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Endoscopic management of pancreatic fistula after enucleation of pancreatic tumors

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Abstract
Introduction Pancreatic fistula (PF) are frequent after pancreatic surgical resection, and particularly after enucleation. Endoscopic treatment might be proposed for postoperative PF, but has never been evaluated after pancreatic enucleation.
Patients and methods From January 2000 to June 2012, 161 patients underwent pancreatic enucleation in our center. In case of PF in the postoperative period, conservative management (somatostatin analogs combined with enteral or parenteral nutrition and drainage) was proposed. If PF persisted after 20 days (output >50 cc/d), endoscopic treatment (pancreatic sphincterotomy and stent placement if evidence of main duct leakage) was proposed. Primary outcome was the delay of PF closure after endoscopic treatment.
Results Ninety-one patients (56 %) developed postoperative PF. PF closed within 3 weeks with conservative management in 78 (86 %) patients. Endoscopic treatment was required in 7 (8 %) patients. Daily PF output was 240 (50–300) mL. Pancreatic sphincterotomy was performed in all patients. A pancreatic stent was inserted in 4 of 5 patients with main pancreatic duct leakage. One patient presented a stent migration requiring a second procedure. No complication of endoscopic treatment was reported. The closure of PF was obtained in all cases, after 13 (3–24) days. Pancreatic stents were removed after 2, 5, 5, and 8 months, respectively. Median postoperative follow-up was 46 (21–70) months. At study endpoint, two patients had small asymptomatic pancreatic collections, four had mild dilatation of main pancreatic duct upstream pancreatic duct leakage, and none developed exocrine pancreatic insufficiency, diabetes, or recurrence of pancreatic tumor.
Conclusions PF occurs in half patients after enucleation. Endoscopic treatment combining pancreatic sphincterotomy and stenting is safe and effective if conservative treatment fails, avoiding a complementary pancreatic resection.

Keywords Pancreatic fistula · Enucleation · Pancreatic sphincterotomy · Pancreatic stent

Abbreviations
PF Pancreatic fistula
ERP Endoscopic retrograde pancreatography

Pancreatectomy might be responsible for both short-term (mainly postoperative PF) and long-term complications (pancreatic exocrine and endocrine insufficiency). Pancreatic enucleation is an alternative technique to standard pancreatectomy which preserves pancreatic parenchyma and decreases the risk of pancreatic insufficiency, but may increase that of PF [1, 2]. While the incidence of PF after conventional pancreatic resection varies between 10 and 15 %, it might reach 20–45 % after enucleation [3–6]. Postoperative PFs are associated with higher risk of infection and bleeding, and increases hospital stay and costs [7].

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Usually, postoperative PFs close within one month under conservative management including administration of somatostatin analogs, artificial nutrition, and adequate drainage [8]. However, spontaneous closure of PF may take even longer and require surgical drainage or even resection. Endoscopic treatment, including pancreatic sphincterotomy associated or not with stenting of the main pancreatic duct, might be an alternative to surgery and has been proposed to treat postoperative PF after distal pancreatectomy [7, 9–13]. However, the specific management of PF after pancreatic enucleation has never been reported.

The aim of this study was to evaluate the results of endoscopic treatment of PF, occurring after pancreatic enucleation.

Patients and methods

Definition of postoperative pancreatic fistula

All patients who underwent pancreatic enucleation between January 2000 and June 2012 in our center were reviewed. Enucleation was considered after surgical exploration, together with intraoperative ultrasonography when needed to localize deep lesions and assess their relationship with the main pancreatic duct. Dissection was performed in contact with the lesion, and hemostasis and pancreatostasis were performed using bipolar cautery and stitches. Peripancreatic drainage was routinely inserted and progressively removed from postoperative day 5. Octreotide (Sandostatin®, Novartis, Rueil-Malmaison, France) was routinely given for 7 days (100 μg subcutaneously three times a day) for prophylaxis of PF. Postoperatively, amylase concentrations were routinely measured in the discharged fluid. A PF was defined as an amylase concentration in the drainage fluid more than 3-fold the upper limit of the normal serum amylase level after postoperative day 3 and was graded according to the recommendations of the International Study Group of PF [14].

Management of pancreatic fistula

In case of postoperative PF, conservative treatment combining enteral or parenteral nutrition and somatostatin analogs with drainage using either the surgical drain or a percutaneous drain was started. When daily output of PF was >50 mL after day 20, CT scan was performed to search for an intra-abdominal collection and endoscopic treatment was proposed.

Endoscopic retrograde pancreatography (ERP) was performed with standard side-viewing duodenoscopy (Olympus) under general anesthesia with endotracheal intubation. In all patients, a sphincterotome (Olympus KD18Q, Rungis, France) was used. The pancreatic leak was first confirmed by pancreatography. Pancreatic sphincterotomy was performed with pure cutting current using an Erbe electrosurgical generator (Erbe, Diegem, Belgium). When pancreatography showed disruption of the main pancreatic duct, a pancreatic stent was inserted. The diameter of pancreatic stent varied according to that of the main pancreatic duct, and its length was adapted to the site of the fistula, with intent to bridge the leakage whenever possible. Prophylactic antibiotics (amoxicillin–clavulanate) were administered during procedure.

Primary outcome

Daily PF output was noted after the endoscopic procedure. The primary outcome was the delay of PF closure after endoscopic treatment. Secondary outcomes included complication rate of endoscopic procedures, duration of hospital stay, presence of collection on imaging, and pancreatic insufficiency or tumor recurrence at study endpoint.

Results

Postoperative fistula after enucleation

Between January 2000 and June 2012, 161 patients underwent pancreatic enucleation at our center (Beaujon Hospital, Clichy, France). Enucleated lesions were located in the head, the corpus and the distal pancreas in 76 (47 %), 32 (20 %), and 53 (33 %) cases, respectively. All surgical procedures included peripancreatic drainage. Postoperatively, amylase concentrations were routinely measured in the discharged fluid.

Ninety-one patients (56 %) presented with a postoperative PF, grade A, B, or C in 59 (65 %), 26 (28 %), and 6 (7 %), respectively. Six (7 %) patients underwent reoperation ($n = 2$) or embolization ($n = 4$) for hemorrhage complicating grade C PF. All leaks were located at the site of enucleation. PF closed spontaneously within 3 weeks under conservative management including parenteral or enteral nutrition, somatostatin analogs, and adequate drainage (inserted at the end of enucleation, or subsequently added by percutaneous approach) in 78 patients (86 %). In seven patients (8 %), conservative management was unsuccessful with a fistula output >50 mL/d at day 20 and an endoscopic treatment was proposed.

Characteristics of patients with endoscopic treatment

The seven patients were four males and three females, of median age 58 (37–75) years with a median BMI of 25

(21–27). All patients underwent laparotomy except one who had laparoscopy. Eight enucleations were performed. One patient had two enucleations for metastases of renal cancer. The other indications for resection included neuroendocrine tumor ($n = 3$), branch duct-intraductal papillary mucinous tumor ($n = 1$), mucinous cystadenoma ($n = 1$), and suspicion of cystic benign tumor ($n = 1$ with a final pathological diagnosis of pseudocyst). The diameter of pancreatic lesions ranged from 6 to 50 mm, located in the head, corpus, or tail of the pancreas in 4, 2, and 2 cases, respectively.

The median delay for the diagnosis of PF was 7 days [1–12]. The median peak of amylase content was 132,000 (23,000–415,000) U/L. At the date of endoscopic treatment, the median fistula daily output was 240 (50–300) mL. A pancreatic collection was seen on CTscan in six patients.

Endoscopic treatment

ERP was performed in all patients who had constant fluid volume after day 20 despite conservative management. A pancreatic sphincterotomy was performed in the seven patients. Pancreatography evidenced a lateral leak from main pancreatic duct in five patients. A pancreatic stent was successfully inserted in four patients and was positioned beyond the site of leakage in one, next to the disruption in one and in the pancreatic collection in two others (double pig-tail stent) (Table 1). In one patient, stent insertion was not possible. No leakage from the main pancreatic duct was evidenced in the two other patients.

Neither complication nor death related to endoscopic procedure was reported.

Short- and long-term outcomes of pancreatic fistula after endoscopic treatment

The median postoperative follow-up was 46 (21–70) months. Two patients presented with other postoperative complications (transient arterial hypertension ($n = 1$) and ischemic cardiac attack ($n = 1$)), resolutive with medical treatment.

The fistula daily output immediately decreased (>50 %) after endoscopic procedure in six patients. In one patient with stent insertion, no improvement of FP output was noted and stent migration was evidenced; a second ERP was performed at day 7 to replace the stent, resulting in FP healing within 6 days. The closure of PF was obtained in all cases, with a median time to closure of 13 (3–24) days. All patients in which the closure time exceeded 13 days had an initial daily output >75 mL. The overall hospital stay was 36 (29–84) days. The longest hospital stay was related to postoperative ischemic cardiac failure in one patient.

In the four patients who had stent insertion, the pancreatic stent was removed at 2, 5, 5, and 8 months, respectively. On CT scan, pancreatic collections decreased in size in all cases. At the end of follow-up, two patients had asymptomatic small pancreatic collections, 13 and 25 mm, respectively. Mild dilatation of main pancreatic duct upstream the pancreatic duct leakage was observed in four patients at the endpoint imaging, corresponding to a healing stricture. No patient developed exocrine pancreatic

Table 1 Results of endoscopic treatment in seven patients who presented pancreatic fistula post-enucleation

Patient	Nature of pancreatic lesion requiring enucleation	Site of enucleation	Endoscopic procedure	Closure of pancreatic fistula	Time to closure (days)	Time to stent ablation (months)	Postoperative follow-up (months)
1	Neuroendocrine tumor	Corpus	PS	Yes	24	–	46
2	Neuroendocrine tumor	Corpus	PS and double pig-tail stent 7 Fr 10 cm	Yes	13	5	49
3	Renal cancer metastases (2 lesions)	Head and tail	PS	Yes	3	–	70
4	Neuroendocrine tumor	Head	PS and double pig-tail stent 7 Fr 5 cm	Yes	21	8	21
5	Branch duct-intraductal papillary mucinous tumor	Head	PS right stent 7 Fr 10 cm	Yes	8	2	89
6	Mucinous cystadenoma	Head	PS	Yes	22	–	23
7	Pancreatic pseudocyst	Tail	PS and right stent 7 Fr 12 cm	Yes	11	5	30

PS pancreatic sphincterotomy

insufficiency or diabetes. No recurrence of pancreatic tumor was observed.

Discussion

To our knowledge, this study is the first series describing endoscopic treatment of PF following pancreatic enucleation. Pancreatic enucleation is the surgical procedure associated with the highest rate of postoperative fistula (20–45 %) [3–6]. In the present study, the rate was even higher (56 %), but grade A fistulas (defined by amylase levels in the drainage fluid exceeding three times the upper limit of serum level) were included. Indeed, this definition has been rarely used in previous series of enucleations. The outcome was commonly favorable using a conservative strategy (86 %), except in six patients who developed bleeding. In seven patients (8 %) in whom PF persisted after day 20, endoscopic treatment (pancreatic sphincterotomy in all patients, in combination with pancreatic stent if the main pancreatic duct was disrupted) was proposed. Our study suggests that endoscopic treatment is technically feasible, safe and successful. No surgical intervention was necessary for additional pancreatic resection

The median closure delay after endoscopic treatment was 13 (3–24) days in the present series, longer than that observed after distal pancreatectomy (4 days) [7]. Two hypotheses might account for this finding. PF occurring after enucleation are supplied both by upstream and downstream pancreatic flow. Moreover, the consistency of pancreatic parenchyma around the operative site was soft and not fibrous.

Modalities of endoscopic treatment are still debated. Some authors suggested to systematically insert a pancreatic stent after sphincterotomy [15]. Dumonceau et al. [16] suggested that small pancreatic stents without pancreatic sphincterotomy could be the best treatment option. However, no comparative studies have been published. In this series, no specific complications were related to pancreatic sphincterotomy. A stent migration occurred in one patient and a second procedure was successful. When pancreatography did not demonstrate leakage from the main pancreatic duct, only pancreatic sphincterotomy was performed. The results were excellent in the two patients, with a single endoscopic procedure (no pancreatic stent to retrieve).

The optimal duration of pancreatic stenting has been controversial. In the present study, the stent was deliberately left in place for a long time after PF closure for calibration and prevention of ductal stricture. Long-term stent placement may cause ductal irregularities mimicking chronic pancreatitis [17, 18]. In our series, no stent-induced damage in the main pancreatic duct was reported, probably due to the small diameter of stents (7 Fr). Four patients developed a duct stricture with upstream dilatation. While inserting a stent through the duct leakage could prevent stricture formation, this is technically difficult and might increase the duration of endoscopic procedure and the risk of post-ERP complications.

Various prophylactic strategies to prevent postoperative PF have been proposed, including glue or different surgical devices [19, 20]. Some series have reported promising results with preoperative pancreatic stenting [21, 22], but this strategy requires general anesthesia, is associated with the risk of post-ERP acute pancreatitis, and its cost-effectiveness has never been demonstrated. Moreover, a randomized study did not confirm the benefit of preoperative stenting, and morbidity was even higher in treated patients [23]. No data on preoperative stenting in patients undergoing enucleation are available. In our series, seven patients (4 %) among the 161 patients who underwent pancreatic enucleation required endoscopic treatment, suggesting that a strategy consisting in systematic preoperative ERP would be useless for 96 % of patients.

Due to the frequent resolution of PF with conservative management, it was decided in our study to wait for 20 days before endoscopic treatment. We could not assess the factors influencing the closure delay due to the small number of patients, but a high daily fistula output before endoscopic treatment was associated with longer closure delay. This finding suggests that endoscopic treatment could be proposed earlier in patients with high daily fistula output. Future studies are required to select the patients who would benefit the most of endoscopic treatment, in order to limit the morbidity associated with PF and to decrease the length hospital stay.

In conclusion, PF occurred in half of patients after enucleation of pancreatic lesions. In cases of unsuccessful conservative management, endoscopic treatment seems feasible, safe, and effective. The best timing of endoscopic treatment remains to be determined in a prospective study.

Disclosures Drs. Frédérique Maire, Philippe Ponsot, Clotilde Debove, Safi Dokmak, Philippe Ruszniewski and Alain Sauvanet have no conflicts of interest or financial ties to disclose.

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