Pancreatic surgery

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Purpose of review
To summarize published research on pancreatic surgery over the past year.

Recent findings
A number of studies aiming to reduce the costs associated with pancreatic surgery were reported. Retrospective analyses confirmed previous findings that neither the routine use of pancreatic duct stents decreases the rate of fistula formation nor does placement of a drain at the time of surgery change the morbidity in patients who develop one. Minimally invasive approaches, both laparoscopic and robot-assisted, are being performed more frequently to remove pancreatic cancers. A randomized trial confirmed that reinforcement of stapled closure during distal pancreatectomy reduces the rate of fistula formation. Controversy remains over whether small pancreatic neuroendocrine tumors need to be surgically resected or can be treated nonoperatively. Patients with chronic pancreatitis should be screened thoroughly before being offered surgical treatment; two studies reported preoperative factors that can be used to identify those most likely to experience pain relief.

Summary
Studies published on pancreatic surgery last year focused on a wide-range of topics. The morbidity and mortality of patients undergoing pancreatic surgery continues to improve, and we anticipate that incorporation of these new findings will lead to even better outcomes.

Keywords
distal pancreatectomy, pancreatic surgery, pancreaticoduodenectomy

INTRODUCTION

Last year (1 March 2012 to 1 March 2013) was another productive time for publications on pancreatic surgery. A *PubMed* search for 'pancreatic surgery' during this interval identified 3142 articles focused on a wide range of topics. In an effort to reduce the overall costs of care, multiple studies identified factors associated with postoperative readmissions. A randomized clinical trial (RCT) revealed that the routine use of staple line reinforcement during distal pancreatectomy significantly reduced the rate of pancreatic fistula formation. Laparoscopic and robot-assisted approaches are used increasingly for both distal pancreatectomy and pancreaticoduodenectomy, even for patients with pancreatic cancer (PDAC). A number of studies contributed to the ongoing uncertainty of whether small pancreatic neuroendocrine tumors (PNETs) require surgical resection. This review highlights these studies (and selected others) that were published last year on pancreatic surgery.

QUALITY MEASURES AND TECHNICAL STUDIES IN PANCREATIC SURGERY

In an effort to decrease the total healthcare costs of patients undergoing pancreatic surgery, many studies identified potential interventions to reduce the number of postoperative hospital readmissions. In a single institution analysis, Gawlas *et al.* [1▪] suggested that readmissions may not be an appropriate measure of quality after pancreatic surgery, as the majority of them were because of the complications directly related to the operation rather than systems processes of healthcare delivery (e.g., coordination of care, discharge planning, etc.). A separate multiinstitution analysis of 1302 patients undergoing pancreatic surgery also found that factors related to the operation – infection, pancreatic leak, nutritional status, and delayed gastric emptying – were the most common causes of readmission [2]. As further support that reducing postoperative complications will reduce costs, Kent *et al.* [3] found

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KEY POINTS

- In an effort to reduce the overall costs of care, multiple studies identified factors associated with postoperative readmissions.
- An RCT revealed that the routine use of staple line reinforcement during distal pancreatectomy significantly reduced the rate of pancreatic fistula formation.
- Laparoscopic and robot-assisted approaches are used increasingly for both distal pancreatectomy and pancreaticoduodenectomy, even for patients with PDAC.
- A number of studies contributed to the ongoing uncertainty of whether small PNETs require surgical resection.

that infections, either wound or related to a pancreatic fistula, were the primary reasons for higher billing.

Many studies aimed to identify preoperative factors that would accurately predict postoperative morbidity. Ragulin-Coyne *et al.* [4] developed a perioperative mortality risk score from preoperative variables that is available online (www.umass.edu/surgery/panc_mortality_custom.aspx). Strikingly, they identified that nationwide inpatient mortality is 5.3%, which is much higher than high-volume pancreatic centers. Callery *et al.* [5] developed a simple 10-point fistula risk score based on intraoperative findings (e.g., pancreatic duct size, texture, etc.) that correlated with fistula development. Interestingly, Kirihara *et al.* [6▪] identified factors on noninvasive CT or MRI – larger predicted remnant pancreatic volume, more visceral adipose tissue, and less skeletal muscle – that were more strongly associated with fistula development than those traditionally implicated (Fig. 1).

The value of a pancreatic duct stent to stent the anastomosis and reduce fistula development has been debated for many years. Results from previous studies are mixed, without definitive evidence to support its routine use. Although there were no RCTs in the literature over the past year, there were two meta-analyses that were informative [7,8]. Both of these studies, on the subgroup analyses of the RCTs, confirmed previous findings that placement of such a stent, either internal or external, across the pancreaticojejunostomy anastomosis does not decrease the incidence of fistula. We agree with these findings and never leave a stent, regardless of duct size or pancreatic texture.

Another issue that has received extensive attention is whether a drain should be left near the pancreaticojejunal anastomosis at the time of surgery. Opponents argue that a drain may actually increase the fistula rate by eroding into the anastomosis. The group from Memorial Sloan Kettering previously completed an RCT on the benefit of leaving a drain. In this year's contemporary analysis, they sought to evaluate the evolution of practice at their institution after that study [9▪]. Correa-Gallego *et al.* found that operative drains still were used in approximately 50% of patients. Patients in whom a drain was left had a longer hospital stay; and higher grade of at least 3 morbidity, fistula, and readmission rates. They concluded from these findings that

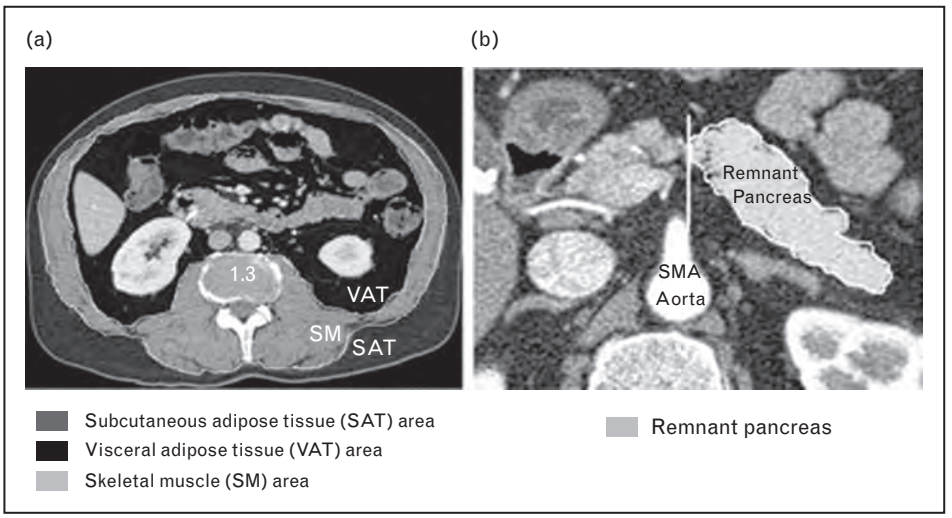

FIGURE 1. (a) SAT, VAT and SM areas were measured at L3 level from preoperative CT (the white line outlines the skeletal muscle area using a graph pen). (b) Measurement of RPV was standardized as occurring at the left border of the superior mesenteric artery, the presumed site of operative transection of the pancreas. RPV, remnant pancreatic volume; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue. [6▪].

routine prophylactic drainage after pancreatic resection can be safely abandoned. Although we find these results provocative, the practice should be tested in an independent RCT across multiple institutions to minimize institutional and surgeon bias.

LAPAROSCOPIC DISTAL PANCREATECTOMY

Laparoscopic distal pancreatectomy (LDP) is regarded as a well tolerated and effective approach for removing benign lesions in the body and tail of the pancreas. These findings were further supported by two meta-analyses completed last year. Venkat *et al.* [10] and Jin *et al.* [11] found that LDP was associated with a significantly lower blood loss and reduced length of stay as compared to open distal pancreatectomy (ODP).

The appropriateness of LDP for removing malignant lesions was addressed by two studies last year. A meta-analysis by Venkat *et al.* [10] combined four retrospective studies to generate composite data, which revealed that there was no difference in margin positivity between LDP and ODP. More lymph nodes (LNs) were harvested in ODP than LDP. In their experiences from 2002 to 2010, Magge *et al.* [12] found that oncologic outcomes of minimally invasive distal pancreatectomy (MIDP) – either LDP ($n=20$) or robotic-assisted distal pancreatectomy (RADP) ($n=8$) – and ODP were equivalent. Although these data suggest that LDP or MIDP may be appropriate for patients with cancer in the body and tail of the pancreas, an RCT is still needed to provide definitive validation of the technique.

Distal pancreatectomy (both ODP and LDP) is associated with as high as a 30% incidence of pancreatic fistula. A number of techniques have been proposed to lower this rate, but without success. However, Hamilton *et al.* [13▪▪] completed an RCT to examine whether routine mesh reinforcement of a stapled closure of the pancreas resection margin reduced the rate of fistula. One hundred patients were randomized. The authors found that staple line reinforcement with Seamguard or Peristrips Dry significantly decreased the rate of International Study Group on Pancreatic Fistula grade B and C leaks from 20 to 1.9% (Fig. 2). 4.8 mm staples were used, and patients were excluded from the trial if their pancreata were too thick for stapled closure. On the basis of these findings, we routinely use mesh reinforcement as an adjunct to stapled closure during LDP and have observed excellent outcomes.

PANCREATIC CANCER CARE

The Massachusetts General Group published a study examining the survival benefit of surgical resection with different degrees of margin clearance [14▪▪]. Using their institutional database of 1705 patients evaluated for PDAC, they found that patients who undergo a microscopic margin positive resection (R1) have better survival than those patients who have locally advanced cancers and do not undergo resection (median survival: 14 vs. 11 months). Patients who have a margin negative (R0) resection fare even better (median 23 months), especially if the cancer does not come within 1 mm of the margin (median 35 months) (Fig. 3). These results stress the importance of diligent surgical technique and intraoperative decision making to maximize the chance of achieving a more than 1 mm negative margin. In addition, they also confirm the importance of a standardized pathologic margin assessment, as the technique (en bloc vs. tangential sampling) has been debated for many years.

It has been shown previously that venous resection (superior mesenteric vein or portal vein) can be

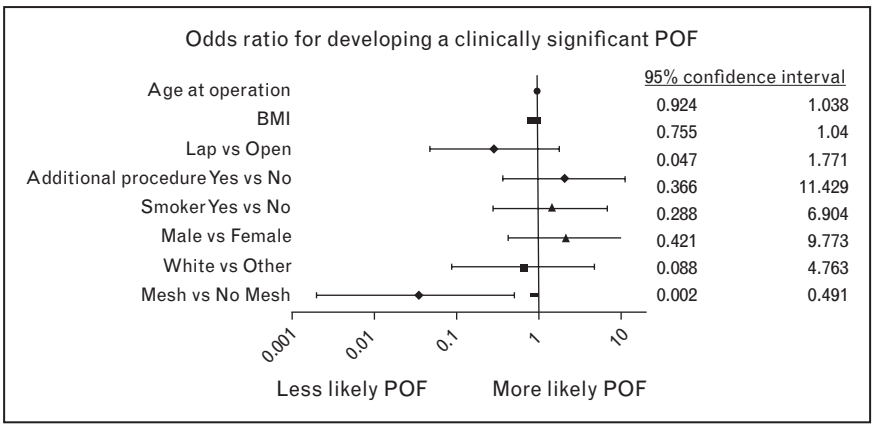

FIGURE 2. Odds ratio for developing a postoperative fistula (POF) by risk category. POF, postoperative fistula. [13▪▪].

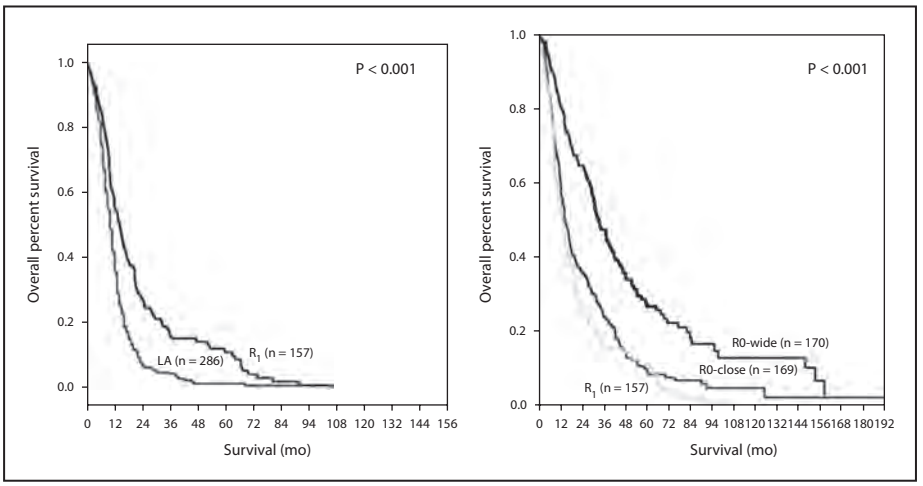

FIGURE 3. (a) Patients undergoing an R1 resection had an improved overall survival compared with those with LA unresectable tumors (median survival of 14 vs 11 months; $P<0.001$). (b) Patients who underwent an R0 resection with close (<1 mm) margins have a worse survival compared with patients who underwent an R0 resection with wide margins (>1 mm) (median survival of 35 vs 16 months; $P<0.001$). [14▪▪].

performed during pancreaticoduodenectomy with acceptable morbidity. These conclusions have been based on multiple independent single institution studies. Two articles published this year incorporated larger databases – the National Surgical Quality Improvement Program Participant User Files [15] and the National Inpatient Sample [16]. Interestingly, both found that vascular resection is associated with a greater frequency of postoperative complications than patients undergoing pancreaticoduodenectomy alone. In an attempt to reduce this morbidity, various techniques for reconstruction have been described. Wang *et al.* [17] were the first to comprehensively assess a primary venous anastomosis, without the need for a vascular graft, and suggest that it can be completed with comparable postoperative morbidity to patients undergoing pancreaticoduodenectomy without vascular resection.

Although less frequently encountered with improvements of noninvasive imaging (CT or MRI), tumors are occasionally found to be unresectable at the time of laparotomy during a planned resection. When this situation arises for head lesions, the surgeon must decide if a palliative biliary or enteric bypass should be performed. Lyons *et al.* [18▪] examine the Memorial Hospital experience with 157 patients who underwent laparotomy without resection from 2000 to 2009. They found that a biliary and/or enteric bypass did not reduce the number of procedures or inpatient hospital days over the remainder of the patients' lifespan. These results suggest that performing palliative surgical bypasses during laparotomy may not be optimal, as biliary and duodenal obstructions usually can be managed successfully with endoscopically placed stents.

Previous studies have revealed that approximately 30% of patients with PDAC die of local tumor burden without bulky systemic metastases. Despite these findings, patients who develop local recurrences after surgical resection are often treated with radiation therapy or chemotherapy; they are not offered repeat surgical removal. Strobel *et al.* [19] have amassed a cohort of 57 patients with isolated local recurrence after resection that underwent repeat laparotomy; 70% were resected, half to negative margins. The survival of the latter group was 30.5 months as compared to 9.4 months in the patients with metastatic disease. Although this strategy is unconventional and the results are preliminary, these findings suggest that repeat resection may be indicated in well selected patients who respond well to treatment and recur a long time after initial resection.

PANCREATIC NEUROENDOCRINE TUMORS

The primary treatment for PNETs is surgical resection. However, many of these tumors have an indolent clinical course and, in select circumstances, it has been suggested that patients may be managed nonoperatively. The challenges with this latter strategy are to define variables that can be measured preoperatively and identify less 'biologically aggressive' tumors. Previous studies suggest that tumor size as measured on noninvasive imaging may be the best measure, as it correlates with LN metastases. Lee *et al.* [20] retrospectively reviewed their experience with 133 patients with PNETs, 77 managed

nonoperatively and 56 who underwent resection. They found that small nonfunctional PNETs usually exhibit minimal or no growth over many years, suggesting that these patients may be managed nonoperatively, particularly those who are poor operative candidates. In addition to nonoperative management, enucleation without nodal sampling is also an option for surgical treatment for these small lesions. This option is further supported by Cauley *et al.* [21] who showed that 45 patients who underwent pancreatic enucleations for small nonmalignant lesions had a decreased risk of short-term and long-term complications compared with larger resections. In contrast, Parekh *et al.* [22] examined the University of California, San Francisco database of 149 resections for PNETs. In this series, one-third of patients with LN metastases had tumors that were less than 3 cm. From these results, they argued that size should not be used as a proxy for nodal involvement and guide to treatment decisions. Until an RCT has been completed, we recommend that PNETs be surgically resected as long as the patient can tolerate an operation.

Gastrinomas are a type of functional PNET that is often difficult to localize on preoperative imaging tests. Most are located in the 'gastrinoma triangle,' which is formed by the cystic duct/common bile duct junction, second and third portion of the duodenum, and the neck of the pancreas. Interestingly, Norton *et al.* [23▪] prospectively studied 58 patients with sporadic gastrinomas (Zollinger–Ellison syndrome, ZES) and negative imaging studies. Each of these patients underwent surgical exploration, and the primary tumor was identified in all but one patient (Fig. 4). Also, liver metastases were found in 7% at the time of surgery. These results suggest that patients with confirmed ZES and no tumor identified on imaging should undergo surgical exploration (rather than continued surveillance) as these tumors can potentially spread to the liver.

SURGICAL TREATMENT OF CHRONIC PANCREATITIS

The most common indication for surgery in patients with chronic pancreatitis is pain. With highly variable rates of reported improvement after surgery, patient selection and the particular procedure performed must be extensively assessed in order to maximize the chances of a desirable outcome. Van der Gaag *et al.* [24] examined their series of 223 patients with chronic pancreatitis who underwent surgical treatment. They found that when the procedure was tailored to the anatomic abnormalities of the pancreas, long-term pain relief could be achieved in up to 90% of patients. Patients who are dependent on opioids and who underwent multiple endoscopic procedures were less likely to achieve a good outcome. Similarly, Ahmed *et al.* [25▪] develop a nomogram to identify patients who have the greatest likelihood of achieving pain relief with an operation. On the basis of their series of 266 patients, the variables associated with persistent

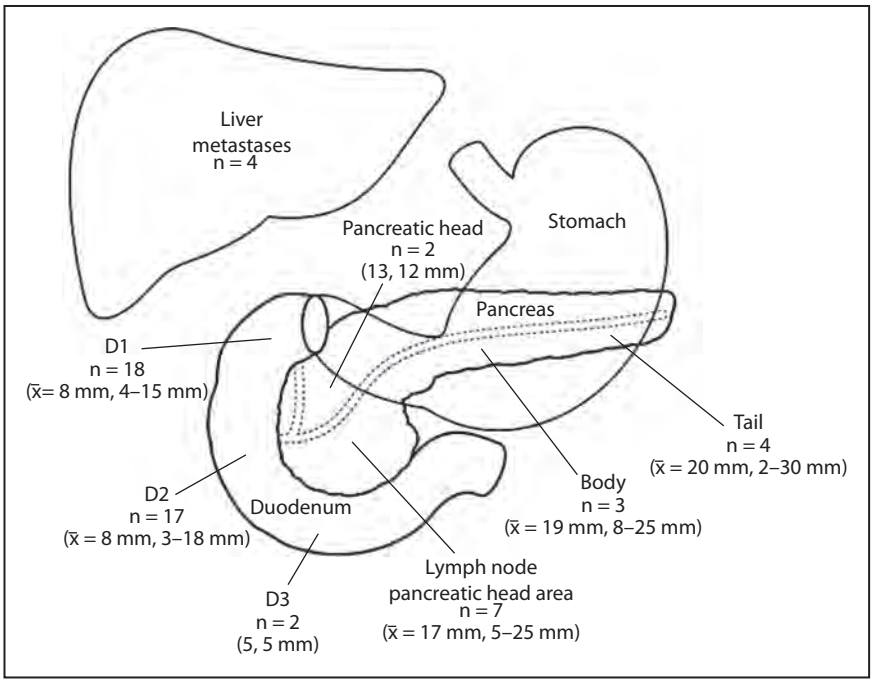

FIGURE 4. The exact location of nonimaged gastrinomas. [23▪].

pain following operation included more than 3 years of pain, preoperative opioid dependence, and more than five endoscopic procedures.

There are a number of surgical procedures that can be performed on patients with chronic pancreatitis. 'Parenchyma-sparing' operations include the Frey or Beger procedures, which have been found to provide similar pain relief in patients with enlarged pancreatic heads, compared with those undergoing pancreaticoduodenectomies. In an RCT, Keck *et al.* [26] found that parenchyma-sparing operations improved pain in two-thirds of patients, equivalent pain relief to those undergoing a pancreaticoduodenectomy. Interestingly, there was no difference between the two groups in preservation of endocrine or exocrine function. Moreover, total pancreatectomy with islet autotransplantation (TP-AIT) is being performed more frequently for patients with chronic pancreatitis refractory to other medical and surgical treatments. Sutherland *et al.* [27] reported on their large series of 409 patients who underwent TP-AIT. They found that 85% of patients experienced pain relief. The islet function was excellent, as 3 years after surgery one-third of patients were completely insulin independent, and one-third had evidence (circulating C-peptide) of at least partial islet function.

ROBOT-ASSISTED PANCREATIC SURGERY

Robot-assisted approaches are more frequently performed for all pancreatic surgery – both distal pancreatectomies and pancreaticoduodenectomies. Although there is a learning curve associated to becoming facile with the procedure, the advantages are that it is associated with a faster recovery and enables better visualization of the surgical field. The group at the University of Pittsburgh has amassed one of the largest series, and Daouadi *et al.* [28▪] directly compared patients who underwent minimally invasive distal pancreatectomy – either with the LDP or RADP. They found that RADP had a significantly lower conversion rate to open than LDP. Of the patients who underwent surgery for PDAC, there was a higher rate of margin negative resections (100 vs. 64%) and a greater lymph node harvest (median: 19 vs. 9) in the RADP group. These results suggest that RADP is associated with better visualization, which translates into less conversion rates and, potentially, a better oncologic operation.

CONCLUSION

This year featured many high-impact research articles on pancreatic surgery. Notable examples were focused on improving the cost-effectiveness of patient care after surgery, management of patients with PDAC and PNETs, incidence of fistula development after distal pancreatectomy, and increasing role of laparoscopy and the robot for all pancreatic procedures. The morbidity and mortality rates of patients after pancreatic surgery has decreased markedly over the last decade; and the survival of patients with PDAC and PNET continues to improve.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 574–575).

1. Gawlas I, Sethi M, Winner M, *et al.* Readmission after pancreatic resection is ▪ not an appropriate measure of quality. Ann Surg Onc 2013; 20:1781–1787.

This study identified that readmissions after pancreatic surgery may not be the best measure of quality, as the majority were because of the complications directly related to the operation rather than postoperative care.

2. Ahmad SA, Edwards MJ, Sutton JM, *et al.* Factors influencing readmission after pancreaticoduodenectomy: a multiinstitutional study of 1302 patients. Ann Surg 2012; 256:529–537.
3. Kent TS, Sachs TE, Callery MP, Vollmer CM Jr. The burden of infection for elective pancreatic resections. Surgery 2013; 153:86–94.
4. Ragulin-Coyne E, Carroll JE, Smith JK, *et al.* Perioperative mortality after pancreatectomy: a risk score to aid decision-making. Surgery 2012; 152 (3 Suppl 1):S120–S127.
5. Callery MP, Pratt WB, Kent TS, *et al.* A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013; 216:1–14.
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This study identified that more visceral adipose tissue, less skeletal muscle, and greater predicted postresection pancreatic remnant were more predictive of postoperative fistula (POF) development than traditional factors (e.g., pancreatic texture and duct size).

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This study validated previous findings that routine placement of an intraoperative drain does not improve the morbidity in patients who develop a POF.

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This study is a RCT revealing that routine use of mesh reinforcement of stapled transection for distal pancreatectomies significantly reduces the rate of clinically significant POF development.

14. Konstantinidis IT, Warshaw AL, Allen JN, *et al.* Pancreatic ductal adenocarcinoma: is there a survival difference for r1 resections versus locally advanced unresectable tumors? What is a 'true' r0 resection? Ann Surg 2013; 257:731–736.

This study reveals that patients who have an R1 resection have better survival than patients with locally advanced disease whose tumors are not resected. Moreover, patients with a wide margin clearance (> 1 mm) have significantly better survival than those with a close margin (< 1 mm).

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This study reveals that palliative surgical bypass at the time of exploratory laparotomy does not decrease patient burden for the remainder of their lives. These results suggest that biliary and enteric obstructions can be treated with endoscopically placed stents.

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This study revealed that patients with ZES and gastrinomas that cannot be identified on preoperative imaging should undergo surgical exploration, as they can all be found at surgery and many have metastatic disease.

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This study revealed that robot-assisted distal pancreatectomy was associated with a higher rate of margin negativity and greater lymph node harvest than laparoscopic approaches for pancreatic cancer.