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Review article

Trends in treatment for pancreatic cancer

Seiki Matsuno, Shinichi Egawa, and Kosuke Arai

First Department of Surgery, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

Abstract Although surgical resection is considered to be the only approach that offers a possibility of cure to patients with pancreatic cancer, the prognosis of the disease has not been improved markedly by any surgical procedures in the past 20 years. Large-scale randomized prospective clinical trials are being conducted in the United States and Italy, comparing standard lymph node dissection with extended lymph node dissection. Although preoperative chemoradiation has various advantages in the treatment of pancreatic cancer, it does not contribute to its downstaging and eventual cure. The combination of leucovorin, 5-fluorouracil (5-FU), and extracorporeal irradiation, however, has been proven to improve the patient's quality of life (QOL). Palliative surgery still requires further research in areas such as the examination of morbidity rates and the duration of bypass effects, now that laparoscopic and endoscopic surgery have both been well developed. Recent biological research has revealed the mechanisms of the carcinogenesis and the progression of pancreatic cancer, and, against this background, we assume that more effective trials will be conducted soon. Immunotherapy with dendritic cells, as well as gene therapy with mutant adenovirus, has already been employed clinically. Pancreatic cancer therapy is now facing new prospects.

Key words Pancreatic cancer · Pancreatectomy · Chemoradiation

Introduction

The therapeutic results in 100,313 patients with pancreatic cancer diagnosed from 1985 to 1995 in the United States, equivalent to approximately 60% of the total number of pancreatic cancer cases in that country during this period, were reported.[1] The report showed that 91% of the patients did not undergo pancreatic resection, while 58% of the patients had been given only symptomatic treatment. In regard to stage IV, which accounts for the largest number of clinical cases of pancreatic cancer, only 2% of the patients underwent surgical resection. Here, it is emphasized that postoperative survival rates were not improved significantly in the past 20 years, even though advances in perioperative patient care, as well as a decrease in postoperative morbidity, have made it possible to perform extended surgical resection. Moreover, neither surgical resection nor postoperative chemoradiation showed any significant improvement in prognosis. These findings appear to indicate that only the detection of this cancer in the early stages, or the development of new therapies, will be effective in improving the prognosis of pancreatic cancer.

In this article, we discuss new therapies for pancreatic cancer, based on recent research.

Preoperative chemoradiation

In recent years, the relative benefits of preoperative chemoradiation, compared with those of postoperative chemoradiation, for locally advanced pancreatic cancer have been suggested by some investigators.[2–4] The advantages of using preoperative chemoradiation for pancreatic cancer are summarized as follows:

1. Preoperative chemoradiation can be employed for any patient because it entails low morbidity.
2. It is possible to target therapeutic effects to the retroperitoneum, which frequently produces a cancer-positive margin after surgical resection.
3. It is possible to avoid unnecessary laparotomy, because distant metastasis becomes apparent in approximately 25% of patients during preoperative chemoradiation.

Offprint requests to: S. Matsuno

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White et al.[5] examined 25 patients with locally advanced pancreatic cancer treated with preoperative chemoradiation (1.8 Gy/day, for 5 weeks, using 5-fluorouracil (FU), mitomycin C, or cisplatin). Five of the patients underwent pancreatic resection, and only 1 of the 5 showed a cancer-negative surgical margin. The surgical margins in the other 4 patients who underwent pancreatic resection were cancer-positive, and no down-staging effect was confirmed. Pisters et al.[6] employed a combination of 30-Gy extracorporeal irradiation and 5-FU before surgery for patients whose pancreatic cancer was regarded as surgically resectable, and they also added intraoperative radiation therapy, at a dose of 10–15 Gy. As a result, they obtained favorable local control, with only mild side effects; the 3-year survival rate of these patients was 23%.

The combination of extracorporeal irradiation and oral administration of leucovorin 25 mg/m^2 and doxifluridine (5-DFUR) 500 mg/m^2 was proven to be effective in patients in whom pancreatic cancer had been judged to be unresectable through intraoperative findings, as well as through computed tomography (CT) diagnosis.[7] This combination treatment was not stopped in any patients because of side effects, and also made it possible for 16% of the patients to undergo surgical resection. The 1-year survival rate for the patients with a surgically resected pancreas was confirmed to be 100%. Therefore, it is believed that this combination therapy should also be taken into consideration from the quality-of-life (QOL) point of view.

Extended resection or standard resection

The question of determining whether we should approach progressive infiltration of pancreatic cancer by surgery has been discussed for a long time. However, no final determination has been achieved, because most studies of this matter have been done retrospectively or have dealt with a small series of patients.[8,9] Recently, some large-scale studies of this problem have been conducted. Mukaiya et al.[10] surveyed findings in 501 patients who had had pancreatic cancer resected at 77 different hospitals in Japan between 1991 and 1994. They reported that, of the patients who had an extended lymph node dissection, 38 were in stage I (43%), 42 were in stage II (54%), and 206 were in stage III (65%). Comparisons of findings in each stage showed no significant differences in prognosis from that in patients with standard dissection, indicating no greater necessity of performing extended lymph node dissection. Yeo et al.[11] carried out a prospective study in a large number of patients in a single hospital, in which they added extended or standard lymph node dissection to pancreatoduodenectomy. All the patients in the extended dissection group (n = 58) underwent distal gastrectomy, while 86% of the patients in the standard dissection group (n = 56) underwent pylorus-preserving procedures. The results showed no significant differences in operative time, amount of blood transfusion, clinical stage, mortality, and morbidity between the two groups. Only 10% of the 58 patients in the extended dissection group were confirmed to have retroperitoneal nodal metastasis, and there were no patients who had nodal metastasis only in the retroperitoneum. The 1-year survival rate in the standard dissection group was 77%, while that in the extended group was 83%. Results for the long-term outcome in these patients are expected in the future.

Pedrazzoli et al.[12] reported a total of 81 patients in a multicenter prospective trial in which patients were randomly allocated to standard lymph node dissection (n = 40) and extended dissection (n = 41). There were no significant differences between the two patient groups in operative time, blood loss, postoperative complications, and mortality as a direct result of surgery. Although no significant difference in prognosis was seen between the two groups, the patients with nodal metastasis in the extended dissection group were confirmed to have higher survival rates than those in the standard group. In the patients without nodal metastasis, there were no significant differences in survival rates between the two groups. If a well trained surgeon, in a hospital with large numbers of patients, performed extended lymph node dissection in patients with nodal metastasis surrounding the pancreas, this would have the possibility of lengthening the period of survival, without much increase in morbidity.

Regarding portal vein resection combined with pancreatectomy, Leach et al.[13] compared results in 75 patients in a single hospital (44 with ordinary pancreatoduodenectomy and 31 with pancreatoduodenectomy with portal vein resection). The results showed no significant differences in survival between the groups. Accordingly, Leach et al.[13] recommended that this combined surgery should be performed if there is portal vein infiltration (regarded as a local factor) in areas where tumors progress, if the infiltrated area can be resected completely. Nagakawa et al.[8] argue that a cancer-free surgical margin results in significant improvement of prognosis, and that extended pancreatic resection, including extended lymph node dissection, should be recommended for pancreatic cancer. Although they reported that 10 of their 39 patients (26.0%) who underwent histologically curative resection with the extended resection procedures survived for 5 years, their analysis was retrospective. In the light of these findings, it appears, unfortunately, that our analyses are not sufficient to determine the truly effective resection factors that contribute to survival.

Palliative surgery and pain control

The objectives of palliative surgery are to improve prognosis by avoiding obstruction of the biliary tract and duodenum, and to improve the quality of life (QOL), by, for example, decreasing the incidence of itching, vomiting, and pain. Sohn et al.[14] analyzed findings in 256 patients in whom laparotomy had been performed for the purpose of pancreatectomy, but in whom the tumors could not be resected. On further examination, it was noted that the reason that the tumors were unresectable was either liver metastasis or peritoneal dissemination in 68% of the patients, while in 32%, the reason was infiltration to the large major vessels. Regarding surgical procedures, a combination of biliary bypass and gastrojejunostomy was performed in 51% of the patients, biliary bypass alone was performed in 11%, and gastrojejunostomy alone was performed in 19%. It was reported that 75% of the patients underwent a neural block of the celiac plexus. The operative mortality caused by palliative surgery was 3.1%, which was considered to show no significant difference from the operative mortality of 1.9% in 512 patients who underwent pancreatoduodenectomy during the same period. These results indicate that palliative surgery can be performed safely. These palliative procedures showed a postoperative morbidity rate of 22%, and an average length of hospital stay of 10.3 days, both of which were confirmed to be lower than the respective findings for the patients with pancreatoduodenectomy. This study showed that the biliary bypass remained effective in 96% of the patients after long-term follow-up, and it was confirmed to have a favorable result when compared with results in patients treated with biliary stents, who had a 17% to 38% recurrence rate of jaundice. Although many people believe that prophylactic gastrojejunostomy increases morbidity, Sohn et al.[14] reported that no difference was seen in morbidity rates between those with and without the procedure, and that only 2% of the patients who had undergone the procedure suffered from a symptom caused by obstruction of the gastrointestinal tract before death.

The role of prophylactic gastrojejunostomy in advanced pancreatic cancer has been discussed for a long time. An analysis of the results of a randomized trial in 87 patients without duodenal obstruction showed that late gastric outlet obstruction developed in 19% of the patients without gastrojejunostomy during a $1^1/_2$-year period, while interval gastric outlet obstruction developed in none of the patients with prophylactic gastrojejunostomy before death.[15] Moreover, the effectiveness of laparoscopic palliative surgery, compared with conventional open procedures, has been confirmed.[16] Laparoscopic palliation has shown a decrease in morbidity, mortality, and in the amount of anodynes consumed.

Pancreatic stent placement was shown to be very effective in relieving pain arising from pancreatic duct obstruction caused by cancer invasion.[17] For patients suffering from continuous severe pain, thoracoscopic splanchnicectomy is confirmed to be an effective method.[18] Many different methods are utilized today to relieve pain.

Chemotherapy

No great effectiveness has been found with chemotherapy in pancreatic cancer.[19–22] Very recently, gemcitabine, an inhibitor of nucleic acid synthesis, was administered to more than 3000 patients with locally advanced or metastatic pancreatic cancer.[23] Among the 982 patients who had available data for tumor response, according to the disease-related symptom improvement (DRSI) index, only 14 patients with complete response (CR) and 104 with partial response (PR) were confirmed (a 12.0% overall response rate). The DRSI index is used to assess the effectiveness of treatment based on a decrease in pain or improvement of the patient's overall physical condition. However, if there is no evidence of either factor, the effectiveness is judged based on a weight gain of more than 7% (excluding edema). The median survival in this study was 4.8 months, and the 1-year survival rate was 15%. Taking into consideration that 80% of the patients were in stage IV, however, phase III trials of gemcitabine are anticipated.

Japanese and Italian groups have reported the results of a phase II trial of docetaxel[24] and those of a phase II trial with intensive weekly chemotherapy using cisplatin (CDDP), 5-FU, epirubicin, and leucovorin.[25] Both trials showed low response rates, 0% and 13%, respectively, indicating no effectiveness in pancreatic cancer. We believe that new drugs with novel mechanisms need to be developed in the future. At the same time, it should be taken into consideration that the conventional assessment systems for drug response rates should be changed, with the adoption of new ones, such as the DRSI index. In regard to QOL, one remarkable report has detailed a specific evaluation system for determining QOL in patients with pancreatic cancer. This is the questionnaire module, QLQ-PAN26 (which consists of 26 different questions regarding such factors as symptoms of pancreatic cancer, side effects of the therapies used, and emotional point of view), to supplement the QLQ-C30 of the European Organization for Research and Treatment of Cancer (EORTC).[26] The use of this system will become necessary, as an international standard, to evaluate the efficacy of various therapies for pancreatic cancer.

Biological therapy

New trials of therapies for pancreatic cancer are being conducted in the clinical setting. Using an endoscopic ultrasound (EUS)-guided fine-needle injection technique, Chang et al.[27] delivered 3–9 $\times$ 10^9 mixed lymphocytes cells (which were cocultures of host and allogeneic donor cells) into nonresectable tumors of the pancreas. There were two patients with PR and one with a minor response, in the eight patients examined; there were no severe side effects, and this treatment produced a median survival of 13.2 months. In one patient, who had liver metastasis prior to therapy, EUS-guided biopsy of the liver lesion after 36 months' follow-up showed no residual cancer cells. EUS-guided drug delivery techniques will be developed and employed clinically in various forms. In 33 patients with resected pancreatic cancer, Nukui et al.[28] compared 16 patients who were treated according to the Gastrointestinal Tumor Study Group (GITSG) protocols with 17 patients who received therapy combining 5-FU, CDDP, and interferon-α (INF-α) with 45–54 Gy extracorporeal irradiation. They reported that the 2-year survival rate in the latter 17 patients was 84%, while the 2-year survival rate in the former 16 patients was 54%. IFN-α has been considered to reinforce the effectiveness of 5-FU, CDDP, and irradiation. Scheithauer et al.[29] used a combination of gemcitabine, epirubicin, and grannulocyte colony-stimulating factor (G-CSF) for 66 patients with distant metastasis; they reported 1 patient with CR and 13 with PR (a 21% response rate), a median survival of 7.8 months, and a 43% rate of symptom improvement. These results confirm that this protocol is more effective than gemcitabine therapy alone. Motoi et al.[30] have shown that a mixed infection of an adenovirus that can grow only in *p53*-deficient cancer cells, together with an adenovirus coding cytokine genes such as interleukin-2 (IL-2) and IL-12, augments the amounts of cytokines by 110–370 times. This treatment produced growth suppression of tumors in a mouse model of severe combined immunodeficiency (SCID) bearing human pancreatic cancer cells. These results will assist us in developing new gene therapies for pancreatic cancer.

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