Retrospective Study

Long-term outcome of pancreatic function following oncological surgery in children: Institutional experience and review of the literature

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Institutional review board statement: The Ethical Committee of "Bambino Gesù" Children's Hospital in Rome approved this study. Our Hospital is an Institute authorized by the Ministry of Health Care for research and clinical study. Therefore, to enroll patients in clinical studies all the parents or tutors give their consent by signature of a specific document when the children are admitted to our Hospital. In this way, we have the consent in line with the indications of our Ethical Committee when the patients are admitted to the hospital.

Informed consent statement: All

Abstract

BACKGROUND
Pancreatic neoplasms are uncommon in children and in most cases they are benign or have low malignant potential. Pancreatoblastoma and solid pseudo-papillary tumor are the most frequent types in early and late childhood, respectively. Complete resection, although burdened by severe complications, is the only curative treatment for these diseases. Pancreatic surgery may result in impaired exocrine and endocrine pancreatic function. However, limited data are available on the long-term pediatric pancreatic function following surgical resection.

AIM
To investigate endocrine and exocrine pancreatic function and growth after oncological pancreatic surgery in a pediatric series.

METHODS
A retrospective analysis of all pediatric patients who underwent surgery for pancreatic neoplasm in our Institution from January 31, 2002 to the present was performed. Endocrine and exocrine insufficiency, auxological and fat-soluble vitamin status (A, D, E and clotting tests) were assessed at diagnosis and at every follow-up visit. Exocrine insufficiency was defined as steatorrhea with fecal elastase-1 < 200 µg/g stool, while endocrine insufficiency was identified as onset of Diabetes or Impaired Glucose Tolerance. Growth was evaluated based on body mass index (BMI) z-score trend.

**RESULTS**

Sixteen patients (12 girls and 4 boys, mean age 10.7 ± 5.3 years), were included. Nine patients (56%) had a neoplasm in the pancreatic head, 4 in the body/tail, 2 in the tail and 1 in the body. Histological findings were as follows: Solid pseudopapillary tumor in 10 patients (62.5%), insulinoma in 2 patients, neuroendocrine tumor in 2 patients and acinar cell carcinoma in 2 patients. The most frequent surgery was pancreatectoduodenectomy (50%). Exocrine failure occurred in 4 patients (25%) and endocrine failure in 2 patients (12.5%). Exocrine insufficiency occurred early (within 6 mo after surgery) and endocrine insufficiency later (8 and 10 years after surgery). Mean BMI z-score was 0.36 ± 1.1 at diagnosis and 0.27 ± 0.95 at the last assessment. Vitamin D was insufficient (< 30 ng/mL) in 8 of the 16 patients during the follow-up period. Vitamins A, E and clotting test were into the normal ranges in all patients.

**CONCLUSION**

Careful and long-term monitoring should follow any pancreatic surgery, to recognize and promptly treat exocrine and endocrine pancreatic insufficiency, which can occur after surgery.

**Key Words:** Pancreatic neoplasms; Pancreatic function; Children; Malabsorption; Pancreatic failure; Growth

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**Core Tip:** There are few published data on pediatric pancreatic neoplasms and, in particular, on the long-term outcome of pancreatic function and growth following surgery. Our findings, based on a retrospective review of 16 patients, showed that the development of exocrine (earlier) and endocrine failure (later) is not rare; careful and long-term monitoring of pancreatic function, can guarantee normal growth during early life.

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**INTRODUCTION**

Pancreatic neoplasms are uncommon in childhood with an incidence rate, as reported in the United States, of 0.018 cases per 100000 people[1]; in most cases they are benign or have low malignant potential[2]. Pancreatoblastoma and solid pseudopapillary tumor (SPT) are the most common histologies in early and late childhood, respectively [1,5,4]. Endocrine tumors, adenocarcinoma, sarcoma, lymphoma and neuroblastoma rarely occur in children. Prognosis, although better than in adults, is strongly influenced by tumor histology, with excellent survival for SPTs (95%) and lower for neuroendocrine tumors (51%), sarcomas (43%) and acinar cell carcinomas (34%)[5]. Complete surgical resection provides the only curative treatment for patients with pancreatic neoplasms, except for lymphoma[6]. Distal pancreatectomy is the preferred...
surgical approach for body/tail neoplasms and pancreatoduodenectomy (PD) for head neoplasms[7-9]. PD, also known as Whipple procedure, is the treatment of choice for pancreatic neoplasms involving the head of the pancreas and the peripancreatic tract[10-13]. It is, however, a very complex surgery with many complications and a high mortality rate, even in adults[14-17]. Pancreatic resections may result in impaired pancreatic, endocrine and exocrine function[7-9,18-22]. Given the great relevance of pancreatic function on nutritional status and growth in childhood, we planned the present study to assess the long-term outcome of exocrine and endocrine pancreatic function, growth and vitamin status following pancreatic resection for neoplasms in our Institution.

MATERIALS AND METHODS

Study design

All consecutive patients, 18 years old or younger, affected by pancreatic neoplasms and who had undergone pancreatic surgery between January 31, 2002 to the present were retrospectively reviewed from our Institutional database. Patients with pancreatic neoplasms had been followed since 2002 by a structured multidisciplinary team consisting of pediatric surgeons, pediatric gastroenterologists, oncologists, endocrinologists, radiologists and dietitians.

All patients with pancreatic neoplasms who had undergone pancreatic surgery were considered eligible.

The following outcomes were selected: (1) Rate of exocrine insufficiency, defined as steatorrhea associated with fecal elastase-1 < 200 µg/g stool[23]; (2) Rate of endocrine insufficiency defined as fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or glycated hemoglobin ≥ 6.5% (≥ 48 mmol/L) for the diagnosis of diabetes and fasting blood glucose 100-125 mg/dL (5.6-6.9 mmol/L) or glycated hemoglobin 5.7%-6.4% (39-47 mmol/mol) for the diagnosis of impaired glucose tolerance (IGT)[24]; (3) Growth based on the body mass index (BMI) z-score trend; the growth charts from the CDC (Centers for Disease Control)[25] were used as a reference; and (4) Rate of fat-soluble vitamin deficiency (A, E, D, clotting test).

Our scheduled follow-up after oncological pancreatic surgery is reported in Table 1. Generally, steatorrhea was assessed before discharge and at every follow-up visit; we employed only fecal elastase to follow the trend of exocrine failure.

Data relating to the study variables were extracted from medical records.

Statistical analysis

Categorical variables were summarized as percentage and continuous variables as mean ± SD. The Mann-Whitney U test was used to compare continuous variables and Fisher’s exact test was used to compare frequencies between groups. A P value of < 0.05 was considered to indicate statistical significance. Statistical evaluation and figures were performed using Graph Pad 6 for Windows.

Ethics

The Ethical Committee of “Bambino Gesù” Children’s Hospital in Rome approved this study. Our Hospital is an Institute authorized by the Ministry of Health Care for research and clinical study. Therefore, to enroll patients in clinical studies all the parents or tutors give their consent by signature of a specific document when the children are admitted to our Hospital. In this way we have the consent in line with the indications of our Ethical Committee when the patients are admitted to the hospital.

RESULTS

Sixteen patients, twelve girls (75%) and four boys (25%) (P = 0.0121), all surviving, fulfilled the study inclusion criteria. Mean age at diagnosis and at the last evaluation were 10.7 ± 5.3 years and 16.6 ± 5.2 years, respectively. Mean follow-up was 5.7 ± 4.3 years. Nine of 16 patients (56%) had a neoplasm in the head of the pancreas (P = NS), and of the remaining 7 patients, 4 had a tumor in the body/tail, 2 in the tail and 1 in the body. Histologies were as follows: SPT in 10 patients (62.5%) (P = NS); the remaining histopathological diagnoses were: Insulinoma in 2 patients, neuroendocrine tumor in 2 and acinar cell carcinoma in the remaining two patients. Mean age at diagnosis was significantly higher in patients with SPT (13.5 ± 2.4 years) than in the
Table 1 Our scheduled follow-up for pancreatic neoplasms after surgery in children

|                                | T1                      | T2                      | T3                      |
|--------------------------------|-------------------------|-------------------------|-------------------------|
| Clinical examination (physical examination, symptoms, weight, height, BMI) | Every 4 mo              | Every 6 mo              | Once a year             |
| Routine lab tests (CBC, liver and kidney function tests, amylase, lipase, bilirubin, albumin, etc.) | Every 4 mo              | Every 6 mo              | Once a year             |
| Vitamin dosage (A, D, E, clotting test) | Every 4 mo              | Every 6 mo              | Once a year             |
| Serological markers (according to the underlying histology) (alpha-FP, Chromogranin-A) | Every 4 mo              | Every 6 mo              | Once a year             |
| Assessment of exocrine pancreatic function (faecal elastase) | Every 4 mo              | Every 6 mo              | Once a year             |
| Assessment of endocrine pancreatic function (fasting blood glucose, glycated hemoglobin, C-peptide) | Every 4 mo              | Every 6 mo              | Once a year             |
| Imaging (abdominal US) | Every 4 mo              | Every 6 mo              | Once a year             |
| Surgical, diabetological and oncological consulting | Every 4 mo              | Every 6 mo              | Once a year             |
| Nutritional assessment (3-d recall dietary assessment and diet optimization by dietitians) | Every 4 mo              | Every 6 mo              | Once a year             |

T1: First year after diagnosis; T2: Second year after diagnosis; T3: Third year to 10 yr after diagnosis (end of follow-up); BMI: Body mass index; CBC: Complete blood count; alpha-FP: alpha-Fetoprotein; US: Ultrasound.

DISCUSSION

Pancreatic neoplasms are rare in childhood and the main treatment, regardless of tumor type, is radical resection[21]. The extent of surgical resection needed for complete debulking is related to the neoplasm site. Whenever possible, less extensive resection is advocated; however, a minority of patients will require resection of the pancreatic head and hepatobiliary reconstruction. Proper discussion of the risks and benefits is particularly difficult due to the lack of literature. In particular, few data are available on the long-term outcome of exocrine and endocrine insufficiency, following surgery. Due to the high relevance of normal absorption in children to guarantee the expected growth course, we investigated, in a series of 16 children with pancreatic tumors who had undergone surgery in the last 19 years, the long-term outcome of exocrine/endocrine function, growth and development of fat-soluble vitamin deficiency. Overall, 25% of patients in the present series developed exocrine failure. In adults, the rate of pancreatic exocrine insufficiency after partial pancreatectomy seems to be higher (about 35%)[19]. In Tables 3 and 4 we summarize the main characteristics of the studies that focused on long-term outcome of pancreatic functions following oncological surgery in children[26-37]. The data showed that the prevalence of exocrine insufficiency in pediatric patients ranged from 0%[29] to 83.3%[33]. Vasudevan et al[27] found exocrine failure rate similar to our finding (23%), while Cheng et al[26] found a much lower rate (8.6%). Park et al[34] reported that six of 8 patients experienced mild steatorrhea.

others (6.2 ± 5.8 years) (P = 0.0167). Abdominal pain was the most frequent presenting symptom (43.7%). PD was the main surgery performed (50% of patients). Exocrine and endocrine insufficiency occurred in 4 (25%) and in 2 (12.5%) of 16 patients, respectively. Two patients developed both exocrine and endocrine insufficiency and 2 only exocrine insufficiency. All patients with exocrine pancreatic failure required supplementation with pancrelipase, which is still ongoing, while 2 patients showed IGT not requiring insulin therapy. All these patients had pancreatic head tumors treated by PD. Interestingly, exocrine insufficiency occurred within the first 6 mo after surgery, while endocrine insufficiency occurred later (8 and 10 years after surgery). With regard to the growth trend, mean BMI z-score at diagnosis was 0.36 ± 1.1 and at the last follow-up was 0.27 ± 0.95 (P = NS) (see also Figure 1 for details). Vitamins A and E and clotting tests were in the normal ranges in all patients. Vitamin D was found to be insufficient (< 30 ng/mL) at some follow-up visits in 8 of the 16 patients. The main characteristics of our patients are detailed in Table 2.
Table 2 Main demographic and clinical characteristics of our patients

| No. | Sex | Age | Histology                  | Symptoms             | Tumor site | Type of surgery    | Length of follow-up | Exocrine pancreatic failure | Endocrine pancreatic failure | Vitamin D insufficiency |
|-----|-----|-----|---------------------------|----------------------|------------|---------------------|---------------------|-----------------------------|-----------------------------|------------------------|
| 1   | F   | 12  | SPT                       | Weight loss          | HEAD       | PPPD                | 10.4 yr            | Yes                         | Yes                         | Yes                    |
| 2   | M   | 9.8 | SPT                       | Occasional diagnosis | BODY       | Distal Pancreatectomy | 6.4 yr            | No                          | No                          | No                     |
| 3   | F   | 17.3| SPT                       | AP                   | HEAD       | PPPD                | 3.9 yr            | Yes                         | No                          | Yes                    |
| 4   | M   | 15.5| Neuroendocrine tumor      | AP                   | HEAD       | PPPD                | 2.3 yr            | No                          | No                          | No                     |
| 5   | F   | 6.6 | Acinar cell carcinoma     | AP+ weight loss      | HEAD       | PPPD                | 11.5 yr           | Yes                         | Yes                         | Yes                    |
| 6   | M   | 4.11| Acinar cell carcinoma     | Not available        | HEAD       | PD                  | 12.3 yr           | Yes                         | No                          | Yes                    |
| 7   | F   | 14.3| SPT                       | Weight loss          | TAIL       | Distal Pancreatectomy | 2 yr              | No                          | No                          | Yes                    |
| 8   | F   | 13.2| SPT                       | AP                   | HEAD       | PPPD                | 9 mo              | No                          | No                          | Yes                    |
| 9   | F   | 3   | Insulinoma                | Hypoglycemia         | HEAD       | Cephalic Pancreatectomy | 11 yr            | No                          | No                          | Yes                    |
| 10  | F   | 11  | SPT                       | AP                   | BODY/TAIL  | Distal Splenopancreatectomy | 2 yr             | No                          | No                          | No                     |
| 11  | M   | 10  | Neuroendocrine tumor      | Screening in Tuberous Sclerosis | BODY/TAIL  | Distal Pancreatectomy | 9 yr              | No                          | No                          | No                     |
| 12  | F   | 15.5| SPT                       | No symptoms          | BODY/TAIL  | Distal Splenopancreatectomy | 2.5 yr           | No                          | No                          | No                     |
| 13  | F   | 13.8| SPT                       | AP                   | HEAD       | PPPD                | 10 yr             | No                          | No                          | No                     |
| 14  | F   | 11.6| SPT                       | No symptoms          | BODY/TAIL  | Distal Splenopancreatectomy | 3.4 yr           | No                          | No                          | Yes                    |
| 15  | F   | 16.2| SPT                       | AP+ weight loss      | TAIL       | Distal Pancreatectomy | 3.8 yr           | No                          | No                          | No                     |
| 16  | F   | 7   | Insulinoma                | Hypoglycemia         | HEAD       | PPPD                | 1 mo              | No                          | No                          | No                     |

F: Female; M: Male; Age: Years at diagnosis; SPT: Solid pseudopapillary tumor; AP: Abdominal pain; PD: Pancreaticoduodenectomy; PPPD: Pylorus preserving pancreaticoduodenectomy; Vitamin D insufficiency: < 30 ng/mL.

In contrast, endocrine insufficiency, described in 40% of adult patients after partial pancreatectomy[19], was observed only in few pediatric patients. We found endocrine failure in 12.5% and Vasudevan et al[27] found endocrine failure in 3%. No patients with endocrine insufficiency were found in seven surveys[28,29,31,33,35-37]. Cheng et al[26] reported that only one patient developed endocrine insufficiency in 104 and Park et al[38] found one in 8 patients. This finding might reflect the larger functional reserve of the endocrine pancreas in young patients[32]. It is possible that the functional reserve could become insufficient many years after pancreatic resection, as confirmed by our two cases who developed endocrine failure after 8 and 10 years after surgery. The two patients who showed IGT not requiring insulin therapy, did not develop islet cell autoantibodies, so we could exclude the diagnosis of latent autoimmune diabetes in adults[38]. This finding suggests that long-term follow-up is crucial to identify endocrine pancreatic failure.

According to our results, previous studies showed that pancreatic exocrine function can occur early (within 2 mo after surgery) following PD but that it may later revert (from 6 mo to 12 mo)[21,22]. Glucose metabolism tends to remain normal for 1 year after PD, but it can worsen after many years[20,22,39].

The magnitude of the pancreatic resection is the main factor influencing the worsening of pancreatic function over the years. Divarca et al[29], found no cases of exocrine and endocrine failure in patients who underwent tumor enucleation. Lindholm et al[33] found a rate of exocrine insufficiency closer to that reported in
Table 3 Summary of the reports included in the literature review

| Ref.                      | Country  | Length of follow-up (yr) | n of cases/M/F (%) | Mean or median age (yr) | Exocrine insufficiency (%) | Endocrine insufficiency (%) |
|---------------------------|----------|--------------------------|--------------------|-------------------------|----------------------------|-----------------------------|
| Present                   | Italy    | 5.7                      | 16 (25/75)         | 10.7                    | 25                         | 12.5                        |
| Cheng et al[26], 2020     | China    | 3.1                      | 104 (31/69)        | 9.9                     | 8.6                        | 1                           |
| Vasudevan et al[27], 2020 | United States | 2.8        | 65                | 13                      | 23                         | 3                           |
| Mizuno et al[28], 2018    | Japan    | 30                       | 1 (M)              | 12                      | 0                          | 0                           |
| Divarci et al[29], 2017   | Turkey   | 3.6                      | 5 (0/100)          | 15                      | 0                          | 0                           |
| d’Ambrosio et al[30], 2014| Italy    | 2.1                      | 5 (40/60)          | 7                       | 20                         | 20                          |
| Laje et al[31], 2013      | United States | 6.7        | 6 (17/83)         | 15                      | 17                         | 0                           |
| Scandavini et al[32], 2018| Sweden   | 6.6                      | 13 (23/77)         | 11.4                    | 31                         | 7.7                         |
| Lindholm et al[33], 2017  | United States | 4.7        | 12 (42/58)        | 9                       | 83.3                       | 0                           |
| Park et al[34], 2016      | Korea    | 10.5                     | 8 (25/75)          | 10.5                    | 75                         | 12.5                        |
| Muller et al[35], 2012    | France   | 4.2                      | 16 (44/56)         | 8.9                     | 6.25                       | 0                           |
| Speer et al[36], 2012     | United States | 1.4        | 11 (36/64)        | 14                      | 9                          | 0                           |
| Yazbeck et al[37], 2010   | Lebanon  | -                        | 1 (F)              | 13                      | 100                        | 0                           |

1 Two patients excluded due to pancreatic trauma.
2 Two patients excluded due to congenital pancreatic malformation and calcifying pancreatitis.
F: Female; M: Male.

Table 4 Overall main characteristics of the reviewed studies

| Onset symptoms (%) | Histology (%) | Type of surgery (%) |
|--------------------|---------------|---------------------|
| Abdominal pain (50)| SPT (64)      | PD (61)             |
| Palpable mass (17) | Pancreatoblastoma (13) | Distal/central pancreatectomy (30) |
| Nausea/emesis (16) | Neuroendocrine tumors (7) | Tumor enucleation (9) |
| Occasional diagnosis (8) | Neuroblastoma (4) | |
| Jaundice (8) | Rhabdomyosarcoma/sarcoma (4) | |
| Diarrhea (1) | Acinar cell carcinoma (4) | |
| Other (3) | | |

SPT: Solid pseudopapillary tumor; PD: Pancreatectoduodenectomy.

adults; interestingly this study included only patients who had undergone PD, as occurred in adults; pylorus-sparing PD can indeed worsen pancreatic function due to insufficient pylorus contraction with consequent stasis within the pancreatic duct and parenchyma destruction[40,41].

Table 5 shows available data in the literature, including data from the present report, to assess associations between exocrine and endocrine insufficiency with tumor site and type of surgery. It can be seen that 93% of all cases of exocrine insufficiency is associated with PD, confirming the results of Lindholm et al[33].
Table 5 Pancreatic function and neoplasm site/surgery

|                         | Overall | Head (%) | Body/tail (%) |
|-------------------------|---------|----------|---------------|
| Exocrine insufficiency  | 35      | 31 (89)  | 4 (11)        |
| Endocrine insufficiency | 5       | 4 (80)   | 1 (20)        |
|                         | Overall | PD (%)   | Other surgery (%) |
|                         | 140     | 106 (76) | 34 (24)       |
| Exocrine insufficiency  | 30      | 28 (93)  | 2 (7)         |
| Endocrine insufficiency | 5       | 4 (80)   | 1 (20)        |

PD: Pancreaticoduodenectomy.

Figure 1 Initial and final body mass index were available in 13 of the 16 patients. BMI: Body mass index; NS: Not significant.

Surgery did not impact on growth course in our patients according to the finding of a previous study[34]. We can argue that the early identification of pancreatic insufficiency and prompt treatment with enzymes is the main strategy to avoid nutritional deficiency and to ensure adequate growth. Early identification of exocrine insufficiency may also prevent the development of fat-soluble vitamin deficiency. Some patients developed vitamin D insufficiency while vitamin A, E and clotting tests remained in the normal ranges in all patients. It can be argued that the low levels of vitamin D may not be exclusively related to exocrine pancreatic insufficiency, in view of the high prevalence of vitamin D insufficiency in the healthy population[42].

CONCLUSION

In conclusion, despite the important limitation of the retrospective design of this study that could have led to missed data, these findings highlight digestive and nutritional issues in a context in which they are frequently disregarded. Careful and long-term monitoring should follow any pancreatic surgery in children. The loss of exocrine function can occur early but it seems to have no impact on the growth course if it is promptly treated. The impairment of endocrine function is less frequent and may take many years to develop.
Research background
Pancreatic neoplasms are very rare in children and available data in this field are limited. Surgery allows the long-term survival of these patients, even if it could lead to complications such as pancreatic insufficiency. Currently there is little evidence on the onset of pancreatic failure and growth trend in children after pancreatic surgery.

Research motivation
We would like to increase knowledge regarding the evolution of pancreatic function after surgical resection in children with pancreatic neoplasms. Currently there is no scheduled follow-up to monitor the long-term complications of pancreatic surgery and in pediatric age it is essential to immediately diagnose the possible onset of pancreatic insufficiency to ensure adequate growth.

Research objectives
The aim of this study was to evaluate the long-term outcome of pancreatic function after pancreatic surgery in children, identify the incidence of endocrine and exocrine pancreatic insufficiency, fat-soluble vitamin deficiency and failure to thrive.

Research methods
We retrospectively analyzed all consecutive pediatric patients diagnosed with pancreatic neoplasms who underwent pancreatic surgery in our institution between January 31, 2002 and the present. Patients were followed by a multidisciplinary team that assessed auxological parameters, clinical symptoms, laboratory and radiological tests at each follow-up visit.

Research results
Sixteen patients (12 girls and 4 boys, mean age 10.7 ± 5.3 years), were included. The most frequent surgery was pancreaticoduodenectomy (50%). Exocrine failure occurred in 4 patients (25%) within 6 mo after surgery, while endocrine failure occurred in 2 patients (12.5%) 8 and 10 years after surgery, respectively. No statistically significant differences were found in BMI z-score at diagnosis and at the last follow-up. Vitamin D was insufficient (< 30 ng/mL) in 8 of the 16 patients while vitamins A, E and clotting test were into the normal ranges in all patients.

Research conclusions
Our study highlights that the development of exocrine and endocrine pancreatic insufficiency after pancreatic surgery is not rare; these potential complications must be adequately identified and treated, as pancreatic enzyme replacement therapy prevents malabsorption and consequent growth failure.

Research perspectives
It is essential to identify and establish a standardized follow-up in pediatric patients, organized by a multidisciplinary team including a surgeon, oncologist, gastroenterologist, endocrinologist, radiologist and dietician.

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