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Brief Communication

Islet autotransplantation in focal intraductal papillary mucinous neoplasms: Evaluating feasibility, safety, and metabolic outcomes in pancreatic resection

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ABSTRACT

Islet auto transplantation (IAT) is a potential therapeutic option for patients undergoing pancreatectomy to preserve endocrine function, but its role in patients with intraductal papillary mucinous neoplasms (IPMNs) remains controversial due to oncological concerns. This study evaluated the feasibility, safety, and metabolic outcomes of IAT in 7 patients with focal IPMNs who underwent pancreatectomy between 2008 and 2023, following the Milan protocol. Primary outcomes included the technical success of islet isolation and the absence of tumor dissemination. Secondary outcomes included insulin independence and metabolic control posttransplant. Islet isolation success was variable, with 4 patients meeting the criteria for transplantation. The average islet yield was 1097 islet equivalents per kilogram of body weight (range: 219-1833 islet equivalents/kg). No patient experienced

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; HbA1c, glycated hemoglobin; IAT, islet autotransplantation; IEQ, islet equivalent; IPMN, intraductal papillary mucinous neoplasm.

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complications related to islet infusion, and there was no evidence of tumor recurrence or metastasis during a mean follow-up of 7.9 years (range: 3.99-11.88 years). IAT recipients demonstrated preserved insulin secretion, whereas nontransplanted patients developed diabetes. These findings support the feasibility and safety of IAT in carefully selected patients with focal IPMNs, providing promising metabolic outcomes. The results open the possibility to initiate larger cohort studies and explore the potential to expand the population of patients who could benefit from this approach.

1. Introduction

Autologous islet transplantation (IAT) has traditionally been employed to prevent postpancreatectomy diabetes in patients undergoing total or partial pancreatectomy for chronic pancreatitis.[1] More recently, the Milan protocol has expanded its indications to selected benign and malignant pancreatic lesions, provided multifocality is excluded.[2,3] However, its application in patients with intraductal papillary mucinous neoplasms (IPMNs) remains controversial due to oncological concerns.[4] IPMNs are premalignant pancreatic lesions that can be broadly classified into those with low malignant potential, typically managed through radiologic or endoscopic surveillance, and high-risk lesions requiring surgical resection due to features such as main pancreatic duct involvement, mural nodules, or rapid cyst growth.[5] Although the latter group provides tissue for IAT, their inherent risk of malignancy raises concerns about the safety of transplanting potentially neoplastic cells. A critical unresolved question is whether the neoplastic potential of an IPMN persists after enzymatic digestion, partial purification, and hepatic infusion during IAT. Further complicating the suitability of IPMNs for IAT are 2 major challenges. First, the multifocal nature of these lesions,[5] often associated with skip areas of varying dysplasia, increases the risk of inadvertently preserving undetected neoplastic foci.[6] This issue is particularly pronounced in tissue regions that appear healthy on imaging, raising concerns about the feasibility of IAT even when the IPMN is presumed to be focal.[7] Second, IPMN-affected pancreatic parenchyma may harbor synchronous or metachronous malignancies,[8] particularly pancreatic ductal adenocarcinoma, necessitating rigorous preoperative evaluation and intraoperative assessment.[9,10] These risks explain why the 2 major IAT protocols, the Minnesota[1] and Milan[2] protocols, list IPMN as a contraindication for IAT outside clinical trials. Although both acknowledge the difficulty of ensuring complete removal of malignant or premalignant cells, the Milan protocol is more permissive, allowing IAT for cases in which multifocality is definitively ruled out through endoscopic ultrasound (EUS).[11] In this study, we present a retrospective cohort of 7 patients with IPMN who underwent IAT at our center using the Milan protocol. This analysis aims to provide preliminary data on the feasibility and safety of IAT in carefully selected IPMN cases, contributing to the existing literature and informing future research directions.

2. Materials and methods

2.1. Study design and patient selection

This retrospective cohort study included patients who underwent IAT at our institution between November 2008 and June 2023. Patients were identified from a prospectively maintained database of individuals undergoing pancreatic surgery and considered for IAT according to the Milan protocol, as previously described.[2,3] The study was approved by the local ethics committee, ensuring compliance with ethical standards for clinical research. All patients provided written informed consent prior to enrollment, which included a detailed explanation of the procedures involved, potential risks, and benefits. In particular, patients were informed about the possibility of IAT as part of their treatment, including the potential risks associated with IAT in cases involving (pre)malignant pancreatic lesions, such as IPMN. The consent also included a clear explanation of the purification process for islets, which was mandated by our institutional protocols, in line with the Milan protocol, to reduce the risk of transferring malignant cells during IAT. The risks of malignant transformation and the possibility of residual cancer in the pancreatic remnant were discussed with the patients as part of the preoperative counseling. The study is registered under ClinicalTrials.gov (NCT01702051).

2.2. Eligibility criteria

Adults (aged $\geq$18 years) with fasting blood glucose levels $<$126 mg/dL and not using glucose-lowering medications were eligible for inclusion. Patients diagnosed with IPMN and undergoing pancreatic surgery were considered after a thorough evaluation of disease extent. Eligible patients had no evidence of multifocal pancreatic neoplasms on preoperative imaging or intraoperative assessment. Additionally, there was no history or suspicion of multiple endocrine neoplasms and no pathological involvement of the pancreatic transection margin, except for low-grade dysplasia. Patients also had to be free of medical conditions that, in the investigator's judgment, would interfere with the safe completion of IAT.

2.3. Preoperative assessment

All patients underwent a comprehensive preoperative evaluation. This included abdominal ultrasonography, as well as

contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging performed on a case-by-case basis, depending on the clinical scenario. EUS with fine needle aspiration was routinely used to assess the characteristics of the IPMN, particularly for lesions exhibiting worrisome features. In addition, patients underwent a series of laboratory tests, including complete blood count, basic metabolic panel, liver function tests, amylase, lipase, endocrine function, and coagulation profile, to further evaluate their overall health status and suitability for surgery.

2.4. Indication for surgery

Patients underwent surgery because of IPMN with high-risk stigmata or worrisome features affecting a single portion of the pancreas. The portion of the pancreas that was processed for IAT had no macroscopic IPMN foci.

2.5. Surgical technique

Pancreas procurement was performed using either open or laparoscopic surgical techniques under general anesthesia. The extent of resection varied from extensive left pancreatectomy to total pancreatectomy or completion pancreatectomy, depending on the location and extent of the IPMN. The blood supply to the pancreas was preserved to minimize warm ischemia time for the islets. The decision to retain or remove the spleen was based on individual patient factors.

2.6. Islet isolation and transplantation

After the removal of the lesion and margin evaluation, the remaining pancreatic segments were transported to the Islet Processing Facility in cold University of Wisconsin preservation solution. The islet isolation and purification process followed the automated method originally introduced by Ricordi for allotransplantation, with local adaptations as previously described.[2,3] The pancreatic duct was cannulated, and the pancreas was enzymatically digested using collagenase NB1 and neutral protease. The digested tissue was then purified using a continuous gradient of Hanks' balanced salt solution–Ficoll on a cell separator. The resulting purified islet fractions were pooled together in Connaught Medical Research Laboratories 1066 medium. Although there is no absolute threshold, we generally do not proceed with infusion if the islet yield is $<$150 islet equivalents (IEQ)/kg, as this number is a critical factor for the outcome. As we performed islet purification, the extended timeline made intraoperative infusion incompatible with the surgical procedure. Therefore, islet culturing was necessary. Finally, the cultured islets were reinfused via the portal vein within 48 hours through percutaneous transhepatic cannulation of the portal vein. Heparin (2000 units) was added to the islet preparation during the isolation process to prevent clot formation. After the surgery, the patient received enoxaparin at a dose of 40 mg, starting 6 hours postsurgery and continued once daily for at least the next 30 days.

2.7. Data collection and outcomes

Data were collected prospectively and analyzed retrospectively. Demographic data, preoperative clinical data, surgical details, islet isolation and transplantation data, and postoperative outcomes were recorded. The primary outcomes of the study included the evaluation of feasibility and safety, considering the absence of tumor dissemination. Secondary outcomes included metabolic parameters, such as insulin independence, glycated hemoglobin (HbA1c) and C-peptide levels, and overall survival.

2.8. Statistical analysis

Descriptive statistics for continuous variables are presented as mean and range and categorical variables as frequencies and percentages. Survival outcomes, including overall disease-free and diabetes-free outcomes, were estimated using Kaplan–Meier curves, with group comparisons made using the log-rank test. The analysis was conducted using GraphPad Prism 5.0 and SPSS version 24.

3. Results

3.1. Patient population

A total of 7 patients (5 female, 2 male) with IPMNs were included in this study (Table 1). The mean age was 65.3 years (range: 46-79), and the mean body mass index was 23.21 kg/m^2 (range: 21.23-27.7). The mean estimated glomerular filtration rate was 78.14 mL/min/1.73 m^2 (range: 40-101). Regarding IPMN classification, 4 patients (57.1%) had branch-duct IPMN, while 3 (42.9%) had mixed-type IPMN. The cyst location varied, with 4 cases (57.1%) occurring in the neck/body of the pancreas, 2 (28.6%) in the head, and 1 (14.3%) in the neck alone. Preoperative radiologic workup included magnetic resonance imaging, EUS, CT, and fine needle aspiration in most cases. Worrisome features were identified in all patients, with cyst size $\geq$ 3 cm being the most common (57.1%), followed by cyst growth $>$5 mm/2 years (28.6%), enhancing thickened cyst wall (28.6%), and acute pancreatitis (14.3%). High-risk stigmata, specifically enhancing mural nodules $\geq$5 mm, were present in 2 patients (28.6%). Surgical management consisted of spleen-preserving distal pancreatectomy in 3 patients (42.9%), laparoscopic distal pancreatectomy and splenectomy in 2 (28.6%), and completion pancreatectomy after pancreatoduodenectomy in 2 (28.6%) because of severe complications due to disruption of pancreatic anastomosis. Completion pancreatectomy occurred on postoperative days 9 and 22, respectively; both patients experienced acute septic conditions, leading to the need for total pancreatectomy. The pathological details of the resected IPMNs are summarized in Table 2. Lesions were predominantly unilocular cystic formations, with patient 7 being an exception, presenting as a multicystic lesion. Lesion sizes ranged from 1 cm to 3.5 cm. The epithelial subtypes were mostly gastric, with patient 6 exhibiting a mixed gastric and intestinal phenotype. Dysplasia varied from low- to intermediate/high-grade (Table 2). Ductal involvement was observed in both the main pancreatic duct and

Table 1
Demographics, clinical-radiologic characteristics, and operative procedures of 7 resected intraductal papillary mucinous neoplasms.

Pt No.	Sex	Age (y)	Weight (kg) BMI (kg/m^2)	eGFR (mL/min/ 1.73 m^2)	Type of IPMN	Cyst location	Preoperative radiologic workup	Worrisome feature	High-risk stigmata	Surgical procedure
1	F	51	61 21.26	69	Branch duct	Neck/body	MRI, EUS, CT, FNA	Cyst growth >5 mm/2 y	-	Laparoscopic distal pancreatectomy and splenectomy
2	F	46	65 23.88	101	Combined	Neck/body	MRI, EUS, FNA	Cyst size ≥3 cm	-	Spleen-preserving distal pancreatectomy
3	F	67	53 21.23	51	Branch duct	Head	EUS, CT, FNA	Enhancing thickened cyst wall	-	Completion pancreatectomy after pancreatoduodenectomy (day +9)
4	M	79	66 23.11	40	Branch duct	Neck	MRI, EUS, CT, FNA	Cyst size ≥3cm	Enhancing mural nodule ≥5 mm	Spleen-preserving distal pancreatectomy
5	M	72	80 27.7	93	Combined	Head	MRI, EUS, CT, FNA	Cyst size ≥3 cm + MPD 5-9 mm	-	Completion pancreatectomy after pancreatoduodenectomy (day +22)
6	F	66	54 22.1	78	Branch duct	Neck	MRI, EUS, FNA	Cyst growth >5 mm/2 y + acute pancreatitis	-	Laparoscopic distal pancreatectomy and splenectomy
7	F	76	62 23.2	95	Combined	Neck/body	EUS, CT, FNA	Cyst size ≥3 cm + enhancing thickened cyst wall + distal atrophy	Enhancing mural nodule ≥5 mm	Spleen-preserving distal pancreatectomy

BMI, body mass index; CT, computed tomography; eGFR, estimated glomerular filtration rate; EUS, endoscopic ultrasound; F, female; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasms; M, male; MPD; main pancreatic duct; MRI, magnetic resonance imaging; Pt, patient; MTC, Microscopic Tumor Cell.

Table 2
Pathology details of 7 resected intraductal papillary mucinous neoplasms.

Pt No.	Lesion description	Size (cm)	Epithelial subtype	Dysplasia	Duct involvement	Distal transection margin	Pancreatic parenchyma
1	Unilocular cystic lesion	1	Gastric	Low/intermediate-grade	Mixed-type IPMN	Negative for MTC + focal low-grade dysplasia	Regular morphology
2	Unilocular cystic lesion	3	Gastric	Low-grade	Branch ducts with focal extension to the main pancreatic duct	Negative for MTC	Mild periductal fibrosis and slight stromal edema
3[a]	Unilocular cystic lesion	2	Gastric	Intermediate/high-grade	Mixed-type IPMN	Negative for MTC + focal low-grade dysplasia	Regular morphology
4	Unilocular cystic lesion	2.3	Gastric	Intermediate-grade	Mixed-type IPMN	Negative for MTC	Regular morphology with mild atrophy and adipose involution
5[a]	Unilocular cystic lesion	-	Undetermined	Low/intermediate-grade	Mixed-type IPMN	Negative for MTC	Mild atrophy and fibrosis with some insular hyperplasia
6	Unilocular cystic lesion	1.8	Mixed gastric and Intestinal	Intermediate-grade	Mixed-type IPMN	Negative for MTC + focal low-grade dysplasia	Regular morphology with mild atrophy, fibrosis, and chronic inflammation
7	Multicystic lesion	3.5	Gastric	Intermediate-grade	Mixed-type IPMN	Negative for MTC, intermediate-grade dysplasia involving the main duct	Regular morphology with limited foci of chronic pancreatitis

IPMN, intraductal papillary mucinous neoplasm; MTC, Microscopic Tumor Cell; Pt, patient.

[a] Pathology details refer to the analysis of tissue obtained after the initial surgical procedure.

branch ducts, with patient 2 showing focal extension from branch ducts to the main pancreatic duct. Focal low-grade dysplasia was observed at the distal transection margins in patients 1, 3, and 6, while case 7 exhibited intermediate-grade dysplasia at the margin, affecting the main duct at the transection site. The surrounding pancreatic parenchyma was generally of regular morphology, but mild pathological changes were noted in some cases. These included mild periductal fibrosis and slight stromal edema in patient 2, mild atrophy, fibrosis, and chronic inflammation in patient 6, and limited foci of chronic pancreatitis in patient 7. These changes likely represent the effect of the IPMN lesions on the adjacent tissue.

3.2. Islet isolation and transplantation

Islet isolation was performed on pancreatic tissue resected from all 7 patients, with pancreas weights ranging from 28 g to 70 g (Table 3). After enzymatic digestion, tissue volumes varied from 4 mL to 25 mL, with IEQ/g of digested pancreatic tissue ranging from 528 (patient 7) to 4793 (patient 5). The isolation index, representing the efficiency of islet extraction, ranged from 0.16 (patient 7) to 0.82 (patient 3). Purification, aimed at removing nonislet cells, resulted in efficiency values ranging from 20% to 85%. The volume of purified tissue varied from 0.3 mL to 5 mL, with final IEQ/g of tissue ranging from 247 (patient 7) to 3399 (patient 5). Patients 1, 2, 4, and 5 achieved successful purification with sufficient islet yields. In contrast, patient 6 had a low islet yield, while patient 3 was excluded due to purification failure. Patient 7 was also deemed ineligible due to an insufficient islet yield combined with a positive distal transection margin indicating intermediate-grade dysplasia, precluding transplantation. After culture, which was performed for 15 to 16 hours, the final islet yields per kilogram of body weight (IEQ/kg) ranged from 219 (patient 6) to 1833 (patient 5). Ultimately, 4 patients (1, 2, 4, and 5) met the criteria for transplantation. These findings highlight the variability in islet isolation outcomes and emphasize the

Table 3
Islet isolation and transplant of 7 resected intraductal papillary mucinous neoplasms.

Pt no.	Pancreas weight	After digestion				After density gradient					Pretransplant culture		Transplantation	
		Tissue volume (mL)	IEQ ($\times 10^3$)	Isolation index	IEQ/g	Tissue volume (mL)	IEQ ($\times 10^3$)	Isolation index	IEQ/g	Purification (%)	Time (h)	IEQ/g	Yes/No	IEQ/kg
1	40	15	103.36	0.52	2584	0.30	78.32	0.59	1,958	85	16	1,384	Yes	923
2	61	25	243.6	0.67	3993	0.50	57.87	0.31	949	30	15	676	Yes	634
3[a]	50	10	95.33	0.82	1907	Discharge for purification failure					No		No	
4	68	20	222.65	0.53	3274	1.5	144.15	0.50	2,120	50	16	1,530	Yes	1,576
5[a]	70	13	331.75	0.69	4739	3	237.91	0.71	3,399	30	16	2,096	Yes	1,833
6	32	4	77.22	0.59	2413	Tissue already purified after digestion				20	19	370	No (discharge for low no.)	219
7	28	5	14.78	0.16	528	5	6.92	0.20	247	-	Discharge for low no. and distal transection margin positive for intermediate-grade dysplasia		No	

IEQ, islet equivalent; Pt, patient.

[a] Details refer to the analysis of tissue obtained after the last surgical procedure.

challenges in obtaining sufficient islet numbers for transplantation after pancreatic resection for IPMN. None of the transplanted patients experienced complications related to islet infusion or exhibited any significant increase in portal vein pressure after the procedure. The recorded portal vein pressures before and after islet infusion were 9.5 ± 2.9 mmHg and 9.5 ± 2.9 mmHg, respectively, indicating stability within a safe range.

3.3. Follow-up

Overall survival, disease-free survival, and diabetes-free survival are presented in Figure 1. Patient 3, who underwent completion pancreatectomy because of pancreatic anastomosis disruption, did not undergo autotransplantation for clinical instability and died 6 days after completion pancreatectomy. In contrast, patient 5, who successfully received the autotransplant, remains alive at 11.88 years of follow-up. Among the patients who underwent partial pancreatectomy (1, 2, 4, 6, and 7), all were alive at the last follow-up, with survival times of 7.02, 3.99, 9.08, 7.69, and 7.57 years, respectively. Notably, none of the patients showed evidence of local disease recurrence or suspicious hepatic lesions suggestive of metastatic progression. All patients who underwent partial pancreatectomy and received an IAT remained diabetes-free at the last follow-up, demonstrating preserved insulin secretion. In contrast, patient 5, who underwent total pancreatectomy, became insulin-dependent but achieved excellent metabolic control, with no severe hypoglycemic events, an HbA1c of 6.4%, low insulin requirements (0.13 U/kg/d), and residual β-cell function, as evidenced by a fasting C-peptide level of 0.6 ng/mL (Fig. 2). All patients who did not receive an IAT developed diabetes. Aside from patient 3, who underwent total pancreatectomy, patients 6 and 7, who had partial pancreatectomy, required treatment with metformin, initiated on days 1485 and 7, respectively. Both achieved discrete metabolic control, with HbA1c levels of 7.4% and 6.5% at the last follow-up (Fig. 2).

4. Discussion

The role of IAT in patients undergoing pancreatectomy for IPMNs remains poorly investigated. A review of the literature identified 3 reported cases of IAT for IPMNs within a larger cohort of 20 patients who underwent extended distal pancreatectomy for benign pancreatic lesions at the Samsung Medical Center in Korea.[12-14] In these cases, the authors implemented multiple strategies to minimize the risk of disease dissemination and recurrence, including preoperative CT and endoscopic retrograde cholangiopancreatography to assess the entire pancreas for multifocality, as well as intraoperative frozen section analysis. Histopathological examination of the tumor revealed a moderate grade of dysplasia, suggesting a relatively low malignant potential. Notably, no cases of recurrence or new-onset pancreatic ductal adenocarcinoma were reported within the entire cohort, including these 3 cases, although follow-up duration varied. To our knowledge, only 1 study has described 2 cases of total

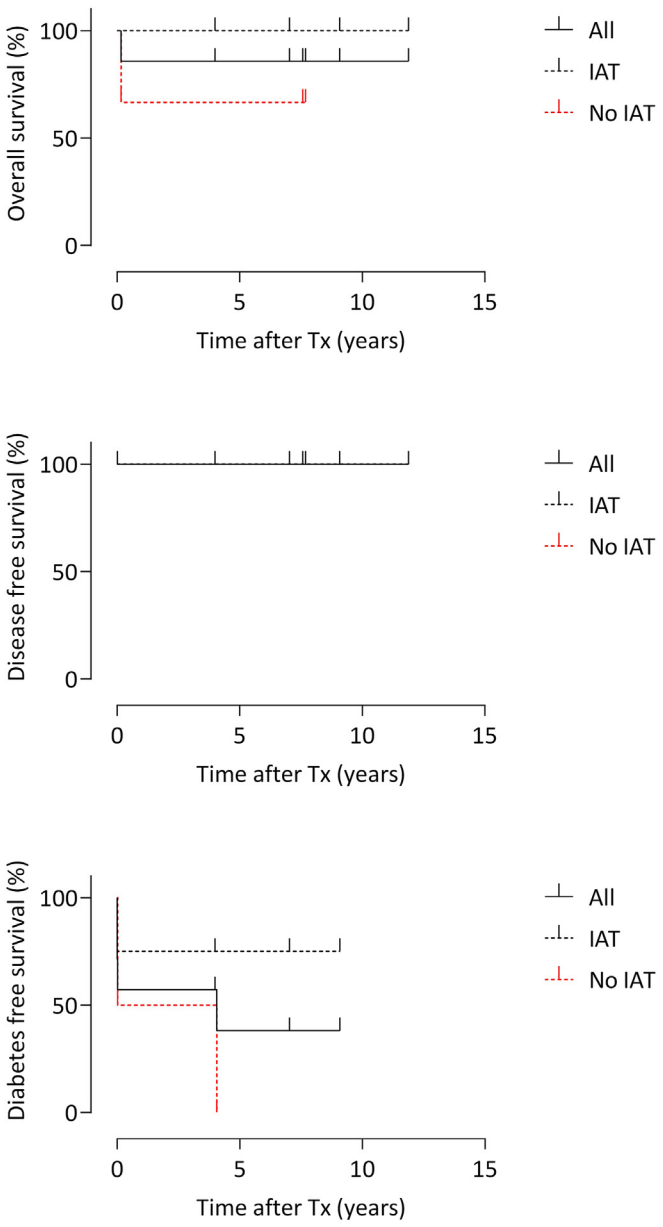

Figure 1. Overall survival, disease-free survival, and diabetes-free survival. Kaplan–Meier survival curves illustrating overall survival, disease-free survival, and diabetes-free survival in the intention-to-treat analysis. The x-axis represents time (years), while the y-axis represents survival probability. Solid lines represent the entire study population, while dotted lines indicate survival outcomes segregated by whether subjects received IAT (black) or not (red). Censored data points are marked with vertical ticks. IAT, islet autotransplantation; Tx, transplantation.

pancreatectomy with IAT for localized IPMN.[3] However, final histopathological details, such as dysplasia grade or subtype classification, were not provided. The authors reported that both patients remained alive at the last follow-up, with a median follow-up of 46 months. Our study aims to expand the limited knowledge in this field by providing further insights into the feasibility and safety of IAT in patients with focal IPMNs

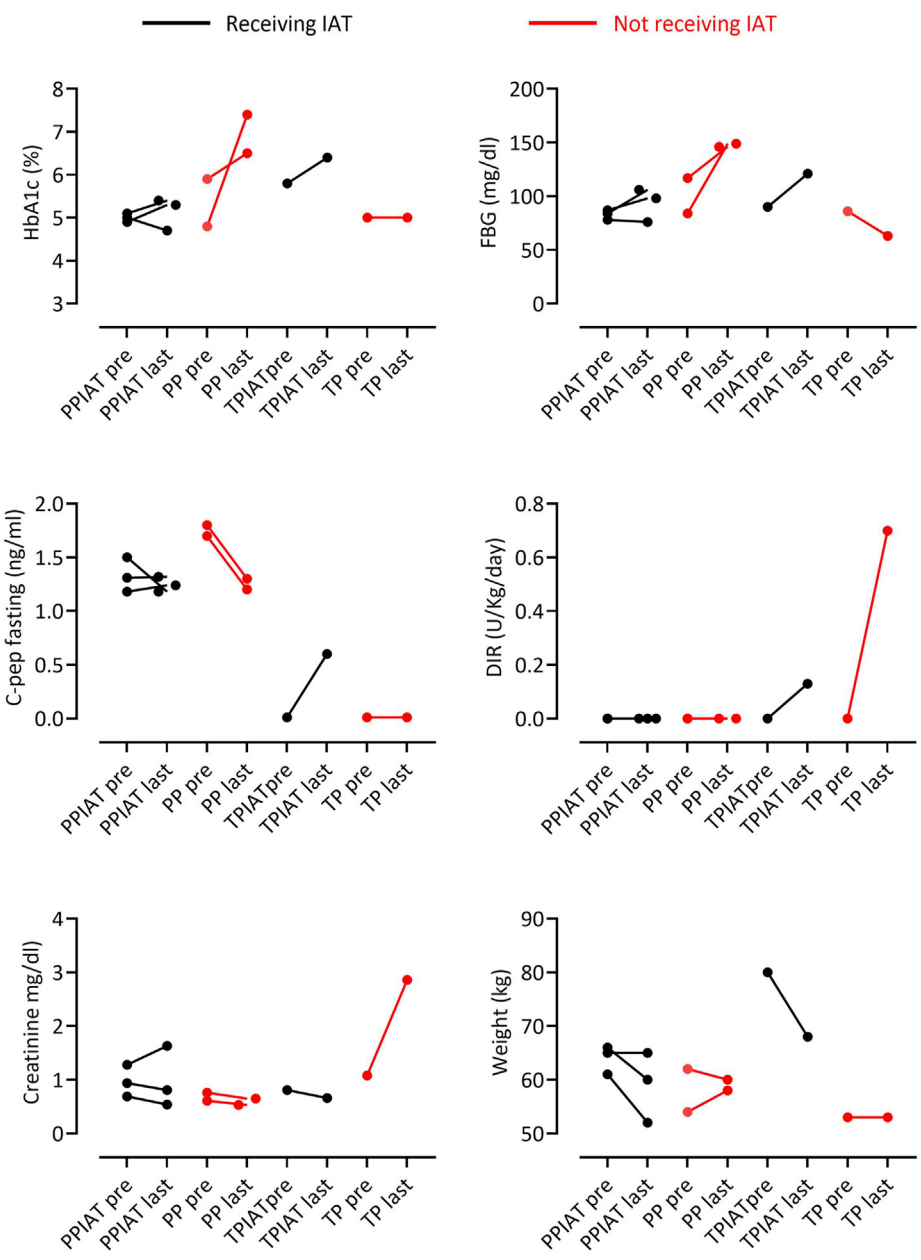

Figure 2. Metabolic follow-up after islet autotransplantation (IAT). Presented are baseline and last recorded values for fasting blood glucose (FBG), glycated hemoglobin (HbA1c), C-peptide, daily insulin requirement (DIR), creatinine, and weight. Data are stratified based on the type of surgery: partial pancreatectomy (PP) or total pancreatectomy (TP), with further segregation by whether patients received IAT. Patients receiving IAT are represented by black, while those not receiving IAT are shown in red.

undergoing pancreatectomy. A key strength of our study is the detailed histopathological analysis, which adds depth to the current understanding of the biological behavior of the disease and informs risk stratification. Our results suggest that, with appropriate patient selection, careful intraoperative management, and strict adherence to protocols, IAT can be performed safely and effectively in this patient population. Importantly, we did not observe any recurrence of disease or an increased risk of metastasis at the transplant site, a critical concern raised by previous studies. Moreover, our metabolic data indicate that IAT has the potential to preserve or restore glucose homeostasis in most patients, a crucial aspect of quality of life after pancreatic resection. A key question that arises from our findings is whether they are sufficient to extend the indications for IAT to patients with multifocal IPMNs. The primary concern here is whether the islet isolation process can effectively remove any neoplastic potential from the tissue. Preclinical models, such as the KrasLSL.G12D/+; p53R172H/+; PdxCretg/+ mouse model, have shown promising results, indicating that pancreatic exocrine tissue may lose its neoplastic potential after islet isolation and transplantation.[15] However, the translation of these findings to human cases remains unclear. While our results support the safety of IAT for focal IPMN, we cannot conclusively determine whether the procedure would be equally safe for multifocal disease. The risk of disseminating malignant or premalignant cells from multifocal lesions during islet isolation remains a significant

concern. Furthermore, a case of malignancy following IAT in a patient with chronic pancreatitis[16] underscores the complexity of the issue, indicating that caution is required, particularly in patients with multifocal or high-risk IPMNs.

Our study is subject to some limitations. First, the number of patients is relatively small, reflecting the inherent challenges in conducting such a study. The single-center nature of this study could also limit the generalizability of our results. Additionally, while the follow-up period is long-term, an even longer observation time would be necessary to fully assess the risk of very late recurrence or metastatic dissemination, given the natural history of these diseases. Furthermore, we observed variability in the outcomes of islet isolation, highlighting certain intrinsic limitations of the procedure that may impact its overall effectiveness. However, the use of strict selection criteria, a standardized protocol, and a multidisciplinary approach helps to mitigate some of these limitations.

In conclusion, our study adds valuable insights into the use of islet IAT in patients undergoing pancreatectomy for focal IPMNs. By providing more detailed data on the technical success of islet isolation, the safety of the procedure, and the metabolic outcomes, our findings build on existing literature and lay the groundwork for larger studies. Although the small sample size and variability in islet isolation outcomes are limitations, the results suggest that IAT can be considered a viable option in carefully selected patients. Further research with larger cohorts and longer follow-up will be essential to refine patient selection criteria and investigate the potential for IAT in patients with multifocal IPMNs.

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Author contributions

L.P., G.B., S.C., and F.A. contributed to conceptualization and study design. R.M., G.C., and A.M. contributed to data collection. D.C., R.C., M.S.L., and F.D.C. contributed to the methods. L.P. and F.A. had access to raw data. R.M. contributed to data curation. L.P. analyzed the data. L.P., M.F., S.P., and A.Z. contributed to data interpretation. Funding was acquired by L.P. L.P. wrote the original draft of the report. F.A., A.Z., and M.F. reviewed and edited the report. F.A. and L.P. were responsible for final submission of the manuscript for publication, and all authors approved the final version before submission. L.P., R.M., and F.A. accessed and verified the underlying study data.

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Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

Data availability

Individual participant data will not be made available. Study protocol, statistical analysis plan, and analytical code will be available from the time of publication in response to any reasonable request addressed to the corresponding author.

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