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Review Article

Systematic review of the clinical significance of lymph node micrometastases of pancreatic adenocarcinoma following surgical resection

Sae Byeol Choi, MD, PhD *, Hyung Joon Han, MD, PhD, Pyoungjae Park, MD, PhD, Wan Bae Kim, MD, PhD, Tae-Jin Song, MD, PhD, Sang Yong Choi, MD, PhD

Department of Surgery, Korea University College of Medicine, Seoul, South Korea

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ABSTRACT

Objectives: The aim of this study is to perform a systematic review of the clinical impact of lymph node micrometastasis in pancreatic adenocarcinoma following surgical resection.
Methods: A systematic review was conducted and published literature were searched using “pancreas or pancreatic” and “cancer or carcinoma or neoplasm”, and “micrometastasis or micrometastses” in the PubMed, EMBAE, and Web of Science.
Results: Thirteen publications with 726 patients and 3701 lymph nodes were included in this systematic review. The detection method was immunohistochemical stains or polymerase chain reaction. The pooled proportion of patients with positive lymph node micrometastasis was 43.1% (95% Confidence interval (CI) 0.254–0.628). The pooled proportion of positive lymph node micrometastasis (number of positive lymph node micrometastasis/total number of lymph nodes examined) was 10.8% (95% CI 4.8–22.6). Among the conventional H &E negative patients, the reported 5-year survival rates of the patients without lymph node micrometastases vs. those with lymph node micrometastases in the ranged from 50% to 61% and from 0% to 36%, respectively Patients with lymph node micrometastasis showed poorer survival (Hazard ratio 4.29, 95% CI 1.27–14.41).
Conclusions: The presence of lymph node micrometastasis is associated with poorer survival. Lymph node micrometastasis is applicable to stratify the risk of recurrence and the need for adjuvant therapy of post-resection patients with pancreatic adenocarcinoma in the conventional H & E lymph node negative patients.
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Introduction

The prognosis of pancreatic adenocarcinoma is poor, and a significant proportion of patients is diagnosed with locally advanced disease and is not eligible for surgical resection [1,2]. Although curative resection is the most important prognostic factor associated with enhanced overall survival, postoperative survival remains poor. Among patients with R0 resection and tumor-free lymph nodes following nodal dissection, both local recurrence and distant metastasis occur frequently [2–6]. This suggests the presence of occult tumor cells that cannot be detected via a routine evaluation.

The known prognostic factors for pancreatic adenocarcinoma following surgical resection include R0 resection, presence of lymph node metastasis, lymph node ratio, perineural invasion, and depth of invasion [2,3,7,8]. Lymph node metastasis is a strongly poor prognostic factor in patients with pancreatic cancer, and the administration of adjuvant chemotherapy should be considered regardless of the performance of complete lymph node dissection [4,7]. According to the American Joint Committee on Cancer (AJCC) 7th edition [9], tumors of different depth of invasion (T1 or T2 or T3) with the presence of regional lymph node micrometastasis are classified as the same stage IIB without distant metastasis.

Routine lymph node metastasis assessments involve histopathologic examination with hematoxylin-eosin (H & E) staining, as this is currently the standard method used to detect the presence of lymph node metastasis. In several cancers, however, the

* Corresponding author. Department of Surgery, Korea University College of Medicine, Korea University Guro Hospital, 80, Guro-dong, Guro-gu, Seoul, South Korea.
E-mail address: csbroad@hanmail.net (S.B. Choi).

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presence of lymph node micrometastases is a useful prognostic marker that avoids under evaluation of the lymph node status [10–12]. Lymph node micrometastasis is defined as a small cluster of invading tumor cells detected by various methods other than H & E staining [10,11,13,14]. This study aimed to perform a systematic review of the clinical impact of lymph node micrometastases of pancreatic adenocarcinoma after surgical resection. This review includes the methods used to detect lymph node micrometastases, detection rate, and clinical impact of lymph node micrometastasis on survival.

Methods

Search strategy

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement Guidelines, which were provided in 2009 by an international study group [15]. A search of published literature in the PubMed, EMBAE, and Web of Science databases was conducted using the following keywords and/or MeSH terms or Emtree: “pancreas or pancreatic” and “cancer or carcinoma or neoplasm”, and “micrometastasis or micrometastases”.

Selection and exclusion criteria

We included studies of lymph node micrometastasis of pancreatic ductal adenocarcinoma following surgical resection, including lymph node dissection. In brief, the criterion used to define lymph node micrometastasis was a metastasis-negative lymph node according to routine hematoxylin and eosin staining that exhibited positivity by other methods such as immunohistochemical staining. Studies that detected tumor cells in tissues associated with circulation, such as the bone marrow, blood, peritoneum, and liver, were excluded. Because the number of cases of lymph node micrometastasis was small and the clinicopathological information was not enough in the articles included micrometastases of non-lymph node sites as well as lymph nodes. However, one study [16] that was designed to investigate micrometastases in the lymph nodes and bone marrow was included in this review because most part of the study focused on lymph node micrometastases and the number of patients to enrolled the study for lymph node micrometastases were 106. Patients who underwent R0 or R1 pancreatectomy were included. No limitation was placed on the locations of lymph nodes, which included regional, para-aortic, and non-site-specified lymph nodes. Furthermore, this review was not limited with regard to the patients' preoperative or postoperative chemo- and/or radiation therapy status. Articles only written in English were included in this review.

Data extraction

Two authors (CSB, HHJ) independently reviewed the search data and identified studies for inclusion after reviewing the themes and abstracts. Related articles by the same author group or those in the same database, recent studies, or studies that included more enrolled patients were included. After determining the studies for inclusion, the following information was obtained: study period, country in which the study was conducted, number of patients enrolled, operative procedures, conventional H&E lymph node metastatis status, methods to detect lymph node micrometastasis, definition of lymph node micrometastasis, pathologic characteristics such as differentiation, depth of invasion (T stage), American Joint Committee on Cancer (AJCC) stage, total numbers of examined patients and those with micrometastasis-positive lymph nodes, total number of lymph nodes examined for the presence of micrometastasis, and number of positive lymph node micrometastases. Survival data, such as 5-year survival rates conducted using the Kaplan–Meier method and hazard ratios (HRs) calculated via Cox proportional hazards models, were also extracted to investigate the clinical impact of lymph node micrometastasis on overall survival. Any discrepancies and queries regarding data collection between the two authors were solved by discussion.

The quality of all publications was assessed using the Newcastle–Ottawa Scale [17]. Of the three categories used in this scale (Selection, Comparability, and Outcome), we used the following for study assessment: “Selection”, 1) selection of patients with lymph node micrometastases, 2) control group for comparison(patients without lymph node micrometastases), 3) and clear definition of lymph node micrometastasis; “Outcome”, 1) patient survival outcomes and2) median follow-up duration of >12months. A study received one star per question, for a maximum score of five stars. The characteristics and quality of the included studies are presented in Table 1.

Statistical analysis

Data and outcomes extracted from each study were pooled and analyzed using Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA). A single weight-adjusted proportion was computed for each variable in each study. The random effect model was used to derive pooled estimates of proportions with 95% confidence intervals (CI) for the explored outcomes. The HRs of prognostic factors identified using the multivariate Cox proportional hazards regression model were fitted to the pooled data set to estimate the associations of prognostic factors with survival; Revman 5.2 analysis software (Cochrane Collaboration, Copenhagen, Denmark) was used for this analysis.

Results

Study characteristics and lymph node micrometastasis detection methods

A total of 485 studies were initially identified; after retrieving 28 articles for full-text appraisal, 13 English-language publications [13,16,18–28] were finally included in this systematic review. The 13 studies were observational cohort studies published from 1997 to 2016. A total of 726 patients and 3701 lymph nodes were included in this systematic review; however, three studies [20,21,28] did not report the total number of examined lymph nodes. Four studies [13,21,27,28] that investigated the presence of micrometastasis included only para-aortic lymph nodes. Four studies included only conventional H & E lymph node negative patients [20,24–26]. And the other studies [13,16,18,19,21–23,27,28] enrolled conventional H & E lymph node positive patients as well as negative patients. Lymph node micrometastasis detection was conducted using immunohistochemical stains [16,22–28], polymerase chain reaction(PCR) [13,18,19], or both methods [20,21]. A summary of the publications is presented in Table 1.

PCR-based genetic screening methods for lymph node micrometastases detect the presence of a mutant allele of the human K-ras gene (codon 12) in the lymph nodes. If the same mutation is found in both the primary tumor and regional lymph nodes, the latter were considered positive for metastasis [13,18–21]. PCR detection of the mutant K-ras codon involved a two-stage PCR/restriction fragment length polymorphism (RFLP) analysis [13,20,21], PCR/non-radioisotopic single-strand conformation polymorphism analysis [18], or PCR with allele specific amplification (MASA) [19].

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