiation therapy. Of those with arterial involvement, 69% achieved an R0 resection. For the arterial arm, the 1-year survival rate was 71% and the median survival time was 29 months. The authors concluded that this chemotherapy regimen combined with radiation therapy can be administered to patients up to 83 years of age and is associated with a

high response rate, a high R0 rate, and prolonged overall survival (18). As evidenced, converting inoperable patients to operable candidates is feasible with neoadjuvant chemoradiation.

While neoadjuvant therapy in general can increase perioperative and postoperative complications, preoperative chemoradiation can reduce the risk of pancreatic fistula. Takahashi *et al.* evaluated 58 patients who underwent distal pancreatectomy, 28 of whom received neoadjuvant gemcitabine-based chemoradiation. Of these patients, 86% did not develop a pancreatic fistula whereas only 33% of patients in the non-neoadjuvant chemoradiation group did not develop a pancreatic fistula. The incidence of clinically significant pancreatic fistula was also lower with the neoadjuvant chemoradiation group (P=0.031) (19). In fact, a National Surgical Quality Improvement database inquiry of 1,562 patients with pancreatic adenocarcinoma showed that of the 199 patients receiving neoadjuvant therapy there was no difference in 30-day mortality and postoperative morbidity (20).

Another concern is local disease progression during neoadjuvant therapy. Varadhachary *et al.* conducted a phase II trial in which 90 patients were enrolled and 79 patients completed neoadjuvant gemcitabine and cisplatin followed by gemcitabine-based radiation prior to surgical resection (21). At the time of publication, only 1 patient had documented isolated local tumor progression at the time of preoperative staging, suggesting that protraction of time with neoadjuvant therapy results in a low incidence of isolated local tumor progression (21).

In a review of the National Cancer Data Base, Colbert *et al.* examined chemoradiation therapy sequencing for resected pancreatic adenocarcinoma in 5,414 patients with pancreatic adenocarcinoma treated at various institutions (22). Of these patients, 277 received preoperative radiation therapy and 5,137 received postoperative radiation therapy. Furthermore, 92.9% received chemotherapy and 7.1% received radiation alone; 56% of patients were stage III; 82% of neoadjuvant radiation patients were found to have negative surgical margins and 72% of postoperative radiation patients achieved negative surgical margins. Overall, 41% and 65% of the preoperative and postoperative radiation therapy patients, respectively, had positive lymph nodes. The median overall survival times for patients who received preoperative and postoperative radiation therapy were 18 and 19 months, respectively. While this is not a prospective randomized study, it does

further inform the debate of which treatment paradigm is more effective.

Conclusions

Neoadjuvant chemoradiation has many potential benefits which have been supported through retrospective and single-institution prospective studies. Trimodality therapy is the preferred method of treatment for pancreatic cancer and the neoadjuvant approach specifically provides the patient with the best chance to complete all three modalities. Despite the lack of multi-institutional randomized data comparing neoadjuvant chemoradiation therapy to adjuvant radiation therapy, there is a body of literature that supports this regimen as the standard treatment approach to pancreatic adenocarcinoma.

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