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BRIEF COMMUNICATION

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Diabetes-free survival after extended distal pancreatectomy and islet auto transplantation for benign or borderline/malignant lesions of the pancreas

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Islet autotransplant is particularly attractive to prevent diabetes after extended pancreatectomy for benign or borderline/malignant pancreas disease. Between 2008 and 2018, 25 patients underwent left extended pancreatectomy (>60%) and islet autotransplant for a neoplasm located in the pancreatic neck or proximal body. Overall, disease-free and diabetes-free survivals were estimated and compared with those observed in 68 nondiabetic patients who underwent distal pancreatectomy for pancreatic neoplasms without islet autotransplant. Median follow-up was 4 years. We observed no deaths and a low morbidity (nonserious procedure-related complications in 2 of 25 patients). Patient and insulin-independent survival rates at 4 years were 100% and 96%, respectively. Glucose homeostasis remained within a nondiabetic range at all times for 19 (73%) of 25 patients. Preoperative glycemic level and insulin resistance were major predictors of diabetes development in these patients. Patients undergoing islet autotransplant had a longer diabetes-free survival than did patients without islet autotransplant ($P = .04$). In conclusion, islet autotransplant after extended pancreatic resection for neoplasms is a safe and successful procedure for preventing diabetes.

KEYWORDS
autotransplantation, clinical research/practice, diabetes, islet transplantation

1 | INTRODUCTION

Islet autotransplant (IAT) has initially been performed to prevent surgical diabetes after total or subtotal pancreatectomy for chronic pancreatitis.[1,2] Additional indications for IAT other than chronic pancreatitis are still controversial[3] and the experience has been limited to small case series.[4-8] One particularly attractive use for IAT is after extended distal pancreatic resection for benign or borderline/malignant lesions located at the neck of the pancreas. In fact, extended left pancreatectomy removing >50% of otherwise healthy pancreatic tissue leads to new-onset diabetes mellitus in 9% to 31% of the patients within a few months postsurgery, and this proportion increases to 20% to 50% during follow-up.[9-14] Although in a limited number of subjects the feasibility and safety of IAT after extended left pancreatic resection have been consistently reported,[4-8] the effectiveness in preventing surgical diabetes remains a matter of

Abbreviations: CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasound; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GIST, gastrointestinal stromal tumor; HbA_{1c}, glycated hemoglobin; HOMA, homeostasis model assessment; HR, hazard ratio; IAT, islet autotransplant; IC, islet count; IEQ, islet equivalent; IFG, impaired fasting glucose; IPMN, intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NFG, normal fasting glucose; PVP, portal vein pressure; PVT, portal vein thrombosis; TCAE, Terminology Criteria for Adverse Events.

discussion. The University Hospital of Geneva reported an insulin independence of 94% at 10 years and normal glucose homeostasis during a 90-month follow-up in 11 of 15 patients who received IAT after an extended pancreatectomy with 75% loss of pancreatic parenchyma.[4,15-20] Conversely, the Samsung Medical Center in Seoul reported that IAT did not significantly decrease the progression to diabetes in 20 patients with 50% to 60% loss of distal pancreatic parenchyma after benign tumor resection. In the present study we report our experience with combined extended left pancreatectomy for neoplasms of the pancreatic neck and IAT, in the attempt to prevent the occurrence of surgical diabetes. Results were compared with those obtained in cohorts of nondiabetic patients who underwent left pancreatic resection for pancreatic neoplasms without IAT.

2 | MATERIAL AND METHODS

2.1 | Patients

From November 2008 to September 2018, all patients scheduled for pancreatic surgery at the Pancreatic Unit of the Department of Surgery of the San Raffaele Scientific Institute (Milan, Italy) were screened to assess whether they were eligible for IAT according to the Milan Protocol (see references 8,21). Moreover, since July 2013, the Islet Processing Facility of the San Raffaele Scientific Institute acted as the remote islet isolation center "on demand" for the Istituto Clinico Humanitas (Rozzano, Italy), and a second surgical site 15 miles away recruited patients according to the same protocol. A total of 113 patients met the criteria for IAT. Thirty-four (30%) of 113 patients were candidates for extended distal pancreatectomy (>60%) and simultaneous IAT for neoplasms of the pancreatic body-neck region and were included in this study. A scheme summarizing the selection process is reported in Figure 1. Local ethics committee approval was obtained for the assessment, islet transplant, and follow-up, with all patients signing an informed consent before study enrollment (NCT01702051). Patients who had a left pancreatic resection in the same period but did not received IAT were also evaluated for diabetes-free, disease-free, and overall survival within a prospective observational study to characterize the clinical signature, risk factors, and etiopathogenetic aspects of pancreatogenic diabetes that we conducted from January 2008 to October 2012.[22] Seven hundred sixty adult incident cases of pancreatic disease (new diagnosis of pancreatic disease, proposed for either curative or not

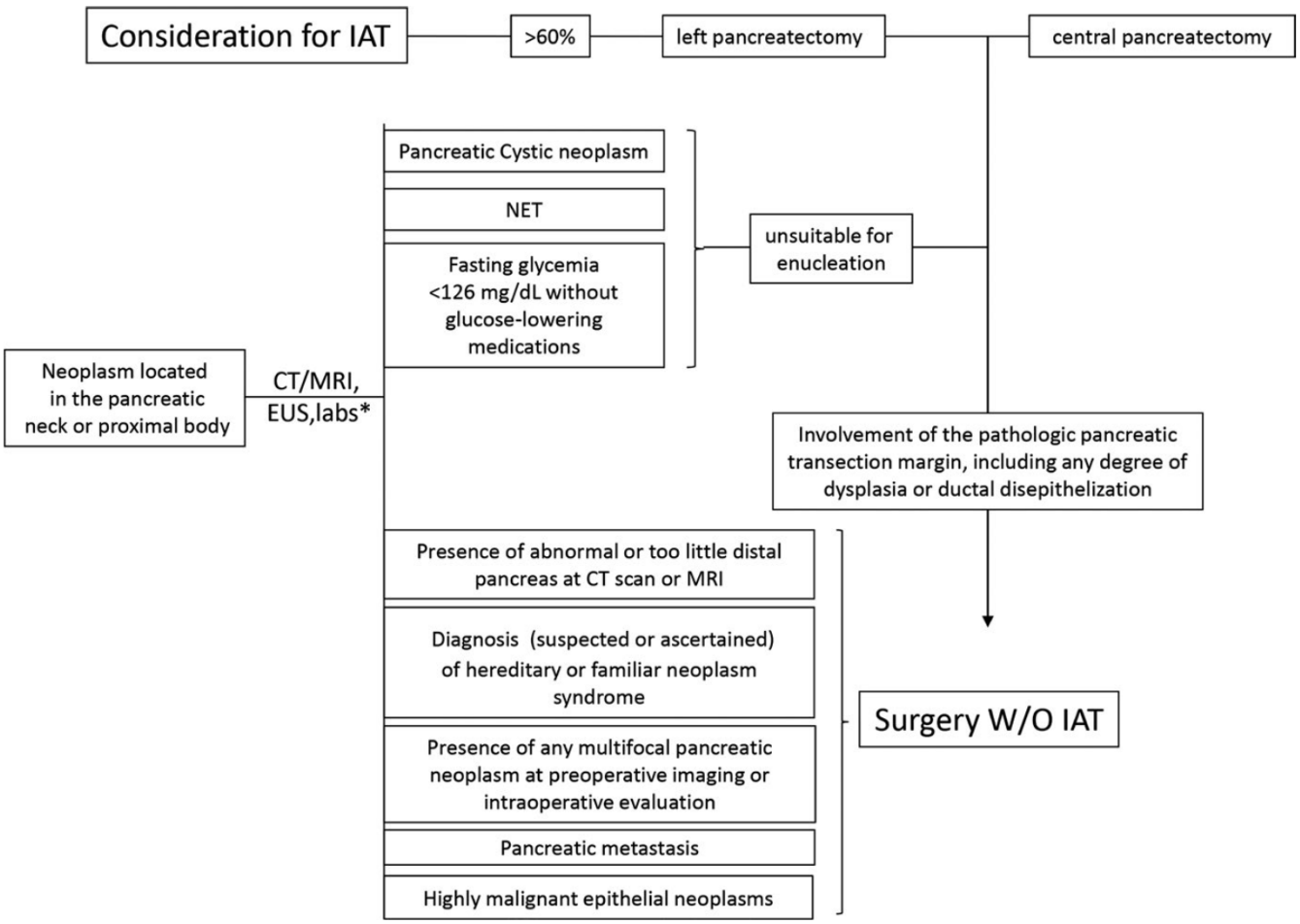

FIGURE 1 IAT screening algorithm for patients with neoplasm located in the pancreatic neck or proximal body. *Complete blood count, basic metabolic panel, liver function tests, amylase, lipase, endocrine function, coagulation profile, tumoral biomarkers. CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; IAT, islet autotransplant

curative surgical treatment) were admitted to the Pancreatic Unit and 624 eligible patients agreed to participate in the study. Of 624 cases, 114 (18.3%) were patients without diabetes who underwent distal pancreatectomy for neoplasms other than pancreatic ductal adenocarcinoma located at the pancreatic neck or proximal body (n = 68, 10.9%). For all participants, medical history, blood biochemistry from the preoperative workup, diabetes-free survival, disease-free survival, and overall survival were recorded.[22]

2.2 | Islet isolation, purification, and transplant

Open or laparoscopic surgery was performed under general anesthesia. The spleen was preserved or removed, as appropriate. If a neoplasm was the reason for pancreatic resection, 1 cm of the pancreatic remnant proximal to the pancreatic margin was resected and sent for frozen section examination to confirm margin negativity.[8,21] The pancreatic tissue for islet isolation was immediately flushed with cold University of Wisconsin preservation solution. Islets were isolated, purified, and transplanted as previously described.[6-8] The purified islets were transplanted back within 48 hours via percutaneous transhepatic cannulation of the portal vein under ultrasonography or fluoroscopic guidance. Islets were counted and their numbers were expressed as absolute number (islet count [IC]) and number of islets normalized to a 150-μm diameter (islet equivalent [IEQ]). Heparin (2000 units) was added to the islet preparation. The patient received enoxaparin at a dose of 40 mg starting 6 hours after the end of the elective surgery and then was administered once daily for at least the next 30 days. After the procedure, glucose levels were tightly controlled (target blood glucose level of 120 mg/dL) for at least 5 days, using continuous intravenous insulin infusion. Assessment of portal vein patency was performed through Doppler ultrasound at postsurgical days 1, 15, and 30. Adverse events related to the islet infusion procedure were recorded and classified according to the Terminology Criteria for Adverse Events (TCAE) In Trials of Adult Pancreatic Islet Transplantation Version 4.1 http://www.isletstudy.org/CITDocs/CIT-TCAE%20V4.pdf. The β-cell function was assessed, as previously described,[6-8,23] by measuring fasting C-peptide (defined as positive for levels ≥0.09 ng/mL; AIA-PACK C-Peptide, Tosoh, Tokyo, Japan), glycated hemoglobin (HbA_{1c}; Bio-Rad Variant II HbA1c analyzer; Bio-Rad Laboratories, Munich, Germany), and fasting plasma glucose (FPG; glucose-oxidase method, Advia 2400; Siemens Diagnostics, Deerfield, IL) and recording average daily insulin requirement.

2.3 | Study definitions

2.3.1 | Diabetes

Study participants were defined as having diabetes if at least 1 of the following criteria was met: FPG ≥126 mg/dL (7.0 mmol/L), HbA_{1c} ≥6.5% (48 mmol/mol), or prescription of diabetes medications. Study participants with an FPG level from 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) were classified as having impaired fasting glucose (IFG). Study participants with FPG level <100 mg/dL (5.6 mmol/L) were classified as having normal fasting glucose (NFG). Insulin independence was defined as no need for exogenous insulin treatment, with adequate glycemic control (ie, HbA_{1c} <7% [53 mmol/mol], fasting capillary glucose levels <140 mg/dL [7.8 mmol/L] >3 times per week and 2-hour postprandial capillary glucose levels <180 mg/dL [10 mmol/L] >4 times per week).

2.4 | Statistical analysis

Data are presented as mean ± SD or median and IQR, according to their distribution. Variables with a normal distribution were compared with the use of 1-way unpaired or paired Student's *t* test. Variables with a nonnormal distribution were compared with the use of a Mann-Whitney *U* test. Categorical variables were compared by using the χ^2 test or Fisher's exact test as appropriate. Survival was estimated according to Kaplan-Meier. Association between variables was assessed by Cox regression analysis. All statistical analyses were performed using SPSS statistical software, version 13.0 (SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Patients and surgery

From November 2008 to September 2018, 32 patients were candidates for extended distal pancreatectomy and simultaneous IAT for lesions of the pancreatic body-neck region. Further, 2 patients were eligible for distal pancreatectomy and salvage IAT after relaparotomy due to a postoperative complication following enucleation. Six (17.6%) of 34 IAT-eligible patients were not transplanted because islet preparations were considered inadequate due to an insufficient number of islets (n = 5, IEQ/kg <50) or bacterial contamination (n = 1). Three (10.7%) of 28 transplanted patients had hereditary pancreatitis (*CFTR* gene mutations) and were not included in the analysis. From January 2008 to October 2012, 68 patients without diabetes were candidates for distal pancreatectomy without IAT for neoplasms of the pancreatic neck or proximal body. Patient characteristics and diagnosis are shown in Table 1. The 2 groups of patients with extended distal pancreatectomy for pancreatic neoplasms were similar in terms of weight, kidney function, glucose control, and pancreatic diseases.

3.2 | Islet isolation and transplant

Islet isolation outcomes are summarized in Table 2. Mean pancreas weight was 42.1 ± 16 g. The median prepurification and postpurification number of islets was 161 700 IEQ (105 320-198 150) and 144 150 IEQ (77 412-164 787 IEQ), respectively ($P = .033$, Wilcoxon signed-rank test). Thus, the median number of IEQ isolated per gram of pancreas was 3669 (3130-4763) prepurification and 3252 postpurification (2175-4334) ($P = .053$). All 25 patients received cultured islets (median time in culture 16 hours). The mean body weight of recipients was 70.1 ± 16 kg, with a

TABLE 1 Patient characteristics

IAT	Yes	No	*P*
Eligible patients	25	68	
Median follow-up (year [95% CI])	4.02 (2.1-5.9)	5.04 (4.54-5.54)	.91
Age (years)	52 ± 14	56 ± 15	.208
Sex (M/F)	7/18	31/37	.126
Body mass index	25.2 ± 4.2	25.4 ± 4.8	.91
Weight (kg)	70.1 ± 16	70.8 ± 15	.98
Fasting plasma glucose (mmol/L)	4.8 ± 0.7	4.7 ± 1.2	.65
Impaired fasting glucose	3/22 (12%)	14/54 (21%)	.34
HbA_{1C} (%)	5.46 ± 0.42	5.42 ± 0.69	.83
Fasting insulin (pmol/L)	84.9 ± 64.6	65.9 ± 45.8	.18
Insulin HOMA2-%B	133 (106-168)	115 (83-177)	.26
Insulin HOMA2-%S	76 (42-117)	91 (64-129)	.25
Creatinine (μmol/L)	71.4 ± 23	73 ± 22.4	.72
Estimated GFR (mL/min/1.73 m^2)	97 ± 30	95 ± 23	.70
Diagnosis			
Pancreatic cystic neoplasm	14/25	25/68	.376
IPMN	2	7	
Serous cystadenoma	3	5	
Mucinous cystadenoma	4	8	
Solid pseudopapillary neoplasm	5	4	
Epithelial cyst	0	1	
NET	11/25	34/68	
Grade 1	7	23	
Ki67 index (%)	1.7 ± 0.5	1.13 ± 0.31	
Mitotic index (HPF)	0.14 ± 0.37	0.26 ± 0.38	
Vascular invasion	2/7	1/23	
Perineural invasion	0/7	1/23	
Lymph node metastases	1/7	0/23	
Extrapancreatic invasion	2/7	1/23	
Grade 2	4	10	
Ki67 index (%)	3.7 ± 1.1	6 ± 5.5	
Mitotic index (HPF)	3.3 ± 3	1.4 ± 1.2	
Vascular invasion	0/4	4/10	
Perineural invasion	0/4	4/10	
Lymph node metastases	0/4	4/10	
Extrapancreatic invasion	2/4	5/10	
Grade 3	0	1	
Ki67 index (%)		70	
Mitotic index (HPF)		80	
Vascular invasion		1/1	
Perineural invasion		1/1	
Lymph node metastases		1/1	
Extrapancreatic invasion		1/1	
Main hormone expressed			
None	6/11	24/34	

(Continues)

TABLE 1 (Continued)

IAT	Yes	No	*P*
Insulin	0/11	6/34	
Glucagon	4/11	3/34	
Somatostin	1/11	1/34	
Others[a]	0/25	9/68	

CI, confidence interval; HOMA, homeostasis model assessment; GFR, glomerular filtration rate; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor.

[a]Kidney metastasis (n = 4), adenosquamous carcinoma of the pancreas (n = 1), acinar cell carcinomas of the pancreas (n = 1), pancreatoblastoma (n = 1), acinar cell carcinomas of the pancreas (n = 1), medullary carcinoma of the pancreas (n = 1), gastrointestinal stromal tumor infiltrating the pancreas (n = 1). Statistical analysis: one-way unpaired Student's *t* test, Mann-Whitney *U* test or χ^2 test, as appropriate.

median transplanted IEQ of 2041 IEQ/kg (1333-2876 IEQ/kg). The volume of islet tissue infused was 2 mL (1-4.5 mL) with a 40% (20%-70%) degree of purification. The site used for transplant was the portal vein for all recipients. Portal vein pressure (PVP) change after infusion of islets was clinically insignificant: the mean preinfusion PVP was 12 (8-14) cm H_2O and the mean postinfusion PVP was 13 (9-15) cm H_2O ($P < .01$). Procedure-related complications occurred in 2 (8%) of 25 patients, with none potentially serious (TCAE score ≥ 3). Specifically, a partial left portal vein thrombosis occurred in 1 patient (treated with low molecular weight heparin with resolution). One subject had a bleeding related to the percutaneous portal vein access procedure (the bleeding did not require intervention). Splenectomy was performed in 11 of 25 patients.

3.3 | Follow-up: patient survival

On September 1, 2018, the median follow-up for distal pancreatectomy and IAT was 4.02 (2.1-5.9) years and all patients were alive (Figure 2). Twenty-four of 25 patients were disease free at their last visit. One patient (NET grade 2, pT3pN0pM0) developed bone and liver metastases at day 783 after surgery, started chemotherapy, and is still alive at day 1176. On the same date, the median follow-up for distal pancreatectomy without IAT for pancreatic neoplasms was 5.04 (4.54-5.54) years and 60 (88.2%) of 68 patients were still alive (Figure 2). Eight patients died after hospital discharge: 1 patient (NET grade 2) died from metachronous lymphoma; 3 patients (serous cystadenoma, NET grade 1, NET grade 2) died from cardiovascular events; 1 patient who already had liver metastases at the time of pancreas surgery (NET grade 2) died because of disease progression; 3 patients (NET grade 2, NET grade 3, gastrointestinal stromal tumor [GIST], n = 1), who were disease free after surgery, died due to the metastatic relapse of their neoplasm. Six additional patients developed a disease recurrence but are still alive: liver metastasis (n = 2, pancreatoblastoma and NET grade 2), nonhepatic metastasis (n = 3; kidney cancer with pancreatic metastasis), and local recurrence (n = 1, intraductal papillary mucinous neoplasm).

3.4 | Follow-up: glucose homeostasis

In distal pancreatectomy with IAT, 6 (27%) of 25 patients developed diabetes at a median of 185 days after pancreatectomy. Regarding the treatment of diabetes, 1 of the 6 patients was treated with insulin (insulin requirement 0.89 U/kg/day), 2

TABLE 2 Islet isolation outcomes in autologous islet auto transplant

Trimmed pancreas weight (g)	36 (31-53)
Digestion	
Digested IC (×10^3)	247.5 (199.3-376.8)
Digested IEQ (×10^3)	161.7 (105.3-198.1)
Digested IEQ/g pancreas	3669.9 (3130-4763)
Digested IEQ/IC	0.53 (0.44-0.73)
Digested tissue volume (mL)	15 (10.6-20)
Purification	
Postpurification IC	213 (144.4-275)
Postpurification IEQ	144.1 (77.4-164.8)
Postpurification IEQ loss (%)	11 (0-31)
Postpurification IEQ/g pancreas	3252 (2175-4334)
Postpurification IEQ/IC	0.59 (0.43-0.82)
Postpurification tissue volume (mL)	2 (1-4.5)
Postpurification purity (%)	20 (20-30)
Pretransplant culture	
Culture time (h)	16 (14.5-16.5)
Postculture IC	206.25 (129-259)
Postculture IEQ	91.62 (55.3-105.2)
Postculture IEQ loss (%)	35 (24-47)
Postculture IEQ/IC	0.43 (0.35-0.64)
Microbiology	
Positive post IAT islet cell culture	3/25 (12%) *Serratia marcescens Sphingomonas paucimobilis Staphylococcus epidermis*
Transplantation	
Islet infused (IEQ/kg)	2041 (1333-2876)
Islet purification (%)	40 (20-70)
Δ Portal vein pressure (cm H_2O)	1 (0-1.5)
Posttransplant complication	2/25
Potentially serious (TCAE score >3)	0/25
Portal vein thrombosis	1 event (partial thrombosis left portal vein)
Liver bleeding	1 event

IC, islet count; IEQ, islet equivalent; TCAE, Terminology Criteria for Adverse Events.

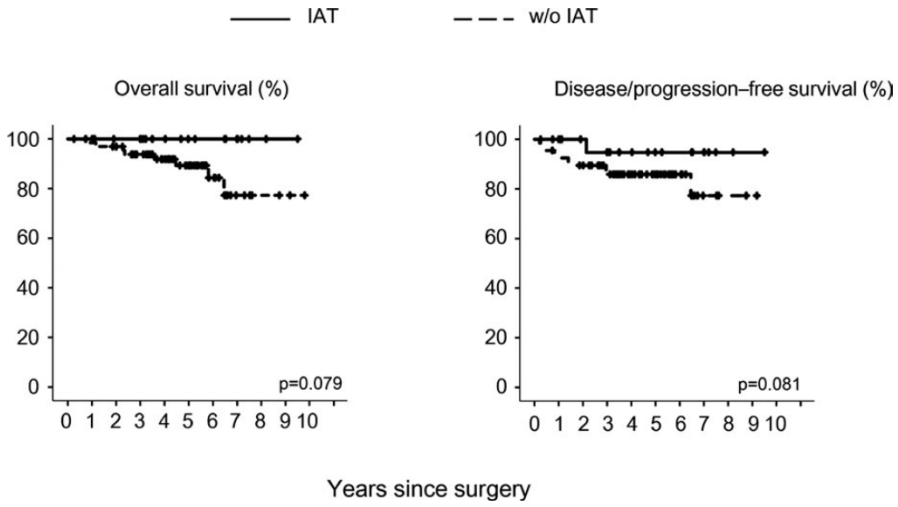

FIGURE 2 Follow-up. Probability of overall survival (left) and disease/progression-free survival (right) after extended distal pancreatectomy combined or not with islet autotransplant, according to Kaplan-Meier. IAT, islet autotransplant

patients were treated with oral diabetes medications (metformin), and 3 patients were treated with lifestyle modifications. Glucose homeostasis remained within the nondiabetic range at all time for 19 (73%) of 25 patients. Diabetes-free, diabetes drug–free, and insulin-free survivals are reported in Figure 3A. In the univariate Cox proportional hazards regression analysis, diabetes development was associated with higher weight/body mass index, higher fasting glucose and insulin levels, lower insulin sensitivity, and shorter islet culture time (Figure 3B). At the last follow-up visit, all 25 patients had a stable HbA_{1c} (6.0% [5.5%-6.4%]) and stable FPG (6.1 mmol/L [5.3-7.1]) and showed sustained insulin production (fasting C-peptide: 1.85 ng/mL [1.26-3.2]), although with significant changes from the presurgical levels (HbA_{1c} = 5.5% [5.1%-5.8%], $P < .001$; fasting C-peptide: 1.86 ng/mL [1.19-2.34], $P = .07$; FPG = 5 mmol/L [4.6-5.1], $P < .001$) (Figure 2C). Severe hypoglycemia was prevented in all patients. We also compared diabetes-free survival of patients with extended distal pancreatectomy with IAT with that of patients who had extended distal pancreatectomy in the same period of time but did not receive IAT. Patients undergoing IAT had a better diabetes-free survival than did patients without IAT ($P = .04$; Figure 4A). Thirty (44.1%) of 68 patients with distal pancreatectomy without IAT for pancreatic neoplasms ($P = .077$ vs patients with distal pancreatectomy and IAT) developed diabetes during follow-up. In addition to the factors described here earlier, higher HbA_{1c}, older age, and male sex were associated with diabetes onset in patients with distal pancreatectomy without IAT for pancreatic neoplasms (Figure 4B). Considering the rule of 10 events per variable in multivariate Cox regression, it was not possible to build a multivariate model that compared diabetes-free survival in the IAT and non-IAT groups factoring in the baseline risk factors that are associated with diabetes in either group. However, we performed an analysis arbitrarily including 3 of the baseline risk factors: HbA_{1c}, FPG, and IFG. Multivariate analysis confirmed HbA_{1c} level (hazard ratio [HR] = 2.73, 95% confidence interval [CI] = 1.16-6.43]; $P = .021$), and non-IAT on the very limits of significance (2.45 [95% CI = 0.91-6.61]; $P = .076$) as variables independently associated with diabetes development but not FPG (1.03 [95% CI = 0.99-1.07]; $P = .123$) and IFG (1.98 [95% CI = 0.54-7.29]; $P = .303$).

4 | DISCUSSION

To our knowledge, this is the largest study describing clinical features and long-term follow-up of patients receiving IAT after extended distal pancreatic resection for benign or borderline/malignant lesions located at the neck of the pancreas. We excluded from our analysis patients with chronic pancreatitis and pancreatic cancer adenocarcinoma because the development of diabetes mellitus after pancreatic resection is likely to reflect the natural course of baseline disease rather than the effects of surgery.[24] Our data demonstrate the feasibility, efficacy, and safety of this approach. Most patients (19 of 25) remained diabetes free during follow-up, while the remaining 6 patients, including 1 patient receiving small doses of insulin, maintained an HbA_{1c} of <7.0%, which is the recommended target for satisfactory glycemic control in patients with diabetes. A longer diabetes-free survival was evident when these patients were compared with a reference population of patients undergoing left pancreatic resection without IAT. The absence of a randomized control group is a limitation of this study, but it would be unethical to randomly deny IAT to patients pancreatectomized at our institution where the procedure is routinely available and approved since November 2008. Considering our control group, 57 (84%) of 68 patients were treated after November 2008, and the choice to perform IAT might have introduced unintentional bias. The decision for not performing IAT in the control group was taken on the basis of medical characteristics like tumor features (ie, pancreatic metastasis and clearly malignant epithelial neoplasm was excluded), patient choice, presence of abnormal or too little distal pancreas at CT scan or MRI, unavailability of isolation facility; while the risk factors for diabetes have not been taken into consideration. As for the risk of disseminating tumor cells to the liver as a consequence of the procedure, we observed that in our cohort of patients the oncologic outcome was not different from that expected without IAT: only 1 patient with a 1.9-cm NET grade

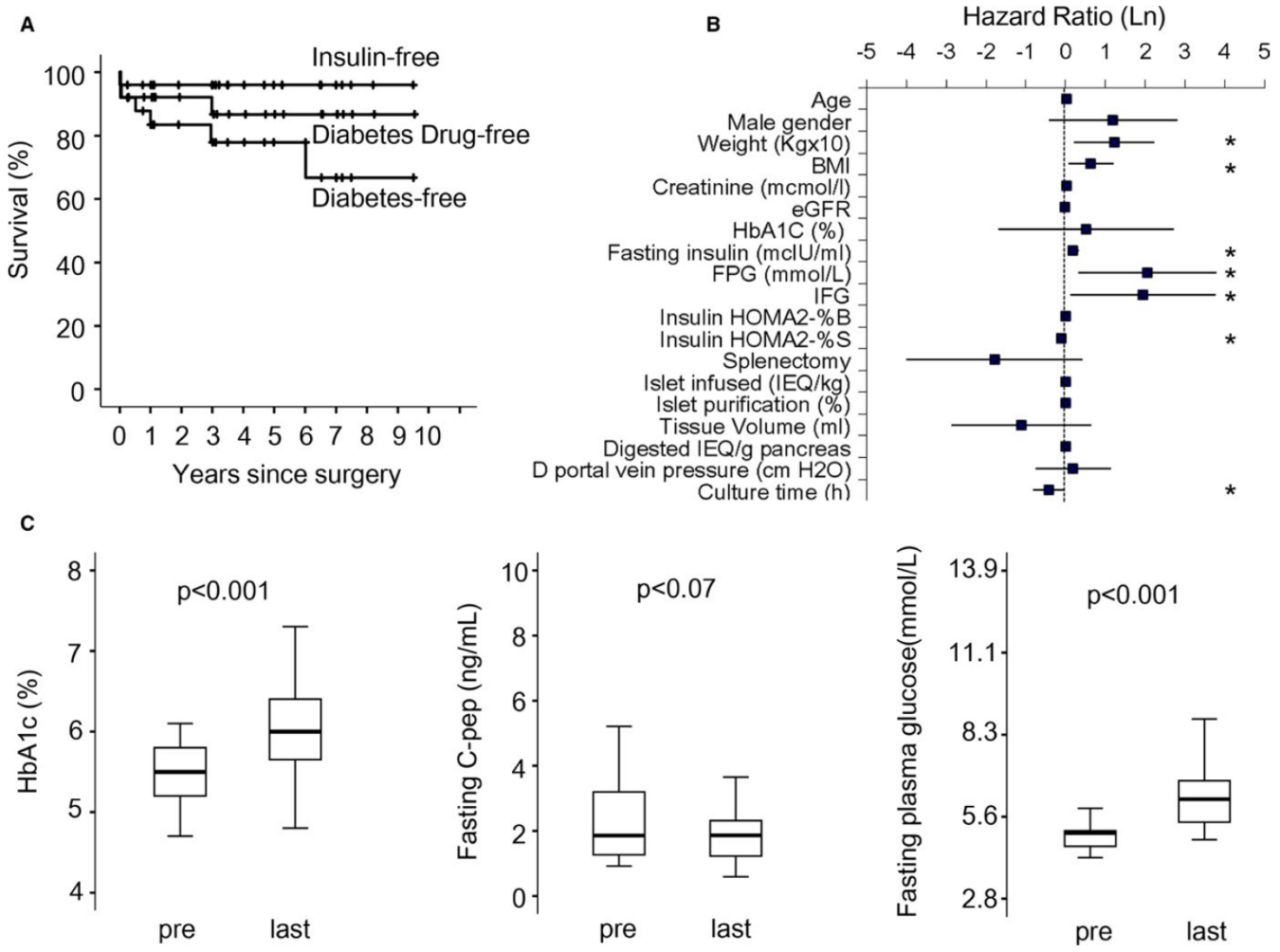

FIGURE 3 Metabolic follow-up. A, Probability of diabetes-free survival, diabetes drug-free survival, and insulin-free survival after IAT, according to Kaplan-Meier. B, Univariate hazard ratios for the development of diabetes. The associations between patient characteristics and diabetes were assessed using Cox regression. All presurgery variables analyzed are presented. Dots represent the hazard ratio after *natural log transformation*; lines limit the 95% confidence intervals. *$P < .05$. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IEQ, islet equivalent; HOMA, homeostasis model assessment; eGFR, estimated glomerular filtration rate. C, Box plots of HbA_{1c}, fasting C-peptide, and fasting glucose plasma presurgery and at the last follow-up visit [Color figure can be viewed at wileyonlinelibrary.com]

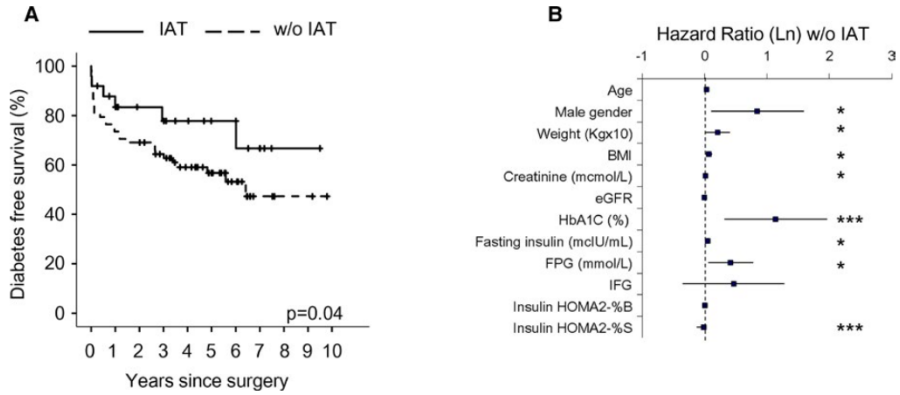

FIGURE 4 Metabolic follow-up. A, Probability of diabetes-free survival after extended distal pancreatectomy combined or not with islet autotransplant, according to Kaplan-Meier. IAT, islet autotransplant. B, Univariate hazard ratios for the development of diabetes. The associations between patient characteristics and diabetes were assessed using Cox regression. All presurgery variables analyzed are presented. Dots represent the hazard ratio after *natural log transformation*; lines limit the 95% confidence intervals. *$P < .05$. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IEQ, islet equivalent; HOMA, homeostasis model assessment; GFR, glomerular filtration rate [Color figure can be viewed at wileyonlinelibrary.com]

2 (MIB-1 index 5%; pT3pN0pM0) developed a metastatic recurrence (liver and bone, day 783 after surgery). This event was interpreted as part of the natural history of the cancer. In fact, he was an HIV-positive subject with disease extended into the peripancreatic soft tissue at the baseline and a positive posterior margin after surgery.

Our results are in agreement with the effectiveness of IAT in preventing diabetes after partial pancreatectomy reported by Ris et al from the University Hospital of Geneva (Switzerland) in a smaller cohort of subjects[4] (ie, 14 patients who had extended pancreatectomy and IAT for benign tumors [10 cystadenomas and 4 NETs]).[4] Their mean islet yields from the tumor resections averaged 5455 IEQ/g pancreatic tissue (higher than in our study), and they reported 94% insulin independence at 10 years and 73% diabetes-free survival at 7.5 years. Unfortunately, the lack of a control group in their work did not allow IAT benefits to be highlighted in quantitative terms. Different conclusions were reported by the Samsung Medical Center[5,25-27] from 20 IAT patients with 50% to 60% loss of pancreatic parenchyma due to benign tumor resection (5 solid pseudopapillary neoplasms, 10 cystadenomas, 3 intraductal papillary mucinous neoplasm, 2 other tumors). Mean islet yields from the tumor resections averaged >5000 IEQ/g, but IAT did not significantly decrease progression to diabetes compared with a control group of patients who declined IAT. It is difficult to understand the reason for this discrepancy. Baseline patient characteristics, islet isolation, and purification appeared similar between the 2 studies with only minor differences. Diabetes was defined with the same criteria. Preoperative glycemic level and insulin resistance were major predictors of diabetes development in both studies. Control groups without IAT appear to be superimposable in terms of diabetes-free survival between the 2 studies. On the other hand, the diabetes-free survival after IAT was worse in the Korean experience than in our study, despite a higher number of transplanted islets. The discrepancy may be explained by the different islet culture time that was at least 24 to 48 hours in the Korean experience and 16 hours in our experience, and we speculate a loss of functional β-cell mass during culture makes islets less efficient for transplant.[28] Beyond the comparison with other centers, the islet culture time deserves further discussion. In fact, among the factors analyzed within our study, culturing islets lead to a better success rate, evidence apparently in contrast with previously published data.[28] These data, however, are not unexpected because short-term pretransplant culture of human islets might help them to recover from stress-related changes and reduce early posttransplant loss,[29] suggesting an U-shaped effect of culture time on clinical outcome. In our cohort the median culture time was 16 hours (range 0-23 hours), a culture time that could still have more of a beneficial than a detrimental impact on islet viability and function.[29] In agreement with this, a culture time between 1 hour and 14 hours showed a favorable effect on the prevalence of insulin independence among islet transplant–only recipients compared with a shorter or longer culture time.[30]

Taken together, our data demonstrate the feasibility, efficiency, and safety of autologous islet transplant for the prevention of surgical diabetes after extended pancreatic resection for pancreatic diseases other than chronic pancreatitis. This approach, which can be accomplished within the framework of a multicenter network, should possibly always be attempted when extended pancreatic resection is performed.

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DISCLOSURE

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

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