

Trial of Neoadjuvant Chemoradiation Therapy for Borderline Resectable Pancreatic Cancer

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ABSTRACT

Purpose : The purpose of this report was to assess therapeutic outcome of neoadjuvant chemoradiation therapy (NACRT) for borderline resectable pancreatic cancer.

Patients and Methods : The subjects were seven patients who underwent NACRT for borderline resectable pancreatic cancer from 2009 to 2013 at our institute. The patients received neoadjuvant chemotherapy with S-1 or gemcitabine in addition to standard fractionated radiation therapy. We retrospectively investigated their therapeutic outcomes.

Results : Resectability after NACRT was 57% (4/7), and these four patients underwent elective pancreatic resection, consisting of pancreaticoduodenectomy (PD) in one patient, distal pancreatectomy (DP) in two and distal pancreatectomy with en bloc celiac axis resection (DPCAR) in one. R0 resection was obtained in all patients who underwent resection. The other three patients did not undergo pancreas resection due to the presence of contraindicating factors such as liver metastases or lung metastases during or just after NACRT. In these patients, the primary lesions decreased in size slightly, but vascular invasion was still observed. Among the four patients who underwent pancreas resection, two are alive without recurrence at 6 and 19 months after starting treatment and one is alive with lymph node metastases at 24 months. The remaining patient died due to carcinomatosa 17 months after the operation.

Conclusion : NACRT for borderline resectable pancreatic cancer seems to be promising in terms of R0 surgical resection, while novel non-surgical treatment for advanced pancreatic cancer is needed to prevent distant metastasis.
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Key words : neoadjuvant chemoradiation therapy, borderline resectable, pancreatic cancer

INTRODUCTION

Surgical resection offers the only possible chance of cure for pancreatic cancer. However, most patients are diagnosed at an advanced stage, and only 10 to 20% of patients are resectable at the time of the initial diagnosis¹. Even for patients who have undergone curative resection

(R0), survival analysis has revealed a poor outcome because of cancer recurrence².

Surgery followed by adjuvant chemotherapy is the standard care for resectable pancreatic cancer. Because of the low resection rate, the role of neoadjuvant chemoradiation therapy in increasing resectability, curability, and finally survival rate for borderline resectable disease is a matter of

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the patient was judged to be resectable, we performed the operation within two to four weeks after the end of NACRT. If the patient was judged to be borderline resectable, on the other hand, we continued to administer chemotherapy at the same frequency until the patient was deemed resectable. Salvage chemotherapy was administered to one patient who was judged to have progressive disease. Treatment effectiveness was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST)⁶. The clinical course after NACRT was evaluated in terms of resectability, curability, recurrence rate and survival.

RESULTS

The seven patients who underwent NACRT were three men and four women with a median age of 67 years (range 56-77 years). The median of the tumors' largest diameters was 41 mm (range 14-80 mm). Clinical staging was determined according to the General Rules for the Study of Pancreatic Cancer (The 6th Edition, Revised Version) by the Japan Pancreas society⁷. Pancreatic cancers were located in the head in two patients and in the body in the other five. NACRT consisted of S-1 in four patients and GEM in three. The reason for borderline resectability was PV invasion in six patients and common hepatic artery invasion in one. There were no cases requiring dose de-escalation, dose skipping or discontinuation of chemotherapy. All patients completed their courses of radiation therapy. As for adverse events, loss of appetite happened in one patient and slight myelosuppression happened in three patients, but none of these events necessitated supportive care. Table 1 shows the patient characteristics and reasons for borderline resectability.

The outcome of NACRT was classified as partial response in three patients, stable disease in one, and progressive disease in three. In all cases of partial response, invasion to the CHA and PV disappeared after NACRT. The case of stable disease retained invasion to the PV, but R0 resection and vascular reconstruction were nevertheless achieved safely. All cases of progressive disease were classified as such due to distant metastatic lesions (liver metastases in two patients and lung metastases in one). In addition, the primary lesions decreased in size slightly after NACRT, but vascular invasion was still observed.

Four of the seven patients (57%) underwent surgical

Table 1. Patient characteristics and factors in borderline resectable cases

Factor		N
Sex (M : F)		3 : 4
Age (years)	Median (range)	67 (56-77)
Size (mm)	Median (range)	41 (14-80)
Location	Ph	2
	Pb	5
Chemotherapy	TS-1	4
	GEM	3
BR factor	PV invasion	6
	CHA invasion	1

(M : male ; F : female ; N : number ; Ph : pancreas head ; Pb : pancreas body ; GEM : gemcitabine ; BR : borderline resectable ; PV : portal vein ; CHA : common hepatic artery)

resection, which consisted of PD in one patient, DP in two, and DPCAR in one. In all four patients who underwent surgical resection, R0 resection was achieved successfully. All surgical patients received adjuvant chemotherapy. Two of the four are alive without recurrence at 6 and 19 months after starting treatment, respectively, and a third patient is alive at 24 months with locoregional lymph node metastases in the abdomen. The fourth patient, who was treated with DPCAR, died due to carcinomatosa at 17 months after starting treatment. All patients who did not undergo surgical resection changed their chemotherapy from GEM to S-1, but all died within six months after starting treatment (Table 2).

DISCUSSION

In patients with resectable pancreatic cancer, the high rate of development of both local recurrence and distant metastases in the early postoperative period is the main reason for poor prognosis. Previously, extended lymphadenectomy was performed for pancreatic cancer to improve outcome, but most randomized controlled trials demonstrated that extended lymphadenectomy in radical PD did not improve long-term survival as compared with standard PD⁸⁻¹¹. These results indicate the limitations of surgery alone for pancreatic cancer. Therefore, multidisciplinary therapy that combines surgical resection with chemotherapy or radiation therapy seems necessary to improve prognosis for pancreatic cancer.

Conventional therapy for pancreatic cancer is surgery

Table 2. Patient characteristics and therapeutic outcomes of patients who underwent neoadjuvant chemoradiation therapy

Age (years)	Sex	Location	Stage	BR factor	Chemo	Response	Operation	Recurrence	Status (months)
56	M	Pb	T4N1 Stage IVa	CHA	GEM	PR	DP-CAR	carcinomatosa	Dead (17)
76	F	Pb	T4N1 Stage IVa	PV	TS-1	PR	DP	Lymph nodes metastasis	Alive (24+)
66	F	Pb	T4N0 Stage IVa	PV	TS-1	PR	DP	None	Alive (19+)
61	F	Ph	T4N0 Stage IVa	PV	TS-1	SD	PD	None	Alive (6+)
77	M	Pb	T4N1 Stage IVa	PV	GEM	PD *Liver metastasis	None		Dead (6)
63	M	Pb	T4N1 Stage IVa	PV	GEM	PD *Lung metastasis	None		Dead (4)
71	F	Ph	T4N1 Stage IVa	PV	GEM	PD *Liver metastasis	None		Dead (5)

(M : male ; F : female ; N : number ; Ph : pancreas head ; Pb : pancreas body ; GEM : gemcitabine ; BR : borderline resectable ; PV : portal vein ; CHA : common hepatic artery ; PR : partial response ; SD : stable disease ; PD : progressive disease ; PD : pancreaticoduodenectomy ; DP : distal pancreatectomy ; DPCAR : distal pancreatectomy with en bloc axis resection ; * : the reason for PD ; Status : prognosis and time from treatment start date)

followed by adjuvant chemotherapy. Unfortunately, patients often cannot receive enough adjuvant therapy because of locally advanced disease or post-operative complications. This difficulty may be overcome by performing neoadjuvant therapy, which allows more patients to receive potentially effective treatment. The effectiveness of neoadjuvant therapy for borderline resectable pancreatic cancer is still controversial. However, several recent reports have suggested that neoadjuvant therapy for borderline resectable pancreatic cancer might improve survival outcome. In 2005, Cunha et al. reported on neoadjuvant chemoradiation therapy in 61 patients with radiographically unresectable pancreatic cancer and concluded that patients whose cancer became resectable achieved prolonged survival, to a degree comparable with survival after resection for initially resectable pancreatic cancer¹². Likewise, in 2008, Katz et al. reported on neoadjuvant therapy in 160 patients classified as borderline resectable. They demonstrated that median survival was 40 months for the 66 patients who completed both surgical resection and neoadjuvant therapy, in contrast to 13 months for the 94 patients who did not undergo pancreatectomy¹³.

The following advantages of NACRT are expected :

first, neoadjuvant therapy is a potentially useful strategy for downstaging borderline resectable pancreatic cancer to allow surgical resection. Second, neoadjuvant therapy can avoid unnecessary surgical resection, it enables the identification of patients who already have occult metastatic disease during neoadjuvant therapy. Finally, neoadjuvant therapy is not affected by the post-operative complications that may delay surgical recovery. Neoadjuvant therapy does have disadvantages, the most serious of which is patient drop-out. In our three patients who could not receive surgical resection due to distant metastases, the treatment protocol we chose emphasized local treatment. In order to avoid treatment-related adverse events, the chemotherapeutic dosages had to be decreased. Radiation therapy is effective for local sites, but its ability to control distant metastasis is poor. In our past experience, chemoradiation therapy has a stronger local reduction effect than chemotherapy alone, but it is associated with a greater frequency of distant metastasis. Of the two types of neoadjuvant therapy for pancreatic cancer, it is controversial whether chemoradiation therapy or chemotherapy alone is more effective. Because it is not clear that neoadjuvant radiation therapy is effective, we plan to emphasize the con-

trol of distant metastases through neoadjuvant chemotherapy alone.

CONCLUSION

NACRT was performed in 57% (4/7), and R0 resection was achieved in all of these cases. NACRT for borderline resectable pancreatic cancer may be a promising means of enabling curative surgical resection, while a novel non-surgical treatment for advanced pancreatic cancer is needed to prevent distant metastasis.

Authors have no conflict of interest.

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