

Systematic review and meta-analysis of prophylactic gastroenterostomy for unresectable advanced pancreatic cancer

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Background: The value of prophylactic gastroenterostomy (usually combined with a biliary bypass) in patients with unresectable cancer of the pancreatic head is controversial.

Methods: A systematic review of retrospective and prospective studies, and a meta-analysis of prospective studies, on the use of prophylactic gastroenterostomy for unresectable pancreatic cancer were performed.

Results: Analysis of retrospective studies did not reveal any advantage or disadvantage of prophylactic gastroenterostomy. Three prospective studies comparing prophylactic gastroenterostomy plus biliodigestive anastomosis with no bypass or a biliodigestive anastomosis alone were identified (altogether 218 patients). For patients who had prophylactic gastroenterostomy, the chance of gastric outlet obstruction during follow-up was significantly lower (odds ratio (OR) 0.06 (95 per cent confidence interval (c.i.) 0.02 to 0.21); $P < 0.001$). The rates of postoperative delayed gastric emptying were similar in both groups (OR 1.93 (95 per cent c.i. 0.57 to 6.53); $P = 0.290$), as were morbidity and mortality. The estimated duration of hospital stay after prophylactic gastroenterostomy was 3 days longer than for patients without bypass (weighted mean difference 3.1 (95 per cent c.i. 0.7 to 5.5); $P = 0.010$).

Conclusion: Prophylactic gastroenterostomy should be performed during surgical exploration of patients with unresectable pancreatic head tumours because it reduces the incidence of long-term gastroduodenal obstruction without impairing short-term outcome.

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Introduction

As potentially curative resection can be offered to only a minority of patients suffering from pancreatic cancer, palliation remains the main line of treatment for this devastating disease. With the introduction of non-operative methods for decompressing the obstructed biliary tree or stomach and duodenum, several alternatives to palliative surgery alone have emerged for the palliation of jaundice, cholangitis and gastric outlet obstruction. However, a clear assessment of the resectability of a locally advanced tumour can only be made based on the findings at surgical exploration. Optimal methods of palliation remain controversial in terms of long-term patient benefit, especially when un-resectability is determined at exploration. Similarly, the results of prospective and large retrospective cumulative analyses comparing surgical

with conservative (interventional) palliation are subject to debate.

A meta-analysis of three studies^{1–3} comparing endoscopic stenting with surgical bypass for malignant biliary obstruction has shown a reintervention rate of 3 (range 0–16) per cent in surgically treated patients and 36 (28–43) per cent in stented patients⁴. This suggests a greater than tenfold increased risk of additional treatment required after endoscopic stenting⁴. On the other hand, a significantly lower complication rate (11 *versus* 29 per cent) and lower procedure-related mortality (3 *versus* 14 per cent) in stented patients was established by Smith and colleagues³. In addition to these findings, a study by Bornman and co-workers⁵ showed no major differences in survival, total hospital stay or complication rate when bypass surgery was compared with treatment by percutaneous endoprostheses. From a technical standpoint, choledochenterostomy

is the standard surgical procedure. This can be based on a meta-analysis by Watanapa and Williamson⁶ that demonstrated a success rate for cholecystoenterostomy of 89 per cent compared with 97 per cent for choledochenterostomy. Furthermore, the advantage of performing a choledochenterostomy is that cholecystectomy and division of the bile duct facilitates dissection and determination of resectability of the tumour.

Although bypass procedures are widely performed, few studies have been conducted to evaluate the value of a prophylactic gastroenterostomy for unresectable pancreatic cancer, especially in the context of a surgical exploration during which unresectability is confirmed and a biliary bypass procedure is performed. The decision to choose conservative or surgical palliation is influenced by the overall health status, the estimated survival, and the expected procedure-related morbidity and mortality. An advantage of a surgical regimen is the ability of a single procedure to provide adequate long-term palliation for the primary symptoms of the disease⁷. However, prophylactic gastrojejunostomy may be hard to justify, as it can be difficult to predict the number of patients with unresectable periampullary carcinoma who will develop pyloroduodenal obstruction in the further course of the disease. As unresectable disease progresses, duodenal obstruction will occur in a significant percentage of patients. Up to 20 per cent develop obstruction after undergoing a single bypass, and nausea and vomiting are present in as many as 30 per cent of patients, as demonstrated in reviews of surgical series^{6,8,9}.

It still remains a clinical challenge to determine which patients would benefit from a surgical procedure that might further shorten their lives or reduce their quality of life. Factors indicating a worse prognosis include American Society of Anesthesiologists grade III, presence of liver metastases and high levels of CA19-9 (over 100 units/ml) and carcinoembryonic antigen (over 10 units/l)¹⁰. However, there is only limited knowledge about which tumours tend to grow locally without metastasizing early, producing a local problem such as gastric or duodenal obstruction, and which tumours induce metastasis-related pathologies that cannot be handled surgically. Whereas the construction of a choledochojunostomy or hepaticojunostomy seems justified for biliary obstruction, especially in the context of surgical exploration for presumed resectable disease, it remains unclear whether a prophylactic gastroenterostomy confers any benefits in terms of quality of life, food intake or weight loss. This review assesses the literature on prophylactic gastroenterostomy for pancreatic cancer; a meta-analysis of the prospectively conducted studies has been performed.

Methods

Two authors (N.H., C.W.M.) independently performed a systematic literature search of the databases of the National Center for Biotechnology Information, the National Library of Medicine and the Cochrane Central Register of Controlled Trials, without language restriction, using the following PubMed search terms: 'gastroenterostomy or gastrojejunostomy or bypass', and 'pancreatic cancer or periampullary cancer'. The last search was performed on 31 August 2008. In addition, the internet and the authors' libraries were searched, using the following medical subject headings: '(advanced) pancreatic cancer', 'pancreaticoduodenectomy', 'Whipple's operation', 'distal pancreatic resection', 'extended pancreatic resection', 'prophylactic bypass', 'double bypass', 'gastroenteric bypass', 'gastroenterostomy', 'duodenal obstruction', 'extrahepatic bile duct obstruction', 'surgical palliation' and 'clinical trials'. Papers deemed relevant by the authors were retrieved, and additional articles were identified by cross-searching the bibliographies of the papers already identified. The articles were stratified into three groups: case reports (which were excluded from this systematic review), retrospective studies and prospective studies.

Data extraction

Relevant studies were analysed according to the type of bypass performed, the number of patients included, morbidity and mortality rates, and the number of clinically relevant gastric outlet obstructions. Data collection and assessment of methodological quality were conducted following recently published protocols¹¹. The conduct and reporting were in accordance with the QUOROM statement¹². The methodological quality was assessed separately for prospective studies (definition of outcome variables and complications, completeness of follow-up and statistical analyses). Heterogeneity was evaluated by analysing comparability of the following items: number of patients, grade or stage of disease, and type of surgery performed.

Inclusion and exclusion criteria

Because of inconsistent surgical strategies and improvements in surgical and perioperative management, studies dating from before 1990 were excluded from the analysis. Case reports and studies lacking control groups were also excluded. Relevant retrospective studies were included in the systematic review. For inclusion in the meta-analysis, trials had to be prospective, comparing a prophylactic

gastroenterostomy, biliary bypass or both with no gastroenterostomy for pancreatic cancer. These trials had to report overall morbidity and mortality, and the number of clinically relevant gastric outlet obstructions.

Statistical analysis

The meta-analysis was performed using the Review Manager (RevMan) software, version 4.2.8 (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration). Gastric outlet obstruction, delayed gastric emptying, and morbidity and mortality in the respective study arms were estimated as a summary odds ratio with 95 per cent confidence interval (c.i.) using the random-effects model of DerSimonian and Laird¹³. Effects on duration of hospital stay were analysed by the weighted mean difference approach. Statistical heterogeneity was assessed using the forest plot and inconsistency statistic (I^2). $P < 0.050$ was considered significant.

Results

The initial search identified 750 studies on prophylactic gastroenterostomy for unresectable pancreatic cancer. Only retrospective and prospective studies dating from after 1990 were included (Fig. 1).

Gastrojejunostomy versus no gastrojejunostomy

Three large reviews have assessed the role of prophylactic gastrojejunostomy in patients with unresectable pancreatic

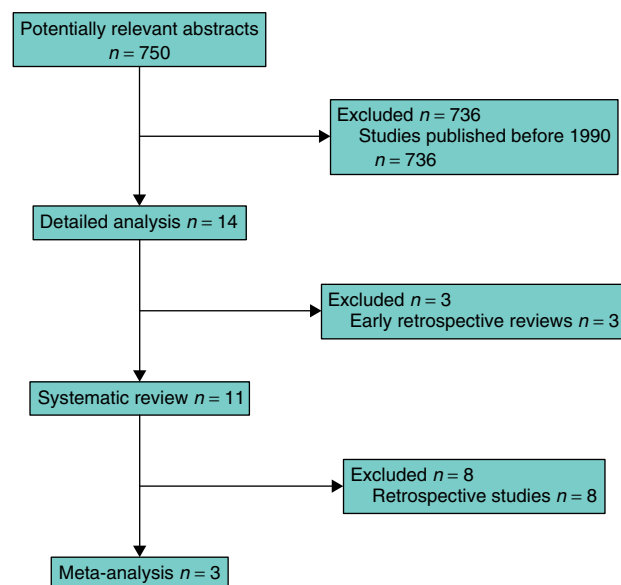


Fig. 1 Number of studies identified and evaluated

cancer (Table 1). A collected series from the literature of over 3300 patients between 1965 and 1983 revealed that at least 16 per cent of those undergoing palliative biliary diversion alone will eventually require reoperation because of duodenal obstruction. The authors concluded that the proportion was high given that these patients were considered at operation to be unlikely to develop duodenal obstruction. Moreover, the search showed that the operative mortality rate was unaffected by additional gastroenterostomy (13 versus 14 per cent)⁸. In a review of over 1600 pancreatic cancers between 1971 and 1990, Watanapa and colleagues⁶ showed that 17 per cent of affected patients had required a gastrojejunostomy before death, and the mortality rate had not increased after an additional biliary bypass (12 versus 14 per cent). The authors favoured gastroenterostomy at the time of initial biliary bypass in patients with unresectable cancer because of the high incidence of subsequent duodenal obstruction and the added risk of postoperative mortality if a second operation is required for such obstruction. Finally, in a review of over 950 patients, Singh and Reber⁹ showed that 21 per cent of patients eventually required gastroenterostomy.

For palliation of unresectable cancer, a French multicentre study by Huguier and co-workers^{15,16} and an American study by Neuberger and colleagues¹⁷ supported a combined biliary and gastric bypass because of the higher incidence of reoperative gastric bypasses in the group undergoing biliary bypass placement alone and an equal mortality rate in the double bypass group. This approach is supported by several other studies^{18–23}. On the other hand, de Rooij and co-workers²³ and Egrari and O'Connell²⁴ proposed selective reoperation for obstruction. They concluded that, because of the rapid progression of pancreatic cancer, prophylactic gastrojejunostomy may well prove unnecessary. These authors, therefore, reserve gastrojejunostomy solely for patients with impending or actual duodenal obstruction^{23,25–27} (Table 2).

Meta-analysis of the prospective studies

Only two prospective randomized studies and one prospective study analysed the potential benefits of a prophylactic gastrojejunostomy. In the study by Lillemoe and colleagues³², 87 patients with unresectable periaampullary cancer were not considered to be at substantial risk of developing duodenal obstruction. They were randomized either to undergo a retrocolic gastrojejunostomy (44 patients) or to receive no prophylactic bypass (43 patients). The head of the pancreas was the commonest tumour site; the commonest reason for unresectability was vascular infiltration,

and the presence of metastases in the liver and peritoneum. The overall postoperative morbidity rate was similar in both groups (32 per cent in the gastroenterostomy group *versus* 33 per cent in the group without gastroenterostomy), as was the mean duration of hospital stay (8.5 *versus* 8.0 days respectively). During long-term follow-up, 19 per cent of patients not undergoing a prophylactic bypass became obstructed and required treatment. On the other hand, the incidence of delayed gastric emptying was similar in the groups (2 per cent), as was the mean survival (8.3 months for both groups).

Another prospective study by Shyr and co-workers³³ concluded that a prophylactic gastrojejunostomy in addition to a biliary bypass was beneficial because, first,

over 30 per cent of patients in the single bypass group developed gastric outlet obstruction during follow-up and, second, operative morbidity and mortality did not increase by performing a double bypass.

The outcome of a prospective randomized controlled trial from the Netherlands gave further support to routine performance of gastrojejunostomy for unresectable periampullary cancer found during explorative laparotomy³⁴. Delayed gastric emptying was the most frequent complication (17 per cent) after double bypass, but this was noted in only one patient (3 per cent) without prophylactic gastrojejunostomy. Nevertheless, the authors clearly demonstrated that this strategy significantly reduced the incidence of late gastric outlet obstruction and relaparotomies without

Table 1 Large retrospective reviews of the literature on palliation of biliary and duodenal obstruction

Reference	Period of review	No. of patients	GE/No GE	Morbidity	Mortality	DGE (%)	Duration of stay	Survival (months)	Late GOO
6	1971–1990	1608	566/1042	n.a.	67 (12)/147 (14)†	20 (6–29)*	n.a.	6.7/7.4	151 of 891 (17)
8	1965–1983	3327	n.a.	n.a.	(13)/(14) for 1144 patients†	n.a.	n.a.	5.9/6.4 for 1266 patients†	532 of 3327 (16)
14	1965–1980	648	n.a.	n.a.	(17)/(18)†	n.a.	n.a.	5.8/6.6†	n.a.

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are range. Morbidity and duration of hospital stay were not specified in any of the reviews. GE, gastroenterostomy; DGE, delayed gastric emptying; GOO, gastric outlet obstruction; n.a., data not available; †not significant.

Table 2 Comparison of additional gastroenterostomy and no gastroenterostomy in patients with advanced pancreatic (head) carcinoma and a biliodigestive bypass: retrospective trials

Reference	Study design	Period of review	No. of patients	GE/no GE	Morbidity	Mortality	DGE	Duration of stay (days)	Survival (months)	Late GOO
16	Multicentre	1982–1988	1770	1134/636	307 (27)/152 (24)‡	138 (12)/104 (16) (<i>P</i> = 0.014)	n.a.	n.a.	8(0)/9(1)* ‡	39 (4)/87 (16) (<i>P</i> < 0.001)
17	Multicentre	1987–1991	1004	530/474	132 (25)/128 (27)‡	69 (13)/62 (13)‡	n.a.	n.a.	10/11* ‡	11 (2)/26 (6)
19	Single centre	1973–1988	340	70/80	n.a.	6 (9)/5 (6)	n.a.	n.a.	n.a.	n.a./20 (25)
23	Single centre	1983–1989	156	118/38	35 (30)/7 (18) (significantly higher)	5 (4)/2 (5)	13 (11)/3 (8)‡	17/14*	n.a.	n.a.
28	Single centre	1972–1990	243	82/34	40 (49)/15 (44)	n.a.	n.a.	n.a.	8/7†‡	n.a.
29	Single centre	1991–1997	256	132/28	37 (28)/4 (14) (<i>P</i> = 0.060)	4 (3)/0 (0)‡	16 (9)/n.a. (16 of 180 with GE)	11.6/9.4‡	n.a.	n.a.
30	Single centre	1983–1994	126	118/6	Overall 33 (27)	Overall 2 (2)	Overall 18 (14)	17 (5–80)	190 (14–830)	14 (11)
31	Single centre	1978–1984	122	14/30	6 (43)/8 (27)	2 (14)/4 (13)‡	3 (21)/n.a.	14(6)/11(5)* n.a.	10/5†‡	0 (0)/2 (7)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.); †values are median. GE, gastroenterostomy; DGE, delayed gastric emptying; GOO, gastric outlet obstruction; n.a., data not available; ‡not significant.

Table 3 Comparison of prophylactic gastroenterostomy and no gastroenterostomy in patients with advanced pancreatic (head) carcinoma: prospective trials

Reference	Study design	No. of patients	GE/no GE	Morbidity	Mortality	DGE	Duration of stay (days)	Survival (months)	Late GOO
32	Randomized, single centre	87	44/43	14 (32)/14 (33)§	0/0§	1 (2)/1 (2)§	8.5(0.5)/8.0(0.5)*§	8.3(0.9)/8.3(1.2)*§	0/8 (19) ($P < 0.010$)
33‡	Single centre	66	44/22	5 (11)/3 (14) ($P = 0.790$)	4 (9)/1 (5) ($P = 0.511$)	5 (11)/2 (9) ($P = 0.777$)	21.5(2.0)/14.6(1.6)* ($P = 0.029$)	6.1(0.7)/9.1(1.1)* ($P = 0.004$)	0(0)/7 (32)
34	Randomized, multicentre	65	36/29	11 (31)/8 (28)§	1 (3)/0§	6 (17)/1 (3) ($P = 0.040$)	11 (4–76)/9 (6–20)† ($P = 0.060$)	7.2 (1–19)/8.5 (3–20)† ($P = 0.150$)	2 (6)/12 (41) ($P = 0.001$)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.); †values are median (range). ‡Double bypass was performed only in patients who had clinical signs and intraoperative findings of gastric outlet obstruction. GE, gastroenterostomy; DGE, delayed gastric emptying; GOO, gastric outlet obstruction; n.a., data not available; §not significant.

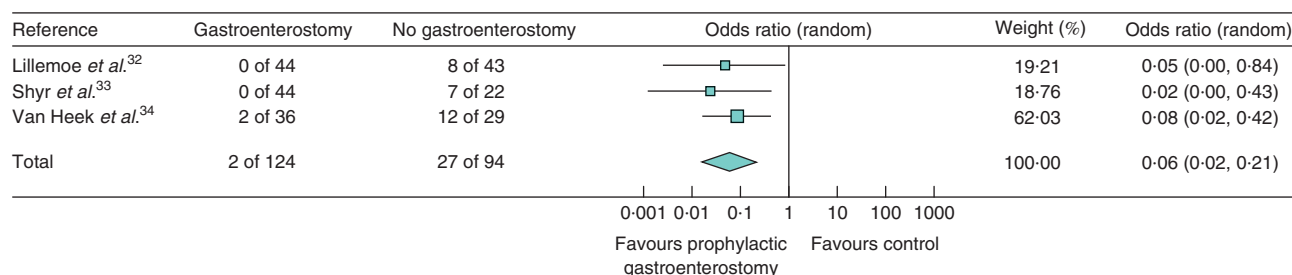


Fig. 2 Meta-analysis of late gastric obstruction. Odds ratio estimates for late gastric obstruction with a prophylactic gastroenterostomy *versus* no gastroenterostomy were calculated using the random-effects model. The diamond represents the overall treatment effect from the study results spanning the 95 per cent confidence interval. Test for heterogeneity: $\chi^2 = 0.61$, 2 d.f., $P = 0.740$, $I^2 = 0$ per cent. Test for overall effect: $Z = 4.39$, $P < 0.001$. Values in parentheses are 95 per cent confidence intervals

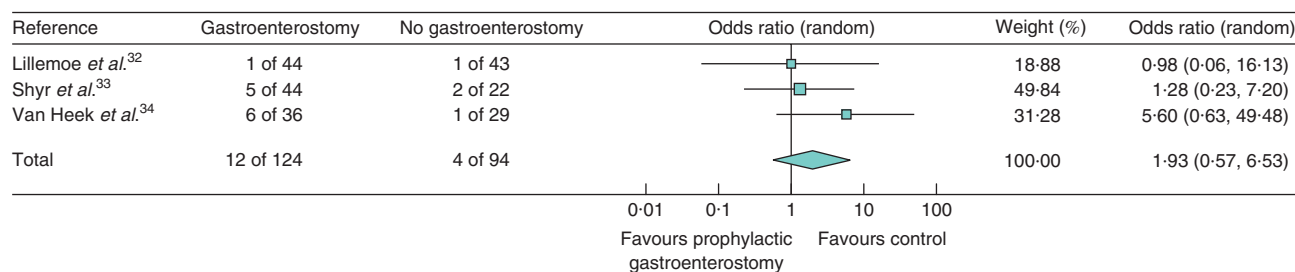


Fig. 3 Meta-analysis of delayed gastric emptying. Odds ratio estimates for delayed gastric emptying with a prophylactic gastroenterostomy *versus* no gastroenterostomy were calculated using the random-effects model. The diamond represents the overall treatment effect from the study results spanning the 95 per cent confidence interval. Test for heterogeneity: $\chi^2 = 1.39$, 2 d.f., $P = 0.500$, $I^2 = 0$ per cent. Test for overall effect: $Z = 1.06$, $P = 0.290$. Values in parentheses are 95 per cent confidence intervals

increasing the overall incidence of postoperative complications. During follow-up, gastric outlet obstruction developed in two (6 per cent) of 36 patients with a double bypass and in 12 (41 per cent) of 29 patients after single

bypass. After double bypass, only one patient had relaparotomy and revision of the gastroenteric anastomosis, whereas six (21 per cent) had relaparotomy with subsequent gastrojejunostomy in the other group³⁴. No major

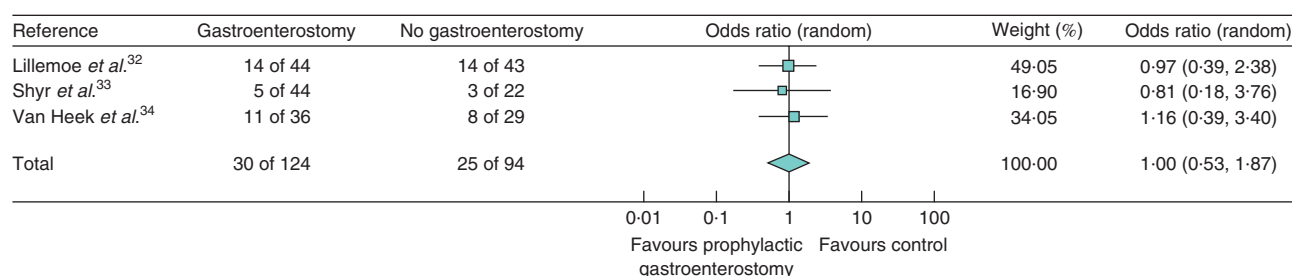


Fig. 4 Meta-analysis of postoperative morbidity. Odds ratio estimates for postoperative morbidity with a prophylactic gastroenterostomy *versus* no gastroenterostomy were calculated using the random-effects model. The diamond represents the overall treatment effect from the study results spanning the 95 per cent confidence interval. Test for heterogeneity: $\chi^2 = 0.14$, 2 d.f., $P = 0.930$, $I^2 = 0$ per cent. Test for overall effect: $Z = 0.01$, $P = 0.990$. Values in parentheses are 95 per cent confidence intervals

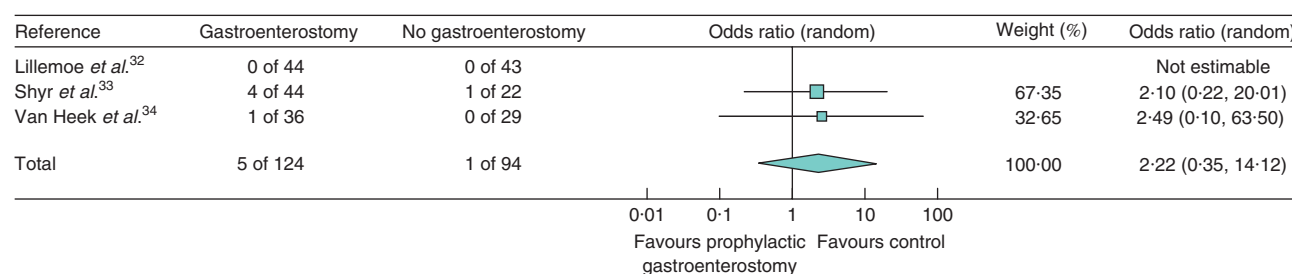


Fig. 5 Meta-analysis of postoperative mortality. Odds ratio estimates for postoperative mortality with a prophylactic gastroenterostomy *versus* no gastroenterostomy were calculated using the random-effects model. The diamond represents the overall treatment effect from the study results spanning the 95 per cent confidence interval. Test for heterogeneity: $\chi^2 = 0.01$, 1 d.f., $P = 0.930$, $I^2 = 0$ per cent. Test for overall effect: $Z = 0.85$, $P = 0.400$. Values in parentheses are 95 per cent confidence intervals

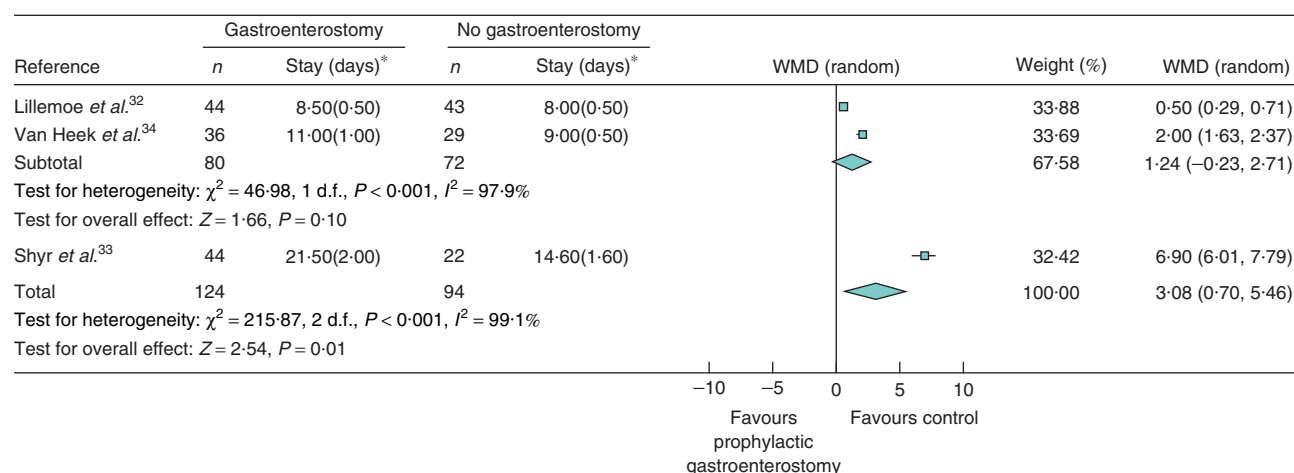


Fig. 6 Meta-analysis of duration of hospital stay. Weighted mean difference (WMD) in duration of hospital stay between patients with a prophylactic gastroenterostomy and patients with no gastroenterostomy was calculated using the random-effects model. The diamond represents the overall treatment effect spanning the 95 per cent confidence interval. Following prophylactic gastroenterostomy, the duration of hospital stay was estimated to be 3 days longer for patients with a double bypass than for those without (WMD 3.1 (95 per cent confidence interval 0.7 to 5.5); $P = 0.010$). Values in parentheses are 95 per cent confidence intervals unless indicated otherwise; *mean(s.d.)

differences were observed in quality of life between the groups, either in the early postoperative period or in the month before death (*Table 3*).

These three studies included a total of 218 patients (124 with prophylactic gastroenterostomy and 94 without). In the group with prophylactic gastroenterostomy, the number of long-term gastric outlet obstructions was significantly lower (OR 0.06 (95 per cent c.i. 0.02 to 0.21); $P < 0.001$) (*Fig. 2*), although the rates of delayed gastric emptying were similar in both groups (OR 1.93 (95 per cent c.i. 0.57 to 6.53); $P = 0.290$) (*Fig. 3*). There were no significant differences with regard to morbidity (OR 1.00 (95 per cent c.i. 0.53 to 1.87); $P = 0.990$) (*Fig. 4*) and mortality (OR 2.22 (95 per cent c.i. 0.35 to 14.12); $P = 0.400$) (*Fig. 5*). Following prophylactic gastroenterostomy, the duration of hospital stay was estimated to be 3 days longer than for patients with no gastroenterostomy (weighted mean difference 3.1 (95 per cent c.i. 0.7 to 5.5); $P = 0.010$) (*Fig. 6*).

Discussion

This meta-analysis has shown palliative prophylactic gastroenterostomy to be a satisfactory option to prevent late gastric outlet obstruction and so provide a better quality of life in a selected cohort of patients. The analysis of prospective studies has demonstrated that such a surgical procedure is associated with low morbidity and mortality.

Palliation for unresectable pancreatic cancer may be achieved by endoscopic, laparoscopic and open surgical approaches, depending on symptoms, overall health status, estimated survival, and expected procedure-related morbidity and mortality^{7,10,35–42}. The advantage of surgical palliation is its ability in a single procedure to provide adequate long-term relief of both bile duct and gastric or duodenal obstruction.

It is interesting to note that in a number of tertiary referral centres the routine practice is to construct a double bypass in patients with unresectable tumour but who are otherwise fit¹⁰. This form of management is underpinned by single-centre experiences showing that a significant number of patients (between 13 and 21 per cent) require a reoperation for gastric outlet obstruction developing later in the course of the disease^{6,9,14}. Other institutions, however, have advocated selective gastric bypass based on clinical judgement of the likelihood of subsequent gastric or duodenal obstruction^{43–45}. Some authors propose performing a surgical bypass only in patients who present with clinically evident obstruction at the time of the construction of a biliary bypass. This concept is based on

the high procedure-related morbidity and mortality rates published between the 1960s and the 1980s^{23–25,27,28,44–48}.

Some authors have tried to identify risk factors for the development of gastric outlet obstruction such as vomiting^{48,49}, tumour size^{45,46,48,50} or expected survival time after surgical intervention^{14,50,51}. Still, the overall incidence of gastric outlet obstruction in patients with only a biliary bypass has been reported to be 3–50 per cent⁵². Large retrospective reviews^{6,9,14} and prospective randomized trials of endoscopic palliation^{1–3,5,52} suggest that 10–20 per cent of patients develop late gastric outlet obstruction. These numbers support the notion that a combination of a biliary and gastric bypass is preferable at the time of exploration.

Delayed gastric emptying is, itself, an important factor compromising quality of life²⁰. The exact pathophysiological mechanisms underlying this problem remain unclear, but it seems that infiltration of the splanchnic nerves by tumour cells may lead to a subsequent functional impairment of gastric motility⁵². Additionally, the age of the patient⁵³ and preoperative duodenal obstruction⁴³ have been shown to be risk factors for a 'non-functioning' gastroenterostomy. The incidence of delayed gastric emptying after gastroenterostomy varies from 9 to 26 per cent^{20,29,43,44,52–54}. However, as the present meta-analysis has shown that a gastroenterostomy can be performed safely, it seems reasonable to argue that, after an appropriate estimation of the life expectancy of the patient¹⁰, a prophylactic gastroenterostomy should be constructed in a selected cohort, namely those who are found to have unresectable disease at exploration and who require a biliary bypass.

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