ORIGINAL ARTICLE

Surgical Management of Insulinomas

Short- and Long-term Outcomes After Enucleations and Pancreatic Resections

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Objective: To analyze the characteristics and outcomes following enucleation and pancreatic resections of insulinomas.

Design: Retrospective cohort study; prospective database.

Settings: Academic, tertiary, and referral centers.

Patients: Consecutive patients with insulinomas (symptoms of hyperinsulinism and positive fasting glucose test) who underwent surgical treatment between January 1990 and December 2009.

Main Outcome Measures: Operative morbidity, tumor recurrence, and survival after treatment.

Results: A total of 198 patients (58.5% women; median age, 48 years) were identified. There were 175 (88%) neuroendocrine tumors grade G1 and 23 (12%) neuroendocrine tumors grade G2. Malignant insulinomas defined by lymph node/liver metastases were found in 7 patients (3.5%). Multiple insulinomas were found in 8% of patients, and 5.5% of patients had multiple endocrine neoplasia type 1. Surgical procedures included 106 enucleations (54%) and 92 pancreatic resections (46%). Mortality was nil. Rate of clinically significant pancreatic fistula was 18%. Enucleations had a higher reoperation rate compared with pancreatic resections (8.5% vs 1%; $P=.02$). Multiple endocrine neoplasia type 1 was significantly associated with younger age at onset ($P<.005$) and higher rates of malignancies and multiple lesions. Median follow-up was 65 months. Six patients (3%; 5 patients had neuroendocrine tumors grade G2) developed tumor recurrence. Four patients (2%) died of disease. New exocrine (1.5%) and endocrine (4%) insufficiencies were associated only with pancreatic resections.

Conclusions: Outcomes following surgical resection of insulinomas are satisfactory, with no mortality and good functional results. Recurrence is uncommon (3%), and it is more likely associated with neuroendocrine tumors grade G2. Insulinomas in multiple endocrine neoplasia type 1 are at higher risk for being malignant and multifocal, requiring pancreatic resections.

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Insulinomas, the most common functioning endocrine neoplasms of the pancreas, are characterized clinically by hypoglycemic symptoms resulting from neuroglycopenia and catecholamine response.[1,2] They usually present as a small, well-demarcated, solitary nodule that may arise in any part of the gland, with an incidence peak in the fifth decade of life.[1-3] Approximately 5% to 10% of patients with insulinomas have multiple endocrine neoplasia type 1 (MEN 1), and these patients frequently have multiple lesions and are at higher risk for malignancy.[3-6] Still, more than 90% of sporadic insulinomas are benign tumors, being treatable by surgical operation.[1,3]

While in the past preoperative localization of insulinoma could be problematic and blind pancreatic resections were performed,[7,8] high-resolution imaging techniques and endoscopic ultrasound currently allow high preoperative detection rates, which is essential in planning the most appropriate surgical strategy.[9-18]

Tumor enucleation is largely performed to treat insulinomas.[3,5] Although associated with a high risk for postoperative complications, this procedure has the advantage of preserving healthy pancreatic parenchyma with a low risk for postoperative pancreatic insufficiency.[19,20] However, when the lesion is embedded deep in the pancreatic tissue or is close to the main pancreatic duct, enucleation should be avoided and formal pancreatic resections performed. The rate of enucleations and pancreatic resections for insulinomas varies among different studies, and

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most of those include a limited number of patients or encompass a wide study period.[1,5,21-24]

Our objective is to analyze the surgical experience of 2 high-volume centers in the management of insulinomas, with a specific focus on different surgical procedures performed (enucleation vs pancreatic resections). Perioperative and long-term functional and oncologic outcomes are analyzed.

METHODS

After obtaining institutional review board approval, prospective databases maintained at the Departments of Surgery of the University of Verona and San Raffaele Hospital were queried to identify patients in whom an enucleation or pancreatic resection for insulinoma was performed between 1990 and 2009.

All patients included in the present series had hypoglycemic symptoms resulting from neuroglycopenia and/or the autonomic nervous system. Diagnosis of insulinoma was based on a positive 72-hour fasting glucose test or low blood glucose associated with high insulin and C-peptide levels.[1-3] European Neuroendocrine Tumor Society criteria for the diagnosis of insulinoma were applied.[3]

Demographic characteristics, preoperative assessment, intraoperative and postoperative data, complications, and pathology were collected. Patients with MEN 1 were included. According to international guidelines, MEN 1 was diagnosed in patients with at least 2 of the 3 major MEN 1–correlated disorders (primary hyperparathyroidism, pituitary adenoma, or pancreaticoduodenal endocrine tumors), patients with 1 typical disorder and positive family history, or cases of positive genetic testing for MEN 1.[25]

Intraoperative ultrasound was performed in selected cases to evaluate tumor morphology and tumor proximity to the main pancreatic duct, as well as to rule out the presence of multiple lesions.

The choice of the surgical procedure was based on location and size of the tumor. Specifically, for small neoplasms located superficially, enucleation was considered. For insulinomas in the neck/proximal body of the pancreas embedded deep in the substance of the gland and/or close to the main pancreatic duct, middle pancreatectomy (MP) was performed according to previously described techniques.[26] In patients who underwent pancreatic resection, octreotide, 0.1 mg, was administered 1 hour prior to the operation and then 3 times a day for 7 days. Perioperative mortality was defined as in-hospital or 30-day death. Pancreatic fistula was classified according to International Study Group on Pancreatic Fistula grading.[27]

The pathologic diagnosis was based on conventional histologic and immunohistochemical examination (chromogranin A and synaptophysin) on surgical specimen. The Ki67 proliferative index was expressed as a percentage based on the count of Ki67-positive cells in 2000 tumor cells in areas of the highest immunostaining using MIB1 antibody (DBA). All cases were further reviewed and classified according to the criteria of the 2000 and 2010 World Health Organization (WHO) classifications[28,29] and staged according to the new TNM classification system.[30]

Patients' follow-up was based on clinical, radiological, and laboratory assessments with yearly intervals.[31] Specific aims of long-term follow-up were to evaluate tumor recurrence and long-term endocrine and exocrine functions. The presence of new-onset diabetes was demonstrated through serum glucose levels and oral glucose tolerance test.[20] New onset of exocrine insufficiency was defined as patients affected by steatorrhea and weight loss requiring oral pancreatic enzymes in the absence of tumor recurrence.

The *t* test and Mann-Whitney *U* test were applied to compare continuous data. χ^2 and Fisher exact tests were used to compare categorical variables. A *P* value of less than .05 was considered statistically significant. Survival analysis was based on the Kaplan-Meier method. Statistical analysis was performed with the SPSS statistical software package (SPSS).

RESULTS

PATIENT POPULATION AND PREOPERATIVE IMAGING

During the study, 198 patients diagnosed as having symptomatic insulinoma were treated. Median age at presentation was 48 years (range, 14-85 years), and the incidence was slightly higher in women (58.5%; 116 patients). Eleven patients (5.5%) had MEN 1. All patients had hypoglycemia-related symptoms. None of the patients had abdominal pain or jaundice. Unintentional weight gain was found in 95 cases (48%). None of the patients in this cohort had previous negative laparotomies for insulinomas.

Overall, in 6 patients (3%), insulinoma could not be preoperatively identified. Multifocal lesions were detected at preoperative imaging in 13 patients (6.5%).

INTRAOPERATIVE FINDINGS

Intraoperative and postoperative data are shown in **Table 1**. Insulinomas were localized intraoperatively in all 198 patients. In the 6 patients without preoperative tumor localization, insulinomas were detected by palpation and intraoperative ultrasound. Multiple lesions were found in 16 patients (8%; median, 2; range, 2-10) and they were located in the head in 1 case, the body/tail in 9 patients, and along the entire gland in the remaining 6. At laparotomy, 2 patients had unresectable bilateral liver metastases.

SURGICAL PROCEDURES

Enucleation was the most common surgical procedure (n=106; 54%), while the remaining 92 patients (46%) underwent pancreatic resections. Distal pancreatectomy was carried out in 56 patients (28%), and 37 of those (18.5%) were spleen preserving. Twenty patients (10%) underwent MP, while pancreaticoduodenectomy and total pancreatectomy were performed in 11 (5.5%) and 2 patients (1%), respectively. Finally, a distal pancreatectomy associated with enucleation in the pancreatic head was carried out in the other 3 patients (1.5%). Overall, 13 procedures were undertaken laparoscopically (6 enucleations and 7 distal pancreatectomies). Most pancreatic resections (80.5%) were performed for insulinomas located in the pancreatic body/tail, while most (56 of 69; 81%) insulinomas of the proximal pancreas underwent enucleation ($P<.001$) (Table 1). Pancreatic resections were significantly associated with longer duration of surgery and a higher number of intraoperative blood transfusions ($P<.001$).

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Table 1. Intraoperative and Postoperative Data of Surgical Complications of 106 Patients Who Underwent Enucleation and 92 Patients Who Underwent Pancreatic Resection for Insulinoma

Variable	Patients, No. (%)			*P* Value
	Overall (N = 198)	Enucleation (n = 106)	Pancreatic Resection (n = 92)	
Tumor site				
Head/uncinate process	69 (35)	56 (53)	13 (14)	<.001
Body/tail	123 (62)	49 (46)	74 (80.5)	
Entire gland	6 (3)	1 (1)	5 (5.5)	
Intraoperative ultrasound	70 (35.5)	39 (37)	31 (34)	.65
Laparoscopic procedure	13 (6.5)	6 (5.5)	7 (7.5)	.78
Duration of surgery, median (range), min	180 (70-540)	180 (70-280)	240 (90-540)	<.001
Intraoperative blood transfusions	20 (10)	3 (3)	17 (18.5)	<.001
Mortality	0 (0)	0 (0)	0 (0)	
Overall morbidity	103 (52)	50 (47.2)	53 (57.5)	.14
Abdominal complications	93 (47)	47 (44.3)	46 (50)	.43
Overall pancreatic fistula	83 (42)	44 (42)	39 (42)	.90
Grade A pancreatic fistula	48 (24)	22 (21)	26 (28)	.13
Grades B and C pancreatic fistulas	35 (18)	22 (21)	13 (14)	
Pancreatitis	11 (5.5)	6 (5.5)	5 (5.5)	.91
Hemorrhage	6 (3)	4 (3.5)	2 (2)	.49
Abdominal collection	26 (13)	17 (16)	9 (10)	.13
Delayed gastric emptying	1 (0.5)	0 (0)	1 (1)	.29
Overall nonsurgical complications	18 (9)	7 (6.5)	11 (12)	.18
Sepsis	9 (4.5)	4 (3.5)	5 (5.5)	.59
Pulmonary complications	13 (6.5)	4 (3.5)	9 (10)	.08
Hospital LOS, median (range), d	12 (4-57)	10.5 (7-57)	12 (4-53)	.44
Reoperation	10 (5)	9 (8.5)	1 (1)	.02
Readmission	6 (3)	4 (3.5)	2 (2)	.51

Abbreviation: LOS, length of stay.

POSTOPERATIVE COURSE

There was no mortality, and overall morbidity was 52%. Table 1 shows postoperative complications. Median length of postoperative stay was 12 days. Overall and grades B and C pancreatic fistula rates were 42% and 18%, respectively, with no differences between patients who underwent enucleation and pancreatic resections. The reoperation rate was significantly higher in the enucleation group (8.5% vs 1%; $P=.02$). Indications for reoperation included intra-abdominal bleeding (n=4), severe acute pancreatitis with infected necrosis (n=3), intra-abdominal abscess associated with grade C pancreatic fistula (n=2), and postoperative acute appendicitis (n=1).

PATHOLOGY

The diagnosis of insulinoma was pathologically confirmed in all surgical specimens. **Table 2** shows pathologic data for the entire cohort. Median tumor size was 15 mm without differences between insulinomas that underwent enucleation and pancreatic resections (14.5 mm vs 15 mm; $P=.24$). Lymphovascular invasion was found in 14 patients (7%). When the 2010 WHO classification was applied, no neuroendocrine carcinomas were identified, being all insulinomas either neuroendocrine tumor (NET) grade G1 (88%) or NET grade G2 (12%). According to the 2000 WHO classification, there were 129 benign insulinomas (65%), 62 tumors with uncertain biological behavior (31.5%), and 7 well-differentiated carcinomas (3.5%). Positive resection margins (R1) were found in 9 patients (4.5%) who had undergone enucleation in 5 cases, MP in 1 patient, and distal pancreatectomy in the remaining 3. Multifocal tumors were found at pathology in 16 patients (8%).

Overall, no lymph node was excised (NX) in 133 patients (67%) who underwent enucleation, MP, or spleen-preserving distal pancreatectomy. NX rates were 87% for enucleation, 75% for middle MP, and 70% for spleen-preserving distal pancreatectomy.

MALIGNANCIES

Malignant insulinomas were found in 7 patients (3.5%) who had undergone distal pancreatectomy in 5 cases and total pancreatectomy in the remaining 2 cases. They all had lymph node metastases, with 2 having concurrent liver metastases. Six tumors were NET grade G2 and 1 was NET grade G1 (all tumors were well-differentiated endocrine carcinomas according to the 2000 WHO classification). Median size of malignant tumors was 45 mm (range, 20-100 mm) with a median Ki67 value of 8% (range, 1%-20%). The 2 patients with unresectable liver metastases from insulinoma had persistent hypoglycemic symptoms after pancreatic resection.

PATIENTS WITH MEN 1

Eleven patients (5.5%) had MEN 1 and were significantly younger than patients who did not have MEN 1

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Table 2. Pathology of Patients Who Underwent Enucleation or Pancreatic Resection for Insulinoma

	Patients, No. (%) (N = 198)
Size, median (range), mm	15 (5-100)
2000 WHO classification[28]	
Benign	129 (65)
UBB	62 (31.5)
WDEC	7 (3.5)
2010 WHO classification[29]	
NET G1	175 (88)
NET G2	23 (12)
NEC	
pTNM staging[30]	
T1	158 (80)
T2	33 (16.5)
T3	5 (2.5)
T4	2 (1)
NX	133 (67)
N0	58 (29.5)
N1	7 (3.5)
M0	196 (99)
M1	2 (1)
R status	
R0	187 (94.5)
R1	9 (4.5)
R2	2 (1)[a]

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; UBB, uncertain biological behavior; WDEC, well-differentiated endocrine carcinoma; WHO, World Health Organization.

[a] In these 2 patients, R2 status is defined by the presence of unresectable liver metastases.

(median age, 31 vs 48 years; $P=.01$). The rate of malignant tumor (27% vs 3%) was significantly higher in patients with MEN 1 ($P<.001$). The presence of MEN 1was associated with a higher rate of multiple lesions (82% vs 4%; $P=.001$), larger tumor size (median diameter, 25 mm vs 15 mm; $P=.002$), and higher rate of lymphovascular invasion (36% vs 5%; $P=.004$). Patients with MEN 1 underwent pancreatic resections (n=9, including 2 total pancreatectomies) more frequently than enucleations. One 26-year-old woman with insulinoma-related symptoms underwent total pancreatectomy for a multifocal endocrine tumor metastatic to peripancreatic lymph nodes and the liver. Interestingly, immunolabelling for insulin showed strong and diffuse positivity only in some of her pancreatic neoplasms, while the remaining were classified as nonfunctioning pancreatic endocrine tumors. Although liver metastases were not resected, there was a complete symptom regression following total pancreatectomy. Therefore, in this case, liver metastases were considered part of multifocal pancreatic nonfunctioning endocrine tumors.

FOLLOW-UP AND TUMOR RECURRENCE

Median follow-up of the entire cohort was 65 months (range, 12-237 months). Six patients (3%) developed tumor recurrence; of these, 2 had MEN 1. Five patients were diagnosed as having NET grade G2 (**Table 3**). Three of these patients had a pN1 NET at initial histology, while the remaining patients had a pNX status because no lymph nodes were removed.

One patient with MEN 1 developed a recurrence in the head of the pancreas. This tumor was presumably a new primary. He underwent pancreaticoduodenectomy, and he remains disease-free 2 years after his second operation. The remaining patients developed liver metastases within 38 months from initial surgery. They underwent chemotherapy and transarterial chemoembolization. Three of these patients died of disease, while the other 2 are alive with stable disease. No patient with R1 resection developed disease recurrence.

The 5- and 10-year disease-free survival rates were 100% and 96%, respectively. Overall, 13 patients died during follow-up, and 4 patients died of disease.

Eight patients (4%) developed postoperative endocrine insufficiency, 1 (1%) after enucleation and 7 (7.5%) after pancreatic resections ($P=.02$). New onset of exocrine insufficiency was found in only 3 patients (3%) after pancreatic resections ($P=.06$).

COMMENT

The results of our study confirm that insulinoma is usually a benign and solitary tumor with a very low recurrence rate after complete surgical excision.[1-3,5,21,24,32] Most neoplasms (88%) were NET grade G1 with no neuroendocrine carcinomas when 2010 WHO classification was applied. Only 7 patients (3.5%) had a malignant tumor, defined by the presence of lymph nodes and/or liver metastases. In this cohort of 198 patients, 5- and 10-year disease-free survival rates were 100% and 96%, respectively. Six patients (3%) developed tumor recurrence after a median follow-up of 65 months. Overall, only 4 patients (2%) died of disease.

Considering the favorable outcomes associated with insulinomas, enucleation and other parenchyma-sparing procedures are advocated by many researchers as appropriate to treat this disease.[1-3,5,32,33] These procedures as well as distal pancreatectomy may be safely performed laparoscopically, and this approach can shorten the hospital length of stay, enhance postoperative recovery, and minimize the cosmetic impact of the surgical wound.[34-37] In this series, enucleation was performed in 54% of cases, while the remaining patients underwent pancreatic resections including spleen-preserving distal pancreatectomies (18.5%) and MPs (10%). Resection of the pancreatic head was performed in only 11 patients (5.5%). These data are in keeping with a review of 383 insulinomas showing a rate of enucleation and pancreaticoduodenal resection of 54% and 5%, respectively.[33] Others have reported a lower rate of enucleations with an increased number of pancreaticoduodenectomies to avoid possible pancreatic duct injuries.[5] In our experience, 81% of insulinomas located in the pancreatic head underwent enucleation compared with 40% of those located in the body/tail. These differences may reflect our reluctance to perform pancreaticoduodenectomy—with its risks for morbidity, mortality, and functional impairment—for a tumor with a favorable outcome in a patient population with a long life expectancy.

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Table 3. Characteristics of Patients Who Developed Tumor Recurrence After Surgical Treatment of Insulinomas

Patient No.	2000 WHO Classification Histology	2010 WHO Classification Histology	pTNM Staging	Surgical Procedure	Ki67 Index, %	MEN 1	R Status	Lymphovascular Invasion	TTR, mo	Site	Status
1	WDEC	NET G2	pT2N1M0	Distal pancreatectomy with splenectomy	19	No	R0	Yes	38	Liver	DOD, 61 mo
2	WDEC	NET G2	pT2N1M0	Distal pancreatectomy with splenectomy	5	Yes	R0	Yes	36	Liver	DOD, 80 mo
3	Tumor with UBB	NET G2	pT1NxM0	Enucleation	5	No	R0	No	24	Liver	Alive, 142 mo
4	Tumor with UBB	NET G2	pT2NxM0	Enucleation	3	No	R0	Yes	36	Liver	DOD, 250 mo
5	Tumor with UBB	NET G1	pT2NxM0	Spleen-preserving distal pancreatectomy	1	Yes	R0	No	72	Pancreatic head	Alive, 96 mo
6	WDEC	NET G2	pT3N1M0	Distal pancreatectomy	15	No	R0	Yes	12	Liver	Alive, 54 mo

Abbreviations: DOD, dead of disease; G, grade; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; TTR, time to recurrence; UBB, uncertain biological behavior; WDEC, well-differentiated endocrine carcinoma.

Overall morbidity was 52% with no mortality. No statistically significant differences were found between enucleations and pancreatic resections in regard to pancreatic fistula and abdominal complications, despite a higher reoperation rate in the enucleation group. Moreover, the rate of pancreatic insufficiency following enucleation was nearly absent as in other series.[19,20,26]

In this cohort, 6 patients developed tumor recurrence; of these, 5 patients had NET grade G2. Interestingly, 2 of these patients had undergone enucleation with no lymph nodes excised (NX status), and they developed liver metastases. It could be supposed that the lack of nodal samples led to an erroneous pathologic diagnosis. Enucleation as well as other parenchyma-sparing procedures may lack adequate lymph node sampling, resulting in a possible tumor understaging.[38] Remarkably, NX rates were 87% for enucleation, 75% for MP, and 70% for spleen-preserving distal pancreatectomy. Whenever enucleation or other parenchyma-sparing procedures are carried out, lymph node sampling of peripancreatic nodes should be performed to increase the oncologic effectiveness of these procedures.

The combination of preoperative imaging, intraoperative ultrasound, and palpation allowed localizing insulinomas in all 198 patients, thus avoiding blind pancreatic resections. Preoperative localization of the tumor is of paramount importance when planning the most appropriate surgical management for these patients.[9,15,39] Currently, the combination of biphasic thin section helical computed tomography and endoscopic ultrasonography has an almost 100% sensitivity in localizing insulinomas.[5,10-12,16,17,39] Pathologic characteristics of insulinomas in this series were similar to the findings reported by others.[1,3,5,21,24] The overall median tumor size was 15 mm and most insulinomas were NET grade G1. Danforth and colleagues[40] found a correlation between size and malignancy (median size of 47 mm in a group of 62 patients). We confirm this data because malignant insulinomas had a median size of 45 mm with a median Ki67 value of 8%. Finally, in this cohort, R1 resection was found in 9 patients (4.5%) but none of them developed tumor recurrence. Similar data are provided by Nikfarjam et al,[5] with an R1 rate of 13% and no recurrences in this group.

Interestingly, insulinomas in the setting of MEN 1 have a specific clinicopathologic profile, showing a more aggressive biological behavior. Multiple endocrine neoplasia type 1 insulinomas were associated with an earlier age at onset and higher rates of malignant neoplasms and multiple lesions. The optimal management of patients with MEN 1 is debated. Although some researchers have suggested a systematic subtotal pancreatectomy associated with enucleation of pancreatic head lesions,[41,42] it is unclear whether this aggressive approach may eventually decrease the risk for tumor recurrence.[3,4,6] In this series among patients with MEN 1, there was only 1 local recurrence after an R0 spleen-preserving distal pancreatectomy for a NET grade G1 pT2NX that was successfully treated with pancreaticoduodenectomy. It is likely that this tumor represents a new primary rather than a real recurrence. Since insulinomas in MEN 1 are at higher risk for being malignant and multifocal, pancreatic resections instead of enucleation should be performed, but the performance of routine subtotal pancreatectomy seems unjustified.[43]

In conclusion, insulinomas are commonly well-differentiated nonmetastatic and unifocal tumors. A combination of endoscopic ultrasonography with high-resolution imaging techniques can identify nearly 100% of insulinomas, optimizing the surgical strategy and avoiding blind resections. About half of patients will require a pancreatic resection; and in high-volume centers, both surgical resections and enucleations are safe, with no mortality and acceptable morbidity. Recurrence is uncommon (3%), and it is more likely associated with NET grade G2. Lymph node sampling should be carried out whenever a parenchyma-sparing procedure is performed to decrease the risk for tumor understaging. Insulinomas in MEN 1 are at higher risk for being malignant and multifocal, thus requiring pancreatic resections.

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Author Contributions: Drs Crippa, Zerbi, and Falconi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Crippa, Zerbi, Di Carlo, and Falconi. *Acquisition of data:* Boninsegna, Capitanio, and Balzano. *Analysis and interpretation of data:* Crippa, Partelli, Balzano, Pederzoli, and Falconi. *Drafting of the manuscript:* Crippa, Capitanio, and Partelli. *Critical revision of the manuscript for important intellectual content:* Crippa, Zerbi, Boninsegna, Partelli, Balzano, Pederzoli, Di Carlo, and Falconi. *Statistical analysis:* Crippa, Boninsegna, and Partelli. *Study supervision:* Zerbi, Balzano, Pederzoli, Di Carlo, and Falconi.

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