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Laparoscopic Pancreas Surgery: Image Guidance Solutions

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Additional information is available at the end of the chapter

Abstract

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related deaths. Surgery is the only viable treatment, but irradical resection rates are still high. Laparoscopic pancreatic surgery has some technical limitations for surgeons and tumor identification may be challenging. Image-guided techniques provide intraoperative margin assessment and visualization methods, which may be advantageous in guiding the surgeon to achieve curative resections and therefore improve the surgical outcomes. In this chapter, current available laparoscopic surgical approaches and image-guided techniques for pancreatic surgery are reviewed. Surgical outcomes of pancreaticoduodenectomy and distal pancreatectomy performed by laparoscopy, laparoendoscopic single-site surgery (LESS), and robotic surgery are included and analyzed. Besides, image-guided techniques such as intraoperative near-infrared fluorescence imaging and surgical navigation are presented as emerging techniques. Results show that minimally invasive procedures reported a reduction of blood loss, reduced length of hospital stay, and positive resection margins, as well as an improvement in spleen-preserving rates, when compared to open surgery. Studies reported that fluorescence-guided pancreatic surgery might be beneficial in cases where the pancreatic anatomy is difficult to identify. The first approach of a surgical navigation system for guidance during pancreatic resection procedures is presented, combining preoperative images (CT and MRI) with intraoperative laparoscopic ultrasound imaging.

Keywords: pancreatic cancer, laparoendoscopic single-site surgery, robotic surgery, image-guided surgery, surgical navigation, near-infrared fluorescence

1. Introduction

Cancer is the second leading cause of death worldwide after heart disease, with 14.9 million cases and 8.2 million deaths in 2013 [1, 2] and the first leading cause of death among adults aged 40–79 years [3, 4]. Worldwide, pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related deaths [2, 3]. The incidence of all types of pancreatic cancer ranges from 1 to 10 cases per 100,000 people and is generally higher in developed countries and among men [1, 2]. This has remained stable for the past 30 years relative to the incidence of other common solid tumors [5]. Each year about 233,000 new cases of pancreatic cancer are diagnosed worldwide [2, 3]. In the United States, the American Cancer Association expected about 48,960 (24,840 men and 24,120 women) cases of incidence in pancreatic cancer in 2015, with a mortality rate of 83% [6]. In Europe, the estimated number of new cases of pancreatic cancer in 2012 was 79,331 and the estimated number of cases of deaths was 78,669 [7, 8], which is almost the double than in the United States. The 5-year survival rate in the world for pancreatic cancer is still very low, with only 6%. In addition, the overall 2-year survival rate is less than 10%, which has hardly improved over the past two decades [3–5]. In fact, in contrast to the stable or declining trends for most cancer types in the United States, a trend analysis for 2001–2010 indicated that death rates are rising for pancreatic cancer [3, 4].
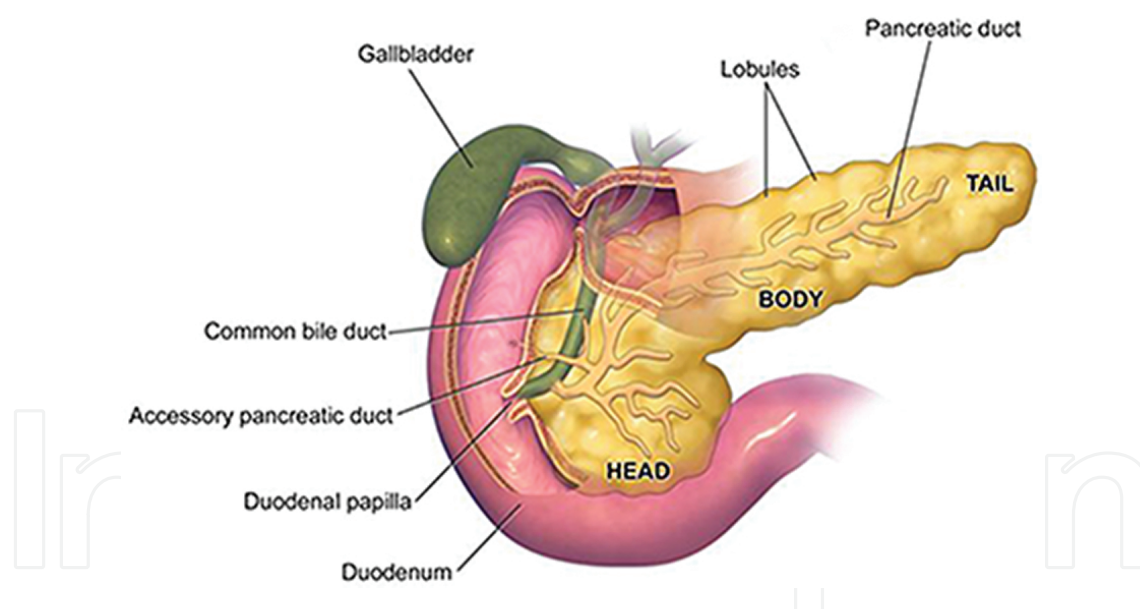

Figure 1. Anatomy of the pancreas. *Source:* "Blausen Gallery 2014". Wikiversity Journal of Medicine. DOI: 10.15347/wjm/2014.010. ISSN 20018762.

Pancreatic tumors are mainly classified as exocrine and endocrine tumors, also known as pancreatic neuroendocrine tumors (NETs). Exocrine tumors are approximately 99% of all primary pancreatic tumors [9] and are divided into ductal adenocarcinomas (80–90% of exocrine tumors), cystic neoplasms, and solid pseudopapillary neoplasms [5, 6, 10]. Ductal adenocarcinomas usually begin in the ducts of the pancreas and are located in the head of the pancreas (60–70%) (**Figure 1**) [10]. Approximately 5–10% of PDA cases are believed to be due

to hereditary conditions, such as hereditary pancreatitis, Gardner syndrome, familial colon cancer, and others [11].

Pancreatic cases are usually diagnosed at an advanced stage but with few treatment options available. This is attributed primarily to a lack of reliable methods for early diagnosis and rapid metastasis of pancreatic cancer [12]. At the time of diagnosis, less than 20% of patients with pancreatic cancer present with localized, potentially curable tumors [13, 14]. Approximately, 30% of patients receive a diagnosis of advanced loco-regional disease. In addition, 30% of patients have local recurrence of tumors after treatment for an early disease [14].

Although there are several available treatments for pancreatic cancer such as ablative techniques, radiation therapies, and chemotherapy, surgery is the only viable treatment. However, only 10–20% of pancreatic tumors are candidates to be surgically resected at diagnosis [10, 15]. The required surgical intervention for pancreatic cancer treatment depends on the location of tumors. Cancers arising in the head of the pancreas require a pancreaticoduodenectomy (Whipple operation), while those in the tail require a distal pancreatectomy with or without splenectomy [16]. Lesions located in the neck and body may require a distal pancreatectomy, pancreaticoduodenectomy or, rarely, a total pancreatectomy. After surgery, patients with no positive resection margins (R0) have the most favorable prognosis [17]. The median survival length reported for resected (R0) pancreatic cancer ranges from 17–27 months and, after a R1 resection, the average survival length is 10.3 months [18]. However, irradical resection of pancreatic cancers still occurs in 35–42% of patients [16, 19]. This survival time is longer in patients with malignant disease localized to the pancreas and less than 3 cm in diameter than in patients with tumors of greater size or with retroperitoneal invasion (6–15 months) [13]. Other factors, such as tumor size, lymph node status, tumor grade and blood vessel invasion, are also correlated with prognosis [20].

The introduction of minimally invasive surgical techniques in the treatment of pancreatic cancer has allowed almost any pancreatic tumor to be operated by laparoscopic or robotic approaches with similar outcomes to the standard approach [21, 22]. Even new approaches such as laparosendoscopic single-site surgery (LESS) are being applied recently in the field of pancreatic surgery [23, 24]. However, there are some limitations that have hindered the wide use of minimally invasive pancreatic surgery, mainly due to the challenges of these kinds of interventions. The retroperitoneal location of the pancreas makes it difficult to reach during surgery. In addition, this glandular organ presents a delicate structure close to major vascular structures. There are also some technical limitations related to minimally invasive surgery (MIS) such as the lack of visual and tactile information. Increasing the capability to visualize tumor margins or to identify small metastatic nodules may significantly improve the surgical procedure to prevent positive resection margins, and therefore, surgical outcomes [25]. Image-guided techniques can provide intraoperative margin assessment and visualization methods, which may be advantageous in guiding the surgeon to achieve curative resections. Some of these emerging modalities are intraoperative near-infrared fluorescence imaging and surgical navigation systems [26, 27]. However, despite the high rate of positive resections in pancreatic surgery, there is limited medical literature regarding the use of navigation systems as a support during pancreatic interventions. In this chapter, the current laparoscopic surgical techniques

and image-guided methods for pancreatic surgery and their associate surgical outcomes will be reviewed.

2. Laparoscopic techniques for pancreatic surgery

Pancreatic cancer is a complex disease, whose optimal treatment depends heavily on careful accurate staging [28]. Surgical resection is still the only potentially curative therapy for pancreatic cancer. However, pancreatic resection is technically challenging and a complex surgical procedure. In this section, the current laparoscopic surgical techniques for pancreatic surgery and their associated surgical outcomes will be reviewed. In order to reach more representative information, only studies published after 2010 and with more than 50 patients included, were taken into account. No limitation in the number of patients was set for the studies using LESS.

2.1. Laparoscopic surgery

2.1.1. Laparoscopic pancreaticoduodenectomy

The first laparoscopic pancreaticoduodenectomy (LPD) was published by Gagner and Pomp in 1994 [29]. They concluded that, although technically feasible, this approach did not confer significant benefit over the conventional open approach in terms of postoperative outcomes or reduced postoperative recovery period. One of the largest barriers of this complex procedure is the reconstruction phase due to the three separate anastomoses to be performed (pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy).

	N	Conv. (%)	Time (min)	EBL (ml)	LHS (days)	Morb. (%)	Mort. (%)	PF (%)	LN (%)	R0 (%)
[30]	53	17	541	195	8	77.3	5.7	13.2	44.2	94.9
[31]	384				10		5.2		4.7	80
[32]	983						5. 1			
[33]	108		379.4	492.4	6					
[34]	65	4.6	368	240	7	40	1.5	16.9	23.1	89
[35]	105	4.7	487.3		15	25	0.9	5.7	12.4	100
[36]	96	3.1					0	28.1		
[37]	75	13.3	551		7	31		9.3		
[38]	137		480.4	592	14.1					
[39]	681				9	39.4	3.8			

N: number of patients; Conv.: conversions; EBL: estimated blood loss; LHS: length of hospital stay; Morb.: morbidity rate; Mort.: mortality rate; PF: pancreatic fistulas; LN: lymph nodes; R0: R0 resection rate.

Table 1. Reported outcomes in laparoscopic pancreaticoduodenectomy.

A summary of the outcomes reported for LPDs are presented in **Table 1**. The average operation time was 486.7 min (range 368–551 min), 8.5% (range 3–17%) conversions, 342.3 ml (range 195–

592 ml) blood loss, 8.9 days (range 6–15 days) hospital stay, 32% (range 25–40%) morbidity, 2.6% (range 0–5%) mortality, 14.7% (range 6–28%) pancreatic fistulas, 21.1% (range 6–28%) harvested lymph nodes, and 89.7% (range 80–100%) R0 resection. The highest rate of conversions reported was due to suspected portal vein involvement [30]. Regarding morbidity rates, the highest rate was caused mainly by surgical site infection, postoperative pancreatic fistula, and intraabdominal access [30]. Myocardial infarctions and positive margins were the main mortality causes [30, 31]. Comparing these results with the conventional open approach [16], LPD leads to an increase in operating time, rate of pancreatic fistulas, and R0 resections; a decrease in estimated blood loss and harvested lymph nodes; and similar results in length of hospital stay, morbidity, and mortality rates.

Most of the studies reported longer operation times using the laparoscopic approach compared to the open approach [30, 35, 37]. Although some studies reported comparable outcomes between open and LPD [30], in general, reduction of blood loss and hospital stay [33, 34] are shown for LPD. In some studies, LPD was associated with equivalent overall hospital cost compared with open pancreaticoduodenectomy [37, 39]. While operating time and supply costs were higher for LPD, it was balanced by reduced cost due to the shorter postoperative hospital stay. A steep learning curve is another aspect associated with LDP and some researchers stated that this procedure should be performed in centers by surgeons with substantial knowledge, experience, and skills [34, 36].

2.1.2. Laparoscopic distal pancreatectomy

Laparoscopic distal pancreatectomy (LDP) was first reported in 1996 by Gagner and Cuschieri [40, 41]. During this intervention, the tail of the pancreas or the tail and a portion of the body of the pancreas are removed. In some cases, the spleen is also removed. This operation is used more often to treat pancreatic NETs found in the tail and body of the pancreas. The determination of resectability is often based on the extent of involvement of the celiac axis [42].

A summary of the outcomes for LDPs are shown in **Table 2**. In brief, the average operation time was 215.2 min, 12% conversion rate, 241.7 ml estimated blood loss, 7.6 days length of hospital stay, 32.5% morbidity rate, 0.3% mortality rate, 21.2% pancreatic fistulas, 10.2% harvested lymph nodes, 89.5% R0 resection, and 46.3% spleen-preserving rate. Comparing these results with the outcomes from conventional open surgery [43, 44], there is a decrease in operation time, estimated blood loss, length of hospital stay, and mortality rate; similar morbidity rates; and an increased rate of pancreatic fistulas and spleen preservation.

Satisfactory oncological outcomes have been reported for LDP in patients with PDA and left-side pancreatic neoplasms [58, 61]. Although some studies reported similar outcomes as open distal pancreatectomy [21], most of the studies reported a clear reduction of blood loss [50, 53, 62, 63, 65] and hospital stay [45, 48, 50, 53, 31, 59, 61–65]. An increase in quality of life is reported when compared to the conventional approach [46]. Similar costs for the laparoscopic and open approaches are reported [63]. The increased OR cost associated with LDP is often offset by the shorter hospitalization and lower overall cost of postoperative care [57].

Regarding the spleen-preserving rate, results stated that it is worth to attempt laparoscopic spleen-preserving DP in patients with a presumed benign to borderline tumor of the body-tail of the pancreas [54]. The most positive results were reported for the splenic vessels preservation technique regarding the conservation of the spleen [51, 66].

	N	Conv. (%)	Time (min)	EBL (ml)	LHS (days)	Morb. (%)	Mort. (%)	PF (%)	LN (%)	R0 (%)	SP (%)
[21]	64	32.8	213	275	8	16		11	8	62	79.6
[45]	535	22.8			7		0		15	86	
[46]	100	23	239	464	7.7	66	0	53		73.3	
[47]	94							0	11		
[48]	71	9.1	250	150	5	28.2	0	11		97.2	15.5
[49]	67	14.9	203	100	6	21	1.5	19	6		
[50]	107	30	193	150	5	27	0	15		97	21
[51]* †	55	9	214.7	342.8	8.2	27.3	0	16			93.4
[51]* †	85	13	199.2	288.9	10.5	38.8	0	26	3		84.7
[52]	132	6.1	156.5	197.4	6	43.2	0.8	21	8	96.2	9.8
[53]	131	31.3	193	262	5	32	0	8	11	100	22.1
[54]	100	2	207		8.7	49	0	27		98	41
[55]	143	5.6	236	334				17			
[56]	902	6.4	316	243	18.9	23.6		66	11		32
[57]	70	7.1	145	113	5.8	49	0	36	5		
[58]	196	2.5	220	250	8	31.9	0	24	10	83.8	
[59]	144	39.5			6.8		0		17	87	
[60]	70	7.1	239		9	25.7	0	19	3	75.7	
[61]	359		195		8	12	0	28	20	91.6	49.6
[62]	82	7	188	70	4	32.9	0	13		97	12
[63]	100	4	214	171	6.1	34	3	17	15	100	25
[64]	73	15	352		5	40	0	22		97	
[65]	45	0	158.7	122.6	7.9	26.7		16			53.3
[66]†	70	0	220	352	10.4	32.9	0	17			100
[67]* †	246	0	193.4	378	8.2	32.5	0	20			54.8
[67]* †	203	0	204.4	328	7.7	25	0	4			

N: number of patients; Conv.: conversions; EBL: estimated blood loss; LHS: length of hospital stay; Morb.: morbidity rate; Mort.: mortality rate; PF: pancreatic fistulas; LN: lymph nodes; R0: R0 resection rate; SP: spleen preserving.
*Two groups.
†Spleen-preserving DP.

Table 2. Reported outcomes in laparoscopic distal pancreatectomy.

With growing surgical experience and refinement in the surgical technique, the indications for LDP have substantially broadened [52]. In this sense, the learning curve appeared to have been completed after 17 procedures [68], but strict selection criteria, high-volume hospital, and experienced team in open pancreatic surgery may play an important role in shortening this learning curve [69].

2.2. Laparoendoscopic single-site surgery

Recent interest in improving cosmetic outcomes has led to laparoendoscopic single-site surgery (LESS) being performed in a variety of procedures. In this sense, LESS is now consolidated as a real alternative to conventional laparoscopic surgery, with numerous studies sustaining its feasibility and therapeutic safety. However, single-site pancreatectomy has been explored and described only in recent years, and therefore, literature is limited to DP procedures and mostly to single case reports or small case series, as it is considered to be a challenging procedure. Only one study has been found for a PD through the single-site approach [70]. In this case, a surgical resection for a malignant melanoma metastatic to the pancreas was performed. The resection was carried out preserving the pylorus. No detailed information about the intervention and surgical outcomes were reported.

	N	Conv. (%)	Time (min)	EBL (ml)	LHS (days)	Morb. (%)	Mort. (%)	PF (%)	LN (%)	R0 (%)	SP (%)
[23]	20		176		2	4	20	20	0	100	90
[24]	14	7.1	166.4	157.1	7.6	0	7.1	0			50
[71]	1	0	330	100	7	1		100	0	100	0
[72]	1	0	170		5		0			100	0
[73]†	1	0	233	<100	3		0			100	100
[74]	12	20	279.8	185	12.2	3	41.6	25		100	33.3
[75]	8	0	145	225	6	2	50	25		100	62.5
[76]*	2	0	232.5	100	7, 5		0	100			
[77]	1	0			5	0			0	100	0

N: number of patients; Conv.: conversions; EBL: estimated blood loss; LHS: length of hospital stay; Morb.: morbidity rate; Mort.: mortality rate; PF: pancreatic fistulas; LN: lymph nodes; R0: R0 resection rate; SP: spleen preserving.
*Two groups.
†Spleen-preserving DP.

Table 3. Reported outcomes in single-site distal pancreatectomy.

The average operation time reported for LESS distal pancreatectomy (**Table 3**) was 218 min (range 145–330 min), 3% (range 0–20%) conversion rate, 144 ml (range 100–225 ml) estimated blood loss, 6 days (range 2–12 days) length of hospital stay, 15% (range 0–50%) morbidity, 0% mortality, 100% R0 resection, and 42% (range 0–100) spleen-preserving rate. Comparing the results with the conventional laparoscopic approach, there is a decreased rate of conversions, estimated blood loss, length of hospital stay, and morbidity; a similar mortality rate; increased average of pancreatic fistulas and R0 resections; and lower spleen-preserving rate.

Barbaros et al. [71] reported the first transumbilical laparoscopic single-site DP in a patient with metastatic lesions on the pancreas. The patient developed a pancreatic fistula. Haugvik et al. [75] compared the results of 8 single-incision DPs with 16 conventional LDPs. They reported no significant differences in operative time, intraoperative bleeding, resection status, and hospital stay between the two groups. Four surgical complications were reported for LESS

and five for the conventional approach, including two patients for each group who developed a pancreatic fistula. There was no conversion to conventional laparoscopic or open surgery in any procedure. No differences between operative and postoperative results were also obtained by Yao et al. [24], who compared the surgical outcomes of 14 transumbilical laparoscopic single-site DPs with seven conventional multiport interventions. One conversion to open surgery and one case of leakage were reported for the LESS interventions. Machado et al. [23] reported 4 cases of pancreatic fistula in a study of 20 DPs. Some cases reported no surgical complications during the intervention [72, 76]. In a case study without using any commercial surgical port for LESS [77], the patient developed fever and leukocytosis after surgery. Bracale et al. [72] presented the first LESS DP for an adenocarcinoma. They reported no postoperative complications after 4 months follow-up.

Spleen preservation is an important issue in patients undergoing DP. However, only a few studies have reported spleen preservation through LESS. Chang et al. [73] reported a case of ransumbilical LESS spleen-preserving DP for a cystic tumor in the body of the pancreas. No surgical complications were reported. In another study, Han et al. [74] compared the results from 12 LESS DPs to 28 cases using a conventional laparoscopic approach. The mean surgery time and hospital stay in the LESS group were significantly longer. The spleen preservation was possible in 60.7% of the patients who underwent the conventional approach and 33.3% for the LESS. No significant differences in intraoperative blood loss, tumor size, conversion rate, and postoperative complications between the two groups were found.

In general, authors stated that single-site laparoscopic PD is a feasible and safe technique [23, 72, 74], which can be successfully performed in selected cases and qualified centers [71, 73]. However, they also stated that it is a very demanding procedure with a steep learning curve [74].

2.3. Robotic surgery

Robotic platforms, as the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), try to overcome many of the key shortcomings of traditional laparoscopy that include monocular vision, limited degrees of freedom, and the effects of pivot and fulcrum, which make complex tasks difficult to master. However, there are also some drawbacks regarding the use of these systems such as the lack of tactile feedback and their cost, including mainte-nance. Since its first reported application in 2003 [78], the application of robotic technology in pancreatic interventions has been increasing. The main benefit of robotic-assisted PD in comparison with LPD may be the ease of intracorporeal reconstruction after a long resection [78].

In the scientific literature, most of the studies regarding the robotic-assisted PD and DP are retrospective reviews and case reports (**Table 4** and **5**). The average operation time reported for robot-assisted PD (**Table 4**) was 489.1 min (range 410–568 min), 10% (range 0–22%) conversion rate, 324 ml (range 250–400 ml) estimated blood loss, 13.4 days (range 9–22 days) hospital stay, 48.6% (range 21–67%) morbidity rate, 3.8% (range 1–7%) mortality rate, 17.4% (range 7–30) pancreatic fistulas, 29% (range 11–70%) harvested lymph nodes, and 91% (range 87–95%) R0 resection. Comparing the results with conventional laparoscopic approach,

operative time, length of hospital stay, and negative resections margins are similar; the rate of conversions, morbidity, mortality, and pancreatic fistulas are increased. Positive results have been obtained for robotic-assisted PD in patients with aberrant or anomalous hepatic arterial anatomy [22]. In a prospective analysis with 150 patients, Polanco et al. [79] concluded that larger body mass index, higher EBL, smaller tumor size and smaller duct diameter are the main predictors of postoperative PF in robot-assisted PD. It appears that the learning curve for robot-assisted PD is attained within 80 cases [80].

	N	Conv. (%)	Time (min)	EBL (ml)	LHS (days)	Morb. (%)	Mort. (%)	PF (%)	LN (%)	R0 (%)
[22]*	112	0	500	250	9.5	63.3	6.7	7	20	92.6
[79]	150	7.3	515	300				17		
[80]	200	6.5	483	250	9	67.5	3.3	17	11	92
[84]	60		410	400	20	35	1.7	13	23	94.7
[85]	50	22	421	394	22			30	70	90
[86]	50	16	568	350	10	56	2	20	36	89
[87]	132	8.3	527	>400	10	21	5.3	17	14	87.7

N: number of patients; Conv.: conversions; EBL: estimated blood loss; LHS: length of hospital stay; Morb.: morbidity rate; Mort.: mortality rate; PF: pancreatic fistulas; LN: lymph nodes; R0: R0 resection rate; SP: spleen preserving.
*Two groups.

Table 4. Reported outcomes in robotic-assisted pancreaticoduodenectomy.

	N	Conv. (%)	Time (min)	EBL (ml)	LHS (days)	Morb. (%)	Mort. (%)	PF (%)	LN (%)	R0 (%)	SP (%)
[45]	535	23			7				3	86	
[82]	100	2	246	150		72	0	42	13	95.7	
[83]	55	0	278.2		12.6	61.8	0	53	58	100	61.8
[87]	83	2.4	256	>200	6	13	0	43	17	97	
[88]†	69	0	150	100	11.6	40.6	0	25	22	100	65.2

N: number of patients; Conv.: conversions; EBL: estimated blood loss; LHS: length of hospital stay; Morb.: morbidity rate; Mort.: mortality rate; PF: pancreatic fistulas; LN: lymph nodes; R0: R0 resection rate; SP: spleen preserving.
†Spleen-preserving DP.

Table 5. Reported outcomes in robotic-assisted distal pancreatectomy.

Regarding robot-assisted DP, the average operation time was 232.6 min (range 150–278 min), 5.5% (range 0–23%) conversion rate, 125 ml (range 100–150 ml) estimated blood loss, 9.3 days (range 6–13 days) hospital stay, 46.9% (range 13–72%) morbidity rate, 0% mortality rate, 40.7% (range 24–53%) pancreatic fistula, 22.6% (range 3–58%) harvested lymph nodes, 95.7% (range 86–100%) R0 resection, and 63.5% (range 62–65%) spleen-preserving rate. Comparing these

results with the conventional laparoscopic approach, there is a decreased conversion rate and EBL; and increased operation time, length of hospital stay, morbidity, rate of pancreatic fistulas, R0 resections, and spleen-preserving rate. Morbid obesity and technical difficulty seem to be the two most common reasons for conversion from robotic-assisted hepatobiliary and pancreatic surgery [81]. It appears that the learning curve for robot-assisted DP is approximately 10–40 cases [82, 83].

3. Image-guided techniques for pancreatic surgery

In order to cope with some of the limitations in MIS and guide the surgeon during the surgical procedure, image-guided techniques have been developed. The lack of tactile feedback and 3D sensation in video-assisted surgery accelerated the need for these techniques. In addition, for the human eye, several pathologies, such as the presence of nonsuperficial tumors, are not easily distinguishable from surrounding normal tissue. This makes, in some occasions, decision-making during surgery a very difficult process. During image-guided surgery, diagnostic imaging is used in conjunction with images from the operative field to improve the localization and targeting of pathologies, as well as to monitor and control treatments. The combination of tracking technologies for recording the position of the patient and the surgical instruments with preoperative and intraoperative images provides a comprehensive assistance tool for guiding any MIS intervention [27, 89–91]. Image-guided technology allows for more precise and accurate procedures, allowing surgeons to decide the best approach to address a specific disease before the intervention [92].

Radical surgical resection of tumor tissue is currently the best chance for cure. However, this option is only suitable for a minority of patients, and surgical procedures are complex with high rates of local recurrence. The presence of microscopic residual tumor tissue at the resection margins is one of the main prognostic factors, and therefore optimizing the surgical procedure to prevent positive resection margins is of the utmost importance. Accordingly, intraoperative margin assessment and visualization techniques, as well as image-guided techniques may be advantageous in guiding the surgeon to achieve curative resections.

3.1. Laparoscopic ultrasound (LUS)

Advances in technology over the last 30 years have seen the application of laparoscopic ultrasound (LUS) expand beyond its initial limited diagnostic role to assisting in tumor staging, guiding intervention, locating lesions intraoperatively, assessing anatomic relationships, and in directed therapy [93–95]. The main application of LUS during pancreatic and liver surgery is providing real-time imaging guidance for resectability assessment and detection of vessel involvement, aiming to decrease the number of irradical resections [95]. The reported overall sensitivity, specificity, and accuracy of combined diagnostic laparoscopy and LUS in predicting resectability has been reported to be 100, 91, and 96%, respectively [96]. LUS should be considered for confirmation of staging of disease when there is a strong suspicion of unresectability and tumor borders are not clearly defined by CT scan [96].

LUS plays an integral part in the management of cystic lesions of the pancreas, particularly the characterization of suspected intraductal papillary mucinous neoplasms (IPMNs) [95, 97, 98]. IPMNs appear as well-defined hypoechoic masses with associated posterior enhancement. The malignant potential of IPMNs is directly related to its relationship with the main pancreatic duct and adjacent blood vessels (**Figure 1**). LUS allows defining the cysts borders (**Figure 2**) and evaluating the relationship of the lesion with the main duct and any major vessels [95, 98, 99].
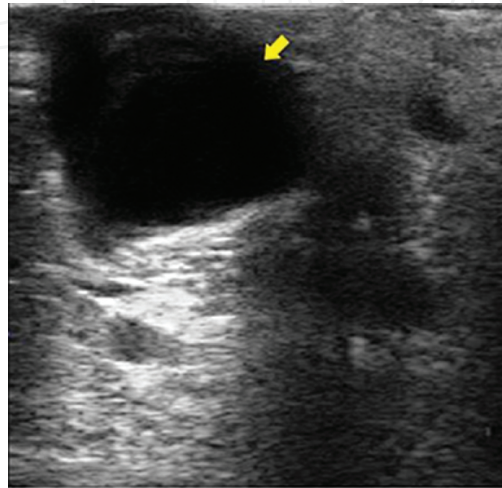
Figure 2. LUS image of a pancreatic cystic tumor. The lesion appears as a hypoechoic mass (yellow arrow).

In the case of pancreatic adenocarcinomas, they appear as a homogeneous hypoechoic mass with poorly defined margins. Large tumors can display a mixed echogenicity. A sensitivity of 90% for assessing positive lymph nodes and 100% for venous invasion have been reported for laparoscopy combined with LUS examination [100]. Regarding NETs, LUS facilitates intraoperative decision-making and demonstrates anatomic details, such as the tumor location and its relation to the adjacent vascular structures and main pancreatic duct [95, 97]. In ultrasound images, NETs typically appear as well-defined, homogeneous, and hypoechoic masses [93]. Findings from LUS inspection help to decide whether to perform either tumor enucleation or resection during laparoscopic intervention [93].

3.2. Fluorescence

Near-infrared (NIR) light (700–900 nm) is a novel imaging technique that can penetrate through several millimeters even centimeters of tissue, revealing targets below the tissue surface [101]. This imaging modality does not use ionizing radiation or direct tissue contact, making it a remarkably safe technique. NIR fluorescent contrast agents can be visualized with acquisition times in the millisecond range, enabling real-time guidance during surgery. Furthermore, as NIR light is invisible to the human eye, it does not alter the look of the surgical field, thus minimizing the learning curve [102]. The main aim of this imaging modality is to fill the gap between preoperative imaging and intraoperative reality.

Fluorescence-guided systems provide an additional tool for diagnosis of pancreatic cancer, real-time image guidance during tumor resection, and inspection to confirm complete resection [103]. This intraoperative modality can assist surgeons to visualize tumors, sentinel lymph nodes, and vital structures in real time [102]. This technology could represent the next step to improving treatment of pancreatic cancer in laparoscopic resections. However, most of the published studies for pancreatic surgery are limited to animal models.

Two main components are needed for fluorescence-guided surgery, fluorescent contrast agents and a NIR camera system. Several intraoperative NIR fluorescence camera systems have been developed for both open and laparoscopic surgery, some of which are commercially available and Food and Drug Administration (FDA) approved [104]. Fluorescent contrast agents contain a fluorescent component (fluorophore), which emits NIR fluorescent light after being excited with a NIR light source. Visualization of the tissue is based on the signal of the contrast agent in the region of interest relative to the background signal, known as signal-to-background ratio.

Indocyanine green (ICG) and methylene blue (MB) are the only NIR fluorophores that are registered with the FDA and the European Medicines Agency for clinical use. ICG emits fluorescent light at ≈800 nm and it is cleared rapidly by the liver and almost exclusively excreted into the bile, permitting imaging of bile ducts. MB has been applied clinically for many years as a visible contrast agent, and when diluted to levels that are almost undetectable to the human eye, MB becomes a fluorophore emitting at ≈700 nm. MB is cleared equally by both liver and kidney, permitting imaging of both bile ducts and ureters. ICG has been shown to accumulate around hepatic metastasis of pancreatic and colorectal cancers [105]. Methylene blue tends to accumulate in NETs after high-dose intra-arterial injection [103, 106]. The chemical structures of both ICG and MB do not allow these agents to be conjugated to tissue-specific, therefore, they are nonspecific NIR contrast agents [102, 107].

Applications of this technique during hepatopancreatobiliary surgery include tumor imaging in liver and pancreas, and real-time imaging of the biliary tree. Pessaux et al. [26] presented a robotic pancreaticoduodenectomy assisted by fluorescence imaging, providing enhanced visualization of the common bile and cystic ducts during the intervention (**Figure 1**). Subar et al. [108] reported a case of a LPD to treat an ampullary lesion in the duodenum. Before the pancreaticojejunostomy, the viability of the margin of the remnant pancreas was assessed with NIR imaging. The NIR technique improved the detection of ischemic tissue of the pancreatic margin after resection. This may lead to an increase in blood supply to the pancreatic anastomosis, and therefore potentially help to decrease the incidence of pancreatic fistulas.

In a study with different pancreatic tumors on three experimental porcine models, we analyzed the usefulness of NIR imaging during laparoscopic pancreaticoduodenectomy and single-site distal pancreatectomy procedures. In two animals, a tumor model was created in the head of the pancreas. In the third animal, the tumor model was developed in the tail of the pancreas. NIR imaging was used as guidance during LPD and LESS distal pancreatectomy. The patency of the hepaticojejunostomy was assessed by means of ICG excretion and fluoroscopic imaging. During surgery, identification of the biliary anatomy and vascular anatomy of the pancreas was possible in all procedures using NIR imaging (**Figure 3**). Biliary excretion of ICG was not clearly visualized during the patency test, but fluoroscopic imaging was positive in one case.
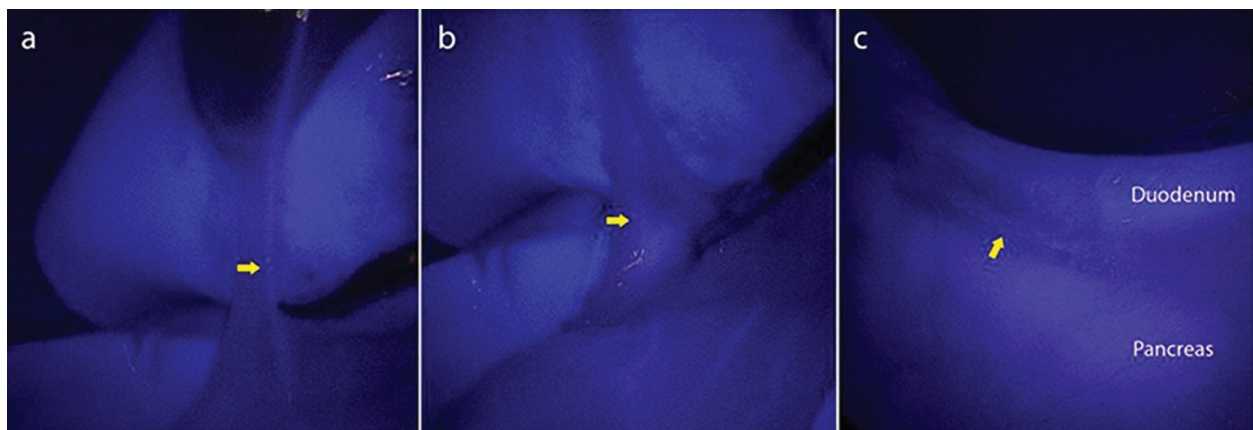
Figure 3. NIR image of biliary and pancreatic anatomy: Cystic artery (a, yellow arrow), cystic duct (b, yellow arrow), and pancreaticoduodenal artery (c, yellow arrow).

To obtain the full advantage of NIR fluorescence imaging for pancreatic cancer visualization, such as tumor imaging, tumor specific NIR conjugated agents need to be designed and tested. The tumor-targeting capability of the fluorophore-conjugated anticarcinoembryonic antigen antibody has been demonstrated in orthotopic models for intraoperative tumor visualization of both primary and metastatic deposits of pancreatic cancer [25, 109]. Metildi et al. [109] concluded that mice treated with fluorescence-guided laparoscopic surgery permitted adequate labeling and distinction of tumor margins before tumor resection, decreasing local recurrence, and increasing survival compared to mice treated with standard bright-light laparoscopic surgery.

3.3. Surgical navigation

Surgical navigation systems (SNS) combine preoperative and intraoperative image information with position and orientation tracking of surgical instruments during the surgical intervention as a surgical decision-making tool helping to improve the safety, accuracy, and efficiency of surgeries [27, 91, 92]. In MIS, due to surgeon having less visual and tactile perception compared to open surgery, image assistance becomes extensively helpful for 3D understanding of the surgical scenario and localization of lesion and essential anatomic structures.

The basic setup of a SNS consists of a preoperative image data (typically MR and CT), a tracking system (mainly electromagnetic or optical), a computer platform with screen, and the respective navigation software [89]. The combination of image-guided surgery with navigation technology consists of several steps, which are critical to ensure safety and accuracy of a procedure [27]: (1) acquisition of preoperative images and visualization for optimal diagnosis and planning, (2) accurate registration of preoperative data to the patient coordinate space and visualization in the OR, (3) intraoperative image acquisition and visualization/fusion with the preoperative images to update for anatomical shifts, and (4) postoperative imaging and visualization for evaluation of the surgical treatment.

Despite the use of navigation systems, abdominal surgery is still a challenging task. Commercial SNS are available for resection and ablation procedures of the liver (example: CAScination AG, Switzerland). However, to the best of our knowledge, no commercial systems are available or studies in the scientific literature have been published regarding the use of SNS for assistance during pancreatic cancer surgery.

We were recently able to demonstrate the usefulness of the CustusX navigation system for image guidance during a patient case, a distal pancreatectomy for the resection of a cystic tumor in the body of the pancreas (unpublished case). CustusX is an open-source navigation research platform for image-guided interventions [91]. This platform has been successfully used for many clinical applications such as neurosurgery, spine procedures, bronchoscopy, endovascular therapy, and laparoscopic procedures like adrenalectomy and lately for liver and pancreas surgery [91, 110–112].

Figure 4. Snapshot of the CustusX platform during a distal pancreatectomy. The tumor is shown in green and the pancreas in yellow. The US imaging is superimposed on the 3D model from a preoperative MRI scan.

Prior to surgery, MR and CT images were acquired and imported into the navigation system software for reconstruction into 3D. The anatomical structures of interest, including the pancreas, tumor, and vessels were segmented semiautomatically [112]. The navigation system was integrated with a LUS probe running on an ultrasound scanner (Ultrasonix, Canada) with digital research interface to the navigation system. The probe was tracked by an electromagnetic sensor integrated in the tip. A probe calibration was carried out in a laboratory using a robotic arm and a well-defined geometric structure in a water tank [113]. An intraoperative registration procedure was carried out to combine the intraoperative LUS with the corresponding preoperative MR and CT images, displaying them simultaneously (**Figure 4**). This enabled the location of the lesion based on multimodal display, providing a useful tool for the surgeons to identify the anatomical structures of interest, meet their relation to other adjacent structures, and define safely and accurately the resection margin during the course of the distal pancreatectomy.

3.4. Augmented reality

Another available technology for intraoperative surgical guidance is augmented reality (AR). In surgery, AR is the fusion of artificial computer-generated images (3D virtual model) generally obtained from preoperative medical imaging and real-time patient images with the aim to visualize unapparent anatomical details. This results in the visualization of internal structures through overlying tissues, providing a virtual transparent vision of surgical anatomy. Potential advantages of the use of this imaging technology in surgery include the delineation of dissection planes or resection margins and the avoidance of injury to invisible structures.

The registration process is one of the main challenges of AR, in which the virtual model and intraoperative images should be merged in real time. In this sense, intraoperative accuracy is highly affected by mobile or deformable structures due to the heartbeat, ventilation, or laparoscopic insufflation.

A method to overlay anatomical information from preoperative CT studies onto the patient's body surface during gastrointestinal, hepatobiliary, and pancreatic surgery was presented by Sugimoto et al. [114]. For enabling the simultaneous display of the gastrointestinal tract and pancreatobiliary duct with associated blood vessels, a carbon dioxide-enhanced virtual multiple detector CT cholangiopancreatography was performed. Manual registration based on physiological markers was used. However, this method does not deal with possible alteration of the patient anatomy during the course of the surgery. A robotic pancreaticoduo-denectomy assisted by AR was presented by Pessaux et al. [26]. In this study, a 3D virtual model of the patient from a preoperative CT scan was manually merged with the stereoscopic images from the da Vinci® robotic system.

4. Conclusions

Pancreatic cancer has a high mortality rate and, at the time of diagnosis, the number of patients with potentially resectable tumors is considerably low. Surgery is still the only viable option for treatment of pancreatic cancer. However, surgical procedures for pancreatic resection are complex and require high surgical expertise. Pancreatic tumors can be treated through laparoscopic surgery with similar outcomes to the conventional approach. In general, studies reported that minimally invasive pancreatic surgery is feasible, safe, and with a steep learning curve. Laparoscopic procedures reported a reduction of blood loss, length of hospital stay, and positive resection margins, as well as an improvement in spleen-preserving rates when compared to open surgery. Laparoendoscopic single-site surgery reduces the blood loss and morbidity, compared with the conventional laparoscopic approach. In robot-assisted pancre-atic surgery, reported surgical outcomes are similar to laparoscopic surgery, with an apparent increase in the splenic preservation rate and negative resection margins.

Laparoscopic pancreatic surgery has some technical limitations for the surgeon such as the reduced tactile and visual information. Besides, intraoperative tumor identification may be a

challenging task in some cases due to the anatomical location of the pancreas, nearby major vascular structures, and frequently inflamed surrounding pancreatic tissue. These limitations may significantly impact the surgical procedure to prevent positive resection margins. Image-guided techniques provide intraoperative margin assessment and visualization methods, which may be advantageous in guiding the surgeon to achieve curative resections, resulting in improved surgical outcomes. Reported cases of fluorescence-guided pancreatic surgery showed that this imaging technique could be beneficial in surgeries where the pancreatic anatomy is difficult to identify. Navigation systems combine preoperative and intraoperative imaging, providing location of the anatomical structures of interest with respect to surgical instruments as well as the extent of the tumor to be addressed, which allows for a safe and precise definition of resection margins. Thus, surgeons will have a comprehensive system to support and guide pancreatic surgeries, with the ultimate goal of improving surgical outcomes and increase the rate of negative resections and the subsequent positive effect on the life expectancy of the patient.

Acknowledgements

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