Peer Review File

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Reviewer A

1. Why were cohorts of locally advanced disease and metastatic disease included to evaluate the association between chemotherapy response and SEMS patency? Both cohorts are such a diverse group that factors pertaining to the local status of the tumor on SEMS patency cannot be ignored. Although patients with locally advanced disease can ultimately undergo curative-intent surgical resection following excellent response to preoperative therapy, <25% do so either because of local/distant progression of disease. Again, all these factors need to be taken in account to generalize the results of this study.

Reply>

We gratefully acknowledge your valuable feedback.

We agree with your insight on disease status. Although SEMS is now recommended for patients with obstructive jaundice who are expected to receive neoadjuvant therapy, it is difficult to evaluate SEMS patency in patients with resectable or borderline resectable pancreatic cancer because of surgical intervention. Therefore, we enrolled patients with unresectable pancreatic cancer who required biliary drainage during their lifetime.

We understand your concern about the different disease statuses between locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer. As you mentioned, surgery is now indicated for <25% of all patients with LAPC. However, LAPC is still considered unresectable, and many studies have combined LAPC and MPC as unresectable cancer.

We have added the abovementioned limitation in the Discussion section.

Before:

Limitation section in Discussion

This study has several limitations. First, it is retrospective in nature with a small number of patients.

After:

Limitation section in Discussion

This study has several limitations. First, it was retrospective in nature and included a small number of patients with LAPC or MPC.

2. The authors need to discuss the criteria used to define locally advanced disease. Was this concordant with the NCCN resectability criteria?

Reply>

We have used the National Comprehensive Cancer Network (NCCN) resectability criteria to define locally advanced disease. We have added a description of the NCCN criteria in the revised manuscript.

Before:

Definitions section in Methods

The duration of SEMS patency was defined as the time between SEMS insertion and SEMS occlusion or revision.

After:

Definitions section in Methods

Pancreatic cancer staging was performed according to the National Comprehensive Cancer Network (NCCN) criteria.(3) The duration of SEMS patency was defined as the time between SEMS insertion and SEMS occlusion or revision.

Reference

3. Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(4):439-57.

3. Why was an arbitrary cutoff of 7months PFS used to define "good" and "poor" chemotherapy response? Also, what criteria did the authors use to define "progression" to chemotherapy? Was it based biochemical, radiological or clinical factors? This should be elaborated on in the methods section.

Reply>

In this study, PFS was 6.4 months, which was consistent with the median PFS reported in previous studies: 5.5–6.4 months in MPC and 7or 8 months in LAPC. Based on these results, we defined the cutoff value as 7 months. We used the RECIST 1.1 to define disease progression.

Before:

Definitions section in Methods

Based on the PFS, good and poor chemotherapy responses were defined as PFS >7 months and PFS <7 months, respectively.

After:

Definitions section in Methods

The median progression-free survival (PFS) of patients with MPC receiving FOLFIRINOX or GnP as the first-line chemotherapy ranged from 5.5 to 6.4 months(4, 5). The median PFS of patients with LAPC receiving FOLFIRINOX or GnP ranged from 7 to 8 months(11). Compared with the aforementioned previous studies, the median PFS in our study was 6.4 months; longer PFS and shorter PFS were defined as PFS ≥ 7 months and PFS < 7 months, respectively. Disease progression was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1(12).

Reference

4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25.

5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.

11. Walma MS, Brada LJ, Patuleia SIS, Blomjous JG, Bollen TL, Bosscha K, et al. Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort. Eur J Surg Oncol. 2021;47(3 Pt B):699-707.

4. There is a major error in the definition of "duration of chemotherapy". The authors wrote "In the multivariate analysis, metastatic cancer and poor chemotherapy response (PFS < 7 months), i.e., shorter duration of initial chemotherapy…" and "Compared with

this study, the current study showed that SEMS patency was affected by the duration of first-line chemotherapy. What does this mean? How is a PFS<7months related to the duration of chemotherapy? Further, they conclude that "SEMS patency was associated with the duration of initial chemotherapy.." which is inherently wrong based on the analysis they presented. This is a major point that the authors need to address. The number of cycles of chemotherapy for each group needs to be clearly delineated.

Reply>

We agree with your comment and have revised the term "duration of initial chemotherapy" and "chemotherapy response" to "progression-free survival" throughout the manuscript and figures.

Before:

Title

Association between chemotherapy response and metal stent patency in patients with advanced pancreatic cancer

Running Title

Running Title: Chemotherapy and SEMS patency in pancreatic cancer

Keywords

Keywords: pancreatic cancer; chemotherapy; Self Expandable Metallic Stents

Background of Abstract

However, limited data regarding the association between SEMS patency and chemotherapy response are available. This study aimed to assess the chemotherapy response and SEMS

patency in patients with advanced pancreatic cancer.

Methods of Abstract

Patients received either gemcitabine plus nab-paclitaxel (GnP) or fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as initial chemotherapy and SEMS within 1 month before or after initial chemotherapy. Good chemotherapy response was defined as progression-free survival (PFS) >7 months.

Results of Abstract

From among the several clinical parameters examined, poor chemotherapy response (PFS < 7 months) (hazard ratio [HR] 2.117 (95% confidence interval [CI] 1.020–4.393), P = 0.044), and metastatic cancer (HR 2.414 (95% CI 1.159–5.018), P = 0.019) were associated with shorter SEMS patency in the multivariate analysis. The median SEMS patency of patients with longer and shorter initial chemotherapy was 14.3 and 7.0 months (P = 0.012), respectively, and that in patients with locally advanced and metastatic cancer was 16.7 and 7.0 months (P = 0.006), respectively.

Conclusions of Abstract

SEMS patency was associated with response of initial chemotherapy in patients with advanced pancreatic cancer who received GnP or FOLFIRINOX.

Fourth paragraph in Methods

Based on the PFS, good and poor chemotherapy responses were defined as PFS >7 months and PFS <7 months, respectively.

Third paragraph in Results

In the univariate analysis for stent patency, age ≥70 years, metastatic cancer, CA 19-9 level ≥37 U/mL, and poor chemotherapy response (PFS < 7 months) were associated with the duration of SEMS patency. In the multivariate analysis, metastatic cancer and poor chemotherapy response (PFS < 7 months), i.e., shorter duration of initial chemotherapy, were associated with the duration of SEMS patency with hazard ratios of 2.412 (95% CI, 1.159–5.018; $P = 0.019$) and 2.117 (95% CI, 1.020–4.393, $P = 0.044$), respectively (Table 2).

Fourth paragraph in Results

When the SEMS patency between the good and poor chemotherapy response groups was compared (Figure 2A), the median SEMS patency of the good chemotherapy response group was significantly longer than that of the poor chemotherapy response group (14.3 vs. 7.0 months, P = 0.012).

Second paragraph in Discussion

Compared with this study, the current study showed that SEMS patency was affected by the duration of first-line chemotherapy. The outcome in the current study agreed with that of the previous study in that the response of chemotherapy affected the SEMS patency.

Second paragraph in Discussion

However, the R-squared value in this study showed that there was a moderate association between PFS and SEMS patency, which suggested that SEMS patency is affected by not only the chemotherapy response but also other clinical factors.

Fourth paragraph in Discussion

Lastly, our study only demonstrated the association between chemotherapy response and stent patency and did not investigate the causal relationship.

Fifth paragraph in Discussion

In conclusion, SEMS patency was associated with the duration of initial chemotherapy in patients with advanced pancreatic cancer who received GnP or FOLFIRINOX. Further studies on the causal relationship between chemotherapy response and duration of SEMS patency are warranted.

After:

Title

Association between progression-free survival and metal stent patency in patients with advanced pancreatic cancer

Running Title

Running Title: PFS and SEMS patency in pancreatic cancer

Keywords

Keywords: pancreatic cancer; progression-free survival; Self Expandable Metallic Stents

Background of Abstract

However, knowledge regarding the association between SEMS patency and progression-free survival (PFS) remains limited. This study aimed to assess PFS and SEMS patency in patients with advanced pancreatic cancer.

Methods of Abstract

Patients received ~~either~~ gemcitabine plus nab-paclitaxel (GnP) or fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as initial chemotherapy and SEMS within 1 month before or after the initial chemotherapy. Longer PFS was defined as PFS ≥7 months.

Results of Abstract

Of the clinical parameters assessed using multivariate analysis, shorter PFS (PFS < 7 months; hazard ratio [HR], 2.117; 95% confidence interval [CI], 1.020–4.393; $P = 0.044$) and metastatic cancer (HR, 2.414; 95% CI, 1.159–5.018; $P = 0.019$) were found to be associated with shorter SEMS patency. The median SEMS patency in patients with longer PFS and those with shorter PFS was 14.3 and 7.0 months ($P = 0.012$), respectively, and that in patients with locally advanced cancer and those with metastatic cancer was 16.7 and 7.0 months ($P = 0.006$), respectively.

Conclusions of Abstract

SEMS patency may be associated with PFS in patients with advanced pancreatic cancer who receive GnP or FOLFIRINOX.

Fourth paragraph in Methods

Longer and shorter PFS were defined as PFS ≥7 months and PFS <7 months, respectively.

Third paragraph in Results

In the univariate analysis of stent patency, age ≥ 70 years, metastatic cancer, CA 19-9 level ≥ 37 U/mL, and shorter PFS were noted to be associated with the duration of SEMS patency. In the multivariate analysis, metastatic cancer and shorter PFS were associated with the duration

of SEMS patency with hazard ratios of 2.412 (95% CI, 1.159–5.018; $P = 0.019$) and 2.117 (95% CI, 1.020–4.393; $P = 0.044$), respectively (Table 2).

Fourth paragraph in Results

When SEMS patency was compared between the longer and shorter PFS groups (Figure 3A), the median SEMS patency of the longer PFS group was found to be significantly longer than that of the shorter PFS group (14.3 vs. 7.0 months; $P = 0.012$).

Second paragraph in Discussion

Compared with the previous study, the present study showed that SEMS patency is affected by PFS. This is likely a reflection of longer durations of initial chemotherapy resulting in a better response, thereby delaying events such as tumor ingrowth. The finding of the present study was consistent with that of a previous study in that patients' response to chemotherapy may affect SEMS patency.

Second paragraph in Discussion

However, the R-squared value determined in this study indicated a moderate association between PFS and SEMS patency, which further suggested that SEMS patency is affected not only by PFS but also other clinical factors.

Fourth paragraph in Discussion

Finally, our study only identified the association between PFS and stent patency but did not investigate the causal relationship.

Fifth paragraph in Discussion

In conclusion, SEMS patency may be associated with PFS in patients with advanced pancreatic cancer who received GnP or FOLFIRINOX. Further studies on the causal relationship between PFS and the duration of SEMS patency are warranted in the future.

5. Was there a difference in the stent revision causes between patients with locally advanced vs metastatic pancreatic cancer? Progression of pancreatic cancer tends to predominantly be distant progression rather than local progression. Please elaborate.

Reply>

The causes of stent revision did not vary between the two groups. We have indicated the causes in the Second paragraph of the Results section.

Before:

Fifth paragraph in Methods

Variables with P <0.05 by univariate analysis were included in the multivariate analysis. The Kaplan–Meier method was used to compare the duration of SEMS patency.

Second paragraph in Results

The most common cause of stent revision was tumor ingrowth or overgrowth (51.3%), followed by sludge formation (38.5%) and stent migration (2.6%). The median stent patency and PFS were 208 (interquartile range [IQR] 136–387 days) and 192 days (IQR, 127–375 days), respectively.

After:

Fifth paragraph in Methods

Data with a P-value of <0.05 in univariate analysis were included in the multivariate analysis. The Kaplan–Meier method was used to compare the duration of SEMS patency. Categorical variables were evaluated using Fisher's exact test.

Second paragraph in Results

The most common cause of stent revision was tumor ingrowth or overgrowth (51.3%), followed by sludge formation (38.5%) and stent migration (2.6%). The causes of stent revision did not vary between the LAPC and MPC groups (tumor ingrowth or overgrowth: 63.6% vs. 46.4%, $P = 0.142$; sludge formation: 27.2% vs. 42.9%, $P = 0.795$; stent migration: 0% vs. 3.6%, $P > 0.99$). The median stent patency and PFS were 6.9 (interquartile range [IQR], 4.5–12.9) and 6.4 (IQR, 4.2–12.5) months, respectively.

6. The PFS/OS and stent-patency rates should be reported in months rather than in days.

Reply>

The PFS/OS and stent-patency rates have been revised to months.

Before:

Results of Abstract

Sixty-one patients (82.4%) underwent endoscopic SEMS insertion. The median stent patency and PFS were 208 and 192 days, respectively, and the median overall survival was 315 days. From among the several clinical parameters examined, shorter PFS (PFS < 7 months) (hazard ratio [HR] 2.117 (95% confidence interval [CI] 1.020−4.393), $P = 0.044$), and metastatic cancer (HR 2.414 (95% CI 1.159–5.018), $P = 0.019$) were associated with shorter SEMS patency in the multivariate analysis. The median SEMS patency of patients with longer and shorter initial chemotherapy was 428 and 211 days ($P = 0.012$), respectively, and that in patients with locally

advanced and metastatic cancer was 501 and 211 days (P = 0.006), respectively.

Second paragraph in Results

The median stent patency and PFS were 208 (interquartile range [IQR] 136–387 days) and 192 days (IQR, 127–375 days), respectively. The median OS was 315 days (IQR, 202–495 days).

Fourth paragraph in Results

When the SEMS patency between the good and poor chemotherapy response groups was compared (Figure 2A), the median SEMS patency of the good chemotherapy response group was significantly longer than that of the poor chemotherapy response group (428 vs. 211 days, P = 0.012). When the SEMS patency between patients with LAPC and MPC was compared (Figure 2B), the median SEMS patency of the LAPC group was significantly longer than that of the MPC group (501 vs. 211 days, P = 0.006).

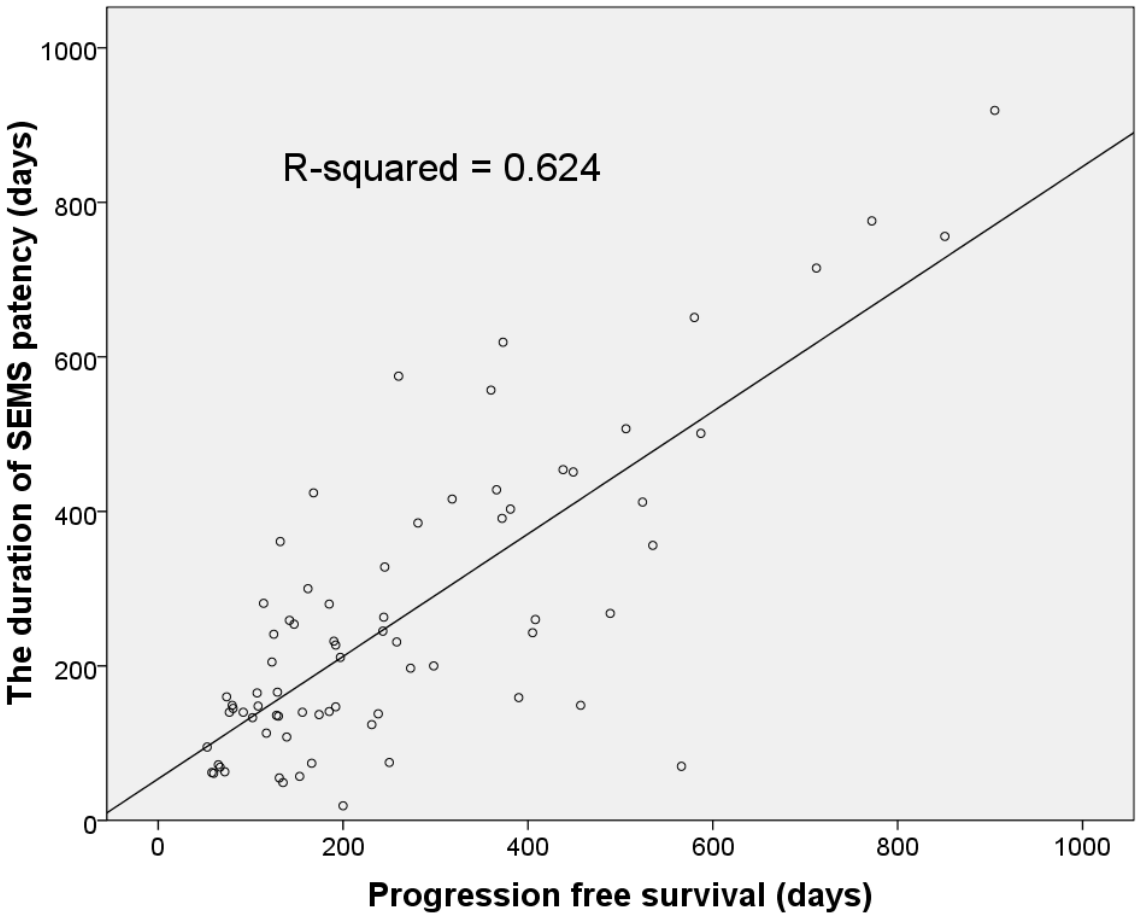
First paragraph in Discussion

Considering the median patency of SEMS, which ranged from 166 to 287 days, the duration of SEMS patency was comparable to the expected survival at that time(18-21). The median stent patency in this study was 208 (IQR, 136–387) days, which was also comparable to that in previous studies. However, SEMS revision is necessary in many patients because the survival of patients has increased with the advent of two recently introduced chemotherapy regimens. Although there were patients with not only MPC but also LAPC, the median PFS and OS in this study were 192 (IQR, 127–375) and 315 (IQR, 202–495) days, which were comparable to those in the previous studies (PFS, 5.5–6.4 months; OS, 8.5–11.1 months)(4, 5).

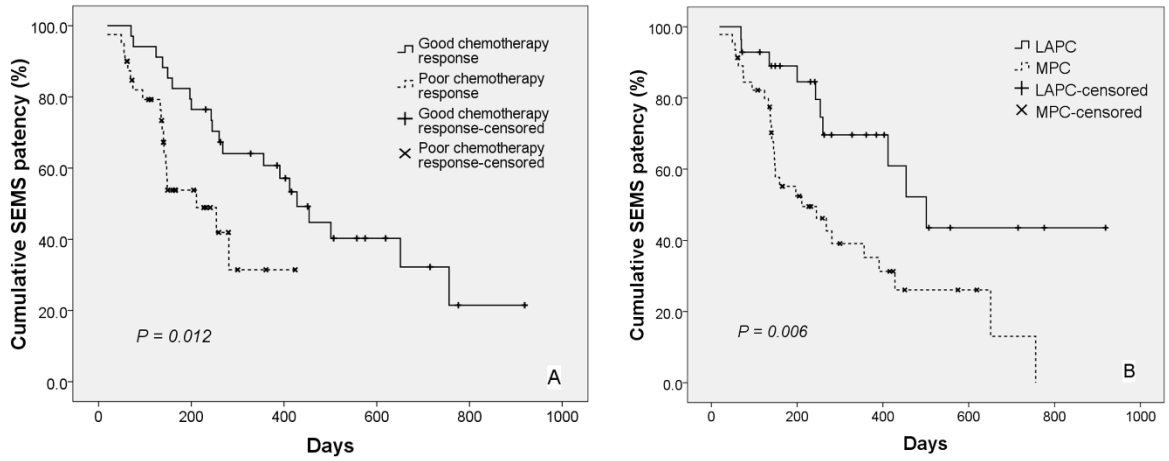
In table 1

	N = 74 (%)
Age (year) (mean, 95% CI)	66.2 (63.7–68.6)
<70	46 (62.2)
≥70	28 (47.8)
Sex	
Male	38 (51.4)
Female	36 (48.6)
Clinical stage	
LAPC	28 (37.8)
MPC	46 (62.2)
Cell type	
Adenocarcinoma	69 (93.2)
Poorly differentiated carcinoma	2 (2.7)
Adenosquamous carcinoma	1 (1.4)
Biopsy not proven	2 (2.7)
Total bilirubin (mg/dL) (mean, 95% CI)	7.2 (5.7–8.7)
CA 19-9 (U/mL) (mean, 95% CI)	1442.8 (586.7–2299.0)
<37	16 (21.6)
≥37	57 (77.0)
First–line chemotherapy	
Gemcitabine plus nab-paclitaxel	16 (21.6)
FOLFIRINOX	58 (78.4)
Stent insertion method	
Endoscopic	61 (82.4)
Percutaneous	13 (17.6)
Stent diameter	
8 mm	9 (12.2)
10 mm	65 (87.8)
Metal stent type	
Covered stent	9 (12.2)
Uncovered stent	65 (87.8)
Stent revision	
Yes	39 (52.7)
No	35 (47.3)
Cause of stent revision	
Tumor ingrowth or overgrowth	20 (51.3)
Sludge formation	15 (38.5)
Stent migration	1 (2.6)
Unknown	3 (7.7)
Stent insertion–chemotherapy period (day) (median, range)	4.0 (–30~30)
Duration of stent patency (day) (median, IQR)	208 (136–387)
Progression-free survival (day) (median, IQR)	192 (127–375)
Progression-free survival	
<7 months	40 (54.1)
≥7 months	34 (45.9)
Overall survival (day) (median, IQR)	315 (202–495)
Median follow-up period (day, range)	420 (57–1101)

In figure 1



In figure 2



In figure legends

(A) The median SEMS patency of the good chemotherapy response group was significantly longer than that of the poor chemotherapy response group (428 vs. 211 days, P = 0.012).

(B) The median SEMS patency of the locally advanced pancreatic cancer group was significantly longer than that of the metastatic pancreatic cancer group (501 vs. 211 days, P = 0.006).

After:

Results of Abstract

Of the patients, 61 (82.4%) underwent endoscopic SEMS insertion. The median stent patency and PFS were 6.9 (IQR, 4.5–12.9) and 6.4 (IQR, 4.2–12.5) months, respectively; the median overall survival was 10.5 (IQR, 6.7–16.5) months. Of the clinical parameters assessed using multivariate analysis, shorter PFS (PFS < 7 months; hazard ratio [HR], 2.117; 95% confidence interval [CI], 1.020–4.393; P = 0.044) and metastatic cancer (HR, 2.414; 95% CI, 1.159–5.018; P = 0.019) were found to be associated with shorter SEMS patency. The median SEMS patency in patients with longer PFS and those with shorter PFS was 14.3 and 7.0 months (*P* = 0.012), respectively, and that in patients with locally advanced cancer and those with metastatic cancer

was 16.7 and 7.0 months (P = 0.006), respectively. The coefficient of determination between stent patency and PFS was 0.624.

Second paragraph in Results

The median stent patency and PFS were 6.9 (interquartile range [IQR], 4.5–12.9) and 6.4 (IQR, 4.2–12.5) months, respectively. The median OS was 10.5 (IQR, 6.7–16.5) months.

Fourth paragraph in Results

When SEMS patency was compared between the longer and shorter PFS groups (Figure 3A), the median SEMS patency of the longer PFS group was found to be significantly longer than that of the shorter PFS group (14.3 vs. 7.0 months; P = 0.012). When SEMS patency was compared between patients with LAPC and those with MPC (Figure 3B), the median SEMS patency of the LAPC group was significantly longer than that of the MPC group (16.7 vs. 7.0 months; P = 0.006).

First paragraph in Discussion

Considering the median patency of SEMS, which ranged from 5.5 to 9.6 months, the duration of SEMS patency was consistent with the expected survival at that time(16-19). The median stent patency in this study was 6.9 (IQR, 4.5–12.9) months, which was also consistent with that of previous studies. However, SEMS revision is necessary in many patients because patient survival has increased with the advent of the two recently introduced chemotherapy regimens. Although there were patients with not only MPC but also LAPC, the median PFS and OS in this study were 6.4 (IQR, 4.2–12.5) and 10.5 (IQR, 6.7–16.5) months, which were consistent with those of the previous studies (PFS, 5.5–6.4 months; OS, 8.5–11.1 months)(4, 5).

In table 1

	N = 74 (%)
Age (years) mean (95% CI)	66.2 (63.7–68.6)
<70	46 (62.2)
≥70	28 (47.8)
Sex, n (%)	
Male	38 (51.4)
Female	36 (48.6)
Clinical stage, n (%)	
LAPC	28 (37.8)
MPC	46 (62.2)
Cell type, n (%)	
Adenocarcinoma	69 (93.2)
Poorly differentiated carcinoma	2 (2.7)
Adenosquamous carcinoma	1 (1.4)
Biopsy not proven	2 (2.7)
Total bilirubin (mg/dL), mean (95% CI)	7.2 (5.7–8.7)
CA 19-9 (U/mL), mean (95% CI)	1442.8 (586.7–2299.0)
<37	16 (21.6)
≥37	57 (77.0)
First–line chemotherapy, n (%)	
Gemcitabine plus nab-paclitaxel	16 (21.6)
FOLFIRINOX	58 (78.4)
Stent insertion method, n (%)	
Endoscopic	61 (82.4)
Percutaneous	13 (17.6)
Stent diameter (mm), n (%)	
8	9 (12.2)
10	65 (87.8)
Metal stent type, n (%)	
Covered	9 (12.2)
Uncovered	65 (87.8)
Stent revision, n (%)	
Yes	39 (52.7)
No	35 (47.3)
Cause of stent revision, n (%)	
Tumor ingrowth or overgrowth	20 (51.3)
Sludge formation	15 (38.5)
Stent migration	1 (2.6)
Unknown	3 (7.7)
Stent insertion–chemotherapy period (days), median (range)	4.0 (–30~30)
Duration of stent patency (months), median (IQR)	6.9 (4.5–12.9)
Progression-free survival (months), median (IQR)	6.4 (4.2–12.5)
Progression-free survival (months), n (%)	
<7	40 (54.1)
≥7	34 (45.9)
Overall survival (months), median (IQR)	10.5 (6.7–16.5)
Follow-up period (months),median (range)	14 (1.9–36.7)

Figure 1

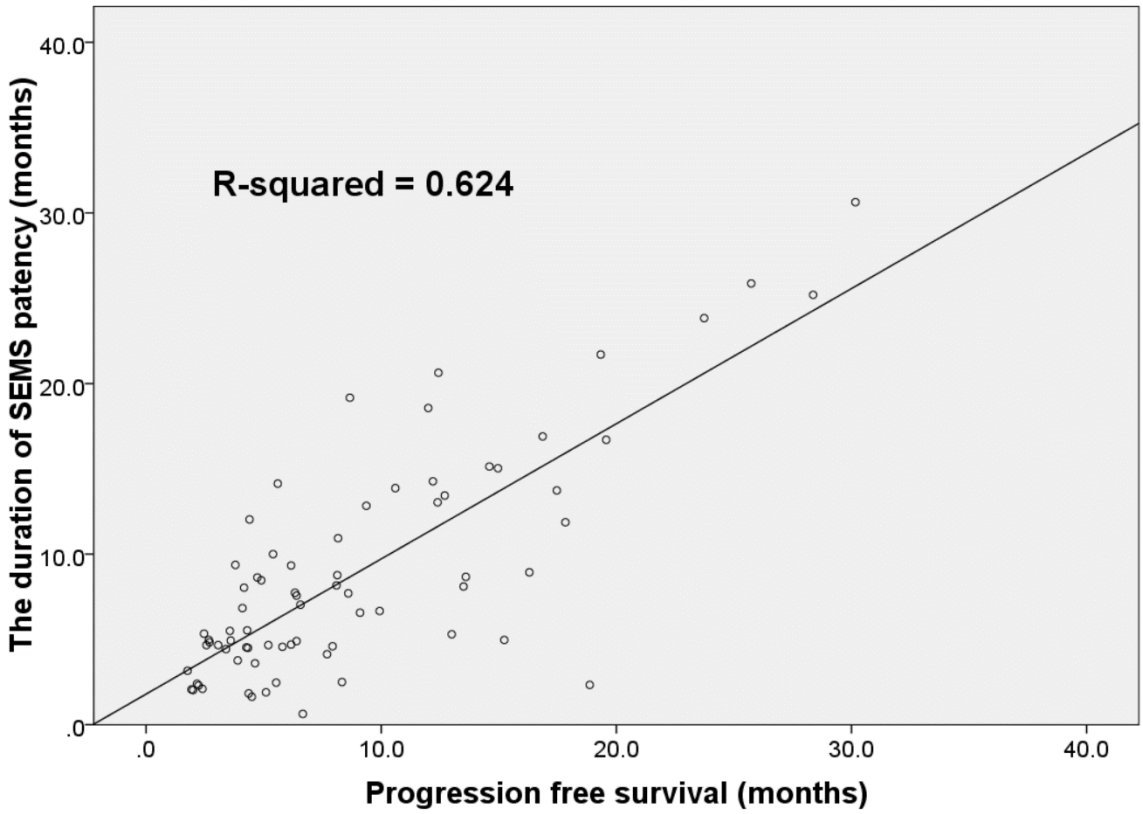
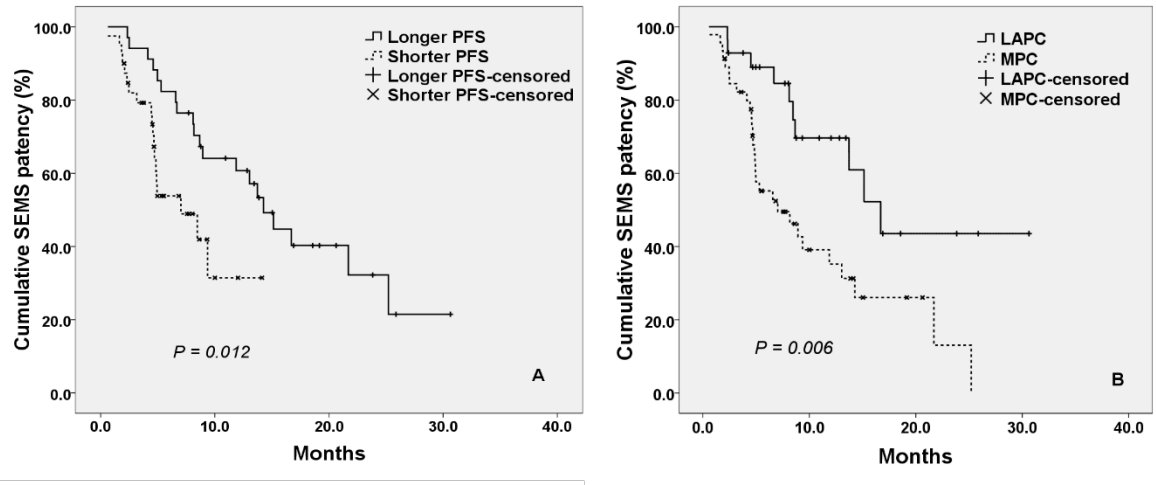


Figure 2



In figure legends

(A) Median SEMS patency of the longer PFS group was significantly longer than that of the shorter PFS group (14.3 vs. 7.0 months, $P = 0.012$).

(B) Median SEMS patency of the locally advanced pancreatic cancer group was significantly longer than that of the metastatic pancreatic cancer group (16.7 vs. 7.0 months, $P = 0.006$).

7. Several grammatical errors; please proof read

Reply>

Thank you for highlighting this issue. The English Editing company Enago (www.enago.com) has re-checked the revised manuscript.

Reviewer B

1. The authors indicate that they reviewed over 1000 charts to end up with the 74 that met inclusion criteria. Ideally, there would be description of how the authors got from 1000 to 74, including how many patients were excluded for various reasons, if possible.

Reply>

We gratefully acknowledge your valuable feedback.

We have checked the exact number of charts and added a study flow chart.

Before:

First paragraph in Methods

Between January 2012 and June 2021, more than 1,000 patients diagnosed with pancreatic cancer at Seoul National University Bundang Hospital and Seoul Metropolitan Government – Seoul National University Boramae Medical Center were examined through a retrospective

review of medical records.

Third paragraph in Methods

Eventually, 74 patients who met the study criteria were included in this study.

After :

First paragraph in Methods

Between January 2012 and June 2021, the medical records of a total of 843 patients diagnosed with pancreatic cancer at Seoul National University Bundang Hospital and Seoul Metropolitan Government – Seoul National University Boramae Medical Center, were reviewed retrospectively.

Third paragraph in Methods

Of the 843 patients with pancreatic cancer, 769 were excluded for the following reasons: 144 had resectable or borderline resectable pancreatic cancer, 134 received initial therapy other than FOLFIRINOX or GnP, and 491 did not undergo SEMS insertion within 1 month before or after chemotherapy. Finally, 74 patients who met the study inclusion criteria were enrolled in this study (Figure 1).

Figure 1

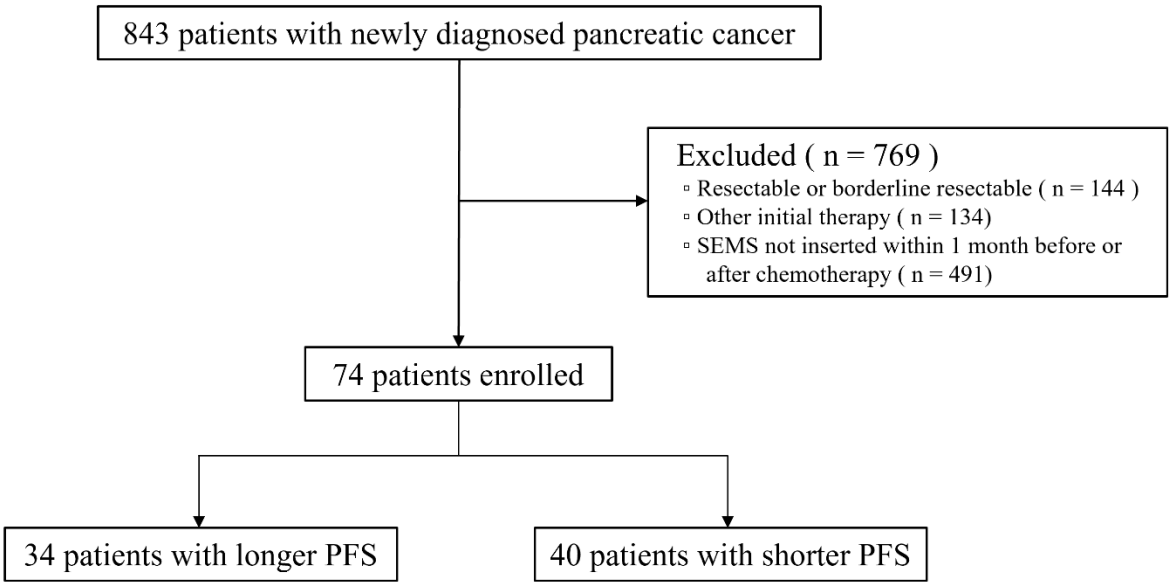


Figure legends

Figure 1. Flowchart of the study.

Of the 843 patients with pancreatic cancer, 74 were finally included in this study. Of them, 34 patients exhibited longer progression-free survival (PFS) and 40 exhibited shorter PFS.

2. The authors report on the association between PFS and stent patency and subsequently describe this as a measure of "chemotherapy response" or "duration of initial chemotherapy." While better chemotherapy response and longer duration of chemotherapy was likely present in patients with better PFS, the authors did not truly analyze chemotherapy response (i.e. biochemical or radiographic response) or duration of chemotherapy (i.e. months/cycles of chemo), so the authors should stick with saying that the association is between PFS and stent patency but then can comment that this is likely a reflection of longer durations of chemo with better response, thereby delaying events such as tumor ingrowth.

Reply>

We appreciate your insightful comment. Because your comment is identical to comment #4 provided by Reviewer A, we would like to ask you to kindly see our response to comment #4.