7. Rosso E, Casnedi S, Pessaux P, Oussoultzoglou E, Panaro F, Mahfud M, Jaeck D, Bachellier P. The role of "fatty pancreas" and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg 2009;13:1845–1851.
8. Ansorge C, Strömmer L, Andrén-Sandberg Å, Lundell L, Herrington MK, Segersvärd R. Structured intraoperative assessment of pancreatic gland characteristics in predicting complications after pancreaticoduodenectomy. Br J Surg 2012;99:1076–1082.
9. Pecorelli N, Balzano G, Capretti G, Zerbi A, Di Carlo V, Braga M. Effect of surgeon volume on outcome following pancreaticoduodenectomy in a high-volume hospital. J Gastrointest Surg 2012;16:518–523.
10. Hashimoto Y, Traverso LW. Incidence of pancreatic anastomotic failure and delayed gastric emptying after pancreatoduodenectomy in 507 consecutive patients: use of a web-based calculator to improve homogeneity of definition. Surgery 2010;147:503–515.
11. Frozanpor F, Loizou L, Ansorge C, Segersvärd R, Lundell L, Albiin N. Preoperative pancreas CT/MRI characteristics predict fistula rate after pancreaticoduodenectomy. World J Surg 2012;36:1858–1865.
12. Hashimoto Y, Sclabas GM, Takahashi N, Kirihara Y, Smyrk TC, Huebner M, Farnell MB. Dual-phase computed tomography for assessment of pancreatic fibrosis and anastomotic failure risk following pancreatoduodenectomy. J Gastrointest Surg 2011;15:2193–2204.
13. Hwang HK, Park JS, Park CI, Kim JK, Yoon DS. The impact of body mass index on pancreatic fistula after pancreaticoduodenectomy in Asian patients on the basis of Asia-Pacific perspective of body mass index. JOP 2011;12:586–592.
14. Callery MP, Pratt WB, Vollmer CM Jr. Prevention and management of pancreatic fistula. J Gastrointest Surg 2009;13:163–173.
15. Lai EC, Lau SH, Lau WY. Measures to prevent pancreatic fistula after pancreatoduodenectomy: a comprehensive review. Arch Surg 2009;144:1074–1080.
16. Motoi F, Egawa S, Rikiyama T, Katayose Y, Unno M. Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. Br J Surg 2012;99:524–531.
17. Okano K, Oshima M, Kakinoki K, Yamamoto N, Akamoto S, Yachida S, Hagiike M, Kamada H, Masaki T, Suzuki Y. Pancreatic thickness as a predictive factor for postoperative pancreatic fistula after distal pancreatectomy using an endopath stapler. Surg Today 2013;43:141–147.
18. Sugimoto M, Gotohda N, Kato Y, Takahashi S, Kinoshita T, Shibasaki H, Nomura S, Konishi M, Kaneko H. Risk factor analysis and prevention of postoperative pancreatic fistula after distal pancreatectomy with stapler use. J Hepatobiliary Pancreat Sci 2013; 20:538–544.
19. Kakita A, Takahashi T, Yoshida M, Furuta K. A simpler and more reliable technique of pancreatojejunal anastomosis. Surg Today 1996;26:532–535.
20. Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, Falconi M, Pederzoli P. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Ann Surg 2007;246:281–287.
21. Tranchart H, Gaujoux S, Rebours V, Vullierme MP, Dokmak S, Levy P, Couvelard A, Belghiti J, Sauvanet A. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. Ann Surg 2012;256:139–145.
22. Lermite E, Pessaux P, Brehant O, Teyssedou C, Pelletier I, Etienne S, Arnaud JP. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. J Am Coll Surg 2007;204:588–596.
23. Noji T, Nakamura T, Ambo Y, Suzuki O, Nakamura F, Kishida A, Hirano S, Kondo S, Kashimura N. Clinically relevant pancreas-related infectious complication after pancreaticoenteral anastomosis could be predicted by the parameters obtained on postoperative day 3. Pancreas 2012;41:916–921.
24. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, Talamini G, Pederzoli P. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010;252:207–214.
25. Tajima Y, Kuroki T, Tsutsumi R, Fukuda K, Kitasato A, Adachi T, Mishima T, Kanematsu T. Risk factors for pancreatic anastomotic leakage: the significance of preoperative dynamic magnetic resonance imaging of the pancreas as a predictor of leakage. J Am Coll Surg 2006;202:723–731.
26. Tajima Y, Matsuzaki S, Furui J, Isomoto I, Hayashi K, Kanematsu T. Use of the time-signal intensity curve from dynamic magnetic resonance imaging to evaluate remnant pancreatic fibrosis after pancreaticojejunostomy in patients undergoing pancreaticoduodenectomy. Br J Surg 2004;91:595–600.
27. Ammann RW, Heitz PU, Klöppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. Gastroenterology 1996;111:224–231.
28. Friess H, Malfertheiner P, Isenmann R, Kühne H, Beger HG, Büchler MW. The risk of pancreaticointestinal anastomosis can be predicted preoperatively. Pancreas 1996;13:202–208.
29. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg 2007;246:1058–1064.
30. Ahmad SA, Edwards MJ, Sutton JM, Grewal SS, Hanseman DJ, Maithel SK, Patel SH, Bentram DJ, Weber SM, Cho CS, Winslow ER, Scoggins CR, Martin RC, Kim HJ, Baker JJ, Merchant NB, Parikh AA, Kooby DA. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. Ann Surg 2012;256:529–537.
31. Gebauer F, Kloth K, Tachezy M, Vashist YK, Cataldegirmen G, Izbicki JR, Bockhorn M. Options and limitations in applying the fistula classification by the International Study Group for Pancreatic Fistula. Ann Surg 2012;256:130–138.
32. Shirakawa S, Matsumoto I, Toyama H, Shinzeki M, Ajiki T, Fukumoto T, Ku Y. Pancreatic volumetric assessment as a predictor of new-onset diabetes following distal pancreatectomy. J Gastrointest Surg. 2012;16:2212–2219.
33. Kirihara Y, Takahashi N, Hashimoto Y, Sclabas GM, Khan S, Moriya T, Sakagami J, Huebner M, Sarr MG, Farnell MB. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. Ann Surg 2013;257:512–519.
34. Fernández-Cruz L, Belli A, Acosta M, Chavarria EJ, Adelsdorfer W, López-Boado MA, Ferrer J. Which is the best technique for pancreaticoenteric reconstruction after pancreaticoduodenectomy? A critical analysis. Surg Today 2011;41:761–766.
35. Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, Hyslop T, Schmidt CM, Rosato EL, Lavu H, Nakeeb A, Pitt HA, Lillemoe KD, Yeo CJ. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 2009;208:738–747.
36. Barakat O, Ozaki CF, Wood RP. Topically applied 2-octyl cyanoacrylate (Dermabond) for prevention of postoperative pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg 2012;16:1499–1507.
37. Tani M, Kawai M, Hirono S, Hatori T, Imaizumi T, Nakao A, Egawa S, Asano T, Nagakawa T, Yamaue H. Use of omentum or falciform ligament does not decrease complications after pancreaticoduodenectomy: nationwide survey of the Japanese Society of Pancreatic Surgery. Surgery 2012;151:183–191.
38. Koti RS, Gurusamy KS, Fusai G, Davidson BR. Meta-analysis of randomized controlled trials on the effectiveness of somatostatin analogues for pancreatic surgery: a Cochrane review. HPB (Oxford) 2010;12:155–165.

Original Paper

# Infection Control for Prevention of Pancreatic Fistula after Pancreaticoduodenectomy

*Shin Kobayashi, Naoto Gotohda, Yuichiro Kato, Shinichiro Takahashi, Masaru Konishi and Taira Kinoshita*

Department of Surgical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Corresponding author: Naoto Gotohda, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan; Tel.: +81-4-7133-1111, Fax: +81-4-7131-4724; E-mail; ngotohda@east.ncc.go.jp

**Key Words:** Pancreaticoduodenectomy; Soft pancreas; Pancreatic fistula; Infection control.

## ABSTRACT

**Background/Aims:** Effectiveness of infection control for prevention of pancreatic fistula (PF) after pancreaticoduodenectomy (PD) is not clear. We analyzed the impact of infection on the development of PF and examined the effect of enhanced infection control to prevent PF. **Methodology:** Amylase level (D-amylase) and bacterial culture (D-culture) of drainage fluid were evaluated on POD 1, 3, 5 and 7, in 90 consecutive patients with soft pancreas who underwent PD. The study period was divided into two periods. The relationship between D-amylase and D-culture was examined, and the clinicopathological factors predicting PF were analyzed in the first period. Then, anti-infection measures were introduced in the second period, and the effect of enhanced infection control was examined. **Results:** Twenty-nine out of 58 patients (50.0%) developed PF in the first period. D-amylase were higher in patients with D-culture infection than in those without it ($p<0.05$). D-amylase above 10,000IU/L on POD1 and D-culture infection on POD3 were independent predictive factors for PF by multivariate analysis ($p<0.01$). After introduction of enhanced infection control in the second period, four out of 32 patients (12.5%) developed PF. The rates of PF and D-culture infection were significantly reduced ($p<0.05$). **Conclusions:** Infection of drainage fluid is related to an increased level of amylase, resulting in PF. Enhanced infection control can effectively prevent PF after PD in soft pancreas.

## INTRODUCTION

Although the mortality after pancreaticoduodenectomy (PD) has decreased to 1-2% with the recent advancement of surgical techniques, perioperative management, and centralization of case volumes, the morbidity still remains as high as 30-60% (1-4). Among those morbidities, pancreatic fistula (PF) is the most feared complication, which can potentially lead to devastating consequences (5-9). Soft pancreas is one of the most important risk factors for PF, and its rate was reported to be as high as 21-32% in soft pancreas (8,10-14). It is well recognized that septic sequelae of PF, such as abscess and pseudoaneurysm, lead to longer hospitalization and even death (5-9). Recently, it was reported that intraperitoneal infection is related to the occurrence of PF. Pratt *et al.* suggested that intraperitoneal infection was a key factor in late-onset PF (7). However, it has not been clear when intraperitoneal infection occurs and how it affects the development of PF. Role of infection control for prevention of PF remained unclear.

We analyzed the impact of infection on the development of PF and examined the effect of enhanced infection control to prevent PF. The aims of this study were: i) to clarify when infection of drainage fluid occurs and how it affects the development of PF; ii) to examine predictive factors for PF; and iii) to verify the effect of enhanced infection control for prevention of PF.

## METHODOLOGY

From July 2008 to December 2010, 142 consecutive patients underwent PD at the Department of Surgery, National Cancer Center Hospital East (NCCHE), Kashiwa, Japan. Among those 142 patients, 90 patients with soft pancreas were enrolled in this study. The texture of the pancreas, either soft or hard, was judged from the intraoperative findings by the operating surgeons. The study period was divided into two periods. The first period was from July 2008 to December 2009, and the second period was from January 2010 to December 2010. Amylase level in drainage fluid (D-amylase) and bacterial culture of drainage fluid (D-culture) were evaluated on postoperative day (POD) 1, POD3, POD5 and POD7. The relationship between D-amylase and D-culture was examined, and the predictive factors for PF were analyzed in the first period. Then, anti-PF measures that were determined according to the predictive factors in the first period were introduced in the second period, and the rates of PF were compared between the two periods. The study protocol was approved by the institutional review board of the National Cancer Center Hospital.

### Surgical technique

For PD, subtotal stomach-preserving pancreaticoduodenectomy (SSpPD) was the procedure of choice at NCCHE. Reconstruction was performed by a modification of the method described by Child (15), with pancreatojejunal anastomosis performed by duct-to-mucosa, end-to-side pancreaticojejunostomy. Pancreatic duct-to-jejunal mucosal anastomosis was performed with 8 to 16 interrupted sutures using monofilament slowly absorbable material (5-0 PDS-II, Johnson&Johnson Co., USA, or 5-0 Maxon, Covidien Co., USA). The pancreatic stump and jejunal seromuscular layer were closely approximated with 3 to 6 interrupted sutures using monofilament non-absorbable material (3-0 Nespylene, Alfresa Pharma Co., Japan) as described

Hepato-Gastroenterology 2013; 60:00-00 doi 10.5754/hge11655

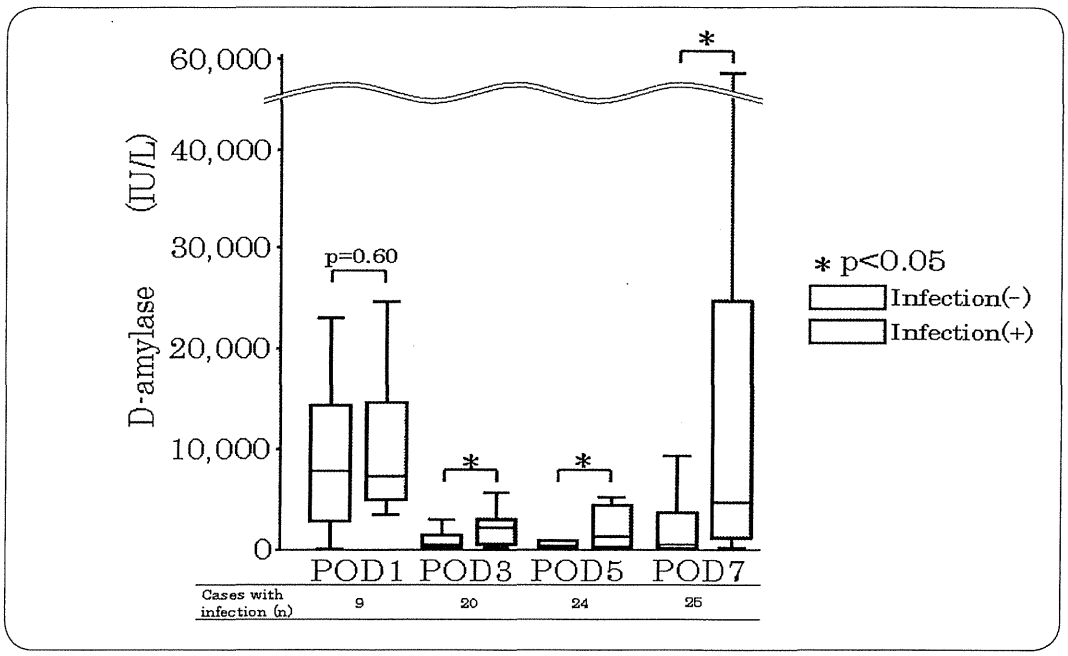


**FIGURE 1.** Amylase level in drainage fluid with and without infection. D-amylase in patients with D-culture infection was significantly higher than that without infection from POD3 to POD7 ($p<0.05$).

**TABLE 1.** ISGPF grade of pancreatic fistula.

| Variables<br>Drain amylase | Fistula (-)<br>≦3 x serum value | Grade A<br>>3 x serum value | Grade B<br>>3 x serum value | Grade C<br>>3 x serum value |
|---|---|---|---|---|
| Clinical condition | Well | Well | Often well | Ill appearance/bad |
| Specific treatment* | No | No | Yes/No | Yes |
| US/CT | Negative | Negative | Negative/positive | Positive |
| Drainage≧3wks | No | No | Usually yes | Yes |
| Signs of infection | No | No | Yes | Yes |
| Readmission | No | No | Yes/No | Yes/No |
| Sepsis | No | No | No | Yes |
| Reoperation | No | No | No | Yes |
| Death | No | No | No | Yes |

ISGPF: International Study Group of Pancreatic Fistula; US: Ultrasound; CT: Computed Tomography; *Specific treatment includes parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
(Adapted with permission from Bassi C, et al. (5))

by Kakita *et al.* (16) a 6-Fr polyethylene tube was placed in the main pancreatic duct as a lost stent. Abdominal lavage was performed with 3,000mL warm saline after digestive tract reconstruction.

### Surgical drains

Two round closed suction drains, either 19-Fr or 24-Fr depending on the operator's preference, were placed near the pancreatic and biliary anastomoses. Drains were usually removed on POD7 in the first period if the drainage fluid was clear and D-amylase was less than three times the upper limit of normal serum amylase level.

### Evaluation of pancreatic fistula

Output of closed suction drains was recorded every day, and any measurable amount, usually above 2-3mL per day, was evaluated for D-amylase and D-culture on POD1 to POD7. The presence and the grade of PF were evaluated according to the classification by the International Study Group of Pancreatic Fistula (ISGPF) (5). Details of the ISGPF classification are described in **Table 1**. The upper limit of serum amylase level at NCCHE

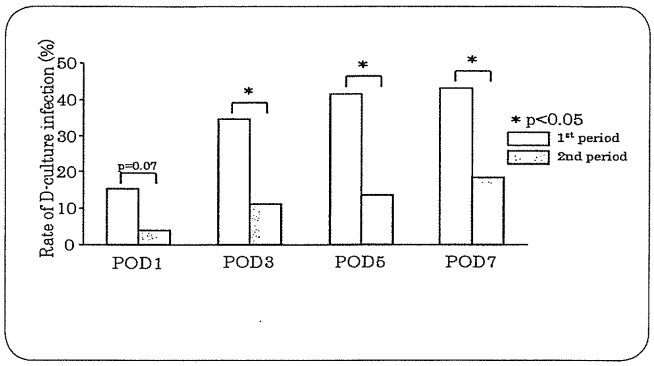


**FIGURE 2.** Rate of drainage fluid infection in two periods. The rate of D-culture infection was significantly reduced in the second period from POD3 to POD7 ($p<0.05$).

**TABLE 2.** Patient characteristics

| Variables | | 1st period (n=58) | | 2nd period (n=32) | | p |
|---|---|---|---|---|---|---|
| **Age** | years* | 70 | (24-87) | 66 | (32-83) | 0.08 |
| **Gender** | male/female | 34 / 24 | | 20 / 12 | | 0.54 |
| **Preoperative biliary drainage** | yes/no | 27 / 31 | | 16 / 16 | | 0.46 |
| **Preoperative bile infection** | yes/no | 17/ 41 | | 9 / 23 | | 0.55 |
| **Indications for operation** | n | | | | | 0.36 |
| Pancreatic origin | | 24 | (41.4%) | 13 | (40.6%) | |
| *Ductal adenocarcinoma* | | 10 | (17.3%) | 6 | (18.8%) | |
| *IPMN* | | 9 | (15.6%) | 5 | (15.6%) | |
| *Neuroendocrine tumor* | | 2 | (3.4%) | | | |
| *SPT* | | 2 | (3.4%) | 2 | ( 6.3%) | |
| *Pancreatitis* | | 1 | (1.7%) | | | |
| Bile duct origin | | 21 | (36.2%) | 12 | (37.5%) | |
| *Bile duct adenocarcinoma* | | 19 | (32.8%) | 12 | (37.5%) | |
| *Benign stricture* | | 2 | (3.4%) | | | |
| Gallbladder adenocarcinoma | | 3 | (5.2%) | 1 | ( 3.1%) | |
| Ampullary adenocarcinoma | | 6 | (10.4%) | 3 | ( 9.4%) | |
| Duodenal adenocarcinoma | | 2 | (3.4%) | 2 | ( 6.3%) | |
| Gastric adenocarcinoma | | 2 | (3.4%) | 1 | ( 3.1%) | |
| **Type of procedure** | n | | | | | 0.31 |
| SSpPD | | 47 | (81.0%) | 28 | (87.5%) | |
| PD | | 7 | (12.1%) | 4 | (12.5%) | |
| HPD (SSpPD+hepatectomy) | | 4 | (6.9%) | | | |
| **Operative time** | minutes* | 350 | ( 2 0 2 - 562) | 344 | (250-717) | 0.90 |
| **EBL** | mL* | 857 | ( 2 4 6 - 3281) | 788 | (161-4884) | 0.33 |
| **Blood transfusion** | yes/no | 14 / 44 | | 5 / 27 | | 0.25 |
| **Pancreatic duct size** | n | | | | | 0.41 |
| <3mm | | 39 | (67.2%) | 20 | (65.6%) | |
| ≧3mm | | 19 | (32.8%) | 12 | (37.5%) | |

*Numerical variables are presented as median (range); IPMN: Intraductal Papillary Mucinous Neoplasm; SPT: Solid Pseudo-Papillary Tumor; SSpPD: Subtotal Stomach-Preserving Pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; HPD: Hepato-Pancreaticoduodenectomy; EBL: Estimated Blood Loss.

**TABLE 3.** Pathogens cultured from drainage fluid in 1st period.

| Pathogen | Patients (n) |
|---|---|
| *Enterococcus faecalis* | 8 |
| *Klebsierra pneumoniae* | 8 |
| *Pseudomonas aeruginosa* | 4 |
| *Enterobacter cloacae* | 3 |
| *Enterococcus faecium* | 3 |
| *Escherichia coli* | 3 |
| *Enterobacter aerogenes* | 2 |
| *Staphylococcus aureus* | 1 |
| 11 other organisms | 11 |

PF: Pancreatic Fistula; EBL: Estimated Blood Loss; PV: Portal Vein.

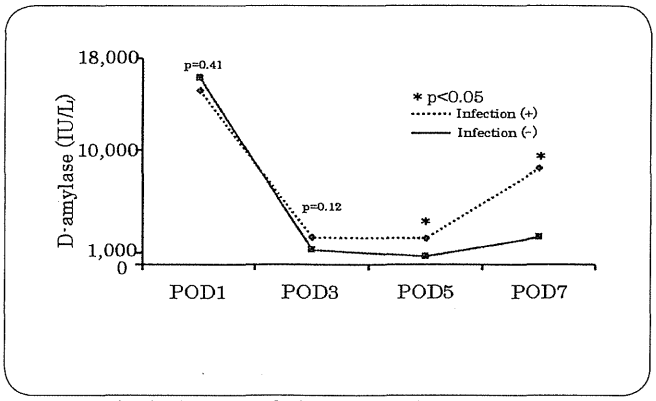


**FIGURE 3.** Amylase level in drainage fluid according to infection status on POD3. The subsequent change in amylase level in patients with D-amylase above 10,000IU/L on POD1 is shown. Amylase level in patients with infection was significantly higher from POD5 to POD7 ($p<0.05$).

was 125IU/L. In this study, any case in which drains were not removed by POD10 because of amylase-rich drainage fluid was considered as grade B irrespective of the drainage volume and length of drain insertion. Grades B/C PF were considered clinically important and were investigated in this study. Neither prophylactic nor therapeutic octreotide was administered for the management of PF.

**Bacterial culture of drainage fluid (D-culture)**

D-culture was performed on POD1, POD3, POD5 and POD7. On each day, a fresh specimen was aspirated from the drainage tube with sterile technique and incubated on sheep's agar plates for 48 hours. Any bacteria that formed $10^5$ colony forming units /mL were analyzed in the present study.

**Other perioperative management**

Preoperative biliary drainage was performed either by percutaneous transhepatic cholangio-drainage (PTCD), percutaneous transhepatic gallbladder drainage (PTGBD), or endoscopic naso-biliary drainage (ENBD), when the serum level of total bilirubin exceeded around 5mg/dL or depending on the operator's preference. Preoperative bile culture was performed, if possible. Prophylactic antibiotics, usually one gram of cefazolin (CEZ), were given to all patients before incision and every three hours only during operation in the first period. They were changed to an appropriate alternative in accordance with the bacteria, if any, found in the preoperative biliary drainage fluid. Other perioperative infection control was performed according to the guidelines issued by the Centers for Disease Control in the United States (17). Oral intake was started with clear liquid on POD1 and soft solid food on POD3. Patients were discharged home after oral intake was fully tolerated and all drains were removed.

**Statistical analysis**

All data were recorded in a database for analysis (Microsoft Excel and SPSS 11.0 J for Windows). Differences between numerical variables were analyzed by Mann-Whitney U-test and those between categorical variables were analyzed by $\chi^2$ statistics. Multivariate analysis was performed with logistic regression test. A $p$ value of less than 0.05 was considered significant.

**RESULTS**

Ninety consecutive patients with soft pancreas, 58 patients in the first period and 32 patients in the second, were enrolled in the present study. Patient characteristics in each period are described in **Table 2**. None of the patient characteristics was statistically different between the two periods.

In the first period, grade B/C PF was found in 29 patients (50.0%); grade B in 26 patients (44.8%) and C in three patients (5.2%). Median value of D-amylase in the first period was 7843IU/L on POD1, 764IU/L on POD3, 306IU/L on POD5, and 1204IU/L on POD7. The number of patients with D-culture infection was nine on POD1, 20 on POD3, 24 on POD5, and 25 on POD7. Pathogens found in D-culture are shown in **Table 3**. Comparison of D-amylase in patients with and without D-culture infection is shown in **Figure 1**. D-amylase was significantly higher in patients with D-culture infection than in those without infection on POD3 to POD7 ($p<0.05$), although the difference was not significant on POD1 ($p=0.60$). Median value of D-amylase decreased from POD1 to POD5 and increased on POD7 irrespective of D-culture infection, but the increase from POD5 to POD7 in patients with D-culture infection was about 30-fold higher than that in those without infection. The only risk factor for increased D-amylase on POD7 from POD5 was D-culture infection on POD7 (odds ratio (OR): 7.2, 95% confidence interval (CI): 1.4-37.4).

To examine predictive factors for PF, clinicopathological factors within five postoperative days were analyzed in the first period (**Table 4**). The cut-off value of D-amylase was established by drawing the receiver operating characteristic curve. D-culture infection on POD3 and D-amylase above 10,000 IU/L on POD1 were independent predictive factors by multivariate analysis (OR: 74.6% and 35.9, 95% CI: 6.4-873 and 3.9-327, respectively). Other factors, such as non-dilated main pancreatic duct, were not significant predictors of PF. Among 36 patients with one or two predictive factors present, 28 patients developed PF, while only one patient developed PF among those without any of the two factors (sensitivity: 96.6%, specificity: 72.4%, positive predictive value: 77.8%, negative predictive value: 95.5%) The only case that developed grade B PF in the absence of the two factors was managed conservatively.

According to the aforementioned results in the first period, we introduced anti-infection measures in the second period (**Table 5**). The number of patients with D-culture infection was one on POD1 (3.1%), four on POD3 (12.5%), five on POD5 (15.6%), and six on POD7 (18.8%), which were significantly fewer than those in the first period on POD3 to POD7 ($p<0.05$) (**Figure 2**).

**TABLE 4.** Analysis of clinicopathological factors predicting pancreatic fistula in 1st period.

| Variable | PF (n=29) | | No PF (n=29) | | *p* value | | Odds ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | univariate | multivariate | |
| Age ≧75 yr | 8 | (93.8%) | 9 | (79.6%) | 0.50 | | |
| Male | 19 | (65.6%) | 15 | (57.1%) | 0.21 | | |
| Preoperative biliary drainage | 12 | (43.8%) | 15 | (59.2%) | 0.30 | | |
| Preoperative bile infection | 10 | (34.5%) | 7 | (24.1%) | 0.28 | | |
| Pancreatic origin | 9 | (37.5%) | 15 | (71.4%) | 0.09 | | |
| Pancreatic ductal adenocarcinoma | 3 | (15.6%) | 7 | (53.1%) | 0.15 | | |
| Operative time ≧360min | 16 | (53.1%) | 10 | (51.0%) | 0.09 | | |
| EBL ≧1200mL | 10 | (6.3%) | 4 | (14.3%) | 0.06 | | |
| Blood transfusion (+) | 7 | (25.0%) | 7 | (32.7%) | 0.62 | | |
| Pancreatic duct ≧3mm | 6 | (28.1%) | 13 | (65.3%) | 0.04 | 0.33 | |
| PV resection | 2 | (6.3%) | 3 | (28.6%) | 0.50 | | |
| Other organ resection | 3 | (9.4%) | 1 | (2.0%) | 0.31 | | |
| D-amylase POD1 ≧10,000IU/L | 21 | (65.6%) | 6 | (12.2%) | < 0.001 | 0.001 | 35.9 (3.9-327) |
| D-amylase POD3 ≧1000IU/L | 20 | (68.8%) | 7 | (14.3%) | 0.001 | 0.59 | |
| D-amylase POD5 ≧1000IU/L | 14 | (53.1%) | 4 | (8.2%) | 0.003 | 0.35 | |
| D-culture infection POD1 (+) | 8 | (25.0%) | 1 | (2.0%) | 0.01 | 0.71 | |
| D-culture infection POD3 (+) | 18 | (59.4%) | 2 | (6.1%) | < 0.001 | 0.001 | 74.6 (6.4-873) |
| D-culture infection POD5 (+) | 20 | (71.9%) | 4 | (16.3%) | < 0.001 | 0.32 | |

PF: Pancreatic Fistula; EBL: Estimated Blood Loss; PV: Portal Vein.

**TABLE 5.** Anti-infection measures that introduced in the 2nd period.

1) Prophylactic antibiotics were changed from CEZ to PIPC.

2) PIPC was administered during and after operation until POD3.

3) Volume of intraperitoneal lavage before fascial closure was increased from 3000mL to at least 5000mL.

4) Surgical drains were removed on POD5/6 if D-amylase on POD1 was below 10,000IU/L and a negative result of D-culture on POD3 was confirmed after 48 hours of incubation.

CEZ: Cefazolin; PIPC: Pentocillin; POD: Postoperative Day; D-Amylase: Amylase Level in Drainage Fluid; IU/L: International Units Per Liter; D-Culture: Bacterial Culture of Drainage Fluid.

Length of surgical drain placement was significantly shortened in the second period from the first period (median; 6 *vs.* 13 days, $p<0.01$). Subsequently, grade B PF was identified in four patients (12.5%) while no patient developed grade C PF in the second period. The rate of PF significantly dropped from 50.0% in the first period to 12.5% in the second period ($p<0.01$) (**Table 6**). During the same period, overall PF rates including both soft and hard pancreas significantly dropped from 39.5% (32/81) to 8.3% (5/60) ($p<0.01$). Postoperative hospitalization was significantly shorter in the second period than in the first period (13 days *vs.* 24 days, $p<0.01$). Other postoperative complications are described in **Table 7**. Only one patient required re-admission, for general malaise. There was one death (1.1%) throughout the entire period, due to liver failure after transarterial embolization for pseudo-aneurysm rupture of the common hepatic artery.

## DISCUSSION

It is widely accepted that infection is related to PF. However, bacterial cultures of drainage fluid have been evaluated only at drain removal or after the development of PF (18-20). It has not been clear when infection occurs

**TABLE 6. Rate of pancreatic fistula in two periods.**

| | 1st period (n=58) | 2nd period (n=32) | *p* |
|---|---|---|---|
| **Pancreatic fistula** | 29 (50.0%) | 4 (12.5%) | <0.01 |
| Grade B | 26 | 4 | |
| Grade C | 3 | 0 | |

**TABLE 7. Other postoperative complications.**

| | 1st period (n=58) | 2nd period (n=32) | *p* |
|---|---|---|---|
| Abdominal fluid collection / abscess | 15 (25.9%) | 4 (12.5%) | 0.26 |
| With antibiotics only | 12 | 4 | |
| With IVR drainage | 3 | 0 | |
| Wound infection / fat lysis | 13 (22.4%) | 2 ( 6.3%) | 0.04 |
| Biliary anastomosis failure | 2 (3.4%) | 0 | 0.58 |
| Pseudo-aneurysm rupture | 3 (5.2%) | 0 | 0.44 |
| Pseudo-membranous colitis | 3 (5.2%) | 0 | 0.44 |
| Liver abscess | 2 (3.4%) | 0 | 0.58 |
| Delayed gastric emptying | 2 (3.4%) | 0 | 0.58 |

IVR: Interventional Radiology.

and how infection affects the development of PF. In this analysis, D-amylase in patients with D-culture infection was significantly higher than that without infection from POD3 to POD7 ($p<0.05$), and the increase in D-amylase from POD5 to POD7 in patients with D-culture infection was about 30-fold higher than that without infection. Pratt *et al.* reported that the presence of infection was a key factor in development of late-onset PF (7), and in our study, D-culture infection on POD7 was the only risk factor for an increase in D-amylase on POD7 from POD5 (OR: 4.4, 95% CI: 1.2-15.6). Our data clearly demonstrated that infection of drainage fluid was related to an increased level of amylase.

In this analysis, D-culture infection on POD3 was the strongest predictive factor for PF in the first period (OR: 74.6, 95% CI: 6.4-873). *Enterococcus faecalis/faecium, Klebsierra pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae/aerogenes* and *Escherichia coli* were the seven most frequent bacteria, accounting for 53.4% of pathogens and 79.3% of cases of D-culture infection in the first period. These enteric organisms were consistent with the results of previous studies (18,20), and were mostly resistant to CEZ. Biliary organisms found after PD were also similar to the above results (21). Preoperative bile infection was significantly related to D-culture infection on POD3 and POD5 in the first period ($p<0.05$). Therefore, we considered that intraoperative bacterial contamination was the main source of D-culture infection, and introduced anti-infection measures in the second period (**Table 5**). The rate of D-culture infection significantly dropped in the second period from POD3 to POD7 ($p<0.05$) (**Figure 2**), and the rate of PF was significantly lower in the second period than in the first period (12.5% *vs.* 50.0%, $p<0.01$) (**Table 5**). A change in D-amylase according to the status of D-culture infection on POD3 was found in patients with D-amylase above 10,000IU/L on POD1 (**Figure 3**). D-amylase in patients with infection significantly increased, with the development of PF, while D-amylase in patients without infection sharply dropped after POD3. It was thus clearly demonstrated that infection of drainage fluid is a key factor in the development of PF, and enhanced infection control effectively prevented PF in the second period. Based on these results, we speculate that there are two physiopathological mechanisms of development of PF in soft pancreas. One is a transient leak, probably from a branched pancreatic duct in the stump, which is manifested as D-amylase above 10,000IU/L on POD1. The other is failure of closure of branched pancreatic ducts due to infection, which presents as D-culture infection on POD3 and a subsequent high D-amylase. Bacterial contamination of surgical field was found to be a risk factor of anastomotic leakage in colorectal surgery (22,23). The same seemed to be true of pancreatojejunal anastomosis. Enhanced infection control effectively minimized the impact of bacteria in the early postoperative period and later prevented the development of PF.

As for the length of surgical drain placement, it was significantly shorter in the second period than in the first period ($p<0.01$). Kawai *et al.* reported that early removal of surgical drains on POD4 prevented infectious complications after PD (18). Our criterion to remove surgical drains on POD5/6 seemed to effectively minimized the occurrence of infectious complication and the development of PF. At the same time, we did not observe any intra-abdominal abscess that required IVR drainage in the second period. Early drain removal on POD4 in all patients required subsequent IVR drainage of intra-abdominal abscess in 7.4% of patients after PD (2). Our enhanced infection control and selective drain removal policy effectively minimized infectious complications as well as prevented subsequent intra-abdominal abscess drainage. We consider that the

status of D-culture infection is the critical factor in the management of PF and advocate selective early drain removal policy.

This analysis has several limitations. It was a single institutional study and the study population was not large. Although the surgical indications, procedures and perioperative management were similar among high-volume centers, the details differed among centers and even among patients. Our results need to be verified in a multi-institutional setting. However, these limitations do not preclude the importance of the present study since our findings were demonstrated with statistical significance. A future perspective is to conduct a prospective multi-institutional study to verify the impact of infection on the development of PF and the effect of infection control for prevention of PF after PD in soft pancreas.

In conclusion, the present study has several important findings: i) Infection of drainage fluid is related to an increased level of amylase; ii) D-amylase above 10,000IU/L on POD1 and D-culture infection on POD3 were independent predictive factors for PF. A transient leak probably from a branched pancreatic duct in the stump and failure of closure of branched pancreatic ducts due to infection are two possible physiopathological mechanisms for the development of PF; iii) surgical drains can be selectively removed early in the absence of these two factors; and iv) enhanced infection control can effectively prevent PF after PD.

## REFERENCES


1. **Reid-Lombardo KM, Farnell MB, Crippa S, et al.:** Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1507 patients: A report from the pancreatic anastomotic leak study group. J Gastrointest Surg 2007; 11:1451-1459.
2. **Kawai M, Tani M, Hirono S, Ina S, Miyazawa M, Yamaue H:** How do we predict the clinically relevant pancreatic fistula after pancreaticoduodenectomy? An analysis in 244 consecutive patients. World J Surg 2009; 33:2670-2678.
3. **Buchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'graggen K:** Pancreatic fistula after pancreatic head resection. Br J Surg 2000; 87:883-889.
4. **DeOliveira ML, Winter FM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien PA:** Assessment of complications after pancreatic surgery. A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006; 244:931-939.
5. **Bassi C, Dervenis C, Butturini G, et al.:** International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8-13.
6. **Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan M, Allen PJ:** Management and outcomes of postpancreatectomy fistula, leak, and abscess: Results of 908 patients resected at a single institution between 2000 and 2005. J Am Coll Surg 2008; 207:490-498.
7. **Pratt WB, Callery MP, Vollmer Jr CM:** The latent presentation of pancreatic fistulas. Br J Surg 2009; 96:641-649.
8. **Yeo CJ, Cameron JL, Maher MM, et al.:** A prospective randomized trial of pancreaticogastostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995; 222:580-588.
9. **Schmidt CM, Choi J, Powell ES, et al.:** Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes: HPB Surg. 2009 published on-line. DOI: 10.1155/2009/404520.
10. **Muscari F, Suc B, Kirzin S, Hay JM, Fourtanier G, Fingerhut A, Sastre B, Chipponi J, Fagniez PL, Radovanovic A; French Associations for Surgical Research:** Risk factors for mortality and intra-abdominal complications after pancreaticoduodenectomy: multivariate analysis in 300 patients: Surgery 2006; 139:591-598.
11. **Sato N, Yamaguchi K, Yokohata K, Shimizu S, Morisaki T, Mizumoto K, Chijiiwa K, Tanaka M:** Preoperative exocrine pancreatic function predicts risk of leakage of pancreaticojejunostomy. Surgery 1998; 124:871-876.
12. **Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT:** Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005; 11:2456-2461.
13. **Lin JW, Cameron JL, Yeo CJ, Rial TS, Lillemoe KD:** Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004; 8:951-959.
14. **Choe YM, Lee KY, Oh CA, Lee JB, Choi SK, Hur YS, im SJ, Cho YU, Ahn SI, Hong KC, Shin SH, Kim KR:** Risk factors affecting pancreatic fistulas after pancreaticoduodenectomy. World J Gastroenterol 2008; 14:6970-6974.
15. **Child CG III:** Carcinoma of duodenum: one-stage radical pancreaticoduodenectomy preserving the external pancreatic secretion, case report. Ann Surg 1943; 118:838-842.
16. **Kakita A, Yoshida M, Takahashi T:** History of pancreaticojejunostomy in pancreaticoduodenectomy: development of a more reliable anastomosis technique: J Hepatobiliary Pancreat Surg 2001; 8:230-237.
17. **Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR:** Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol 1999; 20:247-278.
18. **Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R, Miyazawa M, Uchiyama K, Yamaue H: Early** removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection. Ann Surg 2006; 244:1-7.
19. **Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, Falconi M, Pederzoli P: Amylase** value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula. Ann Surg 2007; 246:281-287.
20. **Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, Talamini G, Pederzoli P:** Early versus late drain removal after standard pancreatic resections. Results of a prospective randomized trial. Ann Surg 2010; 252:207-214.
21. **Kajiwara T, Sakamoto Y, Morohuji N, Nara S, Esaki M, Shimada K, Kosuge T:** An analysis of risk factors of pancreatic fistula after pancreaticoduodenectomy: clinical impact of bile juice infection on day 1. Langenbecks Arch Surg 2010; 395:707-712.
22. **Konishi T, Watanabe T, Kishimoto J, Nagawa H:** Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006; 202:439-444.
23. **Makela JT, KiviniemiH, Laitinen S:** Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Dis Colon Rectum 2003; 46:653-660.

膵癌・胆道癌

診断・治療 Q&A

# Q Borderline resectableの膵癌とは何か詳しく教えてください

高橋進一郎[*1]，小西　大[*2]
国立がん研究センター東病院肝胆膵外科 病棟医長[*1]・科長[*2]
池田公史[*4]，大野　泉[*3]
国立がん研究センター東病院肝胆膵内科[*3]・科長[*4]
小林達伺[*5]
国立がん研究センター東病院放射線診断科 医長[*5]

## A Borderline resectable膵癌の基本概念

膵癌治療において外科的切除は，根治を目指すことが可能な唯一の治療である。膵癌の診療は切除可能性の検討から始まり，遠隔転移を伴う転移性膵癌，重要な血管への浸潤所見を認める局所進行膵癌には内科的治療，それらの所見がない切除可能膵癌には外科的切除と術後補助化学療法を行うことが標準的な膵癌診療と考えられてきた。しかし，高性能なmultidetector-row computed tomography（MDCT）の普及により今まで画像診断では捉えられなかった脈管周囲の微細な軟部陰影が認識可能になると，切除可能膵癌と局所進行膵癌の判断に悩む腫瘍に少なからず遭遇するようになった。これらの多くは，動脈の不整狭窄像は認めないが腫瘍が動脈に密接している。技術的に切除可能だが血管剥離部で腫瘍との距離が確保できずR1（顕微鏡学的断端陽性）が予想される腫瘍である。2006年にMD AndersonのVaradhacharyらは上記のような腫瘍をborderline resectable膵癌と呼称し再発のリスクが高く術前治療が望ましい一群として分類した[1]。NCCNガイドラインではborderline resectable膵癌を定義するとともに，膵癌を切除可能性によって切除不能膵癌，borderline resectable膵癌，切除可能膵癌の3群に分類している[2]。Borderline resectable膵癌は，遠隔転移を有さない膵癌の約1割程度の頻度と考えられ，切除・放射線治療等の局所治療と全身化学療法を組み合わせた集学的治療により予後の改善が期待される。本稿では，borderline resectable膵癌の定義，診断，治療について概説する。

## 定　義

従来，画像による切除可能性の診断には限界があり最終的に切除できたものが切除可能膵癌，切除できなかったものを切除不能膵癌と考えるむきもあったが，現在はMDCTの導入により術前切除可能性診断は可能と考えられている。2012 NCCN Clinical Practice Guidelineによるborderline resectable膵癌の定義を図1に示す。

切除不能膵癌（局所進行膵癌）は腫瘍と主要動脈（上腸間膜動脈，腹腔動脈，総肝動脈）の接する範囲が180度以上の腫瘍である。特殊な場合（腹腔動脈幹合併切除を伴う膵体尾部切除）を除いて主要動脈の合併切除は許容されないため，腫瘍が主要動脈から剥離できない場合は切除不能となる（図2，3）。CT画像上，腫瘍が血管と180度以上で接する場合，95%の割合で動脈と剥離ができず切除不能であったと報告されている[3]。一方切除可能膵癌は主要動脈との間に明らかな脂肪層を有しR0（顕微鏡学的断端陰性）切除が確実に可能な腫瘍である。以上の切除可能膵癌，切除不能膵癌を除いた腫瘍，すなわち主要動脈に半周以内で接しR1切除の可能性が高い腫瘍がborderline resectable膵癌とされている。

**NCCN ガイドライン 2012**
**Borderline resectable膵癌 診断基準**

・遠隔転移がない。

・上腸間膜静脈もしくは門脈の変形，内腔狭小化，動脈浸潤を伴わない不整狭窄，再建可能な小範囲の閉塞。

・肝動脈への腫瘍近接もしくは小範囲の不整狭窄を伴う胃十二指腸動脈不整狭窄(腹腔動脈に腫瘍進展を認めない)。

・上腸間膜動脈に腫瘍が半周以下の範囲で接する。

**図1 Borderline resectable 膵癌の診断基準**

NCCN Clinical Practice Guideline 2012より

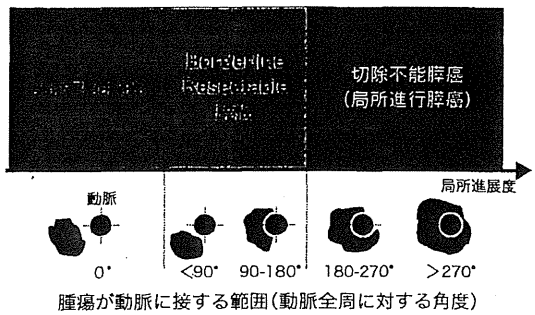


**図2 遠隔転移を有さない膵癌の分類**

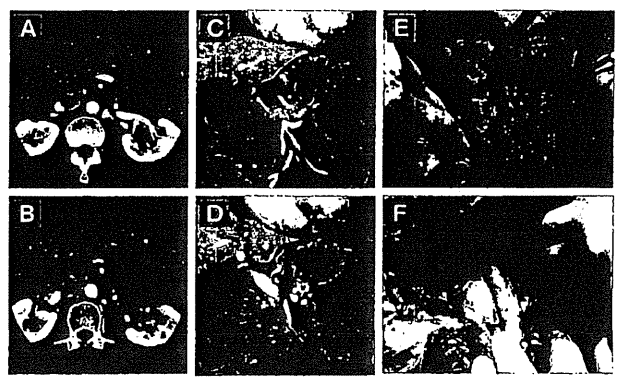


**図3 Borderline resectable膵癌の一例**

A，C：腫瘍浸潤による上腸間膜静脈・脾静脈合流部の狭窄
(A：水平断，C：冠状断)

B，D：腫瘍が上腸間膜動脈へ1/4周程度接する
(B：水平断，D：冠状断)

E，F：S-1併用放射線療法後に亜全胃温存膵頭十二指腸切除・門脈合併切除腎静脈グラフト再建を施行。R0切除後11ヵ月無再発生存中。

門脈・上腸間膜静脈と腫瘍の相互関係によるborderline resectable膵癌の定義はコンセンサスが得られていない。門脈・上腸間膜静脈浸潤は合併切除再建によりR0切除可能な場合があり動脈において用いられた剥離可能性によるロジックは成り立たない。腫瘍と門脈系脈管の境界が明瞭な場合切除可能膵癌，再建不可能な脈管浸潤を有する場合切除不能膵癌は自明だが，再建可能な門脈浸潤を有する腫瘍について切除可能膵癌とborderline resectable膵癌の境界は定まっておらず，米国の主要施設間においても認識に相違がある。本邦では変形を有する片側浸潤までは切除可能とし，再建可能ではあるが隣接する動脈との間でR1切除の可能性がある両側浸潤腫瘍をborderline resectable膵癌と考える施設が多いようである。

## 診　断

膵癌切除可能性診断を行うには動脈，門脈と腫瘍の関係が把握できる詳細な画像が必要となる。16列以上の検出器を搭載したMDCTによる膵臓用プロトコールに則った撮像が望ましい。造影前画像と造影開始後3相(35-45秒；動脈優位相，70-90秒；門脈優位相，180秒前後；平衡相)で撮像する。局所評価にはスライス厚1～3mmの拡大再構成画像やMPR(multiplanar reformation)画像を適宜追加作成して行う。Borderline resectable膵癌を含めた切除可能性の診断はcancer board等のカンファレンスにおいて内科，外科，放射線科，画像系専門職等による協議のうえで行うことが望ましい。

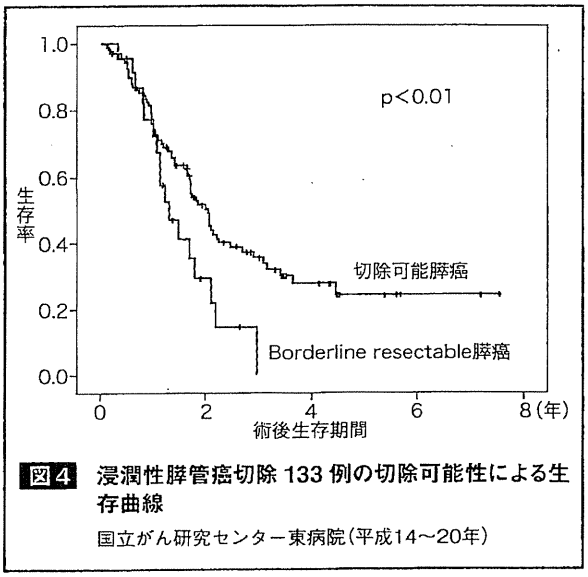


**図4** 浸潤性膵管癌切除133例の切除可能性による生存曲線

国立がん研究センター東病院(平成14～20年)

## 治療

Borderline resectable膵癌の標準治療は定まっていない。しかし局所再発のリスクが高いことから，NCCN Clinical Practice Guidelineでは切除+術後補助療法に加え術前治療が推奨されている。国立がん研究センター東病院の検討では切除後ゲムシタビン中心の補助化学療法を受けたborderline resectable膵癌患者は同様の治療を受けた切除可能膵癌患者と比較し局所再発率が高く予後が不良であった(図4)[4]。顕微鏡学的癌遺残の可能性が高いborderline resectable膵癌に適した治療戦略が必要と思われる。R0切除率の向上と局所再発率の低下をめざし術前化学放射線療法がいくつかの施設で試みられている。MD Anderson Cancer CenterのKatzらは84例のborderline resectable膵癌患者に対し化学放射線療法を中心とした術前治療後膵切除を行い切除率38%，切除例のR0切除割合97%，生存期間40ヵ月と良好な成績を示している[5]。また，最近の局所進行膵癌(切除不能膵癌)とborderline resectable膵癌を対象とした化学放射線療法の小規模研究では，局所進行膵癌と比較してborderline resectable膵癌ではR0切除割合が高く予後が良好であった[6]。これらの結果は術前化学放射線療法を中心とした集学的治療によりborderline resectable膵癌の予後が改善する可能性を示している(図3)。しかし，borderline resectable膵癌における術前化学放射線療法の明らかなエビデンスは確立されていないことから，その有効性と安全性を検証する多施設臨床試験が望まれる。本邦では膵癌補助化学療法研究グループ(JASPAC)においてborderline resectable膵癌を対象とした術前S-1併用放射線療法の第Ⅱ相試験が行われており上記の命題について一定の見解が得られるものと期待される。

## 文献

1) Varadhachary GR, Tamm EP, Abbruzzese JL, et al: Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 13(8): 1035-1046, 2006
2) Network NCC: NCCN Clinical Practice Guidelines in Oncology--Pancreatic Adenocarcinoma. 2012
3) Lu DS, Reber HA, Krasny RM, et al: Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. AJR Am J Roentgenol 168(6): 1439-1443, 1997
4) Takahashi S, Kinoshita T, Konishi M, et al: Borderline resectable pancreatic cancer: rationale for multidisciplinary treatment. J Hepatobiliary Pancreat Sci 18(4): 567-574, 2011
5) Katz MH, Pisters PW, Evans DB, et al: Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg 206(5): 833-846; discussion 846-848, 2008
6) Leone F, Gatti M, Massucco P, et al: Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: A single-institutional experience. Cancer: 2012

Gastric Cancer
DOI 10.1007/s10120-013-0309-z

ORIGINAL ARTICLE

# Survival prolongation after treatment failure of first-line chemotherapy in patients with advanced gastric cancer: combined analysis of the Japan Clinical Oncology Group Trials JCOG9205 and JCOG9912

**Atsuo Takashima · Narikazu Boku · Ken Kato · Kenichi Nakamura · Junki Mizusawa · Haruhiko Fukuda · Kuniaki Shirao · Yasuhiro Shimada · Atsushi Ohtsu**

Received: 21 June 2013 / Accepted: 26 September 2013


**Abstract**
*Background* Two randomized phase III trials of first-line chemotherapy for advanced gastric cancer (JCOG9205 and JCOG9912) conducted by the Japan Clinical Oncology Group used 5-fluorouracil continuous infusion (5-FUci) as the control arm. New active agents (e.g., S-1, irinotecan, and taxanes) were introduced as second-line chemotherapy in the late 1990s after JCOG9205. This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival after adjusting for baseline factors and also investigated the cause of survival prolongation.
*Patients and methods* The subjects were patients assigned to the 5-FUci arms who met the eligibility criteria of both JCOG9205 and JCOG9912. Overall survival (OS), time to treatment failure (TTF), and survival after treatment failure in the first-line chemotherapy (OS-TTF) were compared after adjusting baseline characteristics using the Cox proportional hazard model. Second-line chemotherapy details were also reviewed.
*Results* The combined analysis included 89 and 230 patients in JCOG9205 and JCOG9912, respectively. After adjusting baseline characteristics, TTF was similar between groups (HR 0.95; 95 % CI, 0.73–1.26). However, both OS (HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912. More patients in JCOG9912 received second-line chemotherapy (83 vs. 52 %) with new drugs (77 vs. 10 %) than in JCOG9205. OS-TTF was substantially prolonged in patients who received second-line chemotherapy (HR, 0.66; 95 % CI, 0.46–0.95).
*Conclusion* OS and OS-TTF were longer in JCOG9912 than JCOG9205. Second-line chemotherapy with new drugs is a potential reason for the observed prolongation of survival.

**Keywords** Gastric cancer · Post-treatment failure survival · Second-line chemotherapy

A. Takashima (✉) · K. Nakamura · J. Mizusawa · H. Fukuda
Japan Clinical Oncology Group Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: atakashi@ncc.go.jp

A. Takashima · K. Kato · Y. Shimada
Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan

N. Boku
Department of Medical Oncology, St. Marianna University Graduate School of Medicine, Kanagawa, Japan

K. Shirao
Department of Medical Oncology, Faculty of Medicine, Oita University, Oita, Japan

A. Ohtsu
Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

## Introduction

Although advanced gastric cancer (AGC) cannot be cured by systemic chemotherapy, some randomized controlled trials [1–3] and meta-analyses [4] demonstrate a survival benefit for first-line chemotherapy compared to best supportive care alone. The survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials comparing second-line chemotherapy and best supportive care have demonstrated the survival benefit of second-line chemotherapy [6, 7].

Published online: 26 October 2013

Two randomized phase III trials of first-line chemotherapy for AGC [i.e., Japan Clinical Oncology Group (JCOG) 9205 and JCOG9912] conducted by the JCOG involved 5-fluorouracil continuous infusion (5-FUci) as the control arm. In JCOG9205, a combination of 5-FU plus cisplatin did not confer a survival benefit over 5-FUci alone; 5-FUci was regarded as standard chemotherapy in the 1990s [8]. Thereafter, monotherapy with S-1 exhibited non-inferiority to 5-FUci in JCOG9912 in the 2000s [9]. When these two trials are compared directly, the survival of the 5-FUci arm in JCOG9912 is longer than that in JCOG9205 [median survival times: 7.1 months (95 % confidence interval (CI), 5.8–8.2) vs. 10.8 months (95 % CI, 8.9–12.0), respectively].

The periods of patient accrual for JCOG9205 and JCOG9912 were 1992–1997 and 2000–2006, respectively. In Japan, after some new active agents such as S-1, irinotecan, paclitaxel, and docetaxel were approved for AGC in the late 1990s [10–14], they have been used not only in first-line chemotherapy but in second-line chemotherapy as well. The proportions of patients in the 5-FUci arms in JCOG9205 and JCOG9912 who received second-line chemotherapy were 53 and 78 %, respectively. It is speculated that second-line chemotherapy might have contributed to the prolongation of overall survival (OS) in JCOG9912 compared to JCOG9205.

However, survival is possibly affected by other factors including baseline factors. Furthermore, the details of regimens employed as second-line chemotherapy have not been reviewed in either trial. Therefore, it is necessary to adjust the patient backgrounds of JCOG9205 and JCOG9912 to assess the influence of second-line chemotherapy on survival.

This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival even after adjusting the baseline factors of patients who met the common eligibility criteria. If survival prolongation was evident, we aimed to investigate the underlying causes of survival prolongation.

## Patients and methods

### Patient population

The subjects in this combined analysis were the patients assigned to the 5-FUci arms in JCOG9205 ($N = 105$) and JCOG9912 ($N = 234$). The subjects were selected according to the following eligibility criteria of common to both trials: histologically confirmed unresectable or recurrent gastric adenocarcinoma; adequate self-supported nutrition intake; age 20–75 years; ECOG performance status 0, 1, or 2; no history of chemotherapy or radiotherapy; preserved organ functions; and written informed consent. Patients with intestinal stenosis, who were eligible in JCOG9205 but not JCOG9912, and those with a history of adjuvant chemotherapy, who were eligible in JCOG9912 but not JCOG9205, were excluded from this study.

In both trials, the protocol treatment was continuous infusion of 5-FU (800 mg $m^{-2}$ $day^{-1}$) from day 1 to 5 repeated every 4 weeks until progressive disease or unacceptable toxicity was observed. The tumor response was evaluated by computed tomography and endoscopy every 4 and 8 weeks in JCOG9205 and JCOG9912, respectively.

The study protocol of this ad hoc combined analysis was approved by the Protocol Review Committee of the JCOG as well as the institutional review boards at the institutions of the study chair and study coordinator in compliance with the Japanese Ethical Guidelines for Clinical Studies.

### Statistical analysis

The study endpoints were OS, time to treatment failure (TTF), survival after treatment failure (OS-TTF), the proportions of patients who received second-line chemotherapy, and the type of treatment regimens of second-line chemotherapy.

OS was counted from the date of randomization to the date of death from any cause or was censored at the date of the last follow-up for surviving patients. TTF was defined as the period from the date of randomization to the date of off-treatment from any cause (e.g., death, documentation of disease progression, adverse event, or patient refusal) or was censored at the date of last follow-up for surviving patients on treatment. OS-TTF was calculated by subtracting TTF from OS in each patient or censored in case of survival. OS-TTF was counted as 0 if the protocol treatment (i.e., first-line chemotherapy) was terminated because of death. OS, TTF, and OS-TTF were compared between JCOG9205 and JCOG9912 using the Cox proportional hazard model after adjusting the following baseline factors: age (<65 vs. ≥65 years), sex (male vs. female), performance status (PS, 0–2), macroscopic type (0–5) [15], histological type (intestinal vs. diffuse) [16], prior gastrectomy (+ vs. −), target lesion (+ vs. −), peritoneal metastasis (+ vs. −), and number of metastatic sites (0–2). Prognostic factors for OS-TTF were also analyzed using the Cox proportional hazard model. For Cox regression analysis, all variables were treated as categorical variables.

OS, TTF, and OS-TTF were estimated using the Kaplan–Meier method. All analyses were carried out with SAS release 9.1 (SAS Institute, Cary, NC, USA).

## Results

### Patients

The study schema is shown in Fig. 1. There were 105 and 234 patients assigned to the 5-FUci arms in JCOG9205 and JCOG9912, respectively. Sixteen and 4 patients in JCOG9205 and JCOG9912 were excluded from this combined analysis because they did not meet the eligibility criteria or had missing data. Finally, 319 patients, 89 from JCOG9205 and 230 from JCOG9912, were included in the combined analysis.

The patients' baseline characteristics are shown in Table 1. JCOG9912 contained more patients ≥65 years old, with better PS, and fewer metastatic sites and fewer patients with peritoneal metastasis compared to JCOG9205. Thus, there appear to be substantial differences in patient background between JCOG9205 and JCOG9912.

### Reasons for treatment failure and second-line chemotherapy

The reasons for treatment failure in both trials were similar: disease progression or death in 84 % (disease progression, 68; death, 7/89) and 86 % (disease progression, 197; death, 1/230) in JCOG9205 and JCOG9912, respectively.

Second-line chemotherapy is summarized in Table 2. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 [83 % (190/230) vs. 52 % (46/89), respectively]. The drugs used in second-line chemotherapy largely differed between JCOG9205 and JCOG9912. In JCOG9912, regimens containing new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used as second-line chemotherapy in 178/190 patients (94 %). On the other hand, only 9/46 (20 %) patients received new-generation drugs in JCOG9205.

### OS and OS-TTF

TTF adjusted by the Cox model did not differ significantly between trials [adjusted hazard ratio (HR), 0.95; 95 % CI, 0.73–1.26]. However, both OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912 (Fig. 2a–c).

Subgroup analyses by second-line chemotherapy are shown in Fig. 3. Among the patients with second-line chemotherapy, OS-TTF was remarkably longer in JCOG9912 than JCOG9205 (adjusted HR, 0.66; 95 % CI, 0.46–0.95). On the other hand, among the patients who did not receive second-line chemotherapy, OS-TTF was longer in JCOG9205 than JCOG9912 (adjusted HR, 1.37; 95 % CI, 0.74–2.53).

Multivariate analysis was performed to determine the prognostic factors for OS-TTF. PS ($p < 0.001$), gastrectomy ($p = 0.031$), peritoneal metastasis ($p = 0.015$), and number of metastatic sites ($p = 0.011$) were selected as the prognostic factors for OS-TTF (Table 3).

## Discussion

Even after selecting patients on the basis of common eligibility criteria and adjusting baseline factors, the OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) of the 5-FUci arm was longer in JCOG9912 than JCOG9205.

We tried to align the two groups as much as possible to maximize comparability. Only the patients from the 5-FUci

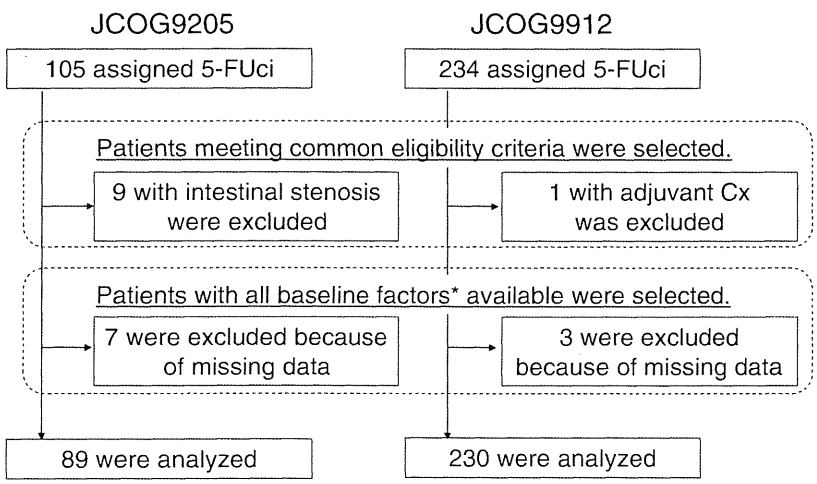


**Fig. 1** Study profile. The baseline factors used in this study were age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *Cx* chemotherapy

**Table 1** Patient characteristics

| | JCOG9205 | | JCOG9912 | | *p* value[a] |
|---|---|---|---|---|---|
| No. of patients | 89 | % | 230 | % | |
| Age (years) | | | | | |
| Median (range) | 63 (27–75) | | 63 (24–75) | | 0.4 |
| <65 | 52 | 58 | 119 | 52 | 0.06 |
| ≥65 | 37 | 42 | 111 | 48 | |
| Sex | | | | | |
| Male | 63 | 71 | 172 | 75 | 0.48 |
| Female | 26 | 29 | 58 | 25 | |
| PS[b] | | | | | |
| 0 | 41 | 46 | 149 | 65 | <.0001 |
| 1 | 33 | 37 | 78 | 34 | |
| 2 | 15 | 17 | 3 | 1 | |
| Macroscopic type[c] | | | | | |
| 0 | 0 | 0 | 5 | 2 | 0.75 |
| 1 | 5 | 6 | 8 | 4 | |
| 2 | 20 | 22 | 53 | 23 | |
| 3 | 45 | 51 | 120 | 52 | |
| 4 | 17 | 19 | 40 | 17 | |
| 5 | 2 | 2 | 4 | 2 | |
| Histological type | | | | | |
| Intestinal | 45 | 51 | 110 | 48 | 0.71 |
| Diffuse | 44 | 49 | 120 | 52 | |
| Gastrectomy | | | | | |
| − | 69 | 78 | 161 | 70 | 0.21 |
| + | 20 | 22 | 69 | 30 | |
| Target lesions | | | | | |
| − | 20 | 22 | 59 | 26 | 0.66 |
| + | 69 | 78 | 171 | 74 | |
| Peritoneal metastasis | | | | | |
| − | 76 | 85 | 143 | 62 | <.0001 |
| + | 13 | 15 | 87 | 38 | |
| Number of metastatic sites | | | | | |
| 0 | 0 | 0 | 2 | 1 | 0.06 |
| 1 | 51 | 57 | 100 | 43 | |
| ≥2 | 38 | 43 | 128 | 56 | |

[a] All *p* values are two sided. The Wilcoxon rank-sum test was used to analyze continuous variables, and Fisher's exact test was used to analyze categorical data

[b] PS was evaluated at treatment initiation in JCOG9205 and at registration in JCOG9912

[c] Japanese Classification of Gastric Carcinoma

arms meeting the common eligibility criteria of both trials were analyzed, and baseline characteristics were adjusted in multivariate analysis. In addition, both trials were conducted by the same study group. The results show that TTF (adjusted HR, 0.95; 95 % CI, 0.73–1.26) and the reasons for treatment discontinuation did not differ between trials. This finding indicates that the impact of the first-line chemotherapy with 5-FUci on OS might be comparable between the two trials.

**Table 2** Second-line chemotherapy

| Second-line chemotherapy | JCOG9205 | | JCOG9912 | |
|---|---|---|---|---|
| + | 46 | 51.7 % | 190 | 82.6 % |
| PTX, DTX, irinotecan, or S-1-containing regimen | 9 | 10.1 % | 178 | 77.4 % |
| PTX/DTX containing | 2 | | 60 | |
| Irinotecan containing | 6 | | 100 | |
| S-1 containing | 1 | | 29 | |
| Other | 37 | 41.6 % | 12 | 5.2 % |
| 5-FU/MTX | 25 | | 7 | |
| 5-FU/CDDP | 6 | | 0 | |
| Other | 6 | | 5 | |
| − | 39 | 43.8 % | 35 | 15.2 % |
| Unknown | 4 | 4.5 % | 5 | 2.2 % |

*PTX* paclitaxel, *DTX* docetaxel, *CDDP* cisplatin, *MTX* methotrexate

To evaluate the effect of second-line chemotherapy, it would be ideal to estimate the time from the start of second-line chemotherapy to death. However, because we did not collect the start date of second-line chemotherapy in the case report form, we adopted OS-TTF as the endpoint. Survival post progression is another endpoint sometimes used to evaluate the effect of second-line chemotherapy. However, protocol treatment is sometimes terminated for reasons other than progression. Moreover, second-line chemotherapy is started before progression. Therefore, we considered OS-TTF to be a more suitable surrogate of the time from the start of second-line chemotherapy than survival post progression.

The present comparison between the two trials performed in different decades is considered to contain some bias. There have been many changes in patient management during this time, leading to better survival in the recent trial. Considering OS was longer in JCOG9912 than JCOG9205, even though TTF did not differ between trials, it can be speculated that patient management after treatment failure might have changed in the era of JCOG9912 compared to that of JCOG9205. One of the major changes that occurred was the availability of antitumor drugs in second-line chemotherapy. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 (83 vs. 52 %, respectively) (Table 2). In particular, new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used more frequently in JCOG9912 than JCOG9205 (77 vs. 10 %, respectively). Moreover, the improvements in OS and OS-TTF from JCOG9205 to JCOG9912 were only observed in the subset of patients who received second-line chemotherapy (HR, 0.66; 95 %

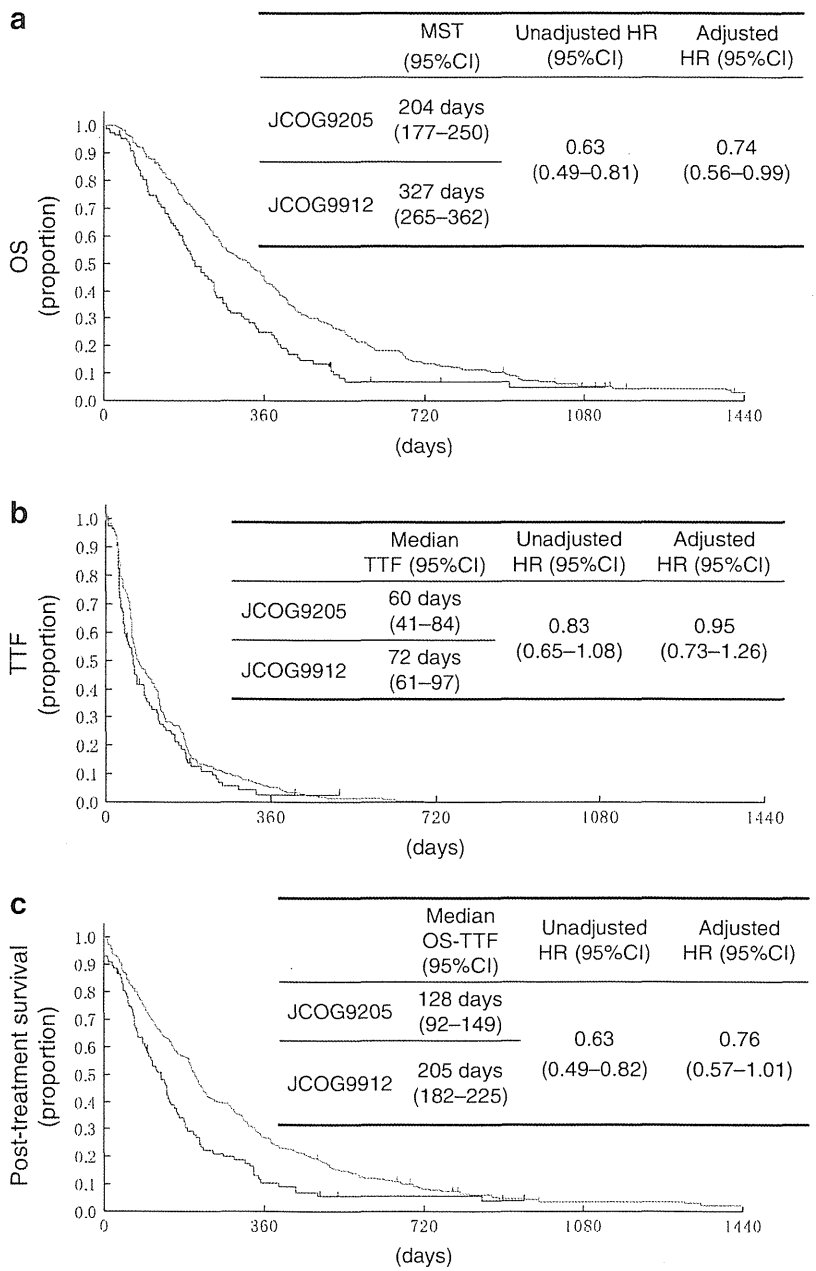


**Fig. 2** Overall survival (OS) (**a**), time to treatment failure (TTF) (**b**), and OS-TTF (**c**). Seven patients and one patient in JCOG9205 and JCOG9912, respectively, who died during first-line chemotherapy, were considered to have events on day 0. Adjustment factors included patient age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *MST* median survival time, *OS* overall survival, *TTF* time to treatment failure

CI, 0.46–0.95) (Fig. 3). These results suggest second-line chemotherapy with new-generation drugs might have contributed to survival prolongation. Kawakami et al. [17] reported the post-progression survival (PPS) of AGC is significantly longer in trials published in 2006 or later than in those published before 2005 published trials (5.34 vs. 3.74 months, $p = 0.001$). The present results corroborate these previous results, further indicating the increasing availability of active drugs in subsequent therapies is a potential reason for the observed survival prolongation.

As mentioned in the Introduction, the survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials compared second-line chemotherapy and best supportive care in AGC (6, 7). The first trial compared best supportive care with irinotecan monotherapy [6]. Irinotecan-treated patients had significantly longer survival (median survival time, 4.0 vs. 2.4 months for patients receiving best supportive care alone; HR, 0.48; 95 % CI, 0.25–0.92). These results suggest second-line chemotherapy with irinotecan confers a survival benefit.

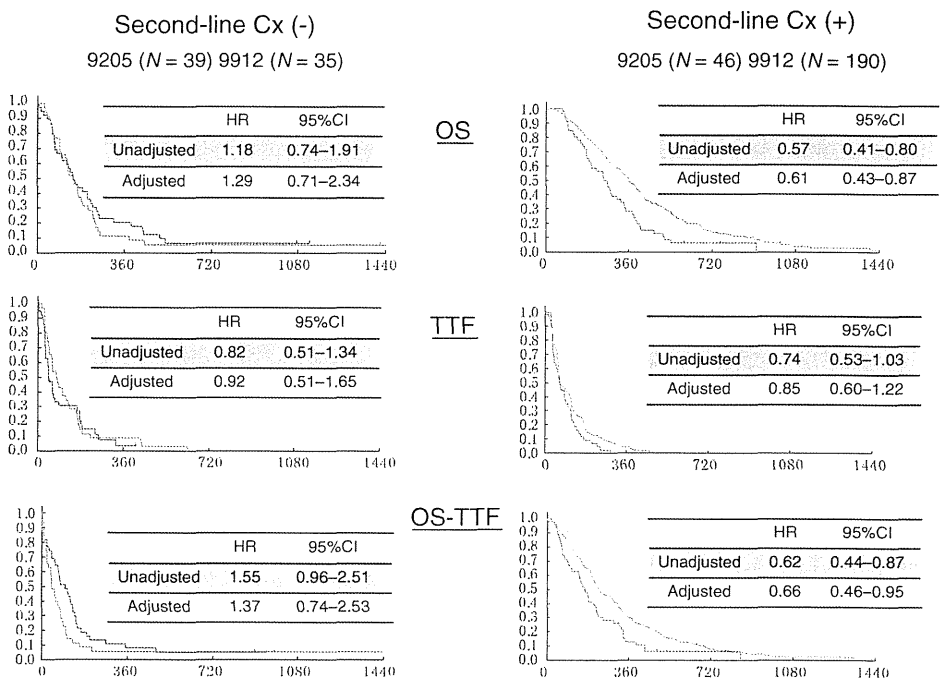


**Fig. 3** Subgroup analyses according to the presence of second-line chemotherapy. Adjustment factors included age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and the number of metastatic sites. *Cx* chemotherapy, *MST* median survival time

**Table 3** Mutivariate analysis of survival after treatment failure

| | HR | 95 % CI | *p* value |
|---|---|---|---|
| Trial | | | |
| JCOG9912 (vs. JCOG9205) | 0.76 | 0.57–1.01 | 0.06 |
| Age (years) | | | |
| ≥65 (vs. ≤64) | 1.04 | 0.82–1.31 | 0.77 |
| Sex | | | |
| Male (vs. female) | 0.84 | 0.63–1.10 | 0.20 |
| Performance status (PS) | | | |
| PS1 (vs. 0) | 1.51 | 1.17–1.95 | <0.0001 |
| PS2 (vs. 0) | 3.67 | 2.11–6.37 | |
| Macroscopic type | | | |
| 1 (vs. 0) | 0.61 | 0.20–1.85 | 0.63 |
| 2 (vs. 0) | 0.53 | 0.21–1.37 | |
| 3 (vs. 0) | 0.67 | 0.27–1.69 | |
| 4 (vs. 0) | 0.61 | 0.23–1.64 | |
| 5 (vs. 0) | 0.54 | 0.15–1.95 | |
| Histological type | | | |
| Intestinal (vs. diffuse) | 0.97 | 0.76–1.24 | 0.78 |
| Gastrectomy | | | |
| + (vs. −) | 0.73 | 0.55–0.97 | 0.03 |
| Target lesions | | | |
| + (vs. −) | 1.08 | 0.80–1.47 | 0.61 |
| Peritoneal metastasis | | | |
| + (vs. −) | 0.70 | 0.52–0.93 | 0.01 |
| Number of metastatic sites | | | |
| 1 (vs. 0) | 2.24 | 0.30–16.8 | 0.01 |
| ≥2 (vs. 0) | 3.26 | 0.43–24.9 | |

However, the study was terminated early because of poor accrual. The second study, which compared treatment with irinotecan or docetaxel to best supportive care, also showed a survival benefit of second-line chemotherapy compared to best supportive care (median survival time, 5.3 vs. 3.8 months for patients receiving best supportive care alone; HR, 0.66; 95 % CI, 0.49–0.89) [7]. This result is currently the only evidence from a completed randomized trial justifying the use of second-line chemotherapy for AGC. Besides these two studies, the present results provide additional evidence supporting a survival benefit of second-line chemotherapy in AGC.

The present combined analysis has some limitations. There may be some other reasons for the prolongation of post-treatment failure survival in this analysis, including better general condition at treatment failure in JCOG9912, recent advances in supportive care, lead-time bias of diagnosis of metastasis, and unidentified baseline factors in first-line chemotherapy; however, these factors could not be adjusted in the analysis. In particular, prognostic factors at the failure of first-line chemotherapy that could strongly influence survival after treatment failure, such as PS, were not collected in either trial.

At present, regional differences in clinical outcomes between Asian and Western countries are major obstacles for conducting global trials for AGC [18]. Although better survival in Asian countries is considered to be mainly the result of a higher proportion of patients who receive second-line chemotherapy than in Western countries, the true reason for this difference remains unknown [19]. The

present study suggests "PS," "gastrectomy," "peritoneal metastasis," and "number of metastatic sites" are strongly associated with OS-TTF. These factors are well-known prognostic factors for OS in advanced gastric cancer patients undergoing first-line chemotherapy. Patient condition before both first- and second-line chemotherapy is speculated to substantially impact OS-TTF as well as OS. Therefore, when comparing OS and OS-TF among various regions, the aforementioned patient background characteristics should be considered in addition to second-line chemotherapy. Moreover, collecting the data of prognostic factors at the time of treatment failure is recommended in future trials to clarify the effect of survival after treatment failure.

In conclusion, the longer OS and OS-TTF in JCOG9912 than in JCOG9205, even after adjusting for baseline characteristics, suggest the increasing availability of active drugs (e.g., irinotecan, taxanes, etc.) in subsequent therapies is a potential reason for the observed survival prolongation.

**Acknowledgments** We express our sincere thanks to all participating patients, investigators, and members of the JCOG Data Center. This study was supported by in part by National Cancer Center Research and Development Fund (23-A-16 and 23-A-19), Grants-in-Aid for Cancer Research (20S-3, 20S-6), and a Grant-in Aid for Clinical Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

**Conflict of interest** The authors have declared no conflicts of interest.

## References

1. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer (Phila). 1993;72(1):37–41.
2. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer. 1995;71(3):587–91.
3. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8(2):163–8.
4. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010;3:CD004064. doi: 10.1002/14651858.CD004064.pub3.
5. Wesolowski R, Lee C, Kim R. Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol. 2009;10(9):903–12. doi:10.1016/S1470-2045(09)70136-6.
6. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer: a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306–14. doi:10.1016/j.ejca.2011.06.002.
7. Kang JH, Lee SI, do Lim H, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30(13):1513–8. doi:10.1200/JCO.2011.39.4585.
8. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21(1):54–9.
9. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009;10(11):1063–1069. doi: 10.1016/S1470-2045(09)70259-1.
10. Nagashima F, Ohtsu A, Yoshida S, Ito K. Japanese nationwide post-marketing survey of S-1 in patients with advanced gastric cancer. Gastric Cancer. 2005;8(1):6–11. doi:10.1007/s10120-004-0306-3.
11. Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, et al. An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol. 1998;21(4):416–9.
12. Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol. 1999;17(1):319–23.
13. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer. 2006;9(1):14–8. doi:10.1007/s10120-005-0351-6.
14. Bang YJ, Kang WK, Kang YK, Kim HC, Jacques C, Zuber E, et al. Docetaxel 75 mg/m$^2$ is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. Jpn J Clin Oncol. 2002;32(7):248–54.
15. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 3rd English edition. Gastric Cancer 2011;14(2):101–112. doi: 10.1007/s10120-011-0041-5. PubMed PMID: 21573743.
16. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
17. Kawakami H, Okamoto I, Hayashi H, Taguri M, Morita S, Nakagawa K. Postprogression survival for first-line chemotherapy in patients with advanced gastric cancer. Eur J Cancer. 2013;49(14):3003–9. doi:10.1016/j.ejca.2013.05.022.
18. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29(30):3968–76. doi:10.1200/JCO.2011.36.2236.
19. Kirk R. Targeted therapies: should we be aghast at the AVAGAST data? Nat Rev Clin Oncol. 2011;8(10):567. doi:10.1038/nrclinonc.2011.115.

Published Ahead of Print on September 16, 2013 as 10.1200/JCO.2012.48.3552
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.48.3552

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study

*Atsushi Ohtsu, Jaffer A. Ajani, Yu-Xian Bai, Yung-Jue Bang, Hyun-Cheol Chung, Hong-Ming Pan, Tarek Sahmoud, Lin Shen, Kun-Huei Yeh, Keisho Chin, Kei Muro, Yeul Hong Kim, David Ferry, Niall C. Tebbutt, Salah-Eddin Al-Batran, Heind Smith, Chiara Costantini, Syed Rizvi, David Lebwohl, and Eric Van Cutsem*

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on September 16, 2013.

Supported by Novartis Pharmaceuticals.

Presented at the 48th Annual Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology, San Francisco, CA, January 19-21, 2012, the 48th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2012, and the 14th World Congress on Gastrointestinal Cancer, Barcelona, Spain, June 27-30, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00879333.

Corresponding author: Atsushi Ohtsu, MD, PhD, Division of Gastrointestinal Oncology/Digestive, Endoscopy, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, 277-8577 Japan; e-mail: aohtsu@east.ncc.go.jp.



0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2012.48.3552

## ABSTRACT

### Purpose
The oral mammalian target of rapamycin inhibitor everolimus demonstrated promising efficacy in a phase II study of pretreated advanced gastric cancer. This international, double-blind, phase III study compared everolimus efficacy and safety with that of best supportive care (BSC) in previously treated advanced gastric cancer.

### Patients and Methods
Patients with advanced gastric cancer that progressed after one or two lines of systemic chemotherapy were randomly assigned to everolimus 10 mg/d (assignment schedule: 2:1) or matching placebo, both given with BSC. Randomization was stratified by previous chemotherapy lines (one *v* two) and region (Asia *v* rest of the world [ROW]). Treatment continued until disease progression or intolerable toxicity. Primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), overall response rate, and safety.

### Results
Six hundred fifty-six patients (median age, 62.0 years; 73.6% male) were enrolled. Median OS was 5.4 months with everolimus and 4.3 months with placebo (hazard ratio, 0.90; 95% CI, 0.75 to 1.08; $P = .124$). Median PFS was 1.7 months and 1.4 months in the everolimus and placebo arms, respectively (hazard ratio, 0.66; 95% CI, 0.56 to 0.78). Common grade 3/4 adverse events included anemia, decreased appetite, and fatigue. The safety profile was similar in patients enrolled in Asia versus ROW.

### Conclusion
Compared with BSC, everolimus did not significantly improve overall survival for advanced gastric cancer that progressed after one or two lines of previous systemic chemotherapy. The safety profile observed for everolimus was consistent with that observed for everolimus in other cancers.

*J Clin Oncol 31. © 2013 by American Society of Clinical Oncology*

## INTRODUCTION

Gastric cancer is the fourth most common malignancy and second leading cause of cancer mortality worldwide, with 989,600 new cases and 738,000 deaths estimated to have occurred in 2008.[1] Although resection may be curative in early-stage disease,[2-4] approximately two thirds of patients present with inoperable or metastatic disease.[5] The exceptions are Japan and Korea, where national screening programs lead to early-stage diagnosis in approximately one half of patients.[6,7] Patients with advanced gastric cancer and distant metastases, who receive systemic treatment with regimens including fluorouracil and related compounds, platinum derivatives, taxanes, or irinotecan, have a 5-year survival rate of less than 5% and median overall survival (OS) less than 12 months.[6,8-10] After failure of first-line therapy, there is little consensus on second- and third-line treatment options, and outcomes are poor[2,8]; in recent phase III trials of second-line chemotherapy for advanced gastric cancer, median OS was only 4.0 to 5.3 months.[11,12] A need exists for effective therapy for patients with advanced gastric cancer whose disease progresses after first-line therapy.

Phosphatidylinositol 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) are activated in 30% and 60% of human gastric carcinomas, respectively.[13,14] PI3K/Akt/mTOR pathway

dysregulation is also associated with chemotherapy resistance[13] and decreased survival.[15-17] These findings suggest the PI3K/Akt/mTOR pathway is frequently activated in gastric cancer and is directly linked to its progression.

The oral mTOR inhibitor everolimus has demonstrated clinical benefit and a tolerable safety profile in several human cancers and tumor syndromes.[18-22] In preclinical models, everolimus inhibited downstream signaling molecules, cell proliferation, tumor growth and vascularization, and peritoneal metastasis.[14,23-27]

In a phase II study of everolimus 10 mg/d in 53 patients with advanced gastric cancer whose disease progressed after one or two previous chemotherapy lines, the disease control rate was 54.7%, median progression-free survival (PFS) per central radiology review was 2.7 months, and median OS was 10.1 months.[28] The phase III GRANITE-1 (First Gastric Antitumor Trial With Everolimus; Clinical Trial No. NCT00879333) evaluated everolimus efficacy and safety in patients with advanced gastric cancer who experienced treatment failure after one or two lines of previous chemotherapy.

## PATIENTS AND METHODS

### Patients

Eligible patients were at least 18 years old with histologically or cytologically confirmed gastric adenocarcinoma, including that of the gastroesophageal junction, and had documented disease progression after one or two previous systemic chemotherapy lines for advanced disease. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq 2$[29] and adequate organ and hematologic function. Exclusion criteria included enteral feeding, malignant ascites requiring drainage, and chronic treatment with immunosuppressive agents.

All patients provided written informed consent before enrollment. The appropriate ethics committees at each participating center approved the protocol. The study was conducted in accordance with the protocol, good clinical practice principles, the Declaration of Helsinki, and all applicable local regulations. A steering committee supervised the conduct of the study. An independent data monitoring committee performed semiannual safety reviews and reviewed interim efficacy results.

### Study Design and Assessment

Patients were randomly assigned at a 2:1 schedule to oral everolimus 10 mg/d or matching placebo. All patients received best supportive care (BSC), defined as care in accordance with local institutional practice, excluding anticancer therapy. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal. The protocol provided guidelines for dose interruption or reduction for adverse events (AEs). An initial dose reduction to 5 mg/d and a subsequent reduction to 5 mg every other day were permitted.

Treatment assignment was determined by a centralized interactive web response system that automated the random assignment of patient numbers to randomization numbers. Randomization numbers were linked to the treatment groups, which were in turn linked to medication numbers. The medication randomization list was produced by Novartis Drug Supply Management using a validated system. Randomization was stratified by the number of previous systemic chemotherapy lines (one *v* two) and region of enrollment (Asia [China, Hong Kong, Japan, Korea, Taiwan, and Thailand] *v* the rest of the world [ROW]). Aside from the independent data monitoring committee, all individuals involved in the study were blinded to treatment assignment.

Tumor response was assessed by the local investigator per the Response Evaluation Criteria in Solid Tumors, version 1.0,[30] every 6 weeks until disease progression; complete (CR) or partial response (PR) required confirmation at least 4 weeks after initial observation. To determine the minimum and maximum concentrations of everolimus in whole blood ($C_{min}$ and $C_{max}$, respectively), venous blood samples were collected predose and 1 and 2 hours postdose on day 1 of week 5. Hematology, biochemistry, and vital signs were assessed at baseline and at each visit. AEs were monitored continuously and assessed using the Common Terminology Criteria for Adverse Events, version 3.0.[31]

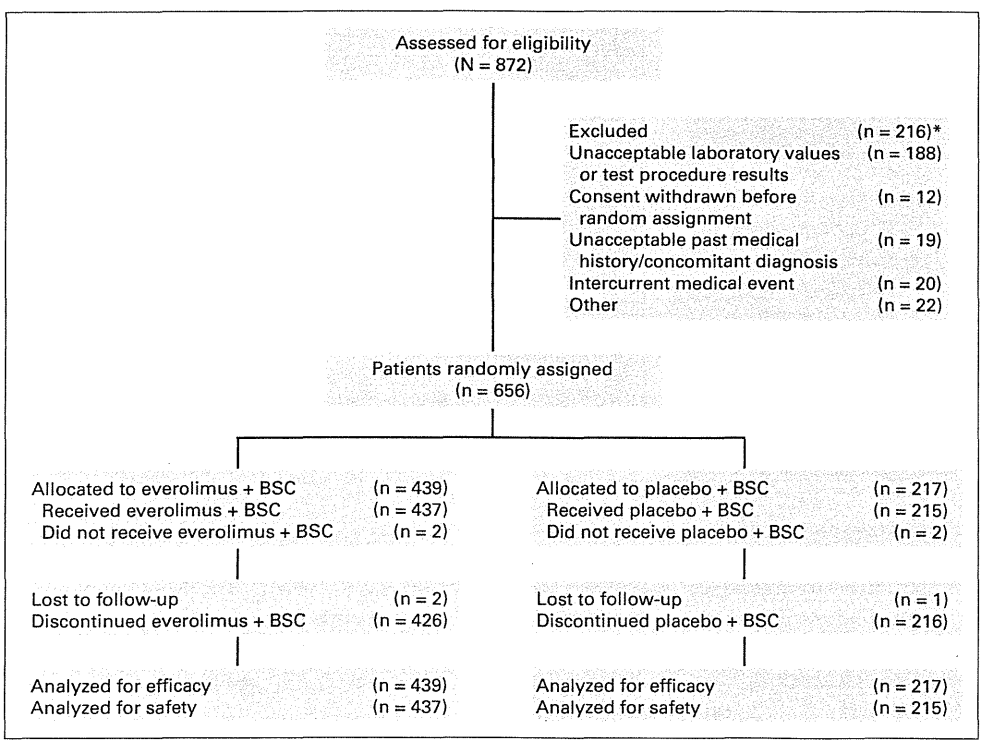


**Fig 1.** CONSORT diagram. (*) Patients could be excluded for more than one reason. BSC, best supportive care.

  