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Review

Intraductal papillary mucinous carcinoma versus pancreatic ductal adenocarcinoma: A systematic review and meta-analysis

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ABSTRACT

Background: Previous studies have indicated that there may be a difference in tumor biology between intraductal papillary mucinous carcinoma (IPMC) and pancreatic ductal adenocarcinoma (PDAC). However, the data are still controversial. The aim of this systematic review and meta-analysis was to summarize and compare the outcome of IPMC and PDAC after surgical resection.

Methods: Studies comparing IPMC and PDAC were identified using Medline and Embase search engines. Primary outcomes of interest were survival and recurrence. Secondary outcomes were clinicopathological characteristics. Meta-analysis of data was conducted using a random-effects model.

Results: A total of 14 studies were included. Pooled analysis revealed an improved 5-year overall survival (OS) for IPMC compared to PDAC (OR 0.23, 95% CI 0.09–0.56). Both colloid and tubular IPMC showed improved 5-year OS compared to PDAC (OR 0.12, 95% CI 0.05–0.25 and OR 0.38, 95% CI 0.26–0.54, respectively). Median survival time ranged from 21 to 58 months in the IPMC group compared to 12–23 months in the PDAC group. No meta-analysis could be performed on recurrence or on time-to-event data. Descriptive data showed no survival difference for higher TNM stages. IPMC was more often found at a TNM-stage of 1 (OR 4.40, 95% CI 2.71–7.15) and had lower rates of lymph node spread (OR 0.43, 95% CI 0.32–0.57).

Conclusion: Available data suggest that IPMC has a more indolent course with a better 5-year OS compared to PDAC. The histopathological features are less aggressive in IPMC. The reason may be earlier detection. However, for IPMC with higher TNM stages the survival seems to be similar to that of PDAC.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis as it is often diagnosed at a late stage and has an unusually aggressive biology [1,2]. Another type of pancreatic tumor is intraductal papillary mucinous neoplasm (IPMN). IPMN is a cystic tumor emerging from the cells lining the pancreatic ducts [3]. An IPMN that has progressed from high-grade dysplasia to adenocarcinoma is referred to as IPMN with an associated invasive carcinoma [3,4], and in this article hence shortened "IPMC".

The relationship between PDAC and IPMN is complex as they can arise independently or be genetically related. Having an IPMN lesion increases the risk of developing PDAC [5]. The anatomical location seems not to adequately state the relatedness between an invasive carcinoma and the IPMN [6].

IPMC can be classified into different histological subtypes based on the invasive component. The most common variants are the tubular and colloid subtypes [3]. The tubular or ductal subtype is often found to be more aggressive and has a morphology almost indistinguishable from conventional PDAC [7]. The colloid subtype demonstrates different morphology and has a better prognosis [8].

Surgical resection is the only potentially curative therapy for IPMC, as well as PDAC. However, only about 20% of PDAC patients are eligible for surgery at diagnosis [9]. The corresponding percentage for IPMC is less clear. The risk of an IPMN being invasive is based on certain preoperative criteria. Those with a low risk undergo surveillance and those with a high risk undergo surgery. In the case of an IPMC on final histopathology, the treatment and follow-up should be the same as for PDAC according to the most recent guidelines [8,10], which includes adjuvant therapy and surveillance to detect recurrence [9,11].

A meta-analysis published in 2014 reported an overall better prognosis for IPMC vs PDAC [12]. However, due to the lack of available data they were not able to compare the IPMC subtypes with PDAC and also did not perform a stage-matched analysis. Furthermore, recent studies indicate a relationship between noninvasive IPMN and PDAC that may be of predictive value (regarding survival [6] and recurrence

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[13]) following surgically resected PDAC. A better understanding of the similarities and differences between IPMC and PDAC may aid in improved risk stratification, patient counseling and postoperative surveillance.

The aim of this systematic review and meta-analysis was to summarize the latest collective evidence on the outcomes for surgically resected IPMC and conventional PDAC.

2. Methods

This study was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [14] and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines [15]. The MOOSE (Meta-analysis of Observational Studies in Epidemiology) checklist was also applied [16]. All stages from study identification to data abstraction were carried out independently by 2 reviewers (LA and AB). Any discrepancies were resolved by consulting a third and fourth reviewer (DA and RA).

2.1. Study identification

A systematic computerized search of relevant studies published between 2000 and December 2018 was conducted using the Medline and Embase databases using a pre-defined protocol and search strategy (available upon request). The search terms “pancreatic ductal adenocarcinoma” or “PDAC” and “IPMN” or “intraductal papillary mucinous neoplasm” and Medical Subject Headings (MeSH) were used. Articles were screened by titles and abstracts. Full text was obtained for potentially relevant articles. No contact with the authors was made. Only studies published in English were included. The literature search was completed in December 2018.

2.2. Study selection

Comparative studies, matched or unmatched, of IPMC and conventional PDAC that had undergone pancreatic surgery were evaluated. Studies were included if they reported comparative measures of at least one of the primary or secondary outcomes.

The exclusion criteria were: studies not reporting data on the selected outcomes; studies without a clear definition of the invasiveness of IPMN or the relation between IPMN and PDAC; studies that included high-grade dysplasia in the IPMC group; studies including patients that had not undergone surgery in the comparative analysis; non-human studies; case-reports and letters; conference abstracts; review articles; editorials; comments. In the case of overlap in patient cohorts of two studies measuring the same outcome, the most recent was included in the meta-analysis.

The overall risk of bias for the enrolled studies was deemed low as they compared types of pancreatic cancer and not different treatments.

2.3. Outcomes

The primary outcomes of interest were survival and recurrence. The following outcomes were reviewed: overall survival (OS); disease-specific survival (DSS); recurrence-free survival (RFS); recurrence rate. Additionally, we were interested in subgroup analysis on data on the primary outcomes made in matched and unmatched samples, between histological subtypes and PDAC, and PDAC with and without concomitant IPMN.

Secondary outcomes regarded the clinicopathological characteristics (age; gender; type of surgery; neoadjuvant therapy; level of carbohydrate antigen 19-9; TNM-stage; histological differentiation; concomitant non-invasive lesion; vascular, lymphatic or perineural infiltration; location; tumor-grade; nodal status; resection status; size of tumor and invasive component) and postoperative management (adjuvant therapy and re-operation). These were evaluated to assess relevant factors impacting the prognosis and primary outcomes.

2.4. Data extraction

Data collected from each eligible study included: first author, year of publication, study location (hospital/s, country), study period, number of IPMC and conventional PDAC, our predefined primary and secondary outcomes as well as the inclusion and exclusion criteria as described above.

2.5. Statistical analysis

The meta-analysis was conducted using the software Review Manager (RevMan, version 5.3: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Due to lack of presentation on time-to-event data, pooled hazard ratio (HR) could not be calculated and the data are presented in a descriptive way. The odds ratio (OR) with 95% CI was calculated for dichotomous variables, including 5-year OS. For survival analyses an event was classified as “death”. Data were extracted directly, or when not reported, the raw data (number of patients and event rates) were used to calculate the OR. The results were considered statistically significant at P level of < 0.05 if the 95% CI did not cross the value 1. A random-effects model was chosen for all analyses due to a majority of included studies being from a single center as well as expected differences in demography, hospital volume, and health care systems. The heterogeneity across studies, assessed using the Higgins' I^2 and chi^2 test, are presented for each analysis.

Parameters directly matched (or when deemed closely related) were not included in pooled analysis with data of unmatched cohorts if not otherwise specified. Median survival time, recurrence time and recurrence rate were presented in a descriptive overview.

3. Results

Our search generated 5578 articles of which 32 full text articles were screened and a total of 14 studies were deemed eligible for inclusion [17–30] (see Fig. 1 and Table 1). Reasons for exclusion were inclusion of high-grade dysplasia [31], selection of specific cases (only patients with recurrence/borderline resectable) [32,33], no postoperative comparison between IPMC and PDAC [34–38], inclusion of patients that had not undergone surgery [39,40], uncertain classification [41,42] same study population in already included study [43], and limited data only for descriptive analysis [44,45]. Additionally, five studies compared PDAC with and without concomitant [6,13,28,46,47]. However meta-analysis on the data of concomitant IPMN could not be performed due to different outcome measures and rather different definitions.

3.1. Primary outcomes

Five studies [17,19,21,25,26] showed survival data from regression analysis. However, pooled analysis could not be performed because only one study presented data on univariable analysis [21]. The results though, shown in a descriptive manner in Table 2, demonstrate a significantly improved survival in IPMC compared to PDAC even in multivariable analysis.

The 5-year overall survival (OS) was significantly better for IPMC compared to PDAC (OR 0.23, 95% CI 0.09–0.56), see Fig. 2 and Table 4. It remained significant even when sub-analyzing those that were matched, not matched, and had exclusion of postoperative death, see Table 4 and supplementary information.

Generally, the studies did show a better prognosis for those with IPMC compared to PDAC with a median survival time of 21–58 months and 12–23 months respectively, Table 3. However, the difference was not significant when comparing lymph node positive disease and that of higher TNM-stage, see Table 3.

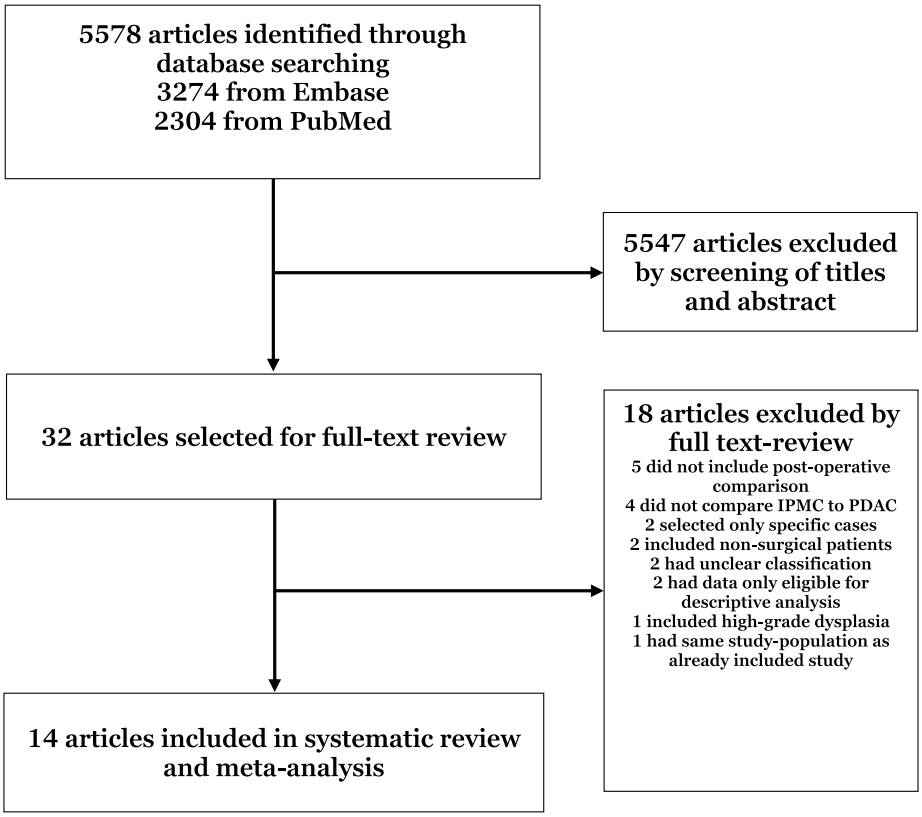

Fig. 1. PRISMA flow chart of the study selection process.

The 5-year OS was significantly different in pooled analysis comparing colloid IPMC and PDAC as well as tubular IPMC and PDAC (OR 0.12, 95% CI 0.05–0.25 and OR 0.38, 95% CI 0.26–0.54 respectively), see Table 4.

Only one study did report a comparison regarding recurrence, see Table 3. In this matched study, 42% of the IPMC and 37% of the PDAC did recur during a mean follow up of 28 and 26 months, respectively [18]. Disease-free months were 28 for IPMC and 12.5 for PDAC ($p < 0.01$) [17].

3.2. Secondary outcomes

Pooled analysis showed no difference regarding gender (OR 1.06, 95% CI 0.97–1.15). Total pancreatectomy was more often performed for IPMC (OR 1.55, 95% CI 1.36–1.77) and a positive resection margin was less frequent in surgery for IPMC (OR 0.53, 95% CI 0.36–0.78). Three studies [19,23,26] were included in both of the aforementioned pooled analyses (five studies in each pooled analysis). Age, tumor size and carbohydrate antigen 19-9 (CA19-9) are shown in a descriptive

Table 1
Overview of studies included in the meta-analysis.

1st author/year/country	Design	Study interval	Staging system	No. of IPMC/ PDAC	Matched	Postoperative mortality excluded
Yamada/2018/Japan [17]	Single RCS	2001–2016	AJCC 7th	73/375	No	NR
Duconseil/2017/France [18]	Multicenter RCS	2005–2012	AJCC 7th	82/164	Yes (stage, LNR, margin status, perineural invasion)	NR
McMillan/2016/USA [19]	Multicenter RCS	1998–2010	AJCC 5-7th (NCDB)	1220/15409	No	Yes (30d)
Takeshita/2012/Japan [30]	Single RCS	1998–2007	NR	17/45	No	NR
Waters/2011/USA [26]	Multicenter RCS	1989–2009	AJCC 7th	113/845	No	NR
Yamaguchi/2011/Japan [28]	Multicenter RCS	1987–2009	JPS	201/7605	No	NR
Yopp/2011/USA [29]	Single RCS	1983–2007	NR	59/59	Yes (nomogram)	NR
Mino-Kenudson/2011/USA [21]	Single RCS	1990–2008	AJCC 6th	61/570	No	Yes (30d)
Wasif/2010/USA [25]	Multicenter RCS	1991–2005	AJCC 6th (SEER)	729/8082	No	NR
Poultsides/2010/USA [23]	Single RCS	1995–2006	AJCC unspecified	132/1128	No	Yes (30d)
Murakami/2009/Japan [22]	Single RCS	1990–2007	AJCC 6th	16/106	No	Yes**
Woo/2008/South Korea [27]	Single RCS	1999–2006	AJCC 6th	19/174	No	Yes (no 30d mortality)
Shimada/2006/Japan [24]	Single RCS	1992–2004	AJCC 5th	18/274	No	-
Maire/2002/France [20]	Multicenter RCS	1987–1999	AJCC 4th	49/49	Yes (age, stage)	Yes (30d)
Overall				2789/34885		

AJCC, American Joint Committee on Cancer; IPMC, intraductal papillary mucinous neoplasms with an associated invasive carcinoma; JPS, Japan Pancreas Society; LNR, lymph node ratio; NCDB, national cancer database; NR, not reported; OS, overall survival; PDAC pancreatic ductal adenocarcinoma; RCS, retrospective cohort study; SEER, surveillance epidemiology and end results.
*Reported in the IPMC group, but not in the PDAC group.

Table 2
Studies presenting survival data using cox regression analysis.

Study	No. of IPMC/PDAC	Univariable HR (95% CI)	Multivariable HR (95% CI)	Co-variates reported in multivariable analysis
Yamada [17]	73/375	0.28 (0.17–0.45)[a]	0.38 (0.23–0.61)	Age < 65 or ≥65, gender, tumor location head vs other, PD vs other, LN status 0 vs 1a/1b
McMillan [19]	1220/15409	-	0.73 (0.68–0.78)[b]	-
Mino-Kenudson [21]	61/570	0.38 (0.26–0.54) Stage matched: 0.43 (0.30–0.62)	0.58 (0.39–0.86)	Tumor type, grade, lymphatic and vascular invasion, margin status
Wasif [25]	729/8082	-	0.76 (0.67–0.87)[b]	Age, tumor location, type of surgery, histology, tumor grade, tumor size, LN status
Waters [26]	113/845	-	0.73 (0.55–0.97)	Age, margin, size ≥ 2 cm, LN status, stage

CI confidence interval; HR, hazard ratio; IPMC, intraductal papillary mucinous neoplasms with an associated invasive carcinoma; LN, lymph node; PD pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma.
[a] Propensity score used in the analysis.
[b] The hazard ratios were inverted for easier interpretation with PDAC as reference.

manner in Table 5. Only one study [18] reported a comparison of CA19-9 levels, which was matched and showed no statistical difference.

IPMC were more often of lower TNM-stage (stage 1 versus higher TNM-stage) (OR 4.40, 95% CI 2.71–7.15) and lower tumor grade (poor vs other) (OR 0.51, 95% CI 0.44–0.59), had less often lymph node spread (OR 0.43, 95% CI 0.32–0.57), perineural invasion (OR 0.25, 95% CI 0.10–0.63), vascular invasion (OR 0.46, 95% CI 0.33–0.64) and lymphatic invasion (OR 0.25, 95% CI 0.03–2.08). IPMC seemed to receive adjuvant therapy in the same extent as PDAC (OR 0.67, 95% CI 0.34–1.30). The results from the pooled analyses are shown in Table 3. Three studies [17–19] explicitly mentioned excluding patients receiving neoadjuvant therapy (Table 3).

4. Discussion

This systematic review and meta-analysis demonstrates an improved survival following surgery for patients with a histopathological diagnosis of IPMN with an associated adenocarcinoma (IPMC) compared to pancreatic ductal adenocarcinoma (PDAC). A total of 14 studies were included, totaling 2,789 patients with IPMC and 34,885 patients with PDAC, respectively. Only patients that had undergone surgery were included as our primary aim was to compare the outcome in patients with a histopathologically confirmed diagnosis.

The pooled analysis showed an improved 5-year OS for IPMC compared to PDAC (OR 0.23, 95% CI 0.09–0.56). Unfortunately, pooled analyses could neither be performed for time-to-event data nor subgroups of AJCC TNM stages. All studies that performed a multivariable regression analysis found a significantly improved survival for IPMC compared to PDAC (Table 2). However, in the descriptive overview in Table 3, the survival differences observed between IPMC and PDAC in the entire cohort do not remain when higher AJCC TNM stages and those with lymph node spread are evaluated. Five-year OS was significantly better for IPMC in matched patients in the pooled analysis. However, there was no significant difference in median survival in the matched study performed by Duconseil et al. [18] or by a matched study from the Mayo Clinic by Schnelldorfer et al. [43].

Pooled analysis showed significantly better 5-year OS when comparing IPMC with tubular differentiation and PDAC (OR 0.38, 95%CI 0.26–0.54), which may be in contrast to former studies. However, only three studies were included in the pooled analysis.

The recurrence rate was seldom presented and only Duconseil et al. [18] reported an actual comparison. Yamada et al. [17] showed that PDAC had significantly lower disease-free survival (DFS) (Table 3). The DFS was comparable between groups in the study by Duconseil et al. [18], but showed a significant difference in the unmatched cohort of Yamada et al. [17]. However, in their series, when stratified by stage, the DFS was not significant in stage I (both in univariable and multivariable analysis), but was significant in stage II (both in univariable and multivariable analysis) [17].

The disease-specific survival (DSS) was compared by Sadakari et al. [44] and Wada et al. [45] in studies that matched for TNM-stage. The former study reported a significantly different 5-year DSS (IPMC 32% vs PDAC 20%, $p = 0.027$), while the latter study showed no statistical difference ($p = 0.11$).

According to the data it seems that PDAC has an inherent aggressive biology with higher incidence of lymph node spread, microinvolvement (vascular, perineural, and lymphatic invasion), more advanced AJCC TNM-stage and higher rate of positive resection margin compared to IPMC (Table 4), which may explain the overall worse survival in PDAC compared to IPMC. Molecular differences between the entities have been shown, taking into account the histological subtype of IPMC [48–50]. However, IPMC seems to be found and thus surgically resected at an earlier stage, which suggests that these lesions are more easily detected at radiological assessments (incidentalomas or found during surveillance of former low-risk classified cyst) and/or more prone to cause symptoms. The reason for finding the lesion was not addressed in

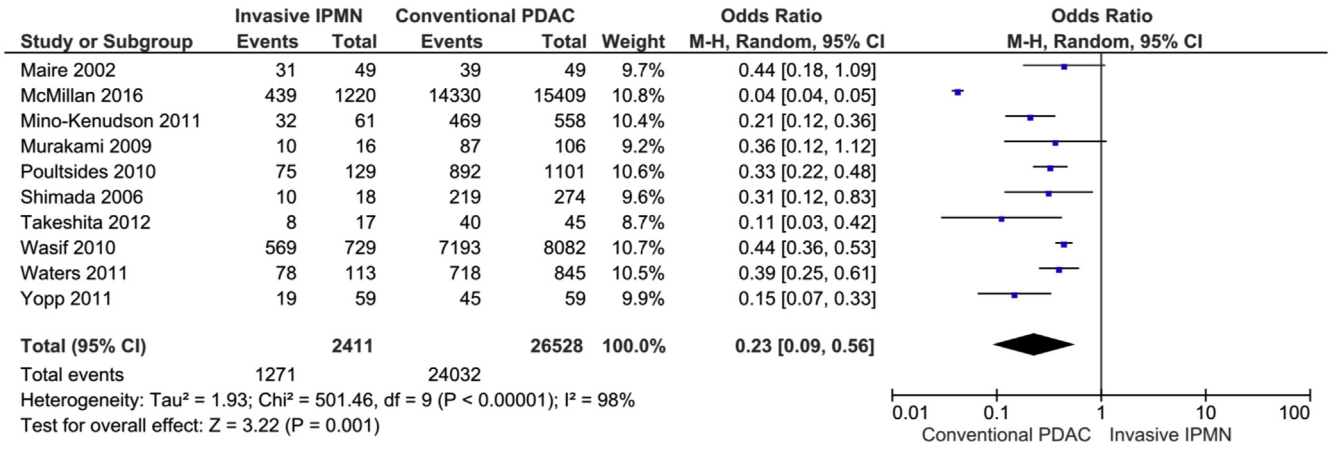

Fig. 2. Five-year overall survival comparing IPMC and PDAC.

any of the included studies.

Total pancreatectomy was more often performed in IPMC compared to PDAC and may indicate the tendency of multifocal disease in IPMC [5].

We were unfortunately unable to compare and analyze PDAC with a "concomitant" IPMN as opposed to PDAC "derived from" IPMN due to differences in definition and data presentation. As previously mentioned, a noninvasive IPMN may have a predictive postoperative value in PDAC [6,13] and it is recommended to try to state the relationship between the PDAC and IPMN [7]. Genetic analysis may be needed to classify relatedness [6,51]. The incidence of synchronous PDAC and IPMN has been described in approximately 5% [39,47,52]. Interestingly, Poultsides et al. [23] explicitly state that no concomitant IPMN was found in their PDAC specimens.

The role of adjuvant therapy could in the scope of this study not be fully investigated. Our pooled analysis showed no difference in the administration of adjuvant therapy. No sub-analysis regarding regimen (chemotherapy and/or radiotherapy) or the impact on survival could be performed. The literature is scarce regarding adjuvant therapy for IPMC, but the existing studies suggest improved survival for IPMC with higher AJCC TNM-stage, lymph node spread or tubular differentiation [18, 19, 53, 54].

Several limitations need to be pointed out. All included studies were of retrospective nature, leading to potential selection bias. Two studies were based on data from databases [19,25], which leads to an increased risk of sampling error. However, they both included large sample sizes. Eight of the 13 included studies had a relatively limited sample size of fewer than 100 patients in the IPMC group. The lack of data and heterogeneity between studies limited our pooled analysis. However, in line with our goal of transparency, all data are descriptively presented. We sought to make sound analysis by taking several factors that largely impact the results into account, such as if the study was matched and if postoperative mortality was excluded. The different versions of AJCC TNM-stage (from the 4th to the 7th version) may impact the comparability between studies. We did only include studies published in English, which entails a risk of missing studies, however, to our knowledge the major guidelines [8,10] also only reference to articles published in English.

5. Conclusion

The findings of this systematic review and meta-analysis demonstrate an improved postoperative survival for IPMC compared to PDAC. The survival benefit for resected IPMC is substantial at earlier stages, a difference that disappears at higher stages. Future prospective studies need to evaluate the benefit of adjuvant therapy for IPMC. The relationship between IPMN and PDAC does also merit further investigation.

Data statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Provenance and peer review.

Not commissioned, externally peer-reviewed.

Ethical approval

Not applicable (systematic review/meta-analysis).

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Author contribution

Study design: LA, RA, DA.
Literature search, study selection and data extraction: LA, AB.
Drafting of manuscript: LA, AB.
Statistical analysis: WT.
Critical revision: RA, DA.

Conflicts of interest

None.

Trial registry number

Registered in Research Registry.
Unique Identifying Number: reviewregistry716.
Hyperlink:
https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5d1cc373555e5c0010dee50a/

Guarantor

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Table 3
Postoperative recurrence and survival data for included studies.

Study	No. of IPMC/PDAC	Matched	Adjuvant therapy	Recurrence rate (%), IPMC/PDAC	Median survival (months), IPMC/PDAC			DFS (months), IPMC/PDAC
					Entire cohort	LN metastasis	Higher TNM stages	
Yamada [17]	73/375	No	Yes*, neoadjuvant excluded	–	–	–	Stage II: 32/23 (NS)	28/12 HR (U): 0.31 (95% CI 0.21–0.47) HR (M): 0.43 (95% CI 0.29–0.64)
Duconseil [18]	82/164	Yes	Yes, neoadjuvant excluded	42%/37%	–	–	–	HR (U)**: 0.61 (95% CI 0.43–1)
McMillan [19]	1220/15409	No	Yes, neoadjuvant excluded	–	29/16.5 (S)	16/14.5 (S)	Stage II: 24.5/17.5 (S) Stage III/IV: 15/13.5 (NS)	–
Takeshita [30]	17/45	No	–	–	–	–	–	–
Waters [26]	113/845	No	–	–	32/17 (S)	–	Stage II a: 23/23 (NS) Stage II b: 20/15 (NS)	–
Yamaguchi [28]	201/7605	No	–	–	46/12 (S)	–	Stage II/III: 46/11 (S)	–
Yopp [29]	59/59	Yes	–	–	–	–	–	–
Mino-Kenudson [21]	61/570	No	–	–	58/18 (S)	–	–	–
Wasif [25]	729/8082	No	–	–	21/14 (S)	15/13 (NS)	Stage II a: (−) (S) Stage II b: (−) (NS)	–
Poultsides [23]	132/1128	No	–	–	43/19 (S)	20/18 (NS)	Stage II: 45/34 (NS) Stage III: 23/19 (NS)	–
Murakami [22]	16/106	No	Yes (1 IPMC/62 PDAC)	50%/-	37.5/13 (S)	–	Stage II a + b: (−) (S)	–
Woo [27]	19/174	No	–	16%/-	–	–	–	–
Shimada [24]	18/274	No	–	–	46/17 (S)	–	–	–
Maire [20]	49/49	Yes	Yes	38%/-	33/22 (S)	–	–	–
Overall	2789/34885				Range: 21–58/12-23	Range: 15–20/13-18		

AJCC, American Joint Committee on Cancer; DFS, disease-free survival; HR (M), hazard ratio in multivariable analysis (included factors may vary between studies); HR (U), hazard ratio in univariable analysis; IPMC, intraductal papillary mucinous neoplasm with an associated invasive carcinoma; NS, no statistical significant difference in log rank test (≥0.05); PDAC, pancreatic ductal adenocarcinoma; S, statistically significant difference in log rank test ($p < 0.05$); TNM, tumor-node-metastasis.
*Chemotherapy only administered to those with PDAC.
**The hazard ratios were inverted for easier interpretation with PDAC as reference.

Table 4
Univariable meta-analysis of 5-year overall survival and clinicopathological variables in patients with PDAC and IPMC.

Parameters	No. of studies	IPMC (event[a])	PDAC (event[a])	Heterogeneity		Overall effect	
				I^2	P	OR (95% CI)[b]	P
Survival data							
5y-OS	10	2411 (1271)	26528 (24032)	98%	< 0.001	0.23 (0.09–0.56)	0.001
5y-OS (matched)	2	108 (50)	108 (84)	68%	0.08	0.25 (0.09–0.73)	0.01
5y-OS[c]	3	860 (657)	9201 (8130)	0%	0.74	0.43 (0.36–0.51)	< 0.001
5y-OS[d]	4	1426 (556)	17174 (15778)	98%	< 0.001	0.17 (0.05–0.67)	0.01
PDAC vs colloid IPMC 5y-OS	3	74 (24)	1718 (1406)	44%	0.17	0.12 (0.05–0.25)	< 0.001
PDAC vs tubular IPMC 5y-OS	3	162 (98)	1718 (1406)	0%	0.69	0.38 (0.26–0.54)	< 0.001
Clinicopathological data							
Gender (male)	11	2520 (1339)	34613 (18418)	0%	0.54	1.06 (0.97–1.15)	0.18
Total vs partial pancreatectomy	5	2267 (290)	25839 (2285)	93%	< 0.001	1.55 (1.36–1.77)	< 0.001
Resection margin (positive)	5	1473 (289)	17236 (4495)	64%	0.03	0.53 (0.36–0.78)	0.001
AJCC TNM1 vs higher	7	2450 (695)	34014 (3729)	93%	< 0.001	4.40 (2.71–7.15)	< 0.001
Tumor grade poor vs other	2	1078 (255)	15611 (5878)	0%	0.64	0.51 (0.44–0.59)	< 0.001
Lymph node spread	10	2503 (1088)	33841 (21301)	85%	< 0.001	0.43 (0.32–0.57)	< 0.001
Perineural invasion	3	212 (124)	1872 (1479)	83%	0.003	0.25 (0.10–0.63)	0.004
Vascular invasion	2	193 (54)	1698 (769)	0%	0.76	0.46 (0.33–0.64)	< 0.001
Lymphatic invasion	2	80 (16)	744 (281)	76%	0.04	0.25 (0.03–2.08)	0.20
Adjuvant therapy							
Adjuvant therapy	6	2169 (1000)	24185 (10315)	95%	< 0.001	0.67 (0.34–1.30)	0.23

AJCC, American Joint Committee on Cancer; I^2, Higgins' test, IPMC, intraductal papillary mucinous neoplasm with an associated invasive carcinoma; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TNM, tumor-node-metastasis.
[a] number of patients with the specific outcome studied.
[b] Result of pooled analysis.
[c] Not matched and excluding postoperative death.
[d] Not matched and including or no report on postoperative death.

Table 5
Reported age, tumor size and carbohydrate antigen 19-9.

Study	Age, mean (SD)		Tumor size in mm, mean (SD)		CA 19-9, mean (SD)	
	IPMC	PDAC	IPMC	PDAC	IPMC	PDAC
Yamada [17]	68 (9.1)	64.5 (9.7)	32.5 (24.1)	NR	346 (981)	NR
Duconseil [18]	67 (1.03)	65 (11.8)	26.7 (1.86)	26 (2.11)	971 (475)	634 (1725)
Waters [26]	68 (41–93)[a]	65 (38–96)[a]	33 (2.2)[c]	30 (1.4)[c]	NR	NR
Mino-Kenudson [21]	70.5 (9.6)	66 (10.4)	Size > 10: 43/61	Size > 10: 522/570	NR	NR
Takeshita [30]	68.5 (25–79)[a]	65.2 (42–79)[a]	NR	NR	NR	NR
Yamaguchi [28]	66.5 (8.4)	63.5 (9.9)	NR	NR	NR	NR
Wasif [25]	64 (13.2)[b]	65 (11.0)[b]	45 (30)	35 (20)	NR	NR
Poultsides [23]	70 (35–85)	67 (32–92)	26 (1–80)[b]	30 (1–155)[b]	NR	NR
Woo [27]	62 (10.0)	61.5 (9.4)	46 (33)	35 (18)	[d]	[d]
Shimada [24]	68 (8)	62 (10)	21 (12)	40 (17)	56% < 37 U/mL	NR
Marie [20]	64 (38–81)[b]	NR	36 (10–130)[b]	NR	16/50 ≥ 2 ULN	NR
McMillan [19]	Age > 76 years: 196/1220	Age > 76 years: 2322/15409	Size > 20: 955/1119	Size > 20: 12528/14253	NR	NR
Yopp [29]	Age > 70 years: 29/59	Age > 70 years: 22/59	Size ≥10: 46/59	Size ≥10: 54/59	NR	NR
Murakami [22]	Age ≥70 years: 11/16	Age ≥70 years: 46/106	Size ≥20: 9/16	Size ≥20: 92/106	NR	NR
Overall	Mean age range: 62–70.5	Mean age range: 61.5–67	Mean size range: 21–45	Mean size range: 26–40	-	-

CA 19-9, carbohydrate antigen 19-9; IPMC, intraductal papillary mucinous neoplasm with an associated invasive carcinoma; NR not reported; PDAC, pancreatic ductal adenocarcinoma; SD standard deviation; ULN, upper limit of normal.
[a] range instead of SD.
[b] median and range instead of mean and SD.
[c] standard error of the mean instead of SD.
[d] CA19-9 > 37 U/mL for the whole cohort and not only in those that underwent surgery (16/29 IPMC, 213/287 PDAC).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.09.014.

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