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Minimally invasive enucleation of pancreatic tumors: The main pancreatic duct is no longer a restricted area

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ABSTRACT

Background: Tumors involving the main pancreatic duct (MPD) used to be a contraindication for enucleation.
Methods: Clinical data of consecutive patients with pancreatic tumors who received laparoscopic or robotic enucleation (LEN or REN) between January 2019 and December 2021 at Fudan University Shanghai Cancer Center were analyzed.
Results: Ninety-six patients were included in the analysis, with 55 in the LEN group and 41 in the REN group, and no conversion to laparotomy. Most tumors were located in the head of pancreas (71.9 %). The tumor diameter (3.1 vs. 1.9 cm) was larger, and more cystic tumors (92.7 % vs. 56.4 %) and more tumors involving the MPD (34.1 % vs. 3.6 %) were observed in the REN group. MPD support tube insertion was performed in 15 cases, with 11 in the REN group and 4 in the LEN group. The incidence of biochemical and grade B postoperative pancreatic fistula (POPF) was both 46.9 %, and no grade C POPF occurred. Among the 45 patients with grade B POPF, 28 cases (62.2 %) were due to carrying drainage tube >3 weeks without additional treatment, and only 4 cases required invasive treatment. For patients with MPD support tube implantation (n = 15), support tube fall-offs were observed in 12 cases, 2 patients had MPD dilatation, and no MPD stricture, stone formation or pancreatic atrophy was observed during follow-up.
Conclusions: The incidence of POPF was high but still controllable without serious complications after minimally invasive enucleation. The MPD is no longer a restricted area, and the robotic system has advantages in handling complex enucleations.

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1. Introduction

Standard surgical procedures for benign or low-grade malignant tumors of the pancreas are associated with a substantial risk of postoperative morbidity and long-term functional impairment, whereas parenchyma-sparing pancreatectomy, such as enucleation, leads to less morbidity and preserves healthy parenchyma as well as exocrine and endocrine function [1]. Enucleation of the pancreas has been reported to be feasible and safe for preserving the normal physiological function of pancreatic patients [2].

With the emphasis on physical examination and the application of high-quality thin-layer scanning techniques, the detection rate for pancreatic tumors continue to rise [3–5]. In addition, there is also a younger age trend. Therefore, based on safe and complete tumor resection and maximal preservation of pancreatic function, there is an urgent need to reduce surgical trauma. Through meta-analyses of data available in the literature, minimally invasive enucleation has the well-known advantages of a minimally invasive approach, such as shorter postoperative hospital stay and lower overall morbidity [6–8].

Although the incidence of serious complications such as postoperative hemorrhage after enucleation is low, postoperative pancreatic fistula (POPF) is still a thorny problem and tumors adjacent to or wrap around the main pancreatic duct (MPD) are considered enucleation contraindications [9,10]. Due to the fear of POPF and the perioperative management that is different from the standard surgical procedure, surgeons are still afraid of minimally invasive enucleation. As a result, minimally invasive enucleation is currently only performed in large pancreatic surgery centers and cannot be widely implemented.

Whether tumors involving the MPD can be minimally invasively enucleated, whether POPF is manageable, and what the long-term

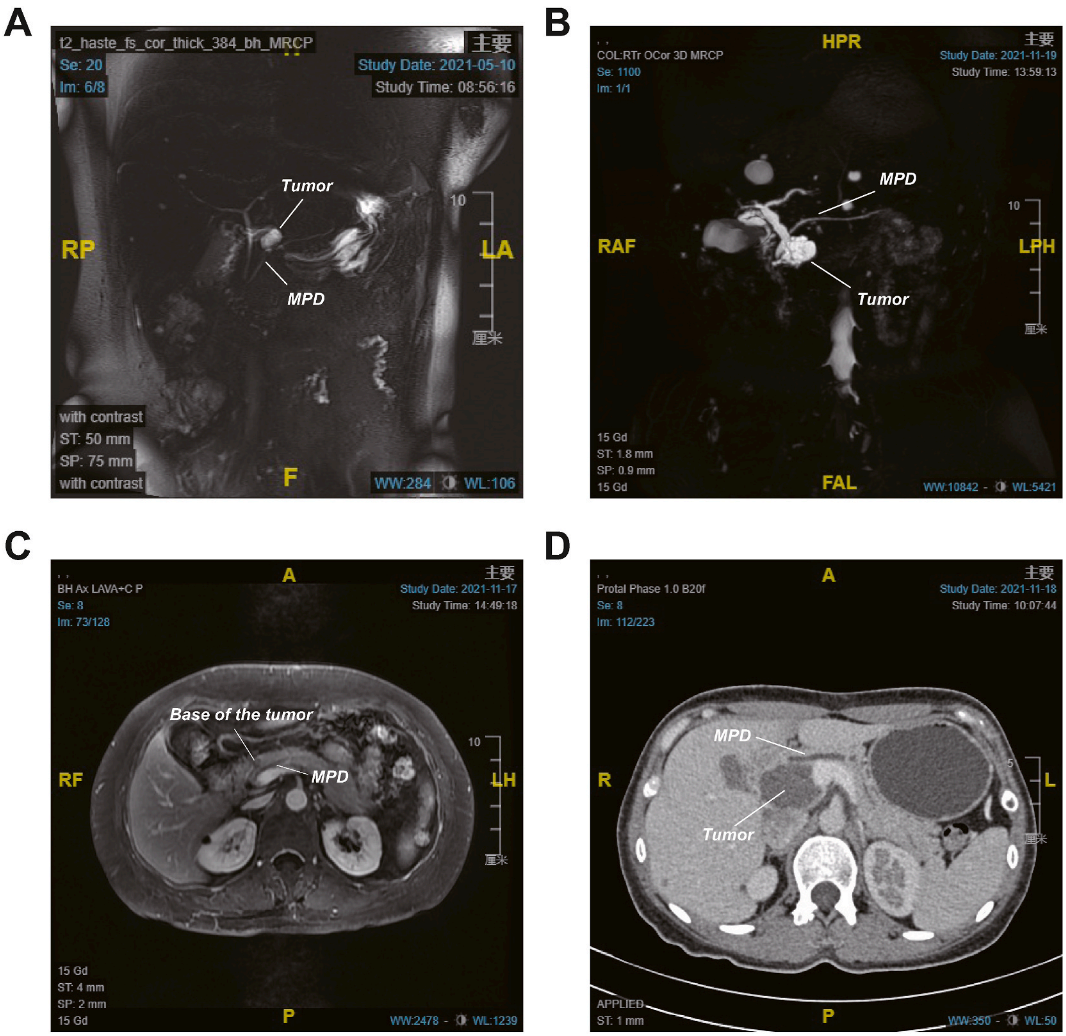

Fig. 1. The positional relationship between the tumor and the main pancreatic duct (MPD).
A: Cephalic side: on the coronal plane, the tumor is located at the cephalic side of the MPD
B: Caudal side: on the coronal plane, the tumor is located at the caudal side of the MPD
C: Ventral side: in the transverse section, the tumor is located at the ventral side of the MPD
D: Dorsal side: in the transverse section, the tumor is located at the dorsal side of the MPD.

prognosis is after repair or reconstruction of the MPD is unclear. This study analyzed the clinicopathological data and perioperative and long-term prognosis information of patients undergoing minimally invasive pancreatic enucleation in our center to determine the feasibility of this technique outside of large pancreatic centers.

2. Methods

2.1. Study population

In this study, consecutive patients who received minimally invasive pancreatic enucleation between January 2019 and December 2021 at Fudan University Shanghai Cancer Center were prospectively collected and retrospectively analyzed. The study was approved by the Shanghai Cancer Center Institutional Review Board, and informed consent was obtained from all patients for their clinical data to be used.

The surgical indications mainly refer to the European evidence-based guidelines on pancreatic cystic tumors [11], the National Comprehensive Cancer Network clinical practice guidelines for neuroendocrine tumors [12], and the experience of our center [13,14]. However, there are still some inconsistencies between available evidence and clinical practice [15]. Studies have shown that surgical removal of correctly identified precursors of pancreatic cancer can improve the prognosis of patients [16–20]. In view of the negative impact of standard surgical procedures on the prognosis of patients, minimally invasive enucleation has less surgical trauma and can benefit more potential high-risk patients. Minimally invasive enucleation was also performed for some young patients whose imaging features, such as tumor diameter, did not meet the standards defined by the guidelines but for whom risk factors (growing fast, with mural nodules, or oppressing pancreatic duct, etc.) were present.

2.2. Preoperative investigations and surgical procedures

Enhanced computed tomography (CT) of the abdomen and enhanced magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography were routinely performed preoperatively to clarify the size of the tumor and the positional relationship between the tumor and the MPD. Fig. 1 shows the four positional relationships between the tumor and the MPD, namely, the cephalic side (Fig. 1A), caudal side (Fig. 1B), ventral side (Fig. 1C), and dorsal side (Fig. 1D).

Minimally invasive pancreatic tumor enucleation includes laparoscopic enucleation (LEN) and robotic enucleation (REN). LEN adopts a leg-split position, and the surgeon stands on the right side of the patient. REN adopts the same position and uses the "six-hole method" to place the trocar. Constant pressure pneumoperitoneum is routinely established. For tumors with a large diameter and complete capsule, we use the tumor-centered approach: an ultrasonic scalpel is employed to completely resect the tumor along the tumor edge (Fig. 2A, ***Supplementary Video 1***). For tumors with a small diameter and no complete capsule close to or wrapped around the MPD, we use the MPD-centered approach: scissors are used to gradually peel off the tumor along the MPD after the support tube is implanted (Fig. 2B, ***Supplementary Video 2***).

For tumors located inside the pancreatic parenchyma and close to the MPD, to avoid damaging or suturing the MPD, we use intraoperative ultrasound for exploration before resection and after suturing the wound (***Supplementary Video 3***). If MPD damage is unavoidable, suture repair (***Supplementary Video 4***) or bridging reconstruction (***Supplementary Video 5***) can be performed after resection of the tumor. For the MPD that needs to be repaired or reconstructed, if there is no combined MPD dilation, our center routinely inserts the MPD support tube and fixes it with interrupted sutures. When placing the support tube, ensure that the distal end

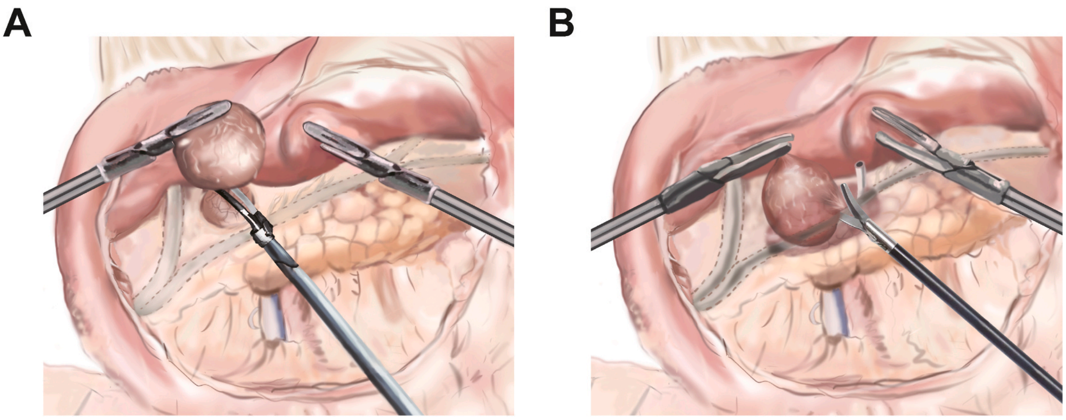

Fig. 2. Minimally invasive surgical approach for pancreatic tumor enucleation.
A: Tumor-centered approach: For tumors with a large diameter and a complete capsule, an ultrasonic scalpel can be used to completely remove the tumor along the tumor edge.
B: Main pancreatic duct-centered approach: For tumors with a small diameter, no complete capsule, close to or around the main pancreatic duct, scissors can be used to gradually peel the tumor along the main pancreatic duct.

of the tube passes through the duodenal papilla to fully reduce the pressure in the MPD. The vascular stump or stump of branched pancreatic ducts on the pancreatic wound is sutured. Most of the wounds are exposed after hemostasis, and a few are covered with ligamentum teres hepatis. Some fish-mouth-like wounds can be closed and sutured, but care should be taken to avoid the formation of dead space, resulting in undrainable effusion. A drainage tube is placed on the cephalic side and on the caudal side of the wound for adequate drainage.

If preoperative testing or intraoperative exploration suggests the presence of a tumor with malignant potential, intraoperative frozen section analysis is used to determine whether a switch to standard surgical procedures. For patients clinically diagnosed with intraductal papillary mucinous neoplasms, routine frozen section analysis of the pancreatic resection margin is performed. If there is a high-grade dysplasia or malignancy present at the surgical margin, further resection is required [11].

2.3. Postoperative management and treatment of complications

For patients who undergo enucleation, our center routinely uses prophylactic octreotide to prevent POPF. On the 4th day after the operation, the patient receives an enhanced CT scan of the abdomen to observe whether there is peritoneal effusion. The standard for removal of the abdominal drainage tube is that the amylase in the drainage fluid is less than 3 times the normal upper limit of serum amylase, or the drainage volume is less than 20 mL for 3 consecutive days, and there is no discomfort such as fever or abdominal pain. For patients with POPF, the indwelling time of the drainage tube should be extended. Drainage volume and amylase values are not contraindications for discharge. If the patient has no fever, abdominal pain, or other symptoms and eats a semiliquid diet without discomfort, he or she can be discharged from the hospital with the drainage tube properly fixed.

Patients with localized effusions that are not in the area of the drainage tube approach should undergo ultrasound or CT-guided puncture and drainage. For postoperative hemorrhage, the treatment method should be selected according to the bleeding site,

Table 1
Preoperative characteristics.

Variable	Number (%)/median (IQR)			
	Whole cohort (n = 96)	LEN (n = 55)	REN (n = 41)	*P* value
Age, years	53.1 (38.2–59.0)	53.5 (40.8–61.3)	44.8 (34.0–58.6)	0.094
Gender, male	30 (31.3)	19 (34.5)	11 (26.8)	0.420
BMI, kg/m^2	23.3 (21.4–25.2)	23.3 (22.9–25.2)	22.3 (20.3–24.7)	**0.017**
Chief complaint				–
Asymptomatic physical examination	75 (78.1)	41 (74.5)	34 (82.9)	
Abdominal distention	9 (9.4)	5 (9.1)	4 (9.8)	
Abdominal pain	9 (9.4)	6 (10.9)	3 (7.3)	
Other[a]	3 (3.1)	3 (5.5)	0 (0.0)	
Pancreatitis, yes	3 (3.1)	3 (5.5)	0 (0.0)	0.258
Diabetes mellitus, yes	7 (7.3)	7 (12.7)	0 (0.0)	**0.019**
History of abdominal surgery, yes	25 (26.0)	12 (21.8)	13 (31.7)	0.275
White blood cell, 10ˆ9/L	5.5 (4.4–6.3)	5.5 (4.2–6.4)	5.4 (4.5–6.3)	0.885
Total bilirubin, μmol/L	8.6 (6.9–12.2)	8.7 (6.8–13.8)	8.5 (7.1–11.6)	0.409
Glucose, mmol/L	5.2 (4.8–5.8)	5.3 (4.9–5.9)	5.0 (4.8–5.6)	0.056
CA19–9, U/mL	11.0 (7.0–18.3)	12.9 (7.6–19.9)	9.9 (6.0–17.0)	0.234
Tumor location				
Head	69 (71.9)	40 (72.7)	29 (70.7)	0.763
Neck	16 (16.7)	8 (14.5)	8 (19.5)	
Body and tail	11 (11.5)	7 (12.7)	4 (9.8)	
Tumor location relative to the MPD				0.374
Caudal and ventral side	37 (38.5)	18 (32.7)	19 (46.3)	
Caudal and dorsal side	27 (28.1)	19 (34.5)	8 (19.5)	
Cephalic and ventral side	22 (22.9)	12 (21.8)	10 (24.4)	
Cephalic and dorsal side	10 (10.4)	6 (10.9)	4 (9.8)	
Tumor diameter, cm	2.2 (1.7–3.2)	1.9 (1.5–2.4)	3.1 (2.0–3.7)	**0.001**
Largest diameter of the tumor base[b], cm	2.1 (1.5–3.0)	1.8 (1.5–2.5)	2.6 (1.9–3.3)	**0.004**
Cystic or solid, cystic	69 (71.9)	31 (56.4)	38 (92.7)	<**0.001**
Distance from tumor to MPD				<**0.001**
With space between MPD	45 (46.9)	33 (60.0)	12 (29.3)	
Clings to MPD but is assessed separable (borderline)	35 (36.5)	20 (36.4)	15 (36.6)	
Cannot be separated or wrap around MPD	16 (16.7)	2 (3.6)	14 (34.1)	
Distance to MPD[c] (n = 45), mm	2.8 (1.5–4.1)	3.0 (1.5–4.1)	2.4 (1.5–4.9)	0.752
MPD diameter, mm	1.5 (1.2–2.2)	1.5 (1.2–2.1)	1.5 (1.1–2.6)	0.894

Abbreviations: IQR, interquartile range; LEN, laparoscopic enucleation; REN, robotic enucleation; BMI, body mass index; CA19-9, carbohydrate antigens 19-9; MPD, main pancreatic duct.

[a] Symptoms related to functional neuroendocrine tumors, such as dizziness, fatigue, diarrhea, etc.

[b] For tumors in which the majority of the tumor body is located within the pancreatic parenchyma, the largest diameter of the tumor base is equal to the tumor diameter; For tumors in which the majority of the tumor body is located outside the pancreatic parenchyma, the largest diameter of the tumor base is smaller than the tumor diameter (Fig. 3 A and B).

[c] The space width for those with space between the tumor and MPD.

bleeding volume and speed. If conservative treatment fails, interventional hemostasis can be selected, and emergency laparoscopic exploration should be performed if necessary. Treatment of delayed gastric emptying requires gastrointestinal decompression, nutritional support, and maintenance of electrolyte and acid-base balance.

2.4. Follow-up and main outcome measures

In this study, patients were followed up every 3–6 months after discharge. For patients with MPD injury and placement of a pancreatic duct support tube, enhanced CT or MRI scans were performed to determine whether the support tube was in place and whether the MPD was dilated, stenotic, or stone-formed. If the ratio of the diameter of the MPD to the width of the pancreatic parenchyma is greater than 0.5, it is defined as pancreatic atrophy [21]. The long-term prognosis, including pancreatitis, frequent diarrhea, exogenous pancreatic enzyme dependence, weight change, new-onset diabetes, and tumor recurrence was followed for 6 months after the operation.

A two-tiered classification system was used for grading dysplasia in mucinous cystadenoma or intraductal papillary mucinous neoplasms [22,23]. The resection margin status was reported according to specific pathological subtypes, with R1 being defined as the presence of tumor cells within <1 mm from the resection margin [24]. Additionally, the Ki-67 index and the 2010 World Health Organization (WHO) grading for neuroendocrine tumors were also recorded. Perioperative complications were defined as clinical events occurring within 90 days after the operation. Specific complications related to pancreatic surgery, such as POPF, postoperative hemorrhage and delayed gastric emptying, were evaluated by the international study group for pancreatic surgery (ISGPS) [25–27]. The degree of other complications was evaluated by the Clavien–Dindo classification system, in which grade III and above complications were defined as major complications [28]. Hospital mortality was defined as death occurring within 90 days after initial surgery, regardless of causes.

2.5. Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables or variables with an abnormal distribution were compared using unpaired Student's *t*-test or the Mann–Whitney *U* test. All analyses were performed using SPSS Statistics 22.0 for Windows (IBM Corp, Armonk, NY, http://www.ibm.com). Two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Preoperative characteristics

As shown in Table 1, 96 patients were included in the analysis, with 55 patients in the LEN group and 41 patients in the REN group. The median age (IQR) was 53.1 (38.2–59.0) years, and female patients were more common (68.7 %). Most of the patients were diagnosed by asymptomatic physical examination. Twenty-six percent of patients had a history of abdominal surgery. Patients in the REN group had a lower BMI than those in the LEN group (22.3 vs. 23.3 kg/m^2, P = 0.017). The preoperative serological tests and tumor markers were normal.

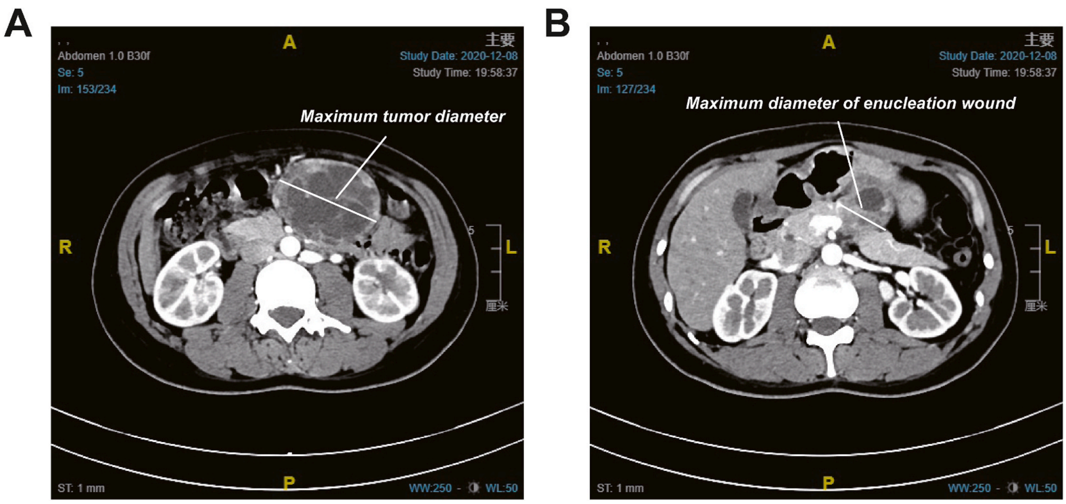

Fig. 3. The diameter of the enucleation wound is not always equal to the maximum diameter of the tumor.
A: The maximum diameter of the tumor
B: The maximum diameter of the enucleation wound indicated by preoperative imaging.

Tumors located in the head (71.9 %) were much more common than those in the neck (16.7 %) and body and tail (11.5 %) of the pancreas. The spatial position of the tumor relative to the MPD (Fig. 1) included 4 situations, namely, caudal and ventral side (38.5 %), caudal and dorsal side (28.1 %), cephalic and ventral side (22.9 %), and cephalic and dorsal side (10.4 %). The tumor diameter (3.1 vs. 1.9 cm, P = 0.001; Fig. 3A) and the largest diameter of the tumor base (2.6 vs. 1.8 cm, P = 0.004; Fig. 3B) of the REN group were greater than those of the LEN group. There were more cystic tumors in the REN group (92.7 % vs. 56.4 %, P < 0.001) and more tumors that could not be separated or wrapped around the MPD (34.1 % vs. 3.6 %). The median MPD diameter was 1.5 mm in the whole cohort.

3.2. *Surgical information and pathological examination*

All patients successfully completed minimally invasive tumor enucleation without intraoperative blood transfusion and conversion to laparotomy. The texture of the pancreas was mostly normal (66.7 %), the texture of another 31.3 % was brittle, and that of another 2.1 % was hard. The majority of the MPDs were not exposed (n = 60), 9 cases were exposed but not injured, and 12 cases had MPD injury and underwent simple suture closure. In addition, suture repair after insertion of the support tube was performed in 15 cases, and the proportion in the REN group was higher than that in the LEN group (26.8 % vs. 7.3 %). After enucleation, 89.6 % of the wound surface was uncovered, and a few wounds were closed by suture (6.3 %) or covered by the ligamentum teres hepatis (4.2 %). The operation time was longer in the REN group than in the LEN group (226.0 vs. 165.0 min, P = 0.004). The median intraoperative blood loss in the whole cohort was 50.0 mL.

Consistent with the results of the preoperative imaging examination, the postoperative pathological results showed that there were

Table 2
Surgical and pathological characteristics.

Variable	Number (%)/median (IQR)			
	Whole cohort (n=96)	LEN (n=55)	REN (n=41)	*P* value
ASA grade				0.156
I	30 (31.3)	14 (25.5)	16 (39.0)	
II	66 (68.8)	41 (74.5)	25 (61.0)	
Pancreatic texture				0.101
Hard	2 (2.1)	1 (1.8)	1 (2.4)	
Normal	64 (66.7)	32 (58.2)	32 (78.0)	
Brittle	30 (31.3)	22 (40.0)	8 (19.5)	
Treatment of MPD				**0.003**
Not exposed	60 (62.5)	41 (74.5)	19 (46.3)	
Exposed but not injured	9 (9.4)	2 (3.6)	7 (17.1)	
Simple suture closure	12 (12.5)	8 (14.5)	4 (9.8)	
Suture repair after insertion of support tube	15 (15.6)	4 (7.3)	11 (26.8)	
Wound surface treatment				0.095
Suture closed	6 (6.3)	1 (1.8)	5 (12.2)	
Covered by ligamentum teres hepatis	4 (4.2)	3 (5.5)	1 (2.4)	
Uncovered	86 (89.6)	51 (92.7)	35 (85.4)	
Operation time, minutes	185.0 (137.5-260.0)	165.0 (119.0-229.0)	226.0 (156.5-298.5)	**0.004**
Blood loss, mL	50.0 (50.0-100.0)	50.0 (50.0-100.0)	50.0 (50.0-100.0)	0.534
Pathologic diagnosis				**<0.001**
Serous cystadenoma	32 (33.3)	13 (23.6)	19 (46.3)	
Mucinous cystadenoma	3 (3.1)	2 (3.6)	1 (2.4)	
Intraductal papillary mucinous neoplasms	30 (31.3)	12 (21.8)	18 (43.9)	
Solid pseudopapillary tumor	3 (3.1)	2 (3.6)	1 (2.4)	
Neuroendocrine tumor	19 (19.8)	19 (34.5)	0 (0.0)	
Other	9 (9.4)	7 (12.7)	2 (4.9)	
Pathological characteristics of different subtypes				
Variable	**Mucinous cystadenoma (n=3)**	**Intraductal papillary mucinous neoplasms (n=30)**	**Solid pseudopapillary tumor (n=3)**	**Neuroendocrine tumor (n=19)**
Dysplasia grading			-	-
low-grade	3 (100.0)	30 (100.0)		
high-grade	0 (0.0)	0 (0.0)		
R status	-	low-grade dysplasia	R0	R0
		30 (100.0)	3 (100.0)	17 (89.5)
Ki-67 index, %	-	-	2.0 (2.0-2.5)	2.0 (1.0-3.0)
WHO grading	-	-	-	
G1				11 (57.9)
G2				8 (42.1)

Abbreviations: IQR, interquartile range; LEN, laparoscopic enucleation; REN, robotic enucleation; ASA, American Society of Anesthesiologists; MPD, main pancreatic duct; WHO, World Health Organization.

more cystic tumors in the REN group (P < 0.001) (Table 2). The pathological characteristics of different subtypes revealed that mucinous cystadenoma and intraductal papillary mucinous neoplasms surgical resection samples, as well as the pancreatic duct margin of intraductal papillary mucinous neoplasms, all demonstrated low-grade dysplasia. All of the three cases of solid pseudo-papillary tumors, and 17 out of the 19 cases of neuroendocrine tumors attained an R0 resection margin. The median Ki-67 index for both tumor types was found to be 2.0 %. Among the neuroendocrine tumors, 11 cases (57.9 %) were classified as WHO grading G1, while 8 cases (42.1 %) were categorized as G2. There were no occurrences of invasive cancer observed in the entire cohort.

3.3. Perioperative prognosis

The total amount of abdominal drainage fluid (TAD) after the operation on days 1, 3, and 5 was 60.0 mL, 31.5 mL, and 23.5 mL, respectively. The abdominal drainage fluid amylase (DFA) after the operation on days 3 and 5 was 3693.5 U/L and 1354.5 U/L. There was no difference in postoperative length of stay (LOS) between the REN group and the LEN group (7.6 vs. 7.8 days, P = 0.894). Forty-seven patients (49.0 %) were discharged with abdominal drainage tubes. After discharge, there were 13 cases of readmission, mainly due to asymptomatic local effusion; 9 patients received conservative therapy, and 4 patients received abdominal paracentesis drainage. The median removal time of all abdominal drainage tubes was 17.0 days (Table 3).

The incidence of severe complications (Clavien–Dindo grade ≥ III) was 4.2 %, and all of them were caused by puncture and

Table 3
Perioperative prognosis.

Variable	Number (%)/median (IQR)			
	Whole cohort (n = 96)	LEN (n = 55)	REN (n = 41)	*P* value
TAD on day 1, mL	60.0 (25.3–90.0)	50.0 (20.0–80.0)	65.0 (30.0–120.0)	**0.048**
TAD on day 3, mL	31.5 (15.0–88.8)	26.0 (15.0–70.0)	55.0 (15.0–104.5)	0.192
TAD on day 5, mL	23.5 (5.0–80.0)	22.0 (5.0–55.0)	30.0 (3.0–156.5)	0.572
DFA on day 3, U/L	3693.5 (980.3–10000.0)	3190.0 (898.0–10000.0)	3868.0 (985.5–10000.0)	0.582
DFA on day 5, U/L	1354.5 (101.0–6273.8)	1347.0 (153.0–6346.0)	1367.0 (12.0–7921.0)	0.838
Postoperative LOS, days	7.7 (6.3–10.6)	7.8 (6.3–10.9)	7.6 (6.4–10.5)	0.894
Discharge with drainage tube, yes	47 (49.0)	29 (52.7)	18 (43.9)	0.392
Readmission, yes	13 (13.5)	5 (9.1)	8 (19.5)	0.140
Reason for readmission				–
Fever	3 (3.1)	0 (0.0)	3 (7.3)	
Abdominal pain	3 (3.1)	1 (1.8)	2 (4.9)	
Asymptomatic local effusion	7 (7.3)	4 (7.3)	3 (7.3)	
Treatment of readmission (n = 13)				–
Abdominal paracentesis drainage	4 (30.8)	2 (40.0)	2 (25.0)	
Conservative therapy	9 (69.2)	3 (60.0)	6 (75.0)	
Removal time of all abdominal drainage tubes, days	17.0 (6.0–33.8)	23.0 (6.0–35.0)	10.0 (6.5–31.5)	0.681
ISGPS POPF grade				0.182
None	6 (6.3)	5 (9.1)	1 (2.4)	
Biochemical	45 (46.9)	22 (40.0)	23 (56.1)	
B	45 (46.9)	28 (50.9)	17 (41.5)	
C	0 (0.0)	0 (0.0)	0 (0.0)	
Sub-classification of POPF grade B (n = 45)				0.600
Abdominal drainage tube>3 weeks without additional treatment	28 (62.2)	19 (67.9)	9 (52.9)	
With abdominal drainage tube >3 weeks and additional drug treatment	13 (28.9)	7 (25.0)	6 (35.3)	
Invasive treatment such as interventional puncture and drainage	4 (8.9)	2 (7.1)	2 (11.8)	
Postoperative hemorrhage severity				**0.012**
None	91 (94.8)	55 (100.0)	36 (87.8)	
Mild	5 (5.2)	0 (0.0)	5 (12.2)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative hemorrhage time (n = 5)				–
Early hemorrhage, ≤24 h	1 (20.0)	0 (0.0)	1 (20.0)	
Late hemorrhage, >24 h	4 (80.0)	0 (0.0)	4 (80.0)	
Blood transfusion, yes	4 (4.2)	0 (0.0)	4 (9.8)	**0.030**
Bile leadage, yes	1 (1.0)	0 (0.0)	1 (2.4)	0.244
Delayed gastric emptying, yes	2 (2.1)	1 (1.8)	1 (2.4)	1.000
Reoperation, yes	0 (0.0)	0 (0.0)	0 (0.0)	–
Death in 90 days, yes	0 (0.0)	0 (0.0)	0 (0.0)	
Clavien-Dindo classification				0.621
None	45 (46.9)	23 (41.8)	22 (53.7)	
I	23 (24.0)	14 (25.5)	9 (22.0)	
II	24 (25.0)	16 (29.1)	8 (19.5)	
III	4 (4.2)	2 (3.6)	2 (4.9)	

Abbreviations: IQR, interquartile range; LEN, laparoscopic enucleation; REN, robotic enucleation; TAD, total amount of abdominal drainage fluid after operation; DFA, abdominal drainage fluid amylase after operation; LOS, length of stay; POPF, postoperative pancreatic fistula.

drainage of peritoneal effusion. No reoperations or deaths occurred within 90 days. In terms of pancreatic-specific complications, biochemical POPF occurred in 46.9 % of patients, grade B POPF occurred in the same proportion of patients, and no grade C POPF occurred. It should be noted that among the 45 patients with grade B POPF, 28 cases (62.2 %) were due to carrying an abdominal drainage tube >3 weeks without additional treatment, and only 4 cases required invasive treatment. There were 5 cases of postoperative mild hemorrhage, 4 of which were late hemorrhage. All cases were cured after conservative treatment such as application of hemostatic agents and/or blood transfusion. One patient had a mild biliary fistula due to excessive bile duct exposure, which was cured after percutaneous transhepatic cholangiographic drainage treatment for biliary decompression. Delayed gastric emptying occurred in 2 cases.

3.4. Long-term prognosis half a year after discharge

The median follow-up time of this study was 17.8 (15.3–19.5) months. During the follow-up period, 5 patients had a history of postoperative pancreatitis, 2 patients had dyspepsia requiring exogenous pancreatic enzymes, 2 patients had new-onset diabetes, and 78.1 % of patients had weight changes within 5 kg (Table 4). No tumor recurrence was observed during the follow-up period.

For patients with MPD support tube implantation (n = 15), 3 patients had a history of pancreatitis, support tube fall-offs into the duodenum were observed in 12 patients during follow-up, and the median period until support tube fall-off was 2.5 months. Among these patients, only 2 had MPD dilatation, and no MPD stricture, MPD stone formation or pancreatic atrophy was observed.

4. Discussion

Because enucleation results in the least loss of normal pancreatic parenchyma and the best preservation of pancreatic functionality and because, even for low-grade malignant tumors, enucleation has similar long-term oncological results to those of standard surgery, enucleation is gradually becoming widely used in clinical practice [24,29,30]. Cauley et al. found that the incidence of endocrine dysfunction (4 % vs. 17 %, P = 0.05) and exocrine dysfunction (2 % vs. 17 %, $P < 0.05$) after enucleation was lower than that of anatomical resection by comparing the results of enucleation in 45 cases with the results of anatomical resection in 90 cases of pancreatic tumors [1]. Kiely et al. followed up 30 patients after enucleation for up to 10 years. No patient had pancreatic endocrine or exocrine dysfunction [29]. In this study, after a median follow-up period of 17.8 months, no patients had frequent diarrhea, 2 patients (2.1 %) had dyspepsia requiring exogenous pancreatic enzymes, 2 patients (2.1 %) had new-onset diabetes, and 78 % of patients had weight changes within 5 kg. We believe that the cases in which patients' weight changes exceeded 5 kg were partly due to the prevention and control of COVID-19. Our research data showed that enucleation has advantages in preserving pancreatic function. Moreover, no tumor recurrence was observed during the follow-up period.

Before laparoscopic and robotic surgery systems were widely used, open enucleation was also a safe and feasible operation for benign or low-grade pancreatic tumors. Wang et al. reported the single-center experience of 142 cases of pancreatic tumor enucleation, most of which involved open surgery (97.9 %). The overall postoperative morbidity was 66.2 %, mainly due to POPF (53.5 %), and grade C POPF was 5.6 %. The incidence rate of Clavien−Dindo above grade III was 8.4 %, including one death (0.7 %) [31]. In the early period of our center, open enucleation was also performed. However, due to concerns regarding POPF, 62.3 % of the surgical wounds following open enucleation were combined with prophylactic Roux-en-Y pancreaticojejunostomy reconstruction [32]. While this approach did indeed reduce the incidence of grade B POPF (17.5 %), it also resulted in prolonged postoperative LOS (12.5 days), leading to severe postoperative hemorrhage and the unfortunate death of two patients. Furthermore, during the follow-up period, we

Table 4
Long-term prognosis half a year after discharge.

Variable	Number (%)/median (IQR)
Whole cohort (n = 96)	
Pancreatitis, yes	5 (5.2)
Frequent diarrhea, yes	0 (0.0)
Dyspepsia requires exogenous pancreatic enzymes, yes	2 (2.1)
Current weight, Kg	
Weight gain more than 5 Kg	10 (10.4)
Weight change within 5 Kg	75 (78.1)
Weight loss more than 5 Kg	11 (11.5)
New-onset diabetes, yes	2 (2.1)
Patients with MPD support tube implantation (n = 15)	
Pancreatitis, yes	3 (20.0)
Support tube fall-off, yes	12 (80.0)
Time of support tube falls off, months	2.5 (1.8–8.3)
MPD dilatation, yes	2 (13.3)
MPD stricture, yes	0 (0.0)
MPD stone formation, yes	0 (0.0)
MPD diameter/Pancreatic parenchyma width	0.1 (0.1–0.2)
Pancreatic atrophy[a], yes	0 (0.0)

Abbreviations: IQR, interquartile range; MPD, main pancreatic duct.
[a] Defined as the ratio of the diameter of the MPD to the width of the pancreatic parenchyma >0.5.

identified cases of gastrointestinal bleeding, and patients reported discomfort in the surgical area. As a result, our center ceased performing open enucleation after 2019. In this study, all patients successfully completed minimally invasive enucleation without conversion to laparotomy, and no reoperation or perioperative death occurred. The median postoperative hospital stay was 7.7 days. There were only 4 cases (4.2 %) of Clavien–Dindo above grade III, and all of these patients received abdominal puncture and drainage guided by ultrasound or CT. There were 5 cases of mild intraperitoneal hemorrhage after the operation, most of which were late hemorrhage of the surgical wound, which were cured after conservative treatment, such as application of hemostatic agents and blood transfusion. These data indicate that minimally invasive enucleation has advantages in terms of surgical safety and postoperative recovery time.

Due to the exposed pancreatic wound, the risk of POPF in enucleation is higher than that in anatomical resection with rates ranging from 20 % to 57 % [8,33–36]. In this study, according to the ISGPS definition of POPF [25], the incidence of biochemical and grade B POPF were both 46.9 %, and no grade C POPF occurred. Although the incidence of POPF after enucleation was high, we believe that this is consistent with clinical practice. In this study, 89.6 % of patients' pancreatic enucleation wounds were exposed, and it was difficult to avoid pancreatic juice outflow. The median amylase content of drainage fluid was 3693.5 U/L on the third day after the operation, which was at least in the category of biochemical POPF in the ISGPS grading standard. Due to the influence of biochemical POPF, patients need their drainage tube period extended after surgery. In this study, 49.0 % of patients were discharged with drainage tubes. If the tube was carried for more than 3 weeks, according to the definition of ISGPS, the case was classified as grade B POPF. In a study by Suzanne M. et al., it was found that after enucleation, 64.5 % of patients had drain amylase levels exceeding three times the upper limit of normal, indicating biochemical POPF, and 38.7 % had drains in place for more than 3 weeks, corresponding to grade B POPF as per the ISGPS criteria. These findings align with our discussion on the incidence and classification of POPF in enucleation procedures [37]. Although the incidence of POPF is remarkable and the condition even inevitable, most of these outcomes are safe and controllable. Moreover, in comparison with standard surgery, enucleation minimizes the loss of normal pancreatic parenchyma and maximally preserves pancreatic function. Therefore, in the long run, the benefits offered by enucleation can outweigh the drawbacks. Only 37.8 % of grade B POPFs (17 out of the whole cohort, 17.7 %) required additional drug treatment or invasive treatment. Considering the technical aspects and wound management differences between minimally invasive enucleation and anatomical resection, we suggest that clinically relevant POPF be limited to grade B POPF cases requiring interventions and grade C POPF cases. The remaining 62.2 % of grade B POPFs (28 out of the whole cohort, 29.2 %) were simply present because the drainage tube had been carried for more than 3 weeks, and should be classified as having biochemical POPF. Our results showed that for patients undergoing minimally invasive enucleation, POPF is controllable, but the ISGPS grading system is not applicable or requires modification.

Early attempts at minimally invasive enucleation were limited to pancreatic body and tail tumors with clear tumor boundaries, protruding from the pancreatic parenchyma and far from the MPD [38,39]. Tumors located deep in the pancreatic parenchyma require higher-level and more challenging minimally invasive surgical techniques [40]. Pauline et al. showed that the incidence of POPF after enucleation was different for tumors at different locations. A tumor located at the uncinate process was a high-risk factor for POPF after enucleation [41]. However, for tumors deep in the pancreatic head, the successful implementation of minimally invasive enucleation can avoid pancreatoduodenectomy [42]. In this study, the incidence of grade B POPF in the head of the pancreas seemed to be higher than that in the neck, body, and tail of the pancreas, but there was no significant difference (52.2 % vs. 33.3 %, $P = 0.096$). In addition to the growth position of the tumor in the pancreas, we believe that the position of the tumor relative to the MPD may be an influencing factor for POPF. Therefore, we divided the tumor position relative to the MPD into four types (Fig. 1, Table 1). The results showed that there was no difference in the incidence of grade B POPF with tumors located at the cephalic or caudal side of the MPD (40.6 % vs. 50.0 %, $P = 0.386$). However, the incidence of grade B POPF in tumors located on the dorsal side was higher than that in tumors located on the ventral side (59.5 % vs. 39.0 %, $P = 0.050$). This is because tumors on the dorsal side of the MPD increase the difficulty of operation and have a greater risk of damaging the MPD. However, with the help of intraoperative ultrasound localization and the operating advantages of the robot system in a narrow space, the tumor can still be safely enucleated.

The most important factor affecting the safety of enucleation seems to be the distance from the tumor to the MPD. Surprisingly, such parameters are rarely described in detail in previous studies, which makes it impossible to accurately assess their actual impact on the incidence of POPF. According to Heeger et al., the risk of POPF seems to increase with the closer the tumor is to the MPD. The incidence of POPF after enucleation of tumors in the deep portion (<3 mm from the MPD) was higher than that in the shallow portion (>3 mm) (73.3 % vs. 30.0 %, $P = 0.002$) [43] Studies have also limited this hazard distance to 2 mm [44,45]. Some studies even indicate that if the tumor is near the MPD, enucleation may be contraindicated [8], and standard resection is preferred to avoid the risk of POPF [46]. However, in these studies, the tumors were at least spaced from the MPD and did not include tumors that were borderline resectable, inseparable, or wrapped around the MPD, rarely involving MPD repair or reconstruction. The divergent patient selection criteria constituted the primary reason for the higher reported POPF incidence in our study compared to previous studies [35]. However, a retrospective analysis of 166 cases of pancreatic tumor enucleation by Strobel et al. showed that even tumors directly adjacent to the MPD can be enucleated safely, although their study also did not include cases wrapped around the MPD [47]. In 2021, Rong et al. introduced the concept of pancreatic duct repair surgery for the first time, and outlined four main procedures: MPD repair, end-to-end pancreatic anastomosis, branch duct intraductal papillary mucinous neoplasms local resection, and MPD replacement [48]. The results of our study will provide additional data support for pancreatic duct repair surgery. In this study, for patients with space between the MPD ($n = 45$), distance was not a risk factor for grade B POPF ($OR = 0.943$, 95 % CI: 0.740–1.201, $P = 0.632$). According to the distance between the tumor and the MPD, we further divided the patients into three types: with space between the tumor and the MPD ($n = 45$, 46.9 %), with the tumor clinging to the MPD but assessed as separable (borderline) ($n = 35$, 36.5 %), and with the tumor unable to be separated or encasing the MPD ($n = 16$, 16.7 %). The proportions of no POPF, biochemical POPF, and grade B POPF of the three above-described types were 11.1 %, 60.0 % and 28.9 % vs. 2.9 %, 31.4 % and 65.7 % vs. 0.0 %, 43.8 % and 56.3 %, respectively

(P = 0.012). Although the incidence of POPF in tumors encasing the MPD is much higher than that of the first two types, enucleation can be performed safely in such patients. During resection, the MPD-centered approach (Fig. 2B, Supplemental Video 2) can be used to carefully dissect the tumor. Even if the MPD is damaged during the operation, it can be repaired (**Supplemental Video 3**) or reconstructed (**Supplemental Video 4**) to restore its continuity as well as the physiological anatomy to the greatest extent. In this study, among patients with MPD support tube implantation (n = 15), grade B POPF occurred in 11 cases, and only 2 of them underwent abdominal puncture and drainage after the operation. Support tube fall-offs were observed in 12 patients during the follow-up, with a median time of 2.5 months and no MPD stricture, stone formation or pancreatic atrophy. In addition, we also observed that the tumor diameter in the REN group was larger than that in the LEN group, and the proportion of cystic tumors and tumors encasing the MPD was also higher, indicating that the robotic system has more advantages in handling complex enucleation. In addition to anatomical factors, pancreatic texture also affects POPF [49,50]. We found that grade B POPF occurred more frequently in a brittle pancreas than in a hard or normal pancreas (66.7 % vs. 37.9 %, P = 0.009).

Although this study demonstrated that minimally invasive enucleation is safe and feasible, we recommend that it be performed at an experienced pancreatic surgery center. Previous studies have reported 16 cases of LEN experience at a single center, among which 3 patients (18.7 %) were converted to laparotomy because the tumor could not be localized during the operation. The postoperative readmission rate was 28.6 %. One patient underwent reoperation for severe postoperative pancreatitis [51]. Although the overall prognosis is good, caution is still needed. After all, severe complications caused by benign tumor surgery are a situation that neither surgeons nor patients want to see.

The main limitation of this study is that it included 32 cases of serous cystadenoma and 30 cases of intraductal papillary mucinous neoplasms, as indicated by postoperative pathological results. This may raise concerns regarding the surgical indications and the potential risks associated with the widespread adoption of this technique. Due to the challenges in preoperative diagnosis of pancreatic cystic tumors, the retrospective nature of the study, and the absence of uniform standards for the follow-up of pancreatic cystic tumors without high-risk symptoms or features across different guidelines, it is possible that some patients included in the study may not meet the absolute indications for surgery as recommended by current guidelines [11,15]. However, it should be noted that these patients constitute a very small proportion of the overall population managed through outpatient surveillance at our center. In Supplementary Table 1, we reviewed the indications or reasons for performing minimally invasive enucleation in the 65 cases of pancreatic cystic tumors. We observed that, in addition to the absolute or relative surgical indications described in the guidelines, 30.8 % of patients were younger than 40 years old, and 53.8 % exhibited extreme anxiety and fear regarding potential malignancy and lifelong follow-up, strongly requesting surgical intervention. An international survey on the clinical application of guidelines for pancreatic cystic tumors revealed that 30 % of surgeons would agree to perform surgery on patients who request it, even if the tumor is considered to have a lower risk of malignancy [15]. Furthermore, in young patients, the risk of pancreatic cystic tumor progression increases over time, along with an increased likelihood of developing indications for surgical resection [52,53]. Therefore, in our clinical practice, we not only provide reassurance and recommend regular surveillance to patients but also consider minimally invasive enucleation for selected patients with worrisome tumor features and strong surgical requests. This approach aims to prevent tumor progression, minimize the extent of pancreatic parenchyma-sparing resection (such as duodenum-preserving pancreatic head resection, spleen-preserving distal pancreatectomy, etc.), and even avoid oncological resections whenever possible. However, due to the low malignant potential of pancreatic cystic tumors and the high rate of complications associated with pancreatic surgery, we must carefully balance the surgical risks of benign lesions with the potential for inadequate treatment of malignancies. Furthermore, we need to consider and evaluate the risks and costs associated with invasive and non-invasive monitoring approaches. Another limitation is that the follow-up period was not long enough to study the effect of minimally invasive enucleation on oncological prognosis and patients' long-term quality of life, as well as the long-term impact of MPD repair or reconstruction on the caudal pancreas. However, we are also conducting a multicenter prospective clinical trial on minimally invasive enucleation with MPD repair or reconstruction (NCT06024343) to gather further data and insights regarding the long-term outcomes.

5. Conclusion

Our study confirmed that minimally invasive enucleation is safe and feasible for the treatment of benign and low-grade pancreatic tumors and can preserve pancreatic function to the greatest extent. The incidence of POPF was high but controllable, without serious complications, and the ISGPS POPF classification does not seem to be applicable for enucleation. The relationship between the tumor and the MPD is the most important factor affecting POPF, but it is no longer an enucleation contraindication. Compared with laparoscopy, the robotic system has advantages in handling complex and difficult enucleations, and this needs to be verified by high-quality clinical randomized controlled trials.

Ethics statement

This study was reviewed and approved by the Shanghai Cancer Center Institutional Review Board, with the approval number: 2309282-11. Informed consent was obtained from all patients for their clinical data to be used.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Zheng Li: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Qifeng Zhuo:** Investigation, Formal analysis, Data curation. **Yihua Shi:** Investigation, Data curation, Conceptualization. **Haidi Chen:** Investigation, Data curation. **Mengqi Liu:** Investigation, Data curation. **Wensheng Liu:** Methodology, Investigation, Data curation. **Wenyan Xu:** Investigation, Data curation. **Chen Chen:** Investigation, Data curation. **Shunrong Ji:** Validation, Supervision, Software. **Xianjun Yu:** Supervision, Project administration, Funding acquisition, Conceptualization. **Xiaowu Xu:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21917.

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