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Review

The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma – A systematic review and meta-analysis

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ABSTRACT

Objectives: To assess the impact of neural invasion/NI on overall survival/OS and tumor recurrence in pancreatic ductal adenocarcinoma/PDAC.
Summary background data: NI is a histopathological hallmark of PDAC. Although some studies suggested an important role for NI on OS, disease-free/DFS and progression-free survival/PFS in PDAC, there is still no consensus on the actual role of NI on survival and local recurrence in PDAC.
Methods: Pubmed, Cochrane library, Ovid and Google Scholar were screened for the terms "pancreatic ductal adenocarcinoma", "pancreatic cancer", "survival", "tumor recurrence" and "perineural invasion". The *P*referred–*R*eporting-*I*tems-for-*S*ystematic-review-and-*M*eta-*A*nalysis/PRISMA-guidelines were used for systematic review and meta-analysis. Articles meeting predefined criteria were critically analysed on relevance, and meta-analyses were performed by pooling univariate and multivariate hazard ratios/HR.
Results: A total number of 25 studies on the influence of NI on tumor recurrence, and 121 studies analysing the influence of NI on survival were identified by systematic review. The HR of the univariate (HR 1.88; 95%-CI 1.71–2.07; $p < 0.00001$) and multivariate meta-analysis (HR 1.68; 95%-CI 1.47–1.92; $p < 0.00001$) showed a major impact of NI on OS. Likewise, NI was associated with decreased DFS (HR 2.53; 95%-CI: 1.67–3.83; $p = 0.0001$) and PFS (HR 2.41; 95%-CI: 1.73–3.37: $p < 0.00001$) multivariate meta-analysis.
Conclusions: Although the power of this study is limited by missing pathological procedures to assess the true incidence of NI, NI appears to be an independent prognostic factor for OS, DFS and PFS in PDAC. Therefore, NI should be increasingly considered in patient stratification and in the development of novel therapeutic algorithms.

Contents

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a dismal 5-year survival rate <5% [1]. Despite intensive research, the median survival time of patients with PDAC has remained nearly constant along the last decades [1]. In curative therapy, surgery followed by adjuvant therapy remains the standard treatment for patients with resectable, non-metastatic PDAC [2]. Nevertheless, rates of failure, i.e. tumor recurrence, after even radical resections are high. Here, several randomized controlled trials including patients treated with curative intention demonstrated failure rates of tumor therapy exceeding 70% [2,3]. Moreover, autopsy results of patients, who were resected for PDAC, showed metastasis and local recurrence rates of 75%–88% [4]. So far, margin status [5], tumor stage and grade [6], lymph node metastasis [7] and invasion into adjacent organs and structures [8], could be identified as important prognostic factors in patients with PDAC.

Neural invasion (Pn) is a pathohistological hallmark of PDAC [9]. Although it is similarly encountered in other solid tumors like colorectal cancer, prostate cancer and gastric cancer, the reported incidence of Pn in PDAC reaches up to 100%, surpassing any known solid tumor [10]. Furthermore, the severity of Pn was reported to be strongest in PDAC when compared to all other gastrointestinal malignancies [10]. This observation implies that Pn is a very characteristic, omnipresent and ominous feature of PDAC [10].

Intractable pain is one of the dominant symptoms of patients with PDAC [11,12]. Here, several studies could show that the severity of Pn is closely associated with the abdominal pain symptoms of PDAC patients [11]. Due to the ubiquitous neuropathic changes in PDAC including Pn, intrapancreatic neural hypertrophy and increased neural density, the pain sensation in PDAC was recognized as neuropathic [11]. Moreover, this neuropathic pain was found to be directly associated with impaired survival in patients with PDAC and identified as a novel prognostic factor in pancreatic cancer [11,12].

Until now, some studies demonstrated that Pn may impact survival and tumor recurrence in PDAC. However, a clear consensus about the exact impact and importance of Pn on overall (OS), disease-free (DFS) and progression-free survival (PFS) has not yet been defined. Whereas some studies could show a strong correlation between Pn and OS [13,14], there were also some studies showing no significant correlation between OS and Pn [15] or even improved OS for patients with Pn [16,17].

Therefore, in the current study, we performed a systematic review of the literature for the influence of Pn on survival, prognosis and local recurrence in PDAC. Furthermore, we conducted a meta-analysis of studies correlating Pn with OS, PFS and/or DFS to reach a conclusive statement on the impact of Pn in PDAC.

2. Methods

2.1. Study design

To perform this systematic review and meta-analysis, we adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) [18] guidelines. As recommended by the PRISMA guidelines, this systematic review and meta-analysis was registrated on the international prospective register of systematic reviews (CRD42016038775). The following databases were systematically screened for literature: Pubmed, Cochrane library, Ovid and Google Scholar. The search strategy included the following items: “pancreatic cancer”, “pancreatic ductal adenocarcinoma”, “neural invasion”, “perineural invasion”, “survival” and “recurrence”. All studies of patients with PDAC that analysed the influence of Pn on survival and/or tumor recurrence were eligible for inclusion.

2.2. Data extraction

After removing duplicates, topics and abstracts were independently screened by three reviewers (SS, IED and FS) for possible inclusion. Articles, which did not show any reference to PDAC or survival, were excluded from further analysis. Studies containing numeric data about the influence of Pn in PDAC on survival and recurrence were included. Studies published in other languages other than English were also excluded.

Full-text articles were analysed for the influence of Pn on OS, DFS and PFS and for data match, and the following inclusion criteria were considered in the systematic review and meta-analysis.

2.2.1. Histological characteristics

Only patients with proven histology of pancreatic ductal adenocarcinoma were included in the study. Publications dealing with other pancreatic tumors were excluded. Moreover, due to a different tumor biology and often a less aggressive clinical course, studies that included solely IPMN-based cancers were excluded from further analysis. Studies that compared the survival intervals or rates between patients without histological signs for neural invasion (Pn0) and patients with neural invasion (Pn1) were included in the meta-analysis.

2.2.2. Survival time

Here, OS was defined as the time between resection and death. DFS was defined as the time interval between resection and tumor