Outcomes From Minimal Access Retroperitoneal and Open Pancreatic Necrosectomy in 394 Patients With Necrotizing Pancreatitis

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Objective: To examine the outcomes from minimal access retroperitoneal pancreatic necrosectomy (MARPN) and open pancreatic necrosectomy (OPN) for severe necrotizing pancreatitis in a single center.

Background: The optimal management of severe pancreatic necrosis is evolving with a few large center single series.

Methods: Between 1997 and 2013, patients with necrotizing pancreatitis at the Liverpool Pancreas Center were reviewed. Outcome measures were retrospectively analyzed by intention to treat.

Results: There were 394 patients who had either MARPN (274, 69.5%) or OPN (120, 30.5%). Complications occurred in 174 MARPN patients (63.5%) and 98 (81.7%) OPN patients ($P < 0.001$). OPN was associated with increased postoperative multiorgan failure [42 (35%) vs 56 (20.4%), $P = 0.001$] and median (inter-quartile range) Acute Physiology and Chronic Health Evaluation II score 9 (6–11.5) vs 8 (5–11), $P < 0.001$] with intensive care required less frequently in MARPN patients [40.9% (112) vs 75% (90), $P < 0.001$]. The mortality rate was 42 (15.3%) in MARPNs and 28 (23.3%) in OPNs ($P = 0.064$). Both the mortality and the overall complication rates decreased between 1997–2008 and 2008–2013 [49 (23.8%) vs 21 (11.2%) $P = 0.001$, respectively; and 151 (73.3%) vs 121 (64.4%), $P = 0.080$, respectively). Increased mortality was independently associated with age ($P < 0.001$), preoperative intensive care stay ($P = 0.014$), and multiple organ failure ($P < 0.001$); operation before 2008 ($P < 0.001$) and conversion to OPN ($P = 0.035$). MARPN independently reduced mortality odds risk (odds ratio = 0.27; 95% confidence interval = 0.12–0.57; $P < 0.001$).

Conclusions: Increasing experience and advances in perioperative care have led to improvement in outcomes. The role of MARPN in reducing complications and deaths within a multimodality approach remains substantial and should be used initially if feasible.

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Pancreatic necrosis develops as a consequence of acute pancreatitis in approximately 20% of patients with infection occurring in around 30% of these cases (range 14%–62%).[1–7] Infected pancreatic necrosis is associated with 8% to 39% mortality rate and substantial morbidity.[1–8] Persistent organ failure beyond 48 hours is the major cause of morbidity occurring in around half of patients with pancreatic necrosis and in up to two thirds of those with superimposed infection.[3–9] Unlike sterile necrosis, infected necrosis generally requires intervention in the form of debridement and/or drainage either surgical or radiological.[7–10]

During the past two decades, the surgical management of infected or potentially infected pancreatic necrosis has undergone considerable changes. Percutaneous catheter drainage, minimal access retroperitoneal pancreatic necrosectomy (MARPN), the step-up approach, and endoscopic transgastric procedures have all been proposed as alternatives to open pancreatic necrosectomy (OPN),[10–21] but the optimal approach addressing pancreatic necrosis cannot be accurately predicted upfront. In a prospective multicenter study,[15] 62% patients with acute necrotizing pancreatitis were adequately managed without any kind of intervention but only 33% patients had infected pancreatic necrosis. In a recent systematic review,[16] it was suggested that up to 64% of patients with infected pancreatic necrosis could be managed by nonsurgical intervention but all the studies were highly heterogeneous. In another systematic review,[17] percutaneous catheter drainage allowed surgical debridement to be avoided in 55.7% of cases. Consequently, the role of surgery as an initial procedure in necrotizing pancreatitis has been progressively called into question. Recent International Association of Pancreatology/American Association of Pancreatology guidelines[18] suggested percutaneous catheter drainage or endoscopic transmural drainage to be the first step in the treatment of infected necrotizing pancreatitis.

Debridement of infected pancreatic necrosis, however, continues to be the mainstay of treatment when percutaneous drainage fails, which is the case in 25% to 75% of patients.[10,13,19–22] OPN is associated with 34% to 95% morbidity and 6% to 25% mortality depending on the series, existing expertise, and the severity of illness at the time of surgery.[2,8,11–13,20,22–24] The experience from OPN has shown that failure to adequately control infected pancreatic necrosis results in a very high mortality, which successful surgical debridement has reduced to <20% in some series.[2,8,11–13] Improved technologies have enabled the development of increasingly minimally invasive procedures. Retroperitoneal video assisted necrosectomy has been performed with 0% to 20% mortality and 10% to 30% complication rate.[10,12,13,17,25–30] We have previously demonstrated

the significant benefits of MARPN compared with OPN in terms of morbidity and mortality.[10] Both modalities have been used in the Regional Pancreas Unit associated with the NIHR Liverpool Pancreas Biomedical Research Unit to treat patients with pancreatic necrosis who were referred to or admitted to our unit with severe acute pancreatitis. The purpose of this study was to reassess patient outcomes after MARPN or OPN on an intention to treat basis and identify predictors of death and postoperative complications.

PATIENTS AND METHODS

All patients undergoing pancreatic necrosectomy in the Regional Pancreas Unit at the Royal Liverpool University Hospital were recorded in a prospectively kept electronic database. Data from January 1, 1997 until the December 31, 2013 were used in this study. Patient characteristics and disease severity have been updated according to revised disease severity classifications by going through individual patient notes. Patient demographics, preoperative, operative, interventional radiology, postoperative data and, the duration of hospitalization and intensive therapy unit (ITU stay) were retrieved. Preoperative data analyzed included the initial and immediate preoperative computed tomography (CT), severity index (SI), [31] the Acute Physiology and Chronic Health Evaluation (APACHE) II score,[32] and organ dysfunction score.[33,34] Physiological and organ dysfunction scores were repeated 24 hours postoperatively. Severe acute pancreatitis was defined by the 2012 Atlanta classification.[35] Outcome measures included overall and procedure related complications and mortality. Mortality was defined as death during admission or during the 3 months after discharge. Operation specific complications include bleeding, pancreatic fistulas, biliary strictures or leaks, gastrointestinal or bowel leaks, ischemic gut, wound complications, intraabdominal abscesses, pseudoaneurysms, and portal vein thrombosis developing in the postoperative period. All remaining complications were categorized as operation nonspecific.

The overall management plan and the indication, type, and timing for any kind of intervention for all of our patients was set in the benign pancreas Multidisciplinary Team (MDT) meeting by a panel of specialist pancreas consultant surgeons, radiologists, and gastroenterologists. A severe acute pancreatitis proforma was completed for every patient referred to our unit. Clinical characteristics and the respective imaging were communicated to our benign pancreas MDT before reaching a consultation. Patients requiring advanced surgical care from the entire north-west UK region, were transferred to our unit upon bed availability. Patients were escalated to a critical care setting for intensive organ support and monitoring whenever required, delaying operative steps as much as possible. Surgical intervention no earlier than 4 weeks after symptom onset was intended unless the clinical state of the patient necessitated earlier necrosectomy or laparotomy for intraabdominal complications not amenable to interventional radiology. Patients with severe acute pancreatitis[35] were managed according to the initial 2002[1] and revised 2013 IAP/APA evidence based guidelines.[18] Endoscopic sphincterotomy was performed early in patients with biliary pancreatitis admitted with or developing acute cholangitis.

A multidetector contrast enhanced CT scan using a pancreatic protocol was undertaken in all patients within 72–96 hours from symptom onset or from hospital admission when the time of onset could not be verified. In patients with diagnostic uncertainty, such as suspicion for visceral perforation or ischemic gut, a CT scan was undertaken immediately on hospital admission. A repeat CT scan was undertaken as dictated by the patient's clinical condition, inflammatory markers (white cell count and C-reactive protein values), or whenever an invasive intervention was considered. Any sharp, abrupt, or gradual rise in these values prompted us to order a repeat CT scan. A CT-guided fine-needle aspiration for bacteriology (CT-FNAB) was advocated for most patients with >30% pancreatic necrosis and no gas, failing to improve after >4 weeks of supportive care (or less if clinically indicated). Aspirates were sent for Gram staining, bacteriology, and fungal culture. Positive stain or cultures were indications for urgent necrosectomy. Infected necrotic tissue was defined as (i) a positive FNAB from pancreatic or peripancreatic necrosis, (ii) a positive sample retrieved during a drainage procedure or a pancreatic necrosectomy, or (iii) the presence of extraluminal gas in a fluid collection or the retroperitoneum on contrast-enhanced CT. Suspected infected necrosis was defined as positive blood cultures, persistent sepsis syndrome, or progressive clinical deterioration despite maximal support in the ITU, without documentation of infected pancreatic necrosis. Patients with confirmed or suspected infected necrosis were evaluated whether they were feasible for a MARPN (left-sided, right-sided, or bilateral). A pigtail catheter placement in interventional radiology was the first step before commencing on MARPNs. Patients with poor access and clinical deterioration or failing to improve with conservative measures were assigned to an OPN.

Patients with sterile pancreatic necrosis also underwent pancreatic necrosectomy if they were unable to eat because of persistent pain and vomiting after 4 to 6 weeks or more hospitalization despite perseverance with nutritional support. Patients showing improvement were discharged and followed up for recurrent symptoms or the development of medium and late complications.[25]

Surgical and Interventional Techniques

Minimal Access Retroperitoneal Pancreatic Necrosectomy

MARPN was performed as previously described.[10,13,25,36] Briefly access to the necrotic cavity was customarily obtained via the left flank with a 12F pigtail catheter inserted under CT-guidance. The path of choice was through the area extending between the lower pole of the spleen and the splenic flexure. In patients with significant (right-sided) pancreatic head necrosis not amenable to left-sided MARPN an anterior duodenal path through the gastrocolic omentum was established and bilateral or right sided procedures were subsequently performed. In patients with pancreatic necrosis tracking down to the left and/or right retroperitoneal gutters, a second drain was introduced to be later used as an accessory track for video assisted pancreatic necrosectomy. Patients with right-sided MARPNs and those with necrosectomies performed though more than one access sites were categorized as complex MARPNs. With the guide wire in place the patient was transferred to the operating theatre and properly positioned so that the access track was approximately horizontal. Depending on the general condition of the patient, the procedure was conducted under general anesthesia or just sedation. Under fluoroscopy, the catheter was exchanged over a guide wire and serial dilatations up to 30 F were routinely performed. An operating nephroscope with a wide-bore operating channel was used for piecemeal removal of pancreatic necrosis and samples were sent for microbiology. Initial debridement was usually restricted by predominant immature necrosis and oozing from the cavity walls. After a first-time MARPN, an irrigating drain, consisting of a 28 F chest drain and a 10 F or 12 F nasogastric tube sutured together, was inserted into the cavity and 0.9 % saline solution used to irrigate the cavity continuously at a rate of 125 mL/h. There were two new modifications from that previously described.[10] (1) The guide wire was kept in place during the whole procedure including the necrosectomy itself and placement of the irrigating drain to avoid the risk of losing the access track. (2) The outer sheath of the nephroscope was

removed to enable larger pieces of necrosis to be removed with the grasping forceps. The MARPN session was then repeated at approximately 7 to 10 day intervals until all the necrosis had been removed and only healthy granulation tissue could be visualized. Pending improvement based on the patient's clinical condition, CT imaging, and laboratory values, the irrigation rate was progressively halved to 30 mL/h then discontinued. A fistulogram was performed to show complete collapse and control of the cavity. The drainage catheter was then downsized using a small nasogastric tube and the patient was discharged home under district nurse care and followed up at 21-day intervals with drain shortening on each visit.

Open Pancreatic Necrosectomy

OPN was performed with postoperative local lavage undertaken as previously described by Beger et al.[37] Postoperative closed irrigation was performed with at least two wide bore drains similar to those described for MARPNs, which were placed in the necrotic cavity through separate small incisions. Packing of the abdomen was not routinely employed. Second look OPNs were reserved for patients who developed specific serious complications of pancreatic necrosis such as ischemic gut.

Interventional Drains

Additional radiologic drains were postoperatively inserted to drain loculated residual fluid collections, areas of evolving necrosis, or symptomatic ascites irrespective of the type of initial treatment.

Endoscopic Ultrasound–guided Procedures

Endoscopic ultrasound (EUS)–guided endoscopic pancreatic necrosectomy was undertaken as an index procedure in the context of a gastroenterology driven protocol in patients with guidewire accessible walled off pancreatic necrosis. A pancreatic surgeon was readily available when a conversion to MARPN was ultimately required. All operations were performed by a single endoscopist using a standard technique to achieve access to the pancreatic necrotic cavity.[21,38] Once the communication between the stomach and the walled-off necrosis was established, a balloon dilatation was performed and a 16 mm, 2 to 3 cm covered metal stent with flared ends was deployed to maintain track patency and active endoscopic removal of debris performed using snares and forceps. No pigtail or naso-pseudocystic drains were left in situ postoperatively and the necrotic cavity was not kept on postoperative irrigation. No repeat sessions were performed.

Statistical Analysis

Outcome measure comparisons between MARPN and OPN were performed by intention to treat. To take into account general improvements in patient care, a time variable was introduced before and after 2008 with a similar number of patients in each period that coincided with our previous report.[10] Frequency counts and percentages were used to summarize categorical variables and median and interquartile range (IQR) for continuous variables. Fisher's exact test and the two-tailed Mann-Whitney U test were used to identify significant differences between groups of patients for categorical and continuous variables respectively. Univariate logistic regression analysis was performed to identify preoperative risk factors associated with mortality and overall complication rate and all risk factors reaching a univariate analysis $P < 0.1$ were included in a multivariate logistic regression analysis. A stepwise selection process was used to identify risk factors independently associated with mortality and overall complication rate and estimate their effect. No imputation was performed for missing data. Analysis was performed on an available case basis using software R version 3.0.1[39] and significance level of $a = 0.05$ was applied for all statistical tests.

RESULTS

Demographics, Etiology, and Preoperative Findings

There were 399 patients with acute necrotizing pancreatitis who underwent pancreatic necrosectomy during the study period but five patients were excluded because of incomplete data. There were 206 patients treated before 2009 and 188 patients after this time

TABLE 1. Demographic and Preoperative Data

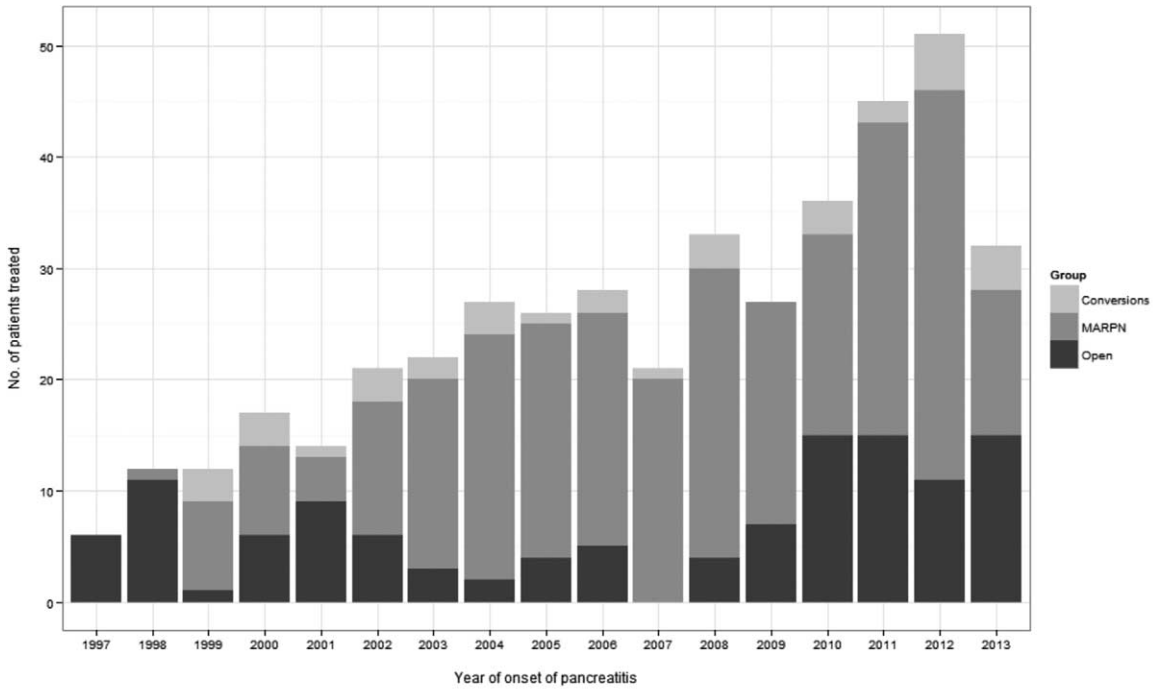
Characteristics	MARPN (n = 274)	OPN (n = 120)	P*
Sex: Male	172 (62.8%)	86 (71.7%)	0.107
Age (y)	59 (46, 69)†	58.5 (42, 70)†	0.550
Missing	1 (0.4%)	0 (0%)	
Admission after Sep 2008	124 (45.3%)	64 (53.3%)	0.155
Etiology of pancreatitis			
Biliary stones	136 (49.6%)	53 (44.2%)	0.294
Ethanol	63 (23%)	37 (30.8%)	
ERCP	15 (5.5%)	5 (4.2%)	
Idiopathic	25 (9.1%)	15 (12.5%)	
Other	11 (4.0%)	5 (4.2%)	
Missing	21 (7.7%)	5 (4.2%)	
Tertiary referrals	213 (77.7%)	76 (63.3%)	0.005
Missing	3 (1.1%)	2 (1.7%)	
Days from admission to transfer	16 (8, 28)†	17 (7.3, 31)†	0.922
Missing	15 (5.5%)	6 (5%)	
Admission CT severity index	8 (4, 9)†	7 (5, 8)†	0.459
Missing	36 (13.1%)	15 (12.5%)	
Admission pancreatic necrosis			
No necrosis	48 (17.5%)	10 (8.3%)	0.006
<30 % necrosis	39 (14.2%)	28 (23.3%)	
30%–50% necrosis	55 (20.1%)	33 (27.5%)	
>50% necrosis	102 (37.2%)	35 (29.2%)	
Missing	30 (10.9%)	14 (11.7%)	
Preoperative CT severity index	9 (7, 10)†	8 (6, 9)†	<0.001
Missing	29 (10.6%)	11 (9.2%)	
Preoperative pancreatic necrosis			
No necrosis	17 (6.2%)	9 (7.5%)	<0.001
<30 % necrosis	28 (10.2%)	27 (22.5%)	
30%–50% necrosis	60 (21.9%)	34 (28.3%)	
>50% necrosis	140 (51.1%)	39 (32.5%)	
Missing	29 (10.6%)	11 (9.2%)	
Preoperative APACHE II score	8 (5, 11)†	8 (4, 11)†	0.656
Severe	128 (46.7%)	57 (47.5%)	0.906
Missing	44 (16%)	16 (13.3%)	
Preoperative MOF	64 (23.4%)	30 (25%)	0.896
Missing	38 (13.9%)	14 (11.7%)	
Preoperative ITU stay	103 (37.6%)	36 (30%)	0.105
Missing	19 (6.9%)	5 (4.2%)	
Preoperative ITU stay (d)‡	14 (5, 25)†	8 (1.5, 18.5)†	0.039
Missing	0 (0%)	1 (0.8%)	
Days to operation‡	29.5 (18, 43)†	24 (12.8, 42.3)†	0.029
Missing	0 (0%)	1 (0.8%)	
Pancreatic necrosis with gas	34 (12.4%)	23 (19.2%)	
FNA positive for bacteriology	94 (34.3%)	15 (12.5%)	
Systemic sepsis	30 (10.9%)	17 (14.2%)	
Other	4 (1.5%)	5 (4.2%)	
Missing	15 (5.5%)	4 (3.3%)	

*Fisher's exact test (two-sided) for categorical data and Mann-Whitney U test (two-sided) for continuous data.

†Median (IQR).

‡Calculated only for patients who stayed in ITU preoperatively.

APACHE indicates Acute Physiology and Chronic Health Evaluation; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; IQR, interquartile range; ITU, intensive therapy unit; MARPN, minimal access retroperitoneal pancreatic necrosectomy; MOF, multiple organ failure; OPN, open pancreatic necrosectomy.



No (%) of Operations	1997 - 2002		2003 - 2008		2009-2013
Open	39 (54%)	p < 0.001	18 (12%)	p < 0.001	63 (36%)
MARPN	33 (46%)		127 (88%)		114 (64%)
Total	72 (100%)		145 (100%)		177 (100%)
Conversions	10 (14%)		12 (8%)		14 (8%)

FIGURE 1. Minimal access retroperitoneal pancreatic necrosectomies (MARPNs), open pancreatic necrosectomies (OPNs), and conversion rate over a 17-year period in one institution.

point. MARPN was performed in 274 patients (69.5%) whereas 120 patients (30.5%) had an OPN (Table 1) (Fig. 1). The preoperative CT severity index was significantly higher in patients submitted to MARPN compared with those who had OPN (9 vs 8, $P < 0.001$), whereas more MARPN patients had >50% pancreatic necrosis on preoperative imaging (51.1% vs 32.5%, $P < 0.001$). There was no difference in preoperative APACHE II scores, the prevalence of preoperative multiple organ failure (MOF), or the need for preoperative ITU stay between the two groups. MARPN patients however tended to spend significantly more time in ITU preoperatively (median of 14 days vs 8 days, $P = 0.039$), with longer hospitalization until the index procedure (median of 29.5 days vs 24 days, $P = 0.029$). Overall, 289 patients were tertiary referrals (73.4%) with the transfer being made in a median of 16 (7.5–30) days from the index admission. More of the tertiary referrals were treated with MARPNs compared with OPN [213 (77%) vs 76 (63.3%), $P = 0.005$]. Biliary stones and excessive ethanol consumption were the two principal etiologies of acute pancreatitis (n = 289, 73.4%).

There were 166 (42.1%) patients who were operated for infected necrosis confirmed preoperatively, 47 (11.9%) patients were operated for acute systemic deterioration caused by sepsis and 153 (38.8%) patients were operated for a complicated pancreatic necrosis and extrapancreatic necrotic fluid collections. These patients who failed to improve under conservative/noninvasive management, developed local complications from an enlarging acute or walled-off pancreatic necrosis and had persistently elevated inflammation markers despite optimal care. Patients who underwent MARPN more frequently had CT-FNAB confirmed infections compared with patients who had OPN (34.3% vs 12.5%), whereas complicated necrotic collections and pancreatic necrosis with gas were both commoner indications among patients having an OPN (46.7% vs 35.4% and 19.2% vs 12.4%, respectively) with an overall $P < 0.001$.

Postoperative Outcomes

Infected pancreatic necrosis was confirmed in 306 pancreatic necrosectomy specimens (77.7%) and were significantly more frequently encountered in patients submitted to MARPN (83.2% vs 65%, $P < 0.001$) (Table 2). Of the 274 patients in whom an MARPN was attempted, 36 (13.1%) patients required conversion to an open necrosectomy. Poor access to the necrotic cavity and inability to dilate the track was the reason in 16 patients, whereas in eight patients there was bleeding (during the initial or the repeat MARPNs), which could not be controlled by conservative measures or interventional radiology. In six patients, there was a perforation either into a hollow viscus or into the peritoneal cavity. In four patients, the debridement achieved was suboptimal and two patients developed ischemic colitis requiring urgent colectomy. All 36 patients were included in the MARPN group of patients on an intention to treat basis.

Five of the 120 patients who had an OPN required additional MARPN procedures to completely remove remaining pancreatic necrosis and were included in the OPN group by intention to treat. Four of these patients had their index procedure in the referring

TABLE 2. Postoperative Outcomes Between the Two Groups

Characteristics	MARPN (n = 274)	OPN (n = 120)	P*
No. of deaths	42 (15.3%)	28 (23.3%)	0.064
Missing	1 (0.4%)	0 (0%)	
No. of complications	174 (63.5%)	98 (81.7%)	<0.001
Missing	2 (0.7%)	0 (0%)	
No. of operation-specific complications	97 (35.4%)	62 (51.7%)	<0.001
No. of operation-nonspecific complications	46 (16.8%)	32 (26.7%)	<0.001†
Missing	2 (0.7%)	0 (0%)	
No. of procedures/patient	3 (2, 4)‡	1 (1, 1)‡	<0.001§
Missing	2 (0.7%)	0 (0%)	
Conversions	36 (13.1%)	5 (4.2%)	0.007
Complex MARPNs			
Dual left-sided MARPN	6 (2.2%)	0 (0%)	—
Bilateral MARPN	9 (3.3%)	0 (0%)	
Right-sided MARPN	0 (0%)	1 (0.8%)	
Percutaneous radiologic abdominal drainage	80 (29.2%)	26 (21.7%)	0.338
Missing	75 (27.7%)	43 (35.8%)	
Infected necrosis at MARPN or OPN	228 (83.2%)	78 (65%)	<0.001
Missing	3 (1.1%)	5 (4.2%)	
Postoperative APACHE II score	8 (5, 11)‡	9 (6, 11.5)‡	<0.001§
Severe	112 (40.9%)	59 (49.9%)	0.146
Missing	51 (18.6%)	21(17.5%)	
Postoperative MOF	56 (20.4%)	42 (35%)	0.001
Missing	40 (14.6%)	21 (17.5%)	
Missing	75 (27.7%)	43 (35.8%)	
Postoperative ITU stay	112 (40.9%)	90 (75%)	<0.001
Missing	8 (2.9%)	0 (0%)	
Postoperative ITU stay (d)‖	12.5 (4, 25.8)‡	6 (3, 16.8)‡	0.018§
Total hospitalization (d)¶	98 (75, 132)‡	71 (40, 103)‡	<0.001§
Missing	22 (8%)	3 (2.5%)	

*Fisher's exact test (two-sided).
†Treating ''unclear'' cases as ''operation related complication.''
‡Median (IQR).
§Mann-Whitney *U* test (two-sided).
‖Calculated only for patients who stayed in ITU postoperatively.
¶Excluding patients who died during hospitalization.
APACHE indicates Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; ITU, intensive therapy unit; MARPN, minimal access retroperitoneal pancreatic necrosectomy; MOF, multiple organ failure; OPN, open pancreatic necrosectomy.

center before being transferred to our unit, with a clear indication for OPN at that time. In two more patients, a laparotomy was done in the referring center, but the necrosectomy achieved was minimal. Both patients were deemed suitable for MARPN based on subsequent imaging and were categorized as MARPNs on an intention to treat basis.

A median (IQR) of 3 (2–4) MARPNs were performed. Difficult cases required more complex MARPN procedures to be performed or additional abdominal drains to be inserted. In nine (3.3%) patients, bilateral MARPNs were needed to achieve adequate access to the pancreatic necrosis. In six (2.2%) patients two left-sided drains were inserted towards the necrotic cavity and video-assisted necrosectomies were later performed from both tracks. One (0.8%) patient had right sided access to the pancreatic necrosis and an ipsilateral video assisted necrosectomy was performed. This patient had had initially an OPN that yielded unsatisfactory results. Percutaneous interventional radiology drains additionally had to be inserted for intraabdominal collections in 80 (29.2%) MARPN and 26 (21.7%) OPN cases. EUS-assisted endoscopic pancreatic necrosectomy was performed acutely in three (0.76%) patients. Two of them were converted to MARPN owing to technical failure and the third was converted to OPN. Six more EUS drainage procedures were performed <1 year from the index (MARPN) procedure to treat symptomatic recurrent walled-off necrosis, successfully in three.

Postoperative mortality was higher, though not significantly, in patients undergoing OPN compared with MARPN (23.3% vs 15.3%, $P = 0.064$). OPN was associated with higher overall (81.7% vs 63.5%, $P < 0.001$) and procedure related complication rate (51.7% vs 35.4%, $P < 0.001$). Postoperatively, 98 (24.9%) patients had MOF with a median APACHE II score of 8 (2–14). Postoperative multiple organ failure was associated more frequently with OPN compared with MARPN (35% vs 20.4%, $P = 0.001$), with OPN patients having higher postoperative median APACHE II scores (9 vs 8, $P < 0.001$). A higher proportion of OPN patients required ITU admission than patients who had MARPN (75% vs 40.9%, $P < 0.001$) but ITU stay was longer in the latter (12.5 days vs 6 days, $P = 0.018$) reflecting the preoperative state. MARPN patients required significantly more prolonged total hospitalization (98 days vs 71 days, $P < 0.001$). Specific complications, persistent pancreatic fistulas (11.7% vs 5.1%, $P = 0.032$) and postoperative sepsis with MOF (25% vs 12%, $P = 0.003$) were significantly more prevalent after OPN, whereas MARPNs were associated with significantly higher postoperative DVT rates (6.6% vs 1.7%, $P = 0.046$) (Table 3).

Comparison of Outcomes Between 1997–2008 and 2009–2013

There was a significant decrease in mortality rates after 2008 falling from 23.8% to 11.2% ($P = 0.001$) (Table 4). This reduction was binary, composed by a reduction both in MARPN-associated

TABLE 3. Details of Postoperative Complications Between the Two Groups

Complications	MARPN (n = 274)	OPN (n = 120)	P*
Bleeding	50 (18.2%)	18 (15%)	0.470
Missing	6 (2.2%)	1 (0.8%)	
Pseudoaneurysm	12 (4.4%)	2 (1.7%)	0.243
Missing	1 (0.4%)	0 (0%)	
Persistent pancreatic fistula	14 (5.1%)	14 (11.7%)	0.032
Missing	2 (0.7%)	0 (0%)	
Upper GI fistula	9 (3.3%)	9 (7.5%)	0.113
Missing	6 (2.2%)	1 (0.8%)	
Lower GI fistula	20 (7.3%)	4 (3.3%)	0.170
Missing	6 (2.2%)	0 (0%)	
Biliary stricture	8 (2.9%)	7 (5.8%)	0.251
Missing	6 (2.2%)	1 (0.8%)	
Ischemic bowel	4 (1.5%)	2 (1.7%)	1.000
Missing	6 (2.2%)	1 (0.8%)	
Clostridium difficile colitis	12 (4.4%)	2 (1.7%)	0.243
Missing	5 (1.8%)	1 (0.8%)	
Ascites	25 (9.1%)	6 (5%)	0.222
Missing	5 (1.8%)	1 (0.8%)	
Portal vein thrombosis	32 (11.7%)	9 (7.5%)	0.282
Missing	5 (1.8%)	1 (0.8%)	
SMV thrombosis	14 (5.1%)	6 (5%)	1.000
Missing	5 (1.8%)	1 (0.8%)	
Myocardial infarction	4 (1.5%)	4 (3.3%)	0.257
Missing	6 (2.2%)	1 (0.8%)	
Stroke	4 (1.5%)	1 (0.8%)	1.000
Missing	5 (1.8%)	1 (0.8%)	
Other cardiac complication	5 (1.8%)	4 (3.3%)	0.465
Missing	5 (1.8%)	1 (0.8%)	
Pulmonary embolism	3 (1.1%)	5 (4.2%)	0.061
Missing	5 (1.8%)	1 (0.8%)	
Deep venous thrombosis	18 (6.6%)	2 (1.7%)	0.046
Missing	5 (1.8%)	1 (0.8%)	
Nosocomial pneumonia	15 (5.5%)	8 (6.7%)	0.647
Missing	5 (1.8%)	1 (0.8%)	
Persistent sepsis and MOF	33 (12%)	30 (25%)	0.003
Missing	5 (1.8%)	1 (0.8%)	
Total†	175 (63.9%)	98 (81.7%)	<0.001
Missing	2 (0.7%)	0 (0%)	

*Fisher's exact test (two-sided).

†No. of patients who experienced at least one complication.

GI indicates gastrointestinal; MARPN, minimal access retroperitoneal pancreatic necrosectomy; MOF, multiple organ failure; OPN, open pancreatic necrosectomy; SMV, superior mesenteric vein.

TABLE 4. Patient Characteristics and Outcomes Before and After 2008

Characteristics	Before 1997–2008 (n = 206)	After 2009–2013 (n = 188)	P*
Age (y)†	58 (44.3, 68)	60 (46.5, 71)	0.122‡
Missing	0 (0%)	1 (0.5%)	
Sex: Male	132 (64.1%)	126 (67%)	0.524
Tertiary referrals	151 (73.3%)	138 (73.4%)	0.729
Missing	5 (2.4%)	0 (0%)	
Days from admission to transfer	19 (8, 32)†	16 (7, 25)†	0.069‡
Missing	14 (6.8%)	7 (2.1%)	
APACHE II score (admission)	10 (6, 13)†	6 (4, 10)†	<0.001‡
Severe	38 (20.2%)	112 (54.4%)	<0.001
Missing	90 (47.9%)	41 (19.9%)	
APACHE II score (preoperative)	9 (5, 12)†	8 (5, 10.3)†	0.113‡
Severe	104 (50.5%)	81 (43.1%)	0.270
Missing	28 (13.6%)	32 (17%)	
CT severity index (admission)	8 (5, 9)†	7 (4.8, 8.3)†	0.301‡
Severe	103 (50%)	89 (47.3%)	0.587
Missing	27 (13.1%)	24 (12.8%)	
CT severity index (preoperative)	9 (6, 10)†	8 (6, 9)†	0.030‡
Severe	134 (65%)	125 (66.5%)	0.720
Missing	25 (12.1%)	15 (8%)	
Preoperative MOF	56 (27.2%)	38 (20.2%)	0.029
Missing	36 (17.5%)	18 (8.5%)	
Admission pancreatic necrosis			
No Necrosis	22 (10.7%)	36 (19.1%)	<0.001
<30 % necrosis	44 (21.4%)	23 (12.2%)	
30%–50% necrosis	30 (14.6%)	58 (30.9%)	
>50% necrosis	84 (40.8%)	53 (28.2%)	
Missing	26 (12.6%)	18 (9.6%)	
Preoperative pancreatic necrosis			
No necrosis	7 (3.4%)	19 (10.1%)	<0.001
<30% necrosis	37 (18%)	18 (9.6%)	
30%–50% necrosis	30 (14.6%)	64 (34%)	
>50% necrosis	107 (51.9%)	72 (38.3%)	
Missing	25 (12.1%)	15 (8%)	
Indication for intervention			
Complicated necrotic collection	57 (27.7%)	96 (51.1%)	<0.001
Pancreatic necrosis with gas	30 (14.6%)	27 (14.4%)	
FNAB positive	70 (34%)	39 (20.7%)	
Systemic sepsis	30 (14.6%)	17 (9.0%)	
Other	3 (1.5%)	6 (3.2%)	
Missing	16 (7.8%)	3 (1.6%)	
Operation type			
MARPN	150 (72.8%)	124 (66%)	0.155
OPN	56 (27.2%)	64 (34%)	
No. of conversions	26 (10.7%)	15 (7.4%)	0.141
Complex MARPNs	6 (2.9%)	10 (5.3%)	0.580
Missing	116 (56.3%)	3 (1.6%)	
Percutaneous radiologic drains	37 (18%)	69 (36.7%)	0.601
Missing	115 (55.8%)	3 (1.6%)	
No. of MARPNs/patient	3 (2, 5)†	3 (2, 4)†	0.075‡
Missing	2 (1%)	0 (0%)	
No. of deaths	49 (23.8%)	21 (11.2%)	0.001
Missing	0 (0%)	1 (0.5%)	
Overall complications	151 (73.3%)	121 (64.4%)	0.080
Missing	0 (0%)	2 (1.1%)	
Operation-related complications	92 (44.6%)	78 (41.5%)	0.543
Unclear	56 (27.2%)	26 (13.8%)	0.001‡
Missing	0 (0%)	2 (1.1%)	
Infected necrosis at necrosectomy	165 (80.1%)	141 (75%)	0.079
Missing	7 (3.4%)	1 (0.5%)	
Postoperative MOF	64 (20.4%)	34 (35%)	0.001
Missing	36 (31.1%)	25 (18.1%)	
Postoperative APACHE II score	8 (5, 11)†	8 (5, 11)†	0.537‡
Severe	94 (45.6 %)	77 (41%)	0.577
Missing	34 (16.5%)	38(20.2%)	

(19.3% vs 10.6%, $P = 0.033$) and OPN-associated mortality (35.7% vs 12.5%, $P = 0.003$). There was also a significant decline in operation nonspecific complications (13.8% vs 27.2%, $P = 0.001$) and a smaller reduction in the overall (64.4% vs 73.3%, $P = 0.080$) and procedure related morbidity (41.5% vs 44.6%, $P = 0.543$). There was a decrease in the median duration of hospitalization (88 days vs 96 days, $P = 0.015$). There was a rise in the proportion of OPNs undertaken (34% vs 27.2%, $P = 0.155$), a decrease in the procedure conversion rate (7.4% vs 10.7%, $P = 0.141$) and a wider application of complex MARPNs (5.3% vs 2.9%, $P = 0.580$), and an increase in the postoperative application of percutaneous radiologic drains (36.7% vs 18%, $P = 0.601$). A lower proportion of patients with preoperative MOF (20.2% vs 27.2%, $P = 0.029$) or > 50% pancreatic necrosis (38.3% vs 51.9%, $P < 0.001$) were submitted to a pancreatic necrosectomy after 2008 with higher prevalence of postoperative MOF (35% vs 20.4%, $P = 0.001$). Although before 2008, FNAB confirmed infected pancreatic necrosis was the primary indication for intervention (34%), complicated necrotic collections were the

TABLE 4. (*Continued*)

Characteristics	Before 1997–2008 (n = 206)	After 2009–2013 (n = 188)	P*
Postoperative ITU stay	99 (48.1%)	103 (54.8%)	0.154
Missing	3 (1.5%)	5 (2.7%)	
Postoperative ITU stay (d)||	13 (4, 30.5)†	6 (3, 17.5)†	0.854‡
Total hospitalization (d)¶	96 (73, 131)†	88 (54, 121)†	0.015‡
Missing	22 (10.7%)	9 (4.8%)	

*Fisher's exact test (two-sided).
†Median (IQR).
‡Mann-Whitney *U* test (two-sided).
§Treating "unclear" cases as "operation related complication."
||Calculated only for patients who stayed in ITU postoperatively.
¶Excluding patients who died during hospitalization.
APACHE indicates Acute Physiology and Chronic Health Evaluation; FNAB, fine-needle aspiration biopsy; IQR, interquartile range; ITU, intensive therapy unit; MARPN, minimal access retroperitoneal pancreatic necrosectomy; MOF, multiple organ failure.

main indication for necrosectomy after 2008 (51.1%) ($P < 0.001$) (Table 4).

Univariate and Multivariate Logistic Regression Analysis

The results of the univariate logistic regression analysis for complications and mortality are summarized in Table 5. Increased risk of complications was associated independently with increasing patient age ($P = 0.015$), male sex ($P = 0.006$), tertiary referral ($P = 0.015$), preoperative ITU stay ($P < 0.001$), insertion of additional percutaneous radiologic drains ($P < 0.001$), and conversion to OPN ($P = 0.005$), whereas independent complication odds risk reduction was associated with use of MARPN ($P < 0.001$), (Table 6). Increased mortality was independently associated with increased patient age ($P < 0.001$), preoperative ITU stay ($P = 0.014$), preoperative MOF ($P < 0.001$), and conversion to open necrosectomy ($P = 0.035$). Independent mortality odds risk reduction was associated with admission after 2008 ($P < 0.001$) and use of MARPN ($P < 0.001$), (Table 6).

DISCUSSION

A very high proportion of our patients were tertiary referrals, representing 289 (73.4%) out of 394 patients treated, with the more conservative approaches not being suitable or having already been utilized before transfer. There was a general reduction in mortality between the earlier and later time periods, secondary to changes in diagnosis (less FNABs), and treatment (increasing application of interventional drains and complex MARPNs, as well as a decreasing MARPN conversion rate), reflecting a more integrated approach. MARPN was the only independent factor associated with a significant reduced odds risk of mortality with an estimated 73% odds risk reduction. This was also observed in relation to complications with MARPN being the only independent factor associated with a similarly large complication odds risk reduction.

Infected pancreatic necrosis, acute complications not amenable to interventional radiology, and deteriorating organ failure in patients with necrotizing pancreatitis are potentially life threatening complications of acute pancreatitis that require intervention.[1,4,5,7,9,18]

TABLE 5. Univariable Logistic Regression: Risk Factors for Complications and Death

	Complications		Death	
Variables	OR (95% CI)	P	OR (95% CI)	P
Age (y)	1.01 (1.00, 1.02)	0.163	1.06 (1.04, 1.08)	<0.001
Sex: Male	1.52 (0.97, 2.37)	0.066	1.27 (0.74, 2.27)	0.398
Admission after September 2008	0.68 (0.44, 1.04)	0.078	0.41 (0.23, 0.70)	0.002
Etiology				
Biliary stones	0.98 (0.63, 1.54)	0.936	0.66 (0.37, 1.14)	0.137
Ethanol	0.76 (0.46, 1.25)	0.267	1.15 (0.61, 2.08)	0.654
ERCP	2.53 (0.83, 10.98)	0.146	2.28 (0.78, 5.96)	0.105
Preoperative APACHE II score	1.12 (1.05, 1.18)	<0.001	1.15 (1.08, 1.23)	<0.001
Tertiary referral	1.49 (0.92, 2.41)	0.102	1.39 (0.75, 2.71)	0.317
Days from admission to transfer	1.01 (1.00, 1.03)	0.101	1.00 (0.99, 1.02)	0.810
Days from admission to first CT	1.01 (1.00, 1.03)	0.174	0.99 (0.97, 1.01)	0.336
CT Severity index (admission)	1.04 (0.95, 1.14)	0.389	1.08 (0.97, 1.21)	0.177
CT Severity index (preoperative)	1.01 (0.90, 1.12)	0.899	1.03 (0.91, 1.18)	0.640
Preoperative MOF	3.99 (2.13, 8.05)	<0.001	6.38 (3.52, 11.81)	<0.001
>50% necrosis (admission)	1.43 (0.89, 2.34)	0.146	1.71 (0.98, 3.00)	0.060
>50% necrosis (preoperative)	1.07 (0.68, 1.69)	0.773	1.34 (0.77, 2.37)	0.301
Preoperative ITU stay	3.09 (1.85, 5.34)	<0.001	3.23 (1.85, 5.74)	<0.001
Indication for intervention				
Complicated necrosis	0.62 (0.40, 0.98)	0.039	0.54 (0.30, 0.96)	0.039
Necrosis with gas	2.17 (1.09, 4.70)	0.036	1.02 (0.46, 2.06)	0.964
FNA positive	0.66 (0.41, 1.06)	0.084	1.20 (0.67, 2.12)	0.527
Systemic sepsis	3.19 (1.41, 8.57)	0.011	2.61 (1.29, 5.10)	0.006
Other	2.97 (0.52, 55.83)	0.311	0.39 (0.02, 1.92)	0.311
Op. type: MARPN	0.40 (0.23, 0.66)	<0.001	0.60 (0.35, 1.03)	0.059
Additional drain	3.47 (2.00, 6.22)	<0.001	1.53 (0.76, 3.06)	0.223
Complex MARPNs	0.71 (0.26, 2.05)	0.515	0.40 (0.02, 2.07)	0.382
Conversion to open	2.85 (1.17, 8.53)	0.035	1.99 (0.87, 4.24)	0.086

APACHE indicates Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; ITU, intensive therapy unit; MARPN, minimal access retroperitoneal pancreatic necrosectomy; MOF, multiple organ failure; OR, odds ratio.

TABLE 6. Multivariable Logistic Regression: Independent Predictors for Complications and Mortality

Variables	OR for Complications (95% CI)	*P*
Complications*		
Age (years)	1.02 (1.00, 1.04)	0.015
Sex: Male	2.47 (1.31, 4.75)	0.006
Tertiary referral	2.47 (1.21, 5.18)	0.015
Preoperative ITU stay	4.20 (2.12, 8.75)	<0.001
MARPN	0.27 (0.13, 0.55)	<0.001
Additional abdominal drainage	4.18 (2.17, 8.41)	<0.001
Conversion to OPN	11.17 (2.57, 82.10)	0.005
Mortality†		
Age (years)	1.08 (1.06, 1.12)	<0.001
Admission after September 2008	0.29 (0.14, 0.59)	<0.001
Preoperative ITU stay	2.83 (1.23, 6.56)	0.014
MARPN	0.27 (0.12, 0.57)	<0.001
Preoperative MOF	4.14 (1.90, 9.34)	<0.001
Conversion to OPN	3.51 (1.05, 11.13)	0.035

*Le Cessie-van Houwelingen goodness of fit test: *P* value = 0.968.
†Le Cessie-van Houwelingen goodness of fit test: *P* value = 0.516.
CI indicates confidence interval; ITU, intensive therapy unit; MARPN, minimal access retroperitoneal pancreatic necrosectomy; OPN, open pancreatic necrosectomy.

Apparently sterile but highly symptomatic necrosis, manifesting as disabling pain, gastric outlet or biliary obstruction, or deteriorating nutrition represent further indications for catheter drainage or a debridement procedure.[9,18,40] Pancreatic necrosis can be managed by many different techniques including open necrosectomy and closed packing,[41] laparoscopic transperitoneal necrosectomy,[42] minimal access retroperitoneal (video assisted) necrosectomy,[10,12,13,17,25–30] endoscopic necrosectomy[24,43,44] or drainage,[45] step-up combination approaches using percutaneous techniques and surgery,[20] or transmural drainage and endoscopic necrosectomy.[46]

The success with catheter only drainage after the report of the step-up approach in 2010 has met with only very limited success in our center and is not possible to quantify in the whole series given that the bulk of our referrals were tertiary.[20] The number of radiological interventional drains either pre- and/or postsurgery increased however form 18.0% to 36.7% indicating a shift in clinical practice. Placing drains transperitoneally will result in drainage of the liquid component whereas the more solid pathogenic component remains, but the contraction can then eliminate the retroperitoneal guidewire access route for MARPN. This accounts for one of the reasons for the relatively small increase in OPN in this series from patients referred from outside our center. For these reasons we would encourage the left retroperitoneal route for drainage of necrotic collections if feasible, thus keeping the MARPN choice viable when required.

When the intended benefits from simple drainage of an acute necrotic collection are poor however, surgical debridement should be implemented as soon as possible. The two approaches that have risen to favor in this regard are the retroperitoneal route (MARPN)[10,12,13,17,25–30] and the endoscopic transgastric necrosectomy.[24,43–45]

Advances in interventional radiology have decreased the numbers of unnecessary laparotomies over the years. When debridement is not amenable to a minimally invasive technique because of poor radiologic access, for other technical reasons, or when other acute intraabdominal conditions come into play, patients were reassigned to OPN. Complex variations to the classic MARPN including bilateral, multiple unilateral, and right-sided procedures have been increasingly performed during the past few years in our unit in an effort to minimize the need for OPN. Similarly, postoperative percutaneous catheter drainage has customarily been used to help manage infectious sequelae after both types of pancreatic necrosectomy. Endoscopic drainage and necrosectomy have been introduced but with limited success in this group of patients. Infected pancreatic necrosis was found in 77.7% of our patients and 83.2% of those undergoing MARPN justifying our decision to perform a necrosectomy,[2,6,41,47,48] whereas the CT-SI score,[6,11,20] the APACHE II score,[6,11] and the prevalence of MOF[6,15] reflect the severity of acute pancreatitis in our series. MOF and not preoperative CT-SI score was independently associated with poor outcome, suggesting the adverse predictive power of systemic against local risk factors in patients with necrotizing pancreatitis. Careful investigation is required in patients with complicated pancreatic necrosis to select those with the higher likelihood of infected pancreatic necrosis. In addition to a reduced overall complication rate, MARPN was associated with significantly lower operation specific complication rates. The longer hospital stay in these patients relates to the later median intervention time point (29.5 vs 24.0 days, $P = 0.029$) and more severe cases surviving and needing a longer recovery period as well as the need to repeat to MARPNs in these cases.

Although there was a general reduction in mortality between the two periods, there has been a steady decrease in the operation related morbidity and in the operation nonspecific complication rate. This means that there was improvement from OPN (12.8% morbidity rate after 2008) in keeping with other studies.[12,23,49–51] Nevertheless patients undergoing MARPN had more severe disease based on preoperative imaging and postoperatively MOF was more common and median APACHE II score was higher after OPN. These findings demonstrate the detrimental effect of OPN on organ function. Conversion from MARPN to OPN increased patient mortality and morbidity significantly (Table 6), and should be avoided if at all possible. As our study is very large and is from a single center (though not a randomized controlled trial) it can compare OPN with MARPN taking into account preoperative risk factors and clearly shows that MARPN is the procedure of choice, although technically this is not possible for mainly access reasons in around 30% of cases.

Our study provides an updated comparison of short-term outcomes between MARPN and OPN in patients with necrotizing pancreatitis. Despite the obvious advantages of MARPNs, this later period of our work has been associated with further decline in postoperative mortality, highlighting a wide margin for quality improvement especially in patients submitted to OPN. In a group of patients who have been principally admitted to another hospital and referred to our unit for definitive treatment (73.3% vs 69%[10]) with increasingly documented infected pancreatic necrosis (77% vs 64.5%[10]), performance of complex MARPNs, postoperative insertion of percutaneous catheters, and conversion from one type of necrosectomy to the other, and liberal repetition of MARPNs until necrosis-free pancreatic margins are achieved, suggest some of the technical reasons for this improvement. Further refinements in the MARPN technology and technique, increasing application of endoscopic necrosectomies and the introduction of hybrid step-up approaches may provide even better results in the future.

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