Pancreatology 19 (2019) 1074–1080

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Efficacy of extended versus standard lymphadenectomy in pancreatoduodenectomy for pancreatic head adenocarcinoma. An update meta-analysis

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ARTICLE INFO

Article history:
Received 9 April 2019
Received in revised form
18 September 2019
Accepted 14 October 2019
Available online 17 October 2019

Keywords:
Pancreatic carcinoma
Pancreaticoduodenectomy
Lymph node dissection
Extended
Standard

ABSTRACT

Background: Surgical resection is the only possible cure for pancreatic cancer, it remains controversial whether extend lymphadenectomy in pancreatoduodenectomy (EPD) is better than standard lymphadenectomy in pancreatoduodenectomy (SPD). The aim of this study was to compare the efficacy of EPD with SPD for pancreatic head adenocarcinoma.

Methods: A specific search of online databases including PubMed, Web of Science, Embase, and Cochrane library was conducted from January 1990 to October 2018. Relative perioperative outcomes were synthesized. Single-arm meta-analysis was also performed.

Results: A total of eight studies involving 687 (342 vs 345) patients were included for analysis in our study. The number of lymph nodes harvested [24.54 vs 13.29; weighted mean difference (WMD) −10.69, $P = 0.000$], operative time (469.84 min vs 354.85 min; WMD -99.09, $P = 0.000$), and diarrhea (postoperative three months) [45.1% vs 18.2%; odds radio (OR) 0.20, $P = 0.014$] were significantly higher in patients who underwent EPD than SPD. The perioperative complications (35% vs 28.8%; OR 0.79, $P = 0.186$), tumor size (3.27 cm vs 3.248 cm; WMD -0.11, $P = 0.256$), lymph node metastasis (66% vs 55.9%; OR 0.71, $P = 0.105$), and positive margin (10.4% vs 11.3%; OR 1.28, $P = 0.392$) were no significant differences between EPD group and SPD group. Extended lymphadenectomy in pancreatoduodenectomy dose not contribute to the overall survival of patients with adenocarcinoma of the pancreatic head [hazard ratio (HR) 0.95; 95% CI 0.78–1.15; $P = 0.61$].

Conclusion: The update meta-analysis shows that EPD failed to improve the overall survival, may even lead to increased morbidity.

Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death [1] and is expected to become the second leading cause by 2030 in the United States [2]. Although considerable progress has been made in improving the survival rate of cancer in the past few decades, there has been no significant improvement in the 5-year survival rate of pancreatic cancer, which only increased from 3.0% in 1975 to 5.4% in 2005 according to SEER [3], and only increased to 8.5% according to the latest data of SEER [4]. Currently, surgical resection is the only possible cure for pancreatic cancer [5]. Fortner [6] first described extended radical lymphadenectomy with pancreatoduodenectomy (PD) as a result of poor prognosis of pancreatic cancer. In the 1980s, PD with enlarged lymphadenectomy became popular in Japan. Histopathology after expanded PD revealed frequent lymph node metastasis in the region between the abdominal trunk and the superior mesenteric artery, suggesting the benefits of expanded lymph node dissection [7–11].

Since then, many studies have debated the impact of enlarged lymphadenectomy on survival. Ishikawa et al. [12] found that PD with enlarged lymphadenectomy seemed to benefit patients with a 5-year survival rate of 28%. Subsequent reports have also shown that radical scalpel has a survival advantage over standard lymphadenectomy [13]. However, a number of studies have shown that enlarged lymphadenectomy cannot prolong the survival period of

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https://doi.org/10.1016/j.pan.2019.10.003
1424-3903/

patients and may increase the incidence of digestive fistula, lymphatic leakage and gastric emptying disorder, which is contrary to the results of earlier studies [14,15]. Although many scholars have conducted some comparative studies, it is uncertain whether extend lymphadenectomy in pancreatoduodenectomy (EPD) is superior to standard lymphadenectomy in pancreatoduodenectomy (SPD). A recent meta-analysis [16] compared the efficacy of SPD and EPD in the treatment of pancreatic head cancer. However, this study included cases of periampullary cancer, which may make the data less convincing. Therefore, only ductal adenocarcinoma of the head of pancreas was included in this meta-analysis.

Methods

Literature search and selection

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. We conducted a systematic and comprehensive literature retrieval of online databases including PubMed, Web of Science, Embase, and Cochrane library, from January 1990 to October 2018 to identify all of Randomized Controlled Trials (RCTs) or observational studies including cohort and case-control studies, which were published in English-language. The search strategy used the terms and combinations as follows: 'carcinoma, pancreatic ductal', 'pancreatic adenocarcinoma', 'pancreatic cancer', 'pancreatic carcinoma', 'pancreaticoduodenectomy', 'lymph node dissection', 'lymph node excision', 'lymphadenectomy', 'extended', 'standard'.

The inclusion criteria were as follows: study population: patients with proven or suspected pancreatic head adenocarcinoma before the operation; intervention: SPD versus EPD; study design: RCTs or observational studies; outcomes measure: This meta-analysis was designed to evaluate two types of outcome: perioperative outcomes (operative outcomes, pathology, morbidity and mortality) and long-term outcomes (overall survival, recurrence patterns). The following were the exclusion criteria: patient groups with ampullary, distal bile duct or duodenal carcinoma, neuroendocrine and serous cystic tumors of the pancreas; case reports, conferences abstracts, commentary literatures, studies lacking control groups.

Data collection and quality assessment

Data collection and the assessment of literature quality were conducted independently by two investigators (WW and YH). All available information, including baseline details, the perioperative outcomes (perioperative complications, diarrhea, pancreatic leak, delayed gastric emptying, intra-abdominal hemorrhage, intra-abdominal abscess, wound infection, operative time, postoperative hospital stay and blood transfusion), the pathologic outcomes (lymph nodes harvested, tumor size, lymph node metastasis, and positive margin), and the long-term outcomes (overall survival rate and local recurrence) were recorded in a Microsoft excel database.

The quality of included RCTs were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) [18]. For quality assessment of included observational studies were assessed by the modified Newcastle-Ottawa Scale (NOS) [19]. Disagreements were resolved by the third investigator (ZT).

Statistical analysis

Dichotomous outcomes were estimated by the pooled odds ratio (OR) with 95% confidence intervals (95% CIs) and continuous outcomes were assessed by the pooled weight mean difference (WMD) or standardized mean difference (SMD) with 95% CIs. Single-arm meta-analyses were performed for SPD and EPD groups. The inter-study heterogeneity was identified by Cochran Chi-square test and I^2, where I^2<50% indicated low heterogeneity and I^2>50% suggested significant heterogeneity. When I^2<50%, a fixed-effects model was used to pool the results, while a random-effects model was utilized when I^2>50%. Funnel plots tests, Harbord tests, Peters tests and Egger tests were used to detect the publication bias. Harbord and Peters tests were recommended for binary variable, and Egger test was recommended for enumeration data [20]. *P* values lower than 0.05 were considered as statistical significance. All the statistical analyses were performed by utilizing STATA software (version 12.0, Stata Corporation, College Station, TX).

Results

Study selection and quality assessment

Following the previous search strategy, the initial search identified 526 potential literatures were obtained from the online database from January 1, 1990, to October 30, 2018. After removal of duplicates, 423 studies remained in total. Then, 372 studies were removed by browsing title and abstract, 42 of the remaining 51 records were excluded with various reasons. Finally, eight studies were included in this meta-analysis [15,21–28], and one study included two articles [15,21] (Fig. 1). The characteristics, quality assessment, and demographics of the included studies were summarized in Tables 1 and 2.

Perioperative outcomes

In single-arm synthesis, although the overall perioperative complications rate in EPD group [35% (95% CI 29.8–40.2)] was higher than SPD group [28.8% (95% CI 23.7–33.8)], the present meta-analysis showed the perioperative morbidity in EPD was not significantly different when compared with SPD (OR 0.79, 95% CI 0.56–1.12, $P = 0.186$), with no heterogeneity ($I^2 = 0$, $P = 0.991$) (Fig. 2A). And there was also no evidence of any difference in mortality between two groups (OR 0.52,95% CI 0.2–1.34, $P = 0.174$) (Fig. 2B).

Nevertheless, diarrhea (postoperative three months) was 18.2% (95% CI 7.2–29.3) and 45.1% (95% CI 9.1–88.1) in SPD group and EPD group, respectively. A random-effects model was chosen in diarrhea because of the high heterogeneity. Our meta-analysis revealed diarrhea in EPD group was significantly higher than in the SPD group (OR 0.20, 95% CI 0.05–0.72, $P = 0.014$). (Fig. 2C).

Due to high heterogeneity, random effects analysis was chosen in operative time, blood transfusion, and postoperative hospital stay. The operative time was 354.85 min for SPD and 469.84 min for EPD (WMD -99.09, 95% CI -146.39 to −51.79, $P = 0.000$) (Fig. 2D). The blood transfusion was 1.16 unit and 1.372 unit (SMD -0.96, 95% CI -2.12 to 0.20, $P = 0.106$) for SPD and EPD, severally (Fig. 2E), the postoperative hospital stay was 26.27 days and 27.10 days, respectively (SMD -0.83, 95% CI -0.79 to 2.46, $P = 0.316$) (Fig. 2F).

Pathologic outcomes

Random effects analysis was performed for lymph nodes harvested and lymph node metastasis due to high heterogeneity, while fixed effects analysis was conducted for tumor size and positive margin with no heterogeneity. The result of meta-analysis for lymph nodes harvested was 13.29 for SPD and 14.54 for EPD. And it

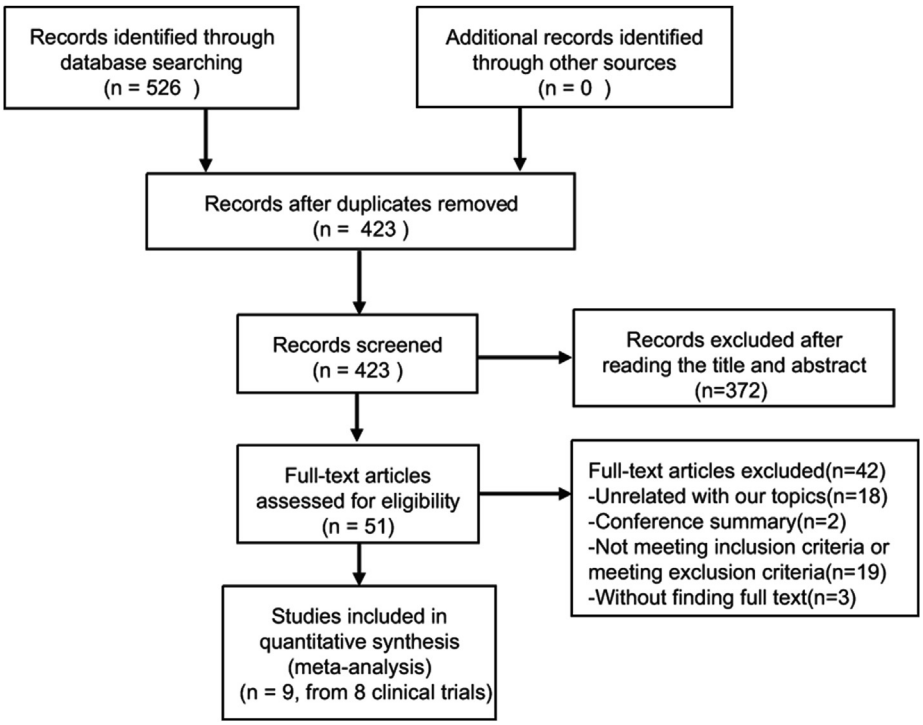

Fig. 1. A flow diagram of the inclusion criteria of studies eligible for meta-analysis.

Table 1
Characteristics and quality assessment of the included studies.

Study	Year	Country	Intervention	Study period	Study type	Quality Score
Ignjatovic et al. [27]	2017	Serbia	SPD vs EPD	2007–2010	Single-center Non-RCT	7
Jang et al. [15,21]	2014,2017	South Korea		2006–2009	Multicenter RCT	[a]
Nimura et al. [22]	2012	Japan		2000–2003	Multicenter RCT	[a]
Takao et al. [23]	2008	Japan		1980–2001	Single-center Non-RCT	6
Farnell et al. [24]	2005	America		1997–2003	Single-center RCT	[a]
Yang et al. [25]	2005	China		1994–2002	Single-center Non-RCT	7
Iacono et al. [28]	2002	Italy		1992–1996	Single-center Non-RCT	6
Pedrazzoli et al. [26]	1998	Italy		1991–1994	Multicenter RCT	[a]

RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial.
[a] RCTs were tested by Cochrane handbook for systematic reviews of interventions, which were shown in the supplementary files.

Table 2
Demographics of the of the included studies.

Study	Number of Patients	Mean Age	Sex (male%)	Postoperative Adjuvant Therapy	AJCC Stage (I/II/III/IV)(%)	R1 Resection (%)
Ignjatovic et al. [27]	30/30	64.5/59.7	46.7/60	No	(10/90/0/0)/(17/76/7/0)	NA
Jang et al. [15,21]	83/86	62/63.4	53/54	Yes	(8/92/0/0)/(3/97/0/0)	15/9
Nimura et al. [22]	51/50	62.7/62.9	59/51	No	(4/96/0/0)/(2/80/0/18)	6/10
Takao et al. [23]	61/40	NA	NA	No	(13/67/7/13)/(3/77/5/15)	35/23
Farnell et al. [24]	38/34[a]	66/67	50/54	Yes	(0/34/66/0)/(0/32/53/15)	24/18
Yang et al. [25]	20/46	58.8/64.2	70/78	No	(25/15/60/0)/(15/18/67/0)	NA
Iacono et al. [28]	13/17	61.3/62.5	64.7/46	NA	(23/15/62/0)/(18/0/82/0)	23/12
Pedrazzoli et al. [26]	40/41	62/59.2	62/59.2	No	(35/5/60/0)/(34/7/59/0)	28/22

Data were described as (SPD)/(EPD) in most blank.
AJCC, America Joint Committee on Cancer; NA, not available.
[a] Four patients in the SPD and three in the EPD, which had an adenocarcinoma associated with features of intraductal papillary mucinous neoplasm, were excluded in Farnell study.

revealed lymph nodes harvested in EPD group was significantly higher than in the SPD group (WMD -10.69, 95% CI -15.21 to −6.17, $P = 0.000$) (Fig. 3A). There was no significant difference in the tumor size (WMD -0.11, 95% CI -0.3 to 0.08, $P = 0.256$) (Fig. 3B), lymph node metastasis (OR 0.71, 95% CI 0.47–1.07, $P = 0.105$) (Fig. 3C), and positive margin (OR 1.28, 95% CI 0.73–2.25, $P = 0.392$) (Fig. 3D).

Survival and recurrence

All of the included studies showed the overall survival in the form of Kaplan-Meier curves. When the studies were analyzed together, there was no statistical difference between the patients who received EPD and those who underwent SPD [hazard ratio

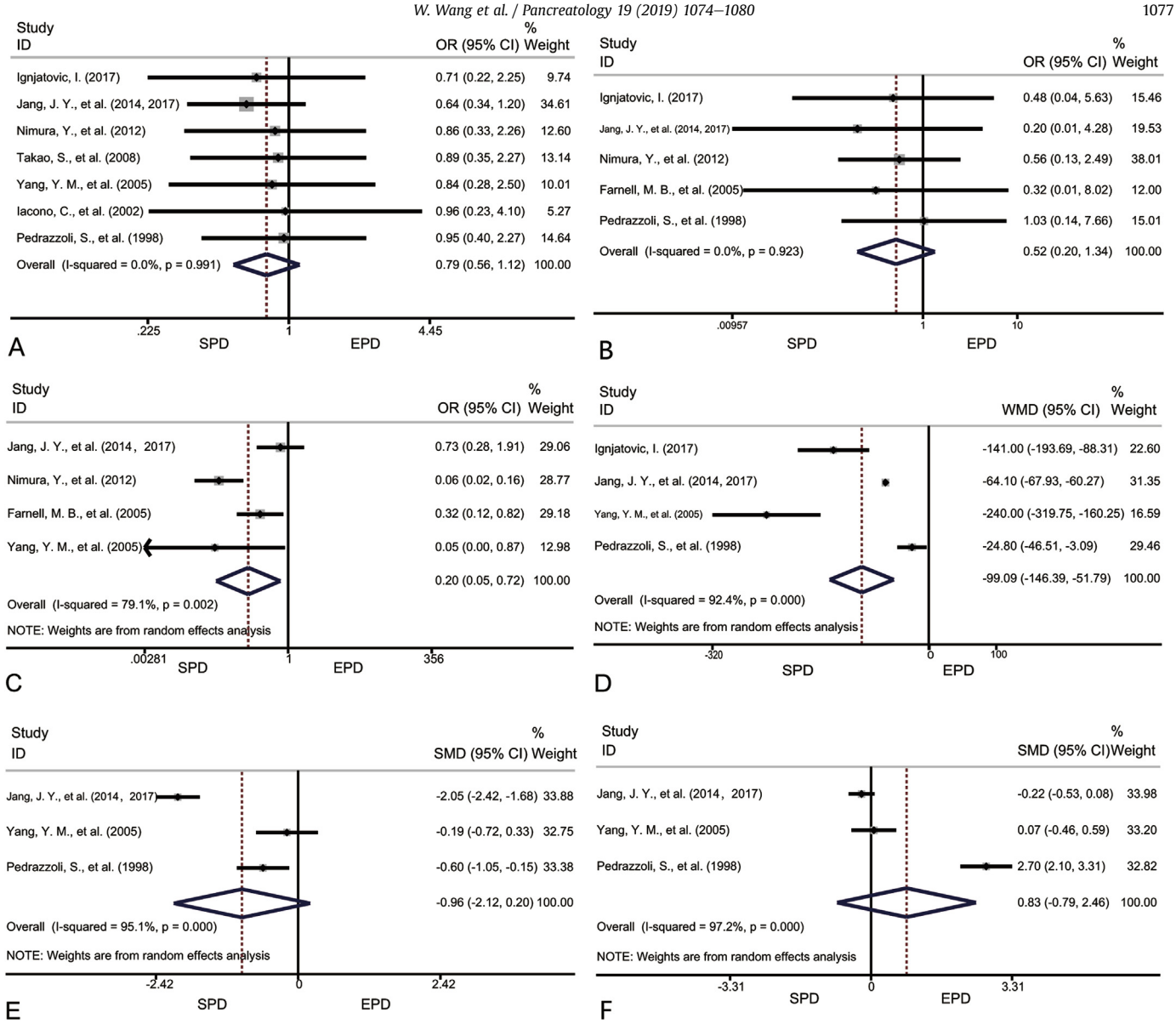

Fig. 2. Forest plot of meta-analysis in perioperative outcomes. A, Forest plot of OR of overall perioperative complications. B, Forest plot of OR of mortality. C, Forest plot of OR of diarrhea (postoperative three months). D, Forest plot of WMD of operative time. E, Forest plot of SMD of blood transfusion. F, Forest plot of SMD of postoperative hospital stay.

(HR) 0.95; 95% CI 0.78–1.15; $P = 0.61$] (Fig. 3E).

Four of the eight trials reported local recurrence after operation. The local recurrence was 36.6% and 25.1% in SPD and EPD, respectively (OR 1.63, 95% CI 0.83–3.21, $P = 0.154$) (Fig. 3F). The date was analyzed by random effects model because of the high heterogeneity.

Subgroup analysis

The overall perioperative complications and survival rate were divided into two subgroups according to the study type (RCT versus non-RCT). There was no significantly different on the total perioperative complications in RCT group (OR 0.76, 95% CI 0.48–1.19, $P = 0.227$), and the same result occurred in the non-RCT group (OR 0.84, 95% CI 0.48–1.47, $P = 0.544$). The subgroup meta-analysis showed that EPD did not improve survival when survival was divided into RCT (HR 1.12, 95% CI 0.87–1.45, $P = 0.368$) and non-RCT (HR 0.75, 95% CI 0.56–1.02, $P = 0.065$). When survival was analyzed by whether absence of postoperative adjuvant treatment (adjuvant therapy versus non-adjuvant therapy), again, EPD did not contribute to the long-term survival (HR 1.27, 95% CI 0.94–1.72, $P = 0.145$, and HR 0.91, 95% CI 0.72–1.14, $P = 0.418$, respectively).

Meanwhile, this meta-analysis indicated no significant difference between two groups in occurrences of perioperative complications, such as pancreatic leak (OR 0.81, 95% CI 0.41–1.58, $P = 0.536$), delayed gastric emptying (OR 1.02, 95% CI 0.55–1.91, $P = 0.946$), intra-abdominal hemorrhage (OR 0.76, 95% CI 0.26–2.27, $P = 0.624$), intra-abdominal abscess (OR 0.91, 95% CI 0.37–2.26, $P = 0.846$), and wound infection (OR 0.79, 95% CI 0.35–1.77, $P = 0.573$). All the results of subgroup analyses were showed in the supplementary files (Fig. S1).

Publication bias and sensitivity analysis

Funnel plots showed the included studies were symmetric distribution. Harbord, Peters and Egger tests proved that potential publication bias did not appear among the studies. Sensitivity analyses verified the robustness of the results. All the results were

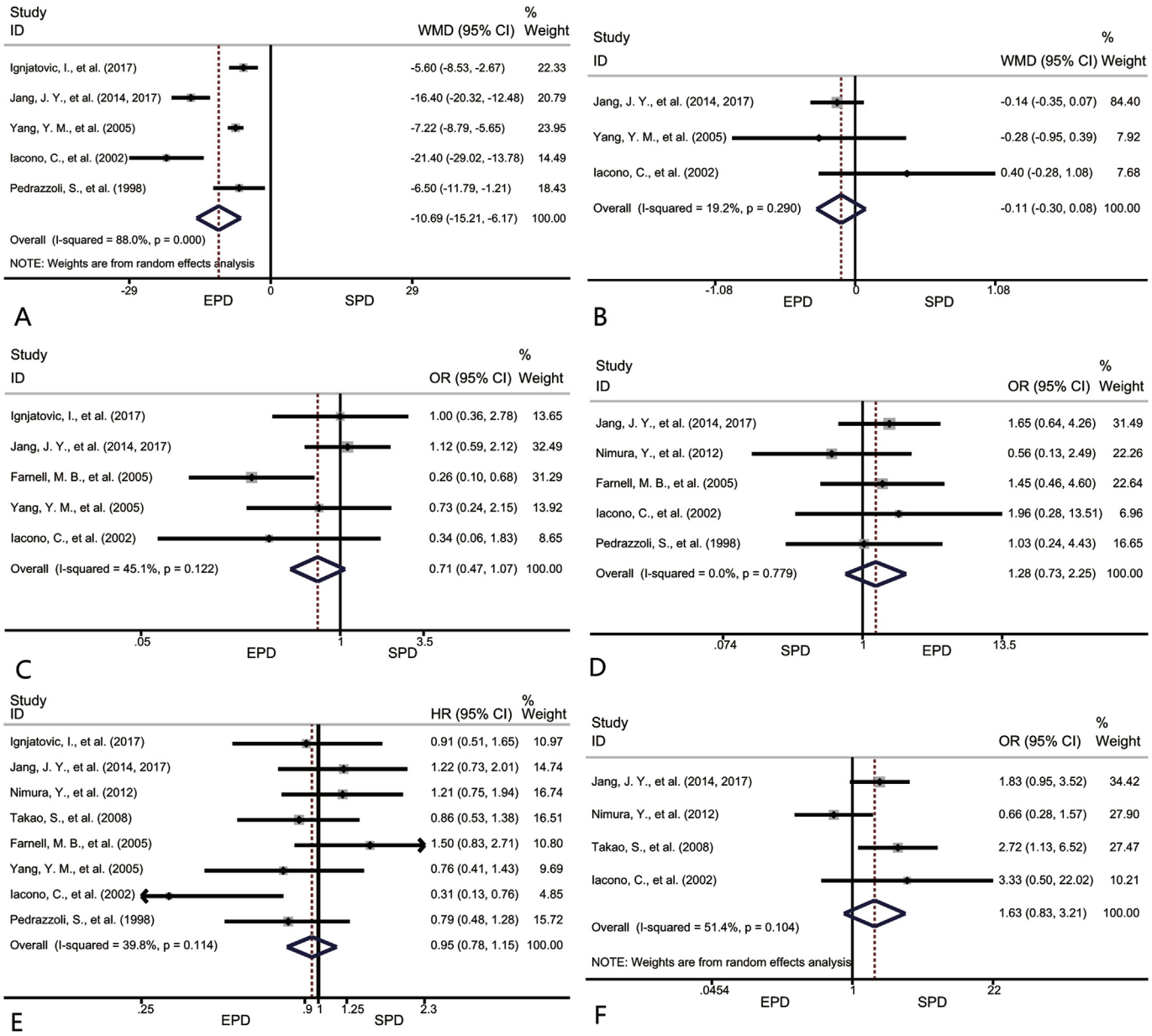

Fig. 3. Forest plot of meta-analysis in pathologic outcomes, survival and recurrence. A, Forest plot of WMD of lymph nodes harvested. B, Forest plot of WMD of tumor size. C, Forest plot of OR of lymph node metastasis. D, Forest plot of OR of positive margin. E, Forest plot of HR of overall survival. F, Forest plot of OR of local recurrence.

presented in the supplementary files (Figs. S2 and S3).

Discussion

This meta-analysis included eight studies with 687 (342 vs 345) cases to compare the short-term and long-term outcomes of SPD and EPD for patients with pancreatic head adenocarcinoma. Previous meta-analyses [16,29–32] included cases of periampullary cancer, which may reduce the credibility of the data. Our meta-analysis was included in the study in strict accordance with the inclusion criteria of patients diagnosed as pancreatic cephalic adenocarcinoma, excluding other periampullary carcinomas. To the best of our knowledge, this is the first meta-analysis on the short-term and long-term outcomes of EPD vs SPD for pancreatic head adenocarcinoma excluding cases of periampullary carcinoma. Although patients with benign tumors and those with periampullary tumors were included in the assessment of morbidity and mortality in the Farnell study, the patients were excluded from the survival analysis.

Just as showed in Table 1, our study included four RCTS and four non-RCTs. Nevertheless, according to the literature quality evaluation results, the non-RCTs were of relatively high quality. Besides, sensitivity analysis was conducted on all the outcomes in the study and showed that the results were not affected by individual studies. Moreover, meta-analysis of RCT is not necessarily superior to non-RCT in terms of evidence level [33]. Among the primary outcomes, subgroup analyses of total complications and overall survival were performed, and the general trend was consistent.

Our study showed that EPD did not contribute to survival when compared with SPD (HR 0.95; 95% CI 0.78–1.15; $P = 0.61$). We also found that diarrhea (postoperative three months) in EPD was significantly higher than SPD, though there was no statistical difference in total complications between the two groups. Moreover, the single-arm synthesis revealed that perioperative complications

rate in EPD group was higher than SPD group (35% vs 28.8%; OR 0.79, $P = 0.186$), subgroup outcomes such as pancreatic leak (12.7% vs 10.9%; OR 0.81, $P = 0.536$), intra-abdominal hemorrhage (6.2% vs 4.4%; OR 0.76, $P = 0.624$), intro-abdominal abscess (7.8% vs 4.6%; OR 0.91, $P = 0.846$) and wound infection (8.1% vs 7.7%; OR 0.79, $P = 0.573$) showed the same trend. It indicated that EPD may even lead to an upward tendency in morbidity, met to the previous studies [16,29,30]. The operative time of EPD was longer than SPD, which meant patients who underwent EPD prolonged exposure to anesthetic agents that may affect the patients postoperative recovery and result in delayed discharge [34].

In this meta-analysis, the number of lymph nodes harvested from EPD was higher than SPD, it was conducive to guiding postoperative adjuvant treatment. Interestingly, Japanese RCT [22] do not include patients receiving adjuvant therapy to avoid confusion of survival benefits, but there may be also ethical issues. The benefits of adjuvant chemotherapy after surgery for pancreatic cancer are well known [35–38], and adjuvant therapy is recommended in the guidelines for the treatment of pancreatic adenocarcinoma in many countries. Nevertheless, more data of tumor recurrence were needed to estimate disease-free survival. Unfortunately, all included studies did not have sufficient data on tumor recurrence. Only four project studies recorded the local recurrence rate, and there was no significant difference in the local recurrence rate between the two groups (OR 1.63, $P = 0.154$). Therefore, more comparative studies are needed to record the details of tumor recurrence in the future. The ongoing multi-center RCT (NCT03081351), which focuses on recording long-term outcomes, will help supplement the relevant records.

Lack of standardized lymph node dissection coverage in the control study may affect the current findings [29]. However, lymph node dissection area in both standard and extended lymphadenectomy groups were not similar to each other in the most included trials. To ensure the high quality of the study, the standardization of the dissected lymph node stations in standard and extended groups should be the primary consideration, especially in multi-center RCT [22]. Fortunately, the international pancreatic surgery research group (ISGPS) reached a consensus in 2014, aiming to remove lymph nodes (LNs) 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, 17b in SPD [39]. The latest several RCTs (NCT02787187, NCT03081351, NCT02928081) determine the scope of SPD and EPD lymph node dissection according to ISGPS expert consensus, which is conducive to the standardization of lymph node dissection scope.

We acknowledge that there were some potential limitations to consider in this study. First, four of the included studies were non-randomized, increasing the risk of potential selection and publication bias. Second, the number of cases included in the study was limited. Third, the treatment within the group was a little different. The extent of lymph node dissection within the group was inconsistent. Moreover, whether postoperative adjuvant therapy or not and different treatment regimens may have some extent effect on the final results. Finally, although there was no heterogeneity in our main results, other results such as the duration of surgery, length of hospitalization, diarrhea and local recurrence were relatively high. Several factors can explain high heterogeneity, such as surgical experiences, different baseline characteristics among the studies, different regions and races.

In conclusion, EPD based on this meta-analysis does not contribute to overall survival, may even lead to increased morbidity. However, this conclusion needs to be tested in high quality multi-center randomized control trials.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.10.003.

Funding

None.

Authorship

WW was responsible for conception and design of the study, data collection and analysis, and manuscript writing. ZT designed the study, performed critical revision and supervised all phases of the study. YH, LW, LY and LY contributed to data collection and analysis.

References

[1] Moutinho-Ribeiro P, Coelho R, Giovannini M, Macedo G. Pancreatic cancer screening: still a delusion? Pancreatology 2017;17(5):754–65.
[2] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74(11):2913–21.
[3] Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review. Bethesda, MD: National Cancer Institute; 1975-2015. https://seer.cancer.gov/csr/1975_2015/. [Accessed April 2018]. based on November 2017 SEER data submission, posted to the SEER web site.
[4] NCI/SEER. 2018. https://seer.cancer.gov/statfacts/html/pancreas.html. [Accessed 1 March 2019]. Accessed.
[5] McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018;24(43):4846–61.
[6] Fortner J. Regional resection of cancer of the pancreas: a new surgical approach. Surgery 1973;73:307–20.
[7] Ishikawa O, Oohigashi H, Imaoka S, Sasaki Y, Kameyama M, Kabuto T, et al. Clinico-pathological study on the appropriate range of pancreatic resection to obtain operative curability of pancreatic head cancer. Nippon Geka Gakkai Zasshi 1984;85:363–9.
[8] Nagai H. An anatomical and pathological study of autopsy material on the metastasis of pancreatic cancer to para-aortic lymph nodes. Nippon Geka Gakkai Zasshi 1987;88:308–17.
[9] Nagakawa T, Konishi I, Higashino Y, Ueno K, Ohta T, Kayahara M, et al. The spread and prognosis of carcinoma in the region of the pancreatic head. Jpn J Surg 1989;19:510–8.
[10] Ishikawa O, Ohigashi H, Imaoka S, Furukawa H, Sasaki Y, Fujita M, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann Surg 1992;215:231–6.
[11] Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer 1993;72:2118–23.
[12] Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg 1988;208:215–20.
[13] Kawarada Y, Yokoi H, Isaji S, Naganuma T, Tabata M, Machishi H, et al. Modified standard pancreaticoduodenectomy for the treatment of pancreatic head cancer. Digestion 1999;60(Suppl 1):120–5.
[14] Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, et al. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta- analysis of 1909 patients. Eur J Surg Oncol 2009;35(1):79–86.
[15] Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg 2014;259(4):656–64.
[16] Orci LA, Meyer J, Combescure C, Bühler L, Berney T, Morel P, et al. A meta-analysis of extended versus standard lymphadenectomy in patients undergoing pancreatoduodenectomy for pancreatic adenocarcinoma. HPB 2015;17(7):565–72.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[18] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[19] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. 2016 [updated March 2011]. 2011, The Cochrane Collaboration.

Available from, Version 5.1. 0. www.cochrane-handbook.org.
[20] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
[21] Jang JY, Kang JS, Han YM, Heo JS, Choi SH, Choi DW, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for pancreatic head cancer: a multicenter prospective randomized controlled study. J Hepatobiliary Pancreat Sci 2017;24:426–33.
[22] Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci 2012;19:230–41.
[23] Takao S, Shinchi H, Maemura K, Kurahara H, Natsugoe S, Aikou T. Survival benefit of pancreaticoduodenectomy in a Japanese fashion for a limited group of patients with pancreatic head cancer. Hepato-Gastroenterology 2008;55:1789–95.
[24] Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–28.
[25] Yang YM, Wan YL, Tian XD, Zhuang Y, Huang YT. Outcome of pancreaticoduodenectomy with extended retroperitoneal lymphadenectomy for adenocarcinoma of the head of the pancreas. Chin Med J 2005;118(22):1863–9.
[26] Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508–17.
[27] Ignjatovic I, Knezevic S, Knezevic D, Dugalic V, Micev M, Matic S, et al. Standard versus extended lymphadenectomy in radical surgical treatment for pancreatic head carcinoma. J BUON 2017;22(1):232–8.
[28] Iacono C, Accordin S, Bortolasi L, Facci E, Zamboni G, Montresor E, et al. Results of pancreaticoduodenectomy for pancreatic cancer: extended versus standard procedure. World J Surg 2002;26(11):1309–14.
[29] Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007;94:265–73.
[30] Dasari BV, Pasquali S, Vohra RS, Smith AM, Taylor MA, Sutcliffe RP, et al. Extended versus standard lymphadenectomy for pancreatic head cancer: meta-analysis of randomized controlled trials. J Gastrointest Surg 2015;19:1725–32.
[31] Sun JF, Yang YX, Wang X, Yu Z, Zhang T, Song J, et al. Meta-analysis of the efficacies of extended and standard pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas. World J Surg 2014;38(10):2708–15.
[32] Ke K, Chen W, Chen YL. Standard and extended lymphadenectomy for adenocarcinoma of the pancreatic head: a meta-analysis and systematic review. J Gastroenterol Hepatol 2014;29(3):453–62.
[33] Abraham NS, Byrne CJ, Young JM, Solomon MJ. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. J Clin Epidemiol 2010;63:238–45.
[34] Harrison OJ, Smart NJ, White P, Brigic A, Carlisle ER, Allison AS, et al. Operative time and outcome of enhanced recovery after surgery after laparoscopic colorectal surgery. J Soc Laparoendosc Surg 2014;18(2):265–72.
[35] Liao WC, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Lancet Oncol 2013;14:1095–103.
[36] Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. J Am Med Assoc 2013;310:1473–81.
[37] Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol 2014;32:504–12.
[38] Mirkin KA, Greenleaf EK, Hollenbeak CS, Wong J. Time to the initiation of adjuvant chemotherapy does not impact survivalin patients with resected pancreatic cancer. Cancer 2016;122:2979–87.
[39] Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156(3):591–600.