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Original article

Survival benefit of conversion surgery for patients with initially unresectable pancreatic cancer who responded favorably to nonsurgical treatment

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Abstract

Background: Conversion surgery (CS) is expected as a new therapeutic strategy for patients with unresectable pancreatic cancer (UR-PC). We analyzed outcomes of CS for patients with UR-PC and evaluated the survival benefit of CS.

Methods: Thirty-four patients diagnosed with UR-PC according to the National Comprehensive Cancer Network guideline underwent CS in our hospital. Resectability was considered by multimodal images in patients who underwent nonsurgical treatment (NST) for more than 6 months. CS was performed only in patients who were judged to be able to undergo R0 resection.

Results: Twenty-six patients had locally advanced PC, and 8 had distant metastases. The median duration of NST was 9 (range, 5-44) months. R0 resection was achieved in 30 patients (88.2%). Six patients (17.6%) showed Evans grade ≥ III. Three- and 5-year overall survival (OS) rates from initial treatment were 74% and 56.9%, respectively, with median survival time (MST) of 5.3 years. Patients with Evans grade ≥ III had a better prognosis than those with Evans grade < III (p=0.0092, Log–rank test).

Conclusions: CS might have survival benefit to patients with UR-PC who responded favorably to NST.

Introduction

Pancreatic cancer (PC) is a representative disease of refractory malignant tumors, and its prognosis is the most dismal among gastrointestinal cancers. The number of patients with PC is increasing worldwide.[1,2] In Japan, the number of deaths caused by PC reached 31,866 in 2015.[3] Recently, although various diagnostic modalities have developed remarkably, detecting early stage of PC is still difficult. Therefore, it is often diagnosed during its advanced stage, and resectable PC accounts for only 10 to 20% of all patients.[4] Furthermore, its prognosis is extremely poor, and the 5-year survival rate is less than 10%.[5] For pancreatic specialists, improving the prognosis of PC is the top priority, but it is obvious that there is a limit to trying to find solutions to surgical resection only. It goes without saying that it is an urgent matter to establish an effective therapeutic strategy combined with multimodal treatment including surgical resection.

In recent years, patients with unresectable malignancies can obtain favorable treatment effect for a certain period of time by nonsurgical treatment (NST) such as chemo(radio)therapy and can convert to surgical resection. This surgical strategy is called

"conversion surgery (CS)."[6,7] Several articles have also been reported for CS in patients with unresectable PC (UR-PC),[8-16] and its prognostic effect to CS have been mentioned. Hereafter, because of the remarkable progress of NST, candidates with UR-PC for CS is expected to increase. However, whether conversion from NST with high treatment effect to CS brings true benefit to patients with UR-PC is unclear.

In this study, patients with UR-PC who underwent CS were retrospectively analyzed, and we aimed to clarify the survival benefit of CS for patients with UR-PC who obtain favorable treatment effect from NST.

Methods

Patients

Forty-three patients with initially UR-PC who responded favorably to NST and were planned to perform CS at the Hokkaido University Hospital Department of Gastroenterological Surgery II from April 2007 to October 2017 were identified. Thirty-four (79.1%) from 43 patients could be performed CS. The remaining patients underwent only

exploratory laparotomy because unresectable lesions were detected during surgery. Five of 9 patients had new hepatic metastases; 2 patients had new peritoneal dissemination. Superior mesenteric artery (SMA) invasion of the tumor exceeded to 180° was comfirmed in 2 patients, intraoperatively. All patients had ductal adenocarcinoma of the pancreas cytologically or pathologically proved by endoscopic ultrasound-guided fine-needle aspiration. Multimodal image findings such as multi-detector row computed tomography, contrast-enhanced ultrasonography, and gadoxetic acid-enhanced magnetic resonance imaging were considered, and we certainly confirmed that all patients had UR-PC initially according to the National Comprehensive Cancer Network (NCCN) guideline version 2.2017.[17] With regard to the common hepatic artery (CHA), we diagnosed UR-PC when safe and complete resection and reconstruction were very difficult because of the tumor extension to the proper hepatic artery. The treatment effect of NST was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[18] Our criteria in CS for patients with UR-PC were as follows: i) treatment effect was evaluated as stable disease (SD), partial response (PR), or complete response (CR) in RECIST version 1.1 by NST for 6 months or more; ii) R0 resection was

possible by multimodal imaging; iii) distant metastatic lesions should be resected when they showed no progression during NST and could be resected completely. If all the metastases were treated with NST, resection of the primary lesion alone was performed. All patients met these criteria. CA19-9 and positron emission tomography maximum standardized uptake values (PET SUVmax) reduction were important tools for evaluating the treatment effect of NST. We did not include a decrease of CA19-9 value in our criteria for CS. However, when planning CS, we referred to a change of CA19-9 value and considered that it was desirable to normalize it if possible. PET was not an indispensable examination. Preoperative and postoperative clinical data were obtained from medical records. Informed consent was obtained from all patients. This study was conducted with the approval of the Hokkaido University Hospital Institutional Review Board (017-0442, UMIN000031131).

NST

As to NST, there were no specific provisions for anticancer drugs and the combined use of radiation. Recently, FOLFIRINOX [5-fluorouracil (5-FU), oxaliplatin, irinotecan, leucovorin] and combination therapy of nab-paclitaxel plus gemcitabine (GnP) were

increasingly used due to the development of new therapies. With regard to the optimal treatment period of NST, we initially adapted “NST for more than 6 months” as the criteria, but according to Satoi et al.,[9] “NST for more than 8 months” was considered preferable if possible since 2014.

CS

CS for patients with PC was defined as follows: “For patients initially diagnosed as UR-PC, favorable responses (SD, PR, or CR) were obtained as results of NST for a certain period; surgical resection converted from NST was performed only when it was judged that R0 resection was possible by considering multimodal image findings in detail.”

Based on detailed examination of multimodal images, we judged that R0 resection is possible when the following findings were found: in case it was possible to diagnose resectable or borderline PC due to a remarkable tumor reduction effect of NST, or in case it could be judged that complete resection was possible with making full use of concomitant major arterial resection even if it was still unresectable PC after NST.

Regarding the extent of resection, initially, all regions where the tumor existed at the

time of initial diagnosis were included; as a result, extended resections, such as concomitant major arterial resection, were performed on patients with locally advanced PC. However, in recent years, high tumor reduction effects could be obtained according to the remarkable progress of NST; in some cases, it was very difficult to diagnose tumor extension correctly because of the influence of NST, even when using multimodal imaging. Given this situation, from 2014, we were positively trying to preserve major arteries by confirming the absence of cancer in the periarterial nerve plexus with intraoperative frozen sections and to minimize surgical invasiveness.

Assessment

The clinical treatment effect of NST was assessed by RECIST version 1.1, [18] and the histologic assessment of the extent of NST response was evaluated by the Evans' grading system.[19] The Clavien-Dindo (C–D) classification was applied to postoperative complications.[20] On evaluation of CA19-9, "increase" was defined that patients who received NST had more than 20% increase of CA19-9 compared with the initial value, and "decrease" was defined more than 30% decrease of it. Others were defined as "no change". Mortality was

defined as death within 90 days after surgery.

Statistical analysis

Continuous variables were reported as median and range. Overall survival (OS) was calculated from the date of initial treatment and CS to the date of last follow-up (censored) or the date of patient death (event). In the same way, disease-free survival (DFS) was also calculated from the date of CS to the date of the last follow-up (censored) or the date of confirmation of reccurence. Survival analysis was plotted according to the Kaplan–Meier method. Differences between the survival curves were analyzed by the generalized Wilcoxon test (G–W) and the log–rank test (L–R). A p-value of < 0.05 was considered significant. All analyses were performed using JMP® Pro (Version 13; SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Of the 34 patients who underwent CS, 16 patients were men and 18 patients were women, and the median age was 64 (range, 43-80) years **(Table1)**. Fifteen patients had tumor

in the pancreatic head region, 9 patients in the pancreatic body, 4 patients in the pancreatic tail, and 6 patients in the two regions (head/body or body/tail). In unresectable tumors, 26 patients (76.5%) had locally advanced PC, and 8 patients (23.5%) had distant metastasis. Among 26 patients with locally advanced PC, tumor contact with CHA was most frequent in 12 patients, SMA in 6 patients, and celiac axis (CA), CA+CHA, and portal vein (PV) in 2 patients. Of the 8 patients with distant metastasis, 5 patients had liver metastasis, 2 patients had para-aortic lymph node metastasis, and 1 patients had peritoneal dissemination.

NST

Eighteen patients received systemic chemotherapy, 13 patients received chemoradiotherapy, and 3 patients received intra-arterial chemotherapy **(Table 1)**. In systemic chemotherapy, gemcitabine and S-1 combination therapy (GS), which is the most common therapy in this study, was given to 10 patients. Three patients received gemcitabine (GEM) alone. GnP regimen and FOLFIRINOX were given to 2 patients, respectively. For 1 patient with peritoneal dissemination, intraperitoneal paclitaxel (PTX) combined with GEM administered intravenously was performed. Intraarterial infusion chemotherapy with GEM

and 5-FU was given in 3 patients. In chemoradiotherapy, radiation therapy was combined with S-1 in 8 patients, with GEM in 3 patients, with GS in 1 patient and with GnP regimen in 1 patient. Total dose and fractions of radiotherapy was 50.4Gy/ 25 fractions (fr) in 11 patients, 45Gy/ 25fr in 1 patient and 30Gy/ 15fr in 1 patient. In addition, systemic chemotherapies were performed before or after chemoradiotherapy. The median NST period was 9 (range, 5-44) months. The treatment effects of PR and SD were evaluated in 24 and 10 patients, respectively. No patients had CR according to preoperative images. Although CA19-9 levels were decreased by NST in 20 patients (58.8%), CA19-9 was elevated in only 1 patient (2.9%).

Surgical outcomes

We performed subtotal stomach-preserving pancreaticoduodenectomy in 12 patients, distal pancreatectomy with en bloc celiac axis resection in 8 patients **(Table 2)**, concomitant CHA resection (CHAR) was in 5 patients, and concomitant portal vein resection was in 25 patients (76.5%). In 4 patients, we could avoid concomitant major arterial resection if the periarterial nerve plexus was cancer negative by intraoperative frozen sections. Including

these 4 patients, R0 resection was achieved in 30 patients (88.2%). The median surgical time in all patients was 504.5 (range, 200-1159) minutes, and median intraoperative bleeding was 997.5 (range, 200-3200) mL. Although complications of C–D classification ≥ IIIa were found in 8 patients (23.5%), no mortalities were reported in all patients. The median postoperative hospital stay was 28 (range, 12-121) days. Histopathologically, Evans grade ≥ III was noted in 6 patients (17.6%), of which 3 patients had pathological CR. Thirty patients (88.2%) could receive postoperative adjuvant chemotherapy, and the median time from CS to induction of adjuvant chemotherapy was 1.8 (range, 0.7-6.5) months. S-1 was given in 18 patients, GEM in 9 patients, GS in 1 patient, nab-PTX in 1 patient and intraperitoneal infusion of PTX combined with intravenous administration of GEM in 1 patient. Nineteen patients (63.3%) could complete adjuvant chemotherapy.

Postoperative recurrence

DFS curve from CS is shown in Figure 1. DFS rates at 1, 3 and 5 years were 82.0%, 41.1% and 34.3%, respectively. Recurrence was confirmed in 18 (52.9%) of 34 patients **(Table 3)**. Five patients had peritoneal dissemination, 4 patients had liver metastasis, 4

patients had lung metastasis, and 3 patients had remnant pancreatic recurrence. The median duration from CS to recurrence was 12.6 (range, 1.6-65) months. Besides, we considered the time to relapse by the recurrence site. The median time to liver metastasis was 4.5 (range, 1.6-5.4) months, peritoneal dissemination was 12.2 (range, 3.2-20.3) months, lung metastasis was 19.1 (range, 4-65) months, and remnant pancreatic recurrence was 13 (range, 11.9-14.7) months. After confirming relapse, 13 patients were performed systemic chemotherapy. GEM alone was received in 5 of 13 patients, GS in 3 patients, TS-1 alone in 2 patients, FOLFIRINOX in 1 patients, GnP regimen in 1 patients and modified 5-FU/leucovorin plus oxaliplatin (mFOLFOX-6) in 1 patients. Two of 3 patients with remnant pancreatic recurrence underwent remnant pancreatic resection. After surgery, GEM alone and FOLFIRINOX were performed, respectively. Intraarterial infusion chemotherapy with GEM and 5-FU was given in 1 patient. One patient with peritoneal recurrence underwent intraperitoneal PTX combined with oral administration of S-1. Best supportive care was selected in 1 patient.

Survival analysis

The survival curve of all 34 patients from initial treatment is shown in **Figure 2A**. The median follow-up period for all patients was 3.25 (range, 1.3 - 12.5) years. The 1-, 3-, 5- and 10-year OS rates were 100%, 74.0%, 56.9%, and 33.2%, respectively. The median survival time (MST) was 5.3 years. Furthermore, there were 19 patients in which 5 years or more had passed from the initial treatment. The survival curve of these 19 patients is shown in **Figure 2B**. The actual 5-year OS was 47.4% with MST of 4.0 years. Moreover, the survival curve of 34 patients from CS is shown in Figure 2C. The 1-, 3- and 5-year OS rates were 80.7%, 51.8% and 46.6%, respectively, with MST of 3.8 years. We compared the survival from initial treatment and CS between the locally advanced group and the distant metastasis group. No significant difference was found between the two groups (G–W p=0.0121, L–R p=0.0971, Figure 3A; G–W p=0.0380, L–R p=0.1606, **Figure 3B**). In the comparison of the survival from the initial treatment and CS according to histologic assessment of the extent of NST response, patients with Evans grade ≥ III had a better prognosis than those with Evans grade < III with a significant difference (G–W p=0.0141, L–R p=0.0092, **Figure 4A**; G–W p=0.0380, L–R p=0.1606, **Figure 4B**).

Discussion

This study revealed the long-term prognosis of patients with UR-PC in whom CS was performed; 1-, 3-, 5- and 10-year OS rates from initial treatment were 100%, 74%, 56.9%, and 33.2%, respectively, with an MST of 5.3 years (**Figure 2A**). So far, several articles related to CS for UR-PC patients have been reported.[8-16] Our results in this study may be the best among these previous articles. These values seemed to indicate the possibility of prognostic improvement effect in CS for patients with UR-PC to a certain extent.

The therapeutic strategy of CS for patients with UR-PC had a relatively short history, and originated from our previous report of 12 patients with UR-PC who responded favorably to NST in 2011.[8] In this study, CS was expressed as “adjuvant surgical therapy.” This cohort included 4 patients with distant metastasis. R0 resection rate was 75%, and 5-year OS from initial treatment was 50%. There were no 5-year survivors in the distant metastasis group, and the locally advanced group had a better prognosis than the distant metastasis group with a significant difference (p=0.0014). Our present study had the longer follow-up observations,

and further cases were added to this previous report. We compared the survival of the distant metastasis group and the locally advanced group in the same manner as reported previously. As a result, although there was a tendency that the prognosis was better in the locally advanced group than in the distant metastasis group, no significant difference was observed (**Figure 3**). On the other hand, in this study, we revealed that the survival of patients with Evans grade ≥ III was significantly better than that of patients with Evans grade < III (**Figure 4**). Until now, there have been reports on the association between histopathological responses to chemo(radio)therapy and prognosis of patients with PC.[21-23] Chatterjee et al.[21] reported that 42 (18.8%) of 223 patients with PC who received neoadjuvant chemotherapy showed Evans grade ≥ III and that they had better survivals than patients with Evans grade < III. Moreover, White et al.[22] referred to the possibility that histological response was useful as a surrogate marker for treatment efficacy. From our results, we consider that it is very useful information in management of patients after CS. However, because it is based on the results of resected specimen, it is difficult to select patients with a high probability of good prognosis before surgery. It is needless to say that further analysis should be necessary in the future.

With advances in surgical techniques, extended resection using a combination of vascular surgical procedures for patients with PC could be performed relatively safe, and studies were also conducted on CS with concomitant resection of major arteries such as CA or CHA. Amano et al.[11] reported that CS could be performed in 13 (76.5%) of 17 patients with locally advanced UR-PC, who received chemoradiotherapy as NST. It is noteworthy in this study that all surgical procedures performed in 13 patients were extended resections with concomitant major arterial resection. Therefore, extended resections with concomitant major arterial resection after chemoradiotherapy were acceptable based on these results: R0 resection rate was 92.3%, complication rate was 61.5%, and 1-year OS was 92.8%. However, the median observation period of this study was 436 (range, 320-1170) days, which was shorter than that in other studies. Therefore, prognostic analysis with long-term follow-up is necessary to discuss the prognostic effect of this surgical strategy. We previously based on extended resection when performing CS. However, given the remarkable progress of NST, obtaining tumor shrinkage is possible. Specifically, in cases of CS, diagnosing the extent of tumor invasion accurately due to the influence of NST was difficult, even if multimodal

imagings were used. Currently, considering this situation, we attempted proactively to minimize surgical invasiveness of CS and avoid concomitant major arterial resection by confirming with intraoperative frozen sections that the periarterial nerve plexus is cancer negative. In this series, it could be performed in 4 patients, and R0 resection was achieved in all cases. However, whether preserving major artery truly minimizes invasiveness of CS and whether this surgical procedure can affect prognosis are unclear. Hence, it is necessary to accumulate more cases, and to have a longer follow-up for patients who undergo “minimally invasive CS.”

In this manner, while the therapeutic effect of CS on patients with UR-PC is investigated, progress of chemo(radio)therapy is remarkable, and FOLFIRINOX or GnP regimen is used as first-line chemotherapy for patients with UR-PC.[12,13,24-26] Hackert et al.[13] reported that patients with UR-PC who received FOLFIRINOX as NST had a higher conversion rate and a better prognosis than those received other regimen and they advocated that FOLFIRINOX should be first-line therapy for patients with UR-PC. As the antitumor effect of these regimens are very high, candidates for CS are expected to increase. However,

at the same time, prognosis of patients with UR-PC who received NST alone was dramatically improved, and MST exceeded 20 months in the latest articles.[27,28] We should always compare survival analysis by NST alone when examining the prognostic effect of CS. CS is the most invasive surgical therapy. Therefore, at least, the prognostic effect of CS must be always better than that of NST alone. In addition, we clarified that some patients had recurrence earlier after CS, of which liver metastasis occurred the earliest (median time to relapse after CS: 4.5 months). For such patients, CS with high invasiveness could not be said as an effective treatment. Further studies including genome analysis are necessary.[29] If diagnosis of early recurrent patients before CS become possible, unnecessary extended surgery can be avoided, and more appropriate treatment for patients with UR-PC can be applied.

This study has some limitations. It was a single-institute and retrospective study with a small number of cases. All previous reports including this study are retrospective studies. We consider that multi-institutional prospective observational study is necessary to establish evidence in the efficacy of CS. Given that only selected patients responded favorably to NST were targeted among all patients with UR-PC, a selection bias existed. In addition, it was

raised as one of limitations that conversion rate was unclear in this series. Nitsche et al.[12] reported that conversion surgery was possible in 4 (28.6%) out of 14 patients with UR-PC who received FOLFIRINOX as NST. On the other hand, Hackert et al.[13] reported that 292 (50.8%) among 575 patients with UR-PC who received NST could be performed CS. According to the characteristics of our hospital, many patients were referred from far away to undergo surgery, and such patients were already diagnosed UR-PC and received NST by previous doctors. We tried to reveal conversion rate in this cohort, but it was very difficult to grasp the accurate number of patients with UR-PC in the same period of this study in the all hospitals. Therefore, we could not indicate conversion rate in this series. Although there were several limitations as described above, the results of this study seemed to indicate the possibility of survival benefit for patients with UR-PC who underwent CS. Moreover, it may be necessary to consider that CS has an important significance as one of options of multidisciplinary treatment.

In conclusion, CS may possibly improve the prognosis of patients with UR-PC. Therefore, CS should be considered for patients with UR-PC who obtained a good response

by NST for a certain period. Multidisciplinary treatment including CS for patients with UR-PC in close cooperation with oncologists, radiologists, and hepato-biliary-pancreatic surgeons is necessary.

Conflict of interest None declared

References

1. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol. 2009;6:699–708.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74:2913–2921.
3. The Editorial Board of the Cancer Statistics in Japan, eds. Cancer Statistics in Japan 2016. Tokyo: Foundation for Promotion of the Cancer Research (FPCR), 2017.
4. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378:607–620.
5. Siegel RI, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2017;67:7–30.
6. Fukuchi M, Ishiguro T, Ogata K, Suzuki O, Kumagai Y, Ishibashi K, et al. Prognostic role of conversion surgery for unresectable gastric cancer. Ann Surg Oncol. 2015;22:3618–624.

7. Yokota T, Kato K, Hamamoto Y, Tsubosa Y, Ogawa H, Ito Y, et al. Phase II study of chemoselection with docetaxel plus cisplatin and 5-fluorouracil induction chemotherapy and subsequent conversion surgery for locally advanced unresectable oesophageal cancer. Br J Cancer. 2016;115:1328–1334.
8. Kato K, Kondo S, Hirano S, Tanaka E, Shichinohe T, Tsuchikawa T, et al. Adjuvant surgical therapy for patients with initially-unresectable pancreatic cancer with long-term favorable responses to chemotherapy. J Hepatobiliary Pancreat Sci. 2011;18:712–716.
9. Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, et al. Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: result of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2013;20:590–600.
10. Opendro SS, Satoi S, Yanagimoto H, Yamamoto T, Toyokawa H, Hirooka S, et al. Role of adjuvant surgery in initially unresectable pancreatic cancer after long-term chemotherapy

or chemoradiation therapy: survival benefit? J Hepatobiliary Pancreat Sci. 2014;21:695–702.

11. Amano R, Kimura K, Nakata B, Yamazoe S, Motomura H, Yamamoto A, et al. Pancreatectomy with major arterial resection after neoadjuvant chemoradiotherapy gemcitabine and S-1 and concurrent radiotherapy for locally advanced unresectable pancreatic cancer. Surgery. 2015;158:191–200.
12. Nitsche U, Wenzel P, Siveke JT, Braren R, Holzapfel K, Schlitter AM, et al. Resectability after first-line FOLFIRINOX in initially unresectable locally advanced pancreatic cancer: a single-center experience. Ann Surg Oncol. 2015;22:S1212–S1220.
13. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: Neoadjuvant therapy with Folfirinox results in resectability in 60% of the patients. Ann Surg. 2016;264:457–463.
14. Sui K, Okabayashi T, Shima Y, Morita S, Iwata J, Sumiyoshi T, et al. Clinical effects of chemoradiotherapy in pursuit of optimal treatment of locally advanced unresectable pancreatic cancer. Br J Radiol. 2017;90:20170165.

15. Hitchcock KE, Nichols RC, Morris CG, Bose D, Hughes SJ, Stauffer JA, et al. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer. World J Gastrointest Surg. 2017;9:103–108.

16. Saito T, Ishido K, Kudo D, Kimura N, Wakiya T, Nakayama Y, et al. Combination therapy with gemcitabine and nab-paclitaxel for locally advanced unresectable pancreatic cancer. Mol Clin Oncol. 2017;6:963–967.

17. Tempero MA, Malafa MP, AI-Haway M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, Version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15:1028–1061.

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–247.

19. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127:1335–1339.

20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.

21. Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, et al. Histologic grading the extent of residual carcinoma following neoadjuvat chemoradiation in pancreatic ductal adenocarcinoma: A predictor for patient outcome. Cancer. 2012;118:3182–3190.

22. White RR, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA, et al. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. Ann Surg Oncol. 2005;12:214–221.

23. Moutardier V, Magnin V, Turrini O, Viret F, Hennekinne-Mucci S, Gonçalves A, et al. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2004;60:437–443.

24. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17:801–810.

25. Nguyen KT, Kalyan A, Beasley HS, Singhi AD, Sun W, Zeh HJ, et al. Gemcitabine/nab-paclitaxel as second-line therapy following FOLFIRINOX in metastatic/advanced pancreatic cancer – retrospective analysis of response. J Gastrointest Oncol. 2017;8:556–565.

26. Muranaka T, Kuwatani M, Komatsu Y, Sawada K, Nakatsumi H, Kawamoto Y, et al. Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. J Gastrointest Oncol. 2017;8:566–571.

27. Choi Y, Oh DY, Kim K, Chie EK, Kim TY, Lee KH, et al. Concurrent chemoradiotherapy versus chemotherapy alone for unresectable locally advanced pancreatic cancer: a retrospective cohort study. Cancer Res Treat. 2016;48:1045–1055.

28. Sudo K, Hara R, Nakamura K, Kita E, Tsujimoto A, Yamaguchi T. Phase II study of induction gemcitabine and S-1 followed by chemoradiotherapy and systemic

chemotherapy using S-1 for locally advanced pancreatic cancer. Cancer Chemother Pharmacol. 2017;80:195–202.

29. Hayashi H, Kohno T, Ueno H, Hiraoka N, Kondo S, Saito M, et al. Utility of assessing the number of mutated KRAS, CDKN2A, TP53, and SMAD4 genes using a targeted deep sequencing assay as a prognostic biomarker for pancreatic cancer. Pancreas. 2017;46:335–340.

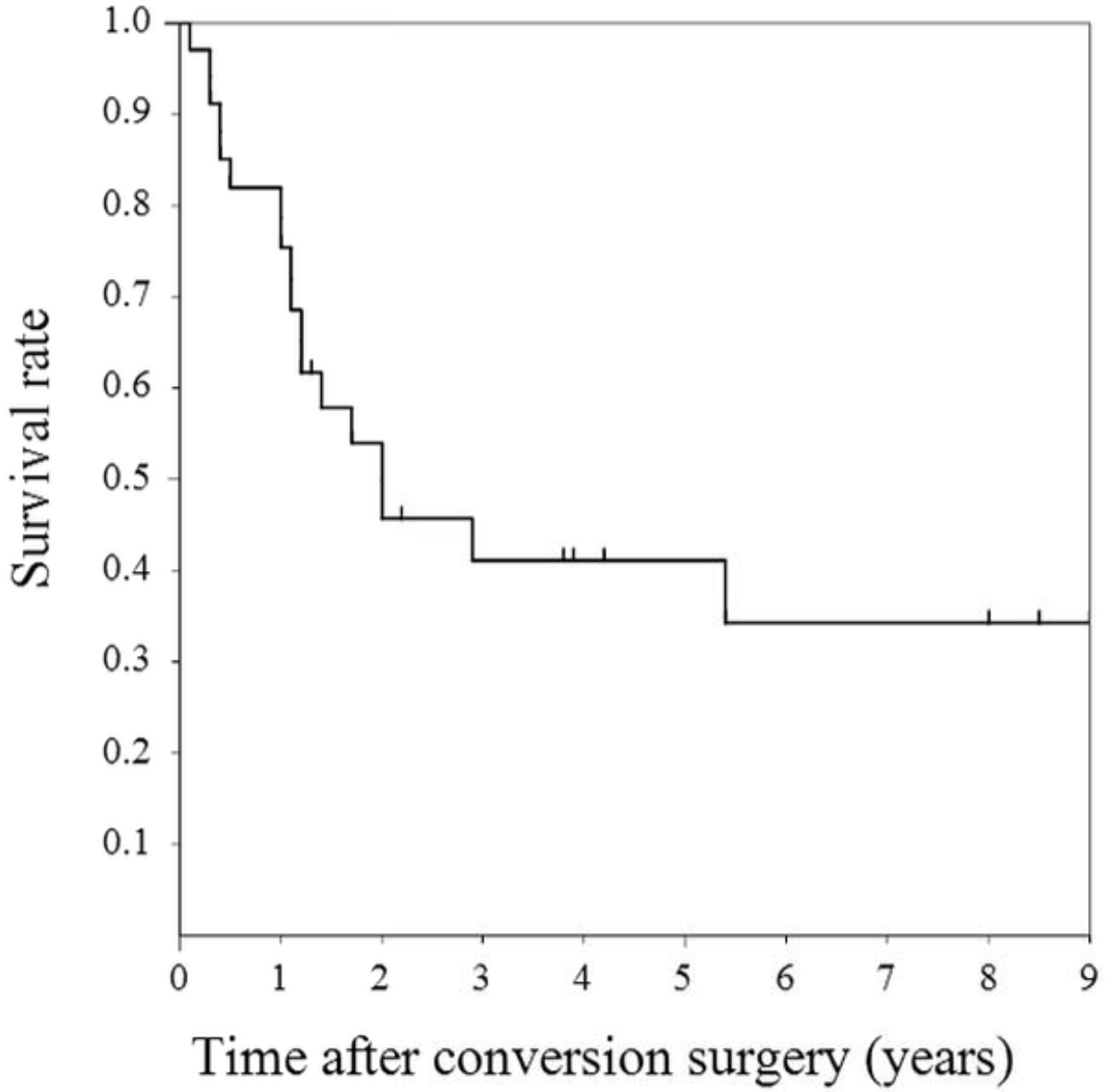
Figure legends

Figure 1 Disease-free survival curve from CS for patients who underwent CS. Disease-free survival rates at 1, 3 and 5 years were 82.0%, 41.1% and 34.3%, respectively. yr, years.

Figure 2 Kaplan–Meier survival curves for patients with unresectable pancreatic cancer who underwent CS. **A:** Overall survival of the 34 patients from initial treatment. **B:** Overall survival of 19 patients for 5 years or more from initial treatment. **C:** Overall survival of the 34 patients from CS. MST, median survival time; yr, years

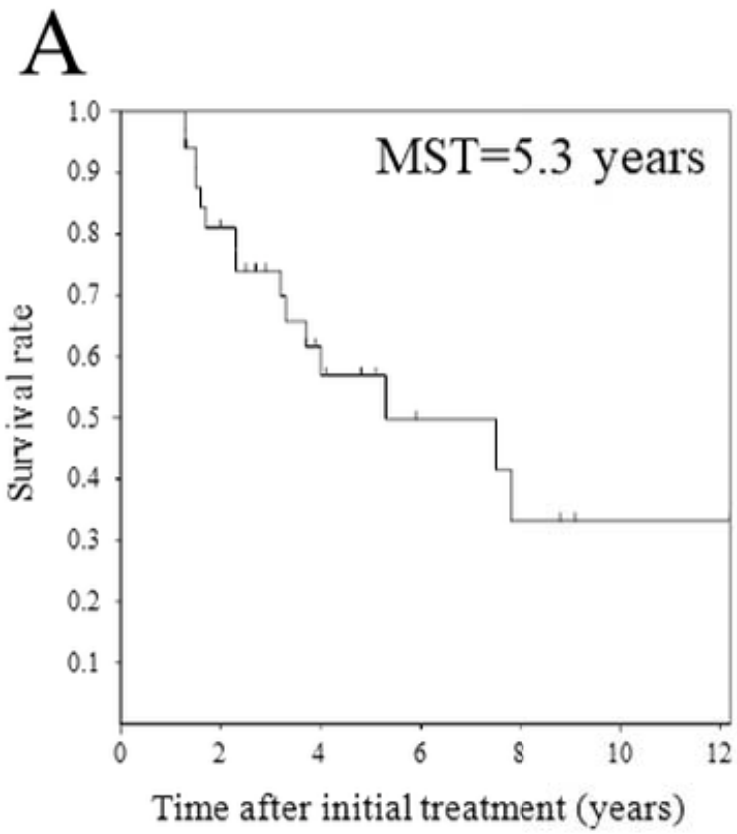
Figure 3 Comparison of the survival curves for patients who underwent CS between the locally advanced group and the distant metastasis group. **A:** Survival curves from initial treatment. **B:** Survival curves from CS. No significant difference was found between the two groups [p=0.0971 (A), p=0.1606 (B), Log–rank test]. G–W test, generalized Wilcoxon test; L–R test, Log–rank test; yr, years

Figure 4 Comparison of the survival curves for patients who underwent CS between those with Evans grade ≥ III and those with Evans grade < III. **A:** Survival curves from initial treatment. **B:** Survival curves from CS. Patients who showed Evans grade ≥ III had a better prognosis than those who showed Evans grade < III [p=0.0092 (A), p=0.0120 (B), Log–rank test]. G–W test, generalized Wilcoxon test; L–R test, Log–rank test; yr, years

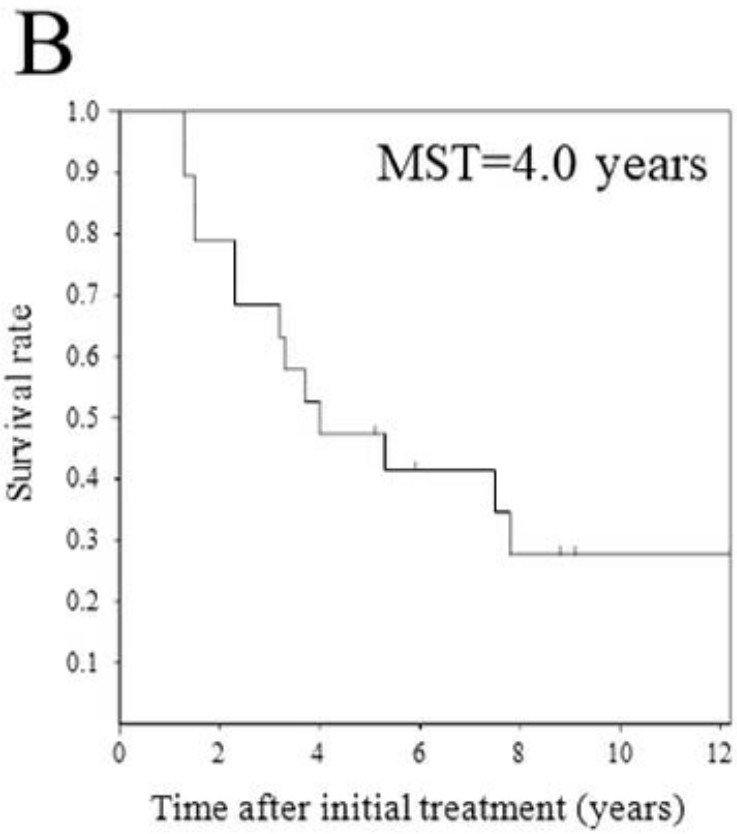


n=34	1yr	3yr	5yr	9yr
No.at risk	25	8	5	2

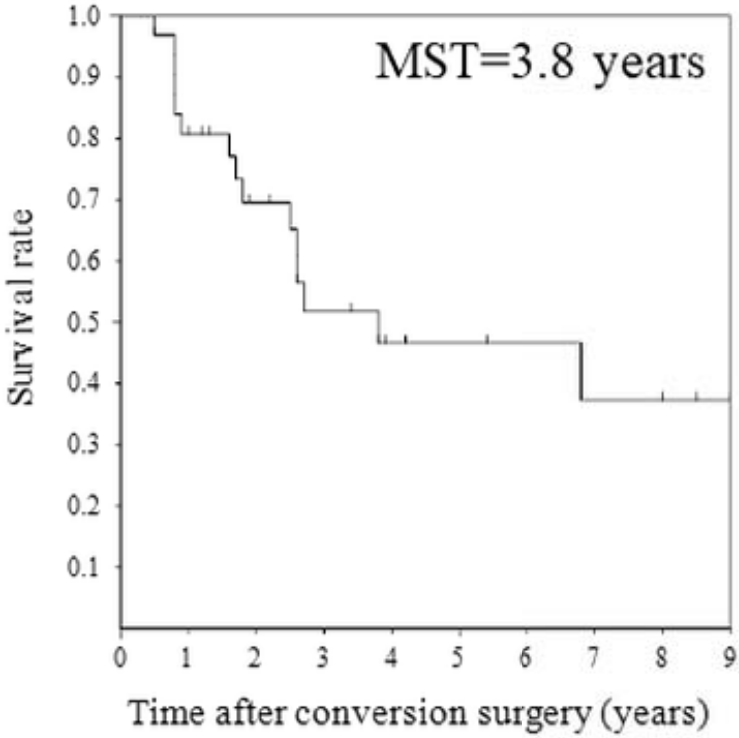
Figure 1



n=34	1yr	3yr	5yr	10yr
No.at risk	34	18	9	2

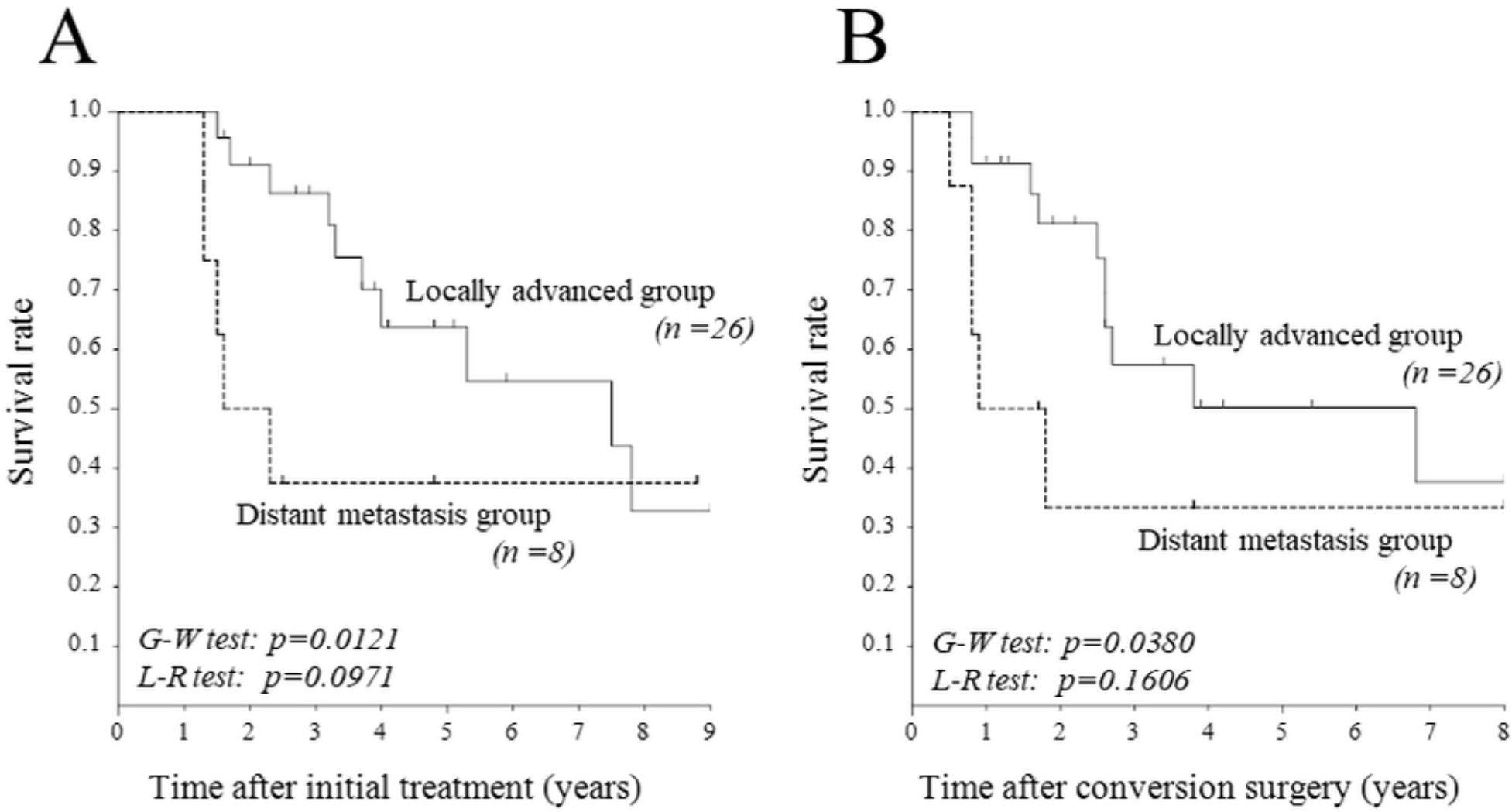


n=19	1yr	3yr	5yr	10yr
No.at risk	19	13	9	2



n=34	1yr	3yr	5yr	9yr
No.at risk	25	11	6	2

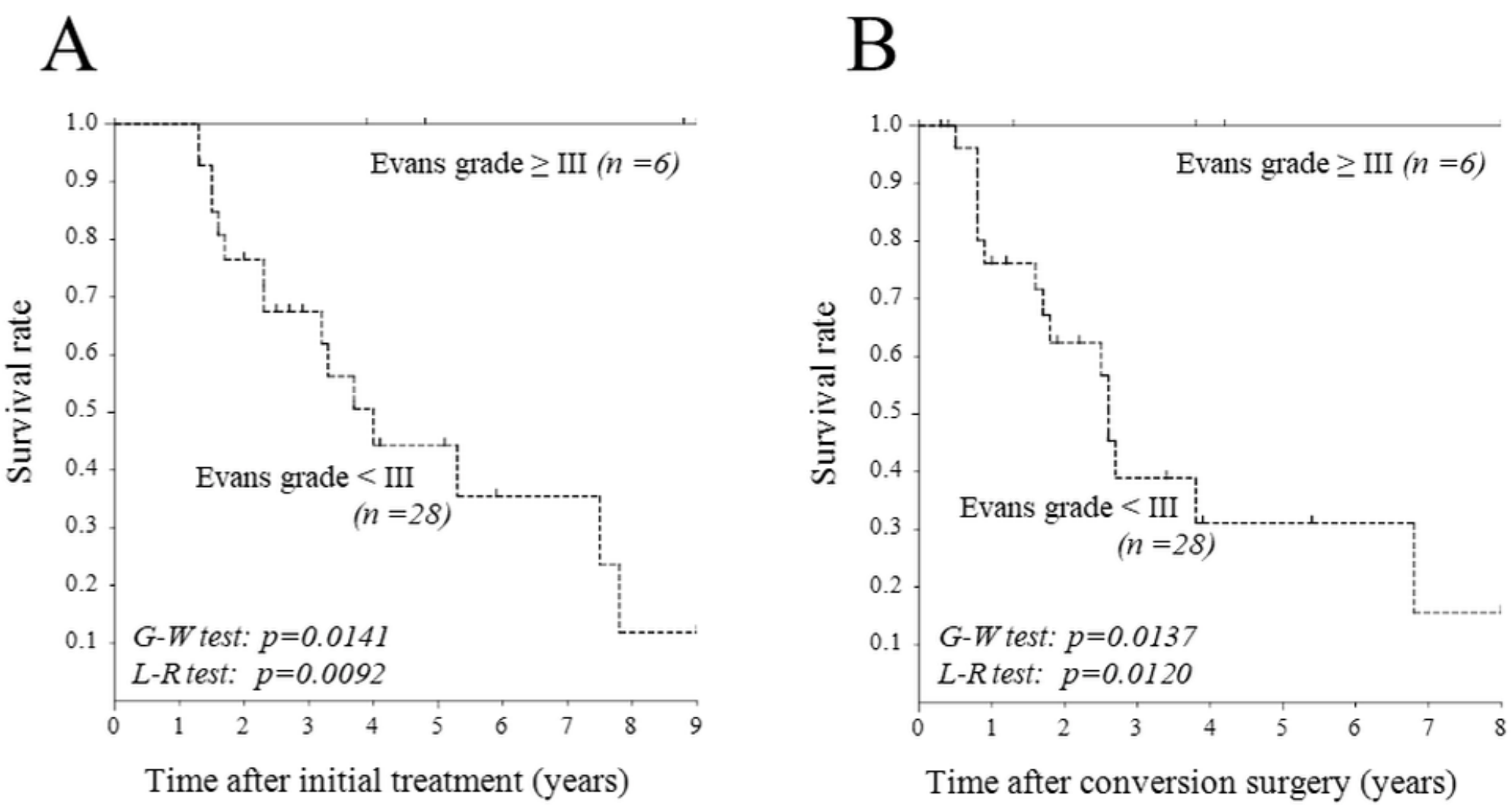
Figure 2



	1yr	3yr	5yr
Locally advanced *(n=26)*			
No. at risk	26	16	8
Distant metastasis *(n=8)*			
No. at risk	8	2	1

	1yr	3yr	5yr
Locally advanced *(n=26)*			
No. at risk	21	9	5
Distant metastasis *(n=8)*			
No. at risk	4	1	1

Figure 3



	1yr	3yr	5yr
Evans grade ≥ III (n=6)			
No. at risk	6	6	3
Evans grade < III (n=28)			
No. at risk	28	12	6

	1yr	3yr	5yr
Evans grade ≥ III (n=6)			
No. at risk	6	5	3
Evans grade < III (n=28)			
No. at risk	19	6	3

Figure 4

Table 1 Characteristics of 34 patients underwent conversion surgery

		n = 34	
Gender (%), male / female		16 (47.1) / 18 (52.9)	
Age, median (range)		64 (43-80)	
Location of tumor (%)	Head	15	(44.1)
	Body	9	(26.5)
	Tail	4	(11.8)
	Head-Body	3	(8.8)
	Body-Tail	3	(8.8)
Unresectable factor (%)	Locally advanced	26	(79.5)
	CHA	12	
	SMA	6	
	CA	2	
	CA+CHA	2	
	PV	2	
	CHA+SMA	1	
	Ao	1	
	Distant metastasis	8	(23.5)
	Liver	5	
	Lung	2	
	Peritoneal dissemination	1	
Nonsurgical treatment (%)	Systemic chemotherapy	18	(53.0)
	Chemoradiation therapy	13	(38.2)
	Intra-arterial chemotherapy	3	(8.8)
Period of non-surgical treatment, months, median (range)		9 (5-44)	
RECIST (%)	SD	10	(29.4)
	PR	24	(70.6)
Change in CA19-9 (%)	Increase	1	(2.9)
	Decrease	20	(58.8)
	No change	13	(38.3)

CHA: common hepatic artery, SMA: superior mesenteric artery, CA: celiac axis, PV: portal vein, Ao: aorta

RECIST: Response Evaluation Criteria In Solid Tumors, SD: stable disease, PR: partial response

Table 2 Surgical outcomes of 34 patients

		n = 34	
Operative procedure of primary tumor (%)	SSPPD	12	(35.3)
	DP-CAR	8	(23.5)
	DP	7	(20.6)
	SSPPD-CHAR	4	(11.8)
	TP-CAR	2	(5.9)
	SSPPD-CHASAR	1	(2.9)
Concomitant major arterial resection (%)		15	(44.1)
Concomitant portal vein resection (%)		25	(76.5)
Operative time, min, median (range)		504.5 (200-1159)	
Intraoperative blood loss, mL, median (range)		997.5 (200-3200)	
R0 resection (%)		30	(88.2)
Postoperative complication (%)		16	(47.1)
Clavien–Dindo classification ≥ IIIa (%)		8	(23.5)
Mortality (%)		0	(0.0)
Evans grade ≥ III (%)		6	(17.6)
Postoperative hospital stays, days, median (range)		28 (12-121)	
Adjuvant chemotherapy (%)		30	(88.2)
Period from CS to adjuvant CTx, months, median (range)		1.8 (0.7-6.5)	
Recurrence (%)		18	(52.9)
Period from CS to recurrence, months, median (range)		12.6 (1.6-65.0)	

SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; DP, distal pancreatectomy

TP, total pancreatectomy; CAR, celiac axis resection; CHAR, common hepatic arterial resection

CHASAR, common hepatic artery and splenic artery resection; CS, conversion surgery

CTx, chemotherapy

Table 3 Details in 18 patients with postoperative recurrence

		n=18	%	Period from CS to relapse, months, median (range)	
Site of recurrence	Peritoneal dissemination	5	27.8	12.2	(3.2-20.3)
	Liver	4	22.2	4.5	(1.6-5.4)
	Lung	4	22.2	19.1	(4.0-65.0)
	Remnant pancreas	3	16.7	13	(11.9-14.7)
	Lymph node	1	5.6	35	-
	Local recurrence	1	5.6	23.6	-
Period from CS to relapse, months, median (range)		12.6 (1.6-65.0)			

CS: conversion surgery