Impact of Pancreatic Margin Status and Lymph Node Metastases on Recurrence after Resection for Invasive and Noninvasive Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Meta-Analysis

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Key Words

Intraductal papillary mucinous neoplasm • Pancreatic margin • Lymph node metastases • Recurrence • Meta-analysis

Abstract

Background: Accurate information is currently lacking regarding the values of positive margins (M⁺) and lymph node (LN) metastases as independent predictors of postoperative recurrence in invasive and noninvasive intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. **Methods:** A comprehensive online literature search identified all types of primary studies that included M⁺ and LN metastases as risk factors and defined recurrence as an outcome in patients with IPMNs. Suitable articles were also identified by manually researching references in qualifying articles. A meta-analysis of the result was performed using a random effects model. **Results:** The recurrence rate in noninvasive IPMNs was 3.72% in patients with negative margin (M⁻) versus 9.56% in those with M⁺ (odds ratio, OR = 0.37, 95% confidence interval, 95% CI: 0.17–0.78, p = 0.010). The recurrence rate in invasive M⁻ IPMNs was 33.85% compared to

53.66% in M⁺ IPMNs (OR = 0.47, 95% CI: 0.25–0.88, p = 0.020). The recurrence rate in invasive IPMNs with positive LN was 76.92% compared to 30.86% with negative LN; OR = 0.15, 95% CI: 0.06–0.37, p < 0.0001). **Conclusions:** M⁺ were associated with disease recurrence in all patients with IPMN, and nodal metastases were significantly associated with recurrence in invasive IPMN.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, defined by the World Health Organization (WHO) in 1996, have been increasingly recognized over the last two decades [1–4]. IPMNs comprise a histologic spectrum ranging from adenoma with mild dysplasia to invasive carcinoma. Increasing molecular and clinical evidence supports the idea that all IPMNs with invasive carcinoma have progressed from adenomas that underwent transformation, possibly reflecting stepwise molecular genetic changes similar to the adenoma-carcinoma sequence seen in colon cancer [5–8].

Patients with noninvasive neoplasms, such as adenomas, borderline, and carcinoma in situ, have a favorable prognosis after surgical resection [9–12]. In contrast, the presence of an invasive component is strongly associated with poor survival [13–15]. Although the overall outcome for IPMN is good, a significant proportion of patients with resected noninvasive IPMN develop pancreatic adenocarcinoma in the pancreatic remnant and subsequently die of disseminated disease [3, 16]. Several recent studies have examined rates, patterns and risk factors for recurrence [3, 9, 14–19]. However, these studies combined noninvasive and invasive IPMNs, for which the rates and patterns of recurrence differ, and failed to detect any association between margin status, lymph node (LN) metastases and recurrence. Furthermore, case series have largely presented small numbers of patients with limited follow-up, and the factors leading to recurrence in these patients are not well understood.

It is reported that positive margins (M^+) for adenomas and borderline lesions closer to adenomas do not warrant subsequent resection [20]. However, there have been reports of invasive carcinomas in association with only mild or moderate dysplasia (adenomas or borderline lesions) within the IPMN in the remnant pancreas [18, 21]. The clinical implications of pancreatic margins with adenomas or borderline lesions are controversial, and surgeons thus remain uncertain about how much pancreas to resect, weighing the risk of recurrence against the morbidity of additional resection.

Evaluation of this issue using randomized controlled trials was not feasible, and individual prognostic studies lack sufficient power to estimate the effects of margin status and LN metastases on recurrence in IPMNs. We therefore performed a meta-analysis to examine the impacts of margin status and LN metastases in IPMNs. The evidence for surgical margins and LN metastases in invasive and noninvasive IPMNs were systematically reviewed to determine their effects on recurrence, and to inform the discussion of management of M^+ and LN metastases in patients with IPMNs.

Methods

Search Strategy

Two authors (K.M.L. and Z.D.W.) independently conducted a systematic literature search of the MEDLINE (PubMed; January 1966 to July 2011) and Embase (January 1988 to July 2011) databases, combining the following terms: (a) ‘intraductal papillary mucinous neoplasm/or intraductal papillary mucinous neoplasms/or intraductal papillary mucinous tumor/or intra-

ductal papillary mucinous tumors’, and ‘pancreas’; (b) ‘recurrence*/or relapse*’, and (c) ‘margin*’, ‘lymph node metastases/or lymph node metastasis/or lymph node involvement’. The date of the most recent search was 4 July 2011. There were no language restrictions. Reference lists from available reviews and selected studies were also cross-searched for additional literature. The articles were stratified into four groups: case reports, reviews, retrospective studies, and prospective non-randomized studies.

Data Collection

Two reviewers independently performed the search in addition to reviewing and extracting data, according to a prespecified protocol. Extracted data included: first author, design, number of patients, margin status and LN metastases in all surgical patients and relapsed patients, and length of follow-up. Disagreement was resolved through arbitration by one reviewer (Y.F.C.).

Inclusion Criteria

Studies were included in our meta-analysis if they reported data allowing calculation of the proportion of recurrence in relation to margin status and LN metastases, and where: (1) subjects were identified as having noninvasive or invasive IPMNs; (2) all were primary tumors; (3) studies used explicit margin definitions or presented detailed margin status or LN metastases for all surgical patients and relapsed patients, and (4) subjects had a minimum median or mean follow-up time of 2 years. When two studies were reported by the same institution, the most recent publication was included.

Exclusion Criteria

Studies were ineligible for this analysis if they: (1) did not present detailed margin status or LN metastases for all surgical patients and relapsed patients; (2) combined invasive and non-invasive IPMNs; (3) presented re-resection data only; (4) were review series or case reports.

Definitions of Variables

Margins

Study-specific information on the definition of the final microscopic margins was extracted and classified using two reported classifications: IPMNs and PanINs. Pathologically, IPMNs and PanINs represent two separate classes of intraductal neoplasia of the pancreas. Most IPMNs are grossly visible neoplasms [22]. In contrast, most PanINs are incidentally detected microscopic lesions [23]. However, the authors in the included studies used the concept of PanINs to describe the margin status in IPMNs after surgical resection at the microscopic level, rather than PanINs themselves in the remnant pancreas. The WHO classification of pancreatic neoplasms reported four successive stages of IPMN: mild dysplasia (adenoma), moderate dysplasia (borderline), severe dysplasia, and invasive carcinoma [4, 24]. The pathologic descriptions of PanIN1, PanIN2 and PanIN3 were defined as epithelium without dysplasia, mild-to-moderate dysplasia, and severe dysplasia, respectively [25]. This meta-analysis combined the evidence on microscopic margins according to the degree

of dysplasia. As in previous studies [17, 19, 26], a standard classification for M⁺ was based on the presence of any degree of dysplasia at the transected margins, including Pan-IN2 (mild-to-moderate dysplasia), and Pan-IN3 (severe dysplasia). Pan-IN 1A or 1B as pathologic lesions of uncertain significance has been reported in two thirds of non-neoplastic pancreases at autopsy, and tends to occur in older subjects [27, 28]. We therefore considered normal columnar epithelium, Pan-IN1A and 1B (epithelium without dysplasia) and epithelial denudation as negative margins (M⁻). The resection margin of total pancreatectomy was also defined as negative.

LN Metastases

LN metastases were diagnosed by pathologists based on the analysis of specimens, rather than by clinicians based on the results of imaging.

Recurrence

Recurrence as a clinical end point was defined as presence of recurrent IPMNs in the pancreatic remnant after surgical resection, or as local, regional, or distant metastatic disease diagnosed in the follow-up period after resection of the neoplasm.

Statistical Analysis

The meta-analysis was performed in line with the recommendations of the Meta-analysis of Observational Studies in Epidemiology and the recommendations of the Cochrane Collaboration, using Review Manager (RevMan) software, version 5.1 (Nordic Cochrane Centre, Copenhagen, Cochrane Collaboration). Odds ratios (ORs) were estimated for dichotomous data, with 95% confidence intervals (CIs). For categorical variables, ORs were combined with the Mantel-Haenszel method using a 'random effect' meta-analysis technique. Values of $p < 0.05$ were considered significant. In surgical research, meta-analysis using the random-effect model has a more conservative value [29, 30], because patient risk profiles and selection criteria for each surgical technique differ among different centers.

The quality of the cohort studies was assessed using the Newcastle-Ottawa Scale [31]. Study quality was evaluated by examining three items: selection of cohort, comparability of cohorts on the basis of the design, and assessment of outcome. Studies achieving six or more stars were considered to be of the highest quality.

Statistical heterogeneity was assessed using funnel plots to evaluate publication bias, and sensitivity analyses for the following subgroups: (a) studies of higher quality with six or more stars, (b) length of follow-up more than 40 months, (c) cohort size >30 patients.

Results

Studies Selected

The initial literature research identified 79 full articles, of which 67 did not meet the inclusion criteria. Most

excluded studies did not provide data on margin status or LN metastases for all surgical patients and relapsed patients. In addition, manual searching of reference lists from available reviews yielded 8 additional studies. Four of the remaining 20 studies were excluded because they were reported by the same institutions as other studies [32–35]. Sixteen studies were therefore included in the final meta-analysis, comprising 9 retrospective cohort studies [12, 18, 19, 36–41], and 7 prospective cohort studies [3, 9, 16, 17, 34, 42, 43]. A review of the data extraction revealed 100% agreement between the two reviewers. Details of the search strategy are presented in figure 1.

The characteristics of the 16 studies are shown in table 1. A total of 1,101 patients with IPMNs were included in this meta-analysis, including 400 (36.33%) invasive IPMNs and 701 (63.67%) noninvasive IPMNs. A total of 218/1,101 (20.96%) patients had positive resection margins, and 52 (39.10%) had LN metastasis in 133 invasive IPMNs. A total of 192 (17.44%) patients reported recurrence, and the length of follow-up ranged from 24 to 65 months. The quality of data reporting was assessed using the Newcastle-Ottawa Scale (table 1).

Impact of Margin Status on Recurrence after Resection for Noninvasive IPMNs

Twelve studies including 701 patients with non-invasive IPMNs were included in this meta-analysis. The overall incidence of recurrence in all patients with noninvasive IPMNs was 4.85%. The recurrence rate in patients with M⁻ and M⁺ was 3.72 and 9.56%, respectively. Analysis of pooled data using the random effects model showed a significant difference in prevalence of recurrence between the two groups (OR = 0.37, 95% CI: 0.17–0.78, $p = 0.010$, fig. 2). There was no significant heterogeneity between the studies ($p = 0.47$). Funnel plots are not shown.

Impact of Margin Status on Recurrence after Resection for Invasive IPMNs

Eleven cohort studies including 339 patients with invasive IPMNs were identified. The incidence of recurrence in all patients with invasive IPMNs was 38.64%. The meta-analysis demonstrated that recurrence after surgical resection occurred in 33.85% of patients with M⁻ (87/257) versus 53.66% with M⁺ (44/82; OR = 0.47; 95% CI: 0.25–0.88, $p = 0.020$; fig. 3). There was no significant heterogeneity between the groups ($p = 0.50$). Funnel plots are not shown.

Fig. 1. Search strategy.

Impact of LN Metastases on Recurrence of Invasive IPMNs

Seven studies were included in the meta-analysis of the impact of LN metastases on recurrence of invasive IPMNs. Recurrence occurred in 40 of 52 LN⁺ patients with invasive IPMNs (76.92%), compared to only 30.86% (25/81) in the LN⁻ group. In the pooled data, the rate of recurrence was significantly higher in LN⁺ patients with invasive IPMNs than in LN⁻ patients (OR = 0.15; 95% CI: 0.06–0.37, $p < 0.0001$; fig. 4). No heterogeneity was detected among the 7 included studies ($p = 0.70$). Funnel plots are not shown.

Sensitivity Analysis

Sensitivity analysis was performed for high-quality studies (≥ 6 stars), studies with length of follow-up > 40 months, and studies with > 30 cases (table 2). Subgroup analysis showed no changes in the ORs and heterogeneities for recurrence in M⁺ patients with noninvasive IPMNs and LN⁺ patients with invasive IPMNs. When low-quality studies (< 6 stars) and those with follow-up durations of < 40 months were excluded, recurrence in patients with invasive IPMNs was not associated with M⁺. However, sensitivity analysis including only studies with cohort sizes of > 30 cases in M⁺ patients with invasive IPMNs revealed significant differences.

Table 1. Characteristics of included studies

Study	Study design	Patients		Margin status		LN ⁺	Recurrence		Follow up, months		Study quality
		inIPMN	nonIPMN	inIPMN	nonIPMN		inIPMN	nonIPMN	inIPMN	nonIPMN	
Sohn et al. [3]	Prospective	52	84	Noninvasive IPMN: 12 Invasive carcinoma: 8	Noninvasive IPMN: 20	28	Invasive/noninvasive IPMN at margin: 12 ^a Tumor free: 11 ^a	Noninvasive IPMN at margin: 2 ^a Tumor free: 5 ^a	24	24	*****
Raut et al. [9]	Prospective	13	22	Noninvasive IPMN: 1	Noninvasive IPMN: 7	5	Negative: 7 LN ⁺ : 4 LN ⁻ : 3	0	61	30.3	*****
Cuillerier et al. [12]	Retrospective	19	26	Disease free: 11 ^b Involved: 8	Disease free: 19 ^b Involved: 7	8	Disease-free margin ^b : 7 Involved margin: 6 LN ⁺ : 8 LN ⁻ : 5	Involved margin: 2	65	65	*****
Salvia et al. [16]	Prospective	58	81	Negative: 28 Adenoma: 2 Borderline: 5 Carcinoma: 3 Invasive carcinoma: 3 Epithelial denudation: 3 TP: 14	Negative: 54 Adenoma: 8 Borderline: 6 Epithelial denudation: 1 TP: 12	24	Negative: 3 Borderline: 2 Epithelial denudation: 2	Negative: 1	40	40	****
Chari et al. [17]	Prospective	40	73	Normal: 11 Mucinous hyperplasia: 9 Dysplasia (Pan-IN2): 2 Cancer: 5 TP: 13	Normal: 37 Denuded: 4 Mucinous hyperplasia: 9 Dysplasia (Pan-IN2): 2 TP: 13	12	Normal/hyperplasia: 12 Dysplasia/cancer: 6 TP: 8	Normal/hyperplasia: 5	45	49	*****
Adsay et al. [18]	Retrospective	14	13	Margin ⁺ for invasion: 1 Margin ⁺ for CIS: 1	Margin ⁺ for IPMB: 2 Margin ⁺ for CIS: 1	4	Negative: 2 LN ⁺ : 2	Margin ⁺ for IPMB: 1 Negative: 1	42	42	****

Table 1. (continued)

Study	Study design	Patients		Margin status		LN ⁺	Recurrence		Follow up, months		Study quality
		inIPMN	nonIPMN	inIPMN	nonIPMN		inIPMN	nonIPMN	inIPMN	nonIPMN	
Wada et al. [19]	Retrospective	25	75	Normal/denuded: 12 Hyperplasia: 4 Dysplasia (Pan-IN2): 2 Cancer (PanIN-3): 1 TP: 6	Normal/denuded: 48 Hyperplasia: 16 Dysplasia (Pan-IN2): 4 TP: 7	8	Normal/denuded: 5 Hyperplasia: 1 Dysplasia (Pan-IN2): 1 Cancer (PanIN-3): 1 TP: 4	Dysplasia (Pan-IN2): 1	56	56	*****
Lubezky et al. [26]	Prospective	23	39	Negative: 16 LD: 2 MD: 1 Invasive cancer: 3	Negative: 31 LD: 8	8	Positive M ⁺ : 4	Negative: 2 LD: 1	37.6	37.6	*****
Azar et al. [36]	Retrospective	7	13	Free: 2 Mild dysplasia: 3 Moderate dysplasia: 2	Free: 8 Mild dysplasia: 5	NA	Mild dysplasia: 3 Free: 1	Mild dysplasia: 1	26.4	56.8	*****
Paye et al. [37]	Retrospective	10	31	Normal: 4 Simple hyperplasia: 1 Atypical hyperplasia: 3 Invasive carcinoma: 2	Normal: 21 Simple hyperplasia: 4 Atypical hyperplasia: 4 Carcinoma in situ: 2	5	Normal: 4 Simple hyperplasia: 1 Atypical hyperplasia: 3 Invasive carcinoma: 2	0	NA	NA	*****
Sugiura et al. [38]	Retrospective	7	23	NA	NA	2	LN ⁺ : 2	NA	60	60	*****
Nara et al. [39]	Retrospective	66	61	Negative: 57 ≥LD: 9	Negative: 49 ≥LD: 12	21	Negative: 17 LD/MD: 1 Invasive cancer: 1 LN ⁺ : 14	0	50	50	*****
Park et al. [40]	Retrospective	35	68	Positive resection margin: 5 ^c		7	LN ⁺ : 5 LN ⁻ : 7	1	26.7	26.7	****
Nakagohri et al. [41]	Retrospective	37	45	Adenoma: 9 Carcinoma: 8	Adenoma: 6 Carcinoma: 1	15	Negative: 9 Adenoma: 1 Carcinoma: 7	Carcinoma: 1	NA	NA	*****

Table 1. (continued)

Study	Study design	Patients		Margin status		LN ⁺	Recurrence		Follow up, months		Study quality
		inIPMN	nonIPMN	inIPMN	nonIPMN		inIPMN	nonIPMN	inIPMN	nonIPMN	
Fujii et al. [42]	Prospective	41	93	NA	Negative: 64 Adenoma: 28 TP: 1	NA	NA	Negative: 6 Adenoma: 3	40.9	40.9	*****
White et al. [43]	Prospective	None	78	None	Negative: 32 Adenoma: 8 Borderline: 7 Carcinoma in situ: 8 PanIN-1/ PanIN-2: 18 Excluded (TP): 5	None	None	Negative: 2 Adenoma: 2 Borderline: 1 Carcinoma in situ: 1	None	40	*****

inIPMN = Invasive IPMN; nonIPMN = noninvasive IPMN; M = metastases; LR = local recurrence; LD = low-grade dysplasia; MD = moderate dysplasia; TP = total pancreatectomy; NA = data not available.

^a Margin status of recurrence was not disclosed directly, but could be calculated according to the data published in this article.

^b Disease-free margins includes patients after TP.

^c Positive resection margins were defined as those with any one among the following at the transection margins: adenoma, borderline tumor, CIS, and invasive carcinoma.

Fig. 2. Forest plot of the impact of margin status on recurrence after resection for noninvasive IPMNs (random effects model).

Fig. 3. Forest plot of the impact of margin status on recurrence after resection for invasive IPMNs (random effects model).

Discussion

IPMNs have attracted wide attention since the establishment of a consensus nomenclature, as evidenced by an increasing number of reports. The management of IPMNs has become increasingly controversial as experience with these tumors has grown, and there is currently no consensus or consistent evidence regarding the value of increased transection margins in reducing recurrence. Furthermore,

there is no consensus on whether involvement of LNs represents a risk factor for postoperative recurrence. This meta-analysis systematically examined the evidence for associations of surgical margins and LN metastases with recurrence in invasive and noninvasive IPMNs. Data synthesis across studies showed that M⁺ significantly increased the odds of recurrence relative to M⁻, and that the rate of recurrence was significantly higher in LN⁺ patients with invasive IPMNs compared to LN⁻ patients.

Fig. 4. Forest plot of the impact of LN metastases on recurrence after resection for invasive IPMNs (random effects model).

Table 2. Sensitivity analysis of impact of pancreatic-margin status and lymph node metastases on recurrence after resection for invasive and noninvasive IPMNs

Subgroup	Patients	Studies	OR (95% CI)	p	HG χ^2	HG P
1. Effect of margin status on recurrence after resection for noninvasive IPMNs						
High-quality studies ≥ 6 stars	453	7	0.21 (0.06–0.81)	0.02*	6.33	0.18
Length of follow-up ≥ 40 months	452	7	0.24 (0.07–0.75)	0.01*	6.60	0.25
Cohort size ≥ 30 patients	666	10	0.37 (0.16–0.84)	0.02*	7.45	0.38
2. Effect of margin status on recurrence after resection for invasive IPMNs						
High-quality studies ≥ 6 stars	175	5	0.61 (0.25–1.52)	0.29	2.97	0.56
Length of follow-up ≥ 40 months	247	7	0.65 (0.30–1.43)	0.28	3.12	0.79
Cohort size ≥ 30 patients	247	5	0.48 (0.24–0.97)	0.04*	2.14	0.71
3. Impact of LN metastases on recurrence for invasive IPMNs						
High-quality studies ≥ 6 stars	54	3	0.21 (0.06–0.71)	0.01*	1.67	0.43
Length of follow-up ≥ 40 months	88	5	0.15 (0.05–0.44)	0.0005*	3.02	0.55
Cohort size ≥ 30 patients	69	2	0.23 (0.07–0.71)	0.01*	0.51	0.48

Asterisk signifies statistically significant outcomes. HG = heterogeneity.

The present meta-analysis reported postoperative recurrence in 4.85% of patients with noninvasive IPMNs, in line with previously published series quoting recurrence rates after surgical resection of 1.3–6.3% [3, 15–17, 19]. Tumor recurrence in the remaining pancreas has been reported after resection for noninvasive IPMNs, but pathologic pancreatic-margin status has not been consistently reported in these cases. Neither of these studies demonstrated an association between margin status and recurrence [3, 9, 15, 16, 19]. Nakagohri et al. [41] and Fujii et al. [42] reported that margins positive for ad-

enomas were not associated with tumor recurrence and International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms of the Pancreas indicated that adenoma at the resected margin did not warrant further resection. However, pooled data in the current study indicated that the odds of recurrence of noninvasive IPMNs after resection were significantly associated with M⁺. Furthermore, available data showed that 53.85% (7/13) of M⁺ in relapsed noninvasive IPMNs were adenomas (mild dysplasia). Accordingly, we and others [3, 17] recommend that patients with IPMNs

should undergo surgical resection to achieve M⁻ with no dysplasia. Although our data did not prove directly that M⁺ cause local recurrence, they suggest that M⁺ are associated with an increased risk of local recurrence.

Recurrence of noninvasive tumors has also been reported, even after complete resection [3, 9, 17, 39, 41]. The incidence of recurrence in patients with M⁻ in this meta-analysis was 3.71%. These recurrences may be the results of residual neoplasms, including multifocal disease, which may have been unrecognized at the time of surgery, or of metachronous development of IPMN. Further detailed histological and molecular studies are needed to clarify this issue [12, 17, 42]. Unfavorable prognoses have been reported for noninvasive intestinal-type IPMNs, with tumor recurrence even after complete resection. However, this observation was uncommon in other types of IPMNs, indicating that intestinal-type IPMNs tend to be diffuse, high-grade lesions with a high probability of recurrence [43]. Prophylactic total pancreatectomy for IPMNs could theoretically solve this problem, but this procedure is only performed in a limited number of patients because of the associated high morbidity and poor postoperative quality of life, including complications such as diabetes and exocrine insufficiency. Because the chance of recurrence from dysplasia at the resected margin, or from multifocal disease in the remnant pancreas is acceptably low, and some recurrence in the isolated pancreatic remnant can be cured by repeat pancreatectomy [28], we recommend that the goal of treatment for noninvasive IPMNs should be complete resection with no dysplasia at the surgical margins, but not prophylactic total pancreatectomy.

According to previous reports, LN metastases occurred in 5–54% of patients with invasive IPMNs [3, 9, 15–17, 34, 37, 40, 41, 44–47]. In the current study, 52 of 133 patients with invasive IPMNs (39.10%) developed LN metastases, which was significantly lower than in those with ductal adenocarcinomas (50–66%). There is no accurate information regarding the independent predictive value of regional LN involvement for postoperative recurrence in invasive IPMNs; however, the present meta-analysis demonstrated a significant association between LN metastases and recurrence. The incidence of recurrence after resection in LN⁺ IPMNs was as high as 76.92%, compared to only 30.86% in the LN⁻ group. Previous studies showed that although LN⁻ IPMNs showed improved survival after resection compared with LN⁻ sporadic pancreatic adenocarcinomas, the natural history of LN⁺ invasive IPMNs mimicked that of LN⁺ sporadic pancreatic adenocarcinomas [48, 49]. Little is

known about the extent of LN dissection. Kobayashi et al. [50] suggested that D2 LN dissection should be recommended in patients with IPMNs with mural nodules demonstrating preoperative imaging findings for invasive carcinomas. D2 LN dissection might also be applied to IPMNs with mural nodules ≥ 10 mm in size, or with imaging findings suggestive of possible LN metastasis. Even in the absence of these factors, peripancreatic LN dissection (D1) at least might be advisable in IPMNs with mural nodules, because of the possibility of invasive carcinoma. Extended LN dissection did not benefit overall survival in patients with pancreatic ductal adenocarcinoma [51, 52]. However, no studies have reported on the effectiveness of extended LN dissection for invasive IPMNs, and further studies concerning the effectiveness of extended LN dissection in patients with invasive IPMNs are therefore needed.

Other authors have shown that the overall disease recurrence rates in patients with invasive IPMNs is 12–68% [3, 15–17, 19]. This meta-analysis revealed that the overall incidence of recurrence was 38.64%, which was much higher than in noninvasive IPMNs. The recurrence rate after surgical resection was significantly lower in the M⁻ group compared to the M⁺ group, and a similar trend towards decreased overall survival in patients with invasive IPMN and carcinoma at the resection margin was observed in the Johns Hopkins series [3]. However, this finding was not reproducible in two of the three subgroups in the sensitivity analysis, and it is possible that several risk factors contribute to recurrence after resection in invasive IPMNs, including LN metastases (mentioned above), as well as vascular and neural invasion. Nevertheless, Chari et al. [17] reported that 70% of patients with recurrence after complete resection had no nodal metastases or perineural or vascular invasion. This suggests that early extrapancreatic spread through micrometastases may occur in invasive IPMNs, as with pancreatic ductal adenocarcinoma. Recurrence in the form of disseminated disease (3.4–44%) is higher than isolated pancreatic remnant recurrence (0–15%) in invasive IPMNs [3, 15–17, 19], possibly be due to the high susceptibility of pancreatobiliary-type IPMNs to develop invasive tubular adenocarcinoma, which is inevitably responsible for the disseminated disease [44]. It is therefore unwise to perform total pancreatectomy to achieve M⁻. In contrast, Cuillerier et al. [12] suggested that total pancreatectomy may be preferred in the absence of manifest peripancreatic LN involvement, as no recurrence was observed in their 3 patients with invasive carcinoma. However, this radical approach needs to be confirmed in

a larger number of patients. Furthermore, the high risk of disease recurrence due to invasive pancreatobiliary-type IPMNs may indicate the requirement for adjuvant therapy.

There were several important limitations of this meta-analysis. First, the studies defined margin status in a variety of ways according to different classification standards, potentially contributing to the heterogeneity of risk ratios among studies. Second, the majority of the original data were not adjusted for potential confounders. The presence of vascular or neural invasion asserted their own independent risks to recurrence in invasive IPMNs. Failure to control for such confounders may lead to overestimation or underestimation of an effect if such factors are also related to the recurrence. Third, the included studies largely presented small numbers of relapsed patients with limited follow-up periods. These limitations of the previously published data could also potentially affect the results of the meta-analysis.

In conclusion, this meta-analysis demonstrated that the association between margins and the risk of recurrence is largely driven by M⁺ in all patients with IPMNs,

and that LN metastases provide a significant contribution to that risk in invasive IPMNs. We therefore conclude that segmental resection of noninvasive IPMNs to achieve M⁻ with no dysplasia is likely to have substantial benefits in terms of long-term local control. Extended LN dissection and pancreatectomy might reduce recurrence in the case of invasive carcinomas. However, prophylactic total pancreatectomy should be performed cautiously in both invasive and noninvasive IPMNs.

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