REVIEW ARTICLE

Outcomes of surgical resection for primary duodenal adenocarcinoma: A systematic review

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Summary   Primary duodenal adenocarcinoma (PDAC) is a rare malignancy. The aim of this study was to evaluate the published evidence for resection with curative intent in patients with PDAC. A literature search was conducted in PubMed and EMBASE databases for eligible studies that reported 5-year overall survival (OS) after surgical resection of PDAC from January 1990 to January 2018. Independent prognostic factors related to OS were evaluated using meta-analytical techniques. Odds ratio (OR) and hazard ratio (HR) with their 95% confidence interval (CI) were calculated as appropriate. Thirty-seven observational studies comprising a total of 1728 patients who underwent resection for PDAC were reviewed. The overall 30-day postoperative mortality was 3.2% (range, 0—16.0%) and the median 5-year OS was 46.4% (range, 16.6—71.1%). Surgical resection significantly improved the prognosis as compared with the palliative therapy (OR 15.76, $P < 0.001$). Lymph node metastasis (HR 2.58, $P < 0.001$), poor tumor differentiation (HR 1.43, $P = 0.05$), perineural invasion (HR 2.21, $P = 0.002$), and lymphovascular invasion (HR 2.18, 95% CI 1.18—4.03; $P = 0.01$) were found to be independently associated with decreased OS after surgical resection. The present study provides evidence that surgical resection can be performed safely for PDAC patients and offers a favorable long-term outcome. Tumor-specific factors have prognostic significance.

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1. Introduction

Primary duodenal adenocarcinoma (PDAC) is a rare malignancy, accounting for 0.3—1% of all gastrointestinal tract malignant tumors.[1] Surgical resection is the only potentially curative treatment, but robust data on the efficacy of this procedure are limited. The published evidence is largely derived from single-center studies with a limited number of patients.[2–17] To achieve greater power in the evaluation of the therapeutic effect and minimize type II statistical error due to small sample sizes, this study sought to systematically review the literature regarding long-term outcomes (5-year overall survival [OS]) of PDAC patients who underwent surgical resection with curative intent. In addition, the independent prognostic factors related to OS were also evaluated using meta-analytical techniques.

2. Methods

2.1. Systematic search strategy

A systematic review of relevant publications from January 1990 to January 2018 was carried out using PubMed and EMBASE databases by using the following search terms: "duodenal adenocarcinoma," "duodenal neoplasms," and "resection." Only articles on humans and in the English language were included for assessment. Reference lists from relevant articles were also manually searched to identify additional studies.

2.2. Criteria for inclusion and exclusion

Studies were considered for inclusion when they reported long-term outcomes (5-year OS) of PDAC patients who underwent surgical resection with curative intent. When multiple publications from the same institution and/or authors were encountered, only the most recent publication was selected. Editorials, comments, letters, non-English language studies and papers presenting data on fewer than 10 patients were excluded.

2.3. Data abstraction and quality assessment

Data were extracted by two authors (Yanming Zhou and Xiaoying Si) independently using predefined criteria, including the first author, publication year, study design, sample size, clinicopathological factors of study population, operative procedures, and 5-year OS. Discrepancies between the two reviewers were resolved by discussion and consensus. Study methodology quality was assessed using the Oxford levels of evidence-based medicine scoring system.[18]

2.4. Statistical analysis

Data are presented as median (range) unless otherwise stated. The meta-analysis was performed using the Review Manager (RevMan) software, version 5.3 (The Cochrane Collaboration, Software Update, Oxford). Odds ratio (OR) and hazard ratio (HR) with their 95% confidence interval (CI) were calculated as appropriate. Statistical significance was set at $P < 0.05$. Between-study heterogeneity was assessed with a χ^2 test and I^2, with $P < 0.1$ being statistically significant. Publication bias was evaluated visually using a funnel plot.

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[19]

3. Results

3.1. Systematic review

A systematic search yielded a total of 37 studies fulfilling the inclusion criteria.[2–17,20–40] Fig. 1 demonstrates a flow diagram of the selection process. Detailed study characteristics are summarized in Table 1. All these publications are retrospective reports (level IV evidence). The total number of patients was 1728 (range, 11—150). Types of surgery were radical resection (e.g., mostly in the form of pancreaticoduodenectomy) in 1350 patients and pancreas-sparing duodenectomy (PSD) in 328 patients, and unknown in 50 in patients. There were 52 (3.2%, range, 0—16.0%) reported 30-day deaths in 1611 patients by 34 studies. Five-year OS was reported in all 37 studies with a median value of 46.4% (range, 16.6—71.1%).

3.2. Meta-analysis

3.2.1. Resection vs. palliation
Twenty-three studies reporting on 1456 patients were included.[4–14,16,17,20,22,24,25,27,29,33,35,37,38] Pooled analysis demonstrated that resection was associated with a significant improvement in 5-year OS (43.4% versus 2.5%, OR 15.76, 95% CI 10.02—24.79; $P < 0.001$). There was no significant heterogeneity between studies ($I^2 = 15\%$, $P = 0.25$) (Fig. 2).

3.2.2. Prognostic factors of survival after resection
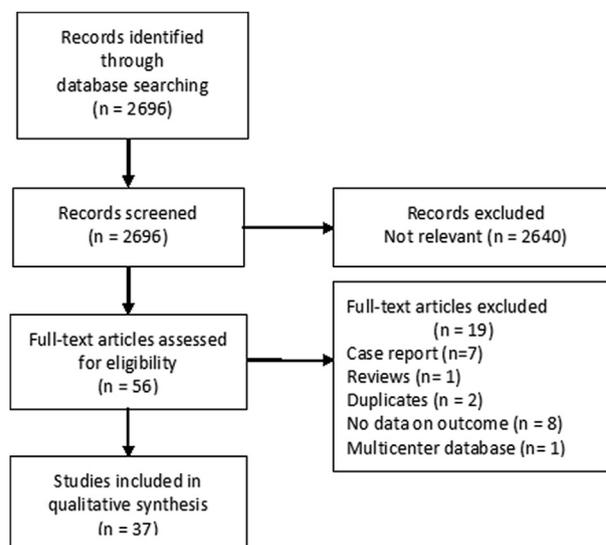Clinicopathological variables that were evaluated for association with OS on multivariate Cox regression analysis in

Figure 1 Flowchart of the search and study selection process.

Table 1 Clinical background of included studies.

Reference	Year	Study period	Region	Patients	OP RR/PSD	LNM (%)	PTD (%)	LVI (%)	Mortality (%)	5-year OS (%)
Lowell[2]	1992	1970–1991	USA	17	8/9	29.4	17.6	—	0	51.9
Delcore[3]	1993	1960–1990	USA	29	21/8	—	—	—	10.3	60.0
Barnes[4]	1994	1967–1991	USA	36	27/9	36.1	—	—	0	54.0
Rotman[5]	1994	1978–1988	France	46	38/8	36.9	—	—	8.7	45.0
Scott-Coombes[6]	1994	1979–1993	UK	17	17/0	—	—	—	5.8	40.0
Sexe[7]	1996	1987–1991	USA	34	34/0	—	—	—	5.8	28.0
Pickleman[8]	1997	1977–1992	USA	17	15/2	47.1	6.2	—	5.9	67.0
Santoro[9]	1997	1980–1994	Italy	65	37/28	—	—	—	7.8	25.0
Ohigashi[10]	1998	1981–1996	Japan	24	24/0	62.5	37.5	—	0	57.0
Bakaeen[11]	2000	1976–1996	USA	68	50/18	32.3	—	—	1.4	54.0
Kaklamanos[12]	2000	1978–1998	USA	37	26/11	48.6	—	—	2.7	37.0
Ryder[13]	2000	1957–1998	USA	31	27/4	—	—	—	6.4	43.0
Tocchi[14]	2003	1980–2000	Italy	25	9/16	—	—	—	16.0	51.0
Sarela[15]	2004	1983–2001	USA	72	56/16	43.0	29.1	—	2.8	71.0
Hu[16]	2006	1993–2003	China	28	11/17	39.3	39.3	—	10.7	42.0
Hung[17]	2007	1994–2005	Taiwan	11	10/1	—	0	—	0	16.6
Hurtuk[20]	2007	1984–2005	USA	31	24/7	42.8	14.2	—	Excluded	42.0
Kelsey[21]	2007	1975–2005	USA	32	20/12	21.8	—	—	6.2	48.0
Lee[22]	2008	1995–2007	South Korea	28	27/1	64.3	14.2	—	0	44.1
Struck[23]	2009	1989–2006	USA	30	25/5	61.5	33.3	—	0	33.3
Han[24]	2010	1990–2006	China	24	18/6	—	—	—	0	24.0
Kawahira[25]	2011	1977–2007	Japan	12	8/4	50.0	—	—	0	65.7
Zhang[26]	2011	1995–2008	China	48	—	—	—	—	0	40.0
Cecchini[27]	2012	1982–2010	USA	103	87/14	48.5	39.7	53.1	2.9	42.0
Liang[28]	2012	1993–2010	Taiwan	36	31/5	72.2	36.1	—	0	27.0
Onkendi[29]	2012	1994–2009	USA	99	70/29	49.3	11.3	—	2.0	43.0
Poultsides[30]	2012	1984–2006	USA	122	122/0	58.2	34.3	63.7	2.4	48.0
Malleo[31]	2012	2000–2009	Italy	25	25/0	52.0	—	40.0	0	71.1
Zenali[32]	2013	1990–2011	USA	68	53/15	48.5	26.5	—	0	55.9
Kim[33]	2014	1995–2010	South Korea	36	31/5	41.7	—	19.4	5.6	46.4
Kato[34]	2014	1992–2011	Japan	35	20/15	31.4	20.0	—	0	63.0
Lee[35]	2014	1999–2009	South Korea	47	44/3	45.0	12.7	53.1	0	60.9
Oyasiji[36]	2015	2000–2013	USA	21	13/8	57.1	33.3	14.3	0	16.7
Solaini[37]	2015	2000–2013	UK	150	132/18	55.7	30.7	45.1	3.3	51.2
Jiang[38]	2016	1999–2014	China	128	112/16	40.5	34.3	28.4	4.3	44.1
Lee[39]	2017	2004–2014	Australia, UK	31	27/4	51.6	38.7	32.2	—	66.5
Sakamoto[40]	2017	1989–2005	Japan	65	51/14	47.8	10.7	—	—	65.0

OP = operative procedure; RR = radical resection; PSD = pancreas-preserving duodenal resection; LNM = lymph node metastasis; PTD = poor tumor differentiation; LVI = lymphovascular invasion; OS = overall survival.

at least three papers were included. Lymph node metastasis (HR 2.58, 95% CI 1.69–3.94; $P < 0.001$), poor tumor differentiation (HR 1.43, 95% CI 1.00–2.05; $P = 0.05$), perineural invasion (HR 2.21, 95% CI 1.35–3.62; $P = 0.002$), and lymphovascular invasion (HR 2.18, 95% CI 1.18–4.03; $P = 0.01$) were found to be independently associated with decreased OS (Fig. 3A–D).

The impact of resection type on OS was evaluated in three studies by univariate analysis.[27,32,38] As shown in Fig. 4, the resection type was not correlated with poor prognosis.

4. Discussion

The present study is important because it represents the largest collective report (n = 1728) on outcomes after surgery of PDAC so far. The findings clearly show that surgical resection of PDAC can be undertaken safely in the majority of patients. The mean postoperative mortality reported in 1611 patients by 34 studies was only 3.2%, which represents the progress in operative and perioperative management. More importantly, resection offers favorable long-term survival with a median 5-year OS rate of 46.4%. As might be expected, survival was significantly higher in patients who underwent surgical resection than that in patients who received palliative therapy. Therefore, an aggressive surgical approach that achieves complete tumor excision should be pursued whenever possible.

Identification of prognostic factors that predict the outcome following surgical resection of PDAC would help stratify patients for appropriate management categories. We found that lymph node metastasis, poor tumor
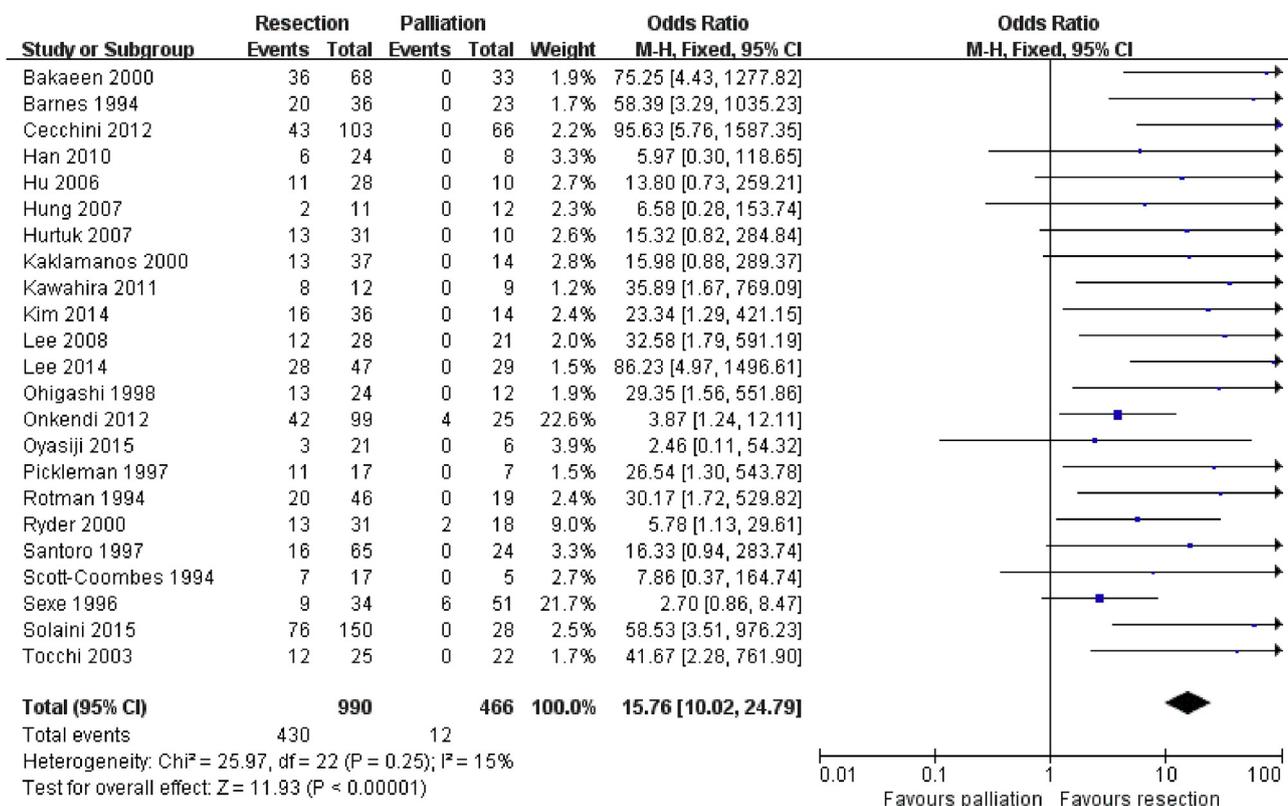
Study or Subgroup	Resection Events	Total	Palliation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bakaeen 2000	36	68	0	33	1.9%	75.25 [4.43, 1277.82]
Barnes 1994	20	36	0	23	1.7%	58.39 [3.29, 1035.23]
Cecchini 2012	43	103	0	66	2.2%	95.63 [5.76, 1587.35]
Han 2010	6	24	0	8	3.3%	5.97 [0.30, 118.65]
Hu 2006	11	28	0	10	2.7%	13.80 [0.73, 259.21]
Hung 2007	2	11	0	12	2.3%	6.58 [0.28, 153.74]
Hurtuk 2007	13	31	0	10	2.6%	15.32 [0.82, 284.84]
Kaklamanos 2000	13	37	0	14	2.8%	15.98 [0.88, 289.37]
Kawahira 2011	8	12	0	9	1.2%	35.89 [1.67, 769.09]
Kim 2014	16	36	0	14	2.4%	23.34 [1.29, 421.15]
Lee 2008	12	28	0	21	2.0%	32.58 [1.79, 591.19]
Lee 2014	28	47	0	29	1.5%	86.23 [4.97, 1496.61]
Ohigashi 1998	13	24	0	12	1.9%	29.35 [1.56, 551.86]
Onkendi 2012	42	99	4	25	22.6%	3.87 [1.24, 12.11]
Oyasiji 2015	3	21	0	6	3.9%	2.46 [0.11, 54.32]
Pickleman 1997	11	17	0	7	1.5%	26.54 [1.30, 543.78]
Rotman 1994	20	46	0	19	2.4%	30.17 [1.72, 529.82]
Ryder 2000	13	31	2	18	9.0%	5.78 [1.13, 29.61]
Santoro 1997	16	65	0	24	3.3%	16.33 [0.94, 283.74]
Scott-Coombes 1994	7	17	0	5	2.7%	7.86 [0.37, 164.74]
Sexe 1996	9	34	6	51	21.7%	2.70 [0.86, 8.47]
Solaini 2015	76	150	0	28	2.5%	58.53 [3.51, 976.23]
Tocchi 2003	12	25	0	22	1.7%	41.67 [2.28, 761.90]
Total (95% CI)		**990**		**466**	**100.0%**	**15.76 [10.02, 24.79]**
Total events	430		12			

Heterogeneity: Chi² = 25.97, df = 22 (P = 0.25); I² = 15%
Test for overall effect: Z = 11.93 (P < 0.00001)

Figure 2 Forest plots for 5-year survival indicating that surgical resection of PDAC is associated with significantly improved survival.

differentiation, perineural invasion and lymphovascular invasion were associated with shorter OS. For patients with these poor prognostic factors, additional strategies may be considered to improve the survival. To the best of our knowledge, no randomized controlled study (RCT) has assessed the role of adjuvant treatment for PDAC. Using the National Cancer Data Base (NCDB), a large population-representative cancer registry, Ecker et al[41] found that patients with lymph node-positive PDAC could gain survival benefits from adjuvant chemotherapy. Adjuvant chemoradiotherapy has been demonstrated to enhance survival of patients with ampullary adenocarcinoma[42]; however, it yielded no beneficial effect for PDAC. A study from Johns Hopkins showed that 5-year OS between patients who received and did not receive adjuvant chemoradiation was comparable.[30] Another study from Duke University compared patients who received surgery alone with those who received either pre- or postoperative chemoradiotherapy and found no significant difference in OS, disease-free survival (DFS) or local control between the two groups.[21] The NCDB analysis revealed that adjuvant chemoradiotherapy did not seem to significantly improve survival as compared with adjuvant chemotherapy, even in high-risk cases.[43]

There is conflicting evidence over the type of resection required for PDAC. One study by Sohn et al[44] demonstrated a significant improvement in 5-year OS in patients undergoing pancreaticoduodenectomy *vs.* patients undergoing PSD (69% *vs.* 0%, P < 0.05). However, these results are not supported by the experience reported by several other authors.[5,11,12,29,38,40] For example, Kaklamanos et al[12] reported on patients undergoing resection for PDAC and found OS was the same after a pancreaticoduodenectomy or PSD. Similarly, a study by Onkendi et al[29] reported a comparison between patients undergoing pancreaticoduodenectomy and patients undergoing PSD, and the result showed no significant difference in 5- and 10-year OS between the two groups. Recently, data of 1611 patients from the Surveillance, Epidemiology, and End Results (SEER) database showed no adverse effects on survival with PSD.[45] After controlling for other factors, the type of surgery does not seem to affect survival as shown by multivariate Cox regression analysis. The pooled data of the present study also confirmed this finding. From the oncological perspective, PSD should be considered if tumor invasion is confined in the duodenal wall, especially for distal duodenal tumors.[11]

A major limitation of the study is the lack of RCT on the subject and the quality of evidence is relatively low. Most studies included fewer than 50 patients over many years. Survival figures for patients undergoing resection have varied widely, with reported 5-year OS ranging from 16.6% to 71.1%, likely due to variation in disease stage and surgical techniques between series. It is commonly felt that favorable prognosis after resection is at least partially due to patient selection (better performance status and limited disease extension). Nevertheless, without resection for PDAC, patient survival beyond 5 years is rare.
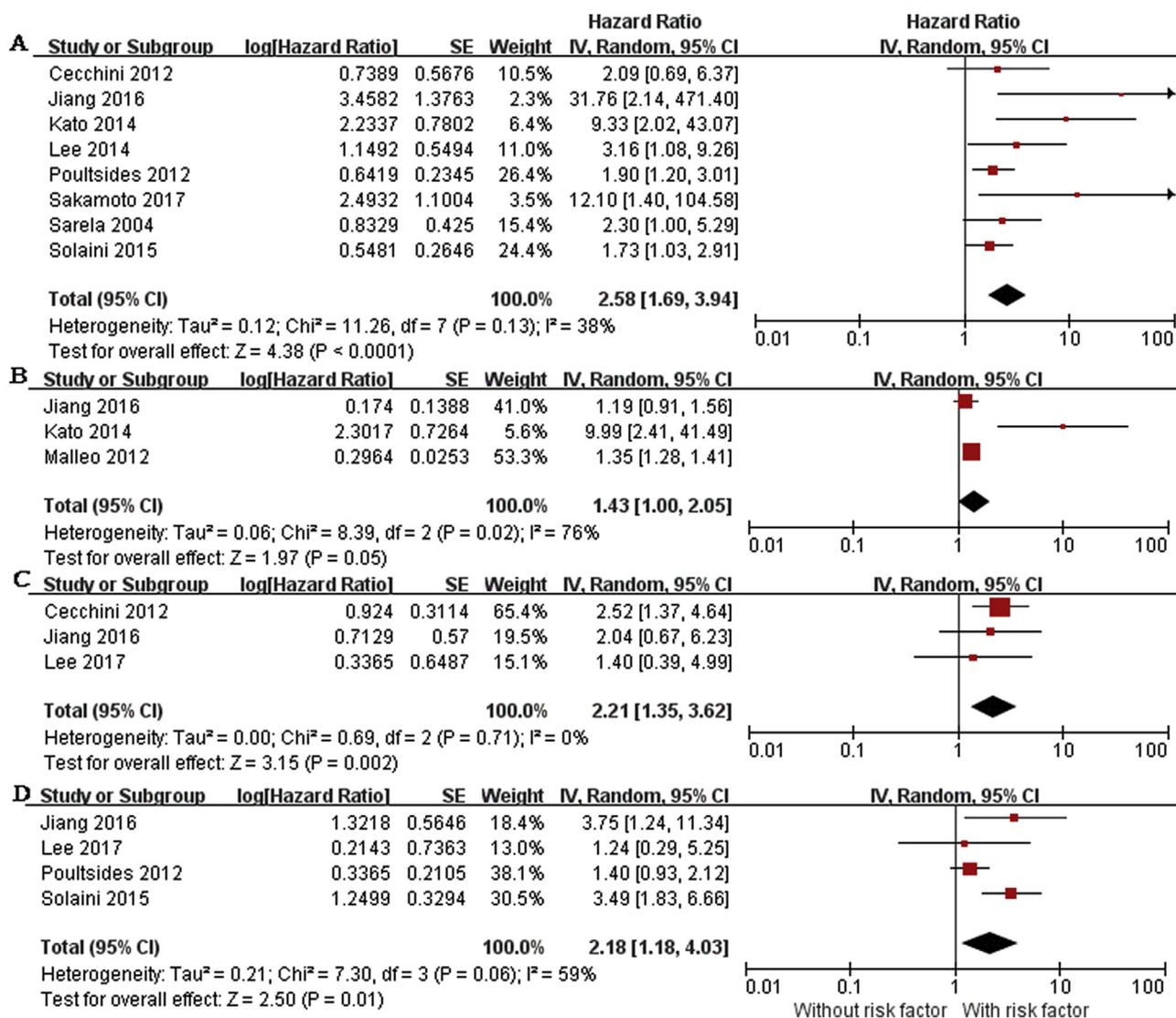
Figure 3   Forest plots of factors associated with OS after surgical resection of PDAC. (A) Lymph node metastasis, (B) poor tumor differentiation, (C) perineural invasion, and (D) lymphovascular invasion.
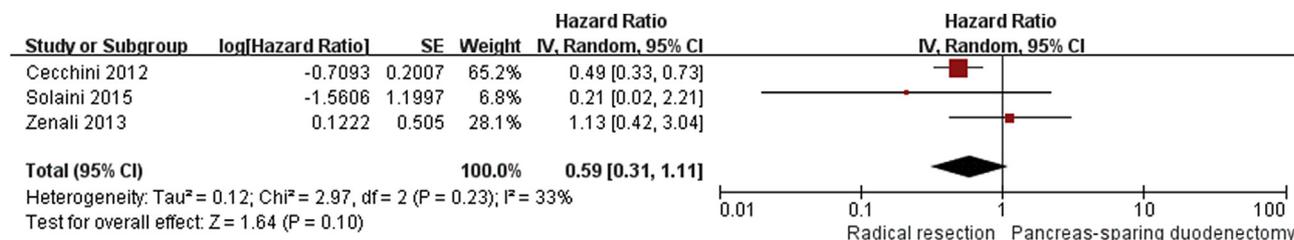

Figure 4   Forest plots for the impact of resection type on overall survival.

In conclusion, surgical resection can be performed safely for patients with PDAC and offers a favorable long-term outcome. The role of adjuvant treatment such as chemotherapy and chemoradiotherapy requires further investigation.

Disclosure

No financial support has been taken for the study.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.04.005.

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