Pancreaticoduodenectomy (Whipple Resection)

Number: 0365

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers pancreaticoduodenectomy (also known as Whipple resection) medically necessary for the treatment of intraductal papillary mucinous neoplasm of the pancreas (IPMN) with high-grade dysplasia or invasive cancer.

Aetna considers the following experimental and investigational because their effectiveness has not been established (i) Preoperative biliary drainage and (ii) The use of omental flap for prevention of post-operative complications following pancreaticoduodenectomy.

Aetna considers pancreaticoduodenectomy (also known as Whipple resection or proximal pancreatectomy) experimental and investigational for the treatment of members with Zollinger-Ellison syndrome because the value of pancreaticoduodenectomy in this condition remains to be established. Furthermore, the morbidity and mortality related to this approach may outweigh its potential benefits.

Policy History

Last Review
05/28/2019
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Next Review: 03/27/2020

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
Aetna considers Braun enterenterostomy medically necessary for lowering the incidence of delayed gastric emptying following pancreaticoduodenectomy.

Aetna considers the use of fibrin sealant integral to the pancreaticoduodenectomy procedure and not separately reimbursed.

Background

Zollinger-Ellison syndrome (ZES) is characterized by severe peptic ulcer disease that results from non-beta islet cell tumors, gastrinomas, of the gastrointestinal tract. The mean age at presentation is 45 to 50 years, and men are affected more often than women. Gastrinomas can be subdivided into tumors that are sporadic, constituting about 75% of patients with ZES, and those that are genetically transmitted and associated with multiple endocrine neoplasia type 1 (MEN 1), constituting about 25% of patients with ZES. Zollinger-Ellison tumors associated with MEN-1 occur at an earlier age than the sporadic tumors and have been characterized by some researchers to follow a more benign course.

Currently, the literature states that proton-pump inhibitors (PPIs) such as lansoprazole (Prevacid) and omeprazole (Prilosec) are the treatment of choice for ZES. For patients who have difficulty controlling gastric acid hyper-secretion with oral PPIs, intravenous pantoprazole (Protonix I.V.) has been reported to be effective. Most ZES patients (93%) maintained effective control of acid output previously established with oral PPIs when switched to twice-daily 80 mg of intravenously administered pantoprazole. In patients with sporadic ZES, the literature suggests that exploratory surgery with tumor resection is also appropriate. According to accepted guidelines, surgical resection of a single gastrinoma may be attempted if there is no evidence that it has spread to other
organs (e.g., lymph nodes or the liver). Gastrectomy to control acid over-production is rarely indicated. However, the role of pancreaticoduodenectomy (Whipple resection, or proximal pancreatectomy) in patients with sporadic gastrinomas and in patients with MEN-1 is controversial. Furthermore, the effect of aggressive surgery, such as the Whipple resection, on survival is unclear.

In a review on surgical treatment and prognosis of gastrinoma, Norton (2005) noted that Whipple pancreaticoduodenectomy results in the highest probability of cure in both sporadic and MEN-1 gastrinoma patients as it removes the entire gastrinoma triangle. However, the excellent long-term survival of these patients with lesser operations and the increased operative mortality and long-term morbidity of Whipple pancreaticoduodenectomy make its current role unclear until further studies are done.

Bartsch et al (2007) stated that gastrinoma is the most frequent functional pancreaticoduodenal endocrine tumor in patients with MEN-1 and a major determinant of mortality in this syndrome. Whether routine surgical exploration should be performed in patients with MEN-1 associated ZES to possibly decrease the malignant spread and eventually increase survival still remains controversial. There is not only disagreement about the indication for surgical exploration, but also what type of procedure should be performed, since sufficient evidence-based data are not available.

In a review on surgical management of ZES, Morrow and Norton (2009) stated that much has been learned about the diagnosis and treatment of ZES, and certain questions require further investigation. Delay in diagnosis of ZES is still a significant problem, and clinical suspicion should be elevated. The single best imaging modality for localization and staging of ZES is somatostatin receptor scintigraphy. Goals of surgical treatment for ZES differ between sporadic and MEN-1-related cases. All sporadic cases of ZES should be surgically
explored (including duodenotomy) even with negative imaging results, because of the high likelihood of finding and removing a tumor for potential cure. Surgery for MEN-1-related cases should be focused on prevention of metastatic disease, with surgery being recommended when pancreatic tumors are greater than 2 cm. The authors noted that the role of Whipple procedure, especially for MEN-1 cases, should be explored further. Laparoscopic and endoscopic treatments are more experimental, but may have a role.

An UpToDate review on “Pancreatectoduodenectomy (Whipple procedure): Techniques” (Reber, 2013) does not mention Zollinger-Ellison syndrome as an indication of pancreaticoduodenectomy. Furthermore, an UpToDate review on “Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)” (Goldfinger, 2013) does not mention pancreaticoduodenectomy as a therapeutic option.

Coolsen and colleagues (2014) stated that few randomized controlled trials (RCTs) have been performed in patients undergoing pancreatic-duodenectomy (PD). An important factor contributing to this is the large number of patients needed to adequately power RCTs for relevant clinical single endpoints. A PD-specific composite end-point (CEP) could solve this problem. The aim of the present study was to develop a PD-specific CEP, consisting of complications related to PD, allowing reduction in sample sizes and improving the ability to compare outcomes. PD-specific CEP components were selected after a systematic review of the literature and consensus between 25 international pancreatic surgeons. Ultimately, prospective cohorts of patients who underwent PD in 2 high-volume HPB centers (London, UK, and Maastricht, NL) were used to assess the event rate and effect of implementing a PD-specific CEP. From a total of 18 single-component end-points, 8 were selected to be included the PD-specific CEP: (i) intra-abdominal abscess, (ii) sepsis, (iii) post-PD hemorrhage, (iv) bile leakage, (v) gastro-
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All 8 components had consensus definitions and a Dindo-Clavien classification of 3 or more. The incidence of the PD-specific CEP was 24.7% in the Maastricht cohort and 23.3% in the London cohort. These incidence rates led to a 2-fold reduction in the theoretical calculated sample size for an adequately powered RCT on PD using this CEP as a primary end-point. The authors concluded that the proposed PD-specific CEP enables clinical investigators to adequately power RCTs on PD and increases the feasibility, comparability, and utility in meta-analysis.

Tenner et al (1996) stated that intraductal mucin-hypersecreting neoplasm (IMHN), also termed mucinous ductal ectasia, is a rare disorder of the pancreas characterized by distension of the pancreatic duct with mucus. This study attempted to clarify the clinical, radiographic, histological, and treatment approaches to this entity. The medical records, radiological imaging studies, and pathology specimens of 8 patients with IMHN seen during a 3-yr period were reviewed. The diagnosis of IMHN was established by findings during ERCP, which included mucin plugging of the papilla, mucin extrusion from the papillary orifice after intraductal injection of contrast medium, mucinous filling defects in the main pancreatic duct, and dilated main and branch pancreatic ducts in the absence of obstructing ductal strictures. All patients presented with an initial clinical diagnosis of acute or chronic pancreatitis, suspected cystic neoplasm, or biliary obstruction. Non-invasive imaging studies such as trans-abdominal ultrasonography or CT and laboratory evaluation did not seem to help in defining the disease. Five patients underwent Whipple resection; pathology included papillary ductal hyperplasia in 1, dysplastic mucinous epithelium in 2, and mucinous cystadenocarcinoma in 2. All 5 patients had associated histological evidence of chronic pancreatitis. All patients are alive and well after 21 to 53 months without
evidence of residual disease. The authors concluded that IMHN has a wide spectrum of clinical, radiological, and histological features. The indolent biologic behavior and favorable prognosis of IMHN suggested that it is one of the most curable forms of pancreatic malignancy.

Paal et al (1999) noted that intraductal papillary-mucinous neoplasms (IPMNs) of the pancreas are rare lesions. These researchers undertook this study to analyze these tumors by focusing on the diagnostic criteria and correlating the histologic features with clinical prognosis. A total of 22 cases of IPMN were retrieved from the Endocrine Tumor Registry of the Armed Forces Institute of Pathology. Blocks or unstained slides were available for histochemical and immunohistochemical studies (including proliferative markers and cell cycle regulators) and K-ras oncogene mutations in 15 cases. Patient follow-up was obtained in all of the cases. IPMN occurs in both genders with a slight male predominance, with a mean age at presentation of 64.4 years (range of 48 to 85 yrs). The patients presented with abdominal pain. The neoplasms were radiologically and grossly cystic, usually (18 cases of 22) located in the head of the pancreas. Histologically, the tumors consisted of intraductal papillary proliferations protruding into and expanding the pancreatic ducts. Invasion into the surrounding pancreatic parenchyma was detected in 15 cases. Chronic pancreatitis was present in all of the cases. p27 immunoreactivity always exceeded the immunoreactivity of cyclin E. K-ras oncogene mutations were detected in 2 cases. Patients were treated with a complete surgical resection (n = 7) or a Whipple procedure (n = 13). Only 2 of 22 patients died of disease (3 died immediately post-operatively and 3 died of unrelated causes), whereas the remaining 14 patients were alive at last follow-up, without evidence of disease, an average of 58.2 months after initial presentation. IPMNs are rare, distinctive neoplasms, with complex intraductal papillae, that can be easily separated from in-situ ductal adenocarcinoma and mucinous cystic
neoplasms. The high ratio of p27 protein to cyclin E supports the excellent prognosis of these neoplasms, despite the presence of invasion and K-ras oncogene mutation.

Fernandez-Cruz et al (2006) stated that the standard surgical procedure for IPMN of the main duct (IPMN-M) or side branch ducts (IPMN-Br) is pancreatectoduodenectomy. IPMN-Br is a more indolent disease with a lower incidence of malignancy. These investigators evaluated the usefulness of organ-preserving pancreatic resections (OPPR) including duodenum-preserving pancreatic head resection (DPHR) and pancreatic head resection with segmental duodenectomy (PHRSD) in patients with IPMN-Br. Surgical outcomes were evaluated in 8 IPMN-Br patients: DPHR was performed in 4 patients and PHRSD was performed in 4 patients. In addition, 13 IPMN patients with Whipple resections were included in the analysis. The incidence of post-operative complications was 38% after Whipple resection, 100% after DPHR and 25% after PHRSD. The mean length of hospital stay was 27 days after DPHR, 22 days after Whipple resection and 16 days after PHRSD. Invasive IPMN was found in 38% of the patients in the Whipple group, and non-invasive IPMN was found in 100% of patients who underwent organ-preserving surgery. The authors concluded that pancreatectoduodenectomy remains the treatment of choice in patients with invasive IPMN. PHRSD appears to be a useful procedure for IPMN-Br located in the head of the pancreas.

Beger et al (2013) stated that cystic neoplasms of the pancreas are being detected and surgically treated increasingly more frequently. Intraductal papillary mucinous neoplasms and mucinous cystic neoplasms (MCN) are primary benign lesions; however, the 5-year risk for malignant transformation has been estimated to be 63% and 15%, respectively. Surgical extirpation of a benign cystic tumor of the pancreas is a cancer preventive measure. The duodenum-preserving total pancreatic head resection technique (DPPHRt) is being used more frequently for cystic...
neoplasms of the pancreatic head. The complete resection of 
the pancreatic head can be applied as a duodenum-preserving 
technique or with segmental resection of the peri-papillary 
duodenum. Borderline lesions, carcinoma in situ or T1N0 
cancer of the papilla and the peri-papillary common bile duct 
are also considered to be indications for segmental resection 
of the peri-papillary duodenum. A literature search for cystic 
neoplastic lesions and DPPHRt revealed the most frequent 
indications to be IPMN, MCN and SCA lesions and 28 % 
suffered from a cystic neoplasm with carcinoma in-situ or a peri- 
papillary malignoma. The hospital mortality rate was 0.52 
%. Compared to the Whipple type resection the DPPHRt 
exhibits significant benefits with respect to a low risk for early 
post-operative complications and a low hospital mortality rate 
of less than 1 %. Exocrine and endocrine pancreatic functions 
after DPPHR are not impaired compared to the Whipple type 
resection.

Aimoto et al (2013) investigated the clinicopathological 
features of borderline resectable invasive carcinomas (BRICs) 
derived from IPMNs and examined the significance of the 
aggressive "surgery first" approach compared with the 
treatment of conventional borderline resectable pancreatic 
ductal adenocarcinomas (BRPDAs). These researchers 
retrospectively studied 7 patients with BRICs derived from 
IPMNs and 14 patients with conventional BRPDAs. Several 
factors were reviewed: initial symptoms, pre-operative 
imaging, serum level of CA19-9, peri-operative factors, 
pathological findings, adjuvant chemotherapy, and outcome. 
All BRICs derived from IPMN were huge tumors (more than 3 
\text{ cm in diameter}) suspected to involve less than 180° of the 
circumference of the vessel. Five patients (71 \%) underwent a 
modified Whipple procedure, and 2 (29 \%) underwent distal 
pancreatectomy. Only 3 patients (43 \%) required vascular 
resection. Curative resection was achieved in all 7 patients, 
who are alive with no evidence of recurrence. There were no 
severe post-operative complications. With regards to the 
pathological IPMN subtype, 2 tumors (29 \%) were gastric and
5 (71%) were intestinal. Only 2 patients (29%) had lymph node metastasis. The final stage was II in 4 (57%) cases and IVa in 3 cases (43%). The 3-year survival rate was 100%.

Tumors of BRICs derived from IPMNs were larger than those of conventional BRPDAs (p < 0.05). The BRICs derived from IPMN less frequently metastasized to lymph nodes (p < 0.05) and were of an earlier stage (p < 0.05) than were conventional BRPDAs. The 3-year survival rate was significantly higher for BRICs derived from IPMNs (100%) than for conventional BRPDAs (19%, p < 0.001). The authors concluded that the BRICs derived from an intestinal or gastric IPMN are less aggressive than conventional BRPDAs and have a more favorable prognosis. In addition, aggressive "surgery first" approach may contribute to this better prognosis.

Furthermore, an UpToDate review on “Diagnosis and treatment of intraductal papillary mucinous neoplasm of the pancreas” (Sheth et al, 2015) states that “Surgery is the only treatment option in patients with intraductal papillary mucinous neoplasm of the pancreas (IPMN) with high-grade dysplasia or invasive cancer …. Surgical series have described a variety of operations for IPMN, including total pancreatectomy, pancreaticoduodenectomy, distal pancreatectomy, and segmental resection of the tumor. The choice of surgery will be determined by the location of the tumor and the extent of involvement of the gland …. The most common operation is pancreaticoduodenectomy (70%) because most tumors are in the head of the pancreas”.

In a meta-analysis, Chen et al (2015a) analyzed the morbidity after pylorus-preserving pancreaticoduodenectomy (PPPD) and pylorus-resecting pancreaticoduodenectomy (PRPD) to determine the optimal surgical treatment of masses in the pancreatic head or peri-ampullary region. A systematic search of databases identifying RCTs from the Cochrane Library, PubMed, EMBASE and Web of Science was performed. Outcome was compared by post-operative morbidity including overall morbidity, pancreatic fistulas, wound infections, post-
operative bleeding, biliary leakage, ascites and delayed gastric emptying (DGE) rate between PPPD and PRPD. The DGE rate in the PRPD subgroups (conventional PD [CPD] and subtotal stomach-preserving PD [SSPPD], respectively) was also analyzed. The results showed that 9 RCTs including 722 participants were included for meta-analysis. Among these RCTs, 7 manuscripts described PRPD as CPD, and 2 manuscripts described PRPD as SSPPD. There were no significant differences in the overall morbidity, pancreatic fistulas, wound infections, post-operative bleeding, or biliary leakage between PPPD and PRPD. There was a lower rate of DGE with PRPD than that with PPPD (relative risk [RR] = 2.15, \( p = 0.03 \), 95% confidence interval [CI]: 1.09 to 4.23). Further subgroup analysis indicated a comparable DGE rate for the CPD but a lower DGE rate for the SSPPD group than the PPPD group. However, the result did not indicate any difference between CPD and SSPPD regarding the DGE rate \( (p = 0.92) \). It is suggested that PPPD is comparable to PRPD in overall morbidity, pancreatic fistulas, wound infections, post-operative bleeding and biliary leakage. The authors concluded that the current data are insufficient to draw a conclusion regarding which surgical procedure is associated with a lower post-operative DGE rate; these conclusions were limited by the available data. They stated that further evaluations of RCTs are needed.

In a Cochrane review, Huttner et al (2016) compared the effectiveness of classic Whipple (CW) operation (pancreaticoduodenectomy) and pylorus-preserving pancreaticoduodenectomy (PPW) techniques for surgical treatment of cancer of the pancreatic head and the peri-ampullary region. These researchers conducted searches on March 28, 2006, January 11, 2011, January 9, 2014, and August 18, 2015 to identify all RCTs, while applying no language restrictions. They searched the following electronic databases on August 18, 2015: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of
Reviews of Effects (DARE) from the Cochrane Library (2015, Issue 8); MEDLINE (1946 to August 2015); and EMBASE (1980 to August 2015). They also searched abstracts from Digestive Disease Week and United European Gastroenterology Week (1995 to 2010); they did not update this part of the search for the 2014 and 2015 updates because the prior searches did not contribute any additional information. These investigators identified 2 additional trials through the updated search in 2015; RCTs comparing CW versus PPW including participants with peri-ampullary or pancreatic carcinoma were selected for analysis. Two review authors independently extracted data from the included trials. They used a random-effects model for pooling data. They compared binary outcomes using odds ratios (ORs), pooled continuous outcomes using mean differences (MDs), and used hazard ratios (HRs) for meta-analysis of survival. Two review authors independently evaluated the methodological quality and risk of bias of included trials according to the standards of the Cochrane Collaboration. These researchers included 8 RCTs with a total of 512 participants. The critical appraisal revealed vast heterogeneity with respect to methodological quality and outcome parameters. Post-operative mortality (OR 0.64, 95 % CI: 0.26 to 1.54; p = 0.32), overall survival (HR 0.84, 95 % CI: 0.61 to 1.16; p = 0.29), and morbidity showed no significant differences, except of delayed gastric emptying, which significantly favored CW (OR 3.03, 95 % CI: 1.05 to 8.70; p = 0.04). Furthermore, these investigators noted that operating time (MD -45.22 minutes, 95 % CI: -74.67 to -15.78; p = 0.003), intra-operative blood loss (MD -0.32 L, 95 % CI: -0.62 to -0.03; p = 0.03), and red blood cell transfusion (MD -0.47 units, 95 % CI: -0.86 to -0.07; p = 0.02) were significantly reduced in the PPW group. All significant results were associated with low-quality evidence based on GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria. The authors concluded that current evidence suggested no relevant differences in mortality, morbidity, and survival between the 2 operations. However, some peri-operative outcome measures significantly favored
the PPW procedure. Given obvious clinical and methodological heterogeneity, future high-quality RCTs of complex surgical interventions based on well-defined outcome parameters are needed.

In a Cochrane review, Gurusamy et al (2016) evaluated the benefits and harms of duodenum-preserving pancreatic head resection (DPPHR) versus PD in people with chronic pancreatitis for whom pancreatic resection is considered the main therapeutic option. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded, and trials registers to June 2015 to identify randomized trials. They also searched the references of included trials to identify further trials. They considered only RCT performed in people with chronic pancreatitis undergoing pancreatic head resection, irrespective of language, blinding, or publication status, for inclusion in the review. Two review authors independently identified trials and extracted data. They calculated the RR, MD, rate ratio (RaR), or HR with 95% CI based on an available-case analysis. A total of 5 trials including 292 participants met the inclusion criteria for the review. After exclusion of 23 participants mainly due to pancreatic cancer or because participants did not receive the planned treatment, a total of 269 participants (with symptomatic chronic pancreatitis involving the head of pancreas and requiring surgery) were randomly assigned to receive DPPHR (135 participants) or PD (134 participants). The trials did not report the American Society of Anesthesiologists (ASA) status of the participants. All the trials were single-center trials and included people with and without obstructive jaundice and people with and without duodenal stenosis, but did not report data separately for those with and without jaundice or those with and without duodenal stenosis. The surgical procedures compared in the 5 trials included DPPHR (Beger or Frey procedures, or wide local excision of the head of the pancreas) and PD (pylorus-preserving pancreaticoduodenectomy or Whipple procedure). The
participants were followed-up for various periods of time ranging from 1 to 15 years. The trials were at unclear or high risk of bias. The overall quality of evidence was low or very low. The differences in short-term mortality (up to 90 days after surgery) (RR 2.89, 95% CI: 0.31 to 26.87; 369 participants; 5 studies; DPPHR: 2/135 (1.5%) versus PD: 0/134 (0%); very low quality evidence) or long-term mortality (maximal follow-up) (HR 0.65, 95% CI: 0.31 to 1.34; 229 participants; 4 studies; very low quality evidence), medium-term (3 months to 5 years) (only a narrative summary was possible; 229 participants; 4 studies; very low quality evidence), or long-term quality of life (more than five years) (MD 8.45, 95% CI -0.27 to 17.18; 101 participants; 2 studies; low quality evidence), proportion of people with adverse events (RR 0.55, 95% CI 0.22 to 1.35; 226 participants; 4 studies; DPPHR: 23/113 (adjusted proportion 20%) versus PD: 41/113 (36.3%); very low quality evidence), number of people with adverse events (RaR 0.95, 95% CI: 0.43 to 2.12; 43 participants; 1 study; DPPHR: 12/22 (54.3 events per 100 participants) versus PD: 12/21 (57.1 events per 100 participants); very low quality evidence), proportion of people employed (maximal follow-up) (RR 1.54, 95% CI: 1.00 to 2.37; 189 participants; 4 studies; DPPHR: 65/98 (adjusted proportion 69.4%) versus PD: 41/91 (45.1%); low quality evidence), incidence proportion of diabetes mellitus (maximum follow-up) (RR 0.78, 95% CI: 0.50 to 1.22; 269 participants; 5 studies; DPPHR: 25/135 (adjusted proportion 18.6%) versus PD: 32/134 (23.9%); very low quality evidence), and prevalence proportion of pancreatic exocrine insufficiency (maximum follow-up) (RR 0.83, 95% CI: 0.68 to 1.02; 189 participants; 4 studies; DPPHR: 62/98 (adjusted proportion 62.0%) versus PD: 68/91 (74.7%); very low quality evidence) were imprecise. The length of hospital stay appeared to be lower with DPPHR compared to PD and ranged between a reduction of 1 day and 5 days in the trials (208 participants; 4 studies; low quality evidence). None of the trials reported short-term quality of life (4 weeks to 3 months), clinically significant pancreatic fistulas, serious adverse events, time to
return to normal activity, time to return to work, and pain scores using a visual analog scale. The authors concluded that low quality evidence suggested that DPPHR may result in shorter hospital stay than PD. Based on low or very low quality evidence, there is currently no evidence of any difference in the mortality, adverse events, or quality of life between DPPHR and PD. However, the results were imprecise and further RCTs are needed on this topic. They stated that future RCTs comparing DPPHR with PD should report the severity as well as the incidence of post-operative complications and their impact on patient recovery. In such trials, participant and observer blinding should be performed and the analysis should be performed on an intention-to-treat basis to decrease the bias. In addition to the short-term benefits and harms such as mortality, surgery-related complications, quality of life, length of hospital stay, return to normal activity, and return to work, future trials should consider linkage of trial participants to health databases, social databases, and mortality registers to obtain the long-term benefits and harms of the different treatments.

Preoperative Biliary Drainage on Complications Following Pancreaticoduodenectomy

In a meta-analysis, Chen et al (2015b) examined the impact of preoperative biliary drainage (PBD) on complications following PD. A meta-analysis was carried out for all relevant RCTs, prospective and retrospective studies published from inception to March 2015 that compared PBD and non-PBD (immediate surgery) for the development of post-operative complications in PD patients. Pooled odds ratio (OR) and 95 % CI were estimated using fixed-effect analyses, or random-effects analyses if there was statistically significant heterogeneity (p < 0.05). A total of 8 RCTs, 13 prospective studies, 20 retrospective studies, and 3 Chinese local retrospective studies with 6,286 patients were included in this study. In a pooled analysis, there were no significant differences between PBD and non-PBD group in the risks of mortality, morbidity,
intra-abdominal abscess, sepsis, hemorrhage, pancreatic leakage, and biliary leakage. However, subgroup analysis of RCTs yielded a trend toward reduced risk of morbidity in PBD group (OR 0.48, CI: 0.24 to 0.97; p = 0.04). Compared with non-PBD, PBD was associated with significant increase in the risk of infectious complication (OR 1.52, CI: 1.07 to 2.17; p = 0.02), wound infection (OR 2.09, CI: 1.39 to 3.13; p = 0.0004), and DGE (OR 1.37, CI: 1.08 to 1.73; p = 0.009). The authors concluded that the findings of this meta-analysis suggested that biliary drainage before PD increased post-operative infectious complication, wound infection, and DGE. They stated that in light of these findings, PBD probably should not be routinely carried out in PD patients.

The Use of Omental Flap for Prevention of Complications Following Pancreaticoduodenectomy

In a meta-analysis, Tian et al (2015) examined the effect of omental flap in PD against post-operative complication. Thorough literature search in Ovid-MEDLINE and EMBASE databases was conducted to identify studies whether the use of Omental Flap to prevent post-operative complications. Review of 14 article candidates, identified 4 eligible articles with a total of 2,971 patients for meta-analysis. Dichotomous data regarding distinction between omental roll-up and non-mental roll-up were pooled using random effects model to obtain the diagnostic ORs and their 95% CIs. There were a total of 1,129 patients in omental roll-up group, 1,842 patients in non-omentum group. Omental roll-up during PD could not prevent post-operative pancreatic fistula (OR = 0.81, 95% CI: 0.40 to 1.63, p = 0.56). It also could not prevent post-operative intra-abdominal bleeding (OR = 0.67, 95% CI: 0.28 to 1.59, p = 0.37). These researchers used the sensitivity analysis that found the pancreatic fistula was lower in the non-omentum roll-up group than in the omental roll-up group (OR = 1.24, 95% CI: 1.03 to 1.50, p = 0.02). The authors concluded that the use of omental roll-up could not decrease the risk of
pancreatic fistula after PD. They stated that further RCTs are needed to identify the effect of omental roll-up technique for PD.

Minimally Invasive Pancreaticoduodenectomy for Peri-Amullary Disease

Chen and colleagues (2017) stated that minimally invasive pancreaticoduodenectomy (MIPD) has been gradually attempted. However, whether MIPD is superior, equal or inferior to its conventional open pancreaticoduodenectomy (OPD) is unclear. These investigators performed a comprehensive review of literature and meta-analysis of MIPD outcomes compared with open surgery. Studies published up to May 2017 were searched in PubMed, Embase, Cochrane Library, and Web of Science. Main outcomes were comprehensively reviewed and measured including conversion to open approach, operation time (OP), estimated blood loss (EBL), transfusion, length of hospital stay (LOS), overall complications, post-operative pancreatic fistula (POPF), delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), re-admission, re-operation and reasons of pre-operative death, number of retrieved lymph nodes (RLN), surgical margins, recurrence, and survival. The software of Review Manage version 5.1 was used for meta-analysis. A total of 100 studies were included for systematic review and 26 (a total of 3,402 cases, 1,064 for MIPD, 2,338 for OPD) were included for meta-analysis. In the early years, most articles were case reports or non-control case series studies, while in the last 6 years high-volume and comparative researches were increasing gradually. Systematic review revealed conversion rates of MIPD to OPD ranged from 0 % to 40 %. The mean or median OP of MIPD ranged from 276 to 657 mins. The total POPF rates vary between 3.8 % and 50 % observed in all systematic reviewed studies. Meta-analysis demonstrated MIPD had longer OP (weighted mean difference [WMD] = 99.4 mins; 95 % CI: 46.0 to 152.8, p < 0.01), lower blood loss (WMD = -0.54 ml; 95 % CI: -0.88 to -0.20 ml; p <
0.01), lower transfusion rate (RR = 0.73, 95 % Cl: 0.57 to 0.94, p = 0.02), shorter LOS (WMD = -3.49 days; 95 % Cl: -4.83 to -2.15, p < 0.01). There was no significant difference in time to oral intake, post-operative complications, POPF, re-operation, re-admission, peri-operative mortality and number of retrieved lymph nodes. The authors concluded that the findings of this study demonstrated that MIPD was technically feasible and safe on the basis of historical studies; MIPD was associated with less blood loss, faster post-operative recovery, shorter length of hospitalization and longer operation time. Moreover, they stated that these findings need to be confirmed with robust prospective comparative studies and randomized clinical trials.

In a systematic review and meta-analysis, Wang and associates (2017) evaluated the feasibility and safety of MIPD versus OPD. Post-operative complications, intra-operative outcomes and oncologic data, and post-operative recovery were compared. There were 27 studies that matched the selection criteria. A total of 1,306 cases of MIPD and 5,603 cases of OPD were included; MIPD was associated with a reduction PPH (OR 1.60; 95 % Cl: 1.03 to 2.49; p = 0.04) and wound infection (OR 0.44, 95 % Cl: 0.30 to 0.66, p < 0.0001). MIPD was also associated with less EBL (mean difference [MD] -300.14 ml, 95 % Cl: -400.11 to -200.17 ml, p < 0.0001), a lower transfusion rate (OR 0.46, 95 % Cl: 0.35 to 0.61; p < 0.0001) and a shorter LOS (MD -2.95 days, 95 % Cl: -3.91 to -2.00 days, p < 0.0001) than OPD. Meanwhile, the MIPD group had a higher R0 resection rate (OR 1.45, 95 % Cl: 1.18 to 1.78, p = 0.0003) and more RLN (MD 1.34, 95 % Cl: 0.14 to 2.53, p = 0.03). However, the minimally invasive approach proved to have much longer OP (MD 71.00 mins; 95 % Cl: 27.01 to 115.00 mins; p = 0.002) than OPD. Finally, there were no significant differences between the 2 procedures in POPF (p = 0.30), DGE (p = 0.07), bile leakage (p = 0.98), mortality (p = 0.08), tumor size (p = 0.15), vascular resection (p = 0.68), or re-operation rate (p = 0.11). The authors concluded that these findings suggested that MIPD was safe, feasible, and
worthwhile. Moreover, they stated that future large, well-designed RCTs with extensive follow-up are needed to further clarify this role.

Kendrick and co-workers (2017) conducted an assessment of the best-evidence and expert opinion on the current status and future challenges of MIPD. These investigators performed a systematic review of the literature and best-evidence on minimally invasive pancreatic resection. Expert panel discussion and audience response activity was used to assess perceived value and future direction. From 582 studies, 26 comparative trials of MIPD and OPD were assessed for perioperative outcomes. There were no RCTs and all available comparative studies were determined of low quality. Several observational and case-matched studies demonstrated longer operative times, but less EBL and shorter LOS for MIPD. Registry-based studies demonstrated increased mortality rates after MIPD in low-volume centers. Oncologic assessment demonstrated comparable outcomes of MIPD. Expert opinion supports ongoing evaluation of MIPD. The authors concluded that MIPD appeared to provide similar perioperative and oncologic outcomes in selected patients, when performed at experienced, high-volume centers. Moreover, they stated that the overall role of MIPD in pancreaticoduodenectomy needs to be better defined. Improved training opportunities, registry participation and prospective evaluation are needed.

Pedziwiatr and colleagues (2017) compared MIPD versus OPD by using meta-analytical techniques. Medline, Embase, and Cochrane Library were searched for eligible studies. Data from included studies were extracted for the following outcomes: operative time, overall morbidity, pancreatic fistula, delayed gastric emptying, blood loss, post-operative hemorrhage, yield of harvested lymph nodes, R1 rate, length of hospital stay, and re-admissions. Random and fix effect meta-analyses were undertaken. Initial reference search yielded 747 articles. Thorough evaluation resulted in 12
papers, which were analyzed. The total number of patients was 2,186 (705 in MIPD group and 1,481 in OPD). Although there were no differences in overall morbidity between groups, these researchers noticed reduced blood loss, DGE, and LOS in favor of MIPD. In contrary, meta-analysis of operative time revealed significant differences in favor of open procedures. Remaining parameters did not differ among groups. The authors concluded that the findings of this meta-analysis suggested that although MIPD took longer, it may be associated with reduced blood loss, shortened LOS, and comparable rate of peri-operative complications. Moreover, they stated that due to heterogeneity of included studies and differences in baseline characteristics between analyzed groups, the analysis of short-term oncological outcomes did not allow drawing unequivocal conclusions. These researchers stated that the existing evidence for the use of laparoscopic surgery in pancreatic head malignancy is very limited and should be interpreted with caution; this supports the concept that further, better quality studies are needed to provide higher level of evidence on the benefits of minimally invasive approach in pancreatic head surgery.

Braun Enteroenterostomy for Lowering the Incidence of Delayed Gastric Emptying Following Pancreaticoduodenectomy

In a prospective RCT, Hwang and associates (2016) examined the clinical impact of Braun anastomosis on delayed gastric emptying (DGE) after pylorus-preserving PD (PPPD). From February 2013 to June 2014, a total of 60 patients were recruited for this study. The incidence of DGE and its risk factors were analyzed according to whether or not Braun anastomosis was used after PPPD; 30 patients were respectively enrolled in No-Braun group and Braun group. A comparative analysis between the 2 groups showed no differences in sex, diagnosis, operation time, hospital stay, or post-operative complications, including pancreatic fistula. Overall DGE developed in 8 patients (26.7 %) in the Braun
group and in 14 patients (46.7 %) in the No-Braun group (p = 0.108). However, clinically relevant DGE (grades B and C) was marginally more frequent in the No-Braun group (23.3 % versus 3.3 %, p = 0.052). In a multi-variable analysis, No-Braun anastomosis was an independent risk factor for developing clinically relevant DGE (OR = 16.489; 95 % CI: 1.287 to 211.195; p = 0.031). The authors concluded that the overall DGE occurrence was not different between the 2 groups. However, No-Braun anastomosis was an independent risk factor for developing clinically relevant DGE.

The authors noted that this study had several limitations. One drawback was the small number of patients (n = 60). According to the reference study's result (i.e., the difference in DGE incidence rates between the Braun and No-Braun groups was 30.8 %), the calculated sample size was small. However, in order to avoid unnecessary randomization, these researchers tried to limit the sample size to the minimum needed for statistical analysis. It was expected that a larger RCT will be conducted based on the current encouraging data to prove the beneficial effect of the Braun anastomosis for reducing clinically relevant DGE following PPPD. In addition, it was interesting to note that, even though this study was designed as an RCT, approximately 40 % of eligible patients did not agree with enrollment. As patients' awareness regarding the potential risks and ethical issues of RCTs is increasing, patients appeared hesitant to get actively involved in them. This issue needs to be considered in planning future RCTs. If effective patient's enrollment were not feasible, the power of the RCT may be limited, and even randomization would not be possible.

In a meta-analysis, Zhou and colleagues (2018) evaluated the impact of Braun enteroenterostomy on DGE following PD. These investigators carried out a systematic review of the literature to identify relevant studies. Statistical analysis was performed using Review Manager software 5.3. A total of 11 studies involving 1,672 patients (1,005 in Braun group and 667
in non-Braun group) were included in the meta-analysis. Braun enterointerostomy was associated with a statistically significant reduction in overall DGE (OR 0.32, 95% CI: 0.24 to 0.43; p < 0.001), clinically significant DGE (OR 0.27, 95% CI: 0.15 to 0.51; p < 0.001), bile leak (OR 0.50, 95% CI: 0.29 to 0.86; p = 0.01), and LOS (WMD -1.66, 95% CI: -2.95 to 0.37; p = 0.01). The authors concluded that Braun enterointerostomy minimized the rate and severity of DGE following PD. Moreover, these researchers stated that more larger-size RCTs are needed to confirm these findings.

The authors stated that this study had several drawbacks. First, significant statistical heterogeneity was detected between studies for some outcomes including the analysis of clinically significant DGE (I² = 55%), largely due to the fact that there were significant variations in each clinical setting regarding surgical technique and peri-operative care. Second, the level of evidence was low, for a considerable number of data came from non-RCTs, knowing that non-RCTs have inherent risk of bias. Finally, long-term outcomes such as the nutritional status were not analyzed in this meta-analysis due to the limited data.

Use of Fibrin Sealant Patch for Reducing the Occurrence of Post-Operative Pancreatic Fistula and Complications Following Pancreaticoduodenectomy

Schindl and colleagues (2018) stated that the potential for a fibrin sealant patch to reduce the risk of post-operative pancreatic fistula (POPF) remains uncertain. In a multi-center study, these researchers examined if a fibrin sealant patch is able to reduce POPF in patients undergoing PD with pancreatojejunostomy. Subjects undergoing PD were randomized to receive either a fibrin patch (patch group) or no patch (control group), and stratified by gland texture, pancreatic duct size and neoadjuvant treatment. The primary end-point was POPF; secondary end-points included complications, drain-related factors and LOS. Risk factors for
POPF were identified by logistic regression analysis. A total of 142 patients were enrolled; 45 of 71 patients (63%) in the patch group and 40 of 71 (56%) in the control group developed biochemical leakage or POPF ($p = 0.392$). Fistulas were classified as grade B or C in 16 (23%) and 10 (14%) patients, respectively ($p = 0.277$). There were no differences in post-operative complications (54 patients in patch group and 50 in control group; $p = 0.839$), drain amylase concentration ($p = 0.494$), time until drain removal (mean (S.D.) 11.6 (1.0) versus 13.3 (1.3) days; $p = 0.613$), fistula closure (17.6 (2.2) versus 16.5 (2.1) days; $p = 0.740$) and LOS (22.1 (2.2) versus 18.2 (0.9) days; $p = 0.810$) between the 2 groups. Multivariable logistic regression analysis confirmed that obesity (OR 5.28, 95% CI: 1.20 to 23.18; $p = 0.027$), soft gland texture (OR 9.86, 95% CI: 3.41 to 28.54; $p < 0.001$) and a small duct (OR 5.50, 1.84 to 16.44; $p = 0.002$) were significant risk factors for POPF. A patch did not reduce the incidence of POPF in patients at higher risk. The authors concluded that the use of a fibrin sealant patch did not reduce the occurrence of POPF and complications after PD with pancreatojejunostomy.

In a Cochrane review, Gong and associates (2018) examined the safety, effectiveness, and potential adverse effects of fibrin sealants for the prevention of POPF following pancreatic surgery. These investigators searched trial registers and the following biomedical databases: the Cochrane Library (2018, Issue 4), Medline (1946 to April 12, 2018), Embase (1980 to April 12, 2018), Science Citation Index Expanded (1900 to April 12, 2018), and Chinese Biomedical Literature Database (CBM) (1978 to April 12, 2018). They included all RCTs that compared fibrin sealant (fibrin glue or fibrin sealant patch) versus control (no fibrin sealant or placebo) in people undergoing pancreatic surgery. Two review authors independently identified the trials for inclusion, collected the data, and assessed the risk of bias. They performed the meta-analyses using Review Manager 5, calculated the RR for dichotomous outcomes (or a Peto OR for very rare outcomes), and the MD for continuous outcomes, with 95% CIs. These
researchers included 11 studies involving 1,462 subjects in the review. Application of fibrin sealants to pancreatic stump closure reinforcement after distal pancreatectomy: They included 7 studies involving 860 participants: 428 were randomized to the fibrin sealant group and 432 to the control group after distal pancreatectomy. Fibrin sealants may lead to little or no difference in POPF (fibrin sealant 19.3%; control 20.1%; RR 0.96, 95% CI: 0.68 to 1.35; 755 participants; 4 studies; low-quality evidence). Fibrin sealants may also lead to little or no difference in post-operative mortality (0.3% versus 0.5%; Peto OR 0.52, 95% CI: 0.05 to 5.03; 804 participants; 6 studies; low-quality evidence), or overall post-operative morbidity (28.5% versus 23.2%; RR 1.23, 95% CI: 0.97 to 1.58; 646 participants; 3 studies; low-quality evidence). The authors were uncertain whether fibrin sealants reduced re-operation rate (2.0% versus 3.8%; RR 0.51, 95% CI: 0.15 to 1.71; 376 participants; 2 studies; very low-quality evidence). There was probably little or no difference in LOS between the groups (12.1 days versus 11.4 days; MD 0.32 days, 95% CI: -1.06 to 1.70; 755 participants; 4 studies; moderate-quality evidence). The studies did not report serious adverse events (AEs), quality of life (QOL), or cost-effectiveness. Application of fibrin sealants to pancreatic anastomosis reinforcement after PD: These investigators included 3 studies involving 251 participants: 115 were randomized to the fibrin sealant group and 136 to the control group after PD. They were uncertain whether fibrin sealants reduced POPF (1.6% versus 6.2%; RR 0.25, 95% CI: 0.01 to 5.06; 57 participants; 1 study; very low-quality evidence). Fibrin sealants may lead to little or no difference in post-operative mortality (0.1% versus 0.7%; Peto OR 0.15, 95% CI: 0.00 to 7.76; 251 participants; 3 studies; low-quality evidence) or LOS (12.8 days versus 14.8 days; MD -1.58 days, 95% CI: -3.96 to 0.81; 181 participants; 2 studies; low-quality evidence). These researchers were uncertain whether fibrin sealants reduced overall post-operative morbidity (33.7% versus 34.7%; RR 0.97, 95% CI: 0.65 to 1.45; 181 participants; 2 studies; very low-quality evidence), or re-
operation rate (7.6 % versus 9.2 %; RR 0.83, 95 % CI: 0.33 to 2.11; 181 participants; 2 studies, very low-quality evidence).
The studies did not report serious AEs, QOL, or cost-effectiveness. Application of fibrin sealants to pancreatic duct occlusion after PD: These investigators included 2 studies involving 351 participants: 188 were randomized to the fibrin sealant group and 163 to the control group after PD. Fibrin sealants may lead to little or no difference in post-operative mortality (8.4 % versus 6.1 %; Peto OR 1.41, 95 % CI: 0.63 to 3.13; 351 participants; 2 studies; low-quality evidence) or LOS (17.0 days versus 16.5 days; MD 0.58 days, 95 % CI: -5.74 to 6.89; 351 participants; 2 studies; low-quality evidence). They were uncertain whether fibrin sealants reduced overall post-operative morbidity (32.0 % versus 27.6 %; RR 1.16, 95 % CI: 0.67 to 2.02; 351 participants; 2 studies; very low-quality evidence), or re-operation rate (13.6 % versus 16.0 %; RR 0.85, 95 % CI: 0.52 to 1.41; 351 participants; 2 studies; very low-quality evidence). Serious AEs were reported in 1 study: more participants developed diabetes mellitus when fibrin sealants were applied to pancreatic duct occlusion, both at 3 months' follow-up (33.7 % fibrin sealant group versus 10.8 % control group; 29 participants versus 9 participants) and 12 months' follow-up (33.7 % fibrin sealant group versus 14.5 % control group; 29 participants versus 12 participants). The studies did not report POPF, QOL, or cost-effectiveness. The authors concluded that based on the current available evidence, fibrin sealants may have little or no effect on POPF in people undergoing distal pancreatectomy. Moreover, these investigators stated that the effects of fibrin sealants on the prevention of POPF are uncertain in people undergoing PD.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pancreaticoduodenectomy (also known as Whipple resection):</td>
</tr>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>48150</td>
<td>Pancreatectomy, proximal subtotal with total duodenectomy, partial gastrectomy, choledochoenterostomy and gastrojejunostomy (Whipple-type procedure); with pancreatojejunostomy</td>
</tr>
<tr>
<td>48152</td>
<td>without pancreatojejunostomy</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>48153</td>
<td>Pancreatectomy, proximal subtotal with near-total duodenectomy, choledochoenterostomy and duodenojejunostomy (pylorus-sparing, Whipple-type procedure); with pancreatojejunostomy</td>
</tr>
<tr>
<td>48154</td>
<td>without pancreatojejunostomy</td>
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<tr>
<td>49905</td>
<td>Omental flap, intra-abdominal (List separately in addition to code for primary procedure)</td>
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<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
<tr>
<td>47533</td>
<td>Placement of biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation; external [not covered for prevention of complications]</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>47534</td>
<td>Placement of biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation; internal-external [not covered for prevention of complications]</td>
</tr>
<tr>
<td>47535</td>
<td>Conversion of external biliary drainage catheter to internal-external biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation [not covered for prevention of complications]</td>
</tr>
<tr>
<td>47536</td>
<td>Exchange of biliary drainage catheter (eg, external, internal-external, or conversion of internal-external to external only), percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation [not covered for prevention of complications]</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- C25.3 Malignant neoplasm of pancreatic duct
- D13.6 Benign neoplasm of pancreas
- D13.7 Benign neoplasm of endocrine pancreas

ICD-10 codes not covered for indications listed in the CPB:

- E16.4 Increased secretion of gastrin [Zollinger-Ellison syndrome]

Bra un enteroenterostomy:

CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>44130</td>
<td>Enteroenterostomy, anastomosis of intestine, with or without cutaneous enterostomy (separate procedure) [Braun enteroenterostomy]</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K91.89</td>
<td>Other postprocedural complications and disorders of digestive system [delayed gastric emptying following pancreaticoduodenectomy]</td>
</tr>
</tbody>
</table>

Fibrin sealant - no specific code:

The above policy is based on the following references:


44. Lucena GCM, Barros RA. Pre-operative biliary drainage in the periampullary neoplasia – A systematic review. Arq Bras Cir Dig. 2018;31(2):e1372.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0365
Pancreaticoduodenectomy (Whipple Resection)

There are no amendments for Medicaid.