Advances in Clinical Medicine 临床医学进展, 2023, 13(12), 20456-20470
Published Online December 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13122879

Hans汉斯

胰十二指肠切除术标准与扩大淋巴结清扫疗效对比的Meta分析

陈　庆[1,2,3,4]，刘　畅[1,2,3,4]，王槐志[1,2,3,4*]

[1]重庆医科大学，重庆
[2]中国科学院重庆绿色智能技术研究院，重庆
[3]中国科学院大学重庆学院，重庆
[4]重庆市人民医院肝胆胰腺外科，重庆

收稿日期：2023年11月25日；录用日期：2023年12月19日；发布日期：2023年12月29日

摘　要

目的：探讨胰十二指肠切除术中行标准清扫淋巴结与扩大淋巴结清扫的安全性与有效性。方法：检索PubMed、Cochrane Library、Embase、SinoMed、中国知网、万方数据库、维普数据库的临床随机对照研究，检索时间为建库时间至2023年4月1日，使用RevMan 5.4.1软件进行统计分析。结果：共计7篇文献、827例患者纳入分析，Meta分析提示EPD组较之于SPD组手术切缘阴性率更高(OR: 0.58, 95% CI: 0.38~0.89, P = 0.01)、淋巴结清扫数量更多(WMD: −10.13, 95% CI: −12.98~−7.28, P < 0.0001)、手术时间更长(WMD: −46.11, 95% CI: −69.54~−22.69, P = 0.0001)，两组在术中出血量、术中输血量、术后住院时长、5年生存期、无病生存期、术后并发症发生率、术后死亡率方面差异无统计学意义(P > 0.05)。结论：EPD组在术后5年生存期、死亡率、术后并发症、无病生存期等与SPD组差异无统计学意义，EPD手术时间更长，可以认为EPD较之于SPD无明显优势，不建议常规行EPD。

关键词

胰十二指肠切除术，淋巴结清扫，R0切除率，术后生存期

Comparison of Standard and Extended Lymph Node Dissection in Pancreaticoduodenectomy: A Meta-Analysis

Qing Chen[1,2,3,4], Chang Liu[1,2,3,4], Huaizhi Wang[1,2,3,4*]

[1]Chongqing Medical University, Chongqing
[2]Chongqing Institute Green and Intelligent Technology, Chinese Academy of Sciences, Chongqing
[*]通讯作者。

文章引用: 陈庆, 刘畅, 王槐志. 胰十二指肠切除术标准与扩大淋巴结清扫疗效对比的 Meta 分析[J]. 临床医学进展, 2023, 13(12): 20456-20470. DOI: 10.12677/acm.2023.13122879

[3]Chongqing School, University of Chinese Academy of Sciences, Chongqing
[4]Department of Hepatopancreatobiliary Surgery, Chongqing General Hospital, Chongqing

Received: Nov. 25th, 2023; accepted: Dec. 19th, 2023; published: Dec. 29th, 2023

Abstract

Objective: To investigate the safety and efficacy of standard lymphadenectomy and extended lymphadenectomy in pancreaticoduodenectomy. Methods: PubMed, Cochrane Library, Embase, SinoMed, CNKI, Wanfang database, and VIP database were searched for randomized controlled trials (RCTs) published from the establishment of the database to April 1, 2023. RevMan 5.4.1 software was used for statistical analysis. Results: A total of 7 articles with 827 patients were included in the analysis. The meta-analysis showed that EPD group had a higher rate of negative surgical margins (OR: 0.58, 95% CI: 0.38~0.89, P = 0.01) and more lymph nodes retrieved (WMD: −10.13, 95% CI: −12.98~−7.28, P = 0.0001), longer operation time (WMD: −46.11, 95% CI: −69.54~−22.69, P = 0.0001). There were no significant differences in intraoperative blood loss, intraoperative blood transfusion, length of postoperative hospital stay, 5-year survival, disease-free survival, postoperative complications, and postoperative mortality between the two groups (P > 0.05). Conclusions: There were no significant differences in 5-year survival, mortality, postoperative complications and disease-free survival between the two groups, but the operation time of EPD was longer. EPD has no obvious advantage over SPD, and it is not recommended to perform EPD routine operation.

Keywords

Pancreaticoduodenectomy, Lymphadenectomy, R0 Resection Rate, Postoperative Survival Time

Copyright © 2023 by author(s) and Hans Publishers Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/
Open Access

1. 引言

胰腺癌是恶性程度非常高，在美国，其死亡率已经超过乳腺癌成为癌症相关死亡的第三大原因。由于胰腺癌具有高侵袭性、高转移性、高复发性等特征，其预后极差，5 年总体生存率仅有 12% [1]。手术切除仍然是胰腺癌的首选治疗方式。

Whipple 等人提出的胰十二指肠切除术(Pancreaticoduodenectomy, PD)是治疗胰腺癌的经典手术方式。Fortner [2]于 1973 年提出了区域性胰十二指肠切除理论，相较于传统 Whipple 手术，该手术方式更广，包括了胰腺周围组织淋巴结、血管旁及后腹膜淋巴结的清扫以达到根治性切除的目的并在随后广泛使用。在 20 世纪 80 年代，日本学者的回顾性研究认为扩大淋巴结的清扫范围能够使患者的术后生存期延长[3] [4]，因此推荐行扩大清扫淋巴结的胰十二指肠切除术。然而，随后的前瞻性随机对照试验认为扩大淋巴结清扫并不能增加患者的总体生存率[5] [6]，而且可能会增加术后并发症的发生率[7]-[12]。因此，关于胰十二指肠切除术是否行扩大淋巴结清扫仍然存在争议。因此，本研究针对上述问题检索已发表的随机对照试验进行 Meta 分析，探讨胰十二指肠切除术标准清扫淋巴结与扩大清扫淋巴结的疗效差异，为制定最佳临床决策提供依据。

2. 资料方法

2.1. 文献检索策略

检索 PubMed、Embase、Cochrane Library、SinoMed、中国知网、万方、维普电子数据库，检索时间为建库至 2023 年 4 月 1 日。使用“主题 + 自由词”方式检索。英文检索词为：“Pancreatic Cancer、Pancreaticoduodenectomy、Lymphadenectomy”。中文检索词为：“胰腺癌”、“胰十二指肠切除术”、“淋巴结清扫”。检索过程中无语言限制。

2.2. 研究资料的纳入及排除标准

纳入标准：1) 研究类型为临床随机对照试验(Randomized Controlled Trial, RCT)；2) 研究对象为胰腺癌患者，主要为胰头癌患者；3) 手术方式均为胰十二指肠切除术并且行 SPD 或 EPD。排除标准：1) 综述、个案报道、回顾性分析、动物试验等非随机对照研究；2) 研究对象非胰腺癌患者，如壶腹部癌；3) 信息不全或无法获取，重复报告等。

2.3. 数据提取

由 2 名研究者独立检索相关文献，使用 EndNote X9 软件排除重复文献，通过阅读题目及摘要，根据纳入及排除标准，初步排除不符合纳入标准的文献。对可能符合要求的文献，获取全文后进行进一步评估。文献数据提取信息包括：1) 一般信息：文献作者、题目、年份、单位、国家；2) 研究特征：患者一般特征，包括平均年龄、性别、随访时间；3) 临床病理特征：肿瘤大小、淋巴结阳性率；4) 手术特征：手术方式、淋巴结清扫范围、淋巴结切除个数、手术时间、术中出血、肿瘤切缘状态；5) 术后结局：生存率、术后并发症、术后住院时间，术后死亡人数等。

2.4. 文献质量评价

2 名研究人员独立采用 Cochrane 协作网推荐的偏倚风险评估工具进行偏倚风险评估，包括以下 7 项：1) 随机序列产生；2) 分配隐藏；3) 研究人员与受试者盲法；4) 结局评估盲法；5) 不全结局数据；6) 选择性报告；7) 其他偏倚。每项包含：Low Risk of Bias (低风险)、Unclear Risk of Bias (风险不明)、High Risk of Bias (高风险) 3 个等级。评价过程中如果出现分歧，则通过讨论或请第三位作者协商解决。

2.5. 统计学方法

采用 Review Manager 5.4 统计软件进行 Meta 分析。计数资料采用比值比(Odds Ratio, OR)作为效应指标，计量资料则用均数差(Mean Difference, MD)作为效应指标。生存分析则采用风险比(Hazard Ratio, HR)作为效应指标，由于 HR 值无法在文献中直接获取，故我们采用 Tierney [13]等人提供的方法，通过提取文献内提供的生存曲线(Kaplan-Meier Curves)数据计算 HR 值及其标准误再进行 Meta 分析。各研究间异质性以 I^2 衡量，$I^2 < 50\%$，表明各研究间异质性较小，采用固定效应模型，$I^2 \geq 50\%$表明异质性过大，采用随机效应模型。各研究间异质性过大或无法判断异质性来源时，仅做描述性分析。$P \leq 0.05$ 被认为差异具有统计学意义。

3. 结果

3.1. 文献纳入

共检索获得文献 1896 篇，其中 PubMed 数据库 462 篇，Embase 数据库 1063 篇，Cochrane Library 68 篇，SinoMed79 篇，中国知网 102 篇，万方数据库 99 篇，维普数据库 23 篇。通过查重、阅读标题、摘要剔除 1879 篇，剩下的 17 篇文献中，剔除非 RCT 文献 2 篇[14] [15]，剔除非胰腺癌 2 篇[16] [17]，剔除

数据不全的早期文献 2 篇[18] [19]。其中，有 3 篇文献[8] [20] [21]是来自美国约翰霍普金斯大学的同一项研究的不同阶段报告，2 篇[5] [22]是来自于韩国的同一项研究的不同阶段报告，故最终将他们视作 2 篇文献纳入，最终纳入 7 篇 RCT 文献，共 827 例患者，其中行标准淋巴结清扫术(Standard Pancreaticoduodenectomy, SPD)患者 409 例，行扩大淋巴结清扫术(Extended Pancreaticoduodenectomy, EPD)患者 418 例，文献检索流程见图 1。

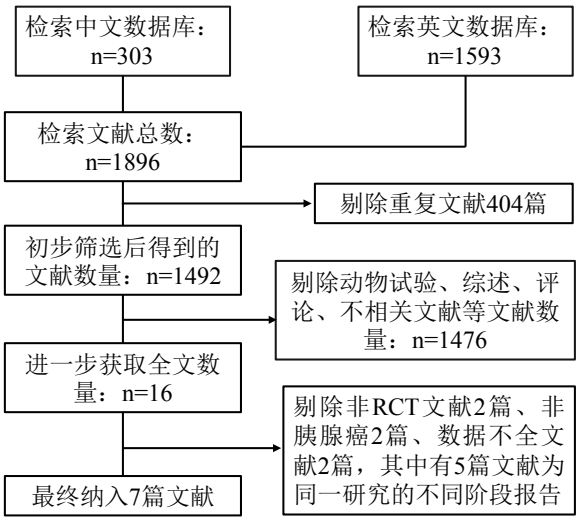

Figure 1. Study selection process
图 1. 文献检索流程图

3.2. 纳入文献偏倚风险评估

根据 Cochrane 手册推荐的偏倚风险评估量表对纳入文献研究进行风险偏倚评估。在随机方法方面，4 篇文献[5] [7] [8] [12]报告了随机序列产生方法，故为低风险，其余文献风险不明。在分配隐藏上，3 篇文献[5] [10] [12]对分配隐藏方案进行了报道，为低风险，其余研究风险不明。在研究者与受试者双盲的评估上，所有研究均未报告双盲，故为高风险。在结局评估盲法上面，2 篇文献[5] [10]为低风险，其余为高风险；在不全数据结局上，5 篇文献[5] [7] [8] [9] [12]无数据缺失为低风险，余为高风险。在选择性报告上，所有文献均未提及，风险不明。所有研究无其他偏倚(见图 2、图 3)。

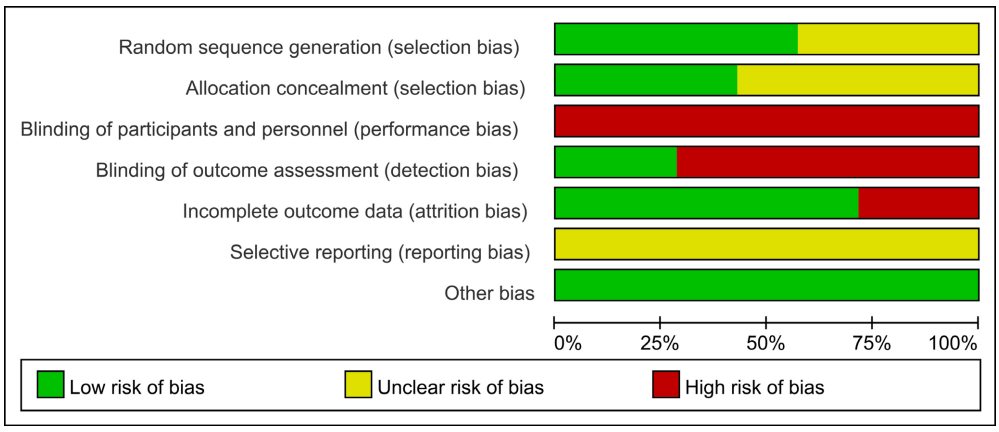

Figure 2. Bias assessment
图 2. 偏倚风险图

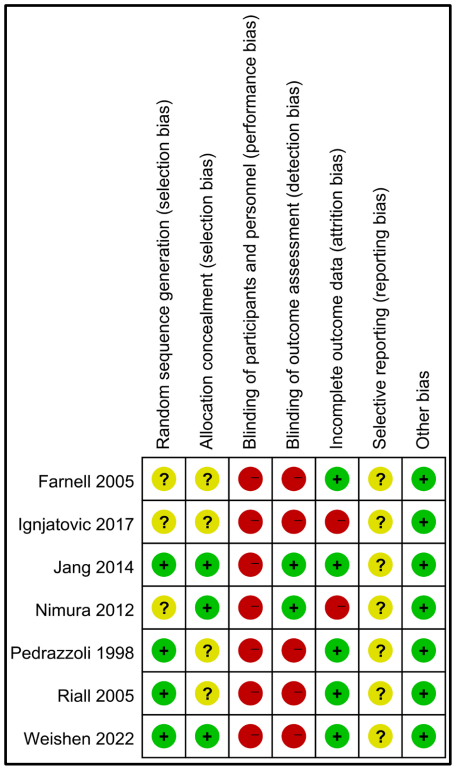

Figure 3. details of bias assessment
图 3. 风险评估详情

3.3. Meta 分析结果

共纳入 7 篇 RCT 文献，827 例患者，其中 SPD 组患者 409 例，EPD 组患者 418 例，纳入文献的一般特征见表 1，其中，Raill 等人[8]的研究包含壶腹部周围癌患者，我们从中提取胰腺癌的相关数据，两组在病理学和人口统计学可比。

Table 1. Characteristic of included literatures
表 1. 纳入文献一般特征

文献	年份	国家	研究类型	分组	人数	男/女	平均年龄	肿瘤大小(cm)	淋巴结阳性
Farnell *et al.*	2005	America	RCT	Standard	40	22/20	64.1	3.1	21
				Extended	39	21/18	64.5	3.1	23
Ignjatovic *et al.*	2017	Serbia	RCT	Standard	30	12/18	64.5 ± 6.1	NR	17
				Extended	30	14/16	59.7 ± 9.3	NR	17
Jang *et al.*	2014	Korea	RCT	Standard	83	49/34	62.0 ± 8.7	2.98 ± 0.84	57
				Extended	86	44/42	63.4 ± 9.5	3.12 ± 0.91	57
Nimura *et al.*	2012	Japan	RCT	Standard	51	32/19	62.7	NR	32
				Extended	50	34/16	62.9	NR	30
Pedrazzoli *et al.*	1998	Italy	RCT	Standard	40	27/13	62.0	3.4	24
				Extended	41	25/16	59.2	2.9	24
Riall *et al.*	2005	America	RCT	Standard	146 (84)	48/ 35	66.2 ± 0.9	3.0 ± 0.1	61
				Extended	148 (83)	43/41	65.2 ± 0.9	2.8 ± 0.1	62
Weishen *et al.*	2022	China	RCT	Standard	81	55/26	63.4 ± 9.3	3.0 ± 0.9	43
				Extended	89	55/34	60.8 ± 9.5	3.2 ± 1.0	47

注：Raill 等人的研究包含壶腹部周围癌患者，其中括号内的为胰腺癌患者。RCT：randomized controlled trial；NR：not reported。

3.4. 手术特征及住院时长

手术及住院相关数据见表 2、表 3，Meta 分析提示：EPD 组手术时间更长(WMD: −46.11, 95% CI: −69.54~−22.69, P < 0.00001)，淋巴结清扫数量更多(WMD: −10.13, 95% CI: −12.98~−7.28, P < 0.0001)，两组差异有统计学意义，二组在术中出血量、术中输血量、住院时长等方面差异无统计学意义(P > 0.05) (见图 4、图 5)。

Table 2. Operation characteristics
表 2. 手术特征

文献	分组	淋巴结清扫范围	手术时长(min)	术中出血(ml)	术中输血(ml)	淋巴结清扫数	切缘阴性
Farnell *et al.*	Standard	3, 4, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17	378.0	NR	NR	15.0	29
	Extended	3, 4, 5, 6, 8a, 8p, 9, 12a, 12b, 12c, 12p, 13a, 13b, 14a, 14b, 14c, 14d, 14v, 1	450.0	NR	NR	34.0	28
Ignjatovic *et al.*	Standard	8a, 13a, 12b1, 12b2, 12c, 13b, 17a, 17b, 14, 14b	305 ± 58.3	NR	NR	18.5 ± 5	NR
	Extended	8a, 8p, 9, 12a1, 12a2, 12b1, 12b2, 12c, 12p1, 12p2, 14a, 14b, 14c, 14d	446 ± 135.2	NR	NR	24.1 ± 6.5	NR
Jang *et al.*	Standard	12 b, 12 c, 13, 17	355.5 ± 12.4	372.3 ± 22.4	20.0 ± 10	17.3 ± 10.6	71
	Extended	5, 6, 8, 9.12a, 12b, 12c, 12p, 12h, 13, 14a, 14b, 14c, 14d, 16a2, 16b1, 17	419.6 ± 13.0	563.0 ± 56.3	50.0 ± 18	33.7 ± 15.1	78
Nimura *et al.*	Standard	13a, 13b, 17a, 17b	426.0	1118	420.0	13.3	48
	Extended	8a, 8p, 9, 12a, 12b, 12c, 12p, 13, 14a, 14b, 14c, 14d, 14v, 16a2, 17	547.0	1680	480.0	40.1	45
Pedrazzoli *et al.*	Standard	5, 6, 8a, 8p, 12b, 13, 17, 18	371.9 ± 49.8	NR	390.0 ± 40	13.3 ± 8.3	29
	Extended	5, 6, 8a, 8p, 9, 12a, 12b, 12c, 12p, 13, 14a, 14b, 14c, 14d, 14v, 16a1, 16a2, 16b1, 17, 18	396.7 ± 49.9	NR	414.0 ± 40	19.8 + 15.1	32
Riall *et al.*	Standard	12b, 12c, 13, 14b, 14v, 17	354.0 ± 6	740 ± 40	100 ± 20	17.0 ± 0.6	67
	Extended	3, 4, 5, 6, 9, 12b, 12c, 13, 14b, 14v, 16a2, 16b1, 17	384.0 ± 6	800 ± 40	100 ± 20	28.5 ± 0.6	79
Wei Shen *et al.*	Standard	5, 6, 8a, 12b, 12c, 13, 14a, 14b, 17	302.5 ± 81.7	416.7 ± 450	738.3 ± 814	16.4 ± 7.5	70
	Extended	5, 6, 8a, 8p, 12a, 12b, 12c, 12p, 13, 13, 14a, 14b, 14c, 14d, 16, 17	315.7 ± 73.0	415.7 ± 317	728.1 ± 640	26.4 ± 9.8	84

NR: not reported.

Table 3. Complications and length of hospital stay
表 3. 并发症和住院时长

文献	分组	人数	总体并发症	胰瘘	胃排空障碍	腹腔感染	术后出血	术后死亡	住院时长
Farnell *et al.*	Standard	40	NR	3	11	2	NR	0	13.0
	Extended	39	NR	5	14	4	NR	1	16.0
Ignjatovic *et al.*	Standard	30	7	4	2	NR	0	1	17.9
	Extended	30	9	7	6	NR	1	2	21.7
Jang *et al.*	Standard	83	36	8	8	6	3	0	19.7 ± 9.4
	Extended	86	28	11	5	6	5	2	22.8 ± 17.1
Nimura *et al.*	Standard	51	10	NR	NR	NR	NR	0	43.8
	Extended	50	11	NR	NR	NR	NR	1	42.4
Pedrazzoli *et al.*	Standard	40	18	5	NR	1	3	2	22.7 ± 1.4
	Extended	41	14	3	NR	1	3	2	19.3 ± 1.1
Riall *et al.*	Standard	146 (84)	24	5	5	2	NR	3	11.3 ± 0.5
	Extended	148 (83)	36	11	13	3	NR	2	14.3 ± 0.8
Wei Shen *et al.*	Standard	81	34	8	1	16	2	0	22.3 ± 12.9
	Extended	89	44	6	1	25	2	2	22.6 ± 12.3

NR: not reported.

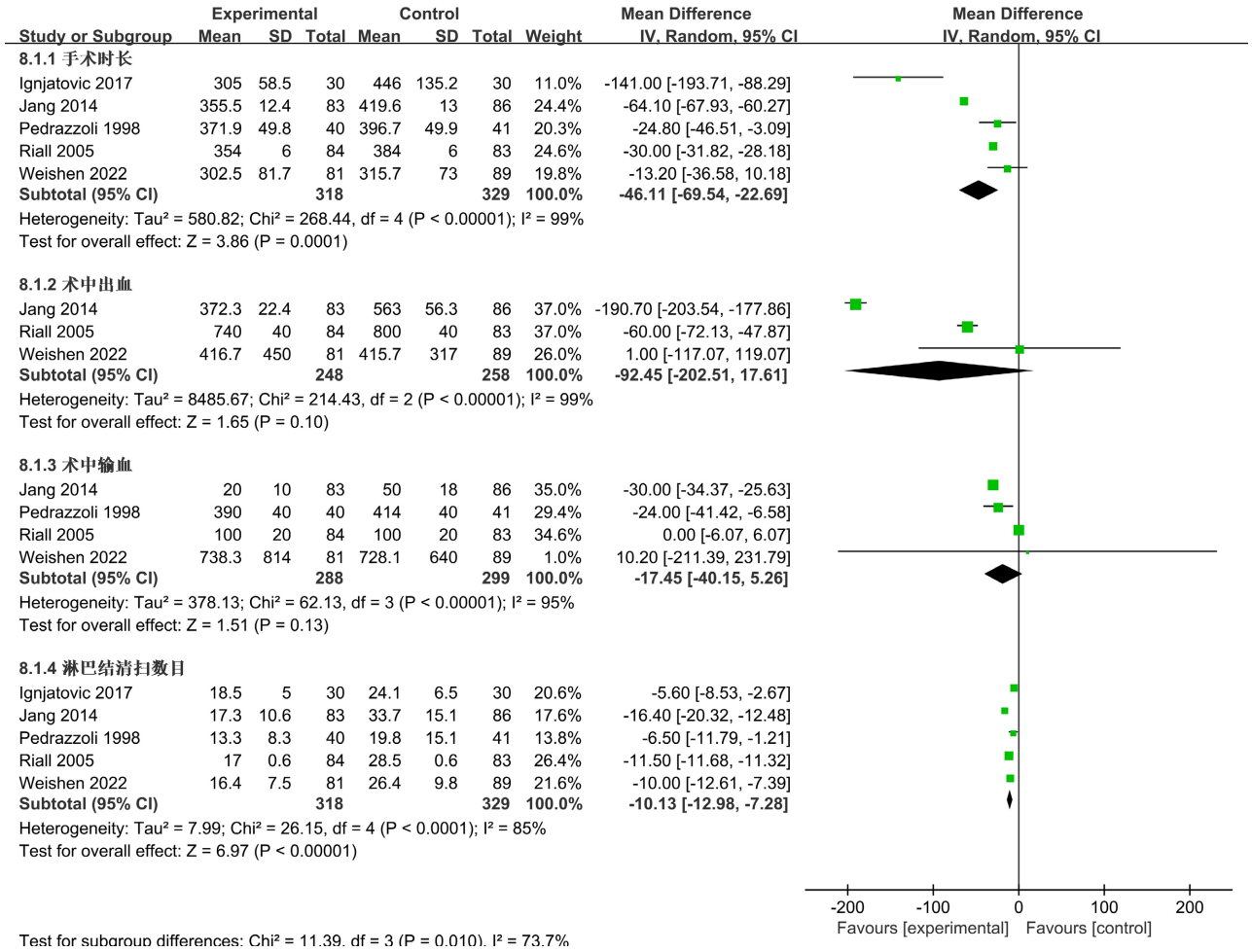

Figure 4. Forest plots of surgical characteristics in the SPD and EPD groups
图 4. SPD 组与 EPD 组手术特征对比的森林图

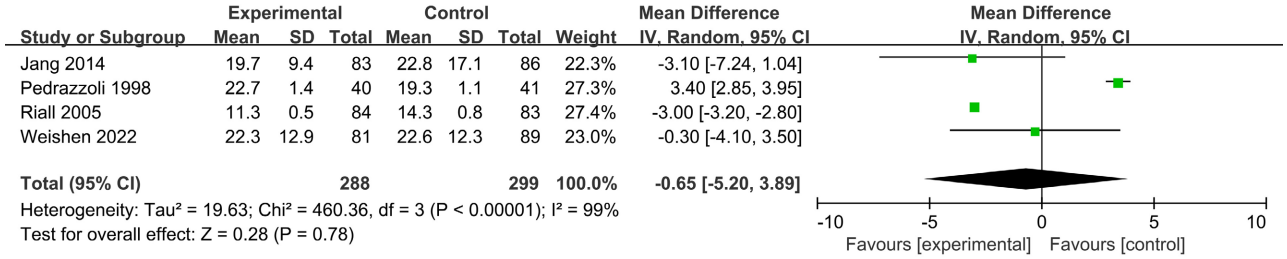

Figure 5. Forest plot of length of hospital stay between SPD and EPD groups
图 5. SPD 组与 EPD 组住院时长对比的森林图

3.5. 术后 5 年生存期

所有研究均以 Kaplan-Meier 曲线形式呈现生存数据，827 例患者剔除术后死亡及失访等 24 例患者后剩余 803 例患者，其中 SPD 组 400 例，EPD 组 403 例患者。Meta 分析结果显示(见图 6)：SPD 组与 EPD 组在术后 5 年生存期上差异无统计学意义(HR: 0.95, 95% CI: 0.80~1.13, P = 0.57)。考虑到患者淋巴结转移情况与术后辅助治疗情况可能对患者生存期产生影响，我们为此进行了亚组分析(见图 7)。

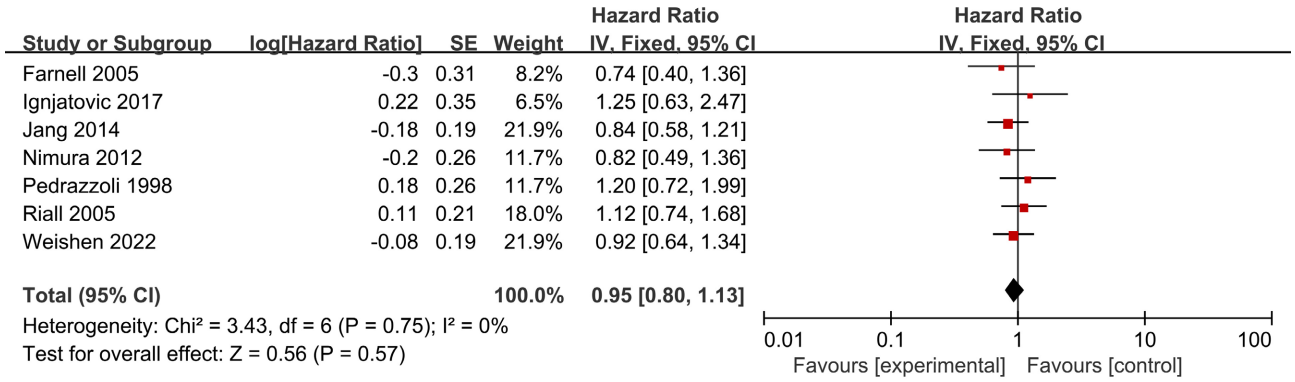

Figure 6. Forest plot of postoperative 5-year survival between SPD group and EPD group
图 6. SPD 组与 EPD 组术后 5 年生存期对比森林图

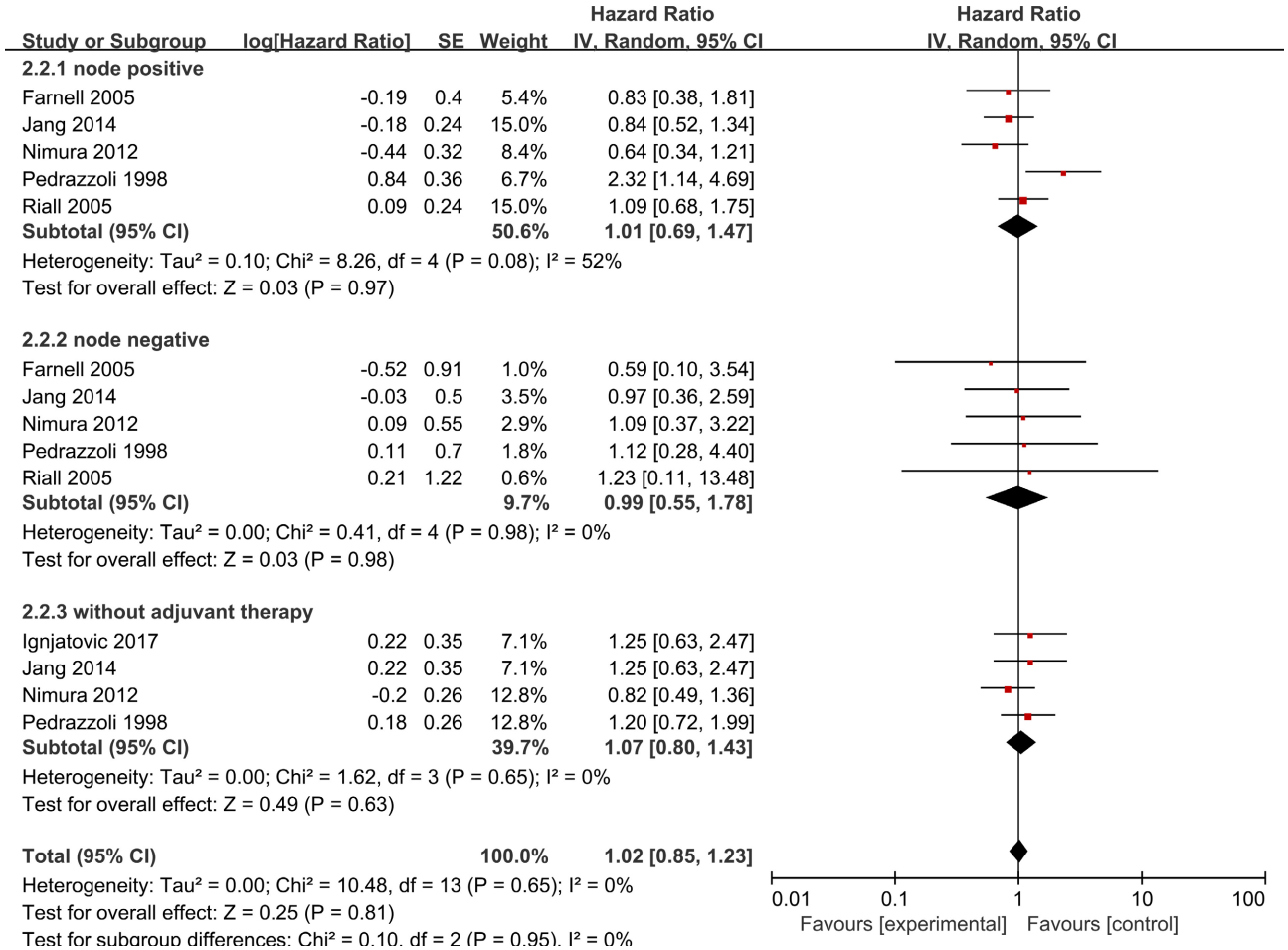

Figure 7. Forest plots for subgroup analysis of postoperative survival in SPD group and EPD group
图 7. SPD 组与 EPD 组术后生存期亚组分析森林图

3.5.1. 淋巴结病检亚组

共 5 项研究报道患者术后淋巴结病检数据。淋巴结阳性 396 例患者，SPD 组 200 例，EPD 组 196 例，淋巴结阴性患者 187 例，SPD 组 92 例，EPD 组 95 例。Meta 分析结果显示：在术后淋巴结病检阳性患者

生存期(HR: 1.01, 95% CI: 0.69~1.47, P = 0.97)、术后淋巴结病检阴性患生存期(HR: 0.99, 95% CI: 0.55~1.78, P = 0.98)上，两组差异无统计学意义(见图 7)。

3.5.2. 术后无辅助治疗亚组

共 4 项研究报道术后无辅助治疗患者生存期数据，共 279 例患者，SPD 组 138 例，EPD 组 141 例。Meta 分析结果显示：两组生存期差异无统计学意义(HR: 1.07, 95% CI: 0.80~1.43, P = 0.63) (见图 7)。

3.6. 无病生存期

3 个研究报道患者无病生存期数据，共 437 例患者，SPD 组 215 例，EPD 组 222 例，Meta 分析结果(见图 8)显示：SPD 组与 EPD 组无病生存期无统计学意义(HR: 0.83, 95% CI: 0.66~1.05, P = 0.11)。

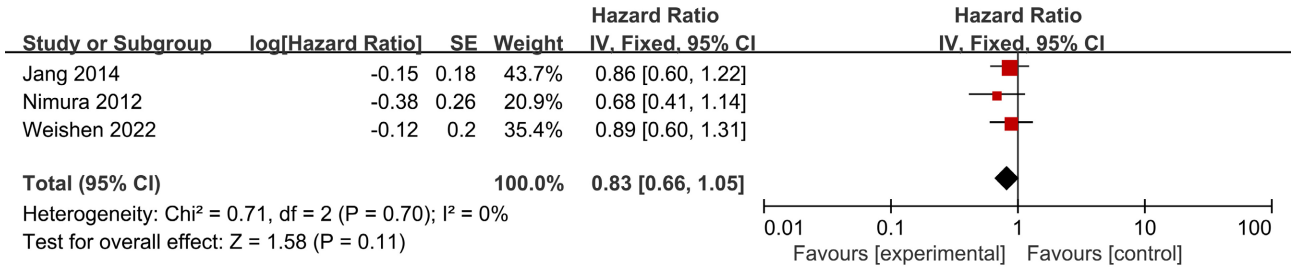

Figure 8. Forest plots of disease-free survival between SPD and EPD groups
图 8. SPD 组与 EPD 组无病生存期的森林图

3.7. 术后并发症

术后并发症数据详见表 3，Meta 分析结果显示：两组在总体并发症(OR: 0.91, 95% CI: 0.67~1.22, P = 0.52)和胰瘘(OR: 0.76, 95% CI: 0.47~1.23, P = 0.27)、腹腔感染(OR: 0.69; 95% CI: 0.40~1.19, P = 0.18)、术后出血(OR: 0.76, 95% CI: 0.31~1.88, P = 0.55)、胃排空障碍(OR: 0.64, 95% CI: 0.37~1.10, P = 0.10)等主要并发症方面(见图 9、图 10)，两组差异无统计学意义。

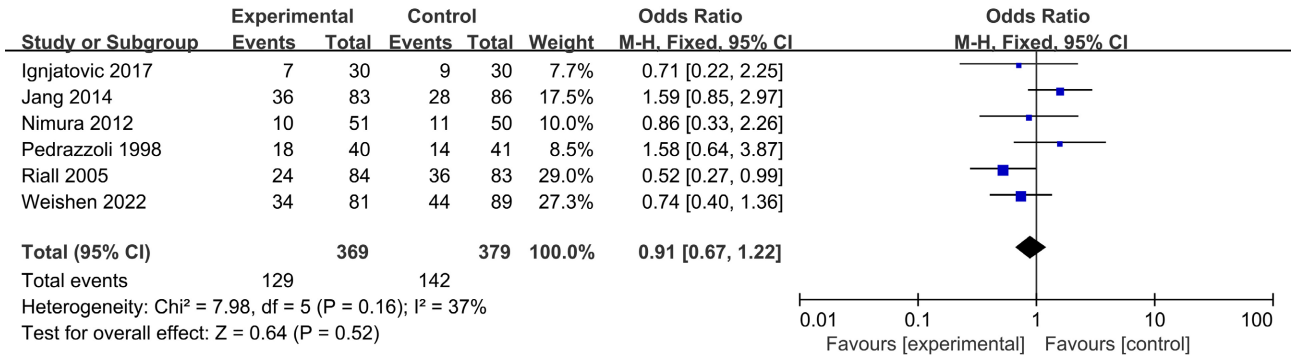

Figure 9. Forest plots of overall postoperative complication rates between SPD group and EPD group
图 9. SPD 组与 EPD 组术后总体并发症发生率森林图

3.8. 术后死亡率

死亡相关数据详见表 3，Meta 分析结果显示(见图 11)：两组在术后死亡率的差异上无统计学意义(OR: 0.57, 95% CI: 0.24~1.38, P = 0.21)。

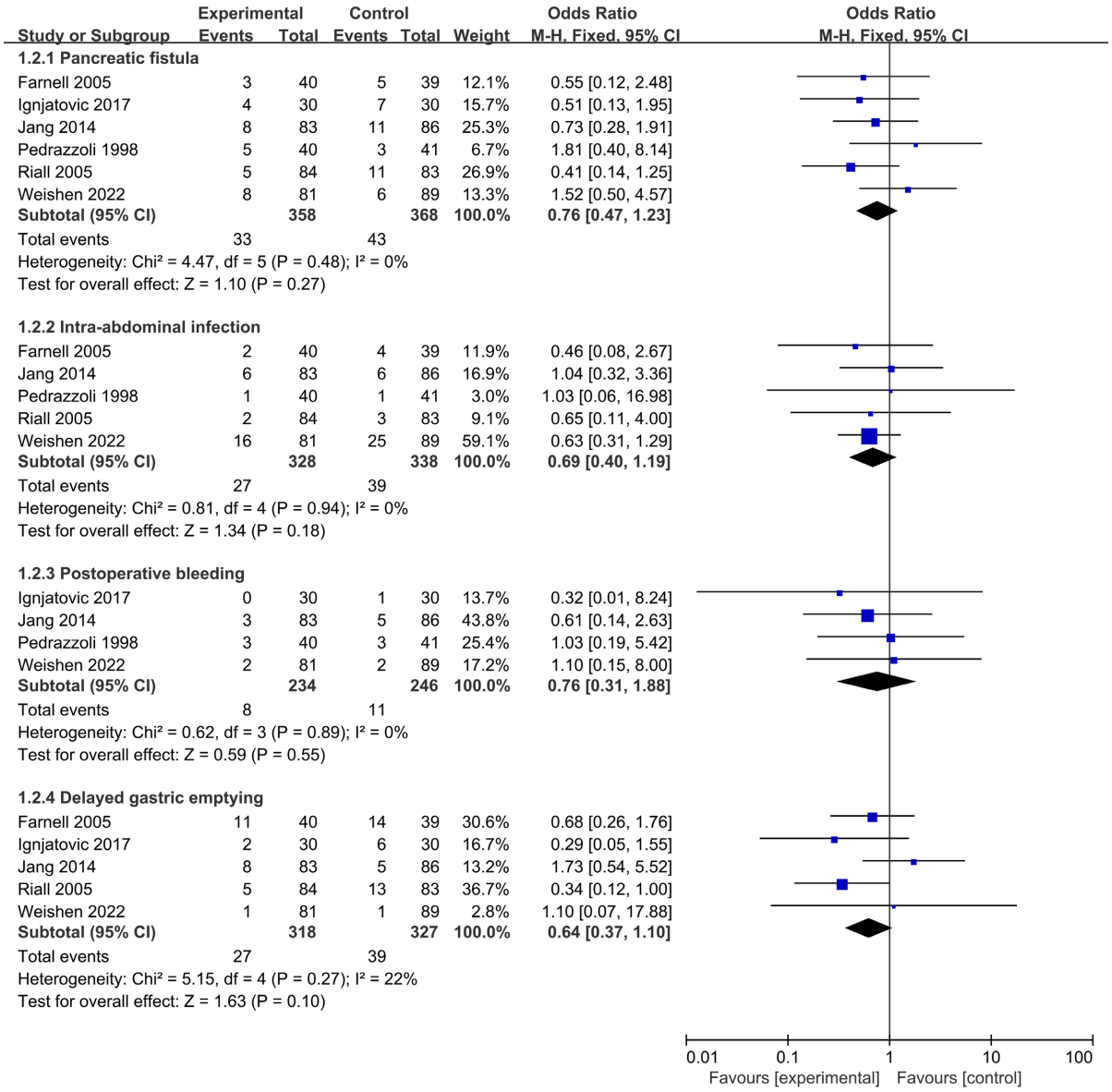

Figure 10. Forest plots of the incidence of major postoperative complications in the SPD and EPD groups
图 10. SPD 组与 EPD 组术后主要并发症发生率森林图

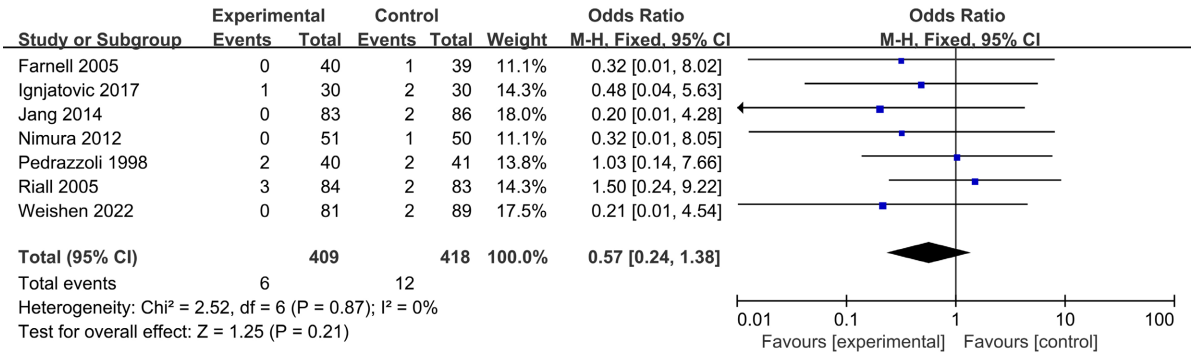

Figure 11. Forest plot of total postoperative mortality between SPD and EPD groups
图 11. SPD 组与 EPD 组总术后死亡率的森林图

3.9. 手术切缘

手术切缘数据见表 2，在手术切缘阴性(R0 切除)上，Meta 分析结果(见图 12)显示：EPD 组切缘阴性率更高，二组差异具有统计学意义(OR: 0.58, 95% CI: 0.38~0.89, P = 0.01)。

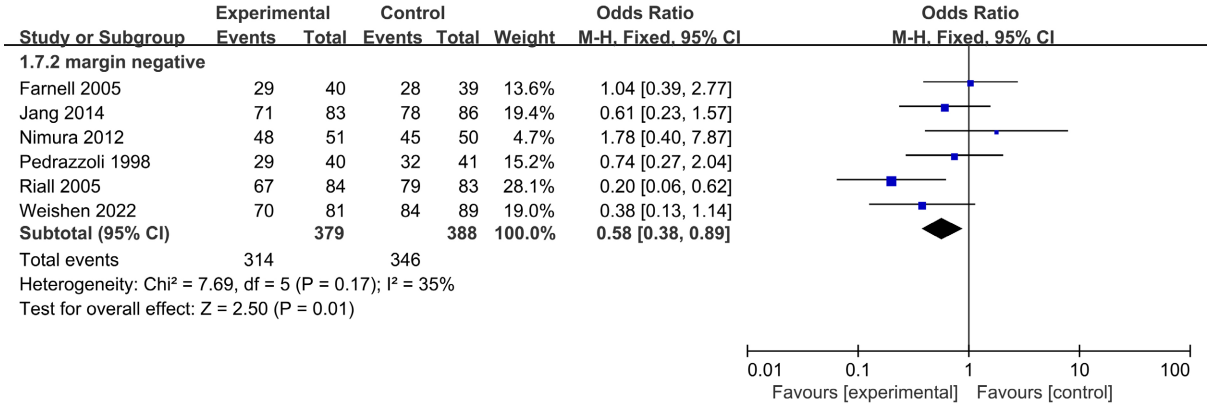

Figure 12. Forest plots of surgical margins in the SPD and EPD groups
图 12. SPD 组与 EPD 组手术切缘的森林图

4. 讨论

胰腺癌恶性程度高，胰十二指肠切除术是胰腺癌的经典手术方式，但在清扫淋巴结范围的问题上还存在争议。上世纪 80 年代，日本学者的回顾性研究发现行扩大清扫淋巴结的胰十二指肠切除术能提高患者的生存率[3] [4]，推荐行扩大清扫淋巴结的胰十二指肠切除术。我们 Meta 结果则表明 SPD 组与 EPD 组在术后 5 年生存期上的差异无统计学意义(P = 0.57)。Pedrazzoli 等人[7]的随机对照试验发现，在淋巴结病检阳性亚组中，EPD 组较 SPD 组生存时间更长，二组差异有统计学意义，而我们的 Meta 分析结果并未发现淋巴结阳性患者生存率有明显的差异(P = 0.97)，同时，我们对淋巴结病检阴性的患者的生存数据进行分析，两者生存率同样无统计学意义。术后辅助治疗可以提高胰腺癌患者的生存率[23] [24] [25]，为了避免其对结果的影响，我们选择对未进行术后辅助治疗的研究进行合并分析，Meta 分析的结果表明，两组的生存期差异无统计学意义。无病生存期是预后的重要标志，在无病生存期方面，EPD 组较之于 SPD 组，两组的差异同样无统计学意义。因此在术后生存期上，我们认为扩大清扫淋巴结并不能使患者获益。

Riall 等人[8] [20] [21]的研究表明，EPD 组在术后胃排空障碍发生率显著高于 SPD 组，一项 Meta 分析[26]结果也支持这个结论，但更多的随机对照试验[10] [12] [22]和 Orci [27]、Kotb [28]等人的 Meta 分析结果则表明两组差异无统计学意义，我们的 Meta 分析结果也表明两组差异无统计学意义。值得注意的是，在 Rial 等人的研究中，EPD 组行远端胃大部切除术的胰十二指肠切除术，SPD 组则行保留幽门的胰十二指肠切除术。我们进一步探讨保留幽门的胰十二指肠切除术是否会影响患者术后胃排空障碍发生率，Hüttner 等人[29]的 Meta 分析表明，保留幽门的胰十二指肠切除术在胃排空障碍发生率要小于传统胰十二指肠切除术，但 Zhou 等人[30] Meta 分析结论则与之相反，Busquets 等人[31]的随机对照试验则表明二者差异无统计学意义，不同研究结论不同，故需更多的高质量临床研究来证实不同手术方式对术后胃排空的影响。在术后死亡率和总体并发症、术后胰瘘、腹腔感染、术后出血等主要并发症方面我们的 Meta 分析结果显示两组差异并无统计学意义。

适当的淋巴结切除有助于控制肿瘤的进展及作为肿瘤分级的依据[32] [33]，同时，手术切缘阴性(R0 切除)患者术后生存期更长且术后复发率更低[34] [35] [36]。我们的 Meta 分析表明较之于 SPD 组，EPD

组 R0 切除率更高，EPD 组淋巴结清扫数量更多，这与 Riall 等人[8]的临床研究结论相同，但更多的随机对照试验[11] [12] [22]和 Meta 分析[37]并不支持这一结论，我们考虑 EPD 组 R0 切除率更高可能与 Riall 等人的研究采用的保留幽门的手术方式有关，但相关研究[29]证实保留幽门的胰十二指肠切除术并不影响 R0 切除率，排除 Raill 等人的研究，两组差异则无统计学意义(P = 0.19)，故我们 EPD 组 R0 切除率更高的结果持保留意见。关于扩大清扫淋巴结和标准清扫淋巴结组是否对手术切缘产生影响，需要更多的临床研究来证实。术中淋巴结的具体清扫个数也存在争议[38]，Huang 等人的队列研究[32]表明最佳清扫数目为 19 个，而 Zhang 等人的最新一项研究[39]表示清除大于 16 个淋巴结能显著提高患者的生存期。同时，淋巴结的清扫个数受手术方法的影响严重，如日本外科医生和病理学家共同合作以识别每个站的淋巴结，结果显示，日本方法比传统方法回收的淋巴结明显更多[40]。因此，关于淋巴结的具体清扫个数，未来需要更多的临床研究与更科学的识别方法来证实。

EPD 组手术时间长，相应术中麻醉时长延长则会给患者带来额外的经济负担[41]。我们探讨了 EPD 组手术时间长的原因，除了本身手术范围更广、操作步骤更为复杂外，还可能与不同地区医师操作熟练程度、采用不同的解剖入路有关。相关研究证实，外科医师手术量越多，其术中出血量与手术时长相应降低[42]，另有研究显示相较于标准入路，动脉先行入路手术时间更短[43]，可以显著降低患者术后出血量及术后并发症发生率[44]。

本研究存尚在以下不足之处，解读结果需谨慎：1) 本研究纳入的研究虽然为证据级别较高的随机对照试验，但研究数量少，仅有 7 项研究，样本量 827 例，纳入研究集中在手术量较少的西方国家，未能真正反映在世界范围内的真实水平；2) 研究质量并未达到理想水平，仅 3 项研究实行了分配隐藏、所有的研究均未实行双盲，部分研究数据不全、随机化方法不明等，这些可能导致偏倚的产生；3) 不同的中心医师水平不一、手术方式及淋巴结清扫范围的不同导致临床异质性较大。

综上，考虑到 EPD 在术后 5 年生存期、死亡率、术后并发症发生率、无病生存期等与 SPD 差异无统计学意义而 EPD 手术时间更长，故我们不建议常规行 EPD。

参考文献

[1] Siegel, R.L., Miller, K.D., Wagle, N.S. and Jemal, A. (2023) Cancer Statistics, 2023. *CA*: *A Cancer Journal for Clinicians*, **73**, 17-48. https://doi.org/10.3322/caac.21763

[2] Fortner, J.G. (1973) Regional Resection of Cancer of the Pancreas: A New Surgical Approach. *Surgery*, **73**, 307-320.

[3] Ishikawa, O., Ohhigashi, H., Sasaki, Y., Kabuto, T., Fukuda, I., Furukawa, H., Imaoka, S., and Iwanaga, T. (1988) Practical Usefulness of Lymphatic and Connective Tissue Clearance for the Carcinoma of the Pancreas Head. *Annals of Surgery*, **208**, 215-220. https://doi.org/10.1097/00000658-198808000-00014

[4] Manabe, T., Ohshio, G., Baba, N., Miyashita, T., Asano, N., Tamura, K., Yamaki, K., Nonaka, A., and Tobe, T. (1989) Radical Pancreatectomy for Ductal Cell Carcinoma of the Head of the Pancreas. *Cancer*, **64**, 1132-1137. https://doi.org/10.1002/1097-0142(19890901)64:5<1132::AID-CNCR2820640528>3.0.CO;2-V

[5] Jang, J.Y., Kang, M.J., Heo, J.S., Choi, S.H., Choi, D.W., Park, S.J., Han, S.S., Yoon, D.S., Yu, H.C., Kang, K.J., Kim, S.G. and Kim, S.W. (2014) 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. *Annals of Surgery*, **259**, 656-664. https://doi.org/10.1097/SLA.0000000000000384

[6] Lin, Q., Zheng, S., Yu, X., *et al*. (2023) Standard Pancreatoduodenectomy versus Extended Pancreatoduodenectomy with Modified Retroperitoneal Nerve Resection in Patients with Pancreatic Head Cancer: A Multicenter Randomized Controlled Trial. *Cancer Communications*, **43**, 257-275. https://doi.org/10.1002/cac2.12399

[7] Pedrazzoli, S., DiCarlo, V., Dionigi, R., Mosca, F., Pederzoli, P., Pasquali, C., Klöppel, G., Dhaene, K., and Michelassi, F. (1998) Standard versus Extended Lymphadenectomy Associated with Pancreatoduodenectomy in the Surgical Treatment of Adenocarcinoma of the Head of the Pancreas: A Multicenter, Prospective, Randomized Study. *Annals of Surgery*, **228**, 508-517. https://doi.org/10.1097/00000658-199810000-00007

[8] Riall, T.S., Cameron, J.L., Lillemoe, K.D., Campbell, K.A., Sauter, P.K., Coleman, J., Abrams, R.A., Laheru, D., Hruban, R.H., and Yeo, C.J. (2005) Pancreaticoduodenectomy with or without Distal Gastrectomy and Extended Retrope-

ritoneal Lymphadenectomy for Periampullary Adenocarcinoma—Part 3: Update on 5-Year Survival. *Journal of Gastrointestinal Surgery*, **9**, 1191-1206. https://doi.org/10.1016/j.gassur.2005.08.034

[9] Farnell, M.B., Pearson, R.K., Sarr, M.G., DiMagno, E.P., Burgart, L.J., Dahl, T.R., Foster, N., Sargent, D.J. and Pancreas Cancer Working Group (2005) A Prospective Randomized Trial Comparing Standard Pancreatoduodenectomy with Pancreatoduodenectomy with Extended Lymphadenectomy in Resectable Pancreatic Head Adenocarcinoma. *Surgery*, **138**, 618-630. https://doi.org/10.1016/j.surg.2005.06.044

[10] Nimura, Y., Nagino, M., Takao, S., Takada, T., Miyazaki, K., Kawarada, Y., Miyagawa, S., Yamaguchi, A., Ishiyama, S., Takeda, Y., Sakoda, K., Kinoshita, T., Yasui, K., Shimada, H. and Katoh, H. (2012) 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. *Journal of Hepato-Biliary-Pancreatic Sciences*, **19**, 230-241. https://doi.org/10.1007/s00534-011-0466-6

[11] Ignjatovic, I., Knezevic, S., Knezevic, D., Dugalic, V., Micev, M., Matic, S., Ostojic, S., Bogdanovic, M., Pavlovic, I. and Jurisic, V. (2017) Standard versus Extended Lymphadenectomy in Radical Surgical Treatment for Pancreatic Head Carcinoma. *Journal of BUON*, **22**, 232-238.

[12] Wang, W., Lou, W., Xu, Z., Chen, H., Shen, Z., Deng, X., Peng, C., Liu, Y. and Shen, B. (2023) Long-Term Outcomes of Standard versus Extended Lymphadenectomy in Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Chinese Multi-Center Prospective Randomized Controlled Trial. *Journal of Advanced Research*, **49**, 151-157. https://doi.org/10.1016/j.jare.2022.09.011

[13] Tierney, J.F., Stewart, L.A., Ghersi, D., Burdett, S. and Sydes, M.R. (2007) Practical Methods for Incorporating Summary Time-to-Event Data into Meta-Analysis. *Trials*, **8**, Article No. 16. https://doi.org/10.1186/1745-6215-8-16

[14] Shao, Q.S., Ye, Z.Y., Li, S.G. and Chen, K. (2008) Radical Pancreatoduodenectomy Combined with Retroperitoneal Nerve, Lymph, and Soft-Tissue Dissection in Pancreatic Head Cancer. *Chinese Medical Journal*, **121**, 1130-1133. https://doi.org/10.1097/00029330-200806020-00018

[15] Qian, L., Xie, J., Xu, Z., Deng, X., Chen, H., Peng, C., Li, H., Chai, W., Xie, J., Wang, W. and Shen, B. (2020) The Necessity of Dissection of No. 14 Lymph Nodes to Patients with Pancreatic Ductal Adenocarcinoma Based on the Embryonic Development of the Head of the Pancreas. *Frontiers in Oncology*, **10**, Article 1343. https://doi.org/10.3389/fonc.2020.01343

[16] Nguyen, T.C., Sohn, T.A., Cameron, J.L., Lillemoe, K.D., Campbell, K.A., Coleman, J., Sauter, P.K., Abrams, R.A., Hruban, R.H. and Yeo, C.J. (2003) Standard vs. Radical Pancreaticoduodenectomy for Periampullary Adenocarcinoma: A Prospective, Randomized Trial Evaluating Quality of Life in Pancreaticoduodenectomy Survivors. *Journal of Gastrointestinal Surgery*, **7**, 1-11. https://doi.org/10.1016/S1091-255X(02)00187-7

[17] Henne-Bruns, D., Vogel, I., Lüttges, J., Klöppel, G. and Kremer, B. (2000) Surgery for Ductal Adenocarcinoma of the Pancreatic Head: Staging, Complications, and Survival after Regional versus Extended Lymphadenectomy. *World Journal of Surgery*, **24**, 595-602. https://doi.org/10.1007/s002689910089

[18] Kremer, B., Vogel, I., Lüttges, J., Klöppel, G. and Henne-Bruns, D. (1999) Surgical Possibilities for Pancreatic Cancer: Extended Resection. *Annals of Oncology*, **10, S**252-S256. https://doi.org/10.1093/annonc/10.suppl_4.S252

[19] Soybel, D.I. (1999) Extended Lymphadenectomy for Carcinoma of the Head of the Pancreas. *Gastroenterology*, **116**, 1499-1500. https://doi.org/10.1016/S0016-5085(99)70520-2

[20] Yeo, C.J., Cameron, J.L., Sohn, T.A., Coleman, J., Sauter, P.K., Hruban, R.H., Pitt, H.A., and Lillemoe, K.D. (1999) Pancreaticoduodenectomy with or without Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma: Comparison of Morbidity and Mortality and Short-Term Outcome. *Annals of Surgery*, **229**, 613. https://doi.org/10.1097/00000658-199905000-00003

[21] Yeo, C.J., Cameron, J.L., Lillemoe, K.D., Sohn, T.A., Campbell, K.A., Sauter, P.K., Coleman, J., Abrams, R.A. and Hruban, R. H. (2002) Pancreaticoduodenectomy with or without Distal Gastrectomy and Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma, Part 2: Randomized Controlled Trial Evaluating Survival, Morbidity, and Mortality. *Annals of Surgery*, **236**, 355-368. https://doi.org/10.1097/00000658-200209000-00012

[22] Jang, J.Y., Kang, J.S., Han, Y., Heo, J.S., Choi, S.H., Choi, D.W., Park, S.J., Han, S.S., Yoon, D.S., Park, J.S., Yu, H. C., Kang, K.J., Kim, S.G., Lee, H., Kwon, W., Yoon, Y.S., Han, H.S. and Kim, S.W. (2017) Long-Term Outcomes and Recurrence Patterns of Standard versus Extended Pancreatectomy for Pancreatic Head Cancer: A Multicenter Prospective Randomized Controlled Study. *Journal of Hepato-Biliary-Pancreatic Sciences*, **24**, 426-433. https://doi.org/10.1002/jhbp.465

[23] Sho, M., Murakami, Y., Motoi, F., Satoi, S., Matsumoto, I., Kawai, M., Honda, G., Uemura, K., Yanagimoto, H., Kurata, M., Fukumoto, T., Akahori, T., Kinoshita, S., Nagai, M., Nishiwada, S., Unno, M., Yamaue, H. and Nakajima, Y. (2015) Postoperative Prognosis of Pancreatic Cancer with Para-Aortic Lymph Node Metastasis: A Multicenter Study on 822 Patients. *Journal of Gastroenterology*, **50**, 694-702. https://doi.org/10.1007/s00535-014-1005-4

[24] Mehtsun, W.T., McCleary, N.J., Maduekwe, U.N., Wolpin, B.M., Schrag, D. and Wang, J. (2022) Patterns of Adjuvant

Chemotherapy Use and Association with Survival in Adults 80 Years and Older with Pancreatic Adenocarcinoma. *JAMA Oncology*, **8**, 88-95. https://doi.org/10.1001/jamaoncol.2021.5407

[25] Mason, M.C., Russell, M.C. and Massarweh, N.N. (2023) Adjuvant Therapy for Pancreatic Adenocarcinoma-Leaving No Rock Unturned. *JAMA Oncology*, **9**, 305-307. https://doi.org/10.1001/jamaoncol.2022.5786

[26] Iqbal, N., Lovegrove, R.E., Tilney, H.S., Abraham, A.T., Bhattacharya, S., Tekkis, P.P. and Kocher, H.M. (2009) A Comparison of Pancreaticoduodenectomy with Extended Pancreaticoduodenectomy: A Meta-Analysis of 1909 Patients. *European Journal of Surgical Oncology*, **35**, 79-86. https://doi.org/10.1016/j.ejso.2008.01.002

[27] Orci, L.A., Meyer, J., Combescure, C., Bühler, L., Berney, T., Morel, P. and Toso, C. (2015) A Meta-Analysis of Extended versus Standard Lymphadenectomy in Patients Undergoing Pancreatoduodenectomy for Pancreatic Adenocarcinoma. *HPB*, **17**, 565-572. https://doi.org/10.1111/hpb.12407

[28] Kotb, A., Hajibandeh, S., Hajibandeh, S. and Satyadas, T. (2021) Meta-Analysis and Trial Sequential Analysis of Randomised Controlled Trials Comparing Standard versus Extended Lymphadenectomy in Pancreatoduodenectomy for Adenocarcinoma of the Head of Pancreas. *Langenbeck's Archives of Surgery*, **406**, 547-561. https://doi.org/10.1007/s00423-020-01999-5

[29] Hüttner, F.J., Fitzmaurice, C., Schwarzer, G., Seiler, C.M., Antes, G., Büchler, M.W. and Diener, M. K. (2016) Pylorus-Preserving Pancreaticoduodenectomy (pp Whipple) versus Pancreaticoduodenectomy (Classic Whipple) for Surgical Treatment of Periampullary and Pancreatic Carcinoma. *Cochrane Database of Systematic Reviews*, **2**, CD006053. https://doi.org/10.1002/14651858.CD006053.pub6

[30] Zhou, Y.M., Lin, L., Wu, L.P., Xu, D.H. and Li, B. (2015) A Case-Matched Comparison and Meta-Analysis Comparing Pylorus-Resecting Pancreaticoduodenectomy with Pylorus-Preserving Pancreaticoduodenectomy for the Incidence of Postoperative Delayed Gastric Emptying. *HPB*, **17**, 337-343. https://doi.org/10.1111/hpb.12358

[31] Busquets, J., Martín, S., Secanella, L., Sorribas, M., Cornellà, N., Altet, J., Peláez, N., Bajen, M., Carnaval, T., Videla, S. and Fabregat, J. (2022) Delayed Gastric Emptying after Classical Whipple or Pylorus-Preserving Pancreatoduodenectomy: A Randomized Clinical Trial (QUANUPAD). *Langenbeck's Archives of Surgery*, **407**, 2247-2258. https://doi.org/10.1007/s00423-022-02583-9

[32] Huang, L., Jansen, L., Balavarca, Y., van der Geest, L., Lemmens, V., Koerkamp, B.G., van Santvoort, H.C., Grützmann, R., Besselink, M.G., Schrotz-King, P. and Brenner, H. (2021) Significance of Examined Lymph Node Number in Accurate Staging and Long-term Survival in Resected Stage I-II Pancreatic Cancer-More Is Better? A Large International Population-Based Cohort Study. *Annals of Surgery*, **274**, e554-e563. https://doi.org/10.1097/SLA.0000000000003558

[33] Zaharia, C., Roalsø, M. and Søreide, K. (2022) The Prognostic Relevance of Examined Lymph Nodes for Accurate Staging of Resected Pancreatic Adenocarcinoma. *Hepatobiliary Surgery and Nutrition*, **11**, 632-635. https://doi.org/10.21037/hbsn-2022-14

[34] Demir, I.E., Jäger, C., Schlitter, A.M., Konukiewitz, B., Stecher, L., Schorn, S., Tieftrunk, E., Scheufele, F., Calavrezos, L., Schirren, R., Esposito, I., Weichert, W., Friess, H., and Ceyhan, G.O. (2018) R0 versus R1 Resection Matters after Pancreaticoduodenectomy, and Less after Distal or Total Pancreatectomy for Pancreatic Cancer. *Annals of Surgery*, **268**, 1058-1068. https://doi.org/10.1097/SLA.0000000000002345

[35] Kelly, K.N., Macedo, F.I., Seaton, M., Wilson, G., Hammill, C., Martin, R.C., Maduekwe, U.N., Kim, H.J., Maithel, S.K., Abbott, D.E., Ahmad, S.A., Kooby, D.A., Merchant, N.B. and Datta, J. (2022) Intraoperative Pancreatic Neck Margin Assessment during Pancreaticoduodenectomy for Pancreatic Adenocarcinoma in the Era of Neoadjuvant Therapy: A Multi-Institutional Analysis from the Central Pancreatic Consortium. *Annals of Surgical Oncology*, **29**, 6004-6012. https://doi.org/10.1245/s10434-022-11804-w

[36] Datta, J., Willobee, B.A., Ryon, E.L., Shah, M.M., Drebin, J.A., Kooby, D.A. and Merchant, N.B. (2021) Contemporary Reappraisal of Intraoperative Neck Margin Assessment during Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Review. *JAMA Surgery*, **156**, 489-495. https://doi.org/10.1001/jamasurg.2020.5676

[37] Ke, K., Chen, W. and Chen, Y. (2014) Standard and Extended Lymphadenectomy for Adenocarcinoma of the Pancreatic Head: A Meta-Analysis and Systematic Review. *Journal of Gastroenterology and Hepatology*, **29**, 453-462. https://doi.org/10.1111/jgh.12393

[38] Ogura, T., Ishida, H., Takahashi, A. and Kawashima, Y. (2022) Importance of an Appropriate Number of Examined Lymph Nodes in Patients with Pancreatic Cancer—The More the Better? *Hepatobiliary Surgery and Nutrition*, **11**, 605-607. https://doi.org/10.21037/hbsn-22-163

[39] Zhang, X., Sun, C., Zhao, L., Niu, P., Li, Z., Fei, H., Wang, W., Guo, C., Che, X., Chen, Y. and Zhao, D. (2023) At Least 16 Lymph Nodes Are Recommended to Examine during Pancreaticoduodenectomy in Ampullary Adenocarcinoma. *American Journal of Cancer Research*, **13**, 340-351.

[40] Ambrosio, M.R., Perotti, B., Battini, A., Fattorini, C., Cavazzana, A., Pasqua, R., Palumbo, P., Gia, L., and Arganini, M. (2022) Surgeon-Pathologist Team Approach Dramatically Affects Lymph Nodes Detection and Improves Patients'

Short-Term Outcome. *Cancers*, **14**, Article 1034. https://doi.org/10.3390/cancers14041034

[41] Vuong, B., Dehal, A., Uppal, A., Stern, S. L., Mejia, J., Weerasinghe, R., Kapoor, V., Ong, E., Hansen, P.D. and Bilchik, A.J. (2018) What Are the Most Significant Cost and Value Drivers for Pancreatic Resection in an Integrated Healthcare System? *Journal of the American College of Surgeons*, **227**, 45-53. https://doi.org/10.1016/j.jamcollsurg.2018.02.015

[42] Park, H.M., Han, S.S., Park, S.J. and Kim, S.W. (2020) Learning Curve for Pancreatoduodenectomy: Can It Be Generalized? *ANZ Journal of Surgery*, **90**, 1414-1421. https://doi.org/10.1111/ans.15874

[43] Pal, S., George, J., Singh, A.N., Mathur, S., Dash, N.R., Garg, P., Sahni, P., and Chattopadhyay, T.K. (2018) Posterior Superior Mesenteric Artery (SMA) First Approach vs. Standard Pancreaticoduodenectomy in Patients with Resectable Periampullary Cancers: A Prospective Comparison Focusing on Circumferential Resection Margins. *Journal of Gastrointestinal Cancer*, **49**, 252-259. https://doi.org/10.1007/s12029-017-9933-x

[44] Jiang, X., Yu, Z., Ma, Z., Deng, H., Ren, W., Shi, W. and Jiao, Z. (2020) Superior Mesenteric Artery First Approach Can Improve the Clinical Outcomes of Pancreaticoduodenectomy: A Meta-Analysis. *International Journal of Surgery*, **73**, 14-24. https://doi.org/10.1016/j.ijsu.2019.11.007