Surgery 173 (2023) 1254–1262

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Outcomes of rescue procedures in the management of locally recurrent ampullary tumors: A Pancreas 2000/EPC study

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https://doi.org/10.1016/j.surg.2022.12.011

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ARTICLE INFO

Article history:
Accepted 13 December 2022
Available online 13 January 2023

ABSTRACT

Background: Ampullary lesions are rare and can be locally treated either with endoscopic papillectomy or transduodenal surgical ampullectomy. Management of local recurrence after a first-line treatment has been poorly studied.
Methods: Patients with a local recurrence of an ampullary lesion initially treated with endoscopic papillectomy or transduodenal surgical ampullectomy were retrospectively included from a multi-institutional database (58 centers) between 2005 and 2018.
Results: A total of 103 patients were included, 21 (20.4%) treated with redo endoscopic papillectomy, 14 (13.6%) with transduodenal surgical ampullectomy, and 68 (66%) with pancreaticoduodenectomy. Redo endoscopic papillectomy had low morbidity with 4.8% ($n = 1$) severe to fatal complications and a R0 rate of 81% ($n = 17$). Transduodenal surgical ampullectomy and pancreaticoduodenectomy after a first procedure had a higher morbidity with Clavien III and more complications, respectively, 28.6% ($n = 4$) and 25% ($n = 17$); R0 resection rates were 85.7% ($n = 12$) and 92.6% ($n = 63$), both without statistically significant difference compared to endoscopic papillectomy ($P = .1$ and 0.2). Pancreaticoduodenectomy had 4.4% ($n = 2$) mortality. No deaths were registered after transduodenal surgical ampullectomy or endoscopic papillectomy. Recurrences treated with pancreaticoduodenectomy were more likely to be adenocarcinomas (79.4%, $n = 54$ vs 21.4%, $n = 3$ for transduodenal surgical ampullectomy and 4.8%, $n = 1$ for endoscopic papillectomy, $P < .0001$). Three-year overall survival and disease-free survival were comparable.
Conclusion: Endoscopy is appropriate for noninvasive recurrences, with resection rate and survival outcomes comparable to surgery. Surgery applies more to invasive recurrences, with transduodenal surgical ampullectomy rather for carcinoma in situ and early cancers and pancreaticoduodenectomy for more advanced tumors.

Introduction

The ampulla of Vater is a specific anatomic structure at the junction of the common bile duct and the main pancreatic duct on a small segment of duodenal wall.[1] Ampullary tumors account for 10% of periampullary lesions[2] and occur sporadically or in the setting of polyposis syndromes such as a familial adenomatous polyposis.[3] Patients can present with obstructive jaundice, cholangitis, bleeding, or weight loss. However, early incidental diagnosis in asymptomatic patients is more frequent.[4] Most ampullary lesions are adenomas[5,6] that have a risk of malignant transformation by an adenoma-to-carcinoma sequence.[7-9] Thus, ampullary lesions should be resected, either endoscopically or surgically with pancreaticoduodenectomy (PDD)[10] or transduodenal surgical ampullectomy (TSA).[11,12] Although surgical interventions demonstrate convincing rates of complete resection, adverse events have to be considered, in particular after PDD. Therefore, endoscopic papillectomy (EP) is recommended as first-line treatment by the European Society for Gastrointestinal Endoscopy for selected noninvasive ampullary lesion (low- and high-grade dysplasia)[13] when R0 resection is feasible. Few data are available regarding treatment of a local recurrence of ampullary tumors whether EP or TSA was performed. In a recent meta-analysis, Heise et al found recurrences rates of 13% after EP and 9.4% after TSA,[14] but recurrence ratea up to 32% has been reported after EP.[15] The management of these local recurrences remain challenging and poorly standardized.

The aim of the present work was to study the management of local recurrence of ampullary tumors after a first-line treatment including EP or TSA with regard to efficacy and complications.

Methods

Inclusion criteria and data collection

This study used data of a multicenter multinational study including 1,422 EPs, 251 TSAs, and 1,189 PDDs from 58 participating centers (Endoscopic vs Surgical Ampullectomy vs Pancreaticoduodenectomy [ESAP] study).[16] All adult patients with a histologically confirmed ampullary neoplasm who underwent an endoscopic or surgical resection were eligible for inclusion. A minimum of 12 months of follow-up after resection was required. The exclusion criteria were periampullary lesions. Out of the whole database, all consecutive adult patients with a local recurrence of an ampullary neoplasm after initial EP or TSA between 2005 and 2018 were identified. By definition of a recurrence, the initial resection margin after EP or TSA was R0, and/or there was no suspicion of a remnant lesion in follow-up endoscopy. Surgery was performed in only high-volume centers (ie, centers performing >20 procedures a year). Each case of a recurrence was discussed and the indication for EP, TSA, or PDD was decided in each center after a multidisciplinary tumor board according to local institutional expertise and patient allocation to medical disciplines.

We collected the medical information from the ESAP study database with additional retrospective medical record review when necessary. Data included age at intervention, sex, comorbidities, concomitant hereditary polyposis syndrome, clinical presentation, size, morphology, and histology of the recurrence. Specific information regarding the interventional procedures was also used. Data were recorded in a preformatted data collection sheet. Adverse events were stratified according to the American Society of

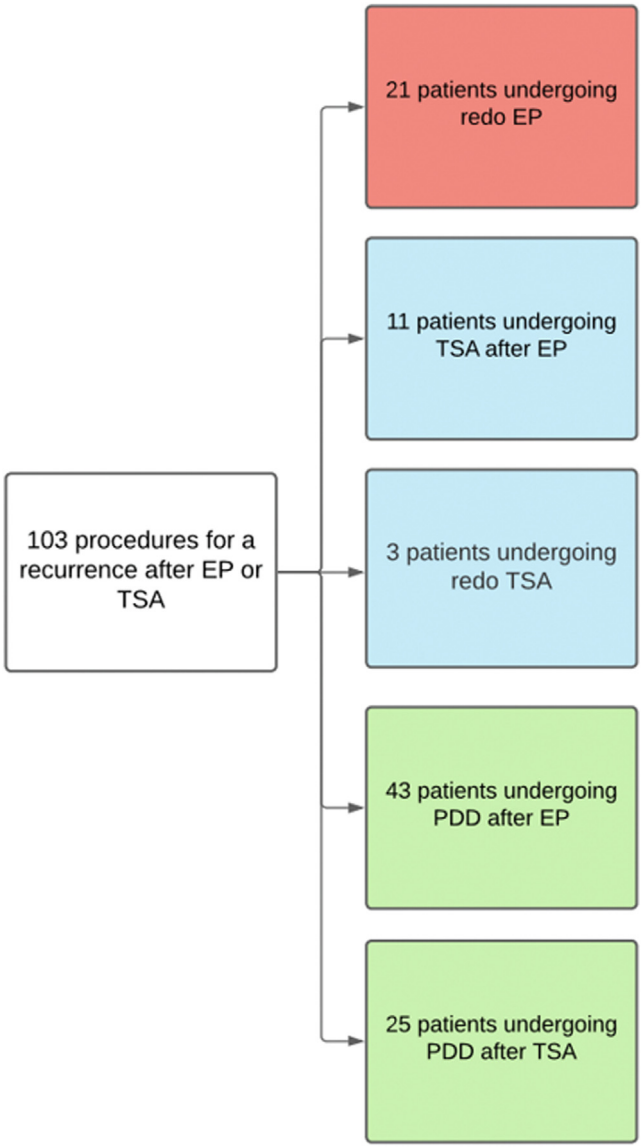

Figure 1. Flow chart of studied population. *EP*, endoscopic papillectomy; *PDD*, pancreatoduodenectomy; *TSA*, transduodenal ampullectomy.

Gastrointestinal Endoscopy (ASGE) complication scale[17,18] for endoscopic procedures, according to the Clavien-Dindo classification[19] for surgical procedures and according to the International Study Group of Pancreatic Fistula for pancreatic fistula classification.[20]

The final study protocol was approved by the ethics committee of the Medical Faculty of the University of Leipzig (455/18-ek) in accordance with the Declaration of Helsinki, the Medical Association's Professional Code of Conduct, and the principles of ICH-GCP guidelines (issued in Jun 1996, ISO14155 from 2012) and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[20,21] Furthermore, local legal and regulatory authorities as well as the medical secrecy and the Federal Data Protection Act were followed.

Statistical analysis

The continuous variables are expressed as median and IQR and/or percentage, as appropriate. The χ^2 analysis or Fisher exact test was used to compare differences in discrete or categorical variables, and the *t* test, ANOVA, or Kruskal-Wallis test was used for the continuous variables. Recurrence was defined as tumor on radiological imaging (lymph node metastases, liver metastases, other metastases) or endoscopic finding in follow-up. Disease-free survival (DFS) was defined as the time between primary procedure and the first evidence of tumor recurrence on imaging/endoscopy. Overall survival (OS) was defined as the time between primary surgery and death or endpoint. Patients were followed up until death or date-point (Jan 2021). Survival probabilities were estimated with the Kaplan-Meier method, and survival was compared between groups with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to evaluate significant recurrence predictors and their relative role in the cohort. Data were analyzed with STATA 16.1 statistical software (StataCorp, LLC, College Station, TX).

Results

Patients and tumors characteristics

Overall, after a median follow-up of 26 months of the whole database, 103 patients presented with local recurrence of an ampullary tumor after a complete resection by first-line local treatment including EP or TSA (Figure 1). Patients' and tumor characteristics are shown in Table I. Briefly, to treat a local recurrence, 21 patients underwent a new EP after EP (20.4%), 11 TSA after EP (10.7%), 3 redo TSA (2.9%), 43 PDD after EP (41.7%), and 25 PDD after TSA (24.3%). For the overall cohort, median age was 64 years, 46% of patients were female, the median body mass index was 24 kg/m^2, and patients were mainly an American Society of Anesthesiologists score of 1 to 2 (62.1%, $n = 64$) with no differences between the groups. Clinical presentation of recurrence was obstructive jaundice in 40 patients (38.8%) and cholangitis in 21 patients (20.4%). Patients in the PDD group were more frequently symptomatic with higher rates of jaundice (48.5%, $n = 33$) and cholangitis (26.5%, $n = 18$) than the TSA and EP groups ($P < .0001$). After first intervention, lesions were mostly noninvasive in EP after EP patients (71.4%, $n = 15$) and invasive in TSA and PDD patients with, respectively, 64.3% ($n = 9$) and 60.3% ($n = 41$). Upon diagnosis, recurrences were usT0/x in 67% ($n = 69$) and usT1 in 21.3% ($n = 22$) of cases. All patients had endoscopic ultrasonography (EUS) at recurrence for local evaluation. Imaging diagnosis data were available for only 83 (81%): data were not retrieved for 3 (4.4%) PDD patients and imaging was not performed for 18 (85.7%) of the redo EP patients. Recurrences were noninvasive at diagnosis biopsy in 71.8% ($n = 74$) of patients.

Intraprocedural parameters

Intraprocedural outcomes are summarized in Table II. Concerning patients undergoing redo EP, 33.3% ($n = 7$) had a biliary duct stent after procedure, 71.4% ($n = 15$) had a pancreatic duct stent after procedure, and 28.6% ($n = 6$) had a complementary argon plasma coagulation (APC) to cauterize residual tissue left after EP. En bloc resection was performed in 10 (47.6%) patients, piecemeal resection in 11 (52.4%) of them.

Within the TSA group, after TSA (2.9%, $n = 3$) or after EP (10.7%, $n = 11$), all procedures were led through laparotomy, and all of them were drained. Transcystic drains were used in 27.2% ($n = 3$) of TSA after EP and 33.3% ($n = 1$) of TSA after TSA.

For patients undergoing PDD, after TSA (24.3%, $n = 25$) or after EP (41.7%, $n = 43$), all procedures were performed through laparotomy except for one that was through laparoscopy. Anastomoses were pancreaticojejunostomy in 51 out of the 68 PDD (75%); all of them were drained. No vascular resection was needed. Median

Table I
Demographic and preoperative characteristics of the 103 patients undergoing a rescue procedure for a local recurrence after management of a first ampullary tumor

	Overall population	EP after EP	TSA		PDD		*P* value (EP vs TSA vs PDD whole group)
			After EP	After TSA	After EP	After TSA	
N (%)	103 (100)	21 (20.4)	14 (13.6)		68 (66)		-
			11 (10.7)	3 (2.9)	43 (41.7)	25 (24.3)	-
Age (y) (IQR)	64 (56–74)	68 (57–74)	65 (55–73)		62 (57–72)		.9
			65 (57–71)	59 (56–68)	65 (57–74)	61 (51–69)	-
Female (*n*, %)	46 (44.7)	9 (42.9)	6 (54.5)	1 (33.3)	18 (41.9)	12 (48)	.07
BMI (kg/m^2) (IQR)	24 (22–28)	26 (25–28)	25 (24–33)		24 (22–28)		.24
			25 (23–34)	30 (29–30)	24 (23–28)	23 (21–26)	-
ASA score 1–2 (*n*, %)	64 (62.1)	13 (61.9)	6 (54.5)	2 (66.6)	30 (69.8)	13 (52)	.9
FAP (*n*, %)	5 (4.9)	4 (19)	1 (9.1)	0	0	0	.003
Time to recurrence (mo) (IQR)	7 (1–21)	15 (1–27)	5 (3–28)		8 (1–17)		.66
			4 (2–9)	43 (24–46)	7 (2–15)	7 (1 - 53)	-
Clinical presentation at recurrence (*n*, %)							< .0001
Jaundice	40 (38.8)	5 (23.8)	2 (18.2)	0	23 (53.5)	10 (40)	
Pancreatitis	8 (7.8)	0	0	0	6 (14)	2 (8)	
Cholangitis	21 (20.4)	1 (4.8)	1 (9.1)	1 (33.3)	13 (30.2)	5 (20)	
Asymptomatic/Other	34 (33)	15 (71.4)	8 (72.7)	2 (66.6)	1 (2.3)	8 (32)	
Diagnostic CT/MRI at recurrence (*n*, %)							
cT0/x	63 (61.1)	2 (9.5)	7 (63.6)	3 (100)	33 (76.7)	18 (72)	.46
cT1	15 (14.6)	1 (4.8)	4 (36.4)	0	8 (18.6)	2 (8)	
cT2	5 (4.6)	0	0	0	2 (4.7)	3 (12)	
cNx	11 (10.7)	3 (14.3)	0	0	3 (7)	5 (20)	.001
cN0	72 (69.9)	0	11 (100)	3 (100)	40 (93)	18 (72)	
Diagnostic endoscopy at recurrence							
- Tumor size (mm) (IQR)	20 (12–26)	20 (10–27)	13 (6–19)	NA	18 (13–25)	20 (18–30)	.56
- Intrabiliary extension (*n*, %)	25 (24.3)	3 (14.3)	4 (36.3)	1 (33.3)	13 (30.2)	4 (16)	
- Intrapancreatic extension (*n*, %)	10 (9.7)	0	0	1 (33.3)	6 (14)	3 (12)	
Recurrence ultrasonography staging (*n*, %)							
US T0/x	69 (67)	20 (95.2)	8 (72.8)	3 (100)	25 (58.1)	13 (52)	.11
US Tis	7 (6.8)	0	0	0	3 (7)	4 (16)	.0004
US T1	22 (21.3)	1 (4.8)	3 (27.2)	0	13 (30.2)	5 (20)	
US T2	5 (4.9)	0	0	0	2 (4.7)	3 (12)	
US NX	39 (37.9)	2 (9.5)	2 (18.2)	1 (33.3)	22 (51.2)	12 (48)	
US N0	61 (59.2)	19 (90.5)	9 (81.8)	2 (66.6)	20 (46.5)	13 (52)	
US N1	3 (2.9)	0	0	0	3 (7)	0	
Diagnosis after first treatment (*n*, %)							
Noninvasive	47 (45.6)	15 (71.4)	3 (27.2)	2 (66.6)	3 (7)	24 (96)	.031
Invasive cancer	56 (54.4)	6 (28.6)	8 (72.8)	1 (33.3)	40 (93)	1 (4)	
Recurrence histological type at biopsy (*n*, %)							
Noninvasive	74 (71.8)	20 (95.2)	10 (90.9)	2 (66.6)	21 (48.7)	21 (84)	.003
Invasive cancer	29 (28.2)	1 (4.8)	1 (9.1)	1 (33.3)	22 (51.3)	4 (16)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *IQR*, interquartile range; *CT*, computed tomography; *EP*, endoscopic papillectomy; *FAP*, familial adenomatous polyposis; *MRI*, magnetic resonance imaging; *PDD*, pancreaticoduodenectomy; *TSA*, transduodenal surgical ampullectomy.

blood loss was 350 mL in the PDD group compared to 150 mL in the TSA and no relevant blood loss in the EP group ($P < .0001$).

Complications following endoscopic and surgical procedures

Complications are displayed in Table III. In the redo EP group, there were 23.8% ($n = 5$) mild/moderate complications according to the ASGE endoscopic adverse events scale. One patient (4.8%) had a severe ASGE complication, that is, duodenal perforation and a severe pancreatitis requiring rehospitalization and transgastric endoscopic drainage of an abdominal collection. The remaining complications were 4 mild pancreatitis (19%), 1 associated with a cholangitis (4.8%), and 1 hemorrhage (4.8%) that needed endoscopic reintervention. The median hospital stay was 6 days, and there was no mortality and no need for surgical intervention.

For TSA patients, complications were mostly Clavien-Dindo grade I to II for TSA after EP (81.8%, $n = 9$) and III to IV for redo TSA (66.6%, $n = 2$). For TSA after EP, complications were 1 (9.1%) biliary stenosis and 1 (9.1%) hemorrhage with the need for 2 reinterventions: 1 surgical (9.1%) and 1 endoscopic (9.1%). For redo TSA, complications were 1 (33.3%) pancreatic stenosis and 1 (33.3%) duodenal fistula with the need for 2 surgical reinterventions (66.6%). Median hospital stay was identical for both groups (14 days), and there was no postoperative mortality.

Concerning PDD, there were 49.5% ($n = 51$) Clavien-Dindo grade I to II complications and the median hospital stay was identical (18 days) for both groups.

In PDD after EP group, there were 27 (62.8%) Clavien-Dindo grade I to II complications: 3 biochemical leaks (7%), 7 grade B PF (16.3%), 4 hemorrhages (9.3%), 8 delayed gastric emptying (DGE) (18.6%), 1 (2.3%) acute pancreatitis, and 1 chyle leak (2.3%). Three grade B PF (7%) were associated with DGE and 1 (2.3%) with hemorrhage. There were 12 (27.9%) Clavien-Dindo III to IV complications: 6 grade C PF (14%), 6 hemorrhages (14%), 5 DGE (11.6%), 1 biliary fistula (2.3%), and 1 duodenal fistula (2.3%). Three grade C PF (7%) were associated with hemorrhages, 3 (7%) with DGE. Biliary fistula was associated with DGE. Reinterventions for Clavien-Dindo IIIa complications were 2 (4.7%) radiological drainages of abdominal collections, and for grades IIIb to IV were 1 (2.3%) radiological drainage and 9 (20.9%) redo surgeries. There was 1 (2.3%) Clavien-Dindo grade V complication due to a hemorrhage with an attempt to radiological embolization that could not prevent death.

In PDD after TSA group, there were 14 (56%) Clavien-Dindo I to II complications: 3 biochemical leaks (12%), 2 chyle leaks (8%), 1 DGE (4%) associated with one of the chyle leaks. There were 3 (12%)

Table II
Intraprocedural parameters of the 103 patients undergoing a rescue procedure for a local recurrence after management of a first ampullary tumor

	Overall population	EP after EP	TSA		PDD	
			After EP	After TSA	After EP	After TSA
N (%)	103 (100)	21 (20.4)	14 (13.6)		68 (66)	
			11 (10.7)	3 (2.9)	43 (41.7)	25 (24.3)
Duodenotomy size (mm) (IQR)	40 (40–50)	-	40 (39–43)	50 (50–50)	-	-
Anastomosis (*n*, %)		-	-	-		
- Pancreaticojejunostomy	51 (49.5)				32 (74.4)	19 (76)
- Pancreaticogastrostomy	17 (16.5)				11 (25.6)	6 (24)
Surgical drain (*n*, %)	81 (78.6)	-	10 (90.9)	3 (100)	43 (100)	25 (100)
Transcystic drain (*n*, %)	8 (7.8)	-	3 (27.2)	1 (33.3)	2 (4.7)	2 (8)
Blood loss (mL) (IQR)	325 (200–600)	-	150 (100–200)	0	350 (280–500)	500 (300–1300)
En bloc EP resection (*n*, %)	10 (9.7)	10 (47.6)	-	-	-	-
Piecemeal EP resection (*n*, %)	11 (10.7)	11 (52.4)	-	-	-	-
BD stent after EP (*n*, %)	7 (6.8)	7 (33.3)	-	-	-	-
PD stent after EP (*n*, %)	15 (14.6)	15 (71.4)	-	-	-	-
Complementary APC (*n*, %)	6 (5.8)	6 (28.6)	-	-	-	-

APC, argon plasma coagulation; *BD*, biliary duct; *EP*, endoscopic papillectomy; *PD*, pancreatic duct; *PDD*, pancreaticoduodenectomy; *TSA*, transduodenal surgical ampullectomy.

Table III
Postoperative outcomes of the 103 patients undergoing a rescue procedure for a local recurrence after management of a first ampullary tumor

	Overall population	EP after EP	TSA		PDD		*P* value (EP vs TSA vs PDD whole group)
			After EP	After TSA	After EP	After TSA	
N (%)	103 (100)	21 (20.4)	14 (13.6)		68 (66)		-
			11 (10.7)	3 (2.9)	43 (41.7)	25 (24.3)	-
Complications (*n*, %)							
- Clavien-Dindo I–II	51 (49.5)	-	9 (81.8)	1 (33.3)	27 (62.8)	14 (56)	1.00
- Clavien-Dindo III–IV	19 (18.4)	-	2 (18.2)	2 (66.6)	12 (27.9)	3 (12)	
- Clavien-Dindo V	2 (1.9)	-	0	0	1 (2.3)	1 (4)	
ASGE endoscopic adverse events (*n*, %)							-
- Mild/moderate	5 (4.9)	5 (23.8)	-				
- Severe/fatal	1 (0.9)	1 (4.8)	-				
Sepsis (*n*, %)	17 (16.5)	1 (4.8)	1 (9.1)	1 (33.3)	12 (27.9)	2 (8)	.25
Acute pancreatitis (*n*, %)	5 (4.9)	4 (19)	0	0	1 (2.3)	0	.009
Delayed gastric emptying (*n*, %)	15 (14.6)	0	0	0	13 (30.2)	2 (8)	.009
Pancreatic fistula (*n*, %)							
- Biochemical leak	6 (5.8)	0	0	0	3 (7)	3 (12)	1.00
- ISGPF B	7 (6.8)	0	0	0	7 (16.3)	0	
- ISGPF C	8 (7.8)	0	0	0	6 (14)	2 (8)	
Biliary fistula (*n*, %)	2 (1.9)	0	0	0	1 (2.3)	1 (4)	1.00
Pancreatic stenosis (*n*, %)	1 (0.9)		0	1 (33.3)	0	0	.14
Biliary stenosis (*n*, %)	1 (0.9)	0	1 (9.1)	0	0	0	.14
Duodenal fistula (*n*, %)	3 (2.9)	1 (4.8)	0	1 (33.3)	1 (2.3)	0	.11
Chyle fistula (*n*, %)	3 (2.9)	0	0	0	1 (2.3)	2 (8)	1.00
Hemorrhage (*n*, %)	13 (12.6)	1 (4.8)	1 (9.1)	0	10 (23.2)	1 (4)	.41
Reintervention needed (*n*, %)							
- Surgical	14 (13.6)	0	1 (9.1)	2 (66.6)	9 (20.9)	2 (8)	.009
- Endoscopic	3 (2.9)	2 (9.5)	1 (9.1)	0	0	0	
- Radiological	5 (4.9)	0	0	0	4 (9.3%)	1 (4)	
Hospital stay (d) (IQR)	15 (9–21)	6 (3–8)	13 (12–22)		18 (13–25)		< .0001
			14 (12–20)	14 (12–24)	18 (13–26)	18 (14–23)	-

ASGE, American Society of Gastrointestinal Endoscopy; *EP*, endoscopic papillectomy; *ISGPF*, International Study Group of Pancreatic Fistula; *PDD*, pancreaticoduodenectomy; *TSA*, transduodenal surgical ampullectomy.

Clavien-Dindo III–IV complications: 2 grade C PF (8%), 1 hemorrhage (4%), 1 DGE (4%), and 1 biliary fistula (4%). Grade C PF were associated with hemorrhage and DGE. Reinterventions were radiological (4%, $n = 1$) and surgical (8%, $n = 2$), all under general anesthesia. The Clavien-Dindo V complication (4%, $n = 1$) was due to a hemorrhage with no reintervention.

Clavien-Dindo grading was mostly I–II between the TSA and PDD groups (71.4% and 60.3%, $P = 1.00$). However, type of reinterventions differed: the EP group had more endoscopic reinterventions (9.5%, $n = 2$), the TSA group had more surgical reinterventions (21.4%, $n = 3$), and the PDD group had more radiological reinterventions (7.4%, $n = 5$; $P = .009$). As expected, median hospital stay was shorter for EP patients with 6 days vs 13 days for TSA and 18 days for PDD ($P < .0001$). Eventually, there was no statistical difference between EP patients with severe to fatal ASGE complications and TSA and PDD patients with Clavien-Dindo ≥III complications ($P = .1$).

For all patients with noninvasive histology at diagnosis of recurrence (Supplementary Table S1), mortality and morbidity were not different between the 3 groups ($P = .99$). The type of reintervention is different, predominantly endoscopic (10%, $n = 2$) for the EP group, surgical for TSA (16.7%, $n = 2$) and radiological for PDD (16.7%, $n = 7$) ($P = .004$). Hospital stay is still shorter for the EP group (7 days vs 13 and 18 days, $P < .0001$).

Pathology results

Pathology outcomes are shown in Table IV. In the redo EP group, tumors were almost all adenomas (95.2%, $n = 20$) except for one

Table IV
Pathology results of the 103 patients undergoing a rescue procedure for a local recurrence after management of a first ampullary tumor

	Overall population	EP after EP	TSA		PDD		*P* value (EP vs TSA vs PDD whole group)
			After EP	After TSA	After EP	After TSA	
N (%)	103 (100)	21 (20.4)	14 (13.6)		68 (66)		-
			11 (10.7)	3 (2.9)	43 (41.7)	25 (24.3)	-
Adenoma (*n*, %)	45 (43.7)	20 (95.2)	9 (81.8)	2 (66.6)	9 (20.9)	5 (20)	< .0001
Adenocarcinoma (*n*, %)	58 (56.3)	1 (4.8)	2 (18.2)	1 (33.3)	34 (79.1)	20 (80)	< .0001
pT stage (*n*, %)							
- Adenoma	45 (43.7)	20 (95.2)	9 (81.8)	2 (66.6)	9 (20.9)	5 (20)	< .0001
- pTis	1 (0.9)	0	0	0	0	1 (4)	
- pT1a	13 (12.6)	1 (4.8)	1 (9.1)	1 (33.3)	7 (16.3)	3 (12)	
- pT1b	9 (8.7)	0	1 (9.1)	0	6 (14)	2 (8)	
- pT2	27 (26.3)	0	0	0	15 (34.8)	12 (48)	
- pT3a	4 (3.9)	0	0	0	3 (7)	1 (4)	
- pT3b	4 (3.9)	0	0	0	3 (7)	1 (4)	
R0 resection (*n*, %)	92 (89.3)	17 (81)	9 (81.8)	3 (100)	42 (97.8)	21 (84)	.2

EP, endoscopic papillectomy; *PDD*, pancreaticoduodenectomy; *TSA*, transduodenal surgical ampullectomy.

(4.8%) that was a pT1a adenocarcinoma. R0 resection rate was 81% ($n = 17$) in the redo EP group.

In the TSA after EP and redo TSA groups, recurrences were adenomas in, respectively, 81.8% ($n = 9$) and 66.6% ($n = 2$). Remaining patients had adenocarcinomas, respectively, 18.2% ($n = 2$) with 9.1% pT1a ($n = 1$) and 9.1% pT1b ($n = 1$) and 33.3% pT1a ($n = 1$). The R0 resection rate was 81.8% ($n = 9$) in the TSA after EP group and 100% ($n = 3$) in the redo TSA group. Concerning both patients who had a R1 resection: the first patient (7.1%) with R1 resection initially had an EP. The R1 resection led to a local recurrence treated with RFA. Unfortunately, follow-up lasted only 2 months, and there were no data afterward. The second patient (7.1%) was initially treated by EP, had no recurrence after R1 resection, and was monitored (imaging and endoscopy) for only 45 months, with no need for another treatment.

In the PDD after EP and PDD after TSA groups, recurrences were adenomas in, respectively, 20.9% ($n = 9$) and 20% ($n = 5$) of cases. Others were adenocarcinomas: pT1a in, respectively, 16.3% ($n = 7$) and 12% ($n = 3$) of cases, and pT2 in, respectively, 34.8% ($n = 15$) and 48% ($n = 12$) of cases. Pancreaticoduodenectomy after EP and after TSA were pN0 in, respectively, 62.8% ($n = 27$) and 96% ($n = 24$). Pancreaticoduodenectomy after EP, however, had 32.5% ($n = 14$) of pN1 and 4.7% ($n = 2$) of N2. R0 resection rate was 97.8% ($n = 42$) in the PDD after EP group and 84% ($n = 21$) in the PDD after TSA group. Concerning the 5 R1 patients: 1 (1.4%), who had initially an EP, was only followed and alive at 72 months. Another one (1.4%), who initially had a TSA, was also only followed and alive at 60 months. One (1.4%), who initially had a TSA, had a local recurrence treated with argon plasma coagulation and was alive after a follow-up of 55 months. The last 2 (2.8%), after an initial TSA, had metastatic recurrences within the first month after the reintervention. They were treated with chemotherapy with 1 alive at 6 months and the other dead precisely 18 days after the first chemotherapy administration.

To sum up, there were more adenocarcinomas in patients having PDD with 79.4% ($n = 54$) vs 21.4% ($n = 3$) for TSA and 4.8% ($n = 1$) for redo EP ($P < .0001$). These adenocarcinomas were pT1a in 14.7% ($n = 10$), pT2 in 39.7% ($n = 27$), and pN0 in 75% ($n = 51$) of PDD patients. There was also more microvascular and lymphovascular invasion in PDD patients with 20.6% ($n = 14$) vs 0 for EP and TSA groups ($P = .01$).

For all patients with noninvasive histology at first biopsy of recurrence (Supplementary Table S2), 56.8% ($n = 42$) of them were adenomas, with 100% of tumors in EP group ($n = 20$), 83.3% of tumors in TSA group ($n = 10$) and only 28.6% of tumors in PDD group ($n = 12$) ($P < .0001$). Repartition of pT stages is similar to total study population in PDD group with pT1 in 28.6% ($n = 12$) and pT2 in 33.3% ($n = 14$) of patients. R0 resection is similar in the 3 groups ($P = .81$).

Survival and recurrence analysis

Survival outcomes are summarized in Table V. For redo EP patients, median follow-up (FU) was 30 months, and recurrences were only local (42.9%). Overall, 42.9% of patients ($n = 9$) recurred. The median time to recurrence was 9 months. Recurrence treatment was APC (14.3%, $n = 3$), endoscopic mucosectomy (19%, $n = 4$), and PDD (9.5%, $n = 2$). Three years DFS and OS were 84% and 100%, respectively.

Overall, 21.4% ($n = 3$) TSA patients had a recurrence, with a median of 1 month to recurrence. In the TSA after EP group, the median FU was 45 months, and recurrences were local (9.1%, $n = 1$) and metastatic (9.1%, $n = 1$). Local recurrence on biliary duct was treated with RFA (9.1%, $n = 1$), with no follow-up thereafter; metastatic recurrence was treated with best supportive care (9.1%, $n = 1$). In the redo TSA group, FU was 23 months, and recurrence was only local on biliary duct in 1 patient (33.3%), treated with repeated APC. The patient died 2 years after first evidence of the local recurrence. Three-year DFS and OS were 68% and 85% for the whole TSA group.

Overall, 19.1% ($n = 13$) PDD patients had a recurrence, with a median of 17 months to recurrence. In the PDD after EP group, median FU was 40 months, and recurrences were local (2.3%, $n = 1$) and metastatic (14%, $n = 6$). All recurrences were treated with chemo/radiotherapy (14%, $n = 6$) except for 1 metastatic recurrence (2.3%, $n = 1$) that was treated with best supportive care. In the PDD after TSA group, median FU was 22 months, and recurrences were local (4%, $n = 1$) and metastatic (20%, $n = 5$). Recurrences were treated with chemo/radiotherapy (12%, $n = 3$) and best supportive care (12%, $n = 3$). Three years DFS and OS were both 87% in the PDD after EP group and 68% and 79%, respectively, in the PDD after TSA group. Recurrence treatment was chemo/radiotherapy in, respectively, 14% and 12% and/or best supportive care in, respectively, 2.3% and 12%.

Recurrences were more frequently metastatic in PDD group with 16.2% ($n = 11$) vs 7.1% ($n = 1$) for TSA group and 0 for EP group ($P = .0001$). Recurrence treatment was also different, with more local therapies (eg, APC, RFA, endoscopic mucosectomy) in the EP and TSA groups compared to more systemic therapies in the PDD group ($P < .0001$).

Three-year OS was not different between the TSA and PDD groups ($P = .51$) and the TSA and EP groups ($P = .2$) or the EP and PDD groups ($P = .09$). Three-year DFS was not different between TSA and PDD groups ($P = .43$), TSA and EP groups ($P = .18$), and PDD and EA groups ($P = .44$) (Supplementary Figures S2 and S3).

For all patients with noninvasive histology at diagnosis of recurrence (Supplementary Table S3), survival outcomes were comparable with those from the whole cohort.

Table V
Survival and recurrence analysis of the 103 patients undergoing a rescue procedure for a local recurrence after management of a first ampullary tumor

	Overall population	EP after EP	TSA		PDD		*P* value (EP vs TSA vs PDD whole group)
			After EP	After TSA	After EP	After TSA	
N (%)	103 (100)	21 (20.4)	14 (13.6)		68 (66)		-
			11 (10.7)	3 (2.9)	43 (41.7)	25 (24.3)	-
Median follow-up (mo) (IQR)	32 (13–61)	30 (17–62)	33 (15–59)		34 (10–61)		.96
			45 (15–67)	23 (18–23)	40 (11–61)	22 (10–56)	-
second recurrence (*n*, %)							
Local	13 (12.6)	9 (42.9)	1 (9.1)	1 (33.3)	1 (2.3)	1 (4)	.0001
Metastatic	12 (11.7)	0	1 (9.1)	0	6 (14)	5 (20)	
Time to recurrence (mo) (IQR)	10 (2–30.5)	9 (6–32)	1 (0–1)		17 (7–26)		.22
			0 (0–1)	0 (0–1)	22 (12–28)	15 (13–16)	-
Disease-free survival at 3 y	79%	84%	73%		87%	68%	-
Overall survival at 3 y	88%	100%	100%		87%	79%	-
Recurrence treatment (*n*, %)							
APC	4 (3.9)	3 (14.3)	0	1 (33.3)	0	0	< .0001
RFA	1 (0.9)	0	1 (9.1)	0	0	0	
Endoscopic mucosectomy	4 (3.9)	4 (19)	0	0	0	0	
TSA	0	0	0	0	0	0	
PDD	2 (1.9)	2 (9.5)	0	0	0	0	
Chemo/Radiotherapy	9 (8.7)	0	0	0	6 (14)	3 (12)	
Best supportive care	5 (4.9)	0	1 (9.1)	0	1 (2.3)	3 (12)	

APC, argon plasma coagulation; *EP*, endoscopic papillectomy; *IQR*, interquartile range; *PDD*, pancreaticoduodenectomy; *RFA*, radiofrequency ablation; *TSA*, transduodenal surgical ampullectomy.

Discussion

Ampullary tumors are rare neoplasms, and their therapeutic management is challenging with a low level of evidence. Scientific literature on management of recurrence after a first-line treatment is even more scarce, and treatment of local recurrences of ampullary lesions are based mainly on local expertise. In a recent meta-analysis, Heise et al found recurrences rate of 13% after EP and 9.4% after TSA,[14] and a recurrence rate up to 32% has been reported after EP. These recurrence rate depends on the quality of the initial procedure and, of course, patients and tumor selection, which remain highly challenging despite exhaustive preoperative workup including computed tomography, magnetic resonance imaging, duodenoscopy, and EUS.[15] Current endoscopic guidelines recommend EP for selected patients (ie, for those with a small lesion (<30 mm) with no sign of carcinoma, no ulceration, soft tissue, and clear margins).[22] Invasive cancers, in particular advanced stages, should be treated surgically with PDD. Transduodenal surgical ampullectomy seems to have satisfying oncological results in pTis and pT1a N0 tumors,[23] with better surgical outcomes than PDD [24] when R0 resection can be achieved. Nevertheless, there is no recommendation or scientific evidence for the treatment of local recurrences of ampullary lesions. So far, the role of surgery and local therapy in locally recurrent ampullary lesions has not been evaluated, and the few data available associate palliative surgery of symptomatic periampullary recurrences with a high morbidity of 86% and a short median of survival of 45 days.[25,26] Other authors highlight the efficiency, in terms of local control and survival, of proton beam radiation and chemotherapy on invasive local and unresectable recurrences.[25,27] Therefore, concerning management of recurrences in a nonpalliative setting, no consensual role for local therapy and/or surgery is based on evidence and is often drive by local expertise.

First, we must underline the difficulty of adequate preoperative assessment and selection of patients for EP versus TSA versus PDD. Best candidates for redo local treatment are patients with small lesions, with no ulceration, with no invasive lesion on biopsy and EUS, and with pT1a lesion (lesion limited to the Vater ampulla or Oddi sphincter and not invading the duodenal submucosa according the last WHO classification of ampullary lesions). Consequently, redo EP or TSA, procedures carrying a low morbidity, could also be considered as a macrobiobsy to best select patient for PDD. Transduodenal surgical ampullectomy, in case of doubt, could be associated with lymphadenectomy to better assess early invasive lesion. In case of R1 resection or R0 resection of invasive lesion at risk of nodal involvement (ie, lesion pT1b and above), PDD should be performed in order to avoid local or distant metastatic resection. The assessment of T stage on EP can be challenging because there is coagulation artifact. In the present study, the indication for the 3 different procedures was decided in each center after a multidisciplinary tumor board. It is indeed known that the management of ampullary lesions depends, of course, on patients and tumors characteristics but also on the local institutional expertise and patient allocation to medical disciplines. Consequently, their rescue scenario reflects indeed the real-life practice.

Endoscopy remains one of the most used treatment options for noninvasive lesions and early ampullary cancers.[28] In a recent study, Takahashi et al[29] suggest that incomplete endoscopic resection (ie, R1) of pTis to pT1b ampullary lesions are associated with ampullary lesions recurrences after EP. In their cohort, noninvasive recurrences were managed with EP, whereas invasive recurrences were managed with PDD or BSC, and only 1 recurrent patient had a second retreatment. However, they did count data from both R1 resection and recurrences, which is not the case in our study. Therefore, they advocate for surgical treatment of recurrences with intraductal extension and/or invasive recurrence. Both APC and RFA need to be carefully evaluated for the treatment noninvasive residual lesions,[30] but their role in recurrence treatment of ampullary lesions is not known. In our cohort, RFA was used to treat 1 (9.1%) local recurrence on the biliary duct for a TSA after EP.

Considering our results, it appears that patient selection is key in the management of patient after first EP/TSA to decide whether redo EP, TSA, or PDD is the best option, knowing the different morbidity of these 3 procedures. Preprocedural careful evaluation of recurrence with cross-sectional imaging and endoscopic ultrasound is mandatory. Pancreaticoduodenectomy is the most common procedure performed in this series. This may be because most patients had symptomatic recurrence, with lesions suspected to be invasive on preoperative biopsy and EUS. This might have led

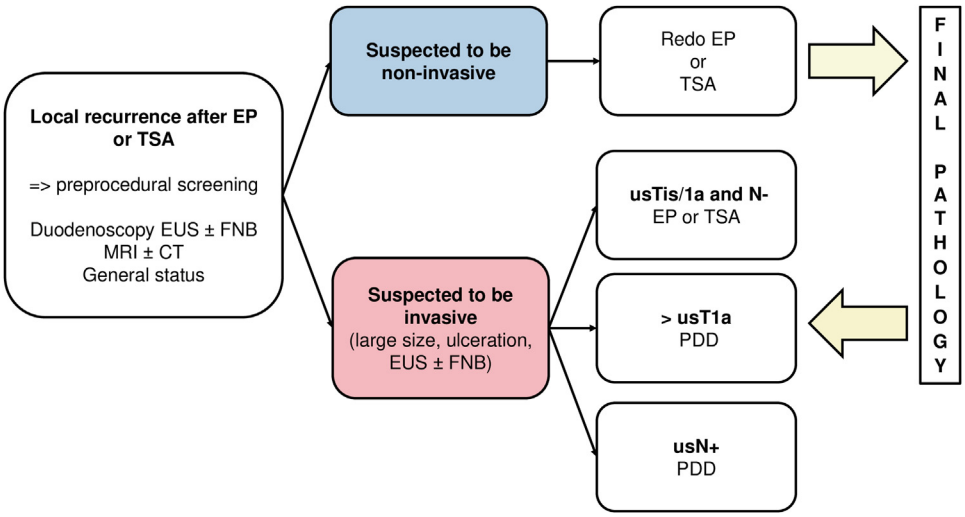

Figure 2. Algorithm proposal for the management of locally recurrent ampullary tumors. *CT*, computed tomography; *EP*, endoscopic papillectomy; *EUS*, endoscopic ultrasonography; *FNB*, fine needle biopsy; *MRI*, magnetic resonance imaging; *PDD*, pancreatoduodenectomy; *TSA*, transduodenal ampullectomy.

clinicians to perform a radical resection. Additionally, redo SA or EA is challenging, and some centers or physicians might have preferred a more conventional procedure such as PDD. In our opinion, redo TSA or redo EA should be part of the armamentarium of a high-volume pancreatic center. Active and long-term follow-up after treatment of ampullary lesion is important and may allow detection and treatment of early noninvasive recurrences.

Redo EP seems to be efficient, with a high R0 rate (81%, $n = 17$) and 28.6% ($n = 6$) complications with only 1 (4.8%) being severe/fatal according to the ASGE scale. Transduodenal surgical ampullectomy, after EP or TSA, also had a high R0 rate (85.7%, $n = 12$), with mainly minor (ie, Clavien-Dindo grade I to II) complications (71.4%, $n = 10$). Clavien-Dindo grade III to IV complications (28.6%, $n = 4$) seem to have occurred mainly after redo TSA after an initial TSA. This might be explained by technical difficulties on an already opened duodenum. Pancreaticoduodenectomy, after EP or TSA, had a high R0 rate (92.6%, $n = 63$), which is intuitive, considering it is the most radical procedure. However, it is not different from the redo EP and TSA group ($P = .2$), although, usually, more advanced lesions are being operated with PDD. Complications were mostly Clavien-Dindo grade I to II (60.3%, $n = 41$), and this is the only group with mortality (2.9%, $n = 2$).

Our data indicate that noninvasive recurrences from tumors initially treated with EP or TSA (ie, low- and high-grade dysplasia) should preferably undergo a new EP or TSA to achieve R0 resection because this was associated with fewer complications and excellent disease-free survival. PDD seems to be more suitable for invasive T1b and above. Patients' general condition must also weigh in the procedure choice, especially given the morbidity of PDD. We therefore propose the following algorithm (Figure 2): redo EP is recommended for noninvasive recurrences after extensive preoperative workup including computed tomography or magnetic resonance imaging, duodenoscopy and EUS (eventually with biopsy), and intraductal endoscopy in selected cases. Pancreaticoduodenectomyshould be recommended for invasive recurrences, especially when lymph node invasion is at risk or suspected or when R0 resection cannot be achieved by EP or TSA. Redo TSA and TSA after first EP is suitable for invasive recurrences, limited to stages usTis or 1, with no lymph node invasion. In addition, TSA can be performed with lymphadenectomy in case of uncertain lymph node status. Nevertheless, redo TSA is technically challenging. It is important to consider the final pathology, to propose a salvage PDD.

Our study has some limitations. First, this is a retrospective work. However, we analyzed a rare situation of a rare disease that may have the potential of an underpowered analysis. On the other hand, a prospective study in such a constellation will hardly ever become reality. Of course, in this multicentric retrospective work, a selection bias cannot be excluded, and patients were often treated according to local resource. This is also of interested, because this reflects the "real-world" practice and represents a great variety of management despite the absence of uniformization in the management of the patients and the performed procedures. Nevertheless, this is, to our knowledge, the largest series to provide evidence on the management of local ampullary tumor recurrences.

To conclude, we provide evidence for the management of recurrent ampullary lesions after endoscopic or surgical interventions. Our data indicate that EP is an adequate therapy for noninvasive recurrences or early cancers if technically feasible. Transduodenal surgical ampullectomy is an acceptable alternative, and PDD should be reserved for invasive lesions with nodal involvement. Eventually, ampullary lesions recurrences can be treated with a comparable algorithm as the initial lesion.

Funding/Support

This work was performed and written as part of a project of the eighth Pancreas 2000 program funded and organized by the European Pancreatic Club.

Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Acknowledgments

The authors would like to thank Down Swibold for its constant and long-term support.

Supplementary materials

Supplementary materials associated with this article can be found in the online version https://doi.org/10.1016/j.surg.2022.12.011.

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