論　文　内　容　要　旨

Prognostic Impact of Para-Aortic Lymph Node Micrometastasis in Pancreatic Ductal Adenocarcinoma

(膵癌における傍大動脈リンパ節微小転移の予後への影響)

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内容要旨

Background. The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) remains dismal. Surgical resection remains the only curative treatment for patients with PDAC. However, even if patients undergo complete surgical resection, the overall 5-year survival rate is reported to be 28%. One of the reasons for the dismal prognosis of resectable PDAC is the high frequency of lymph node metastasis that has been reported to be present in 48–80% of patients with resectable PDAC. Lymph node metastasis of PDAC primarily involves peripancreatic nodes and eventually spreads to distant lymph nodes, including the para-aortic lymph nodes (PALNs). Several prior reports demonstrated that lymph node metastasis was one of the independent risk factors for poor prognosis in patients with PDAC. In recent years, the prognostic impact of lymph node micrometastasis has been reported in a variety of cancers, including esophageal cancer, gastric cancer, colon cancer, and biliary tract cancer. However, only a few reports have demonstrated the clinical value of regional lymph node micrometastasis in PDAC. Moreover, reports evaluating the clinical value of PALN micrometastasis in resected PDAC are extremely rare. Therefore it is still unclear whether micrometastasis of PALNs in PDAC is tantamount to PALN metastasis detected by hematoxylin and eosin (HE) staining.

Methods. This is a retrospective cohort study based on a prospectively maintained institutional database of all patients with PDAC who underwent surgical resection for PDAC at the Department of Surgery, Hiroshima University Hospital, Hiroshima, Japan, from May 1999 to November 2015. A total of 242 patients with PDAC who underwent radical pancreatectomy with PALN dissection were eligible for this study. PALNs were dissected from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery, and from the right margin of the inferior vena cave to the left margin of the abdominal aorta. Lymph node micrometastasis was diagnosed when tumor cells with a largest dimension of 0.2–2 mm or a single tumor cell or a cluster not greater than 0.2 mm of isolated tumor cells were initially detected by CAM 5.2 immunohistochemistry but not by conventional HE staining. The relationship between PALN status and overall survival (OS) was analyzed.

Results. Of the 242 enrolled patients, 25 (10 %) had PALN metastasis detected by HE, and 21 (9%) had PALN micrometastasis not detected by HE but identified by CAM 5.2 immunohistochemistry. The median number of harvested PALNs was 3 (range 1–26). PALN micrometastasis cases included single tumor cells (n = 6) and small clusters of tumor cells (n = 15), while tumor cells with a largest dimension of 0.2–2 mm were not found. Based on PALN status, patients were classified into three groups: PALN no metastasis (n = 196), PALN micrometastasis (n = 21), and PALN HE-positive (n = 25). Univariate OS analysis

demonstrated that portal vein/superior mesenteric vein resection (p <.001), blood transfusion (p = .005), adjuvant chemotherapy (p <.001), tumor size (p = .002), tumor differentiation (p = .014), regional lymph node metastasis (p <.001), R factor (p =.002), UICC pT factor (p = .007), and PALN status (p <.001) were significantly associated with OS. Median survival time for patients in the PALN no metastasis, PALN micrometastasis, and PALN HE-positive groups were 38.9, 17.0, and 17.2 months, respectively. Univariate analysis revealed that patients with PALN micrometastasis (p = .004) and PALN HE positivity (p = .003) had a significantly shorter OS than those without PALN metastasis, whereas no significant difference was observed between the two former groups (p = .874). In multivariate analysis, Portal vein/superior mesenteric vein resection (hazard ratio [HR] 2.08, 95 % confidence interval [95 % CI] 1.42–3.04, p < .001), lack of adjuvant chemotherapy (HR 2.43, 95 % CI 1.60–3.63, p < .001), tumor differentiation (HR 1.60, 95 % CI 1.10–2.37, p = .015), regional lymph node metastasis (HR 1.70, 95 % CI 1.09–2.72, p = .019), PALN micrometastasis (HR 1.89, 95 % CI 1.01–3.28, p = .046), and PALN HE positivity (HR 1.89, 95 % CI 1.10–3.11, p = .023) were identified as independent risk factors for poor OS. Within a subset of 46 patients in the PALN HE-positive or PALN micrometastasis groups, patients who received adjuvant chemotherapy had significantly longer OS than those who had not (p = .002). Multivariate analysis revealed that lack of adjuvant chemotherapy (HR 2.58, 95 % CI 1.10–6.20, p = .029) was independently associated with poor OS.

Conclusions. The prognosis of patients with PALN micrometastasis was extremely poor as well as HE-positive PALNs. However, postoperative adjuvant chemotherapy may contribute to improving the prognosis of PDAC patients with PALN metastasis.