

Critical analysis and systematization of rat pancreatectomy terminology¹

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DOI: <http://dx.doi.org/10.1590/S0102-865020160100000010>

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ABSTRACT

PURPOSE: To critically analyze and standardize the rat pancreatectomy nomenclature variants.

METHODS: It was performed a review of indexed manuscripts in PUBMED from 01/01/1945 to 31/12/2015 with the combined keywords “rat pancreatectomy” and “rat pancreas resection”. The following parameters was considered: A. Frequency of publications; B. Purpose of the pancreatectomy in each article; C. Bibliographic references; D. Nomenclature of techniques according to the pancreatic parenchyma resection percentage

RESULTS: Among the 468, the main objectives were to surgically induce diabetes and to study the genes regulations and expressions. Five rat pancreatectomy technique references received 15 or more citations. Twenty different terminologies were identified for the pancreas resection: according to the resected parenchyma percentage (30 to 95%); to the procedure type (total, subtotal and partial); or based on the selected anatomical region (distal, longitudinal and segmental). A nomenclature systematization was gathered by cross-checking information between the main surgical techniques, the anatomic parameters descriptions and the resected parenchyma percentages.

CONCLUSION: The subtotal pancreatectomy nomenclature for parenchymal resection between 80 and 95% establishes a surgical parameter that also defines the total and partial pancreatectomy limits and standardizes these surgical procedures in rats.

Key words: Pancreatectomy. Systematized Nomenclature of Medicine. Anatomy. Rats.

Introduction

The insulin discovery in 1921, its pancreatic production and the association of its disability with the development of hyperglycemia were crucial events to pursue experimental models that reproduce the diabetes mellitus¹.

The pancreatic physiological properties in *anima mobile* and the need to perform a surgical procedure in this organ, mainly as result of inflammatory, ischemic and neoplastic morbid conditions, have made mandatory the research with animal models^{2,3} in order to improve surgical techniques and to better understand the local and systemic organic repercussions.

Over the decades, the models performed in rats resulted in a wide spectrum of terminology variations³⁻⁶, many of which overlapped. The current references about this subject refer to multiple description methods, making difficult the comprehension of the surgical procedure.

In order to aid the understanding of technical variations, the purpose of this study is to critically analyze and to standardize the rat pancreatectomy variants nomenclature.

Methods

It was performed a bibliographic research on indexed articles in PubMed from 01/01/1945 until 31/12/2015, whose inclusion criteria was the presence of any pancreatectomy techniques in rats. The combined keywords used were “rat pancreatectomy” and “rat pancreas resection”.

Based on the contents analysis (title, abstract, text and bibliographic references), in each paper, the following parameters were gathered and evaluated: A. frequency of publications, in a five-year organization method; B. objective with the pancreatectomy in each article, arranged in sixteen generic indications and compared between endocrine and exocrine pancreas; C. bibliographic references that guided the performed pancreatectomy technique in each article; D. nomenclature of techniques according to the pancreatic parenchyma resection percentage.

Results

In PubMed, 468 papers fulfilled the inclusion criteria. In 54% of the manuscripts (n=253), the abstract, the text content,

and also the title were simultaneously found. In 28% of the cases, there were only an abstract with title available, whereas in 18% only the title was found. In the period 1945-1980, 41,8% of the articles presented the full text available, however, in the period 1981-2015, this percentage rises to 98.9%.

A. Frequency of publications

After organizing the frequency of publications in five years intervals, two peaks of different interest were identified. The first one was in mid-1960s and the second one in the end of the twentieth century, after a slowly rise. There was also a decrease in papers production on the subject in the last 15 years (Figure 1).

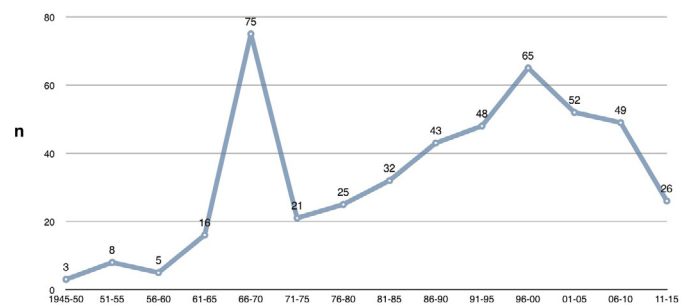


FIGURE 1 - Five-year progression of rat pancreatectomy scientific production.

B. Purpose of the pancreatectomy in each paper

The individualized references assessment showed the purpose of the pancreatectomy in 199 of 468 articles (42.5%) and the top sixteen were evaluated (Table 1). The vast majority of papers without the aim of the pancreatectomy in experimental research were published until the 1980s, during which various information were scarce or unavailable.

TABLE 1 - Objectives with the pancreatectomy in 199 articles.

Purpose of the pancreatectomy	n
Diabetes mellitus induction	86
Expression and/or gene regulation study	29
Post-pancreatectomy metabolic effects	26
Pancreatic regeneration	12
Cell regeneration	11
β cells adaptation study	6
Hormonal action	5
Isolate pancreatic islets	5
Cell proliferation	5
Non-pancreatic organs effects	4
Drug action	2
Pancreatic cancer study	2
Pancreatic function	2
Insulin resistance	2
Intestinal absorption	1
Pancreatectomy description/study technique	1

In 87% of the 199 valid manuscripts, the endocrine function was studied, whereas in 13% it was the exocrine one. In most different periods of the seventy years gathering data covered by this review, the diabetes mellitus induction was the most frequent purpose of pancreatectomy (Table 1). In the last decade, the genes expression and regulation was the second most frequent indication of pancreatectomy.

C. Bibliographic references that guided the performed pancreatectomy technique

In 208 out of 468 valid papers (44%), it was identified at least one reference of a pancreatectomy technique. From the 208 papers, five were highlighted with fifteen or more citations, consisting 76% (158/208) of the total cited (Table 2). In these five most cited references, four of them used male rats and three used Sprague-Dawley lineage.

TABLE 2 - Rat pancreatectomy research articles with 15 or more citations.

	Year	Technical description	Other basic reference quote	Proposed technical changes	Resected parenchyma percentage	Lineage	Rat average weight	Rat gender	Number of citations (n = 158)
Foglia ²	1944	Yes	Yes	Yes	95%	Unspecified	Unspecified	Male	27
Skow ³	1957	Yes	Yes	Yes	95% e 99,5%	Unspecified	110-150g	Female	15
Bonner-Weir ⁴	1983	Yes	Yes	No	90%	Sprague-Dawley	90-110g	Male	52
Bonner-Weir ⁵	1993	Yes	Yes	No	90%	Sprague-Dawley	95-125g	Male	34
Hosokawa ⁶	1996	Yes	Yes	No	90%	Sprague-Dawley	100g	Male	30

D. Techniques nomenclature

The pancreatectomy method and/or extension could be identified nearly in 80% of the 468 valid papers. Twenty terms were found to define the pancreatic resection. Fourteen of them specified the percentage of pancreatic parenchyma resection

ranging from 30 to 95%. Three others comprised generic terms like total, subtotal and partial and the last three was named according to the anatomical region such as distal, longitudinal and segmental (Table 3).

TABLE 3 - Nomenclature of the rat pancreatectomy techniques identified in 468 research articles.

Terms Found	n
Pancreatectomy 30%	2
Pancreatectomy 40%	1
Pancreatectomy 45%	1
Pancreatectomy 50%	18
Pancreatectomy 60%	29
Pancreatectomy 60-70%	2
Pancreatectomy 70%	19
Pancreatectomy 70-80%	1
Pancreatectomy 80%	8
Pancreatectomy 85%	3
Pancreatectomy 85-95%	3
Pancreatectomy 90%	150
Pancreatectomy 90-95%	2
Pancreatectomy 95%	25
Longitudinal Pancreatectomy	1
Partial Pancreatectomy	54
Segmental Pancreatectomy	1
Distal Pancreatectomy	1
Subtotal Pancreatectomy	2
Total Pancreatectomy	49
Pancreatectomy (unspecified)	96

Discussion

Reviews on surgical technique of the pancreas are frequent in medical practice^{7,8}, but uncommon in veterinary and experimental surgery^{9,10}. For a comparison of results, the standardization of nomenclature is fundamental¹¹.

Although the series raised mainly reflects the period after 1980 when 98.9% of papers were available, we decided for the inclusion of texts available since 1945, given the relevance of the technical aspects described previously.

The Figure 1 disclosed two peaks corresponding to the substantial increase in publications over 75 years. The induction of diabetes mellitus was the more common purpose of the pancreatectomy in both peaks. In the 1960-1970 decade this fact concomitantly occurred in the period of development of techniques for organs transplantation and in the decades of 1980-2000 it corresponded to isolation and transplantation of pancreas islets^{12,13}. After these both phases of scientific development, the

indication of pancreatectomy focused on the study of genes expression and regulation gained relevance¹⁴, but did not prevent the progressive decrease of publications started 15 years ago, resembling, nowadays, the frequency found at the 80s.

Pancreatic rat has anatomical features very different from human species¹⁵. The parenchyma of this organ appears as a sheet of intraperitoneal tissue, not always uniform, but uninterrupted extending from the periduodenal mesentery to the hilum of the spleen, and continuing along the great gastric curvature, reaching the periesplenic mesentery site. The existing mesoduodenum allows pancreatic mobility and the approach of the two faces of duodenal pancreatic lobe, while in *anima nobile* this organ is covered by visceral peritoneum that keeps it fixed in a retroperitoneal topography. Pancreatic rat has four segments (gastric, spleen, duodenal and parabiliar)^{15,16}. These characteristics make difficult the three-dimensional understanding and description of the rat pancreatic syntopy, especially for those familiar only with the human anatomy.

In the absence of standardization of nomenclature to characterize the pancreatectomy in rats, our study was guided by the estimated percentage of withdrawn tissue, sometimes by the name of the surgical procedure, or even considering only a subdivision of the body into segments. Thus, in view of the overlays in the scientific literature on the subject (Table 3), the authors intended to make an evaluation of techniques in order to systematize the terminology.

The first pancreatectomy in rats was described in the literature and attributed to Shapiro and Pincus¹⁷. Different variations have been published^{2,3,17,18}, but it has been found that to create a diabetic rat permanently would require extensive resections, associated with high mortality, which limited the use of models. Surpassing these limitations, we highlight Foglia², Scow³ and Richards¹⁶, which established concepts and technical principles accepted and cited up to today. Among the most important ones we emphasize: (1) segmental division of rat pancreas; (2) the approximate relationship between total pancreatic mass and the mass of each segment; (3) technique of digital dissection aided by gauze or cotton; (4) the care not to injure anatomical structures (pancreatobiliary duct and pyloric artery); (5) need to preserve pancreatoduodenal arcade along the medial aspect of the duodenum; (6) the parabiliar segment resection technique; (7) regenerating behavior of rat pancreas after subtotal resection; (8) the technique of total pancreatectomy in two times and (9) standardization of pre and postoperative care.

The investigation of principles that challenged the viability of pancreatectomy in rats in their early stage of

development had in the diabetes induction its dominant focus^{2,3,17}. The consequence of the described techniques brings us as repeated pattern intraoperative maneuvers where the pancreatic parenchyma is resected with the objective to preserve the adjacent anatomy, but not pancreatic tissue itself. Thus, the pancreatic portion withdrawal is distorted and there is no concern or need of any special treatment for residual pancreatic stump. Its references^{2,3,16} were consolidated in the first peak of production in the seventies of the last century (Figure 1).

In the second peak of production in the nineties, Bonner^{4,5} and Hosokawa⁶ were the most cited references, highlighting the delicacy of pancreatic handling, and detailed the quantity, weight and functional capacity of the tissue resected. However, it is noteworthy that its technical bases and bibliographical sources take us back to the authors that preceded those^{2,3,16}.

With respect to the top 16 different techniques of pancreatectomy, diabetes mellitus induction was also the most common. These findings were consistent with the focus of research with therapeutic intent for the control of this disease, which is one of the greatest health problems in the world, even in this millennia¹.

Supporting the interest directed to diabetes mellitus, it was evidenced a prevalence of pancreatectomy studies in rats with the endocrine pancreas (87% x 13%). We believe that due to the differentiated ability to regeneration of the exocrine pancreas of the rat, further studies may improve the knowledge regarding surgical healing after resection, considering the high morbidity and mortality in pancreatic surgery, in humans beings^{3,5,7,8}.

Citations of references that guided the technique used to pancreatectomy in rats were identified in 44% of the studies (n = 208). Again, this limitation is due to, in part, by the lack of accessibility of full texts. In this expressive set of information, five manuscripts comprised 77% of citations²⁻⁶. Significant is to point out that two of these five references were produced by the same author (Bonner-Weir)^{4,5}. Among the five most cited references, the male Sprague Dawley rat was used in three. This can be attributed to the fact that the males of this lineage have a weight of around 450 to 500g and could, in thesis, facilitate surgical manipulation.

The sample of 468 articles in 70 years of research showed twenty (20) different terms used to define the type of pancreatectomy (14 by percentage of parenchyma removed, 3 by name of the surgical procedure and 3 referred to the anatomical location). It is noteworthy that 96 items had only the term “pancreatectomy” without other definition because of the access only to the abstracts.

While performing a pancreatectomy in rats, the anatomical references of pancreatic segments are not always very clear^{15,16}.

The parabiliary segment is well delimited by the duodenum and the pancreatobiliary duct, but its volume is variable and it depends on the duct path. If the duct is located farther from the duodenal arch, this segment will have a tendency to have a larger mass estimated in 10% of total parenchyma, but if it is nearer, the mass of this segment is estimated in 5% of the total¹⁶. The boundary between the duodenal segment and the set composed of gastrosplenic segments is well defined by the path of the portal and superior mesenteric vein. However, the boundary between the gastric segments and spleen may not be so clear, since the flat pancreatic tissue lies just below and along the splenic artery but also above it, close to the greater curvature of the stomach (Figure 2)^{8,16}.

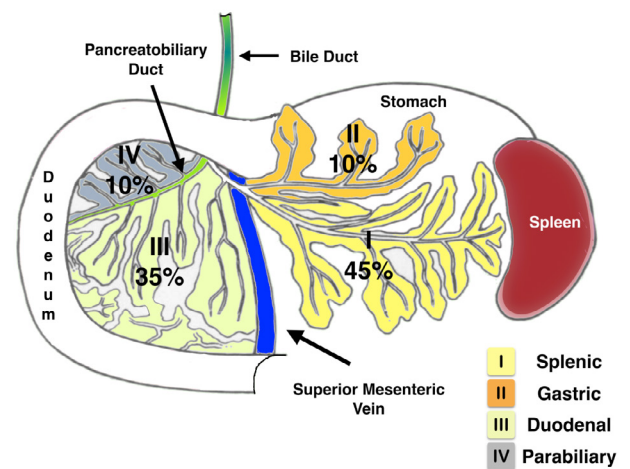


FIGURE 2 - Segmental division of the rat pancreas and relative mass percentages: I. Splenic Segment; II. Gastric Segment; III. Duodenal Segment; IV. Parabiliary Segment. Richards and Fitzgerald⁸.

Regarding the approximate mass division of the pancreatic segments Richards and Fitzgerald’s work still remain as the principal reference, although there may still exist some divergence^{16,18}. The referred authors measured the approximate mass percentage of each segment. The splenic segment accounts for 45% of the parenchymal mass and the duodenal segment for 35% of the pancreatic parenchyma. Together the parabiliary segment and the gastric segment account for 10% of the pancreatic tissue mass (Figure 2).

Given the multiplicity of concepts and criteria used to define the pancreatectomy in rats and considering that this knowledge is often applied to translational research, is understood to be justifiable to propose a basic nomenclature that does not conflict with what has been described, but tries to make it uniform and facilitate future researches on this issue. Therefore,

we propose to systematize the nomenclature enlighten the terms: partial, subtotal and total pancreatectomy.

Partial Pancreatectomy is considered as the group of resections that compromises less than 80% of the parenchyma¹⁹⁻²², including, in a variable way, portions of the splenic, gastric and duodenal segments. Thus, the resection extends from the tissue that is adjacent to the spleen to the gastric and duodenal segments, with a safety margin, sparing noble areas capable of triggering severe local complications. Therefore, the anatomical limit of the parenchymal resection preserves the parabiliary segment, the pancreatic duct and the pancreaticoduodenal vascular arcade. Thereby, it was chosen to include in the denomination of partial pancreatectomy those named as distal pancreatectomy, longitudinal pancreatectomy, segmental and partial, as well as the percentages of 30% to 79% of pancreas resection. In this research, we found that the partial pancreatectomy is mainly associated with the resection of 50 to 70% of the parenchyma.

We also considered subtotal pancreatectomy the resections which contains 80 to 95% of the pancreatic mass^{4-6,23,24}. We included in this classification the complete excision of the gastric and splenic segments and the majority (if not all) of the duodenal segment until the adjacencies of the pancreaticobiliary duct and the pancreaticoduodenal vascular arcade, with the preservation of the parabiliary segment. The explanation for the maintenance of a margin of resection between 80 to 95% by subtotal pancreatectomy is not only due to anatomical parameters sparing critical areas, but also based on careful technique to avoid damage threatening the rat's life. The rat may develop diabetes without developing severe exocrine pancreas insufficiency. Therefore in the modality of subtotal pancreatectomy most of the times prevailed the 90% resection^{4,5}.

We considered the total pancreatectomy as the resections that remove more than 95% of the pancreatic parenchyma. It may seem conflictive the use of the term "total pancreatectomy" while we admit to keep some percentage of the parenchyma. This surgical procedure is technically difficult because of it requires a minimum amount of pancreatic tissue remained (less than 5%)³, in order to protect the duodenal viability and preserve the biliary drainage. Moreover, although the "total pancreatectomy" aims indeed the complete resection, after a few weeks control studies demonstrate the presence of a residual parenchyma due to the peculiar capacity of the pancreas regeneration, in rats^{2-5,24}. This procedure may be performed in one or two steps^{3,25}. When performed in two steps, the parabiliary segment is removed in the first operation and the resection of the splenic, gastric and duodenal segments is completed in the second surgical procedure. It is

important to emphasize that the incidence of biliary and duodenal complications is higher in this total resections in comparison to the other surgical modalities even if the main biliary duct and the vascular arcade are gently dissected. So it is not surprising that total resections has progressively fallen out of use^{3,25}.

Conclusion

The denomination of subtotal pancreatectomy for the 80 to 95% parenchymal resections in rats standardizes the surgical nomenclature, which defines the limits of the partial and total pancreatectomies.

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Received: Jun 14, 2016

Review: Aug 15, 2016

Accepted: Sep 16, 2016

Conflict of interest: none

Financial sources: FAPERJ and CNPq

¹Research performed at Center of Experimental Surgical, Department of Surgery, School of Medicine, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.