RESEARCH ARTICLE

Influence of Perineural Invasion on Survival and Recurrence in Patients with Resected Pancreatic Cancer

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Abstract

Background: Perineural invasion (PNI) has been reported as one of the sources of locoregional recurrence in resected pancreatic cancer (PC). However the impact of PNI in resected pancreatic cancer remains controversial. The purpose of this study was to determine the association between PNI status and clinical outcomes. Methods: Publications were identified which assessed prognostic significance of PNI status in resected pancreatic cancer up to February 2013. A meta-analysis was performed to clarify the association between PNI status and clinical outcomes. Results: A total of 21 studies met the inclusion criteria, covering 4,459 cases. Analysis of these data showed that intrapancreatic PNI was correlated with reduced overall survival only in resected pancreatic ductal adenocarcinoma (PDAC) patients (HR=1.982, 95%CI: 1.526-2.574, *p*=0.000). Extrapancreatic PNI was correlated with reduced overall survival in all resected pancreatic cancer patients (HR=1.748, 95%CI: 1.372-2.228, *p*=0.000). Moreover, intrapancreatic PNI status may be associated with tumor recurrence in all resected pancreatic cancer patients (HR=2.714, 95%CI: 1.885-3.906, *p*=0.000). Conclusion: PNI was an independent and poor prognostic factor in resected PDAC patients. Moreover, intrapancreatic PNI status may be associated with tumor recurrence.

Keywords: Perineural invasion - prognosis - pancreatic nerve plexus - pancreatic ductal adenocarcinoma

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Introduction

Pancreatic cancer is a malignancy with a very poor prognosis. Patients with resectable pancreatic cancer comprise a small subgroup of the overall population from around 15 to 20% (Mancuso et al., 2006). But the patients receiving curative surgery still have a poor prognosis due to local recurrence, hepatic and lymph node metastasis (Sperti et al., 1997; Gebhardt et al., 2000). Perineural invasion(PNI), which was described as the spread of cancer cells in the perineural spaces of the nerves (Kayahara et al., 2007; Liebig et al., 2009), has been reported as one of the sources of local recurrence in resected pancreatic cancer (Pour et al., 2003). And PNI is regarded as a prominent characteristic of pancreatic cancer, because the incidence of PNI is particularly high in pancreatic cancer among varied cancers (Bapat et al., 2011), which can be partially explained by the strong neurotropic effects of cancer cells and the close proximity of the pancreas to several neural plexuses (Stolinski et al., 1995; Pour et al., 2003; Ceyhan et al., 2010).

The PNI status has been reported to be a significant prognostic predictor for survival after surgery (Ozaki et al., 1999; Kazanjian et al., 2008; Sergeant et al., 2009; Ben et al., 2010; Sahin et al., 2012; Xie et al., 2013), however, several studies showed that PNI was not a prognostic parameter (Pawlik et al., 2007; Schiffman et al., 2011; Jamieson et al., 2012; Turrini et al., 2013). A systematic review (Garcea et al., 2008) analysed studies detailing outcomes following resection for PDAC from 1980 to 2008 and showed that meta-analysis of yearly survival data for PNI did not achieve statistical significance. Although thirteen studies related to PNI were found in the review, only five studies included 1 year, 3 year and 5 year survival data. In addition only 481 patients were included in the meta-analysis. In order to address the controversial issues, we performed a meta-analysis to determine the association between PNI status and clinical outcomes.

Materials and Methods

Search strategy

Two authors(J.F.Z and R.H) independently performed a systematic literature search of the following databases: PubMed, Embase and Cochrane Library (last search up to February 2013). The search strategy was based on combinations [("nerve invasion" or "perineural invasion") and "pancreatic cancer" and ("prognosis" or "survival")] in all fields. It was performed with no article type restriction and limited to English. Articles were also

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identified by hand searching for references and using the related articles function in PubMed.

Inclusion criteria and exclusion criteria

All pancreatic cancer types underwent curative operation were eligible for inclusion and no restrictions were placed on patient characteristics or study design. Studies were eligible according to the criteria:(1) assay of primary resected pancreatic cancer specimens and/or extrapancreatic nerve tissue specimens. (2) subjects had a minimum or mean follow-up time of two years. (3) analysis in clinical outcomes including overall survival(OS), disease-free survival(DFS), progression-free survival(PFS) and recurrence-free survival(RFS) using multivariate proportional hazards modeling that adjusted for clinical prognostic factors. (4) reporting of the resulting hazard ratios(HR) including 95% confidence intervals(CI). When two studies were reported including same patients totally or partly by the same institution, the publication including more patients was included.

Studies were ineligible according to the criteria: (1) other periampullary tumors (ampullary, distal cholangiocarcinomas, duodenal adenocarcinomas). (2) impossible to extract the data regarding at least one of clinical outcomes. (3) the curative surgery prior to 1980s were excluded, because OS of PDAC patients undergoing pancreatoduodenectomy in 1970s was significant different from patients in 2000s (Winter et al., 2006).

Data extraction

Two authors independently performed the search according to a prespecified protocol. Extracted data included: first author, year of publication, study design, pathology, number of cases reported, location of PNI, clinical outcomes and quality of study. Disagreement was resolved through arbitration by one reviewer (Y.W.S).

PNI

PNI was defined as cancer cell invasion to the perineural space between the perineurium and endoneurium of the peripheral nerve (Koide et al., 2006; Liebig et al., 2009). Where a cancer nest included nerves without direct contact between them, were excluded from PNI. Intraneural invasion was also included in PNI.

The degree of PNI was defined microscopically as follows: ne0, no perineural invasion; ne1, perineural invasion was difficult to find with only one to three occurrences in the lesions; ne2, perineural invasion was easy to find, in between ne1 and ne3; and ne3, perineural invasion was even easier to find, with more massive occurrences in the lesions and extension beyond the border of the main tumor mass. We regarded ne1 to ne3 as perineural invasion and ne0 as no perineural invasion.

Pancreatic nerve plexus invasion

PNI in pancreatic cancer was classified into intrapancreatic nerve invasion and pancreatic nerve plexus invasion, according to the position on pancreatic neural route (Kanehara, 1996). The pancreatic nerve plexus was classified into the plexus pancreaticus capitalis, branching to pancreas head, and the splenic plexus, branching to pancreas body and tail. We also regard "extrapancreatic perineural invasion" and "peripancreatic neural invasion" as pancreatic nerve plexus invasion.

Intrapancreatic nerve invasion

In most included studies, PNI actually means intrapancreatic nerve invasion. We also regard "intrapancreatic perineural invasion" as the same meaning.

Recurrence

The patten of recurrence was divided into two categories: (1) recurrence in the abdominal cavity, defined as either a locoregional or a peritoneal recurrence; (2) distant recurrence, defined as cancer recurrence in a distant organ (Takahashi et al., 2012). We employed DFS , PFS and RFS as clinical outcomes related to tumor recurrence in resected pancreatic cancer.

Statistical analysis

All statistical analyses were performed using Statistical Analysis System software (STATA 11.0). For individual studies, the data of outcome measure were summarized by the HR and its 95% CI. The heterogeneity of all involved studies was assessed by a statistical value I^2. A random-effects (DerSimonian-Laird method) or fixed-effects (Mantel-Haenszel method) model was used to calculate pooled effect estimates in the presence ($I^2 \leq 50\%$) or absence ($I^2 > 50\%$) of heterogeneity. The impact of PNI status on survival analysis was considered to be statistically significant if the 95% CI for the overall HR did not overlap 1. Conventionally, an observed HR>1 implied a worse survival for the group with PNI(+).

Heterogeneity

The quality of non-randomised studies was assessed using the Newcastle-Ottawa scale (Higgins et al., 2010), by examining patient selection methods, comparability of study groups and assessment of outcome. Studies achieving six or more stars from a maximum of nine were considered to be of higher quality.

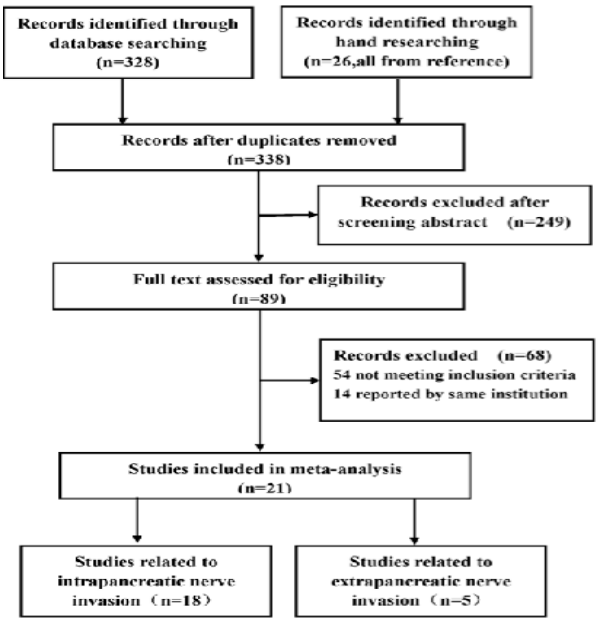

Figure 1. Identification Process for Eligible Studies

Table 1. Characteristics of Included Studies

First author (year)	Study design	Pathology	Num of pantient	Location of PNI		Clinical outcomes	Study quality
				PNI(+)	PNI(-)		
Peng C(2012)	Retro cohort	1	47	23	2	1	6
Sahin IH (2012)	Retro cohort	2	473	71	1	1	7
Jamieson NB(2012)	Retro cohort	1	159	14	1	1	5
Xie H (2012)	Retro cohort	1	77	41	1	1,3	6
Takahashi H(2012)	Retro cohort	2	56	54	1	2	5
Turrini O(2012)	Retro cohort multicenter	2	685	47	1	1	7
Murata Y(2011)	Retro cohort	2	46	9	1	1	7
Kim R (2011)	Retro cohort	2	48	36	1	1,3	6
Lee SH(2011)	Retro cohort	1	57	10	1	1	5
Bachellier P(2010)	Case matched controlled	2	39	13	1	1	4
Ben QW(2010)	Retro cohort	1	55	39	1	1	7
Murakami Y(2010)	Retro cohort	1	31	72	2	1	7
Sergeant G(2009)	Retro cohort	1	119	18	1	1,2	7
Nagai K (2009)	Retro cohort	1	28	25	1	1	7
Schiffman SC(2009)	Retro cohort	2	297	68	1	1	7
Kato K (2009)	Retro cohort	2	145	25	1	1	6
Kazanjian KK(2008)	Retro cohort	1	112	70	1	1	5
Nakagohri T(2006)	Retro cohort	2	88	12	1	1	6
Pawlik TM(2006)	Retro cohort	2	682	67	1	1	6
Mitsunaga S(2005)	Retro cohort multicenter	1	35	66	2	1,2	8
Ozaki H(1998)	Retro cohort	2	126	67	1	1	6

Pathology: 1. PDAC; 2. pancreatic cancer; Outcomes: 1. OS; 2. DFS; 3. PFS; Location of PNI: 1. intrapancreatic nerve invasion; 2. pancreatic nerve plexus invasion

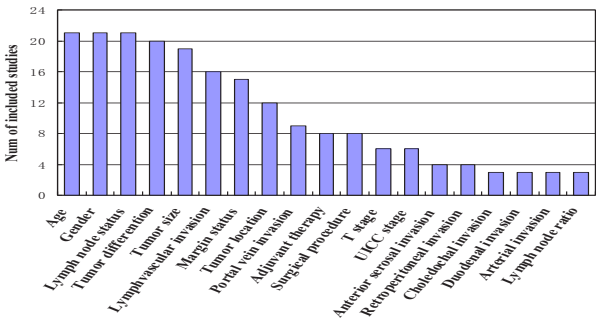

Figure 2. Clinicopathologic Factors of Studies Included in Meta-analysis Except PNI

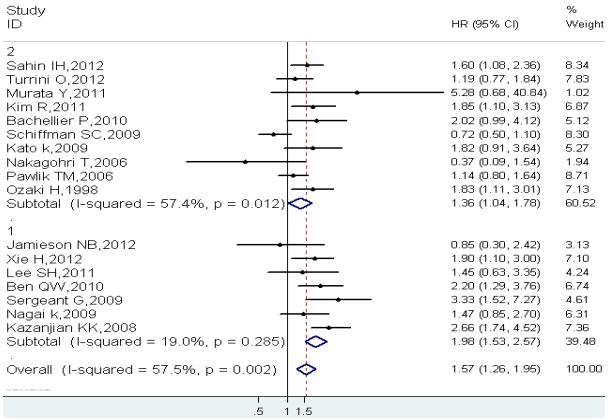

Figure 3. Forest Plot of the Impact of Intrapancreatic PNI Status on OS

Publication bias

Assessment of publication bias was investigated for each of the pooled study groups mainly by the Egger's linear regression test. As supplement approach, the trim and fill method was also applied to assess the potential publication bias, when $P>0.05$ was considered that there was no publication bias in the study.

Results

Characteristics of included studies

The initial literature research identified 89 full articles (Figure1), of which 54 did not meet the inclusion criteria. 14 of the remaining 35 studies (Kim et al., 2006; Murakami et al., 2008; Balentine et al., 2010; Chu et al., 2010; Kanda et al., 2010; de Jong et al., 2011; Jamieson et al., 2011; Kneuertz et al., 2011; Maithel et al., 2011; Singal et al., 2011; Chatterjee et al., 2012; Watanabe et al., 2012; Xie et al., 2012; Fisher et al., 2013) were excluded because they were reported by the same institutions as other studies. 21 studies (Ozaki et al., 1999; Mitsunaga et al., 2005; Nakagohri et al., 2006; Pawlik et al., 2007; Kazanjian et al., 2008; Kato et al., 2009; Nagai et al., 2009; Sergeant et al., 2009; Ben et al., 2010; Murakami et al., 2010; Bachellier et al., 2011; Kim et al., 2011; Schiffman et al., 2011; Cheng et al., 2012; Jamieson et al., 2012; Lee et al., 2012; Murata et al., 2012; Sahin et al., 2012; Takahashi et al., 2012; Turrini et al., 2013; Xie et al., 2013) were included in the final meta-analysis, comprising one case matched controlled study and 20 retrospective cohort studies (Table 1). A total of 4459 patients were included in this meta-analysis.

Except PNI, 19 clinicopathologic factors were incorporated in three or more of the included studies' multivariate analyses (Figure 2). Four studies considered between seven and eight clinical covariates, twelve studies considered between nine and ten covariates, five studies included more than ten covariates.

Impact of intrapancreatic nerve invasion on OS

Eighteen studies (Seventeen studies related to OS and one studie only related to DFS) including 4178 patients

Table 2. Main Characteristics of 18 Studies Relating to Intrapancreatic PNI

First author(year)	OS		DFS		PFS	
	Num	HR (95%CI)	Num	HR (95%CI)	Num	HR (95%CI)
Sahin IH (2012)	544	1.60(1.08-2.36)				
Jamieson NB (2012)	173	0.85(0.30-2.42)				
Xie H (2012)	118	1.9(1.1-3.0)			81	3.1(1.6-5.8)
Takahashi H (2012)			110	2.48(1.11-5.52)		
Turrini O (2012)	932	1.19(0.77-1.84)				
Murata Y (2011)	55	5.28(0.68-40.84)				
Kim R (2011)	84	1.85(1.10-3.13)			84	2.02(1.03-3.99)
Lee SH (2011)	67	1.45(0.63-3.35)				
Bachellier P (2010)	52	2.02(0.99-4.12)				
Ben QW (2010)	94	2.199(1.287-3.758)				
Sergeant G (2009)	137	3.328(1.524-7.267)	137	3.785(1.621-8.835)		
Nagai K (2009)	53	1.47(0.85-2.7)				
Schiffman SC (2009)	365	0.72(0.5-1.1)				
Kato K (2009)	170	1.82(0.91-3.64)				
Kazanjian KK (2008)	182	2.66(1.74-4.52)				
Nakagohri T (2006)	100	0.37(0.09-1.54)				
Pawlik TM (2006)	749	1.14(0.8-1.64)				
Ozaki H (1998)	193	1.83(1.11-3.01)				

Table 3. Main Characteristics of 5 Studies Relating to Extrapancreatic PNI

First author (year)	OS		DFS	
	Num	HR(95%CI)	Num	HR(95%CI)
Peng C (2012)	70	1.822(1.01-3.289)		
Murakami Y (2010)	103	1.93(1.03-3.62)		
Kato K (2009)	177	1.61(1.01-2.55)		
Nakagohri T (2006)	100	1.80(1.07-3.05)		
Mitsunaga S (2005)	101	1.7(1.0-3.0)	101	1.0(0.6-1.7)

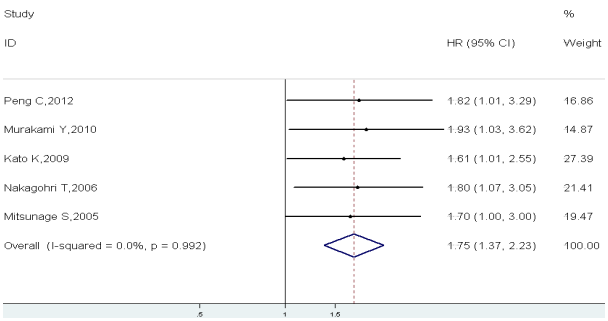

Figure 4. Forest Plot of the Impact of Extrapancreatic PNI Status on OS

with intrapancreatic nerve invasion were included (Table 2). The overall incidence of intrapancreatic PNI was 78.8% (range: 50.9%-91.9%). The included studies were divided into two subgroup according to pathology: PDAC group (subgroup=1) and PC group (subgroup=2). Pooled data of multivariate analysis showed a significant difference between two PNI status on OS (HR=1.566, 95%CI: 1.261-1.945, p=0.000) (Figure 3). But there was a significant heterogeneity in overall group (p=0.002, I^2=57.5%). Egger's test showed no significant publication bias (P=0.425). The meta-analysis of PDAC subgroup showed a significant difference between two PNI status on OS (HR=1.982, 95%CI: 1.526-2.574, p=0.000). And there was no significant heterogeneity in PDAC subgroup (p=0.285, I^2=19.0%). The meta-analysis of PC subgroup also showed a significant heterogeneity, which is similar to total group.

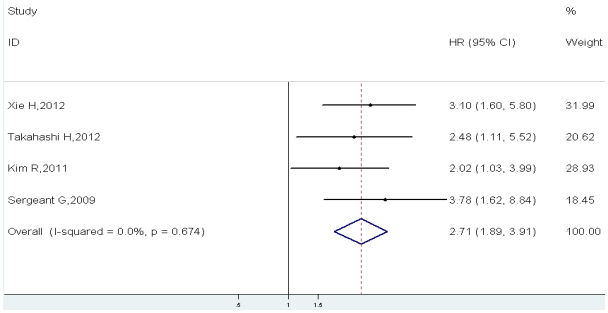

Figure 5. Forest Plot of the Impact of Intrapancreatic PNI Status on DFS or PFS

Impact of pancreatic nerve plexus invasion on OS

Five studies including 551 patients with pancreatic nerve plexus were included (Table 3). The overall incidence of extrapancreatic PNI was 35.4% (range: 26.0%-67.1%). The meta-analysis also showed a significant difference between two PNI status (HR=1.748, 95%CI: 1.372-2.228, p=0.000) (Figure 4). There was no significant heterogeneity (p=0.992, I^2=0.0%). But Egger's test showed slight publication bias (P=0.037).

Impact of intrapancreatic PNI on recurrence

There are two studies related to DFS, two studies related to PFS and no study related to RFS included. The meta-analysis showed a significant difference between two PNI status (HR=2.714, 95%CI: 1.885-3.906, p=0.000) (Figure 5). There was no significant heterogeneity (p=0.674, I^2=0.0%) or publication bias (P=0.644)

Discussion

Pancreatic cancer is characterized by extremely high frequency of PNI. Several detailed pathohistologic studies (Nagakawa et al., 1992a; Nakao et al., 1996) have shown that PNI is one of the causes of locoregional recurrence in resected pancreatic cancer. But the prognostic value of PNI is not clear. In the Japanese staging systems for pancreatic cancer (Kanehara 2003), extrapancreatic nerve plexus invasion was considered as T4 stage. In contrast

to the Japanese system, UICC stage classification (Sobin et al., 2002) does not consider neural invasion as an independent factor. This meta-analysis systematically examined association between PNI status with OS in resected pancreatic cancer. We considered that different pathological types result in a significant heterogeneity in the meta-analysis of intrapancreatic PNI on OS. Compare with PDAC, the most common type of pancreatic cancer, several studies had proved that other pathological types of pancreatic cancer have better prognosis, such as neuroendocrine carcinoma (Winter et al., 2006), intraductal papillary mucinous neoplasm(IPMN) with invasive cancer (Waters et al., 2011), adenosquamous carcinoma (Boyd et al., 2012). We concluded that intrapancreatic PNI is an independent predictor of outcome in resected PDAC patients. In fact, multivariate analysis revealed that patients with PNI-positive tumors were approximately twice as likely to die from PDAC when compared with their stage-matched, PNI-negative counterparts. But the impact of intrapancreatic PNI for the other pathological types was not clear because of significant heterogeneity. Meanwhile extrapancreatic PNI was an independent and poor prognostic factor in all pancreatic cancer patients, which increased 75% risk to die from pancreatic cancer.

Moreover, this meta-analysis revealed that patients with intrapancreatic PNI-positive tumors were 2.7 times risk to recurrence when compared with PNI-negative tumors. Only one included study (Mitsunaga et al., 2005) analysed the relationship between extrapancreatic PNI and DFS, and showed that extrapancreatic PNI was an independent predictor of OS, but not DFS. Shimada et al. (2011) also showed extrapancreatic nerve plexus invasion was not an independent predictor of DFS, but intrapancreatic nerve invasion was. And the studies showed positivity for extrapancreatic PNI significantly increased with an increase in the incidence of intrapancreatic PNI, suggesting that plexus invasion is an extension of intrapancreatic neural invasion, as in the previous reports (Kayahara et al., 1991; Nagakawa et al., 1992b; Mitsunaga et al., 2007).

It was reported that the occurrence of PNI in 75% of cases of stage I disease (Nagakawa et al., 1991; Nakao et al. 1996), suggesting that this pattern of tumor spreading is an early event. Shimada et al. (2011) showed there was no statistical difference of DFS between ne0, 1 patients with lymph node metastases and ne2, 3 patients without lymph node metastases. So PNI may be helpful to identify high-risk patients in early stage, especially for patients with negative lymph node metastasis.

To achieve complete clearance of nerve plexus, standard pancreatoduodenectomy with extended lymphadenectomy had been finished. Compare to standard pancreatoduodenectomy, extended lymphadenectomy involved para-aortic node dissection and autonomic nerve dissection around the superior mesenteric artery. Two randomized controlled trials(RCTs) in American (Farnell et al., 2005) and Japan (Nimura et al., 2002) supported that extended lymphadenectomy provided no survival benefit, but a higher incidence of diarrhea.

In contrary to surgery alone, adjuvant therapy is recommended to treat patients with pancreatic cancer more effectively. A meta-analysis (Ren et al., 2012) showed a significant benefit with regard to DFS and median OS for adjuvant chemotherapy after resection for advanced pancreatic cancer. Takahashi et al. (2012) analyzed the histopathological indicators significantly associated with surgical outcome in the setting of preoperative chemoradiation therapy and showed the status of PNI is significantly associated with DFS and clearly predict locoreginal or peritoneal recurrence. French authors (Barbier et al., 2011) showed preoperative chemoradiation allows for less perineural, lymphatic and vascular invasion, leading to less locoregional recurrence, but does not increase survival, mainly for reasons of metastatic spread. So preoperative chemoradiation may decrease the occurrence of PNI and locoregional recurrence. In addition, several studies (Maithel et al., 2011; Xie et al., 2012; Xie et al., 2013) showed that the status of PNI is significantly associated with OS in univariate analysis. But they analysed the patients with postoperative adjuvant chemotherapy and showed the status of PNI is not significantly different on OS in univariate analysis,. We presumed that postoperative chemotherapy may increase the survival of patients with PNI(+) to an extent similar to PNI(-), which need more study to support.

Defects which reduced the quality of the studies included the lack of explicit definition of PNI, inconsistent surgical methods and different adjuvant treatment. As mentioned, we regarded ne1 to ne3 as perineural invasion. But in most of included studies, the author only defined the status of PNI as "present" or "absent" and "yes" or "no" without any microscopical details. Lack of standardization in all the studies may have resulted in heterogeneity.

Attempts to achieve an R0 resection lead to more extensive operations. Resection and reconstruction of segments of the portal-mesenteric vein is accepted. Involvement of the celiac, hepatic, or superior mesenteric arteries has commonly been considered a contraindication to resection of locally advanced pancreatic cancer (Mollberg et al., 2011). One included study (Bachellier et al., 2011) was reported that 34 patients underwent an extended pancreatic resection with arterial resection. We included the study because it corresponded to "resecected pancreatic cancer". But different standard of resectability and surgical methods will lead to potential bias.

Adjuvant treatment is a standard form of treatment option for PDAC and has been shown to improve the 5-year survival and to delay the time to tumor recurrence in patients who underwent curative surgery (Stocken et al., 2005; Regine et al., 2006; Squadroni et al., 2010). So adjuvant chemotherapy might partly influence significance of the clinical outcomes. In addition, different types of adjuvant treatment will influence clinical outcomes and lead to potential bias.

In summary, this meta-analysis demonstrated that intrapancreatic and extrapancreatic PNI were independent and poor prognostic factors in resected PDAC patients. Intrapancreatic PNI may be associated with tumor recurrence in all pancreatic cancer. It will be helpful to identify high risk patients earlier and guide clinical therapy to determine the status of PNI in resected pancreatic cancer.

Acknowledgements

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