

# 論文内容要旨

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

(膵頭部癌における上腸間膜動脈左側リンパ節の微小転移を含めた  
転移の予後への影響)

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主指導教員：高橋 信也教授  
(医系科学研究科 外科学)

副指導教員：大毛 宏喜教授  
(広島大学病院 感染症学)

副指導教員：村上 義昭准教授  
(医系科学研究科 外科学)

岡田 健司郎

(医歯薬保健学研究科 医歯薬学専攻)

**Background and Aim.** Pancreatic cancer is one of the most lethal human cancers. 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, 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.

**Materials and Methods.** Medical records of consecutive patients with pancreatic head cancer who underwent pancreatectomy 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 administered to these patients.

All the LNs included in the standard lymphadenectomy indicated by the International Study Group on Pancreatic Surgery (ISGPS) 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. 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. 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. 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. Survival analyses on clinicopathological factors were performed with univariate and multivariate methods.

**Results.** 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 pancreatectomy 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, 92 patients (55%) had resectable (R) and 74 patients (45%) had borderline resectable (BR) pancreatic cancer. 29 patients (17%) received neoadjuvant chemotherapy. Sixteen patients (10%) experienced postoperative complications. 121 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 administered to 137 patients (78%). Among the enrolled 166 patients, 20 patients (12%) had SMA-LN-It metastasis detected by HE (SMA-LN-It HE-positive). Of the remaining 146 patients with SMA-LN-It HE-negative, 8 patients (5%) had SMA-LN-It micrometastasis detected by CAM 5.2 including 2 with single type and 6 with cluster type. Based on SMA-LN-It status, patients with pancreatic head cancer were classified into three groups: SMA-LN-It no metastasis (n=138), HE-positive (n=20) and micrometastasis (n=8). In comparisons of SMA-LN-It 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-It status.

In overall survival (OS) analysis, no significant difference was found between patients with SMA-LN-It HE-positive and micrometastasis group with MST of 13.1 and 19.1 months, respectively (p=.861). When SMA-LN-It HE-positive and micrometastasis groups were united, SMA-LN-It HE-positive or micrometastasis group experienced significantly shorter OS than SMA-LN-It no metastasis group with MST of 14.1 and 31.3 months, respectively (p=.015). In 123 patients with LN metastasis or SMA-LN-It micrometastasis, however, no significant difference in OS was found between SMA-LN-It no metastasis and HE-positive or micrometastasis groups (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-It 3 status (p=.046), SMA-LN-It 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-It 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. Within a subset of 28 patients with SMA-LN-It HE-positive or micrometastasis, univariate OS analysis demonstrated that age (p=.023), histologic grade (p=.003) and adjuvant GS chemotherapy (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.

**Conclusions.** SMA-LN-It HE-positive and micrometastasis was found in 12% and 5% of eligible patients, respectively. SMA-LN-It 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-It metastasis and micrometastasis.