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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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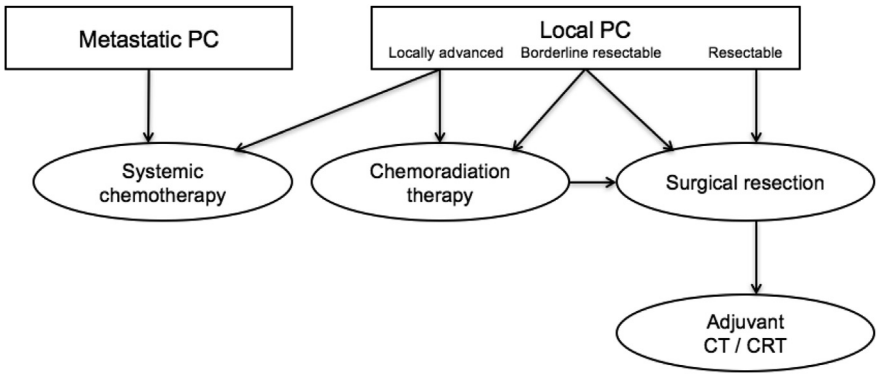

Fig. 1. The treatment of pancreatic cancer (PC: pancreatic cancer, CT: chemotherapy, CRT: chemoradiation)[3]

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

rate of 38% for 31 patients treated with 50.4 Gy conventially fractionated with 4 day infusion of 5-FU and bolus infusion of mitomycin C on the second day. Median survival was 45 months in patients who underwent potentially curative resection.[21] Eastern Cooperative Oncology Group (ECOG) used a similar therapeutic regimen with 53 patients, and only 24 of 41 patients scheduled for surgery were managed with curative resection. Among these patients median survival was 15.7 months.[22] With the limited efficacy of 5-FU, investigators also evaluated RT used concurrently with neoadjuvant gemcitabine. Level I data from the CONKO-001 trial established the role of gemcitabine as an adjuvant therapy. M.D. Anderson Cancer Center reported results from a trial which used gemcitabine (400 mg/m^2/week) concurrently with neoadjuvant RT (30 Gy/10 fractions). Seventy-four percent of 86 patients underwent resection with a 5-year overall survival rate of 36%.[23] Small et al reported a 1-year overall survival rate of 76% for patients with initially resectable pancreatic cancer treated with full dose gemcitabine (1000 mg/m^2) combined with RT (36 Gy/15 fractions) and reported the tolerability of full dose gemcitabine with RT.[24]

Until now, margin-negative pancreatectomy has been the only known cure for the disease. However, only up to 10%–20% of the patients have a resectable tumor, and R0 resection rate ranges between 32, and 71 percent[19,25]. Positive margins after surgery have been associated with significantly worse survival, similar to that of the patients with inoperable disease.[19] Therefore, much of recent data on neoadjuvant therapy has focused on borderline resectable tumors to achieve a higher probability of margin-negative resection. M.D. Anderson Cancer Center published a series of their patients with borderline resectable disease treated with neoadjuvant therapy and reported that 56% of surgical specimens had less than 50% viable tumor cells.[26] They found that 41% of the patients had undergone resection with grossly negative margins and in 94% of them negative surgical margins were histopathologically confirmed. Furthermore, median survival time was 40 months for the patients undergoing resection compared with 13 months for those not receiving surgery ($p < 0.001$). Fox Chase Cancer Center showed similar results. Patients who underwent therapy followed by surgery had an 85% rate of margin-negative resections.[27] These data suggest that neoadjuvant therapy for borderline resectable pancreatic cancer may improve the likelihood of an R0 resection, however randomized trials are needed to test this approach.

4. Chemoradiotherapy for locally advanced unresectable disease

Approximately 30%–40% of the newly diagnosed pancreatic carcinoma cases are classified as locally advanced, non-resectable, non-metastatic cancers, and those with involvement of major blood vessels and regional lymph nodes. Currently, concurrent chemoradiation has been suggested as a standard first line treatment option, even though there are still debates on this modality.

GITSG has demonstrated that split course RT amounting to a total dose of 40–60 Gy with concurrent 5-FU bolus was superior to RT alone. Median survival time was 5.5 months for RT alone (60 Gy) versus 8.3 months for concurrent therapy (40 Gy + 5-FU) and even better with dose escalation therapy (11.3 months for 60 Gy + 5-FU).[28] Subsequently it has been demonstrated that an SMF regimen (streptozocin, mitomycin C, 5-FU) yielded a significantly inferior survival outcome for patients with unresectable disease than 5-FU chemoradiation delivered up to 54 Gy followed by SMF chemotherapy (1-year overall survival 41% vs. 19%, 2-year overall survival 18% vs 0%).[29]

Similar to neoadjuvant strategies, with its potent radiosensitizing effects, combination of gemcitabine with RT has been suggested as an ideal treatment for locally advanced pancreatic carcinoma with efficient locoregional control and substantial systemic effects. A dose of 40 mg/m^2 twice weekly in combination with RT up to a total dose of 50.5 Gy was examined by the Cancer and Leukemia Group B (CALGB) in a phase II study of 39 patients. After chemoradiation, patients without disease progression received gemcitabine alone at weekly doses of 1000 mg/m^2 for 5 cycles. Grade 3/4 toxicity identified in 69% of these patients. The median survival time was 8.2 months.[30] Small et al treated locally advanced pancreatic carcinoma patients with full dose gemcitabine concomitantly used with RT (36 Gy/10 fractions, 3 cycles of gemcitabine). With a median 47% of 1-year overall survival rate, this study was one of the first trials showing the safety of full dose gemcitabine in combination with RT.[24]

An ECOG phase III trial attempted to assess the benefit of RT combined with gemcitabine in the unresectable pancreatic cancer population, but it was terminated prematurely because of poor accrual. Although, adding RT to gemcitabine significantly improved survival rates, grade 4 toxicity was also significantly higher in the chemoradiation arm.[31]

The M.D. Anderson Cancer Center retrospectively examined 114 patients with locally advanced pancreatic carcinoma treated with combination of RT (30 Gy/10 fractions) with either concurrent 5-FU (200–300 mg/m^2/week) or gemcitabine (250–500 mg/m^2/week). Patients receiving gemcitabine developed significantly higher incidence rates of severe acute toxicity requiring a hospital stay of more than 5 days with mucosal ulceration with bleeding, Some patients missed more than 3 doses of gemcitabine and gemcitabine toxicity also resulted in surgical intervention or death. However, no statistically significant difference was detected between chemotherapeutic agents.[32]

5. RT with targeted therapeutic agents

As a recently popular treatment modality disease-targeted therapeutic agents have been tested in the treatment of chemoradiation for pancreatic carcinoma. Promising results were found especially for epidermal growth factor receptor (EGFR) agents.

The overexpression of EGFR and gene amplification were detected in 60% of the patients with pancreas carcinoma.[33] Erlotinib is a reversible tyrosine kinase inhibitor of EGFR.[34] Trials evaluated erlotinib in combination with chemoradiotherapy in the treatment of pancreatic carcinoma. Herman et al conducted a phase II trial for resectable pancreatic cancer patients to demonstrate progression free (PFS), and overall survival (OS) rates with the use of erlotinib in combination with chemoradiation and chemotherapy. Patients had been treated with erlotinib (100 mg daily) and capecitabine (800 mg/m^2/twice daily) concurrently with intensity modulated radiotherapy (IMRT) (50.4 Gy/28 fractions) after surgery followed by gemcitabine (1000 mg/m^2 on days 1, 8 and 15, then every 28 days) for 4 cycles. The PFS and OS were 15.6 and 24.4 months, respectively.[35] In a phase I trial with erlotinib, gemcitabine and paclitaxel had been used concurrently with RT for locally advanced pancreatic cancer, Iannitti et al reported a median survival of 14 months. Three different dosages of erlotinib had been tried, and daily dose of 50 mg was found to be more tolerable in combination with gemcitabine, paclitaxel and RT.[36] Duffy et al showed the results of phase I trial in non-operable pancreas carcinoma patients treated with erlotinib (100 mg/daily), gemcitabine (40 mg/m^2/30 min twice weekly) and RT (50.4 Gy/28 fractions over 5.5 weeks). Partial remission (PR) and stable disease rates were 35% and 53%, respectively.[37]

Cetuximab is a monoclonal antibody that specifically binds to the EGFR. In in vivo and in vitro studies, it has been shown to

enhance radiosensitivity, promote radiation induced apoptosis, decrease cell proliferation, inhibit regeneration of radiation - induced defect site and also tumor angiogenesis.[38] Fiore et al applied weekly cetuximab and gemcitabine (300 mg/m^2) concurrently with RT (50.4 Gy/28 fractions) to 34 patients. They found PR and SD rates of 24% and 52%, respectively. Median survival was 15.3 months.[39] Rembielak et al designed a phase II trial with cetuximab (first dose of 400 mg/m^2 followed by 250 mg/m^2 weekly) and RT (50.4 Gy/28 fractions). They reported that the treatment had been well tolerated and most patients (71%) had experienced acute toxicities of grade 1 or 2. Six months after the treatment only 33% of them had been free from metastatic progression. Median overall survival was 7.5 months (1 year 33% and 3 year 11%).[40]

Panitumumab is a EGFR-related monoclonal antibody. A phase I trial was designed for evaluating addition of panitumumab to gemcitabine based chemoradiotherapy in patients with locally advanced pancreatic cancer. Fourteen patients were treated with panitumumab (1–2.5 mg/kg/weekly for 6 weeks) combined with gemcitabine (300 mg/m^2/weekly for 6 weeks) and RT (50.4 Gy/28 fractions) followed by gemcitabine 1000 mg/m^2 until progression. Maximum tolerable panitumumab dose was 1.5 mg/kg. Grade 3 toxicities during treatment were neutropenia (33%), fatigue (17%), nausea and vomiting (17%). PFS was 8.9 months.[41]

Bevacizumab is a monoclonal antibody related to vascular endothelial growth factor (VEGF). Studies evaluated bevacizumab with chemoradiation for pancreas carcinoma. Van Buren et al tested the efficacy of bevacizumab with RT in a phase II trial for resectable pancreatic carcinoma. Fifty-nine patients had been treated with gemcitabine (1500 mg/m^2) plus bevacizumab (10 mg/m^2) every 2 weeks for 3 cycles followed by RT (30Gy/10 fractions) and bevacizumab. Pancreatic resections were performed in 73% of the patients and margin-negative outcomes were observed in 88% of those patients. Median overall survival times before, and after the resection had been 16.8, and 19.7 months, respectively while corresponding median PFS times had been 6.6 months, and 12.9 months, respectively.[42] Small et al conducted a phase II trìal for patents wìth localised pancreatic carcinoma in that patients had received gemcitabine 1000 mg/m^2 (day 1 and 8, 7 doses) and bevacizumab 10 mg/kg (every 2 week, 5 doses) in combination with RT (36 Gy). Patients with resectable tumors had undergone surgery 6–8 weeks after the last dose of bevacizumab. Maintenance doses of gemcitabine and bevacizumab had been delivered to patients who had unresected tumors without disease progression. Median PFS and OS times had been 9.9 and 11.8 months, respectively.[43]

6. Conclusion

Pancreatic carcinoma is a malignancy with poor prognosis. Patients are diagnosed at an advanced stage of the disease therefore, multidisciplinary approach is needed. Improved survival benefit and R0 resection possibility have been shown with chemoradiation for locally advanced and borderline resectable disease. The effectiveness of 5-FU and gemcitabine has been demonstrated on chemoradiation for locally advanced and borderline resectable disease. RT used in combination with EGFR and VEGF activity inhibiting agents are also promising.

Conflict of interest

The authors have declared that no competing interests exist.

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