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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Lan Sun, MD, PhD, Chief Physician, Professor, Department of Oncology, The People's Hospital of Bishan District, Chongqing 402760, China. sunlan6203@163.com

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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Retrospective Study

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

Giulia Bolasco, Teresa Capriati, Chiara Grimaldi, Lidia Monti, Maria Debora De Pasquale, Ippolita Patrizia Patera, Marco Spada, Giuseppe Maggiore, Antonella Diamanti

ORCID number: Giulia Bolasco 0000-0002-6929-3943; Teresa Capriati 0000-0002-2464-0913; Chiara Grimaldi 0000-0003-3551-9286; Lidia Monti 0000-0002-8601-2621; Maria Debora De Pasquale 0000-0003-1082-6810; Ippolita Patrizia Patera 0000-0002-8509-9876; Marco Spada 0000-0003-0796-6847; Giuseppe Maggiore 0000-0001-8201-2416; Antonella Diamanti 0000-0002-3926-0729.

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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.

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Giulia Bolasco, Teresa Capriati, Giuseppe Maggiore, Antonella Diamanti, Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Chiara Grimaldi, Marco Spada, Division of Hepatobiliopancreatic Surgery, Liver and Kidney Transplantation, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Lidia Monti, Radiology Department, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Maria Debora De Pasquale, Hematology/Oncology Department, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Ippolita Patrizia Patera, Endocrinology and Diabetes Unit, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Corresponding author: Antonella Diamanti, MD, Doctor, Hepatology, Gastroenterology and Nutrition Unit, "Bambino Gesù" Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, Rome 00165, Italy. antonella.diamanti@opbg.net

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

study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement:

There is no conflict of interest associated with the senior author or other coauthors and their contributions to this manuscript.

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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 pseudo-papillary 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 pancreaticoduodenectomy (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 [1,3,4]. 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 pancreaticoduodenectomy (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 periampullary 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 $< 200 \mu\text{g/g}$ stool[23]; (2) Rate of endocrine insufficiency defined as fasting blood glucose $\geq 126 \text{ mg/dL}$ ($\geq 7.0 \text{ mmol/L}$) or glycated hemoglobin $\geq 6.5\%$ ($\geq 48 \text{ mmol/L}$) for the diagnosis of diabetes and fasting blood glucose $100\text{--}125 \text{ mg/dL}$ ($5.6\text{--}6.9 \text{ mmol/L}$) or glycated hemoglobin $5.7\%\text{--}6.4\%$ ($39\text{--}47 \text{ mmol/mol}$) 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 \pm 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 ($P = \text{NS}$), 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%) ($P = \text{NS}$); 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, <i>etc.</i>)	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 (fecal 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.

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 ($P = \text{NS}$) (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](#).

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.

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 mo	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 mo	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*[34] 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. Divarçı *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 <i>et al</i> [26], 2020	China	3.1	104 (31/69)	9.9	8.6	1
Vasudevan <i>et al</i> [27], 2020	United States	2.8	65	13	23	3
Mizuno <i>et al</i> [28], 2018	Japan	30	1 (M)	12	0	0
Divarçı <i>et al</i> [29], 2017	Turkey	3.6	5 (0/100)	15	0	0
d'Ambrosio <i>et al</i> [30], 2014	Italy	2.1	5 (40/60)	7	20	20
Laje <i>et al</i> [31], 2013	United States	6.7	6 (17/83)	15	17	0
Scandavini <i>et al</i> [32], 2018	Sweden	6.6	13 (23/77)	11.4	31	7,7
Lindholm <i>et al</i> [33], 2017	United States	4.7	12 (42/58)	9	83.3	0
Park <i>et al</i> [34], 2016	Korea	10.5	¹ 8 (25/75)	10.5	75	12.5
Muller <i>et al</i> [35], 2012	France	4.2	² 16 (44/56)	8.9	6.25	0
Speer <i>et al</i> [36], 2012	United States	1.4	11 (36/64)	14	9	0
Yazbeck <i>et al</i> [37], 2010	Lebanon	-	1 (F)	13	100	0

¹Two patients excluded due to pancreatic trauma.

²Two 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)	
	Pancreatic islet cells cancer (1)	
	Other (3)	

SPT: Solid pseudopapillary tumor; PD: Pancreaticoduodenectomy.

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 (%)
	235	149 (63)	106 (37)
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.

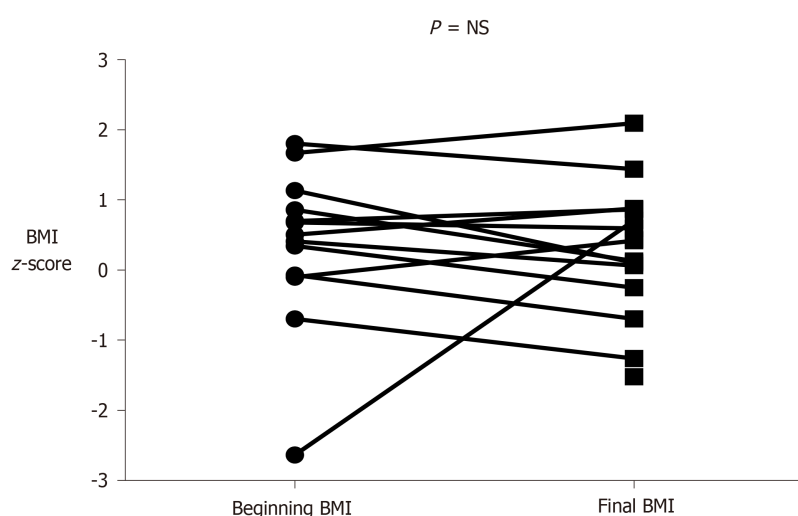


Figure 1 Initial and final body mass index were available in 13 of the 16 patients. BMI: Body mass index; NS: Not significant.

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.

ARTICLE HIGHLIGHTS

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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