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Clinical impact of conversion surgery in patients with locally advanced pancreatic cancer

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Abstract

Background : Unresectable pancreatic cancer cases that were converted to resection after non-surgical treatment have been reported as conversion surgery (CS). Long-term survival following CS has been reported. We aimed to evaluate patient outcomes following CS for locally advanced pancreatic cancer (LA-PC).

Materials & Methods : We retrospectively reviewed the data of 61 patients with LA-PC who visited Tokyo Medical University Hospital between February 2010 and April 2018. We evaluated the resectability status every three months using multimodal imaging and planned CS in cases considered eligible for R0 resection.

Results : Among 61 patients diagnosed with LA-PC, 22 patients (36.0%) underwent CS. The conversion rate was significantly higher in cases with lower median CA19-9 values before treatment initiation and at three months after initiating non-surgical treatment ($p=0.046$, $p=0.002$). Patients who underwent CS had significantly longer median survival time than those who did not (45.0 vs 13.0 mo, $p<0.001$).

Conclusions : CS may improve the prognosis of patients with LA-PC who respond to non-surgical treatment.

Introduction

The prognosis of patients with pancreatic cancer is generally poor[1]. However, in recent years, the prognosis of these patients has improved due to the introduction of novel and effective chemotherapy. There have been many reports on conversion surgery (CS) after the alteration of the tumor status from unresectable to resectable following chemotherapy or chemoradiotherapy. The prognosis of patients with unresectable pancreatic cancer who underwent resection after treatment has been reported to be better than that of patients who did not undergo resection after treatment[2)3)]. However, the clinical benefits of CS remain controversial.

This study aimed to evaluate the benefit of CS for patients with initially locally advanced pancreatic cancer (LA-PC).

Material and Methods

Study Population

The initial patient pool included all patients with LA-PC treated at Tokyo Medical University hospital between January 2010 and April 2018. Resectability status was assessed using multi detector computed tomography (MDCT) according to the National Comprehensive Cancer Network (NCCN) guidelines, version 2.2017[4]. LA-PC was defined as follows : Head/uncinate process pancreatic cancer : tumor contact with the superior mesenteric artery (SMA) of greater than 180 degrees, celiac trunk (CA) or contact with the first jejunal SMA branch ; Body and tail pancreatic cancer : tumor contact with the superior mesenteric artery (SMA) or

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celiac trunk (CA) of greater than 180 degrees, and tumor contact with celiac trunk (CA) and aortic involvement.

All patients had a histological diagnosis of pancreatic ductal adenocarcinoma (PDAC) based on the biopsies performed before treatment or specimen resection. During chemotherapy or chemoradiotherapy, most of these patients were tested for CA19-9 levels every month and the tumor resectability status was reassessed using MDCT, which evaluated the effect of non-surgical treatment. The patients flow chart is shown in Fig. 1. Patients who could not attend follow-up or undergo evaluation of the effect of treatment by images were excluded. We used radiation therapy until October 2016 and shifted to more effective systemic chemotherapy thereafter. The effect of non-surgical treatment was evaluated using multimodal imaging based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. We planned CS in cases in which the tumor had shrunk and R0 resection was possible. We established two groups, one for LA-PC patients who underwent CS and the other for LA-PC patients who did not undergo CS, then compared outcomes. This retrospective study was approved by the ethics committee of the Tokyo Medical University Institutional Review Board (IRB approval number : SH4034).

Date collection

Data on the following variables were collected : (1) pretreatment factors (sex, age, tumor location and size, presence of lymphadenopathy, serum albumin, CA19-9 levels, chemotherapy regimens, radiation therapy, and resection) ; (2) tumor response following non-surgical treatment based on the RECIST criteria (complete response ; partial response ; stable disease ; or progressive disease) and CA19-9 levels. (3) operation methods (pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy) ; (4) pathological diagnosis (lymph node status, surgical margin status, and pathological evaluation according to the Evans classification) ; and (5) postoperative outcomes. Overall survival time was calculated starting from the time of the first treatment to the last follow-up or death (intention-to-treat analyses).

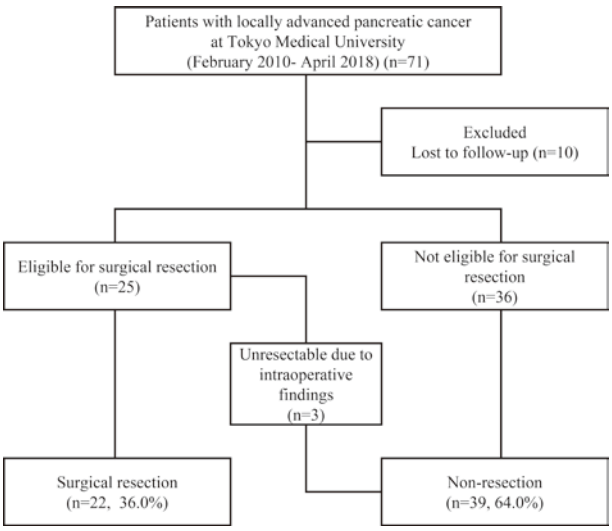

Fig. 1 Flowchart of patient selection

Statistical analysis

All statistical analyses were performed using the chi-square test and the Mann-Whitney U test. The overall survival (OS) was analyzed using the Kaplan-Meier method, and the log-rank test was used for comparison between the two groups. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and p-value <0.05 was considered statistically significant.

Results

Patients

The patient flowchart for this study is shown in Fig. 1. A total of 71 patients were diagnosed with LA-PC according to NCCN guidelines ; of these, 61 patients received non-surgical treatment followed by evaluation of the effect of non-surgical treatment, whereas 10 patients were lost to follow-up and were excluded.

Twenty-five patients (40.9%) were eligible for CS after presenting a favorable response to non-surgical treatment. The indication for CS after non-surgical treatment was based on the RECIST criteria, and there were 25 cases in which R0 resection could be achieved. CS was performed in 22 patients (36.0% of all LA-PC patients, 88.0% of those eligible for resection). Three patients could not undergo CS because of intraoperative findings (peritoneal dissemination). Tumor location was at the side of the pancreas head (n =15, 68.1%), and median tumor size was 3.1 cm (2.2-6.7). The median value of CA19-9 levels at initial presentation was 117 U/mL (1.3-5,556.0).

Chemotherapy regimens were gemcitabine-based protocol as the first chemotherapeutic regimen for all patients. No patients received FOLFIRINOX. During chemotherapy, radiation therapy was administered in 7 patients (31.8%) in the resected group and 8 patients (20.5%) in the non-resected group. The mean time from the beginning of chemotherapy or chemoradiotherapy to resection was 5.0 months.

The median value of CA19-9 levels at 3 months after the beginning of non-surgical treatment was 24.3 U/mL (0.6-675.6) among the resected patients, which was significantly lower than that of non-resected patients (76.5 U/mL [1.0-9439.0] ; p=0.001).

We performed pancreaticoduodenectomy in 13 patients (59.1%), distal pancreatectomy in 7 patients (32.0%), and total pancreatectomy in 2 patients (9.0%). Three cases of major arterial resection occurred in distal pancreatectomy with en bloc celiac axis resection, while 1 case

Table 1 Patients' characteristics

	Resection (*n*=22)	Non-Resection (*n*=39)	*p* value
Age (years)	65.5 (43-78)	69.6 (46-84)	0.212
Sex			0.348
Male	10 45.5%	25 64.1%	
Female	12 54.5%	14 35.9%	
Tumor location			0.097
Ph	15 68.1%	18 46.1%	
Pbt	7 32.9%	21 53.9%	
Tumor diameter, mm,	3.1 (2.2-6.7)	3.2 (1.6-7.5)	0.348
Lymph node metastasis			0.121
Positive	9 40.9%	15 39%	
Negative	13 51.1%	24 61.5%	
Pretreatment albumin (g/dL)	3.9 (3.2-4.5)	3.9 (3.0-4.9)	0.769
Pretreatment CA19-9 levels (U/mL)	117 (1.3-5,556.0)	290.1 (3.0-16,110.0)	0.046
CA19-9 levels (U/mL) after 3 months	24.3 (0.6-675.6)	76.4 (1.0-9,439.0)	0.002
Tumor reduction rate (%)	22.8 (+3.4-50.6)	9.4 (+64.4-30.3)	<0.001
RECIST			
Complete response	0	0	
Partial response	8 36.4%	2 5.2%	
Stable disease	14 63.6%	27 69.2%	
Progressive disease	0	10 25.6%	
Radiation therapy			0.325
Radiation therapy	7 32.9%	8 20.5%	
Without Radiationtherapy	15 68.1%	31 79.5%	

Ph pancreas head, *Pbt* pancreas body and tail, *CA19-9* carbohydrate antigen 19-9, *RECIST* Response Evaluation Criteria In Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* pancreaticoduodenectomy, *CRT* chemoradiotherapy

involved superior mesenteric artery resection and reconstruction due to intraoperative findings. R0 resection was achieved in 16 patients (72.7%). The operation time was 393 min (range 221-1,000), and the intraoperative blood loss was 680.5 mL (range 20-15,530). There were no cases of mortality. Postoperative outcomes and pathological findings are shown in Table 2.

A pathological evaluation was performed according to the Evans classification, resulting in 12 patients (27.3%) with Grade I tumors, 12 patients (54.5%) with Grade IIa tumors, 2 patients with Grade III tumors, and 2 patients (9.0%) with Grade IV tumors. A total of 20 patients (90.9%) received postoperative adjuvant therapy. The remaining 2 patients could not be introduced to postoperative therapy due to a decline in the activities of daily living (ADL). Although we analyzed the differences in prognosis for each regimen of postoperative therapy (Gemcitabine; *n*=7, tegafur/gimeracil/oteracil (S-1); *n*=12, Gemcitabine+nab-paclitaxel (GnP); *n*=1), we found that there were no significant differences for each regimen (data not shown). Among the 20 patients who received adjuvant therapy, 13 were able to continue the same regimen for 6 months. The remaining 6 patients found it difficult to continue adjuvant therapy because of decreased ADL or needed a regimen change due to recurrence.

Survival analysis

The median observation period in the resected group was 30 (range, 6-50) months. The median survival from the beginning of non-surgical treatment was 45.0 months for the resected group and 13.0 months for the non-resected group ($p < 0.001$; Fig. 2). Sixteen patients (72.7%) developed recurrence during the follow-up period after resection. The primary site of recurrence was a distant organ in all patients (liver [$n = 2$], lymph nodes [$n = 3$], lung [$n = 4$], and peritoneal dissemination [$n = 7$]).

The median postoperative RFS in the resected group was 15.0 months (95% CI, 5.2-24.0). Postoperative survival was significantly longer in patients with normal CA19-9 levels after neoadjuvant therapy than in patients with elevated CA19-9 levels ($p = 0.001$) (Fig 3).

Discussion

In this study, we examined the prognosis of patients with pancreatic cancer who underwent CS. The long-

Table 2 Surgical results and pathological findings

	(*n* = 22)
Operative procedures	
PD	13 59.0%
DP	7 31.8%
TP	2 9.0%
PV/SMV resection	12 54.5%
Major arterial resection	4 18.1%
Operation time (min)	393 (221-1,000)
Intraoperative blood loss (mL)	680.5 (20-15,530)
Post-operative complications Clavien-Dindo >IIIa	3 13.6%
Pancreatic fistula (grade B/C)	4 18.1%
Mortality	0 0.0%
Resction margin status	
R0	16 72.7%
R1	6 27.3%
Lymph node metastasis	
Yes	18 81.9%
No	4 18.1%
Evans classification	
I	6 27.3%
IIa	12 54.5%
IIb	0 0.0%
III	2 9.0%
IV	2 9.0%
Postoperative adjuvant chemotherapy	20 90.9%
GEM	7 35.0%
S-1	12 60.0%
GnP	1 5.00%
Recurrence	16 72.7%
Liver metastasis	2 12.5%
Lung metastasis	4 25.0%
Lymph node metastasis	3 18.8%
Peritoneal dissemination	7 43.7%

PD pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *PV* Portal vein, *SMV* Superior mesenteric vein ; *GEM* Gemcitabine, *GnP* the combination of nanoparticle albumin-bound paclitaxel and gemcitabine

term prognosis of patients with CS was significantly better than that of patients without CS.

Compared to other carcinomas, pancreatic cancer has a poor prognosis, and the 5-year survival rate is extremely low in patients with unresectable tumors[1]. However, in recent years, advances in chemotherapy have improved the prognosis of pancreatic cancer, and some studies have reported that long-term survival can be achieved after treatment with CS[2)3)5-8]. Although there is currently no consensus on the timing of resection after treatment, Satoi et al. reported a better prognosis in patients who underwent CS after >8 months of nonsurgical treatment[2].

Operation time and blood loss tend to be higher in conversion surgeries than in conventional pancreatic cancer surgery, but no significant differences in complication rates have been observed. Thus, CS may be safely performed. Some reports have indicated that CA19-9 levels and nutritional status are associated with the prognosis and outcomes of patients with pancreatic cancer[9)10)]. Fluctuations in CA19-9 levels after treatment or surgery were shown to predict therapeutic efficacy and prognosis[11-13)]. Boone et al. stated that the CA19-9 response was associated with R0 ratio, pathology results, and OS in all patients who underwent neoadjuvant therapy for pancreatic cancer before resection[12]. Bergquist et al. concluded that neoadjuvant chemotherapy should be administered to patients with high CA19-9 levels, including

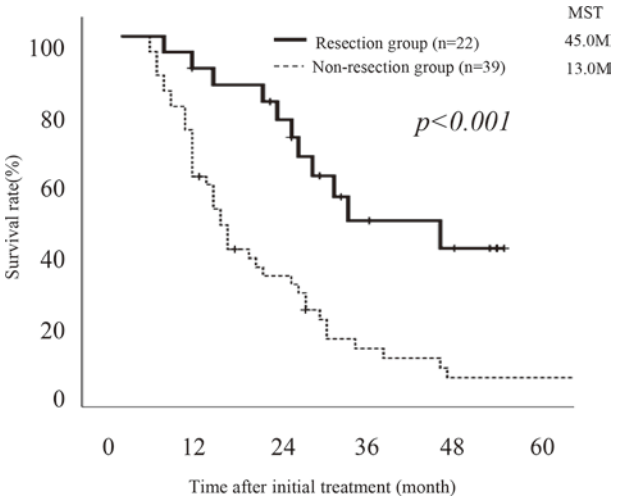

Fig. 2 The overall survival from the start of initial treatment of patients who did and did not undergo conversion surgery. The median survival was significantly better in the resected group than in the unresected group (45.0 vs 13.0 months, p=0.004).

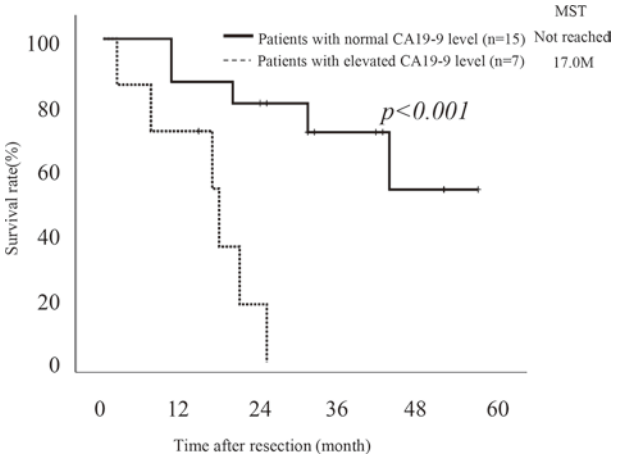

Fig. 3 The comparison of postoperative overall survival between patients with normal level of CA19-9 value after neoadjuvant therapy and patients with above normal levels of CA19-9 values after neoadjuvant therapy. The median survival was significantly better in patients with normal levels of CA19-9 value (not reached vs 17.0 months, p=0.001).

those with resectable cancer[11]. In addition, Dong et al. reported that serum CA19-9 levels, age, and histological classification were independent prognostic factors for OS in patients with resectable pancreatic cancer, and the optimal cutoff for CA19-9 was reported to be 338.45 U/mL[9]. In patients with early recurrence after pancreatectomy, it has been reported that a preoperative CA19-9 level of ≥100 U/mL is a risk factor for early recurrence after resection[14)15)]. Thus, for resectable pancreatic cancer and borderline resectable pancreatic cancer, some studies have reported CA19-9 to be a prognostic factor, and a link was predicted between the timing and indication of CS. However, no significant difference was observed in this study.

This study has several limitations, including its small sample size, retrospective nature, and limited follow-up period. In addition, as another limitation, various non-surgical treatments were included ; therefore, an accurate evaluation was difficult. Further accumulation of cases, follow-up, and prospective studies are needed.

Conclusion

In conclusion, improving prognosis by performing CS in patients with initially unresectable pancreatic cancer may be possible. However, the indication and timing of CS is unclear. Therefore, further prospective studies are needed to identify the indication and timing of CS.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1) Siegel RL, Miller KD, Jemal A : Cancer statistics, 2018. CA Cancer J Clin **68**(1) : 7-30, 2018. PMID : 29313949. DOI : 10.3322/caac.21442
2) Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, Eguchi H, Sho M, Wada K, Shinchi H, Kwon AH, Hirano S, Kinoshita T, Nakao A, Nagano H, Nakajima Y, Sano K, Miyazaki M, Takada T : Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments : results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci **20**(6) : 590-600, 2013. PMID : 23660962. DOI : 10.1007/s00534-013-0616-0
3) Kato K, Kondo S, Hirano S, Tanaka E, Shichinohe T, Tsuchikawa T, Matsumoto J : Adjuvant surgical therapy for patients with initially-unresectable pancreatic cancer with long-term favorable responses to chemotherapy. J Hepatobiliary Pancreat Sci **18**(5) : 712-716, 2011. PMID : 21455748. DOI : 10.1007/s00534-011-0391-8
4) Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, Benson AB 3rd, Binder E, Cardin DB, Cha C, Chiorean EG, Chung V, Czito B, Dillhoff M, Dotan E, Ferrone CR, Hardacre J, Hawkins WG, Herman J, Ko AH, Komanduri S, Koong A, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Scaife C, Thayer S, Weekes CD, Wolff RA, Wolpin BM, Burns J, Darlow S : Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw **15**(8) : 1028-1061, 2017. PMID : 28784865. DOI : 10.6004/jnccn.2017.0131

5) Barugola G, Partelli S, Crippa S, Capelli P, D'Onofrio M, Pederzoli P, Falconi M : Outcomes after resection of locally advanced or borderline resectable pancreatic cancer after neoadjuvant therapy. Am J Surg **203**(2) : 132-139, 2012. PMID : 21824596. DOI : 10.1016/j.amjsurg.2011.03.008
6) Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, Wuthrick E, Williams TM, Reardon J, Ellison EC, Bloomston M, Bekaii-Saab T : Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg **22**(4) : 1153-1159, 2015. PMID : 25358667. DOI : 10.1245/s10434-014-4225-1
7) Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, Strobel O, Jäger D, Ulrich A, Büchler MW : Locally advanced pancreatic cancer : neoadjuvant therapy with Folfirinox results in resectability in 60% of the patients. Ann Surg **264**(3) : 457-463, 2016. PMID : 27355262. DOI : 10.1097/SLA.0000000000001850
8) Strobel O, Berens V, Hinz U, Hartwig W, Hackert T, Bergmann F, Debus J, Jäger D, Büchler MW, Werner J : Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. Surgery **152**(3) : S33-S42, 2012. PMID : 22770956. DOI : 10.1016/j.surg.2012.05.029
9) Dong Q, Yang XH, Zhang Y, Jing W, Zheng LQ, Liu YP, Qu XJ : Elevated serum CA19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma : a pilot study. World J Surg Oncol **12** : 171, 2014. PMID : 24890327. DOI : 10.1186/1477-7819-12-171
10) Glazer ES, Rashid OM, Pimiento JM, Hodul PJ, Malafa MP : Increased neutrophil-to-lymphocyte ratio after neoadjuvant therapy is associated with worse survival after resection of borderline resectable pancreatic ductal adenocarcinoma. Surgery **160**(5) : 1288-1293, 2016. PMID : 27450715. DOI : 10.1016/j.surg.2016.04.039
11) Bergquist JR, Puig CA, Shubert CR, Groeschl RT, Habermann EB, Kendrick ML, Nagorney DM, Smoot RL, Farnell MB, Truty MJ : Carbohydrate antigen 19-9 elevation in anatomically resectable, early stage pancreatic cancer is independently associated with decreased overall survival and an indication for neoadjuvant therapy : A National Cancer Database study. J Am Coll Surg **223**(1) : 52-65, 2016. PMID : 27049786. DOI : 10.1016/j.jamcollsurg.2016.02.009
12) Boone BA, Steve J, Zenati MS, Hogg ME, Singhi AD, Bartlet DL, Zureikat AH, Bahary N, Zeh HJ 3rd : Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. Ann Surg Oncol **21**(13) : 4351-4358, 2014. PMID : 25092157. DOI : 10.1245/s10434-014-3842-z
13) Williams JL, Kadera BE, Nguyen AH, Muthusamy VR, Wainberg ZA, Hines OJ, Reber HA, Donahue TR : CA19-9 Normalization during pre-operative treatment predicts longer survival for patients with locally progressed pancreatic cancer. J Gastrointest Surg **20**(7) : 133142, 2016. PMID : 27114246. DOI : 10.1007/s11605-016-3149-4
14) Hosokawa Y, Nagakawa Y, Sahara Y, Takishita C, Katsumata K, Tsuchida A : Serum SPan-1 is a significant risk factor for early recurrence of pancreatic cancer after curative resection. Dig Surg **34**(2) : 125-132, 2017. PMID : 27658221. DOI : 10.1159/000449041
15) Sugiura T, Uesaka K, Kanemoto H, Mizuno T, Sasaki K, Furukawa H, Matsunaga K, Maeda A : Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma. J Gastrointest Surg **16**(5) : 977-985, 2012. PMID : 22411488. DOI : 10.1007/s11605-012-1859-9

局所進行膵癌患者における Conversion surgery の臨床的意義

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【要旨】【背景】 切除不能膵癌のうち非外科的治療が奏功し切除へ移行した症例は conversion surgery（CS）として報告されており、CS 後の長期生存が報告されている。局所進行膵癌（LA-PC）に対する CS の治療成績を評価することを目的とした。
【対象と方法】 2010 年 2 月から 2018 年 4 月の間に東京医科大学病院を受診した LA-PC 症例 61 例を対象に後方視的に検討した。3 か月おきに画像検査を行い切除可否の評価を行い、R0 切除を達成しうると考えられる症例に CS を予定した。
【結果】 LA-PC と診断された 61 例のうち、22 例（36.0%）に対して CS を行った。手術へ移行できた症例では移行できなかった症例と比較して治療前および非外科的治療 3 か月後の CA19-9 値の中央値が優位に低かった（p=0.046, p=0.002）。CS を施行できた症例ではできなかった症例と比較して生存期間が優位に延長していた（45.0 か月 vs 13.0 か月、p<0.001）。
【結論】 CS は非外科的治療に奏功した LA-PC 症例の予後を改善する可能性がある。

〈キーワード〉 Conversion surgery、膵癌、切除不能膵癌