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Is there any role for minimally invasive surgery in NET?

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Abstract Neuroendocrine tumors (NET) represent the variability of almost benign lesions either secreting hormones occurring as a single lesion up to malignant lesions with metastatic potential. Treatment of NET is usually performed by surgical resection. Due to the rarity of NET, surgical treatment is mainly based on the experience and recommendations of experts and less on the basis of prospective randomized studies. In addition, the development and establishment of new surgical procedures is made more difficult by their rarity. The development of laparoscopic-assisted surgery has significantly improved the treatment of many diseases. Due to the well-known advantages of laparoscopic surgery, this method has also been increasingly used to treat NET. However, due to limited comparative data, the assumed superiority of laparoscopic surgery in the area NET remains often unclear or not yet proven. This review focuses on the present usage of laparoscopic techniques in the area of NET. Relating to the current literature, this review presents the evidence of various laparoscopic procedures for treatment of adrenal, pancreatic and intestine NET as well as extraadrenal pheochromocytoma and neuroendocrine liver metastases. Further, this review focuses on recent new developments of minimally invasive surgery in the area of NET. Here, robotic-assisted surgery and single-port surgery are promising approaches.

Keywords Neuroendocrine tumors · Laparoscopy · Minimally invasive surgery · Adrenal · Liver · Pancreas · Robotic surgery

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1 Introduction

Neuroendocrine tumors are a very variable entity of tumors, sharing their neural crest origin. Due to a wide variability of these tumors, treatment options are very much defined according to their stage or, in other words, their potential of malignancy. Minimally invasive techniques are common standard in contemporary surgery. Without doubt, they have a high potential when choosing surgical treatment options for neuroendocrine tumors, since there is wide variability from almost benign lesions either secreting hormones or occurring as multiple lesions up to malignant lesions with metastasizing potential. Classical minimally invasive techniques use modern endoscopic instruments and are able to reduce scar size of open surgery to incisions of only 5, 10 or 15 mm. An increment of these techniques is single port surgery where only one small incision is used for the whole operation with a single port. In recent years robotic surgery has become the most important innovative type of surgery, which gives the surgeon's hand a new dimension. Due to the also minimally invasive access through ports, it is a matter of debate whether the technique is more or less a "minimally invasive type" of open surgery.

75% of neuroendocrine tumors occur in the abdominal regions. This review discusses mainly the surgical treatment option of tumors occurring in the abdominal and retroperitoneal regions. Due to the completely different type of surgical treatment in cervical, thoracic and brain region neuroendocrine tumors occurring there are not in the scope of this review.

2 Adrenal and extraadrenal pheochromocytoma (paraganglioma) surgery

As the first laparoscopic (partial) adrenalectomy was described in the year 1992 [1], it has become the gold standard in adrenal surgery in the following years. As demonstrated for other surgical procedures, laparoscopic adrenalectomy has significant advantages regarding postoperative pain, hospital length of stay and morbidity thus increasing patient satisfaction and comfort [2–5]. Elfenbein et al. published a retrospective analysis comparing the open and laparoscopic approach by using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) [4]. Here, a total of 3100 patients were included. After adjustment for patient- and procedure-related factors, the laparoscopic approach showed significantly lower postoperative morbidity and shorter length of stay compared to patients undergoing an open procedure. These findings were similar for all indications for adrenalectomy, including malignancy. Conzo et al. considered the first 30 operations as part of the learning curve and claim that 40 operations are needed to master the laparoscopic procedure [3].

Retroperitoneoscopic (partial) adrenalectomy represents the second commonly used approach for minimally invasive adrenal surgery. The first retroperitoneoscopic adrenalectomy was described in year 1995 by Walz et al. [6]. Indeed, much of the credit for the development as a standard procedure is referred to the work of Martin Walz in Essen, Germany. His group published a series of 560 posterior retroperitoneoscopic adrenalectomies performed from 1994 to 2006 [7]. The mortality was 0%. Major complications occurred in 1.3% of patients and minor complications occurred in 14.4%. 8.9% had neoplasms over 6 cm in diameter. Over this period of time the mean operation time significantly declined from 106 to 40 min. Eleven cases were converted to open adrenalectomy. Reasons were failure to progress, adhesions or obesity. Similar results supporting the retroperitoneoscopic approach could be shown by the group of Berber et al. [8]. The principal advantages and disadvantages of the laparoscopic and the retroperitoneoscopic approach are clearly defined [2, 7, 9]: Fundamental advantages of the laparoscopic procedures are the familiar situs and the possibilities of inspection of the abdomen. The retroperitoneoscopic operations, on the other hand, are also technically feasible without restrictions e.g. after previous abdominal operations. The posterior access of retroperitoneoscopic adrenalectomy allows a bilateral adrenalectomy without repositioning the patient. The retroperitoneal methods use direct access to the adrenal gland, which eliminates the preparation of intraperitoneal organs and their possible injury. A further issue favoring the retroperitoneal procedure is the low intraoperative influence on hemodynamics in contrast to the usual increase in peripheral resistance under pneumoperitoneum.

Regarding comparative studies on minimally invasive adrenalectomy, the superiority of either method could not be exactly demonstrated [10–13]. This is due to methodological approaches, low patient numbers, inclusion of learning curves and the number of available methods. Currently, there is no single investigation comparing all four operating procedures used for minimal invasive adrenal surgery: i) anterior transabdominal laparoscopic, ii) lateral transabdominal iii) retroperitoneoscopic lateral and iv) retroperitoneoscopic posterior. In a prospective randomized trial comparing lateral retroperitoneoscopic and lateral laparoscopic adrenalectomy, Rubinstein et al. could show that patient's convalescence time was halved by using the retroperitoneal approach (2.3 instead of 4.7 weeks) [14]. But, there were no differences in operating time, blood loss, analgesic requirement, hospital stay, conversion and complication rate. Dickson et al. compared two groups of patients with pheochromocytoma (n = 23) who underwent either posterior retroperitoneoscopic or lateral transabdominal adrenalectomy [13]. Time of surgery, blood loss, and hospitalization time were significantly shorter or reduced after posterior retroperitoneoscopic adrenalectomy, although these were the first patients retroperitoneally operated in Houston. In addition, the authors observed a highly significant lower pain load of patients that underwent retroperitoneoscopic adrenalectomy. Low postoperative pain after retroperitoneoscopic operations was also observed by other authors [15, 16]. A possible explanation could be the absence of injury to the peritoneum minimizing the risk of postoperative intraperitoneal fluid collections. Interestingly, when laparoscopically experienced surgeons have switched to the retroperitoneoscopic method, they also hold on to it [13, 17]. For retroperitoneoscopic approaches CO2 pressures up to 28 mmHg are needed in order to allow the creation of a sufficiently wide space. A wanted side effect of this pressure is the compression of small venous vessels resulting in a dry operation field. Walz et al. maintain that even in cases of an adrenal venous lesion no relevant bleeding could occur [7]. On the other hand high CO2 pressures may increase the risk of gas embolism. However, these problems were not clinically evident till now. Walz et al. listed tumors larger than 7 cm and a body mass index (BMI) of greater than 45 as contraindications for retroperitoneoscopic resection in their trails [7]. In these cases complete resection of adrenal tumors cannot be ensured due to the small retroperitoneal operating field.

To further reduce the morbidity of minimally invasive surgery, laparoendoscopic single site surgery (LESS) has been developed. LESS was first reported in 1998 for cholecystectomy [18]. Through the development of new techniques and instruments, such as multichannel single-access ports, novel curved instruments and thin flexible laparoscopes, LESS became also relevant for minimally invasive adrenal surgery. Authors reported LESS transumbilical adrenalectomy to be extremely minimal-invasive due to the virtually invisible surgical scar within the umbilicus [19–21]. However, LESS requires more advanced techniques and more experience from the surgeon because the surgical instruments are introduced adjacent and parallel to each other and the surgeon has a limited range of motion. Due to this, extra operation time is needed compared to a multiport laparoscopic procedure [22]. Walz et al. introduced a single access retroperitoneoscopic adrenalectomy (SARA) in order to minimize morbidity and improve cosmetics in the retroperitoneoscopic access [16]. In a case control study with 47 patients, which underwent SARA, the group reported significantly less pain and shorter hospital stay compared to the conventional retroperitoneoscopic adrenalectomy. However, SARA takes a significantly longer time to perform (about 15 min) [16]. Postoperative morbidity and complication rates were similar. Although Walz et al. highlighted SARA as a new milestone in minimally invasive endocrine surgery, the results of prospective randomized studies have to be shown [16].

Robotic-assisted adrenalectomy represents another interesting field of further development of minimally invasive adrenal surgery. The first robotic-assisted adrenalectomy was reported by St. Julien et al. in 2006 [23]. Nordenstrom et al. published a series of 100 robotic-assisted adrenalectomies using the DaVinci™ Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) [24]. The group argues that the DaVinci™ robotic system provides better 3D perception, a superior ergonomic working position for the surgeon, seven degrees of freedom of movement, motion scaling and tremor elimination [24]. In that series of 100 robotically assisted adrenalectomies the median console time was 88 min, decreasing in accordance with the learning curve of the technique [24]. In this series perioperative complication rates were comparable to previously published data. A systematic meta-analysis by Brandao et al. including 600 patients (277 robotic-assisted and 323 laparoscopic) showed no significant differences in conversion rate, operation time and complication rate [25]. In the laparoscopic group there was a significantly longer hospital stay and also a higher estimated blood loss. However, this meta-analysis included only one randomized clinical trial with low quality [25]. A further meta-analysis including 116 patients by Economopoulos et al. confirmed these findings [26]. On the other hand the group of Economopoulos et al. observed a significantly longer operation time for robotically assisted adrenalectomy. Brunaud et al. showed that after a learning curve of 20 cases, robotic-assisted adrenalectomy has similar perioperative outcomes compared to lateral transperitoneal adrenalectomy [27]. In year 2010, Berber et al. were the first who introduced robotic posterior retroperitoneal adrenalectomy in a series of 8 patients. They subjectively observed that dissection was felt to be easier with the robotic technique owing to the improved dexterity of the instruments [28]. Further published patient series, in which robotic posterior retroperitoneal adrenalectomy was performed for adrenal tumors, confirmed the safety and feasibility of the procedure [29–31]. Recently, Kahramangil et al. published the first study comparing posterior retroperitoneal and lateral transabdominal approaches in robotic adrenalectomy. The group found similar postoperative outcomes for both robotic approaches (regarding blood loss, conversion rate, length of hospital stay and 90-day morbidity). However, the posterior retroperitoneal robotic approach resulted in a significant shorter operation time (p = 0,005) and less postoperative pain (p = 0,001) [32].

In conclusion, despite all the methodological and substantive weaknesses of the comparative studies presented so far, it is clear that minimally invasive adrenal surgery is characterized by reduced perioperative morbidity and virtually no mortality. Here, current data suggest superiority of the retroperitoneoscopic approach. An assessment of the single access procedure appears to be premature. First results show that the perioperative pain load can be reduced further. The robotic processes are still in their early stages. Relevant advantages of these cost-intensive methods have not yet been apparent.

In the last century surgical treatment of pheochromocytoma was associated with very high mortality rates (up to 48%) due to intraoperative hypertensive crises [33]. For note, during surgery catecholamine surges of pheochromocytoma may exceed normal values by 1.000 to 1.500 times [34]. Since the introduction of the preoperative α-adrenergic receptor blockade, mortality rate has significantly declined (1%). However, till now, there is no evidence from randomised controlled trials regarding effectiveness of preoperative α-adrenergic receptor blockade [33, 35]. Furthermore, Walz et al. recently published a retrospective analysis of 303 patients and found no difference between patients with or without preoperative α-adrenergic receptor blockade regarding hemodynamic conditions and perioperative complications [36]. Significant historical improvement of mortality rates might be reasoned by many factors as utilization of laparoscopic/retroperitoneoscopic approaches, improved diagnostic, perioperative monitoring (e.g. invasive arterial blood pressure measurement (IBP)) and hemodynamic management (that allow better handling of hypertensive episodes intraoperatively) [37]. Despite the poor evidence situation, preoperative α-adrenergic receptor blockade is still recommended according to the Endocrine Society Clinical Practice Guideline and should be at least started 10–14 days before surgery [33]. Based on the data from Groeben et al. and lack of evidence, however, the general recommendation for perioperative α-adrenergic receptor blockade, as a prophylactic treatment, should be questioned. It should be also noted that the use of α-adrenergic receptor blockade is not without side effects. Beside α-adrenergic receptor blockade calcium channel blockers can be used as an add-on drug to further control blood pressure preoperatively. Generally, a target blood pressure of less than 130/80 mmHg is recommended based on retrospective data [33]. Coadministration of β-adrenergic receptor blockers might be necessary to control tachycardia after administration α-adrenergic blockers. In addition preoperative treatment should also include high-sodium diet and fluid intake to prevent hypotension after tumor removal [33]. Based on retrospective studies preoperative high-sodium diet and fluid intake reduce the risk of postoperative hypotension and also prevent orthostatic hypotension before surgery [33, 34]. During surgery IBP and central venous access are obligate in order to detect and treat hemodynamic instability (HDI). In a retrospective analysis, Kieman et al. identified increasing tumor size and open resection as risk factors for HDI [38]. In addition, open adrenalectomy was also associated with increased complications, use of postoperative vasopressors and hospital stay [38]. After resection blood pressure, heart rate and plasma glucose levels should be closely monitored for 24–48 h as hypertension/hypotension and rebound hypoglycemia are the major potential postoperative complication [33].

For pheochromocytoma and extraadrenal pheochromocytomas (paraganglioma) there are scarcely any comparative data comparing open versus minimally invasive surgery due to their rarity. Walz et al. have published the largest series of minimally invasive treated patients with pheochromocytoma and retroperitoneal extraadrenal pheochromocytomas in a prospective clinical study including 161 patients [39]. Here, tumor size ranged from 0,5 to 12 cm. The group showed that minimally invasive surgery - including laparoscopic and retroperitoneoscopic approach - for treatment of both adrenal pheochromocytoma and extraadrenal pheochromocytoma is safe and feasible. In a prospective randomized comparison of laparoscopic versus open adrenalectomy for pheochromocytoma including 22 patients, Tiberio et al. advocate the laparoscopic procedure due to significantly less blood loss, shorter operating time, and significantly shorter hospital stay [5]. Based on these data, minimally invasive adrenalectomy is recommended for surgical treatment of pheochromocytoma [39]. However, till now there are no prospective randomised studies comparing open versus minimally invasive adrenalectomy. According to the Endocrine Society Practice Guideline, invasive pheochromocytoma or tumors larger than 6 cm should be treated by open resection in order to ensure complete resection [33]. However, the recommendation regarding the tumor size should be critically questioned on the basis of available data [39–41]. Retrospective studies and experience from specialized centers showed that minimally invasive surgery for treatment of pheochromocytomas is safe and feasible regardless of tumor size [39–42]. The groups of Roe et al. al and Carter et al. showed that laparoscopic treatment of larger pheochromocytomas (>6 cm) is associated with similar operative time, blood loss, complications and recurrence rate as smaller ones [40, 41]. In addition, it must be mentioned at this point that – in contrast to cortical malignancies - tumor size of pheochromocytomas does not predict malignancy reliably [39, 43].

10–15% of pheochromocytomas are located extraadrenal and are defined as extraadrenal pheochromocytoma or paraganglioma. The risk of malignancy is 20–30% (compared with a 10% risk of malignancy for adrenal pheochromocytomas) [39, 44]. Extraadrenal pheochromocytoma may appear anywhere along the sympathetic chain mostly adjacent to the aorta at or from just above the level of the renal hilum to the aortic bifurcation. Walz et al. and Goers et al. showed that patients with extraadrenal pheochromocytoma also benefit from laparoscopic resection [39, 44]. Based on their data the authors state that laparoscopic resection should be the preferred surgical approach for treatment of extraadrenal pheochromocytoma [39, 44]. The most suitable minimally invasive procedure (laparoscopic versus retroperitoneoscopic) depends on the localization of the tumor. While tumors below the renal veins are more accessible for laparoscopic procedures, extraadrenal pheochromocytoma in the upper retroperitoneum (above the renal veins) can be well treated by the retroperitoneoscopic procedure [39].

Bilateral pheochromocytomas are observed in syndromic diseases (MEN2, von Hippel-Lindau (VHL)), patients with mutations in the succinate dehydrogenase complex subunit D (SDHD) gene or neurofibromatosis type 1 (NF1). Here, bilateral cortical sparing techniques have been successfully testes and increasingly performed by specialized centers [20]. In order to preserve normal function of the adrenal cortex the surgeon leaves a small amount (at least one-quarter to one third) of unilateral or bilateral adrenal tissue [20]. Here, minimally invasive surgery might be the best approach because it enables the best view and light to the adrenal gland. In addition, the retroperitoneoscopic approach allows bilateral adrenalectomy without patient repositioning, which decreases operation time.

In summery, minimally invasive surgery should be declined as standard treatment of adrenal and extraadrenal pheochromocytomas regardless of tumor size and localization. Even more, Kiernan et al. constitute that open surgery is a major driver of adverse perioperative outcomes [38]. However, due to the rarity of pheochromocytoma, experience with minimally invasive procedures is limited (mostly to specialized centers).

3 Pancreatic surgery

In year 1994, minimally invasive pancreatic surgery was first demonstrated by a report on laparoscopic pylorus-preserving pancreatoduodenectomy by Gagner and Pomp and by a report on laparoscopic pancreatic left resection by Cuschieri [45, 46]. Following this initial experiences, technical feasibility and safety of laparoscopic pancreatic surgery has been demonstrated by case reports, single and multicenter cohort studies and retrospective comparative studies [47–51]. However, the first published studies did not differentiate between various benign and malignant pathologies of the pancreas. This might be due to the initially low number of series and cases for individual pancreatic pathologies in the area of minimally invasive surgery [51]. Especially regarding the entity of pancreatic neuroendocrine tumors (PNET), the incidence is low (about 5% of all pancreatic tumors with an incidence of 2–3 per 100,000 individuals per year). Consequently, it is difficult to generate sufficient comparative data on minimally invasive surgery in the area of PNET.

Drymousis et al. reviewed studies conducted from 1994 to 2012 reporting on laparoscopic and open pancreatic surgery of patients with PNET. They analyzed eleven studies with a total of 906 patients including 10 retrospective studies and one prospective non-randomized trial. In summary, the laparoscopic method was associated with a significant lower overall complication rate, shorter length of hospital stay (about 5 days) with no differences in pancreatic fistula rates, operative time or mortality. Nine studies reported a conversion rate of 9–41% [51]. In a series of 49 patients from a single institution, Fernández-Cruz et al. additionally showed that laparoscopic pancreatic surgery is safe and feasible for malignant neuroendocrine pancreatic tumors [52]. In all resected PNET negative resection margins by the laparoscopic method could be achieved [52]. However, these studies did not clearly differentiate between different available laparoscopic procedures and different entities of PNET.

Patients with secreting PNET are mostly diagnosed at early stage of disease with small tumor sizes. Most secreting tumors are insulinoma, which are 80–90% benign. Due to their usually small size when diagnosed, parenchyma-preserving limited pancreatic resection or so called pancreatic enucleation (PE) is the approach to pursue [53]. PE has the advantage to preserve pancreas parenchyma and function. According to consensus and literature guidelines, PE provides the method of choice in tumors on or directly under the surface the pancreas with a distance to the main duct of at least 2–3 mm and a tumor size smaller than 2 cm [53, 54]. But, if a plane between the tumor capsule and the pancreatic parenchyma cannot be easily identified, resection is recommended instead of enucleation [55].

In contrast to secreting PNET, non-functional PNET represent a poorly understood group of pancreatic lesions that have more aggressive behavior [54]. According to consensus and literature guidelines, only non-functional PNET smaller than 2 cm in size with an absence of locoregional and distant metastases can be treated by enucleation [53, 54]. In contrast, a watch and wait strategy instead of surgical treatment can be proposed in selected patients, like high risk patients or elderly [53]. Surgical resection should still be recommended for young and healthy patients [53]. In contrast, there are data that provide a watch and wait strategy for young patients affected by MEN1 syndrome who have non-functioning PNET <2 cm [53, 56]. According to the ENETS Consensus Guidelines for Standard Care in NETs lymphadenectomy should routinely be performed for non-functional PNET larger than 2 cm. However, the differentiation of a benign lesion from a malignant lesion based on the size of the tumor should be executed with caution, as even small tumors can show malignant behavior and presence of lymph node metastases [54, 57]. In contrast, Yoo et al. suggest that the oncological significance of lymph node metastases in G1-non-functional PNET is overestimated, as they did not show any adverse effects on oncological outcome when lymph node dissection was dispensed with. So, the group claims that local lymph nodes dissection should not be recommended as routine procedure for G1-non-functional PNET [58].

Laparoscopic approach for PE was initially described by Ganger et al. [59]. Since then, series of clinical experiences described feasibility for treatment of PNET [54, 60]. However, clinical experience included mostly small series, due to the rarity of neuroendocrine pancreatic tumors eligible for laparoscopic PE. Zhang et al. reported the largest retrospective study comparing laparoscopic versus open PE for pancreatic neoplasm (15 laparoscopic PE and 22 open PE). For laparoscopic PE, they observed a significantly shorter operating time (about 38 min), lower estimated blood loss, shorter first flatus time and shorter hospital stay. Postoperative outcome, including morbidity, mortality, occurrence of grade B/C pancreatic fistula (20% for laparoscopic PE versus 36,4% for open PE) was similar among both groups. During the follow-up (median 47 months) no local recurrence or distant metastasis occurred in both groups [61]. It should be noted that there is a relevant risk for occurrence of pancreatic fistula after PE. In the literature, occurrence of pancreatic fistula after PE varies. Karaliotas et al. reported comparable occurrence of pancreatic fistula in open and laparoscopic PE [62]. In contrast, Sa Cunha et al. reported that pancreatic fistula rate was significantly lower in laparoscopic than in open PE [63]. Costi et al. retrospectively analyzed the outcome of patients with PNET that underwent laparoscopic PE either in the pancreatic head or in the pancreatic tail. His group showed that morbidity rate and operation time was superior for laparoscopic PE of the pancreatic head [64]. Confirming these results, Zhang et al. showed that laparoscopic enucleation of lesions in the pancreatic head provided more favorable perioperative outcomes [61]. For reported and cited studies it has to be noted, that most of them included only the initial experience of laparoscopic PE. So, superiority of laparoscopic PE might be confirmed with further experience.

For PNET of the pancreatic body and tail, laparoscopic distal pancreatectomy (LDP) can be an alternative. However, to our knowledge there are no data comparing laparoscopic PE versus LDP for small size tumors at or just below the surface of pancreas. Especially in cases of potential malignancy, large tumor size or proximity to the main pancreatic duct, LDP is the method of choice for lesion located in the pancreatic body and tail. Particularly, distal pancreatectomy (DP) is the most commonly used surgical procedures completed by the laparoscopic method at present. The laparoscopic approach is relatively straightforward without any reconstruction of the alimentary tract and can be easily performed within a short time [65]. The approach of LDP was first described in 1994 by Cuschieri [46]. In the following years, case reports, series reports, retrospective analysis and cohort studies suggested that LDP is feasible and safe for the treatment of both benign and malignant tumors of the distal pancreas [65–67]. Regarding resection margins and lymph node yield in the area of oncologic surgery, data show that LDP is at least non-inferior compared to open distal pancreatectomy [66]. Venkat et al. analyzed 18 studies including 1814 patients comparing open versus laparoscopic distal pancreatectomy. Here, overall complication rate was lower for the laparoscopic approach. Regarding operation time, margin positivity, occurrence of pancreatic fistula and mortality, there was no difference in both approaches [65]. De Rooij et al. analyzed nationwide data from the Netherlands comparing laparoscopic and open distal pancreatectomy for benign and malignant pancreatic tumors. In this analysis 64 patients that underwent laparoscopic surgery were included. They demonstrated the superiority of the laparoscopic approach regarding occurrence of major complications and length of hospital stay. Additionally, the survey showed that 85% of surgeons welcomed the laparoscopic approach [67]. However, data comparing laparoscopic and open distal pancreatectomy were mainly derived from retrospective analysis and cohort studies and after matching patients, differences of outcome and hospital stay were not statistically significant [67]. For this reason, the group argues that superiority of the laparoscopic procedure has not yet been proven. Additionally, the group refers to case mixed studies, which have not confirmed the presumed benefits of LDP compared to the open approach [68, 69]. In order to further investigate the safety and feasibility of LDP, the group is currently conducting a prospective randomized trial comparing LDP versus the open procedure (LEOPARD-Trial) [70]. However, the LEOPARD trial and other cited studies for distal pancreatectomy relate not only to PNET alone, but also to other pancreatic pathologies as carcinoma. Because of their rarity, there are virtually no comparative studies that consider the operative and perioperative outcome separate for PNET. However, since the LDP is one of the most frequently used surgical procedures for the treatment of PNET, the evidence of this procedure has been examined more closely in this review, which also included other pathologies of the pancreas.

Patients with insulinoma in context of MEN1-syndrome can also benefit from laparoscopic approaches. However, laparoscopy can also lead to failure of treatment. Because of loss of tactile sensation, multiple tumors within the pancreatic parenchyma presumably cannot be identified. Of note, virtually all patients with MEN1-syndrome have multiple lesions and additional non-functional PNET [71]. Here, both preoperative endoscopic and intraoperative ultrasonography are indispensable. For single lesions located in the pancreatic head and pancreatic tail, spleen preserving distal pancreatectomy combined with PE could be declared as a standard approach with published cure rates from 83%–100% [57].

According to the literature aggressive therapy should be performed for malignant NET, including lymphadenectomy and even resection of liver metastasis [53]. For PNET located in the pancreatic head or the duodenum, which are not suitable for enucleation, pylorus-preserving pancreatoduodenectomy (PPPD) has to be performed. However, during the laparoscopic approach, there are difficulties and challenges in both the resection and the reconstruction phase. Because of this, laparoscopic PPPD is currently only performed by highly specialized surgeons in highly specialized centers. In addition, the learning curve described in the literature is relatively shallow [72]. Retrospective analysis showed feasibility of laparoscopic PPPD with complication rates comparable to the open procedure. Some data even suggest that advantages of laparoscopic approaches such as less pain, shorter hospital stay, and quicker recovery are the same for laparoscopic PPPD [50, 73–75]. However, until now there are no prospective randomized trials comparing the laparoscopic versus the open procedure. Due to limited data, the role of laparoscopic PPPD in the area of PNET remains to be elucidated. When comparing open versus laparoscopic pancreatic surgery in the area of PNET following postoperative complication and mortality rates should be regarded as minimal. Acceptable rates according to ENETS Consensus Guidelines for Standard Care in Neuroendocrine Tumors are: postoperative complication rate of 50% with a mortality rate of 5% for pancreatoduodenectomy and 1% for distal pancreatectomy [53].

Finally, total duodenopancreatectomy is one of the most radical and invasive procedures for the curative treatment of a malignant neuroendocrine tumor of the pancreas. This procedure can be necessary for curative treatment of multifocal neuroendocrine pancreatic tumors in patients as it might occur in syndromic patients of MEN-1 and von Hippel-Lindau syndrome. In individual cases, a laparoscopically assisted minimally invasive total pancreatectomy has been successfully used to treat multifocal PNET [48]. However, there are no comparative data on laparoscopic total pancreatectomy in the area of PNET.

PNETs occur as hereditary multi-organ tumor disease next to MEN1 also in von Hippel-Lindau disease (VHL). Patients and physicians are confronted with a multi-disciplinary challenge, since in VHL hemangioblastomas occur in the cerebellum, brain stem, spinal cord and retina, but also renal clear cell carcinomas and pheochromocytomas are frequent. A timely well adjusted and a distinct decision for an adequate approach is essential. The cut-off for the risk of metastases due to PNETs are lesions of 30 mm or more [76]. Surgical techniques are not different to those used in sporadic PNETs. Reported series are limited, since VHL-associated PNETs are rare, but endoscopic removal has been reported [77].

In summary, the majority of published studies share a limited experience without long-term follow-up. LDP and laparoscopic PE are the most commonly performed procedures for treatment of PNET. Both procedures might be a promising treatment for insulinoma or non-functional PNET. However, due to the rarity of PNET, it may be difficult to provide valid data based on prospective randomized data analyzing individual procedures for treatment.

Leading to a new era in minimally invasive pancreatic surgery, robotic-assisted distal pancreatectomy was first reported in 2002 by Melvin et al. [78]. Additionally, his group reported the first case study using the DaVinci™ robotic surgical system for resecting of a PNET. For distal pancreatectomy, the robotic assisted approach is believed to be helpful e.g. increasing spleen-preservation rate, due to better depth perception (3D), seven degrees of freedom of movement, motion scaling and tremor elimination [79–81]. Regarding time-consuming pancreatic procedures, superior ergonomic working position of the surgeon and tremor compensation represents a further advantage for robotic-assisted surgery.

Zhang et al. analyzed 43 patients undergoing robotic-assisted distal pancreatectomy for treatment of PNET and compared them with 31 patients that underwent LDP for treatment of PNET in a retrospective design. Operating time, length of resected pancreas, postoperative length of hospital stay and rates of conversion to open distal pancreatectomy, pancreatic fistula, transfusion and reoperation were not statistically different [82]. They also showed that robotic-assisted distal pancreatectomy was associated with a significantly higher overall spleen preservation rates (79.1 vs. 48.4%, $P = 0.006$). Additionally, oncological outcomes in this series were superior for the robotic-assisted distal pancreatectomy group with a larger lymph node harvest for G2 and G3 PNET (3.5 vs. 2, $P = 0.034$) [82]. Daouadi et al. retrospectively analyzed the clinical data of 124 patients between 2004 and 2011 and confirmed these findings. Additionally, they found a lower rate of conversion to open distal pancreatectomy for robotic-assisted distal pancreatectomy (0% in RDP vs. 16% in LDP; $P < 0.05$) and shorter operating time (293 ± 93 min in RDP vs. 372 ± 141 min in LDP; $P < 0.01$), respectively [80]. However, for patients scheduled for splenectomy, robotic-assisted distal pancreatectomy had no advantages over LDP regarding intraoperative and postoperative outcomes. [80] In contrast, Lai et al. found that robotic-assisted distal pancreatectomy required a longer operation time than LDP (221.4 min vs. 173.6 min; $P = 0.026$) [83]. Similar results could be demonstrated by Ryan et al., who performed a prospective observational study [84].

In contrast, the experience of robotic-assisted PPPD is limited. In centers with appropriate expertise, the perioperative mortality was between 0 and 5%. Pancreatic fistula occurred between in 0 and 35% of cases, which corresponds essentially to the results of open surgery [85, 86]. Boone et al. examined the learning curve and showed a significant improvement in conversion rate after the first 20 performed procedures (35% vs. 3.3%). Additionally, they found significantly lower rates of pancreatic fistula after 40 performed procedures (27.5% vs. 14.4%). After overcoming the learning curve, a conversion rate of 3.3%, a mortality of 3.3%, a grade B/C pancreatic fistula rate of 6.9%, an R0 resection rate of 91.4% and a mean lymph node yield of 26 was observed [87].

In conclusion, robotic-assisted pancreatic resection is a promising technique for overcoming the limitations of laparoscopic surgery. The experience with the method is limited, especially with regard to PNET. Significant long-term data are missing. The perioperative results published so far are at least equal to those of open and laparoscopic surgery, with the restriction of a selection bias and the learning curve. Additionally, it has to be noted that the costs of the robotic surgery systems are still high, which could be one of the greatest clinical obstacle.

4 Intestinal surgery

Due to their rarity, the surgical recommendations for the treatment of NET of the intestinal tract are mainly based on the experiences of specialized surgeons and less on prospective randomized trials. With regard to the role of minimally invasive surgery for treatment of intestinal NET, there are only very few comparing open to minimally invasive surgery. The following is an overview of the possibilities of the minimally invasive surgical approach to the duodenum, the small intestine and the large intestine.

Duodenal NET accounts for about 5% of all NET of the gastrointestinal tract [88]. Due to their low rate of distant metastasis (9–15%), they have an excellent prognosis [88]. For small tumors (<1 cm) endoscopic resection is recommended [89]. However, for tumors between 1 and 2 cm there is no clear recommendation. For those endoscopic and surgical resection can be discussed. Another treatment option was presented by Tsujimoto et al. and Abe et al. [90, 91]. They declare that there is a high risk of perforation when performing endoscopic mucosal resection for carcinoid of the duodenum, especially when achieving sufficient surgical margins. The group introduced an endoscopic full-thickness resection of the duodenum under laparoscopic control. In detail, after laparoscopic mobilization of the duodenum, the duodenal serosa at the site of the lesion was suctioned under laparoscopic observation. Then, a full-thickness resection of the duodenum was performed. After confirming that margin negative resection has been achieved, the duodenal defect was sutured by laparoscopic hand-suturing technique. A radical resection should always be considered for tumors >2 cm, even in case of distant metastases [92]. Pylorus-preserving pancreatectomy is the procedure of choice. The role of minimally invasive surgery for pylorus-preserving pancreatectomy has been already presented above.

40% of all gastrointestinal NETs are located in the jejunum and ileum, most commonly in the terminal ileum. However, 25–30% contain multiple lesions. A carcinoid syndrome is only present in 5–10% of small bowel NET. Small tumors of <1 cm in size have a risk of 5% for lymph node involvement [92]. In contrast, tumors larger than 1 cm often metastasize. Surgical resection is the treatment method of choice for small bowel NET. Because of a high risk for lymph node metastasis even in small tumors, central lymph node resection should be always performed [92]. In addition, simultaneous cholecystectomy is recommended to avoid possible side-effects from adjuvant antineoplastic therapy [93]. Patients with unresectable liver metastases also benefit from an resection of the primary tumor [94]. The role of laparoscopy in the therapy of small bowel NET can be regarded as low, especially since there are hardly any studies on this. In the course of the operation, a minilaparotomy must be usually performed to remove the tumor and the lymph nodes from the abdomen. However, NET located in the jejunum or ileum can be easily resected through a minilaparotomy by itself and laparoscopy might be not necessary at all. In addition, the whole jejunum and ileum can be easily examined by the same minilaparotomy in order to manually and visually detect further lesions. However, laparoscopy may be used at the beginning of an operation to examine the abdominal cavity, especially the liver.

NET of the appendix are often diagnosed accidentally in the context of appendectomies, which are carried out on the basis of the suspicion of an acute appendicitis. Here, the incidence of NET as a random finding is about 0.3–1.1% [95]. Because NET of the appendix are often located in the tip, the whole tumor is often excised with sufficient surgical margins, so that often no further therapy is necessary [92, 96]. Suarez-Grau et al. analyzed 42 patients with appendiceal carcinoid that underwent appendectomy for suspected acute appendicitis. 7 of these patients required colon resection due to dissemination or colonic involvement. The 5-year survival was over 95% with no recurrence, emphasizing that appendectomy is a sufficient surgical treatment [97]. At this point, it is assumed that laparoscopic appendectomy is preferable to the open procedure although there are few data on open versus laparoscopic appendectomy for treating NET of the appendix. In a retrospective analysis of a series of 39 patients, Bucher et al. could show that laparoscopic appendectomy is safe with similar long-term results compared to those of conventional appendectomy [98]. However, tumor sizes larger than 2 cm, tumors located at the base of the appendix, infiltration of the mesoappendix, goblet cell carcinoids, Ki-67 index >2%, angio- or neuroinvasion or involved surgical margins after appendectomy, should be followed by oncologic right-sided hemicolectomy [92, 96, 99]. However, high level evidence as long-term longitudinal prospective studies is missing [96]. Right-sided hemicolectomy can also be performed laparoscopically, as shown for adenocarcinoma of the colon being as good as, if not superior, to the conventional open approach [100–103]. However, there are only few cases published, in which laparoscopic right-sided hemicolectomy was the surgical treatment for NET of the appendix [96, 104, 105].

Rectal neuroendocrine tumors are the third most frequent NETs with 12.4% [106, 107]. Tumors smaller than 1 cm can usually be resected by endoscopic procedures and have an excellent prognosis. Conventional transanal excision, transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS) are available methods. In the case of TEM, the operation area is shown endoscopically by a wide-lane rectoscope. The rectoscope is connected to the operating table via a support arm system so that a stable exposure of the operating field is achieved. Up to three surgical instruments can be inserted simultaneously. Prerequisite for TEM is a constant gas expansion during the entire operation by an automatic, pressure-controlled gas insufflation. Moore et al. retrospectively analyzed 171 patients with different rectal neoplasms that underwent either TEM or conventional transanal excision. They could show that TEM was more likely to yield clear margins and a non-fragmented specimen compared with conventional transanal excision. In addition, recurrence was less frequent after TEM [108]. This might be due to improved TEM instruments, better exposition and improved visibility [109]. In 2010, Atallah et al. were the first to introduce TAMIS as a method for resection of rectal tumors [110]. In this method, a Single Incision Laparoscopic Surgery (SILS)-Port is introduced transanally. After a pneumorectum has been established via the SILS-Port system, surgery can be performed via usual laparoscopic instruments. One of the advantages of this method is that the standard laparoscopic instruments can be used, thereby saving costs. In addition, visualization and dissection of the entire circumference of the rectum are possible. Recent studies confirmed safe and effective results for TAMIS regarding early and oncologic outcomes with an R1 rate of 5,6% [109, 111–113]. The best method for closure of the rectal wall defect after a full-thickness excision is still debated. In a multicenter trial Hahnloser et al. compared morbidity and incontinence rates between patients undergoing either the suture or a left-open technique after resection of rectal tumors by TAMIS. The group failed to demonstrate any significant differences between the 2 groups [114]. However, there are no comparative clinical studies or randomized control trials comparing TEM versus TAMIS, especially with regard to rectal NET. Janebdar et al. recently published a video report of TAMIS for excision of rectal carcinoid and showed the feasibility this method in the area of rectal NET [115]. In the case of a tumor size of 1–2 cm without infiltration of the muscularis propria, the therapy is controversially discussed in the literature [116]. Guidelines consider a local resection for patients with low mitotic rate (<2/10 high power field (HPF)) and without infiltration of the muscularis propria acceptable [117]. Scherubl et al. recommend a local resection in tumors with no risk factors up to a size of 1.5 cm [118]. If the clinician decides in favor of a local tumor removal in these patients, a full-thickness resection must be carried out using conventional transanal excision, TEM or TAMIS, depending on the size of the tumor and expertise. Because of the low evidence in rectal NET of this size, the patient must be included in the therapy decision. However, for tumor sizes larger than 1 cm in size, radical surgical resection is generally recommended, because of a high metastasis risk of up to 70% [106, 117]. If endoscopic therapeutic options are excluded, anterior resection of the rectum or abdomino-perineal rectum extirpation should be performed. Comparative data on the laparoscopic versus the open procedure in rectal resection are manifold in colorectal adenocarcinoma. However, there is a general consensus that the results can also be transferred to NET [92]. A Cochrane review by Breukink et al. found that laparoscopy for rectal carcinoma provides less blood loss, less pain and shorter hospital stay [119]. A prospective randomized multicenter study including 1.044 patients with rectal cancer by Bonjer et al. considered laparoscopic rectal surgery as the best option for the surgical treatment of rectal cancer due to less blood loss, quicker recovery, less pain, shorter hospital stay, and equivalent oncological outcomes [120]. Jeong et al. confirmed these findings in a randomized controlled trial [121]. To our knowledge, Takatsu et al. were the first who have analyzed short- and long-term outcomes of laparoscopic total mesenteric excision for NET of the rectum [122]. In a retrospective analysis they have analyzed 77 patients with rectal NET that underwent laparoscopic rectal resection with total mesenteric excision (TME). Anastomotic leakage occurred in 6,5%. Anal preservation was achieved for all patients. There were no perioperative deaths. The 3-year overall survival rate was 97,8% [122]. Regarding the robotic-assisted approach, Kim et al. recently published their results of a phase II prospective randomized controlled trial comparing robotic-assisted versus laparoscopic surgery for rectal cancer. They found no significant differences with regard on TME quality, mortality, morbidity, bowel function recovery and quality of live. There was a significant better sexual function 12 months postoperatively in the robotic-assisted group [123]. The respective advantages and disadvantages of robotic surgery have already been mentioned. Again, cost efficiency must be considered as a disadvantage.

5 Liver metastasis surgery

Clearly, there is a role for hepatic surgery in metastatic NET. The role of minimally invasive hepatic resection in metastasized NET is characterized by the same principles as in open resection. At present, two main "groups" of hepatic metastases with clearly defined indications have evolved: colorectal and neuroendocrine [124–129]. For all other secondary liver malignancies there is an ongoing debate regarding patient selection.

Generally, laparoscopic liver resection has to follow the basic surgical principles for open liver resection. There are three criteria for resectability in hepatic surgery: oncologic, technical and functional resectability. While the oncologic resectability is undisputed as stated above, the technical resectability (mainly limited by anatomic structures such as large vessels or bile ducts) has to be individually determined before deciding to indicate minimally invasive surgery. In some instances high vascularization of metastases can be a risk factor for intraoperative bleeding and laparoscopy therefore must be carefully indicated.

According to Frilling et al. there are three patterns of metastatic spread of NETs to the liver: single metastasis of any size (type I); isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved (type II); and disseminated metastatic spread, with both liver lobes always involved or a single lesion of varying size and virtually no normal liver parenchyma (type III) [124].

The following forms of laparoscopic resections address mostly type I metastases: Atypical resection and segmental resection. Especially suitable for laparoscopic resections are subcapsular lesions, lesions in segment 1, segments 2 and 3 (left lateral segment), segments 4b, 5 and 6. Furthermore also central lesions and right cranial segments 7/8 have been shown to be accessible via minimally invasive procedures [130]. For large type I or some type II lesions, anatomic resections such as right hemihepatectomy (segments 5–8) and left hepatectomy (segments 2–4) can technically be carried out laparoscopically under routine circumstances. For all large tumors or tumors involving both liver lobes functional resectability becomes crucial: Generally, in a totally healthy liver up to 75–80% of liver volume can be resected. In patients with a long history of chemotherapy (as mainly seen in colorectal metastases) the remaining liver remnant has to be greater than 40% [131]. Lastly, in cirrhotic livers (mainly seen in association with hepatocellular carcinoma) the liver remnant has to be larger than 50% together with the absence of ascites or portal venous hypertension to perform save surgery. In cases with small future liver remnant (which can be easily determined preoperatively using CT planimetry) even laparoscopic two-stage resections [132, 133] or so-called „*in situ* split "resections have been described [134]. The unifying principle in these concepts is to wait for liver regeneration before resection of the remaining tumor e.g. in the contralateral lobe in a second stage operation.

In summary, functional resectability can be achieved using the aforementioned techniques in type II lesions because enough healthy liver parenchyma is present. In type III lesions a sufficient reserve of functioning parenchyma is not present. Type III lesions therefore have to be regarded as unresectable.

From a scientific point of view, specific data on laparoscopic resection for NET liver metastases are scarce. Only one study focuses exclusively on the open versus laparoscopic approach in neuroendocrine metastases: [135]. More data on the efficacy of a laparoscopic approach can be derived from pooled analyses after the laparoscopic resection of non-colorectal liver metastases, which include NET as primary tumor origin [136, 137]. None of them have shown that NET hepatic metastases have inferior outcomes after laparoscopic surgery compared to open surgery.

There is one drawback when treating NET liver metastases with minimally invasive surgery: It is their detectability during surgery. Clinically, neuroendocrine liver metastases have a different appearance on CT, MRI and PET scans compared to e.g. colorectal liver metastases. This translates also in a different macroscopic appearance during surgery. In many instances they are difficult to visualize even using modern HD laparoscopic equipment. Since tactile feedback is missing in laparoscopy (e.g. the surgeon cannot "feel" the lesion with his fingers) laparoscopic intraoperative ultrasound is mandatory. Even using high-resolution probes, not always all preoperatively diagnosed lesions can be visualized during laparoscopy. Contrast enhanced ultrasound (CEUS) today is not yet standard of care during intraoperative imaging, although promising results have been published [138]. Hence, if there is a discrepancy between preoperative and intraoperative imaging, it is still advisable to convert to open surgery providing better assessment of resectability mainly by manual palpation.

On the other hand, if the surgery is intended to remove a single specific large lesion for amelioration of symptoms ("debulking"), patients may especially benefit from the minimally invasive approach. Not only by reduced postoperative pain and hospital stay, but also because repeat liver resections are greatly facilitated if postoperative adhesions are minimal due to a laparoscopic initial approach. The feasibility of repeat surgery in recurrent intrahepatic metastases was recently described by Spolverato et al. [139].

Much like in colorectal cancer, the laparoscopic approach can be applied in simultaneous resections of the primary and also for the metastasis. So simultaneous minimally invasive treatments of the primary and the metastasis in select cases are no contradictions.

As has been shown for other non-colorectal liver metastases, laparoscopic liver resections, in the hand of an experienced team, can achieve favorable perioperative results without compromising long-term benefit. Surgical criteria of technical, functional and oncological resectability have to be respected. Thus, if technical contraindications to a minimally invasive approach exist, open surgery must always be considered.

6 Conclusion

Today, minimally invasive surgery plays a relevant role in treatment of NET. Even more, according to current data and guidelines laparoscopic procedures should be clearly preferred for some entities of NET (in contrast to the corresponding open procedure). Laparoscopic surgery clearly provides advantages in terms of postoperative convalescence, extent of pain, length of hospital stay, patient's satisfaction and occurrence of incisional hernias, while preserving surgical-oncological principles. Due to the rarity of NET, comparative data on minimally invasive surgery versus open surgery are scarce and the generation of new data on the basis of prospectively randomized trials is made more difficult. Consequently, many developments in minimally invasive therapy of NET are based on data and experience gained from other tumor entities (e.g. adenocarcinomas) and transferred to NET. In particular, this is true for pancreatic, liver, and colorectal surgery.

In the future, robotic-assisted surgery could overcome existing limitations of laparoscopic surgery. Robotic-assisted surgery provides better depth perception (3D), an ergonomic working position for the surgeon, seven degrees of freedom of movement, motion scaling and tremor elimination. However, the robotic processes are still in their early stages and relevant advantages of the cost-intensive method have not yet been apparent.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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