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Review

Chemoradiation of pancreatic carcinoma

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ABSTRACT

Pancreatic carcinoma is a malignancy with a poor prognosis and the 4th. most common cause of cancer-related deaths. Patients are usually diagnosed at advanced stage of the disease. Surgical resection remains the only potentially curative therapy, as only 20% of the patients present with disease are amenable to resection. Surgery, chemotherapy, radiotherapy and palliative therapies are therapeutic options. Multidisciplinary approach is needed for every stage of the disease. Researches showed an improved survival benefit of radiotherapy (RT) and chemotherapy (CT) combination for locally advanced unresectable pancreatic carcinoma compared to RT or CT alone. In an attempt to improve survival, the efficacy of chemoradiation (CRT) after surgery compared to observation has been tested in several trials. Neoadjuvant CRT achieves a higher probability of margin negative R0 resection. Currently, both 5-FU and gemcitabine have been used concurrently with RT, and also targeted agents (erlotinib, cetuximab, panitumumab, bevacizumab) have been also evaluated.

1. Introduction

Pancreatic carcinoma is a malignancy with poor prognosis, and the 4th. most common cause of cancer-related deaths. The American Cancer Society estimated 53.070 new cases of pancreatic cancer and 41.780 pancreatic cancer –related deaths in the United States for the year 2015.[1] More than 200.000 deaths around the world are related to pancreatic carcinoma.[2] Most cases occur in patients between 60 and 80 years of age and rarely before the 4th decade.[3] Male versus female ratio is 1.3:1 and it is most common in black race.[4] Five-year overall survival rates of pancreatic cancer patients decreased 6% in USA. Most patients present with advanced disease. Surgery offers the only means of cure, and unfortunately after diagnosis only 20% of the patients present with tumors amenable to resection.[5] The 5 year-overall survival rates for patients undergoing pancreatic resection is 25–30% for node negative and 10% for node positive disease.[4] Five-year survival rate of the patients presenting with metastatic disease is only 5%.[6]

Ductal adenocarcinomas are the most common histopathological type, accounting nearly 95% of all malignant tumors.[7] Risk factors of pancreatic carcinoma include cigarette smoking, alcohol consumption, chronic pancreatitis, obesity, diabetes mellitus, cholecystectomy, gastrectomy and helicobacter pylori infection.[8] Ten percent of this malignancy may be familial. The risk of cancer is greater among patients with a positive family history.[9]

Surgery, chemotherapy, radiotherapy and palliative therapies are therapeutic options. Multidisciplinary approach is needed for every stage of the disease (Fig. 1). Randomised trials have shown an improved survival benefit of the radiotherapy (RT) and chemotherapy (CT) combination for locally advanced unresectable pancreatic carcinoma compared to RT or CT alone.[10] This review presents the chemoradiation studies related to pancreatic carcinoma.

2. Adjuvant chemoradiotherapy

Early recurrences and low survival rates after pancreaticoduodenectomy in 10%–20% of pancreatic carcinoma patients with localized disease, indicate the need for adjuvant interventions.

Griffin et al analyzed the patterns of treatment failure in 36 patients after curative resection for pancreatic carcinoma. Two and 5-year survival rates among these patients were 32 and 17%, respectively. The median survival time was 11,5 months. In all patients treatment failure is associated with presence of metastases intraabdominal (100%), and peritoneal (42%) cavities, and liver leading to hepatic failure (62%).[11]

Willet and colleagues, analyzed patterns of failure after pancreaticoduodenectomy performed for periampullary carcinoma

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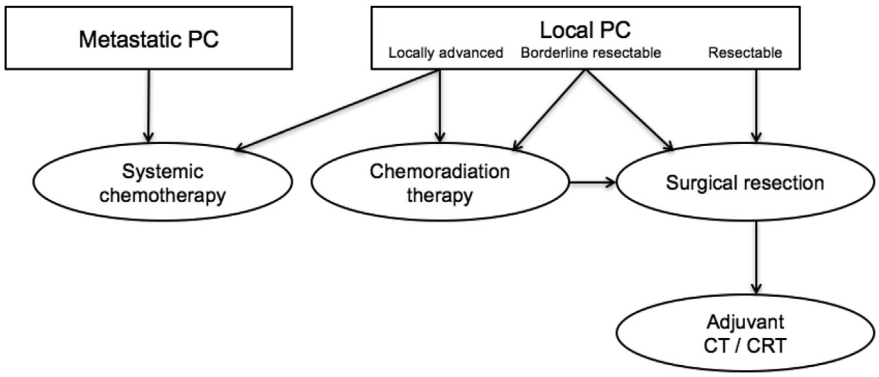

Fig. 1. The treatment of pancreatic cancer (PC: pancreatic cancer, CT: chemotherapy, CRT: chemoradiation)[3]

in 41 patients. They observed local control of 88% in situ disease, T1 or T2 stage compared with 44% for T3 or T4 stages. Patients with lymph node positivity, and negativity had local control rates of 47, and 87%, respectively moderately differentiated tumors had a better local control rate as compared with patients with poorly differentiated tumors (5-year local control rate 81% vs 0%).[12]

For the patients undergoing a potentially curative pancreatoduodenectomy, 3 major sites of disease relapse dominate:

- the bed of resected pancreas,
- the peritoneal cavity and
- the liver.

Therefore, tumor stage, grade and resection margin status are the predictors of survival after surgery.

A randomized trial conducted by the Gastrointestinal Tumor Study Group (GISTG) showed improved overall survival with the use of adjuvant CRT followed by adjuvant CT after definitive surgery (40 Gy split course RT concomitantly with iv bolus 5-FU 500 mg/m^2 on the first 3 days and then weekly for 2 years after RT). Patients who had undergone surgery alone had a median survival of 11 months versus 20 months in the treatment group ($p = 0.03$). Two-year overall survival was 42% with chemoradiotherapy arm versus 15% with surgery alone.[13]

The European Organization for Research and Treatment of Cancer (EORTC) designed a randomized trial to compare surgery alone or surgery plus postoperative chemoradiotherapy. Contrary to GISTG trial, 5-FU was not given after chemoradiotherapy. In the chemoradiation arm the median survival time was 17 months versus 13 months in the surgery alone arm. Although no statistically significant difference was observed between two arms, the trial has been criticized for its lack of any mention of the surgical margin positivity, lack of quality assurance, inclusion of pancreatic and periampullary carcinomas, and insufficient statistical power for subanalysis.[14,15]

Another important trial is the European Study Group of Pancreatic Cancer (ESPAC-1) study, which had a complex design. The effects of adjuvant chemotherapy and chemoradiation in patients with resected pancreatic cancer were evaluated. The patients were randomized to (a) observation after surgery, (b) concomitant chemoradiation alone (40 Gy split course RT with 500 mg/m^2 5-FU iv bolus during the first 3 days), (c) chemotherapy alone (leucovorin 20 mg/m^2 bolus followed by 5-FU 425 mg/m^2 for 5 days, repeated every 28 days for 6 cycles), (d) chemoradiation followed by 6 cycles of adjuvant 5-FU/leucovorin treatment. By contrast, for patients receiving chemoradiotherapy, a negative impact on survival was observed while a survival advantage for adjuvant chemotherapy was achieved. This trial was criticized for several reasons as follows its design was considered inappropriate for sequential therapy analysis, RT details were inadequate (30% of the patients did not receive RT or treatment differed from planned treatment) and RT schedule followed a split course.[16]

Another randomized Radiation Therapy and Oncology Group (RTOG 97-04) trial evaluated whether gemcitabine (1000 mg/m^2/week) before and after 5-FU based chemoradiation (50.4 Gy/28 fractions) would provide superior outcome to 5-FU (250 mg/m^2/day) before and after 5-FU based chemoradiation. The 3-year overall survival times (20.5 vs 17 months), and rates (31 vs 22%) had been indicated for the gemcitabine and 5-FU arms with an intergroup difference which almost reached statistical significance ($p = 0.09$).[17]

After the criticized results of historical randomized trials, further studies were conducted to see if adjuvant chemoradiation may be beneficial. Thus, a phase III randomized NCT01013649 trial is still ongoing in the United States which should be completed by the year 2020. Nevertheless, the impact of chemoradiation on overall survival after pancreaticoduodenectomy was evaluated in a multicenter retrospective study reviewing 955 patients. Median overall survival times was 40 months for patients treated with chemoradiation compared with 25 months for those receiving chemoradiation and 29 months for patients treated only with adjuvant chemotherapy ($p < 0.001$). In the population treated with adjuvant chemoradiation 5-year overall survival was 41% compared with 26% in patients treated with chemotherapy alone.[18]

3. Neoadjuvant chemoradiotherapy

The high frequency of disease recurrences and the low survival rates associated with surgical resection of pancreatic carcinoma have been usually attributed to residual tumor cells left at the surgical margins and lymph node involvement. Many institutions have studied adjuvant therapy to prevent high locoregional and distant recurrences. However, postoperative adjuvant therapy could not be performed in 24%–56% of the patients because of delayed recovery after major surgery, medical comorbidity and disease progression. Thus, recent researches have focused on preoperative neoadjuvant strategies. Sequencing chemoradiation before surgery may provide theoretical advantages. RT with neoadjuvant therapy could be more effective with normal vascular blood flow, the risk of peritoneal seeding with surgery could be reduced, response to chemoradiation could be demonstrated in vivo, unnecessary surgery could be avoided for rapidly progressive biological tumors and metastatic patients that were staged before surgery.[19,20]

Fox Chase Cancer Center, evaluated neoadjuvant chemoradiation for periampullary tumors. They found a resectability