



Limited resection vs. pancreaticoduodenectomy for primary duodenal adenocarcinoma: a systematic review and meta-analysis

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Abstract

It is well known that surgery is the mainstay treatment for duodenal adenocarcinoma. However, the optimal extent of surgery is still under debate. We aimed to systematically review and perform a meta-analysis of limited resection (LR) and pancreaticoduodenectomy for patients with duodenal adenocarcinoma. A systematic electronic database search of the literature was performed using PubMed and the Cochrane Library. All studies comparing LR and pancreaticoduodenectomy for patients with duodenal adenocarcinoma were selected. Long-term overall survival was considered as the primary outcome, and perioperative morbidity and mortality as the secondary outcomes. Fifteen studies with a total of 3166 patients were analyzed; 995 and 1498 patients were treated with limited resection and pancreaticoduodenectomy, respectively. Eight and 7 studies scored a low and intermediate risk of publication bias, respectively. The LR group had a more favorable result than the pancreaticoduodenectomy group in overall morbidity (odds ratio [OR]: 0.33, 95% confidence interval [CI] 0.17–0.65) and postoperative pancreatic fistula (OR: 0.13, 95% CI 0.04–0.43). Mortality (OR: 0.96, 95% CI 0.70–1.33) and overall survival (OR: 0.61, 95% CI 0.33–1.13) were not significantly different between the two groups, although comparison of the two groups stratified by prognostic factors, such as T categories, was not possible due to a lack of detailed data. LR showed long-term outcomes equivalent to those of pancreaticoduodenectomy, while the perioperative morbidity rates were lower. LR could be an option for selected duodenal adenocarcinoma patients with appropriate location or depth of invasion, although further studies are required.

Keywords Duodenal cancer · Duodenal adenocarcinoma · Surgery · Limited resection · Pancreaticoduodenectomy

Introduction

Duodenal adenocarcinoma is a rare tumor that accounts for less than 0.5% of all cases of gastrointestinal cancer. Nevertheless, the duodenum is the most common location for adenocarcinoma of the small bowel, followed by the jejunum

and the ileum [1–5]. Duodenal adenocarcinoma has a reported 5-year survival rate for resected tumors of 25–75% [6–23], which is significantly better than that of other periampullary cancers. Surgery is the mainstay treatment for duodenal adenocarcinoma and several surgical strategies, including endoscopic resection, partial (wedge) resection, segmental (limited) resection, and pancreaticoduodenectomy (PD), are used to treat duodenal adenocarcinoma depending on the location or the depth of tumor invasion. Although PD enables a more extensive removal of the regional lymph nodes, it is often associated with a higher incidence of postoperative morbidity and mortality when compared with segmental resection [24]. Partial (wedge) resection and segmental resection are usually indicated for select tumors with no risk of lymph node metastasis but are not suitable for endoscopic resection [25, 26]. Even though the incidence

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of such tumors has increased because of the advances in endoscopic and radiologic diagnostic modalities, the optimal extent of surgery for duodenal adenocarcinoma remains an issue for debate.

The aim of this study was to perform a systematic review and meta-analysis of studies that compared limited resection (LR) with PD for patients with primary duodenal cancer, with long-term overall survival as the primary outcome and perioperative morbidity and mortality as the secondary outcomes.

Materials and methods

The PRISMA [27] checklist for systematic reviews and meta-analyses were followed to conduct this study.

Information resources

An electronic database search was performed to identify published studies from inception to January 2020 using PubMed and the Cochrane Library.

Search strategy

Both free text and MESH terms were used for searching relevant studies. The keywords used were ‘duodenal neoplasm’, ‘duodenal cancer’, and ‘duodenal adenocarcinoma’ combined with ‘pancreatoduodenectomy’, ‘pancreaticoduodenectomy’, ‘duodenal neoplasms/surgery’, ‘duodenopancreatectomy’, ‘partial resection’, ‘segmental resection’, ‘limited resection’, and ‘simple resection’ using the Boolean operator ‘AND’ (Fig. 1).

Inclusion criteria

To be included in the analysis, the studies had to include:

1. A comparison between LR and PD
2. Primary adenocarcinoma of the duodenum at diagnosis (clearly documented)
3. Adverse early postoperative events including 30-day postoperative mortality, overall postoperative complications, such as procedure related complications (anastomosis leakage, pancreatic fistula, biliary fistula, fluid collection, and abscess) and general complications (wound infection, ileus, acute renal failure, urinary tract infections, delirium, and respiratory, and cardiovascular complications)
4. Long-term outcomes including overall survival

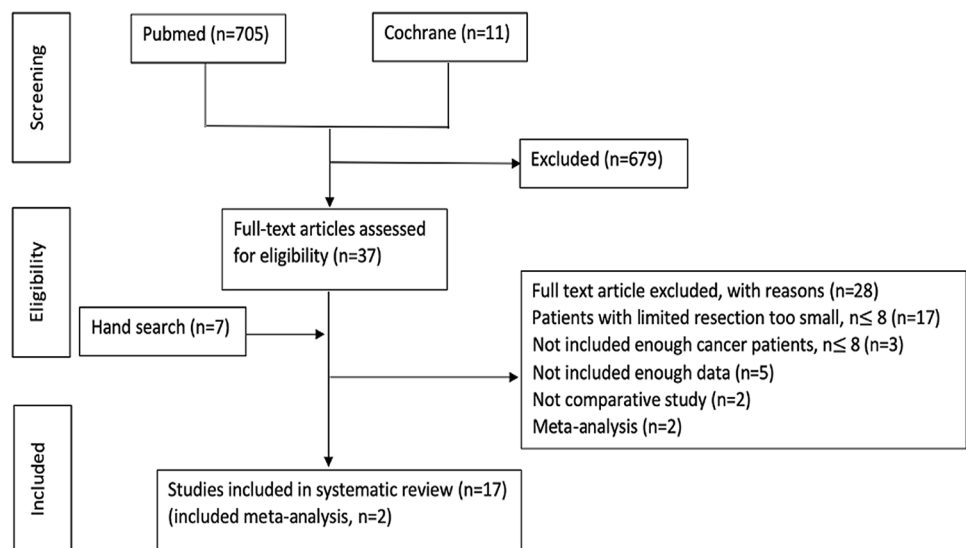
Exclusion criteria

Studies were excluded from the analysis if: (a) the outcomes of interest were not clearly reported; (b) it was impossible to extract or calculate the necessary data from the published results; and (c) the sample size was ≤ 8 .

Data extraction

Five reviewers (P.B., R.H., S.N, S.K, and H.E) independently extracted the following data variables from each study: first author, country, year of publication, study population characteristics including age and gender, study design, inclusion and exclusion criteria, length of follow-up, and number of subjects undergoing LR and PD. There was 100% agreement on the collected data among the five reviewers.

Fig. 1 Article selection process



Statistical analysis

Meta-analysis was conducted by the Review Manager (Rev-Man) Meta-analysis software, v. 5.1.6. The 95% confidence intervals (CIs) were calculated as estimates of precision for odds ratio (OR). The statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. The dichotomous variables were analyzed based on ORs with 95% CI. For the outcomes being considered, the reference categories were selected such that an $OR < 1$ favored the LR approach. The studies were weighted in the meta-analysis by the inverse variances of their effect estimates, that is, the validities of the included studies. Heterogeneity was considered not statistically significant when the Cochrane Q test P value was > 0.1 . The I^2 statistic, a transformation of the Q test, was used to assess the consistency of the effect sizes. In case of heterogeneity, meta-analysis was performed using the random-effects model. In addition, an I^2 value of less than 25% was defined as low heterogeneity, a value between 25 and 50% was defined as moderate heterogeneity, and a value of $> 50\%$ was defined as high heterogeneity [28]. In cases of I^2 values less than 30%, fixed effects models were used throughout. Analysis of long-term survival was performed by obtaining the numbers at risk and combined with either the quoted survival rates or the values read from enlarged plots of the Kaplan–Meier curves to produce the estimates. Where numbers at risk were not quoted, constant censoring over the period of follow-up was assumed in the estimation. A meta-analysis of long-term survival from the included studies using hazard ratios could not be performed because only one study (Cloyd et al.) [19] reported the hazard ratio between the LR and PD groups. The other included studies may have had an insufficient number of patients to perform a multivariate analysis. Funnel plots with an Egger test were used to screen for publication bias.

Assessment of study quality

The methodological quality of all the included studies was assessed with the validated Newcastle–Ottawa scale [29]. Studies scoring > 6 were considered to be high quality and the maximum score was 9.

Definition LR was defined as one of following surgical procedures: transduodenal excision [30], partial/full thickness resection (wedge resection) or pancreas-sparing segmental duodenectomy (PSD) [31–35]. PD (Whipple's procedure) [36] is the standard procedure to treat periampullary tumors and other benign disorders that require removal of the distal bile duct, the duodenum (or some parts of the stomach), and the head of the pancreas. Morbidity was classified using the Clavien–Demartines–Dindo system [37]. Postoperative pancreatic fistula (POPF), post pancreatectomy hemorrhage

(PPH), and delayed gastric emptying time (DGE) were defined according to the International Study Group (ISGPF) criteria [38–40]. Postoperative mortality was defined as death within 30 days of surgery from any cause.

Results

Selection of trials and patient's characteristics

Fourteen studies were retrospective cohort studies and one was a prospective cohort study. No randomized controlled trial was found in our search. The Newcastle–Ottawa scale (NOS) was used for quality assessment.

This analysis comprised 15 studies with a total of 3166 patients, of which 995 patients (31.4%) were treated by LR and 1498 patients were treated by PD (Tables 1 and 2). The patient classifications for each surgical procedure according to tumor depth and location are summarized in Supplementary Table 3. Patients who were selected for LR had a higher percentage of tumors in the third and fourth portion of the duodenum (available data from five studies) and a slightly higher percentage of T1-stage tumors (available data from three studies). The indications for LR and classification of LR procedures are summarized in Supplementary Table 4. Most of the indications for LR were tumors located in the third or fourth portion of the duodenum and a T1a/T1b-stage tumor.

Perioperative outcomes

To evaluate the safety of the procedure of the LR group and the PD group, the ORs of postoperative mortality and morbidity were calculated using the data extracted from the 13 included studies, including 951 patients in the LR group and 1340 patients in the PD group.

Morbidity

The meta-analysis showed more a favorable result in the LR group than in the PD group in terms of overall morbidity (OR: 0.33, 95% CI 0.17–0.65) and occurrence of postoperative pancreatic fistula (OR: 0.13, 95% CI 0.04–0.43) (Fig. 2a, b).

Mortality

The meta-analysis showed no significant difference between the LR group and the PD group in terms of mortality (OR: 0.96, 95% CI 0.70–1.33) (Fig. 3). It should be noted that the patients in the study by Cloyd et al. [19] had a markedly higher weight than other studies; therefore, we performed a sensitivity analysis after excluding the data from the Cloyd

Table 1 Demographic and study characteristics of the studies included in the meta-analysis

Author	Study period	Country	Study design	Age (mean, range)	Male gender (N,%)	Number of patients (N,%)		
						Total	LR	PD
Joesting (1981)	1937–1977	USA	Retrospective cohort	–	56 (53.8%)	104	13 (12.5%)	40 (38.5%)
Barnes (1994)	1967–1991	USA	Retrospective cohort	^a 56(30–83)	44 (65.7%)	67	9 (13.4%)	27 (40.3%)
Santoro (1997)	1980–1994	Italy	Retrospective cohort	56(25–88)	47 (52.8%)	89	26 (29.2%)	37 (41.6%)
Sohn (1998)	1984–1996	USA	Retrospective cohort	61.4(33–89)	32 (58%)	55	13 (23.6%)	35 (63.6%)
Bakaeen (2000)	1976–1996	USA	Retrospective cohort	62	51 (50.5%)	101	18 (17.8%)	50 (49.5%)
Kaklamanos (2000)	1979–1998	USA	Retrospective cohort	61(23–96)	33 (52.4%)	63	12 (19.0%)	25 (39.7%)
Tocchi (2003)	1980–2000	Italy	Retrospective cohort	57.6(42–73)	26 (55.3%)	47	16 (34%)	9 (19.1%)
Cecchini (2012)	1982–2010	USA	Retrospective cohort	^a 67(22–91)	93 (55%)	169	14 (8.2%)	87 (51.5%)
Onkendi (2012)	1994–2009	USA	Retrospective cohort	65(33–87)	75 (59%)	124	28 (22.6%)	46 (37%)
Kato (2014)	1992–2011	Japan	Retrospective cohort	^a 64(47–77)	25 (71.4%)	35	15 (42.9%)	20 (57.1%)
Rangelova (2015)	2006–2011	Sweden	Prospective cohort	–	–	389	20 (5.1%)	81 (20.8%)
Cloyd (2015)	1988–2010	USA	Retrospective cohort	–	745 (46.2%)	1611	746 (46.3%)	865 (53.7%)
Jiang (2016)	1999–2015	China	Retrospective cohort	–	78 (69.9%)	201	16 (8%)	112 (55.7%)
Kohga (2017)	2002–2014	Japan	Retrospective cohort	–	42 (65.6%)	64	33 (51.6%)	31 (48.4%)
Lee (2018)	2004–2014	Australia, UK	Retrospective cohort	^a 64(36–82)	20 (42.6%)	47	16 (34%)	33 (70.2%)

LR limited resection, PD pancreaticoduodenectomy

^aData in median

study, which showed that the LR group had a more favorable outcome compared to the PD group in terms of mortality (OR: 0.39, 95% CI: 0.16–0.94) (Supplementary Fig. 5).

Long-term outcomes

Overall survival was calculated using the data extracted from Kaplan–Meier curves from eight studies including 855 patients in the LR group and 1101 patients in the PD group.

The meta-analysis showed no significant difference in overall survival between the LR group and the PD group (OR: 0.61, 95% CI 0.33–1.13; Fig. 4).

Publication bias and quality of the included studies

The results of the test for publication bias are presented in Supplemental Figs. 1–4. A publication bias in term of mortality may exist in this present study ($P = 0.05035$). The

results of the quality assessment test of the included studies are shown in Fig. 5. Eight studies had a low risk of bias and seven studies had an intermediate risk of bias.

Discussion

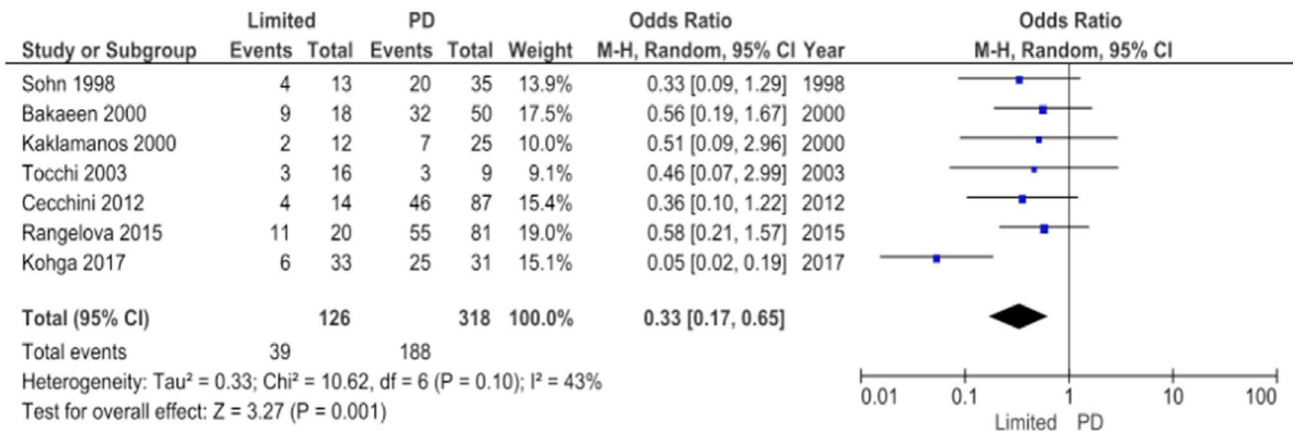
Negative margin resection with regional lymphadenectomy is the only therapeutic option to cure duodenal adenocarcinoma and should be attempted to achieve long-term survival [12, 41]. Patients' survival greatly depends on regional lymph node metastases. Patients with regional lymph node metastasis had a significantly shorter survival time than without [3, 13, 14, 16, 20, 41–46] and lymph node metastasis was also an independent prognostic factor in many studies [13, 14, 20, 41–45, 47]. On the contrary, T stage, tumor size, and location were not associated with patient outcomes [12, 13, 41, 48–50]. Several controversies exist regarding the

Table 2 Demographic and study characteristics of the studies included in the meta-analysis

Author	Tumor location (N, %)							Tumor depth (N, %)							Follow up (Median, month)	Outcome
	D1	D2	D3	D4	Tis	T1	T2	T3	T4							
Joesting (1981)	Supraampullary 8 (9%)	Periampullary 38 (42%)	Infraampullary (49%)	Infraampullary 45	–	–	–	–	–	–	–	–	–	–	OS5	
Barnes (1994)	Supraampullary 1 (2.8%)	Periampullary 22 (61.1%)	Infraampullary (36.1%)	Infraampullary 13	–	–	–	–	–	–	–	–	–	–	MS, OS5, DFS5	
Santoro (1997)	Supraampullary 14 (15.7%)	Periampullary 56 (62.9%)	Infraampullary (21.3%)	Infraampullary 19	–	–	–	–	–	–	–	–	–	–	OS1,2,3,4,5	
Sohn (1998)	0	Periampullary 34 (70.8%)	Infraampullary (29.2%)	Infraampullary 14	–	–	–	–	–	–	–	–	–	36	OS1,2,5	
Bakaeen (2000)	3 (4.4%)	50 (73.5%)	9 (13.2%)	6 (8.8%)	2 (3%)	7 (10%)	14 (20%)	26 (38%)	19 (28%)	24	–	–	–	–	OS3,5	
Kaklamanos, (2000)	6 (16.2%)	19 (51.4%)	9 (24.3%)	3 (8.1%)	0	2 (5.4%)	9 (24.3%)	21 (56.7%)	5 (13.5%)	–	–	–	–	–	MS, OS5	
Tocchi (2003)	0	0	37 (78.7%)	10 (21.2%)	0	0	14 (29.8%)	19 (40.4%)	14 (29.8%)	24	–	–	–	–	MS, OS5	
Cecchini (2012)	10 (9.7%)	72 (69.9%)	10 (9.7%)	11 (10.6%)	–	–	–	–	–	26.5	–	–	–	–	MS, OS3,5	
Onkendi (2012)	8 (6.5%)	76 (62.3%)	25 (20.2%)	15 (12.1%)	0	6 (6.1%)	9 (9.2%)	44 (44.9%)	39 (39.8%)	–	–	–	–	–	MS, OS2,5,10	
Kato (2014)	6 (17.1%)	24 (68.6%)	4 (11.4%)	1 (2.9%)	0	16 (45.7%)	1 (2.9%)	7 (20%)	11 (31.4%)	39	–	–	–	–	MS, OS5	
Rangelova (2015)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Perioperative	
Cloyd (2015)	–	–	–	–	0	143 (8.8%)	152 (9.4%)	535 (33.2%)	705 (43.7%)	41.9	–	–	–	–	MS, OS5	
Jiang (2016)	5 (3.9%)	113 (88.3%)	9 (7%)	1 (0.8%)	0	9 (7.1%)	25 (19.5%)	36 (28.1%)	58 (45.3%)	20	–	–	–	–	MS, OS1,3,5	
Kohga (2017)	4 (6.3%)	33 (51.6%)	2 (3.1%)	Ampulla 25 (39.1%)	0	64 (100%)	0	0	0	–	–	–	–	–	Perioperative	
Lee (2018)	6 (12.8%)	27 (57.4%)	13 (27.7%)	1 (2.1%)	0	1 (3.2%)	8 (25.8%)	12 (38.7%)	9 (29%)	23.5	–	–	–	–	MS, OS5	

MS median survival, OS overall survival, DFS disease free survival, D1 1st portion of duodenum, D2 2nd portion of duodenum, D3 3rd portion of duodenum, D4 4th portion of duodenum; Tis-High-grade dysplasia/carcinoma in situ, T1 tumor invades the lamina propria or submucosa, T1a tumor invades the lamina propria, T1b tumor invades the submucosa, T2 tumor invades the muscularis propria, T3 tumor invades into the subserosa or nonperitonealized perimuscular tissue without serosal penetration, T4 tumor perforates the visceral peritoneum or directly invades other organs or structures

a



b

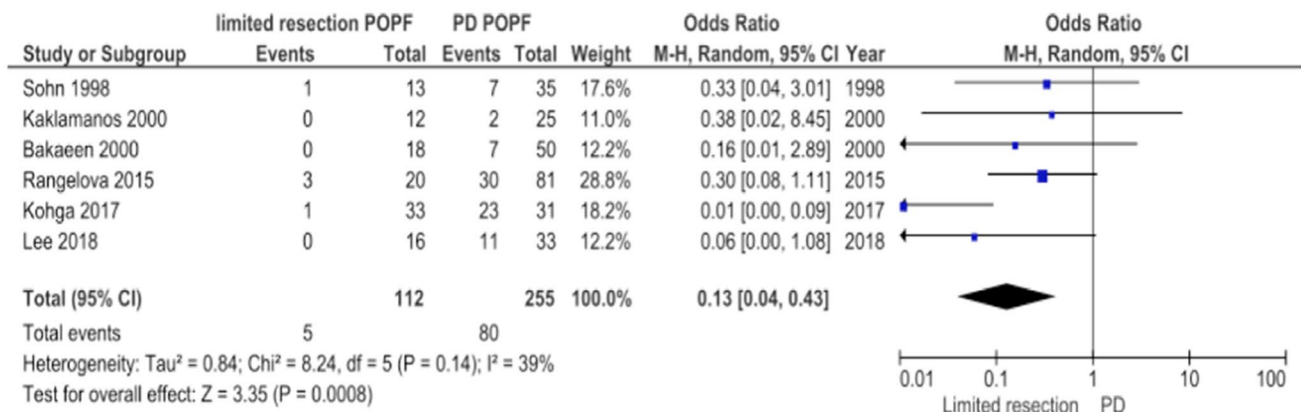


Fig. 2 a Results of the meta-analysis on overall morbidity after limited resection versus after pancreaticoduodenectomy. **b** Results of the meta-analysis on POPF after limited resection versus after pancrea-

ticoduodenectomy. *LR* limited resection, *PD* pancreaticoduodenectomy, *CI* confidence interval, *POPF* postoperative pancreatic fistula

optimum extent of surgery for regional lymphadenectomy. Several authors [12, 17, 51–54] recommend PD over LR to treat duodenal adenocarcinoma because it has a greater possibility of removing all lymph node metastases. However, patients treated through PD have higher morbidity and mortality rates than those treated through LR, despite the recent advances in surgical techniques and postoperative care. LR was recommended to treat tumors that are located within the distal part of the duodenum and reportedly resulted in lower morbidity and mortality with satisfactory long-term overall survival [6–8, 13–15, 55]. However, this approach may result in incomplete regional lymphadenectomy which could affect patient survival [56]. On the other hand, there

is another opinion that the number of resected lymph nodes does not differ between LR and PD [14, 47].

This systematic review and meta-analysis compared the two surgical strategies used for the management of patients with duodenal adenocarcinoma. We aimed to find the most appropriate treatment to decrease postoperative morbidity and mortality (as morbidity may cause a lower survival rate [57]), and increase long-term survival. The results showed that the LR group had lesser overall postoperative morbidity and POPF, no significant difference in overall mortality, and comparable long-term overall survival compared to the PD group. However, the results of this meta-analysis may be affected by selection bias, as patients who underwent

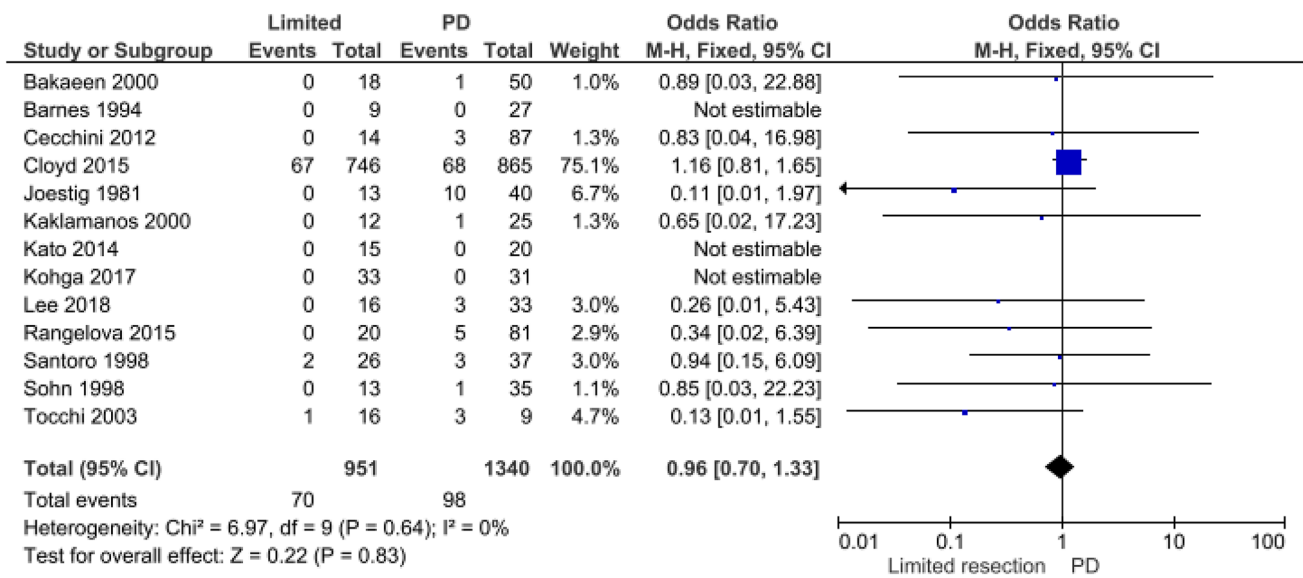


Fig. 3 Results of the meta-analysis on mortality after limited resection versus after pancreaticoduodenectomy

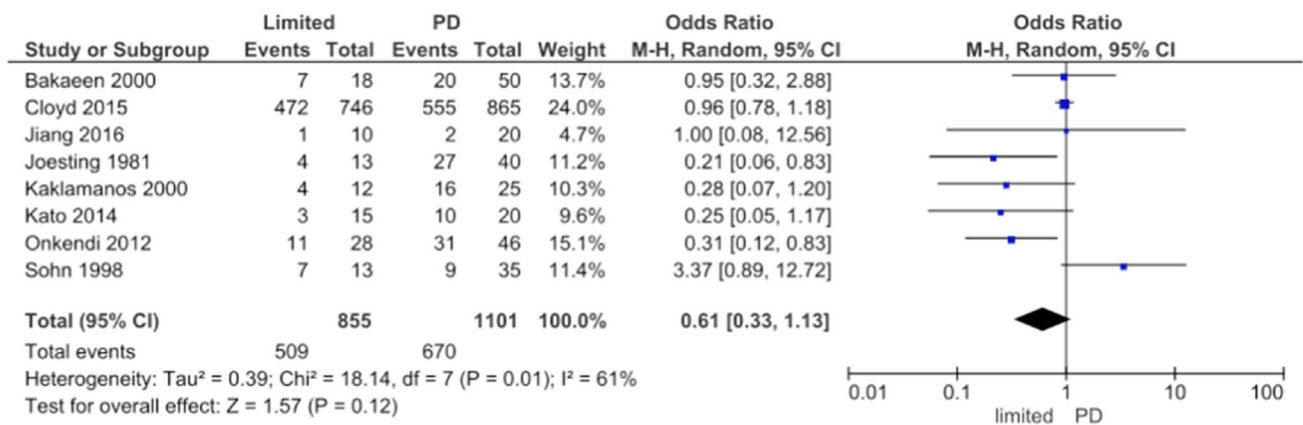
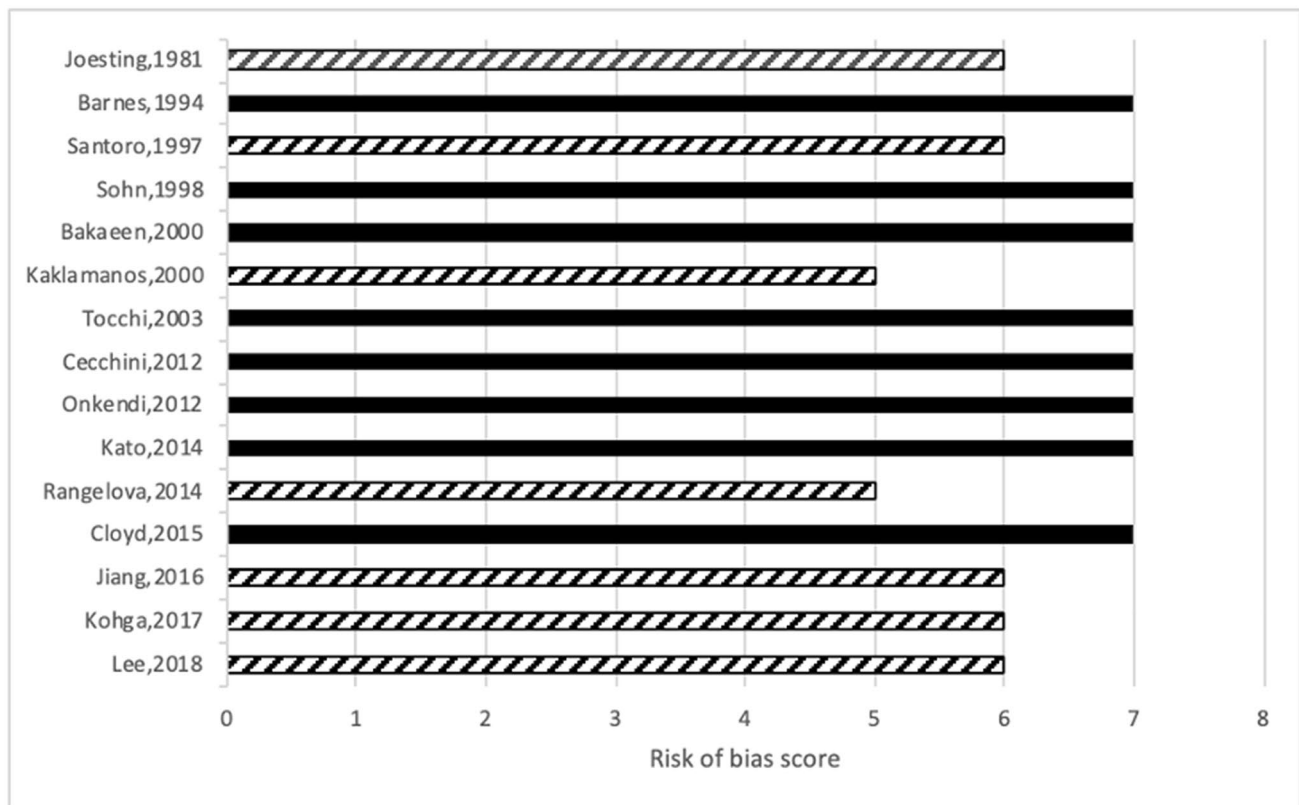


Fig. 4 Results of the meta-analysis on overall survival rate after limited resection versus after pancreaticoduodenectomy

LR had a higher number of tumors in distal portions of the duodenum and superficial (T1) lesion than the PD group. Therefore, it is a matter of decision-making by the surgeon to choose which patients should undergo LR or PD. Further, when considering the risk of nodal metastasis based on the depth of tumor invasion and the pattern of lymph node metastases, Salera et al. [45] showed that no patients with T1 tumors had lymph node metastasis and the prevalence of pN1 disease was significantly associated with pT (depth of tumor) category. Kato et al. [18] also reported the absence of lymph node metastasis when the tumor was limited to the mucosa or submucosa. Sakamoto et al. [58] and Kato et al. [18] determined the distribution of lymph node metastasis based on tumor location or tumor depth of invasion in the duodenum which included anterior and posterior pancreatoduodenal, infrapyloric, common hepatic, pericholedochal

and superior mesenteric arterial, and para-aortic. These findings indicate that tumors located deeper than the mucosa have a greater risk of metastasizing to the regional lymph nodes. Therefore, PD is still the standard treatment in primary duodenal adenocarcinoma and is recommended for all tumors that have invaded to the submucosa to ensure complete regional lymphadenectomy. Additionally, LR can be recommended in select patient with superficial lesions located in suitable locations that allow LR to be safely performed (e.g., locations other than second portion of the duodenum).

The major limitation of this review is that most of the included studies were retrospective with a small sample size. Indeed, no randomized controlled trial was included. Therefore, this study suffered from selection biases and other confounding factors, such as the difference in tumor



▨▨▨▨▨ Intermediate risk of bias ■ Low risk of bias

Fig. 5 Quality assessment of included studies based on the Newcastle–Ottawa scale

biology and aggressiveness in each patient, which affected the accuracy of the comparison between the two surgical approaches. Also, due to the lack of detailed data from the included studies in this meta-analysis, a comparison between the two groups stratified by tumor depth (T categories) and tumor location was not possible. According to the Funnel plot for the comparison of mortality for all studies of LR versus PD (Supplementary Fig. 3), although the p value was marginally not significant, this was likely to have a publication bias (test for funnel plot asymmetry: $P = 0.05035$).

Therefore, the recommendations based on our study's results may not be fully conclusive, but nonetheless, may still provide a reference for a surgeon's decision-making to treat primary duodenal carcinoma.

Conclusion

Negative margin surgical resection and regional lymphadenectomy are the only appropriate therapeutic approaches for duodenal adenocarcinomas. Although the standard treatment for duodenal cancer is PD, the long-term

outcomes are comparable between LR and PD, with the perioperative morbidity rates being lower for LR, provided negative margins can be ensured and regional lymphadenectomy can be performed. Therefore, LR with dissection of the regional lymph nodes may be a suitable option for some selected patients depending on the tumor location and depth of invasion, although further studies are required.

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Compliance with ethical standards

Conflict of interest statement The authors have no conflicts of interest to declare.

Ethical approval The authors have no ethical conflicts to disclose.


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