Journal of Gastrointestinal Surgery (2019) 23:2100–2109
https://doi.org/10.1007/s11605-019-04359-x

2018 SSAT QUICK SHOT PRESENTATION

Prognostic Significance of Lymph Node Metastasis and Micrometastasis Along the Left Side of Superior Mesenteric Artery in Pancreatic Head Cancer

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Received: 26 February 2019 / Accepted: 1 August 2019 / Published online: 13 August 2019

Abstract

Backgrounds and Objectives Although metastasis in lymph nodes along the left side of superior mesenteric artery (SMA-LNs-lt) is sometimes found, survival benefit of SMA-LN-lt dissection for pancreatic head cancer is still unclear. The purpose of this study is to evaluate the prognostic significance of SMA-LN-lt metastasis and micrometastasis.

Methods A total of 166 patients with pancreatic head cancer who underwent pancreatectomy with lymphadenectomy including SMA-LNs-lt between 2002 and 2017 were reviewed retrospectively. Micrometastasis was evaluated by immunohistochemistry.

Results Twenty patients (12%) had SMA-LN-lt metastasis detected by hematoxylin and eosin (HE) staining, and eight patients (5%) had micrometastasis. Patients with SMA-LN-lt HE-positive or micrometastasis group experienced significantly shorter overall survival (OS) than those without ($p = .015$). In multivariate analysis, SMA-LN-lt HE-positive or micrometastasis ($p = .034$), portal vein resection ($p = .002$), histologic grade 2/3 ($p = .046$), LN metastasis ($p = .002$), and lack of adjuvant chemotherapy ($p < .001$) were independent risk factors. Within a subset of SMA-LN-lt HE-positive or micrometastasis group, lack of adjuvant chemotherapy ($p = .003$) was the independent poor prognostic factor.

Conclusions In pancreatic head cancer, the rate of SMA-LN-lt HE-positive and micrometastasis was found in 12% and 5%, respectively. Adjuvant chemotherapy may contribute to improvement of prognosis in patients with LN metastasis including SMA-LN-lt metastasis and micrometastasis.

Keywords Pancreatic head cancer · Superior mesenteric artery · Lymph node metastasis · Micrometastasis · Adjuvant chemotherapy

Introduction

Pancreatic cancer is one of the most lethal human cancers.[1–3] High frequency of lymph node (LN) metastasis is one of the reasons for this dismal prognosis. Metastasis in LNs along the superior mesenteric artery (SMA-LNs) is sometimes found in patients with pancreatic head cancer. Although LNs around the right side of the SMA should be dissected as a standard lymphadenectomy during pancreatectomy for pancreatic head cancer,[4] the left side of SMA-LNs (SMA-LNs-lt) is out of the range for standard lymphadenectomy and not commonly dissected during pancreatectomy for pancreatic head cancer. Therefore, studies focused on SMA-LN-lt metastasis in pancreatic cancer rarely performed and survival benefit of SMA-LN-lt dissection is still unclear. In addition, the frequency of SMA-LN-lt micrometastasis and its prognostic value in patients with pancreatic head cancer have never been reported. The current study aimed to investigate the frequency of SMA-LN-lt metastasis detected by hematoxylin and eosin (HE) staining and micrometastasis detected by immunohistochemical staining and evaluate its prognostic significance of SMA-LN-lt metastasis and micrometastasis in patients who received potentially curative resection for pancreatic head cancer.

Synopsis In pancreatic head cancer, pancreatoduodenectomy with SMA-LN-lt dissection and adjuvant chemotherapy may contribute to the improvement of prognosis in patients with lymph node metastasis including SMA-LN-lt metastasis and micrometastasis.

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Materials and Methods

Study Design

Medical records of consecutive patients with pancreatic head cancer who underwent pancreatoduodenectomy (PD) or total pancreatectomy (TP) with curative intent at the Department of Surgery, Hiroshima University Hospital, Hiroshima, Japan, between May 2002 and November 2017, were reviewed retrospectively. All patients underwent R0 or R1 resection and had confirmed pathological diagnosis of pancreatic ductal adenocarcinoma. During this study period, adjuvant gemcitabine plus S-1 (GS) chemotherapy was administrated to these patients. Since 2009, neoadjuvant chemotherapy was administered to patients with borderline resectable pancreatic head cancer. The study protocol and informed consent form were consistent with the recommendations of the Declaration of Helsinki and approved by the Institutional Review Board of Hiroshima University.

Surgical Procedure and Pathological Examinations

Pylorus-preserving pancreatoduodenectomy (PPPD) was used as a standard surgical procedure for pancreatic head cancer. PD with anterectomy could be selected according to the extent of the cancer. TP was also performed when the cancer invaded the whole pancreas. Portal vein or superior mesenteric vein (PV/SMV) resection was performed if separation of the tumor from the PV/SMV was impossible. All the LNs included in the standard lymphadenectomy indicated by the International Study Group on Pancreatic Surgery (ISGPS)[4] were dissected. With regard to SMA-LNs, circumferential dissection including not only along the right side but also the left side of the SMA was performed (Fig. 1a, b). Dissected SMA-LNs-lt were removed from pancreatoduodenal specimen and sent for permanent histological examination separately. In contrast, the SMA plexus was completely preserved to prevent postsurgical diarrhea and associated weight loss. Intraoperative pathological assessment of pancreatic margins was performed by frozen section analysis. When the pancreatic margin was positive for cancerous cells, further resection of the pancreas was performed. All resected LN specimens were cut into complete serial 2-mm slices along the longest axis, and the slices were formalin-fixed, paraffin-embedded, and stained with HE staining. Tumor stage, LN metastasis, and the final stage were determined based on the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC) 8th edition[5] and American Joint Committee on Cancer (AJCC) 8th edition.[6]

Immunohistochemical Analysis of SMA-LN-lt Micrometastasis

SMA-LN-lt micrometastasis was investigated by immunohistochemistry with anti-cytokeratin (CAM 5.2) in the SMA-LN-lt sections diagnosed as absent of metastasis by HE staining. The endogenous peroxidase activity in the tissue was suppressed by placing in methanol containing 0.3% hydrogen peroxide for 30 min. Antigens were activated with 0.1% trypsin at 37 °C for 30 min. Then, sections were incubated with the primary monoclonal antibody, CAM 5.2 (Becton Dickinson, San Jose, CA) (1:5 dilution), at room temperature for 60 min. The sections were deparaffinized with xylene and rehydrated through graded

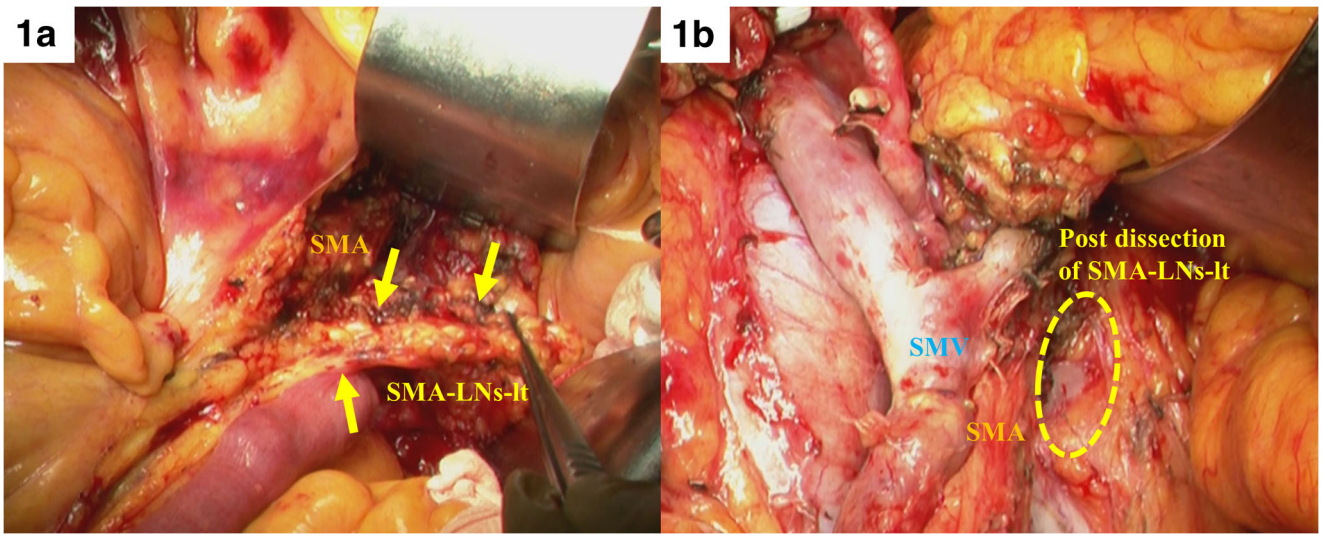

Fig. 1 Surgical findings during pancreatoduodenectomy. **a** Lymphadenectomy of SMA-LNs-lt (arrow). **b** Pancreatoduodenectomy with circumferential dissection including not only along with the right side but also the left side (circle) of the SMA. The SMA plexus was completely preserved. SMA-LNs-lt, lymph nodes along the left side of superior mesenteric artery; SMV, superior mesenteric vein; SMA, superior mesenteric artery

concentrations of ethanol. Next, the sections were incubated with the secondary antibody, EnVision HRP Labelled Polymer, anti-mouse, at room temperature for 60 min. The sections were also deparaffinized and rehydrated. Reaction products were visualized with diaminobenzidine as the chromogen and sections were counterstained with hematoxylin. No significant staining was observed in the negative control sections. In this study, SMA-LN-lt micrometastasis was defined as metastatic tumor cells that were detected by immunohistochemical staining of CAM 5.2 monoclonal antibody, but were not detected by routine histological examination using HE staining. Immunostained tumor cells found in SMA-LNs-lt were classified into two types: the single type, a single cancer cell metastasis (Fig. 2a), and the cluster type, a cluster of cancer cells (Fig. 2b).

Survival

Patients were followed regularly at 3 to 6-month intervals with blood tests, or computed tomography. Overall survival (OS) time for each patient was calculated from time of surgery to time of death or last follow-up. For patients who died, survival time after surgery and cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded. The failure event for OS was defined as death from any cause. Survival analyses on clinicopathological factors were performed with univariate and multivariate methods.

Statistical Analysis

The clinicopathological variables were compared using a chi-squared test and Fisher's exact test, as appropriate. Survival curves were constructed based on the Kaplan-Meier method, and significant differences in survival curves were determined by univariate log-rank analysis. Factors found to be significant on univariate analysis were subjected to multivariate analysis with a Cox proportional hazards model. Differences were considered significant at $p < .05$. All statistical calculations were carried out using JMP statistical software, version 12.0 (SAS Institute, Cary, NC).

Results

Characteristics of Patients and Pathologic Assessment

A total of 389 consecutive patients with pancreatic cancer underwent surgical resection (R0 or R1 resection) between May 2002 and November 2017. Of these 389 patients, 257 patients received PD or TP for pancreatic head cancer. Of these 257 patients, separated SMA-LNs-lt were available in 166 patients and the other 91 patients whose SMA-LN-lt specimens were not clearly confirmed as SMA-LNs-lt were excluded. These 166 patients included 78 males and 88 females with the mean age of 69 years (range 37–91). According to the National Comprehensive Cancer Network preoperative resectability definition,[7] 92 patients (55%) had resectable (R) and 74 patients (45%) had borderline resectable (BR) pancreatic cancer. Twenty-nine patients (17%) received neoadjuvant chemotherapy. The median operative time was 352 min (range 203–613 min) with median intraoperative blood loss of 831 ml (range 100–8345 ml). Time to harvest SMA-LNs-lt was a few minutes. Sixteen patients (10%) experienced postoperative complications, and 33 patients (20%) were administrated antidiarrheal medications due to postoperative

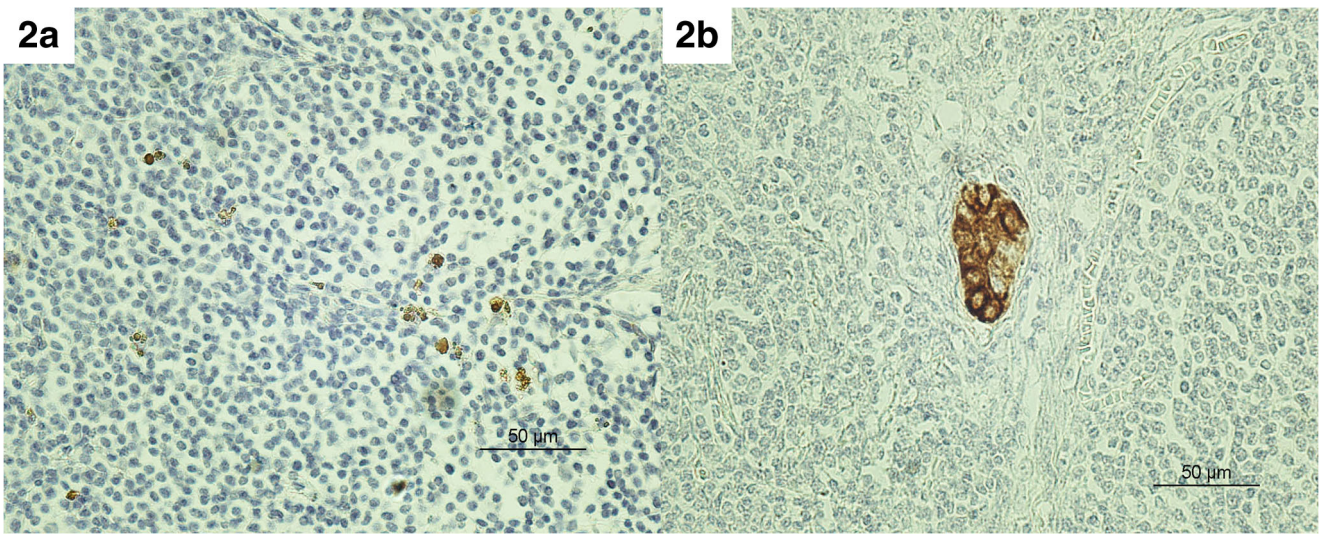

Fig. 2 Immunohistochemical staining with CAM 5.2 for SMA-LN-lt micrometastasis. **a** The single type; a single cancer cell metastasis (original magnification × 400). **b** The cluster type; a cluster of cancer cells (original magnification × 400). SMA-LN-lt, lymph node along the left side of superior mesenteric artery

diarrhea. One hundred twenty-one patients (73%) had positive LNs. The median number of harvested and metastatic LNs was 27 (range 3–66) and 2 (range 0–17), respectively. Adjuvant GS chemotherapy was administrated to 137 patients (78%), and 109 patients (66%) completed full cycle of GS adjuvant chemotherapy. Among the enrolled 166 patients, 20 patients (12%) had SMA-LN-lt metastasis detected by HE (SMA-LN-lt HE-positive). Of the remaining 146 patients with SMA-LN-lt HE-negative, 8 patients (5%) had SMA-LN-lt micrometastasis detected by CAM 5.2 including 2 with single type and 6 with cluster type. Based on SMA-LN-lt status, patients with pancreatic head cancer were classified into three groups: SMA-LN-lt no metastasis ($n = 138$), HE-positive ($n = 20$), and micrometastasis ($n = 8$). The median number of positive LNs in patients with SMA-LN-lt no metastasis, HE-positive, and micrometastasis was 1 (range 0–14), 7 (range 2–17), and 1 (range 0–14), respectively. Ninety-four patients (68%) of SMA-LN-lt no metastasis patients and all the SMA-LN-lt HE-positive patients had other positive LNs except SMA-LNs, whereas two patients (25%) of SMA-LN-lt micrometastasis had negative LNs. All the 8 patients who had SMA-LN-lt micrometastasis experienced recurrence including 5 with liver 3 with lung and 2 with local recurrence, and 7 patients died. The median survival time (MST) of the 8 patients was 19.1 months. In comparisons of SMA-LN-lt status with clinicopathological factors, resectability status ($p = .016$), LN metastasis ($p < .001$), R factor ($p = .012$), and UICC pStage ($p < .001$) were significantly associated with the SMA-LN-lt status (Table 1).

Survival Analysis

Survival curves among SMA-LN-lt 3 status were demonstrated in Fig. 3a. No significant difference in OS was found between patients with SMA-LN-lt HE-positive and micrometastasis group with MST of 13.1 and 19.1 months, respectively ($p = .861$). When SMA-LN-lt HE-positive and micrometastasis groups were united, SMA-LN-lt HE-positive or micrometastasis group experienced significantly shorter OS than SMA-LN-lt no metastasis group with MST of 14.1 and 31.3 months, respectively (Fig. 3b, $p = .015$). In 123 patients with LN metastasis or SMA-LN-lt micrometastasis, however, no significant difference in OS was found between SMA-LN-lt no metastasis and HE-positive or micrometastasis groups (Fig. 3c, $p = .197$). Univariate OS analysis demonstrated that preoperative resectability status ($p = .001$), surgical procedure ($p = .003$), PV/SMV resection ($p < .001$), histologic grade ($p = .026$), LN metastasis ($p < .001$), SMA-LN-lt 3 status ($p = .046$), SMA-LN-lt 2 status ($p = .015$), R factor ($p = .012$), UICC pT factor ($p = .005$), UICC pStage ($p < .001$) ,and adjuvant GS chemotherapy ($p < .001$) were significantly associated with OS. A multivariate analysis identified PV/SMV resection (hazard ratio [HR] 2.19, 95% confidence interval [95% CI] 1.34–3.62, $p = .002$), higher histologic grade (grade 1 vs 2/3) (HR 1.69, 95% CI 1.01–2.91, $p = .046$), LN metastasis (HR 2.64, 95% CI 1.39–5.43, $p = .002$), SMA-LN-lt HE-positive or micrometastasis (HR 1.82, 95% CI 1.05–3.05, $p = .034$), and lack of adjuvant chemotherapy (HR 2.63, 95% CI 1.59–4.32, $p < .001$) as independent risk factors for poor OS (Table 2). Within a subset of 28 patients with SMA-LN-lt HE-positive or micrometastasis, univariate OS analysis demonstrated that age ($p = .023$), histologic grade ($p = .003$), and adjuvant GS chemotherapy (Fig. 3d, $p < .001$) were significantly associated with OS. In addition, the MSTs of patients with adjuvant GS chemotherapy in R and BR group were 39.5 and 24.3 months, respectively. In multivariate analysis, lack of adjuvant GS chemotherapy (HR 4.37, 95% CI 1.65–12.4, $p = .003$) was the independent prognostic factors for poor OS (Table 3).

Discussion

In the current study, prognostic significance of micrometastasis in SMA-LNs-lt was investigated using CAM 5.2 immunohistochemistry in addition to that of metastasis detected by HE staining. The current results concluded that SMA-LN-lt HE-positive or micrometastasis was the independent poor prognostic factor in patients with pancreatic head cancer. Although LN micrometastasis in pancreatic cancer using immunohistochemical staining has been reported by some investigators, its prognostic impact varied among them. Some of them have shown that LN micrometastasis was one of the significant prognostic factors,[8–10] while others suggested that it did not impact on survival.[11, 12] This discrepancy could be caused by the differences of the ranges of LN dissection and the LN areas where micrometastases were investigated.

In the current study, we focused on HE-positive and micrometastasis of SMA-LNs-lt in pancreatic head cancer. Some randomized-control trials demonstrated that the complete resection of SMA-LNs as part of an extended lymphadenectomy for pancreatic head cancer had not been shown the survival benefit.[13–15] In addition, the consensus statement from the ISGPS suggested that only LN stations along the right side of the SMA were included in a standard lymphadenectomy, but SMA-LNs-lt were not.[4] Therefore, SMA-LNs-lt are seldom dissected during surgical resection for pancreatic head cancer, and the frequency of SMA-LN-lt metastasis and prognostic significance of SMA-LN-lt dissection have never been reported. Nonetheless, patients with isolated LN metastasis in SMA-LNs-lt detected by preoperative imaging or local recurrence nearby SMA-LNs-lt after pancreatectomy are sometimes found.[16, 17] Based on these findings, we hypothesized that circumferential dissection of SMA-LNs may contribute to local control of pancreatic head cancer in this area, and have been performed SMA-LNs-lt dissection with complete preservation of SMA plexus.

Table 1 Patient demographics and clinicopathological factors among three groups, including SMA-LN-lt no metastasis, HE-positive, and micrometastasis ($n = 166$)

Factors	No. of patients (%)	SMA-LN-lt 3 status			*p* value
		No metastasis ($n = 138$)	HE-positive ($n = 20$)	Micrometastasis ($n = 8$)	
Age					
< 70	90 (54)	78	9	3	.391
≥ 70	76 (46)	60	11	5	
Gender					
Male	78 (47)	64	10	4	.941
Female	88 (53)	74	10	4	
Tumor location					
Ventral	145 (87)	119	19	7	.476
Dorsal	21 (13)	19	1	1	
Preoperative CA19-9 level (U/ml)					
Median (range)	106 (2–47,470)	71 (2–47,470)	516 (2–42,060)	122 (2–3595)	.403
Resectability status					
Resectable	92 (55)	82	9	1	.016
Borderline resectable	74 (45)	56	11	7	
Surgical procedure					
PD/PPPD	159 (96)	133	19	7	.588
TP	7 (4)	5	1	1	
PV/SMV resection					
Yes	79 (48)	60	13	6	.053
No	87 (52)	78	7	2	
Tumor size (cm)					
< 3	67 (40)	55	7	5	.397
≥ 3	99 (60)	83	13	3	
Histologic grade					
G1	45 (27)	33	8	4	.125
G2/3	121 (73)	105	12	4	
LN metastasis					
Yes	121 (73)	95	20	6	< .001
No	45 (27)	43	0	2	
R factor					
R0	111 (67)	93	10	8	.012
R1	55 (33)	45	10	0	
UICC pT factor					
T1/2	127 (77)	106	14	7	.586
T3/4	39 (23)	32	6	1	
UICC pStage					
I/II	105 (63)	96	3	6	< .001
III/IV	61 (37)	42	17	2	

SMA-LN-lt, lymph node along the left side of superior mesenteric artery; *HE*, hematoxylin and eosin staining; *CA19-9*, carbohydrate antigen 19-9; *PD*, pancreatoduodenectomy; *PPPD*, pylorus-preserving pancreatoduodenectomy; *TP*, total pancreatectomy; *PV*, portal vein; *SMV*, superior mesenteric vein; *LN*, lymph node; *UICC*, International Union Against Cancer

The current results demonstrated that SMA-LN-lt HE-positive and micrometastasis were found in 12% and 5% of eligible patients, respectively. Although no prior studies have shown the frequency of SMA-LN-lt HE-positive and micrometastasis, this result suggested that SMA-LN-lt HE-positive and micrometastasis could be found just a little less than the right side of SMA-LN HE-positive and micrometastasis which was reported as 2–55.2%[10, 13, 18] and

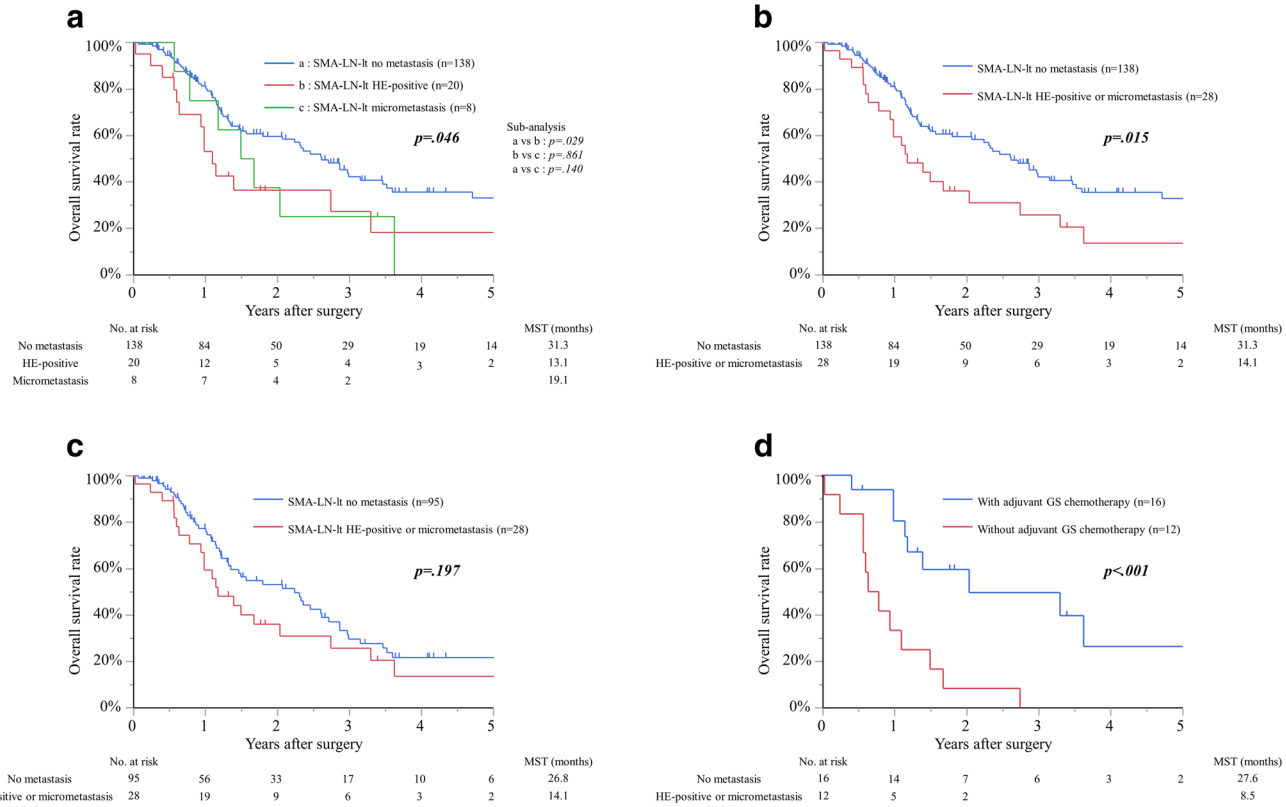

Fig. 3 Overall survival curves. **a** Overall survival curves among three groups, SMA-LN-lt no metastasis, HE-positive, and micrometastasis group. SMA-LN-lt status was significantly associated with OS ($p = .046$). Patients with SMA-LN-lt HE-positive group experienced significantly shorter OS than those with no metastasis ($p = .029$), whereas no significant difference was found between HE-positive and micrometastasis groups ($p = .861$). **b** Overall survival curves between SMA-LN-lt no metastasis and HE-positive or micrometastasis groups. Patients with SMA-LN-lt HE-positive or micrometastasis experienced significantly shorter OS than no metastasis group ($p = .015$). **c** Overall survival curves between SMA-LN-lt no metastasis and HE-positive or micrometastasis groups in 123 patients with LN metastasis or SMA-LN-lt micrometastasis. No significant difference was found between SMA-LN-lt no metastasis and HE-positive or micrometastasis groups ($p = .197$). **d** Overall survival curves of patients with or without adjuvant GS chemotherapy in patients with SMA-LN-lt HE-positive or micrometastasis group. Patients with adjuvant GS chemotherapy experienced significantly shorter OS than those without ($p < .001$). SMA-LN-lt, lymph node along the left side of superior mesenteric artery; HE, hematoxylin and eosin; LN, lymph node; GS, gemcitabine plus S-1; MST, median survival time

11.1–38.4%,[9, 10] respectively. In analyzing the comparisons between clinicopathological factors and SMA-LN-lt 3 status, SMA-LN-lt HE-positive or micrometastasis was more likely to be found in BR compared with R pancreatic head cancer. Also, patients with SMA-LN-lt HE-positive had higher pStage than those with SMA-LN-lt no metastasis or micrometastasis.

The current results revealed that the patients with SMA-LN-lt micrometastasis experienced poor OS that was similar to the patients with SMA-LN-lt HE-positive. All the 8 patients with SMA-LN micrometastasis had early recurrence within 2 years, and 7 patients died from distant metastasis. These findings suggested that SMA-LN-lt micrometastasis might be tantamount to SMA-LN-lt HE-positive. In addition, the current OS analysis demonstrated that MST of patients with SMA-LN-lt HE-positive or micrometastasis was only 14.1 months, and it was one of the independent risk factors for poor OS. However, within a subset of patients with LN metastasis, no significant difference in OS was found between SMA-LN-lt no metastasis and HE-positive or micrometastasis groups. This may be due to small number of patients with SMA-LN-lt HE-positive or micrometastasis. To discuss the prognostic significance of SMA-LN-lt dissection, further studies including larger number of patients would be needed.

The multivariate analysis in 28 patients with SMA-LN-lt HE-positive or micrometastasis revealed that lack of adjuvant GS chemotherapy was the independent prognostic factors for poor OS. Since SMA-LNs-lt is out of the range for standard lymphadenectomy, its metastasis would be defined as distant metastasis. However, the MST of patients with SMA-LN-lt HE-positive or micrometastasis who received adjuvant GS chemotherapy was 27.6 months, which appear to be longer than those of patients with unresectable pancreatic cancer treated with non-surgical therapy, including chemotherapy and chemoradiotherapy.[19–23] Therefore, combination of surgical resection with lymphadenectomy including

Table 2 Univariate and multivariate overall survival analysis of prognostic factors for patients with pancreatic head cancer ($n = 166$)

Factors	Univariate analysis			Multivariate analysis		
	No. of patients (%)	MST (months)	*p* value	HR	95% CI	*p* value
Age						
< 70	90 (54)	32.9	.162			
≥ 70	76 (46)	18.8				
Gender						
Male	78 (47)	21.5	.594			
Female	88 (53)	29.4				
Resectability status						
Resectable	92 (55)	35.8	.001	1.04	0.64–1.72	.870
Borderline resectable	74 (45)	15.8				
Surgical procedure						
PD/PPPD	159 (96)	29.4	.003	2.08	0.75–4.89	.147
TP	7 (4)	11.8				
PV/SMV resection						
Yes	79 (48)	14.6	< .001	2.19	1.34–3.62	.002
No	87 (52)	35.8				
Tumor size (cm)						
< 3	67 (40)	32.9	.463			
≥ 3	99 (60)	24.8				
Histologic grade						
G1	45 (27)	39.5	.026	1.69	1.01–2.91	.046
G2/3	121 (73)	17.9				
LN metastasis						
Yes	121 (73)	–	< .001	2.64	1.39–5.43	.002
No	45 (27)	21.5				
SMA-LN-lt 3 status						
No metastasis	138 (83)	31.3	.046			
HE-positive	20 (12)	13.1				
Micrometastasis	8 (5)	19.1				
SMA-LN-lt 2 status						
No metastasis	138 (83)	31.3	.015	1.82	1.05–3.05	.034
HE-positive or micrometastasis	28 (17)	14.1				
R factor						
R0	111 (67)	31.3	.012	1.04	0.64–1.67	.874
R1	55 (33)	14.5				
UICC pT factor						
T1/2	127 (77)	34.4	.005	1.54	0.88–2.63	.129
T3/4	39 (23)	13.7				
UICC pStage						
I/II	105 (63)	35.6	< .001			
III/IV	61 (37)	14.5				
Adjuvant GS chemotherapy						
Present	109 (66)	35.6	< .001	2.63	1.59–4.32	< .001
Absent	57 (34)	13.6				

MST, median survival time; *HR*, hazard ratio; *CI*, confidence interval; *CA19-9*, carbohydrate antigen 19-9; *PD*, pancreatoduodenectomy; *PPPD*, pylorus-preserving pancreatoduodenectomy; *TP*, total pancreatectomy; *PV/SMV*, portal or superior mesenteric vein; *LN*, lymph node; *SMA-LN-lt*, lymph node along the left side of superior mesenteric artery; *UICC*, International Union Against Cancer; *GS*, gemcitabine plus S-1

Table 3 Univariate and multivariate overall survival analysis in patients of SMA-LN-lt HE-positive or micrometastasis group ($n = 28$)

Factors	Univariate analysis			Multivariate analysis		
	No. of patients (%)	MST (months)	*p* value	HR	95% CI	*p* value
Age						
< 70	12 (43)	32.9	.023	1.71	0.57–5.47	.344
≥ 70	16 (57)	13.1				
Gender						
Male	14 (50)	13.1	.845			
Female	14 (50)	19.1				
Resectability status						
Resectable	10 (36)	13.7	.450			
Borderline resectable	18 (64)	15.4				
Surgical procedure						
PD/PPPD	26 (93)	16.7	.187			
TP	2 (7)	10.6				
PV/SMV resection						
Yes	19 (68)	13.7	.252			
No	9 (32)	32.9				
Tumor size (cm)						
< 3	12 (43)	18.4	.811			
≥ 3	16 (57)	11.8				
Histologic grade						
G1	12 (43)	32.9	.003	3.19	0.99–12.1	.053
G2/3	16 (57)	9.3				
R factor						
R0	18 (64)	16.7	.325			
R1	10 (36)	11.5				
UICC pT factor						
T1/2	21 (75)	20.1	.115			
T3/4	7 (25)	11.8				
UICC pStage						
I/II	9 (32)	20.1	.817			
III/IV	19 (68)	13.7				
Adjuvant GS chemotherapy						
Present	16 (57)	27.6	< .001	4.37	1.65–12.4	.003
Absent	12 (43)	8.5				

MST, median survival time; *HR*, hazard ratio; *CI*, confidence interval; *CA19-9*, carbohydrate antigen 19-9; *PD*, pancreatoduodenectomy; *PPPD*, pylorus-preserving pancreatoduodenectomy; *TP*, total pancreatectomy; *PV/SMV*, portal or superior mesenteric vein; *UICC*, International Union Against Cancer; *GS*, gemcitabine plus S-1

SMA-LN-lt dissection and subsequent adjuvant chemotherapy possibly contribute to improved survival compared with non-surgical treatment. On the other hand, the most serious concern for extended dissection of SMA-LNs was severe postoperative diarrhea. In the current study, the SMA plexus in all enrolled patients was completely preserved that was confirmed by the intraoperative findings. In result, the current study demonstrated the rate of postoperative diarrhea was limited to 20% and adjuvant chemotherapy was received completely in 66% of enrolled patients. These were comparable with some previous reports on PD with standard lymphadenectomy.[4] Based on these results, pancreatectomy with lymphadenectomy including SMA-LN-lt dissection for pancreatic head cancer seemed to be acceptable from the viewpoint of pursuing curative resection as well as keeping the quality of life and maintaining the tolerability for adjuvant chemotherapy.

This study had some limitations. First, the analysis was retrospective study in nature and was based on a relatively small number of patients at a single institution. Second, this

study had selection bias of the enrolled patients. In most patients, SMA-LN-lt specimens were separated from main pancreatoduodenal specimens at surgery. However, those of the 91 excluded patients were not confirmed as SMA-LNs-lt because they were not separated from main specimens or could be mixed with other parts of LNs. Third, although the prognosis of patients with SMA-LN-lt metastasis and micrometastasis who received adjuvant chemotherapy seemed to be better in this study, to prove the survival benefit of SMA-LN-lt dissection, reappraisal of the significance based on prospective further studies including larger number of patients would be needed.

Conclusions

In the current study, SMA-LN-lt HE-positive and micrometastasis was found in 12% and 5% of eligible patients, respectively. SMA-LN-lt HE-positive or micrometastasis was the independent risk factor for poor prognosis in patients who received potentially curative pancreatectomy for pancreatic head cancer. Adjuvant chemotherapy may contribute to improvement of prognosis in patients with LN metastasis including SMA-LN-lt metastasis and micrometastasis.

Authors' Contributions Study concepts: Kenjiro Okada, Yoshiaki Murakami, Naru Kondo, Kenichiro Uemura, Naoya Nakagawa, Shingo Seo, Shinya Takahashi, and Taijiro Sueda.

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Compliance with Ethical Standards The study protocol and informed consent form were consistent with the recommendations of the Declaration of Helsinki and approved by the Institutional Review Board of Hiroshima University.

Conflict of Interest The authors declare that they have no conflict of interest.

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