Technical aspects of paediatric robotic pancreatic enucleation based on a case of an insulinoma

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Background: Insulinomas are rare insulin-producing pancreatic neuroendocrine tumours leading to severe episodes of hypoglycaemia. Surgery is the predominant curative therapy.

Methods: We report here the first paediatric case of an insulinoma of the pancreatic body resected completely robotically under ultrasound guidance in a 10-year-old male with multiple endocrine neoplasia type 1. The port set-up was adapted for the narrowed dimensions of the paediatric peritoneal space. We comment on technical key steps for the organ-preserving procedure that was performed in close proximity to critical anatomic structures, with supporting video. Preoperative diagnostics, including endoscopic ultrasound, to determine surgical management are highlighted.

Results: Following an uneventful post-operative course, the boy was discharged on day 11 with normalised glucose-metabolism. A pseudocyst developing after 4 weeks was treated with endoscopic stenting.

Conclusions: The applicability of a robotic surgical system in limited space conditions such as found in the paediatric abdominal cavity is demonstrated here for pancreatic surgery.

Abstract
1 | INTRODUCTION

Insulinomas are rare neuroendocrine neoplasms of the pancreas with a prevalence of one to three cases per million per year. Due to uncontrolled insulin secretion, patients typically present with symptoms of hypoglycaemia, neuroglycopenic symptoms and symptom relief with glucose administration. The incidence of multiple endocrine neoplasia type 1 (MEN 1) is one in 30,000 people. MEN 1-associated tumours mainly occur in three sites: pituitary and parathyroid glands and foregut neuroendocrine tissue. The mean age of symptomatic insulinoma in MEN 1 is the third decade of life. The occurrence of symptoms during childhood is rare.

Localisation of the tumour by computed tomography (CT) is the preferred initial option followed by endoscopic ultrasound (EUS) or 68Ga-DOTATOC PET-MRI.

The predominant curative therapy is surgical resection, especially for solitary lesions. Most insulinomas can be enucleated because of a surrounding capsule. The surgical approach for these tumours using minimally invasive techniques, including laparoscopy or robotic technology, is promising. At present, such procedures are only established in a limited number of hospitals worldwide and rarely reported in the current literature particularly due to the low incidence of hormone-active pNETs. However, with increased experience and availability of robotic systems in visceral surgery, minimal access strategies are gaining wider acceptance for the surgical treatment of pNETs. Robotic surgery in children is uncommon and mainly used in paediatric urology. Experience with robotic pancreatic surgery in children is rare.

As a centre with extensive experience in the surgical management of congenital hyperinsulinism and solitary insulinomas, we report here the first case of a paediatric insulinoma of the pancreatic body with complete robotic excision in a 10-year-old boy.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and consent to participate

According to local ethical regulations (Ethics committee of the Heinrich Heine University, Düsseldorf, Germany) ‘case reports are not prospectively planned research projects on or with people, but retrospective case descriptions of medical actions. Therefore, the ethics committee is not responsible for evaluating case reports’ and consequently is waiving the necessity of an ethical approval for case reports. Written informed consent for publication was obtained from the patient’s parents.

2.2 | The case

A 10-year-old boy, 159 cm, 46 kg, suffered from an absence-like condition in the morning, 1½ years before presentation. After breakfast, the symptoms vanished. Another event was a confused state of mind after a day of normal school activity and football training in the afternoon but without a meal. The father had tumours surgically resected in the pituitary gland and parathyroid gland and was subsequently diagnosed with MEN 1. The boy inherited the genetic mutation c.473C>A p (Ala158Asp) from his father.

2.3 | Preoperative diagnostics

Sonography and MRI alone were inconclusive but because of the suspected MEN 1 and fasting symptoms the boy was referred to DOTATOC-PET MRI at a specialised centre. A suspicious region of about 1.5 cm in diameter with high metabolic activity was detected in the pancreatic body (Figure 1A) and the boy was referred to our clinic of paediatric surgery.

To define the precise surgical anatomy, transabdominal sonography and EUS were used by the gastroenterologist with the surgical team in the endoscopy suite. Detailed anatomical positioning of the insulinoma in relation to the landmark structures was demonstrated. Whereas transabdominal ultrasound examination was not suitable to show the lesion, EUS was superior in determining the Insulinoma in its dimensions as well as its association to the surrounding vital structures such as visceral vessels and the pancreatic main duct. Upper endoscopy (Olympus GF UCT 180) and EUS (with 7.5 MHz) were uneventfully performed under general anaesthesia. A single solid lesion (diameter 15 mm), with a slightly hyperechogenic pattern, was clearly detected in the body of the pancreas, positioned ventral to the splenic vein, with a minimum distance of 3–4 mm away from the pancreatic main duct and a minimum distance of 5–7 mm from the superior mesenteric vein (data were not shown). The sharp outer border of the lesion suggested a capsule. The surrounding pancreatic tissue was compressed without signs of infiltration. Pancreatic duct diameter was normal (2 mm) in the entire organ. Colour Doppler imaging revealed significant arterial vessels surrounding the lesion (Figure 1B).

2.4 | Robotic system and surgical technique

Surgery was performed with the DaVinci Xi® system (Intuitive Surgical) which is connected to a TruSystem® 7000dV OR-table (TRUMPF Medizin Systeme) enabling integrated table motion without necessity...
of detaching the robotic device. Intraoperative Doppler ultrasound was used, with a Rob12C4 Robotic Transducer ultrasound probe (BK Medical) with a flexible wired head, introduced via the assist port and positioned and angled with the robotic controlled ProGrasp clamp. Instead of a horizontal supraumbilical straight line we used a V-shaped arrangement of the four robotic ports (4 mm × 8 mm; Figure 2A) to adopt the shorter distances of anatomic landmarks on the abdominal surface to intra- and retroperitoneal structures such as stomach, transverse colon and ultimately the pancreatic body in the paediatric abdomen as compared with adults’ anatomy. Between port 1 on the right upper abdomen and port 2 located 3–4 cm more medially, a 12 mm assist trocar was placed infra-umbilically (Figure 2A). All ports were positioned with a distance of 6.5–7.5 cm to each other. Pneumoperitoneum was set to a pressure of 9–10 mmHg.

The patient was positioned in an 11° head down and side-neutral orientation on the OR-table providing an ideal position for exposing the pancreas subsequent to opening the lesser sac. The dorsal gastric wall was temporarily fixed to the abdominal wall with a monofil suture retracting and opening up the lesser sac in ventro-cranial direction (video). Further, the latter manoeuvre avoided unnecessary occupation of one of the three robotic instruments for gastric retraction enabling superior handling of the pancreas and its surrounding structures. Next, the pancreas was completely exposed ventrally. Further, the caudal rim of the pancreatic body region was dissected exposing the supermesenteric and splenic vein as well as the supermesenteric artery. Dissection of the layers and transection of the insulinoma covering pancreas parenchyma was mainly performed with the monopolar scissor. Isolated vessels were electrically sealed with the bipolar Maryland-clamp prior to transection.

As expected, a protrusion of the pancreatic body next to the superior mesenteric vein to the left and ventral of the splenic vein was found. With the intraperitoneal ultrasound probe, this protrusion was further examined (Figure 2B and video). Preoperative assessment of the pancreatic lesion determined by EUS was confirmed including proximity to the main pancreatic duct and neighbouring major vascular structures (Figure 2C and video). The lesion was correlated to the visible pancreatic surface defining the access point for pancreatic dissection.

To ease tilting and lifting of the lesion, a monofil z-suture was placed grasping the capsule of the insulinoma (Figure 2D and video). The latter suture served as a handle for the grasper so avoiding taking hold of the tumour capsule and thus a lower chance of its rupture. For separation and continued mobilisation of the encapsulated insulinoma, we adopted technical lessons learned during open procedures of isolating insulinomas. In that respect, tumour isolation was mainly achieved utilising the tip of the Maryland clamp and the scissor as blunt dissection devices rather than for cutting the tissue (video). During the preparation of the pancreas and especially in the course of enucleation of the insulinoma along the capsule, minimal electric power was used. Subsequent to full mobilisation, the specimen, contained within a bag, was removed through the assisting trocar incision without extending it. After securing local haemostasis, a 16Ch silicon Robinson drain was placed behind the stomach next to the area of pancreatic excision. The key steps of the procedure are shown in the supplemental video to this article (link: https://youtu.be/-mtDzitYgtI).

3 | RESULTS

3.1 | Clinical course

Total console time was 110 min. Estimated blood loss was minimal. The boy was admitted routinely to the intermediate care ward. He recovered quickly without post-operative pancreatic fistula. Preoperative fasting insulin level in the morning was 7.2 μU/l (reference:
3–17 µU/l), and the blood glucose level was 46 mg/dl (reference fasting range: 65.0–100.0 mg/dl). Post-operative fasting blood glucose level was 95 mg/dl. Insulin was not measured post-surgery as preoperative values were normal. The drain was removed on post-operative day 4 and the patient was discharged 11 days after surgery. Blood sugar levels stayed normal since completion of the surgery. The patient developed a small symptomatic pseudocyst presenting with slight abdominal pain at the site of resection, diagnosed 4 weeks following pancreatic surgery, which was managed with trans-gastric drainage. Dislocation of the trans-gastric stent resulted in recurrence of the cyst which was subsequently drained by endoscopic stenting of the pancreatic duct. The boy went back to school after 4 days of hospitalisation. The stent was removed after 8 weeks and on a routine check, without symptoms, the pseudocyst was not detectable.

3.2 | Histopathology

The frozen section procedure confirmed the diagnosis of an insulinoma with a minimal capsule and R0 resection. In the final pathological evaluation, the macroscopic solitary, round, well-demarcated tumour was 17 mm in diameter (Figure 3A). Microscopically, the tumour showed a trabecular growth pattern (Hämatoxylin-Eosin-staining; Figure 3B) with a Ki-67 proliferation index of 8% (data were not shown) and demonstrated rare mitotic figures (1/10 high power fields with a diameter of 0.55 mm). The immunophenotype was characterised by strong intensity for synaptophysin (data were not shown), moderate intensity for chromogranin A (Figure 3C) and varying intensity for insulin (Figure 3D). Taken together, this histopathological pattern resulted in the diagnosis of a functional, well differentiated pancreatic
neuroendocrine neoplasm, PNet G2 (=insulinoma) with a TNM-Classification of Malignant Tumours of pT1, L0, V0 and no residual tumour (R0).

4 | DISCUSSION

Insulinoma as the predominant type of pancreatic NeuroEndocrine Tumor (pNET) has the highest incidence in the fifth and sixth decades with a median of 47 years of age and occurs extremely rarely in paediatric patients.\(^{11-13}\)

4.1 | Pre- and peri-operative diagnostics

Imaging is critical not only to support the diagnosis of an insulinoma but also for localisation and to plan the surgical strategy. Here, we applied three advanced methods for localisation of the lesion: 68Ga-DOTATOC PET/MRI, EUS and robotically guided intraoperative ultrasound. A study on 141 pNET patients demonstrated that the overall sensitivity, specificity and accuracy of 68Ga-DOTATOC PET/CT for diagnosing patients with pancreatic neuroendocrine tumours were 86%, 79% and 85%, respectively.\(^{14}\) In addition, this method was demonstrated to be highly sensitive for the identification and exact localisation of insulinomas which can guide better surgical exploration.\(^{15}\)

Since transabdominal ultrasound did not lead to tumour detection, we utilised transoral EUS including duplex to obtain superior information concerning localisation and determination of the positional relationship of the lesion to surrounding anatomical structures, the fundamental prerequisite for optimal surgical strategy. EUS is a minimally invasive, highly accurate imaging modality for the pancreas and the detection of pancreatic lesions. Most solid pancreatic lesions are depicted as a heterogeneous hypoechoic mass. The median sensitivity of EUS for the detection of pancreatic tumours is in the range of 94%.\(^{16}\) In addition, the sensitivity of EUS was shown to be superior to that of CT (98% vs. 74%) and also superior to transabdominal ultrasound (94% vs. 67%). For the detection of pancreatic tumours smaller than 20 mm in size, EUS had higher sensitivity than contrast-enhanced CT (94.4% vs. 50.0%, n = 36). Based on the results of these studies, EUS is widely used as a superior diagnostic option for patients with suspected pancreatic lesions worldwide.\(^{17}\)

![Figure 3](image-url) Pathology of the insulinoma. (A) The macro-pathology of the resected specimen. Histopathology: (B) Representative HE-staining. Further staining for specific targets was applied to evaluate the immuno-histochemical pattern of an insulinoma. The resected tumour was positive for chromogranin A (C) and insulin (D).
In minimally invasive surgery for pancreatic lesions smaller than 2 cm, such as the insulinoma treated in our case, intraoperative ultrasound localisation and determination of positional relationship to relevant surrounding anatomical structures is critical. The precision of these diagnostic measures compensates palpation that is impossible and enables to identify the anatomic landmarks required for successful completion. Critical information includes tumour proximity to the pancreatic duct as well as localisation in relation to major structures such as splenic vessels behind the pancreatic neck and superior mesenteric vein. This is in accordance with observations that intraoperative ultrasound is able to detect insulinoma tumours located in all sections of the pancreas overall with higher specificity when compared to preoperative imaging diagnostics. In a recent report of 24 curative tissue sparing pancreatic resections in focal congenital hyperinsulinism, specificity of intraoperative ultrasound for localisation of such lesions was 1.0 with a sensitivity of 0.8. Intraoperative ultrasound provides substantial information on localisation, complemented by duplex studies to determine surrounding vessel architecture. Thus, we employed the console’s dual visual/ultrasound image platform as augmented reality implementation. The latter simplified localisation of the insulinoma confirmed proximity to the main pancreatic duct and neighbouring major vascular structures and ultimately precisely confirmed the anatomy of the pancreatic body. Whether fluorescence-guided surgery based on indocyanine green imaging in the near-infrared spectrum has the potential to complement peri-surgical guidance strategies needs to be further evaluated. A report on initial experience with this technique demonstrated to be promising. This is noteworthy, as the here utilised robotic system integrates the foundation for such navigation concepts.

4.2 Surgery

Parenchymal sparing strategies such as enucleation may bear the potential to improve short- and long-term post-operative outcomes when compared to resection of small benign and premalignant pancreatic lesions. Partial anatomical resections are associated with a higher frequency of newly acquired post-operative diabetes as well as exocrine pancreatic insufficiency when compared to pancreatic enucleation. Therefore, surgical enucleation appears to be a valid and effective option for insulinomas, allowing preservation of long-term pancreatic function especially important for children whose normal parenchyma is still developing. In a very recent propensity-score matched pair analysis, pancreatic enucleation provided satisfying long-term outcomes with low chance of new onset of a post-surgical diabetes mellitus. Noteworthy, the evaluation of the quality of life was comparable to the general population.

Ore et al. specified the requirements for the indication to enucleate pancreatic lesions rather than formal pancreatic resection: (1) benign tumours (no evidence of malignant disease); (2) isolated lesions; (3) distance between tumour and main pancreatic duct ≥ 3 mm (no focal stricture or dilation); (4) insulinomas and gastrinomas <2 cm in size; and (5) non-functioning-pNETs when <1–2 cm and low Ki67 mitotic index. Hence, insulinomas of a limited size are excellent candidates for enucleation. A single centre experience of surgical resection for hyperinsulinism or non-functioning pNETs >1 cm in size in adults was reported. The group of 12 patients with a minimally invasive approach, either laparoscopic (n=8) or robotic-assisted (n=4), demonstrated comparable outcome with respect to rate of complications when compared with 21 open access procedures. In contrast to the minimal access interventions, the open approach group demonstrated higher blood loss, hospital stay and operating time. Accordingly, propensity score-matched analyses in a cohort of 60 open versus 60 robotically performed enucleations of pancreatic neuroendocrine tumours of limited size below 2 cm reported results in favour of the robotic approach.

In a recent summary of 65 paediatric cases derived from 16 studies and case reports, respectively, distal pancreatectomy and pancreaticoduodenectomy were the typical therapeutic procedures. Only one of the four enucleations in this overview was applied as minimal invasive procedure in a laparoscopic manner. However, considering the poor tolerability for operative trauma and anaesthesia in children, faster and less traumatic surgical procedures are preferred in these vulnerable patients. Furthermore, the advantage of utilising miniaturised instruments of a robotic surgical system with all levels of manual motion freedom combined with 3D vision for pancreatic surgery seems the ideal surgical strategy for limited space conditions such as the paediatric abdominal cavity. So far, only two paediatric patients were reported as having robotically assisted procedures to treat paediatric insulinomas. One as a distal pancreatectomy (the first application of a robotic surgery system in paediatric insulinoma) and one as enucleation of the pancreatic tail. However, both cases still utilised laparoscopically controlled dissection devices realising the surgery as robotic-laparoscopic hybrid-technique (linear stapler and laparoscopic ultrasonically activated scalpel, respectively).

In our surgical strategy, ports were exclusively utilised for introduction and retraction of material (suture material, swabs, tissue particles, ultrasound probe and suction), while no further instruments or devices were introduced or manipulated via the assist port. Since tissue manipulation is very different in paediatric pancreatic surgery when compared with adult interventions, we suggest adopting technical ‘ABC’ rules for focal hyperinsulinism in robotic-assisted pancreatic enucleation: A – avoid the main duct, B – blunt dissection strictly along the capsule were possible and C – cautious use of electrical coagulation. Still, we observed the development of a delayed pancreatic fistula 6 weeks after surgery which was timely treated with transgastric drainage plus endoscopic stenting of the pancreatic main duct. However, it needs to be discussed, whether preoperative endoscopic stenting is warranted as an additional safety measure to reduce the post-operative risk of developing a pancreatic fistula.

This is the first report of a minimally invasive surgical intervention to successfully treat a paediatric insulinoma solely with robotically controlled instruments. Robotic surgical systems allow delicate pancreatic surgery under limited space conditions such as the paediatric abdominal cavity and therefore seem to be a superior surgical strategy in such cases.
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CONFLICT OF INTEREST
I hereby declare that I do not have any conflicts of interest regarding this case report.

DATA AVAILABILITY STATEMENT
The data generated during and/or analysed during the current case report are available from the corresponding author on reasonable request.

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