Pancreatic cancer is currently the fourth leading cause of cancer-related deaths in men and women, and has one of the lowest 5-year relative survival rates among all cancer sites—8% at all stages (1). Pancreatic cancer deaths are even projected to increase dramatically to become the second leading cause of death from cancer before 2030 (2). These data illustrate the fatal prognosis of the disease. Complete tumor resection is the only potentially curative option for pancreatic cancer patients and the resection of precursor lesions should be performed at the correct point of time to achieve long-term survival (3).

Pancreatic surgery is a complex, technical procedure regarding diagnostic, surgical and perioperative aspects. Its centralization in specialized institutions has led to acceptable mortality rates below 5% (4,5). Highly standardized surgical techniques and perioperative care are required to achieve low morbidity and mortality rates. However, despite tremendous refinements in the operative...
Pylorus-preserving PD versus classic Whipple procedure

Pylorus preservation in PD was initially proposed with the aim to prevent postgastrectomy dumping syndrome and to better preserve the physiological gastrointestinal function with potential benefit on digestion and nutritional status in the long term (17,18). However, opponents of pylorus-preserving PD have questioned its oncological adequacy so that the preservation of the pylorus in cancer patients has been a controversial issue for years. In addition, an increased incidence of DGE was observed in patients undergoing pylorus-preserving PD (19-22). However, depending on trials designs and definitions of outcomes, frequencies of DGE varied considerably between the studies, ranging between 5% and 57% (23).

Postoperative morbidity, mortality and survival

When comparing pylorus-preserving PD and classic Whipple procedure with regard to postoperative morbidity and survival, results from non-randomized studies are highly inconclusive (24-30). With the growing recognition of evidence-based surgery, randomized controlled trials (RCTs) comparing both procedures emerged, followed by systematic reviews and meta-analyses summarizing the existing literature (31-33). Between 1998 and 2015, eight RCTs comparing both procedures in patients with pancreatic and peripancreatic carcinoma were published (Table 1) (20-22,34-38). A currently updated Cochrane review, gives an excellent summary and critical appraisal of the existing evidence (39). Meta-analyses showed no significant difference between the two procedures regarding mortality, overall survival and relevant parameters of morbidity including pancreatic fistula, postpancreatectomy hemorrhage and biliary leakage (39). The only exception is DGE for which significantly increased rates were shown in patients following pylorus-preserving PD compared to the classic Whipple procedure. In contrast, intraoperative blood loss, operation time, and red blood cell transfusions were significantly reduced in pylorus-preserving PD which may be referred to the lower extent of resection (39).

Limitations of evidence

The validity of meta-analyzed data is limited because of considerable clinical and methodological heterogeneity among the studies included. For instance, inter-study

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differences in definitions of outcome parameters limit the comparability of trial results. None of the existing RCTs adhered to today’s commonly accepted definition of the International Study Group of Pancreatic Surgery (ISGPS) for DGE (40). This complicates the interpretation of trial results and therefore, conclusions must be drawn with caution. Furthermore, bias results from limitations in trials design and conduct, e.g., lack of blinding and justification of sample size. This is of particular importance in relation to DGE which cannot be regarded as an objective outcome parameter and thus, its evaluation is highly prone to bias within a non-blinded study design (41). The two largest RCTs reported comparable incidences of DGE (36,37), whereas five other RCTs with smaller sample sizes favored the classic Whipple procedure (20-22,34,38). Considering that none of the trials was powered to test a difference in DGE rates, treatment effects may be wrongly estimated.

Overall quality of life was shown to be similar in patients undergoing pylorus-preserving PD and classic Whipple procedure (34,35,37). Moreover, appetite and weight were better preserved in the pylorus-preserving group (34,35). However, data on quality of life and nutritional status are sparse and heterogenous owing to different questionnaires used and different time points for follow-up.

Pylorus-preserving versus pylorus-resecting PD

After the introduction of pylorus-resecting PD, Hayashibe and co-workers were the first to report outcomes of pylorus-preserving PD compared to the pylorus-resecting operation in 2007 (42). Since then, several non-randomized and randomized trials on this topic have succeeded. Pylorus

<table>
<thead>
<tr>
<th>References</th>
<th>Study group size</th>
<th>Recruitment period</th>
<th>Outcomes</th>
<th>DGE definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloechle et al. 1999</td>
<td>ppPD: 23; CW: 21</td>
<td>Not stated</td>
<td>Operation time: + (ppPD); blood loss: NS; mortality: NS</td>
<td>DGE: + (CW); POPF: /; Not stated</td>
</tr>
<tr>
<td>Seiler et al. 2005</td>
<td>ppPD: 64; CW: 66</td>
<td>1996–2001</td>
<td>Operation time: + (ppPD); blood loss: + (ppPD); mortality: NS</td>
<td>DGE: NS; POPF: NS; LOS: NS</td>
</tr>
<tr>
<td>Taher et al. 2015</td>
<td>ppPD: 12; CW: 8</td>
<td>2003–2005</td>
<td>Operation time: + (ppPD); blood loss: /; mortality: NS</td>
<td>DGE: NS; POPF: NS; LOS: NS</td>
</tr>
</tbody>
</table>

PpPD, pylorus-preserving pancreaticoduodenectomy; CW, classic Whipple procedure; DGE, delayed gastric emptying; POPF, postoperative pancreatic fistula; LOS, length of hospital stay; NS, no significant difference; +, superiority; /, not stated; ISGPS, International Study Group of Pancreatic Surgery; NGT, nasogastric tube; RCT, randomized controlled trial.
resection under preservation of the stomach has been shown to reduce DGE rate significantly in one RCT (43) and six non-randomized comparative trials (42,44-48). In contrast, superiority of pylorus resection was not shown in four other comparative studies including two RCTs (49-52). Hiyoshi et al. evaluated gastric emptying and nutritional status after both procedures during a 12-month period (53). In this study, gastric emptying was evaluated by 13C-acetate breath test before and after surgery. Interestingly, gastric emptying time in the pylorus-preserving group was better preserved than in the pylorus-resecting group when compared to the preoperative function indicating faster gastrointestinal passage after pylorus resection. After body weight decreased significantly in patients in both study groups during the first 6 postoperative months, body weight and body mass index recovered better in the pylorus-preserving group compared to the pylorus-resecting group. The authors concluded that pylorus-preserving PD better preserves physiological gastrointestinal function and long-term nutritional status. However, with only 8 patients in the pylorus-resecting group and 33 patients in the pylorus-preserving group, selection bias must be considered in this study (53).

**Resection of the pylorus does not reduce DGE**

In the years 2014 and 2015, five meta-analyses summarizing the existing evidence on pylorus-preserving versus pylorus-resecting PD were published, and all of them favored pylorus resection in terms of DGE rate (48,54-57). In contrast, a current blinded RCT including 188 patients failed to show superiority of pylorus resection regarding DGE and other relevant outcome parameters (52). This currently largest RCT was designed and planned with the attempt to overcome the limitations of previous trials with non-blinded trial designs and missing adherence to consensus definitions for outcome parameters. We currently performed a systematic review and meta-analysis to give an update of critically appraised and quantitative data on the effectiveness and safety of pylorus-preserving compared to pylorus-resecting PD (58). Table 2 summarizes the available randomized trials. Meta-analysis of the three existing RCTs showed no significant statistical difference between the two procedures for DGE and other relevant outcome parameters including postoperative pancreatic fistula, postpancreatectomy hemorrhage, intra-abdominal fluid collection/abscess, bile leakage, wound infection, pulmonary complications, mortality, reoperations, perioperative blood loss, duration of operation, and length of hospital stay (58). To account for differences in reconstruction techniques, sensitivity analyses were performed. It was shown that the way of the duodeno-/gastroenteric reconstruction route, i.e., antecolic versus retrocolic reconstruction, and pancreaticojunostomy versus pancreaticogastrostomy did not substantially alter the results. It was also shown, that the methodological quality of existing non-randomized studies was rather poor. In our own experience, pylorus resection revealed to be superior to pylorus preservation with regard to DGE in a non-randomized series published in 2013 (44), whereas these data could not be confirmed in a previous randomized trial with larger sample size and blinded study design (52).

Regarding late postoperative outcomes, there is evidence from randomized studies that long-term nutritional and diabetic status, and quality of life are comparable in patients following pylorus-preserving and pylorus-resecting PD (51,59). However, Kawai et al. observed an increased incidence of peptic ulcers following pylorus resection (59). Considering that patients did not undergo routine endoscopy this trend may be underestimated and should be addressed in further studies.  

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**Table 2** RCTs comparing pylorus-preserving and pylorus-resecting PD

<table>
<thead>
<tr>
<th>References</th>
<th>Study group size</th>
<th>Recruitment period</th>
<th>Outcomes</th>
<th>DGE definition</th>
</tr>
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<tbody>
<tr>
<td>Kawai et al. 2011 (43), Japan</td>
<td>ppPD: 64; prPD: 66</td>
<td>2005–2009</td>
<td>Operation time: NS; blood loss: NS; mortality: NS</td>
<td>DGE: + (prPD); POPF: NS; LOS: NS</td>
</tr>
</tbody>
</table>

PpPD, pylorus-preserving pancreaticoduodenectomy; PrPD, pylorus-resecting PD; DGE, delayed gastric emptying; POPF, postoperative pancreatic fistula; LOS, length of hospital stay; NS, no significant difference; +, superiority; ISGPS, International Study Group of Pancreatic Surgery; RCT, randomized controlled trial.
Improvements in methodological quality of surgical trials

In line with the above mentioned randomized trials comparing pylorus-preserving PD and classic Whipple procedure, the existing RCTs comparing pylorus-preserving and pylorus-resecting PD have limitations arising from clinical and methodological heterogeneity, e.g., differences in postoperative management of nasogastric tube removal and start of enteral feeding. Nevertheless, data from latest RCTs illustrate the efforts undertaken to minimize these limitations during the last decade. Regarding DGE and postoperative pancreatic fistula, ISGPS adherence was given in all RCTs comparing pylorus-preserving and pylorus-resecting PD (43,51,52). Moreover, advancements in trial design aspects are obvious. Sample size justification was based on assumptions on the primary endpoint DGE in each study. Blinding of participants, personnel and outcome assessors was reported in one RCT (52)—to give just some of the important improvements.

Future perspectives

While minimal-invasive distal pancreatectomy has gained wide acceptance, open surgery is still the standard approach in PD. Nevertheless, numbers of laparoscopic and robotic PD are increasing in specialized institutions. In a large multi-institutional series including 211 patients undergoing robotic PD and 817 patients undergoing open PD, pylorus-preservation was performed significantly more often in open surgery (60). According to the center’s standard for the open procedure, the pylorus was also preserved in patients undergoing laparoscopic PD (61,62). Wellner et al. showed that laparoscopic pylorus-preserving PD is equivalent to the open procedure regarding postoperative complications, but also showed significantly reduced transfusions and a trend towards shorter operation time, reduced DGE rate, and shorter hospital stay (62). However, long-term outcomes are sparse and further studies are needed to confirm the potential advances of minimal-invasive PD with or without pylorus preservation and to evaluate the oncological adequacy of the procedure in cancer patients.

Summary

Pylorus preservation has gained popularity over the classic Whipple procedure as operation times and intraoperative blood loss were shown to be reduced while relevant short- and long-term outcomes are not affected. Occurring in up to 61% of patients, DGE is the most frequent complication after either procedure. Based on meta-analysis of randomized studies, the classic Whipple procedure is deemed to be superior to pylorus-preserving PD regarding DGE. However, the validity of data is limited as adherence to the ISGPS definition was not given and blinding was lacking in the existing RCTs. This is of particular importance because DGE is prone to bias within non-blinded study designs and missing standards for DGE definition and management. Inter- and intra-study differences in DGE prophylaxis and treatment can further distort trial results. Based on the existing level I evidence studies, there is no convincing benefit of the classic Whipple procedure compared to pylorus-preserving PD—consequently, the pylorus should be preserved whenever possible in patients undergoing pancreatectomy. Considering that pylorus resection does not reduce DGE and long-term data on pylorus-preserving versus pylorus-resecting PD are sparse, removal of the pylorus should no longer be performed as a preventive measure. But, in case of tumor infiltration or concern for sufficient blood supply, pylorus resection in combination with or without distal gastrectomy may be preferred depending on the surgeon’s preference and the individual patient’s situation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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50. Akizuki E, Kimura Y, Nibuoka T, et al. Prospective nonrandomized comparison between pylorus-preserving and subtotal stomach-preserving...


