

Adenocarcinoma of the pancreas: the rationale for neoadjuvant therapy

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Abstract. The survival of patients with pancreatic cancer is dismal: tumor's resection is possible in only 10-20% of patients. This has prompted clinical studies with chemotherapy and/or radiotherapy designed to increase the number of patients eligible for surgery, to maximize local tumor control and to improve the length of survival. Since postoperative chemoradiation is often delayed in these patients due to morbidity and prolonged recovery time associated with surgery, investigators are assessing the efficacy of chemoradiation before pancreatic resection in patients with potentially resectable pancreatic carcinoma or the potential to downstage locally advanced pancreatic cancer to resectable tumor. The analysis of several clinical trials published so far shows that results are conflicting and not definitive. No randomized clinical studies have been reported. Moreover, neoadjuvant therapy rarely leads to surgical downstaging allowing for potentially curative pancreatic resections. Novel multimodality approaches are required, and patients should be entered on clinical, controlled trials.

Key words: Pancreas, pancreatic cancer, neoadjuvant therapy

Introduction

Pancreatic carcinoma accounts for the fifth most common cause of cancer death in United States (1), with an overall five-year survival rate of 1-3% (2). Traditionally surgical resection has been considered the only way to "cure" pancreatic adenocarcinoma. However, fewer than 20% of patients present with tumors that are amenable to resection, and 5 year survival after potentially curative resection is less than 20% (3). Most patients have either occult metastatic disease or residual local disease following resection, and both distant and locoregional patterns of recurrence are common (4). Strategies designed to improve the surgical outcome, such as postoperative adjuvant therapy, for patients with gastrointestinal malignancies have been under investigation for decades. In pancreatic cancer,

the advantage of postoperative therapy for patients undergoing resection is still somewhat controversial, although multimodality therapy appears to improve local control and survival over surgery alone both in prospective (5, 6), and retrospective studies (3). However, reports of adjuvant therapy for pancreatic cancer remark the inherent difficulties of this approach; approximately 20% of patients do not receive benefits of multimodality therapy due to death, complications, or delayed recovery (7).

Rationale for neoadjuvant therapy

The logic behind neoadjuvant chemoradiotherapy is basically the following: treat all patients with potentially resectable disease, observe tumor biology

during the time between the diagnosis and the completion of preoperative therapy, and resect those patients who remain with resectable disease. Several considerations support the preoperative use of chemoradiation (8). First, positive gross or microscopic posterior margins of resection are common after pancreaticoduodenectomy; therefore surgery alone is inadequate for local tumor control. Second, chemoradiation is received by all patients (delayed postoperative recovery does not affect the delivery of multimodality therapy) and it is received at a time when oxygen supply to the tumor is the greatest. Third, occult metastases are given the opportunity to become detectable allowing these patients to avoid the morbidity of resection. Fourth, preoperative therapy may downstage some unresectable tumors to resectable lesions. Finally, some data suggest that preoperative chemoradiation decreases the incidence of pancreatojejunal anastomosis fistula (9).

An important consideration in planning neoadjuvant trials is the definition of resectable disease. Generally, helical computer tomography scanning (CT) accurately assess the relationship of the tumor to the adjacent structures. In the absence of extrapancreatic metastatic disease, a pancreatic tumor is considered (radiographically or intraoperatively) resectable or locally advanced based on the relationship of the primary tumor with the superior mesenteric vein (SMV) or superior mesenteric-portal vein confluence (SMPV) or to the superior mesenteric artery (SMA) and/or coeliac Trunk (8). Infact, resection and reconstruction of SMV or SMVP are possible, without increased morbidity: the survival rate is reported similar to the standard resection (10). Moreover, the concept of "resectable" tumor may vary among surgeons, depending on their experience and aggressiveness. Standardized definition of resectable and locally advanced pancreatic cancer based on objective radiologic criteria are critical in view of planning prospective clinical trials and necessary for the reliable interpretation of survival data from retrospective reviews. Other criteria to define locally advanced or resectable tumor based, for example, on surgeon's assessment at the time of laparotomy, could be incorrect, because the local extent of the tumor before transection of the pancreas and mobilization of SMPV is inaccurate.

Prior to starting with neoadjuvant treatment, confirmation of malignancy is required for all patients, in order to avoid unnecessary toxicity of chemoradiation. Biopsy is generally easily taken by CT-guided percutaneous or by endoscopic ultrasound-guided biopsy or FNA.

The majority of patients with adenocarcinoma of the pancreatic head present with jaundice due to common bile duct obstruction; this requires nonoperative biliary decompression with an endoscopic or percutaneous biliary stent. Although some Authors reported an increased chemoradiation-related morbidity (38% biliary stent obstruction and cholangitis) and subsequent increased operative morbidity and mortality (11, 12), this was not confirmed by Others (3, 13).

Neoadjuvant therapy for potentially resectable pancreatic cancer

The results of the studies concerning neoadjuvant strategies in "potentially" resectable pancreatic carcinoma are listed in Table 1 (11, 14-21). Radiotherapy was performed as standard fractionation (40 to 50 Gy, 1.8 Gy/fraction per day) or as rapid fractionation (30 Gy, 3 Gy/fraction per day) to decrease treatment related toxicity. Concomitant chemotherapy was based on 5-FU administration (sometimes in continuous infusion): other drugs tested with or without 5-FU were mitomycin C, cisplatin, gemcitabine, and paclitaxel. Among 327 evaluable patients, 113 (34%) showed significant treatment related toxicity that required to stop or modify the treatment; 87 patients (27%) required hospitalization, mostly for cause-related to biliary stent obstruction and cholangitis. At restaging after chemoradiation, 73 patients (22%) showed disease progression and were not operated. A total of 239 patients (73%) underwent laparotomy: 59 (18%) patients showed non-resectable disease (liver and/or peritoneal metastases) and 180 (55%) were finally resected. In 54 patients the resection included one or more adjacent structures (the mesenteric-portal vein in 44, the hepatic artery in 4, hepatic segment in 4, and the colon in 5). Median survival time ranged from 12.0 to 25 months; one series reported an actuarial 5-year survival of 28% (18), and another a 5-year survi-

Table 1. Neoadjuvant studies in patients with potentially resectable pancreatic carcinoma

Authors	Nr	Radiotherapy	Chemotherapy	Survival Median (mo)
Yeung et al., 1993 (14)	24	50.0 Gy	5-FU + Mito - C	NA*
Spitz et al., 1997 (15)	91	50.4 Gy or 30.0 Gy	c5-FU	19.2
Pisters et al., 1998 (16)	35	30.0 Gy + IORT	5-FU	25.0
Hoffman et al., 1998 (11)	53	50.4 Gy	5-FU + Mito - C	15.7
Mehta et al., 2001 (17)	15	50.4 Gy	5-FU	12.0
White et al., 2001 (18)	53	45.0 Gy	5-FU	NA**
Breslin et al., 2001 (19)	132	50.4 Gy or 30.0 Gy	5-FU, GEM, Paclitaxel	21.0
Moutardier et al., 2002 (20)	19	45.0 Gy or 30.0 Gy	5-FU, CDDP	20.0
Pisters et al., 2002 (21)	35	30.0 Gy + IORT	Paclitaxel	12.0

IORT = intraoperative radiation therapy.

5-FU = 5-Fluorouracil; Mito-C = Mitomycin; GEM = Gemcitabine; CDDP = Cisplatin.

NA = not available; * = actuarial 5-year survival 16%; ** = actuarial 5-year survival 28%

val probability of 16% (14). Almost all series reported surgical margins free of tumor at pathologic examination; disease progression involved distant sites (liver and lung), with a good control of local-disease progression (only about 10%). However, Spitz et al. (15) reported a similar treatment toxicity, patterns of tumor recurrence, and survival between patients with pancreatic cancer who underwent preoperative or postoperative chemoradiation. A phase II study involving radiotherapy, continuous infusion of 5-FU, and mitomycin-C conducted by the Eastern Cooperative Oncology Group (11) resulted in low resectability rate and poor survival results (probably because of the advanced stage of most resected cancers). This emphasizes the need for careful preoperative staging and assessment that should possibly include laparoscopy and/or other methods, such as endoscopic ultrasound or positron emission tomography.

Chemoradiation therapy for locally advanced pancreatic cancer

Chemoradiation has been administered to patients with locally advanced, unresectable pancreatic cancer in order to prolong survival, and more recently, to downstage advanced locoregional disease to allow surgical resection. The results of 10 published series (22-31) focusing on neoadjuvant strategies in locally advanced pancreatic cancer are reported in Table 2. Radiotherapy was performed in almost all studies as a

standard fractionation (45 to 55 Gy); chemotherapy included 5-FU and/or mitomycin-C, streptozotocin, dipyrindamole, cisplatin, and gemcitabine. Among 339 evaluable patients, 315 (93%) completed chemoradiation treatment, and 224 (71%), at restaging, were excluded from the surgical exploration because of disease's progression or poor medical conditions. Ninety-one (27%) patients underwent surgical exploration and 55 patients were resected: in 19 patients, the resection included also a venous resection (n=15), and/or arterial resection (n=9), and colonic resection (n=2). There were 11 complete response and 34 partial response. Median survival time was 11.5 months (range 8-34 months). Despite some objective responses, survival time seems not to be improved by neoadjuvant therapy (27, 28). Moreover, in some studies (28) review of preoperative imaging of patients submitted to pancreatic and vascular resection, showed an incorrected tumors staging. The available literature suggests that it is unlikely that 5-FU based chemoradiation schedules can convert unresectable to resectable lesions, and thereby increase the number of patients who can be cured with multimodality therapy. Other radiosensitizers drugs should be tested alone or in association with 5-FU in chemoradiation protocols. Gemcitabine, in association with radiation, showed high toxicity in one study(28), while it was well tolerated, with promising results, in other experiences (29, 32). In our experience 24 patients with locally advanced, unresectable pancreatic adenocarcinoma underwent radiotherapy (54 Gy), continuous infusion of

Table 2. Studies with neoadjuvant therapy in patients with locally advanced pancreatic carcinoma

Authors	Nr	Radiotherapy	Chemotherapy	Response	Resection Nr	Survival Median (mo)
Jessup et al., 1993 (22)	16	45 Gy	c 5-FU	NA	2	8
Kamthan et al., 1997 (23)	35	54 Gy	5-FU, STZ, P	PR = 9 CR = 6	5	15
Todd et al., 1998 (24)	38	NO	c 5-FU, Mito - C, Dipyridamole	PR = 14 CR = 1	4	15,5
White et al., 1999 (25)	25	45 Gy	5-FU, Mito - C, P	CR = 1	5	12
Wanebo et al., 2000 (26)	14	45 Gy	5-FU, P	CR = 2	9	16
Kastl et al., 2000 (27)	27	55,8 Gy	5-FU, Mito - C	NA	10	11
Crane et al., 2001 (28)	51	33 Gy	GEM	PR = 6	6	11
Epelbaum et al., 2002 (29)	20	50,4 Gy	GEM	PR = 4		
	3	8				
Kim et al., 2002 (30)	87	NR	5-FU, GEM	PR = 1	1	11
Arnoletti et al., 2002 (31)	30	50,4 Gy	5-FU, Mito - C, GEM	NA	14	34

NA = not available; NR = not reported

5-FU = 5-Fluorouracile; Mito-C = Mitomycin-C; STZ = Streptozotocin; CDDP = Cisplatin; GEM = Gemcitabine.

PR = partial response; CR = complete response

5-FU (200 mg/m²) and gemcitabine (250 mg/m²/week); after restaging no complete or partial response were observed and 14 patients experienced stable disease. No patient underwent resection.

Conclusions

A number of clinical trials have attempted to improve the survival of patients with pancreatic carcinoma with neoadjuvant therapy involving various combination of chemotherapy and radiotherapy. However, the studies have involved relatively small numbers of patients, and no randomized controlled trial has yet been reported. The advantage, if any, over postoperative adjuvant therapy has yet to be defined. The optimal schedule for the combined use of chemotherapy and radiation has not been established so far. The studies have shown the feasibility of preoperative chemoradiation with acceptable toxicity and little or no effect on surgical morbidity. A variable number of patients (10-15%) may have converted from unresectable to resectable disease. However, success in achieving local control with neoadjuvant therapy must be viewed cautiously: it does not necessarily mean improved survival or better quality of life. Downstaging of truly advanced pancreatic cancer to resectable disease is a rare event and needs more effective locoregional therapies.

There is evidence that preoperative chemoradiation overtreats a considerable number of patients (one fourth of patients has metastatic disease at restaging); so, a more accurate selection of the patients candidate to this approach is necessary.

Despite a few promising studies suggesting improved survival in some cases, conclusive clinical investigation are needed. Whenever possible pancreatic cancer patients eligible for neoadjuvant therapy should be placed on clinical, prospective controlled studies.

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