

ORIGINAL ARTICLE

The allocation of pancreas allografts on donor age and duration of intensive care unit stay: the experience of the North Italy Transplant program

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Keywords

islet transplantation, organ allocation, organ donors, pancreas transplantation.

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Conflict of interests

The authors have declared no conflict of interests.

Received: 28 October 2013

Revision requested: 24 November 2013

Accepted: 9 December 2013

Published online: 17 January 2014

doi:10.1111/tri.12261

Summary

Starting in 2011, the North Italy Transplant program (NITp) has based on the allocation of pancreas allografts on donor age and duration of intensive care unit (ICU) stay, but not on donor weight or BMI. We analyzed the detailed allocation protocols of all NITp pancreas donors (2011–2012; $n = 433$). Outcome measures included donor characteristics and pancreas loss reasons during the allocation process. Twenty-three percent of the 433 pancreases offered for allocation were transplanted. Younger age, shorter ICU stay, traumatic brain death, and higher eGFR were predictors of pancreas transplant, either as vascularized organ or as islets. Among pancreas allografts offered to vascularized organ programs, 35% were indeed transplanted, and younger donor age was the only predictor of transplant. The most common reasons for pancreas withdrawal from the allocation process were donor-related factors. Among pancreas offered to islet programs, 48% were processed, but only 14.2% were indeed transplanted, with unsuccessful isolation being the most common reason for pancreas loss. Younger donor age and higher BMI were predictors of islet allograft transplant. The current allocation strategy has allowed an equal distribution of pancreas allografts between programs for either vascularized organ or islet transplant. The high rate of discarded organs remained an unresolved issue.

Introduction

Vascularized pancreas and islet transplantation have both entered the clinical arena as beta-cell replacement therapies for selected cases of type 1 diabetes [1]. Both transplants are the only proven treatments to restore normoglycemia in patients with type 1 diabetes [2,3]. In recent years, the 5-year graft function rate was 72% for vascularized pancreas–kidney transplant and 55% for vascularized pancreas after kidney transplant or vascularized pancreas transplant alone [4]. Based on these results, vascularized pancreas transplantation has become the most commonly procedure for beta-cell replacement in patients with type 1

diabetes. On the other hand, over the last decade, islet transplantation has become increasingly safe and effective in stabilizing glycemic control in long-term, normalizing HbA1c and lowering the risk of secondary complications in patients with type 1 diabetes [2,5]. Recent advances in islet transplantation have markedly improved the 5-year insulin independence rates, which in several independent centers is reported around 50% [6–10], placing islet transplantation, although when performed in highly selected centers, on a par with vascularized pancreas transplant alone. Therefore, organ-sharing organizations are increasingly facing the dilemma of how to allocate donor pancreases to two credible procedures for beta-cell replacement [1]. Currently,

there are no worldwide accepted criteria for the allocation of pancreas allografts, and organ-sharing organizations are proposing different strategies in different countries [11]. A donor quality index for vascularized pancreas has been proposed using sophisticated statistical analysis, and the data have been condensed and are available as an App on iPhone. Despite this in the “real life,” this approach does not work appropriately [12,13] both because many refusal reasons are not in agreement and because criteria like BMI and age cannot be applied in all world regions without taking in consideration differences in the median donor age and in the prevalence of obesity.

The North Italy Transplant program (NITp) is one of the three organ procurement and transplant coordinating organizations in Italy. It serves an area of ca 19 million inhabitants in Northern Italy, including six of the 20 Italian regions (Lombardia, Veneto, Trentino, Friuli-Venezia Giulia, Liguria e Marche). NITp comprises 129 procuring units, 43 transplant programs in 16 hospitals (15 kidney, five kidney–pancreas, nine liver, six heart, two heart–lung, five lung, one intestine), and two islet isolation facilities, hosting both islet and pancreas transplantation centers. To allow the coexistence of islet transplantation with vascularized pancreas transplantation, NITp has recently reassessed donor selection criteria and allocation procedures. In the last 2 years, the NITp has considered age and length of ICU stay, but not donor weight or BMI, as criteria for the allocation of pancreas allografts: pancreas allografts from donors 3 to 50 years old and with ≤ 4 days of ICU stay were “prioritized” for vascularized organ transplant, while pancreas allografts from donors older than 50 years and/or with > 4 days of ICU stay were “prioritized” for islet isolation. The aim of this study is to analyze how this approach worked in the clinical practice reporting the results and the outcome of all pancreas donations in the years 2011–2012.

Materials and methods

NITp allocation system

In the NITp pancreas allocation algorithm, pancreases are offered to vascularized organ transplantation if the donor is aged 3–17 years or 18–50 years *and* stayed in the ICU ≤ 4 days. The following nonbinding exclusion criteria were also considered, with the final decision made on a case-by-case basis by the senior surgeon at the transplant center being offered the pancreas allograft: amylase > 300 U/l, one or more episodes of cardiac arrest and (nor)adrenaline, and dobutamine or dopamine use. NITp protocols regulate allocation of pancreas allografts to different vascularized pancreas programs. The first four donors every month are allocated to simultaneous pancreas and kidney transplantation programs: allocation is based on ABO blood groups for recipient with less than four HLA mismatches. Local

centers have the first option to accept a pancreas allograft, followed by centers within the region and by centers within the entire NITp area. Pancreases not accepted for simultaneous pancreas and kidney transplantation or obtained in excess of the first four donors are offered for pancreas transplantation alone, and allocation is based on ABO blood groups, independently from the number of HLA mismatches. Pancreas allografts not accepted for simultaneous pancreas and kidney transplantation or pancreas transplantation alone are offered for islet isolation. Pancreas allografts are directly offered for islet isolation if the donor meets the following criteria: age 18–50 years *and* ICU stay > 4 days or 51–65 years independently by ICU stay. Local centers have the first option to accept a pancreas allograft for islet isolation. If there is no isolation facility at the local center, the pancreas is offered to one of the two NITp facilities, alternating the facilities for the first and the second half of every month.

The pancreas that is not allocated in NITp, nor as vascularized or as islet transplantation, is proposed to the other Italian regions only if they meet the eligibility criteria for the pancreas as a whole transplant. This is because in other Italian regions, there are no centers with active islet transplant programs. In the period considered, no pancreases from NITp were accepted into extra-NITp regions.

Study design, data source, and management

The study is a descriptive analysis of variables routinely collected by NITp. The analysis is based on two data sources: (i) the NITp database in which medical information on organ donors is recorded and (ii) the handwritten NITp allocation forms recording details about the allocation process, for example the time when a transplant center was contacted, whether the organ was accepted, and, if not, why it was not accepted. We included in our analysis all heart-beating donors entered in the NITp database from January 1, 2011 to December 31, 2012 ($n = 1060$) who had no contraindication for pancreas recovery and whose pancreas was eligible for allocation ($n = 433$). Of the 627 heart-beating donors not considered in the analysis, 442 were not proposed for age (435 over 65 and 7 under 3 years), 84 for an increased risk of infection (meningitis, bacteraemia, HCV positivity, HBsAg positivity), seven for an increased risk for cancer (cancer present or past that did not constitute a criterion of absolute exclusion of the donor), five for an unacceptable risk determined after the proposal of organs (tumor or infection), 19 for an indefinable risk (lack of donor’s medical history, behavioral risk factors, drug use, sexual risk), 29 for the late opposition by family (after the proposal of organs), 12 for the presence of diabetes, and 29 for the evident nonclinical suitability (prolonged cardiac arrest, very poor condition, extremely high amylasemia,

very high amine dosage, extremely long stay in intensive care).

Data sources

We queried the NITp database for data of the pancreas donors included in this study [age (years), sex (male/female), BMI (kg/m²), cause of death (traumatic/nontraumatic), length of ICU stay (days), cardiac arrest and (nor) adrenaline, and dobutamine or dopamine use] and, for those allografts that were not transplanted, the step where the organ was lost (i.e., when the organ was offered for allocation process, at the time of recovery or prior to transplantation/isolation). Data were exported to a Microsoft Excel spreadsheet where we entered the reasons for organ loss that was abstracted from the handwritten NITp allocation forms. If it was not possible to identify an unambiguous reason for refusal or loss, the reason was entered as “unknown.”

Statistics

Statistical analyses were carried out using SPSS 13 (SPSS Inc, Chicago, IL, USA). Median and interquartile range (IQR) were computed for all continuous variables, counts, and percent for categorical variables. The characteristics of transplanted and pancreas allografts lost in the allocation process were compared using chi-squared test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. A logistic regression model was used to assess the association between donor characteristics and pancreas transplant. The multivariate analysis was performed including variables that were significant at the $P < 0.2$ level in the univariate analysis. All tests were conducted using an alpha level of 0.05 to indicate statistical significance.

Results

Loss of pancreas allografts in the allocation process

Of 433 pancreases offered for allocation, 157 (36%) were initially offered for vascularized organ transplantation and 276 (64%) for islet transplantation. As shown in Fig. 1, 101 of the 157 organs offered for vascularized pancreas transplantation were withdrawn from the allocation process: six were refused and then offered for islet isolation, 57 were lost prior to recovery, and 38 were recovered and then refused ($n = 10$) or offered for islet isolation ($n = 28$). Consequently, a total of 34 pancreases initially offered for vascularized organ transplantation were shifted to islet transplantation. Of the 276 plus 34 pancreases offered for islet isolation, 161 were withdrawn from the allocation

process: 138 were lost before recovery and 23 after recovery. The remaining 149 pancreases were processed for islet isolation and 105 lost because of the low islet yield or insufficient purification. In summary, 100 (23.1%) of 433 pancreas allografts offered for allocation were transplanted: $n = 11$ vascularized pancreas transplantations alone, $n = 40$ simultaneous vascularized pancreas–kidney transplantations, $n = 5$ vascularized pancreas transplantations combined with transplantation of other visceral organs, and $n = 44$ islet transplantation.

Donor characteristics

Baseline characteristics of donors and their association with the probability for a pancreas allograft of being transplanted are presented in Table 1 and Fig. 1. Univariate analysis including all 433 pancreas allografts showed that younger donor age, shorter ICU stay, traumatic brain death, and higher eGFR were associated with transplantation (Fig. 2). The multivariate analysis confirmed younger age [risk ratio (95% confidence interval), 0.51 (0.36–0.72); $P < 0.001$] as independently associated with transplantation, with shorter ICU stay [0.91 (0.82–1.001), $P = 0.067$] and higher eGFR [1.087 (0.99–1.19), $P = 0.095$] close to statistical significance. When we analyzed the pancreas allografts offered for vascularized organ transplantation, younger age and lower BMI were associated with transplantation in the univariate analysis. The multivariate analysis confirmed only younger age as being independently associated with transplantation [0.746 (0.565–0.986), $P = 0.039$]. When we analyzed the pancreases offered for islet transplantation, univariate analysis showed that younger age, higher BMI, and traumatic brain death were associated with transplantation. The multivariate analysis confirmed younger age [0.59 (0.36–0.95); $P = 0.033$] and higher BMI [1.65 (1.06–2.6), $P = 0.028$] as independently associated with transplantation.

Reasons of pancreas loss during the allocation process

The followed categorization was developed to group the reasons for refusal or loss of the pancreas allografts:

1. Donor-related reasons: (i) medical and social history, as conveyed via fax or phone to the deciding transplant physicians/surgeons, and (ii) macroscopic organ quality based on (a) surgical inspection at the time of recovery, or (b) surgical inspection in the transplant center (except for recovery-related trauma or damage);
2. Recipient-related reasons (e.g., positive cross-match or not transplantable recipient);
3. Logistics reasons (e.g., organ transfer problems or lack of local capacity);

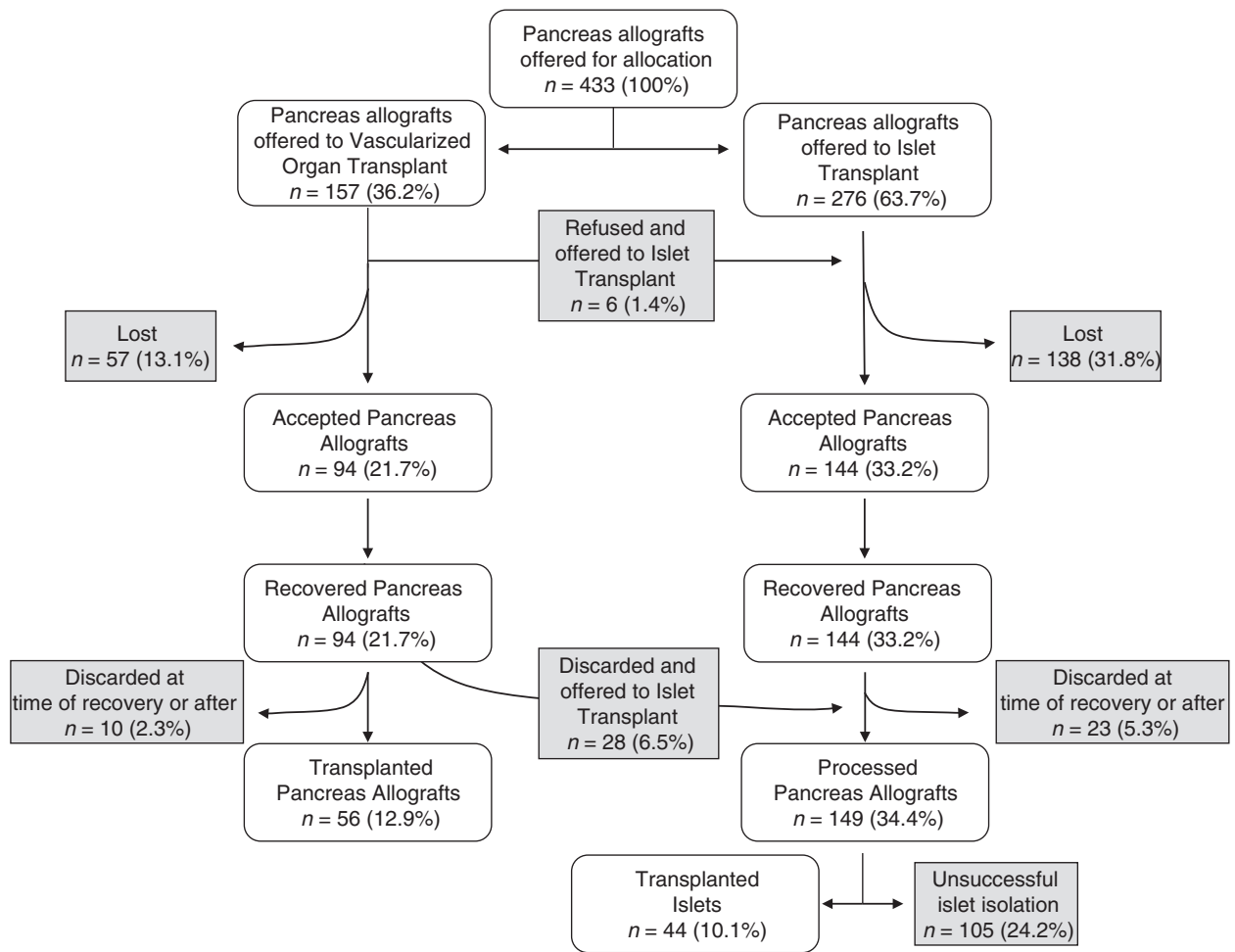


Figure 1 Pancreas allograft allocation flow. In the gray boxes we report the number of lost organs at each step of the allocation process, regardless of the specific reason. Data for NITp donors between 2011 and 2012.

4. Technical reasons, that is, surgical aspects related to recovery (e.g., organ damage because of the recovery procedure).

Donor-related reasons for pancreas loss were most common among pancreas allografts offered for vascularized organ transplantation than among pancreas allografts offered for islet transplantation (40.6% vs. 12.8%, $P < 0.001$). On the other hand, an unsuccessful isolation was the main reason (39.5%) for the loss of a pancreas allograft offered for islet transplantation. Moreover, logistics reasons were significantly more common as the cause for loss among pancreas allografts offered for islet isolation than for those offered for vascularized organ transplantation (13.5% vs. 2.0%, $P < 0.01$), while the frequency of recipient-related and technical reasons was similar for pancreas allografts offered for vascularized organ transplantation and pancreas allografts offered for islet isolation. Finally, we were unable to identify an unambiguous cause for the refusal or loss of the organ that was offered for allocation in

21.8% of the pancreas allografts offered for vascularized organ transplant and 11.6% of those offered for islet isolation, ($P < 0.05$; Table 2).

Pancreas allografts shifted from vascularized organ to islet transplantation

The allocation process produced a subgroup of pancreas allografts ($n = 34$) originally offered for vascularized organ transplantation and subsequently shifted as second choice to islet transplantation. The characteristics and the final outcome of this subgroup of pancreas allografts were compared with the pancreas allografts offered to islet transplantation as first choice (Table 3). In this subgroup, donors were younger and with a better kidney function, and, not surprisingly, the percentage of transplanted organs was higher than for the pancreas allografts originally offered for islet transplantation (27% vs. 13%, respectively, $P = 0.038$).

Table 1. Characteristics of donors of transplanted or not transplanted pancreas allografts.

	All pancreas allografts		Pancreas allografts offered to vascularized organ transplant programs		Pancreas allografts offered to islet transplantation programs	
	Not transplanted	Transplanted	Not transplanted	Transplanted	Not transplanted	Transplanted
N	333	100	101	56	266	44
Age (years)	51 (16)	39 (23)***	40 (24)	31 (16)*	54 (12)	47 (18)**
Sex (males)	182 (55%)	54 (54%)	55 (54%)	33 (59%)	147 (55%)	21 (48%)
Weight (kg)	72 (17)	70 (20)	70 (20)	70 (22)	75 (15)	75 (20)
BMI (kg/m ²)	24.7 (4.6)	24.2 (4.5)	23.9 (4.9)	23.1 (4.6)	24.8 (4.5)	25.7 (6.6)
ICU stay (days)	3 (4)	2 (3)**	3 (3)	2 (3)*	3 (4)	2 (4)
Cause of brain death						
Traumatic (%)	73 (22)	37 (37)**	37 (37)	24 (43)	45 (17)	13 (29)*
Nontraumatic (%)	260 (78)	63 (63)	64 (63)	32 (57)	221 (83)	31 (71)
Cardiac arrest (%)	101 (30)	19 (19)	23 (23)	12 (21)	84 (32)	7 (16)
Creatinine (μM)	79 (44)	70 (35)*	64 (45)	67 (35)	79 (44)	75 (40)
Estimated GFR (ml/min/1.73 m ²)	86.7 (45.9)	96 (149)**	100 (55)	108 (59)	84 (44)	91.8 (60)
Vasopressor use (%)						
None	144 (43)	40 (40)	37 (37)	22 (39)	119 (45)	19 (43)
1	116 (35)	34 (34)	39 (39)	24 (44)	88 (33)	8 (19)
>1	73 (22)	26 (26)	25 (25)	10 (17)	59 (22)	17 (38)
Vasopressor use (%)						
(Nor)adrenaline	111 (59)	36 (60)	41 (64)	21 (62)	84 (57)	14 (56)
Dopamine	77 (41)	23 (38)	22 (34)	10 (29)	62 (42)	13 (52)
Dobutamine	12 (6)	4 (7)	5 (8)	3 (9)	9 (6)	1 (4)

Data are presented as median and interquartile range (IQR) for continuous variables and counts and percent for categorical variables. **P* < 0.05; ***P* < 0.01; ****P* < 0.001, Transplanted versus not transplanted pancreas allografts.

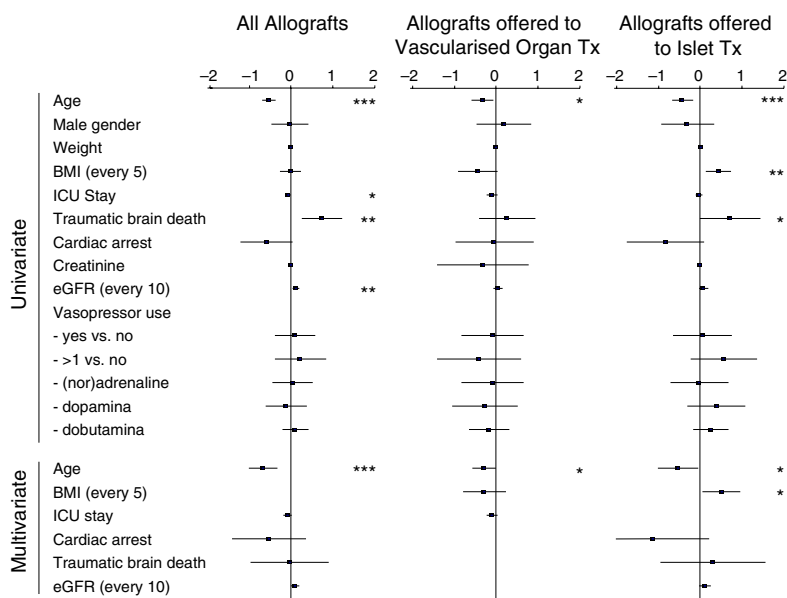


Figure 2 Univariate and multivariate odds ratios for the pancreas transplantation. The associations between baseline donor characteristics and pancreas allograft outcome (Transplanted vs. Not Transplanted) in all pancreas allografts offered for allocation, or according to the allocated program (vascularized pancreas or islet transplantation) were analyzed using logistic regression. All analyzed variables are presented. Dots represent the odds ratio after natural log transformation, lines the 95% confidence intervals. The multivariate analysis was performed including variables which were significant at the *P* < 0.2 level in the univariate analysis. **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

Table 2. Reasons for the loss of pancreas allografts during the allocation process.

	Pancreas allografts offered to vascularized organ transplant programs			Pancreas allografts offered to islet transplantation programs		
	Before recovery	After/during recovery	Total (%)	Before recovery	After/during recovery	Total (%)
Family declined organ donation after pancreas allocation	14	–	14 (13.8)	15	–	15** (5.6)
Unknown	7	15	22 (21.8)	15	16	31* (11.6)
Donor-related criteria						
Unfavorable laboratory test (e.g., lipase, amylase)	13	8	21	10	1	11
Any transmissible diseases	8	–	8	9	2	11
Pancreatic disease	5	4	9	9	1	10
Resuscitation	1	–	1	–	–	0
Traumatic damage	1	1	2	2	–	2
Total			41 (40.6)			34*** (12.8)
Recipient-related criteria						
Recipient not available/not transplantable	13	7	20	43	–	43
Total			20 (19.8)			43 (16.2)
Logistic criteria						
Lack of capacity of transplant center	1	1	2	35	1	36
Total			2 (2)			36** (13.5)
Technical criteria						
Organ damage due to recovery or packing failure	–	2	2	–	2	2
Total			2 (2)			2 (0.7)
After isolation						
Unpurified					70	70
Low number					35	35
Total						105 (39.5)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; Pearson chi-squared test.

Discussion

NITp host both islet and pancreas transplantation centers

Starting in 2011, the North Italy Transplant program (NITp) introduced a new allocation system considering age and length of ICU stay, but not donor weight or BMI, for pancreas allografts. Pancreas allografts from donors 3 to 50 years old and with ≤ 4 days of ICU stay were “prioritized” for vascularized organ transplant, while pancreas allografts from donors older than 50 years and/or with > 4 days of ICU stay were “prioritized” for islet isolation. The results showed that this approach allows an equal distribution between vascularized organ and islet transplantation programs, but the underutilization of pancreas allografts remains a major problem (only 23% of the offered pancreas allografts were transplanted). This is not surprising, given that a similar low utilization has also been reported in the United States [14,15] and in the Eurotransplant region [12], despite criteria for vascularized pancreas donor acceptance or refusal and for stratification of donors have been proposed in the field for many years.

Criteria and thresholds for allocation were chosen by NITp on the basis of both theoretical and practical reasons. Donors younger than 18 years of age have always been considered poor islet donors because of the difficulty of isolat-

ing the islets [16,17]. At the other end of the spectrum, pancreas allografts from older donors yield high numbers of islets, but in vascularized organ transplantation are associated with significantly lower graft survival and higher morbidity [12,18–21]. Generally, the age cutoff defining an “old” donor is set at 45–50 years. Considering the increasing age of organ donors in Italian population, the NITp selected age 50 to avoid an excessive restriction of pancreas allocation for vascularized organ transplantation. The length of ICU stay has been reported to negatively affect the outcome of vascularized pancreas transplantation [22], and it is one of the factors determining the “Pre-procurement Pancreas Suitability Score” (P-PASS) developed by the Eurotransplant network [23]. For this reason, the NITp selected an ICU stay ≤ 4 days as a cutoff defined according to NITp practice and to the international literature. With regard to body weight or BMI, obese donors have an increased beta-cell mass, thus yielding high islet numbers after isolation [17,24,25]. On the other hand, obese individuals are also poor donors of pancreas allografts for vascularized pancreas transplant because of a high risk of technical transplant failure [15,26]. On this basis, a BMI $> 30 \text{ kg/m}^2$ has been proposed as a pancreas allocation criterion [24,27], and, in 2005, the US organ procurement agency modified the criteria for allocation of pancreata

Table 3. Donor characteristics of pancreas allografts allocated to islet isolation, either as first allocation or following refusal by a vascularized pancreas transplantation program.

	Pancreas allografts offered directly to islet transplantation programs	Pancreas allografts offered to islet transplantation programs after being refused by a vascularized organ transplantation program	<i>P</i>
Donor characteristics			
<i>N</i>	276	34	
Age (years)	54 (12)	41.5 (23)	<0.0001
Sex (% males)	148 (54%)	20 (59%)	0.59
Weight (kg)	75 (18)	72 (23)	0.55
BMI (kg/m ²)	25.27 (4.4)	24.25 (5.6)	0.1
ICU stay (days)	3 (5)	4 (5)	0.84
Cause of brain death			
Traumatic (%)	49 (18)	9 (27)	
Nontraumatic (%)	227 (82)	25 (73)	0.24
Cardiac arrest (%)	84 (30)	7 (21)	0.38
Creatinine (μM)	82 (44)	61 (29)	0.014
Estimated GFR (ml/min/1.73 m ²)	84 (41)	113 (39)	0.002
Donation process sequence (%)			
Loss before recovery	132/276 (48)	6/34 (18)	0.001
Loss after/during recovery	17/144 (12)	6/28 (21)	0.22
Loss after isolation	92/127 (72)	13/22 (59)	0.21
Transplanted pancreas	35/276 (13)	9/34 (27)	0.038

Data are presented as median and interquartile range (IQR) for continuous variables and counts and percent for categorical variables. Bold values indicate <0.05.

from deceased donors, with pancreas from donors aged 50 years or more and BMI >30 being primarily intended for islet transplantation. This BMI-based strategy is not applicable within NITp because of a low number of obese donors, reflecting a lower prevalence of obesity in Italian population. Considering the 2011–2012 period, only 43 (10.6%) of the pancreas allografts offered for allocation were from donors with a BMI >30 kg/m², and, if we had applied the US criteria, only 25 (5.8%) of the pancreas allografts would have been allocated to islet transplantation and four indeed transplanted.

An objective of this study was also to describe the steps and reasons why pancreas allografts offered for allocation were lost in the allocation process and to analyze donor characteristics associated with pancreas transplant. More than one relevant result has emerged from the analysis of data. First, the reasons for pancreas loss were different

between organs offered for vascularized organ or islet transplantation. In the vascularized organ transplantation, programs 35% (56/157) of the offered pancreas allografts were indeed transplanted with the most common reason for pancreas loss being donor-related factors. In the islet transplantation programs, 48% (149/310) of the offered pancreas allografts were processed, but only 14.2% indeed transplanted, with unsuccessful isolation being the most common reason for pancreas loss. These results underline the major weaknesses of the two different approaches to beta-cell replacement: the subjective assessment of donor characteristics resulting in the refusal of pancreas allografts offered for vascularized pancreas transplant [12,13] and the relatively low successful isolation rate (31.6%) in islet processing.

Second, there seem to be room for improving the number of pancreas allografts that is lost in the allocation process. Pancreas allografts lost because of logistic reasons (13.5% and 2% of the pancreas allografts offered for islet and vascularized organ transplantation, respectively) and refusal of a center due to its lack of capacity are, in principle, avoidable. Moreover, for a significant number of the pancreas allografts offered for allocation, it was impossible to identify an unambiguous reason why the organ was indeed lost in the process. It is possible that a combination of unfavorable donor characteristics led to the refusal of the allograft offer, although this may simply reflect the absence of objective standardized donor criteria and cutoffs. On the other hand, very few pancreas allografts were not used because transplant surgeons found them to be damaged during the recovery procedure (i.e., technical reason), confirming the high standards of surgical capabilities for pancreas procurement in the NITp network.

Third, younger age emerged as the most relevant donor characteristic associated with pancreas allograft transplantation, both for islet and vascularized organ programs. This makes the case that donor selection criteria on the basis of age, that is, allocation rules, may need to be redefined in the near future. The influence of the age is difficult to assess in the case of islet transplantation. In the past, older donors provided similar or even higher islet yield [16,17,28]; however, all these studies estimated the performances of the isolation procedure using the number of pancreas allografts accepted for isolation as the denominator, that is, without taking into account the organ selection during the allocation process. Furthermore, pancreas allografts from young donors have always been prioritized to vascularized pancreas transplantation, leaving to islet isolation only the organs that were rejected by solid organ transplantation programs, that is, less ideal organs for the isolation of islets. When the proportion of pancreas allografts successfully transplanted was computed taking into account the entire allocation process, as in this study, a younger donor age

can be even more relevant for the final outcome of the pancreas allografts offered for allocation. This is confirmed by the analysis of pancreas allografts shifted from a vascularized organ to an islet transplantation program. In this subgroup of pancreas allografts, the donors were significantly younger and the proportion of transplanted allografts was significantly higher than for pancreas allografts offered as first choice to islet transplantation. Recently, also qualitative concerns were raised for islets obtained from older donors. A negative correlation between donor age and islet function in preclinical models has been reported [29,30]. Accordingly, the only islet transplantation series reporting a consistent achievement of insulin independence after islet infusion from a single-donor have used strict donor selection criteria, limiting donor age to <50 years [7,31,32].

These results and the increasing recognition that pancreas allografts previously considered suitable and keenly accepted for islet isolation were indeed marginal [1] will inevitably widen the overlap between the pools of pancreas donors for the two programs. In the near future, it would seem reasonable to redefine which donors should be directed primarily to vascularized pancreas transplantation and which to islet isolation, with the aim to treat the largest possible number of patients, increasing the proportion of pancreas allografts indeed transplanted, therefore maximizing the clinical success of both transplant programs.

Authorship

MC and LP: participated in research design, in data analysis, and in the writing of the paper. RN, NdeF, RM, FD, AM, AD, and MS: participated in the performance of the research, data analysis, and writing the manuscript.

Funding

This study was supported by the Italian Minister of Health (Programma Ricerca Trapianti 2008) to MC and LP, Italian Minister of Health (Ricerca Finalizzata RF-2009-1469691) and EU (HEALTH-F5-2009-241883-BetaCellTherapy).

References

- Berney T, Johnson PR. Donor pancreata: evolving approaches to organ allocation for whole pancreas versus islet transplantation. *Transplantation* 2010; **90**: 238.
- Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation* 2011; **91**: 373.
- Boggi U, Rosati CM, Marchetti P. Follow-up of secondary diabetic complications after pancreas transplantation. *Curr Opin Organ Transplant* 2013; **18**: 102.
- Gruessner AC, Sutherland DE, Gruessner RW. Long-term outcome after pancreas transplantation. *Curr Opin Organ Transplant* 2012; **17**: 100.
- Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care* 2012; **35**: 1436.
- Vantyghem MC, Kerr-Conte J, Arnalsteen L, et al. Primary graft function, metabolic control, and graft survival after islet transplantation. *Diabetes Care* 2009; **32**: 1473.
- Bellin MD, Kandaswamy R, Parkey J, et al. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. *Am J Transplant* 2008; **8**: 2463.
- Maffi P, Scavini M, Soggi C, et al. Risks and benefits of transplantation in the cure of type 1 diabetes: whole pancreas versus islet transplantation. A Single Center Study. *Rev Diabet Stud* 2011; **8**: 44.
- Shapiro AMJ, Toso C, Imes S, et al. Five-Year Results of Islet-Alone Transplantation Match Pancreas-Alone Transplantation with Alemtuzumab, Tac/MMF, with Strong Suppression of Auto and Alloreactivity. 13th World Congress 2011 of the International Pancreas and Islet Transplant Association (IPITA), Prague 2011.
- Bellin MD, Barton FB, Heitman A, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant* 2012; **12**: 1576.
- Ris F, Toso C, Veith FU, Majno P, Morel P, Oberholzer J. Are criteria for islet and pancreas donors sufficiently different to minimize competition? *Am J Transplant* 2004; **4**: 763.
- Loss M, Drewitz KP, Apfelbacher CJ, et al. Why offered pancreases are refused in the allocation process—a descriptive study using routine data from eurotransplant. *Transplantation* 2013; **95**: 1134.
- Wiseman AC, Wainright JL, Sleeman E, et al. An analysis of the lack of donor pancreas utilization from younger adult organ donors. *Transplantation* 2010; **90**: 475.
- Andreoni KA, Brayman KL, Guidinger MK, Sommers CM, Sung RS. Kidney and pancreas transplantation in the United States, 1996–2005. *Am J Transplant* 2007; **7**: 1359.
- Krieger NR, Odorico JS, Heisey DM, et al. Underutilization of pancreas donors. *Transplantation* 2003; **75**: 1271.
- Lakey JR, Warnock GL, Rajotte RV, et al. Variables in organ donors that affect the recovery of human islets of langerhans. *Transplantation* 1996; **61**: 1047.
- Nano R, Clissi B, Melzi R, et al. Islet isolation for allotransplantation: variables associated with successful islet yield and graft function. *Diabetologia* 2005; **48**: 906.
- Schenker P, Wunsch A, Ertas N, et al. Long-term results after simultaneous pancreas-kidney transplantation using donors aged 45 years or older. *Transplant Proc* 2008; **40**: 923.

19. Salvalaggio PR, Schnitzler MA, Abbott KC, et al. Patient and graft survival implications of simultaneous pancreas kidney transplantation from old donors. *Am J Transplant* 2007; **7**: 1561.
20. Boggi U, Del Chiaro M, Signori S, et al. Pancreas transplants from donors aged 45 years or older. *Transplant Proc* 2005; **37**: 1265.
21. Stegall MD, Dean PG, Sung R, et al. The rationale for the new deceased donor pancreas allocation schema. *Transplantation* 2007; **83**: 1156.
22. Douzdjian V, Gugliuzza KG, Fish JC. Multivariate analysis of donor risk factors for pancreas allograft failure after simultaneous pancreas-kidney transplantation. *Surgery* 1995; **118**: 73.
23. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to recognize a suitable pancreas donor: a eurotransplant study of procurement factors. *Transplant Proc* 2008; **40**: 1275.
24. Matsumoto I, Sawada T, Nakano M, et al. Improvement in islet yield from obese donors for human islet transplants. *Transplantation* 2004; **78**: 880.
25. Brandhorst D, Hering BJ, Brandhorst H, Federlin K, Bretzel RG. Body mass index is an important determinant for human islet isolation outcome. *Transplant Proc* 1994; **26**: 3529.
26. Humar A, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE. The impact of donor obesity on outcomes after cadaver pancreas transplants. *Am J Transplant* 2004; **4**: 605.
27. Sa GP, Sogayar MC, Eliaschewitz FG, et al. Islet versus pancreas transplantation in Brazil: defining criteria for pancreas allocation decision. *Islets* 2011; **3**: 352.
28. Niclauss N, Bosco D, Morel P, et al. Influence of donor age on islet isolation and transplantation outcome. *Transplantation* 2011; **91**: 360.
29. Ihm SH, Matsumoto I, Sawada T, et al. Effect of donor age on function of isolated human islets. *Diabetes* 2006; **55**: 1361.
30. Balamurugan AN, Chang Y, Bertera S, et al. Suitability of human juvenile pancreatic islets for clinical use. *Diabetologia* 2006; **49**: 1845.
31. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA* 2005; **293**: 830.
32. Hering BJ, Kandaswamy R, Harmon JV, et al. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. *Am J Transplant* 2004; **4**: 390.