Original article

Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort

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Background: **Insulinomas are found in 10–15 per cent of patients with multiple endocrine neoplasia type 1 (MEN1) and lead to life-threatening hypoglycaemia. Surgical outcome and the optimal surgical strategy for MEN1-related insulinoma are unknown.**

Methods: **Patients with MEN1-related insulinomas were identified in 46 centres in Europe and North America between 1990 and 2016. Insulinomas were considered localized if the lesion was in the pancreatic head or body/tail. Patients with pancreatic neuroendocrine tumours throughout the pancreas were suspected of having multifocal insulinoma. The primary outcome was postoperative hypoglycaemia, defined as persistent hypoglycaemia, or recurrent hypoglycaemia caused by a new insulinoma or insulin-producing liver metastases. Hypoglycaemia-free survival was estimated by the Kaplan–Meier method.**

Results: **Ninety-six patients underwent resection for MEN1-related insulinoma. Sixty-three and 33 patients had localized and multifocal insulinomas respectively. After a median follow-up of 8 (range 1–22) years, one patient (1 per cent) had persistent disease and six (6 per cent) had developed recurrent disease, of whom four had a new insulinoma. The 10-year hypoglycaemia-free survival rate was 91 (95 per cent c.i. 80 to 96) per cent. Of those with localized disease, 46 patients underwent pancreatic resection and 17 enucleation. One of these patients had persistent disease and one developed recurrent insulinoma. Among patients with multifocal disease, three developed new insulinomas and two developed insulin-producing liver metastases.**

Conclusion: **Surgery for MEN1-related insulinoma is more successful than previously thought.**

*Members of the International MEN1 Insulinoma Study Group are co-authors of this article and may be found under the heading Collaborators

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Introduction

Insulinoma is a pancreatic neuroendocrine tumour (pNET) that produces insulin and leads to symptomatic and life-threatening hypoglycaemia[1]. Currently, surgical resection is the only curative treatment[2,3]. Some 4–8 per cent of insulinomas are associated with multiple endocrine neoplasia type 1 (MEN1), a rare hereditary disorder occurring in two to three per 100 000 people[4,5]. Patients with MEN1 develop pNETs with a very high and age-related penetrance. These pNETs are insulin-producing in 10–15 per cent of patients[6–8]. Patients with MEN1-related insulinoma are often young and have multiple pNETs, making the decision regarding the extent of surgery complicated[9].

Localization of the insulin-producing pNET is a major challenge in the presence of a diffuse background of non-functioning pNETs (NF-pNETs) in MEN1. Extensive resections were initially proposed, such as 80 per cent resection of the pancreas left of the superior mesenteric/portal vein, with subsequent enucleations of pNETs in the pancreatic head[8,10]. Although persistent and recurrent hypoglycaemia seem uncommon after this aggressive approach, the procedure

is associated with pancreatic insufficiency[8,10,11]. The sensitivity of CT and MRI has improved, and the availability of endoscopic ultrasonography (EUS) has increased. In addition, glucagon-like peptide-1 receptor (GLP-1R) imaging using ^{68}Ga-DOTA-exendin-4 ([Nle^{14}, Lys^{40}(Ahx-DOTA-^{68}Ga)NH$_2$] exendin-4) PET/CT, an emerging localization technique, might overcome the difficulties of localizing MEN1-related insulinomas[12]. These advances in preoperative localization raise the question of the optimal surgical procedure for MEN1-related insulinomas, taking both short-term cure of hypoglycaemia and long-term risk of recurrence into account.

The European Neuroendocrine Tumour Society (ENETS) and the MEN1 clinical practice guidelines[2,3] lack well grounded recommendations regarding the optimal surgical strategy because there is limited evidence. In the case of a single pNET on CT, MRI or EUS, the ENETS guidelines[3] recommend pancreas-sparing surgery, based on two single-centre studies[13,14] that included only 13 and eight patients with MEN1 respectively. Persistence or recurrence of hypoglycaemia has been reported in 25–50 per cent after enucleation and 2·6–20 per cent after extensive resection[11,13,15]. Most data are, however, based on old and small single-centre series[9–11,13,15,16], hampering comparisons between surgical strategies. In the only population-based cohort study[17], a higher risk of recurrent hypoglycaemia was observed after enucleation (33·3 per cent) than after distal pancreatectomy (8·7 per cent), but 42 per cent of the patients had surgery before 1990. Studies often also failed to differentiate between recurrent hypoglycaemia because of insulin-producing liver metastases and new insulin-producing pNETs.

The aim of this study was to provide evidence for surgical decision-making in patients with MEN1-related insulinoma. The risk of recurrence after pancreatic surgery was investigated in a comprehensive international cohort of patients with MEN1-related insulinoma.

Methods

This study was an international collaboration between 40 hospitals in Europe and six in North America. Patients with MEN1 were identified in the hospital databases using ICD-9/10 codes for MEN1 and insulinoma. Eligible patients underwent surgery for insulinoma between 1990 and 2016, had a pNET tumour confirmed histologically, and follow-up for at least 1 year after surgery. The MEN1 diagnosis was established either by genetic testing, family history or clinically, according to most recent practice guidelines[2]. Patients who underwent total pancreatectomy and those with distant metastases at diagnosis were excluded. Clinical and demographic data were collected by review of medical records in a standardized manner using predefined definitions. The medical records were examined by an investigator at the collaborating institution and discussed with the coordinating investigators. The study protocol was approved by the medical ethics committees or institutional review boards of all participating centres.

Insulinoma diagnosis

The presence of an insulinoma was based on a positive 72-h supervised fasting test[18,19]. If no test was performed, the diagnosis was based on symptoms or signs of hypoglycaemia with concomitant biochemical endogenous hyperinsulinaemic hypoglycaemia, according to clinical practice guidelines[18,19]. The date of diagnosis was based on the date of the supervised 72-h fasting test or the date of symptoms accompanied by endogenous hyperinsulinaemic hypoglycaemia.

Insulinoma localization

The evaluation for MEN1-related insulinoma was dependent on the surgeon's preference and availability of localization techniques in each centre at the time of surgery. Generally, conventional imaging (CT, MRI, EUS) was undertaken before surgery, eventually followed by more invasive techniques, such as arterial (calcium) stimulation venous sampling or GLP-1R receptor imaging. Most importantly, intraoperative findings, based on intraoperative ultrasonography and/or bimanual palpation, were used to localize the insulinoma and subsequently guide intraoperative surgical decision-making.

Based on all preoperative and intraoperative findings, the insulinoma was localized to the pancreatic head or body/tail, or the surgeon suspected multifocal insulinomas in both the head and body/tail. Subsequent surgical decisions were based on whether during surgery the surgeon considered the insulinoma to be localized (suspected to be located in pancreatic head or body/tail) or possibly multifocal (insulinomas in both pancreatic head and body/tail).

Surgical strategy

Patients with localized insulinoma underwent enucleation, Whipple/pylorus-preserving pancreatoduodenectomy (PPPD) or distal pancreatectomy. In these patients, enucleation was compared with resection (distal pancreatectomy or Whipple/PPPD).

Patients with multifocal insulinomas underwent combined procedures involving the pancreatic head and

Table 1 Baseline characteristics of multiple endocrine neoplasia type 1 study cohort undergoing insulinoma surgery

	Overall (n = 96)	Localized insulinoma (*n* = 63)	Multifocal insulinoma (*n* = 33)
Age at insulinoma diagnosis (years)*	30 (5–81)	31 (5–81)	30 (14–61)
Age at surgery (years)*	32 (6–82)	32 (6–82)	31 (13–62)
Aged less than 21 years at insulinoma surgery			
Yes	15 (16)	8 (13)	7 (21)
No	81 (84)	55 (87)	26 (79)
Sex ratio (M : F)	38 : 58	24 : 39	14 : 19
Diagnosis			
Fasting test	64 (67)	43 (68)	21 (64)
Clinical and biochemical	32 (33)	20 (32)	12 (36)
No. of pNETs on conventional imaging (*n* = 91)			
0	4 (4)	3 (5)	1 (3)
1	45 (49)	31 (52)	14 (45)
2	19 (21)	12 (20)	7 (23)
≥3	23 (25)	14 (23)	9 (29)
Distribution of pNETs on conventional imaging (*n* = 92)			
None	4 (4)	3 (5)	1 (3)
Head only	11 (12)	6 (10)	5 (16)
Body/tail only	51 (55)	39 (65)	12 (38)
Multifocal (head and body/tail)	26 (28)	12 (20)	14 (44)
Size of largest pNET on preoperative imaging (mm)* (*n* = 79)	20 (4–90)	20 (4–60)	22·5 (10–90)
pNET ≥ 2 cm on preoperative imaging (*n* = 81)			
None	36 (44)	26 (50)	10 (34)
Head	13 (16)	6 (12)	7 (24)
Body/tail	29 (36)	19 (37)	10 (34)
Head and body/tail	3 (4)	1 (2)	2 (7)
Suspected lymph node metastases on preoperative imaging (*n* = 92)	1 (1)	1 (2)	0 (0)
Time interval of surgery			
1990–2006	48 (50)	29 (46)	19 (58)
2006–2016	48 (50)	34 (54)	14 (42)
Type of resection			
Enucleation	17 (18)	17 (27)	0 (0)
Multiple enucleations	3 (3)	0 (0)	3 (9)
Distal pancreatectomy	41 (43)	41 (65)	0 (0)
Distal pancreatectomy and enucleation	26 (27)	0 (0)	26 (79)
Whipple/PPPD	5 (5)	5 (8)	0 (0)
Whipple/PPPD and enucleation	2 (2)	0 (0)	2 (6)
Whipple/PPPD and distal pancreatectomy	2 (2)	0 (0)	2 (6)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). pNET, pancreatic neuroendocrine tumour; PPPD, pylorus-preserving pancreatoduodenectomy.

body/tail, including multiple enucleations, distal pancreatectomy plus enucleation of a pNET in the pancreatic head, Whipple/PPPD plus enucleation and Whipple/PPPD plus distal pancreatectomy. In such patients, distal pancreatectomy combined with enucleation of tumour in the head of the pancreas was compared with multiple enucleations, Whipple/PPPD plus enucleation or Whipple/PPPD plus distal pancreatectomy. In addition, patients who underwent one or multiple enucleations were compared with those who had other resections.

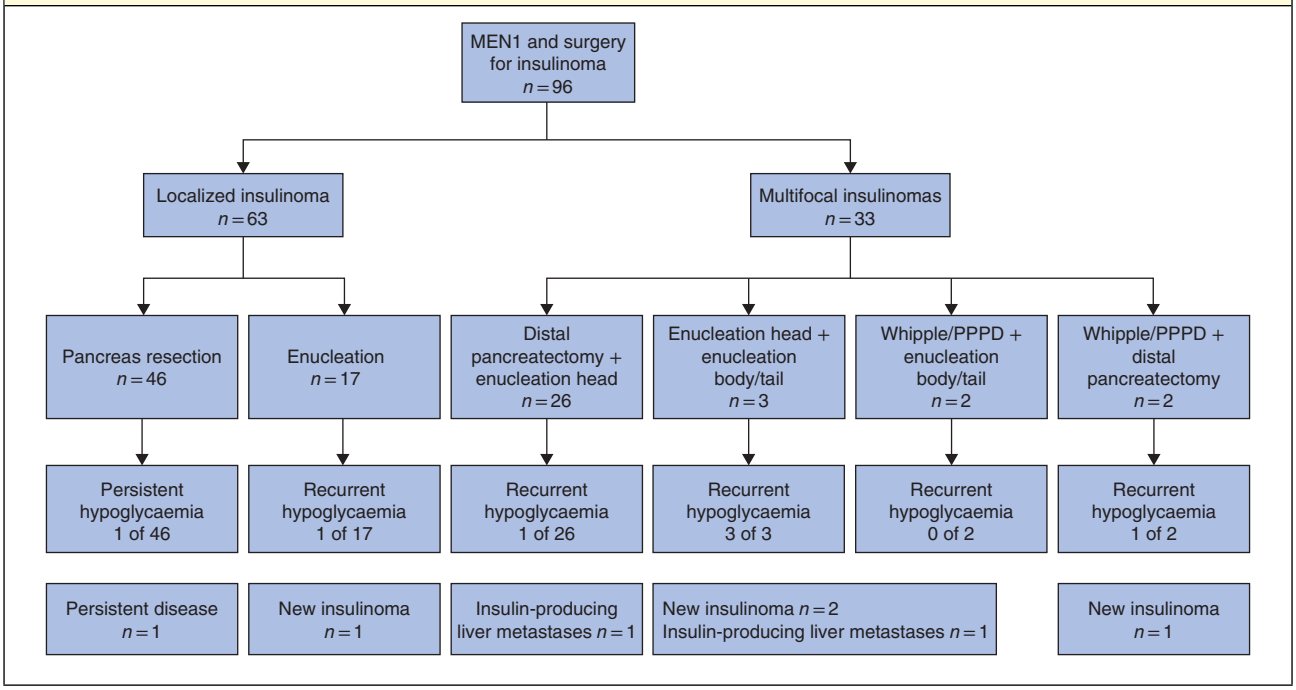
Pathology

The total number of pNETs, number of immunohistochemically insulin-positive pNETs in the head and body/tail, size of the largest insulin-positive pNET of the head and body/tail, and number of tumour-positive locoregional lymph nodes were registered.

Postoperative and long-term outcomes

The primary outcome was hypoglycaemia at 3 months after surgery. Patients with hypoglycaemia within 3 months of

Fig. 1 Study flow chart showing insulinoma location, surgical procedures and postoperative hypoglycaemia



MEN1, multiple endocrine neoplasia type 1; PPPD, pylorus-preserving pancreatoduodenectomy.

surgery were considered to have persistent disease. Insulinoma recurrence was defined as recurrence of hypoglycaemia more than 3 months after surgery owing to a new insulinoma in the remaining pancreas. Patients with recurrence of hypoglycaemia and newly diagnosed liver metastases were considered to have insulin-producing liver metastases.

Secondary outcomes were early and late complications after surgery. Postoperative pancreatic fistula (POPF), postpancreatectomy haemorrhage (PPH), bile leak and delayed gastric emptying (DGE) were graded according to the International Study Group of Pancreatic Surgery (ISGPS) classification[20–23]. Clavien–Dindo grade III–IV postoperative complications within 30 days after surgery, or during the hospital stay, were recorded[24]. Postoperative mortality was defined as death within 30 days of surgery. Exocrine pancreatic insufficiency was defined by use of pancreatic enzyme supplementation for at least 6 months. New-onset diabetes was defined as the use of antidiabetic medication for 6 months or more after surgery.

Statistical analysis

Data are presented as median (range) or count (percentage). The time to recurrence of hypoglycaemia and insulinoma was assessed using Kaplan–Meier analysis[25], and hypoglycaemia- and insulinoma-free survival probabilities were estimated. Follow-up started on the date of insulinoma surgery and ended on the date of hypoglycaemia or insulinoma recurrence, last follow-up or death. Analyses were done separately for patients with localized *versus* multifocal disease, and for patients with one or more enucleation(s) and those who had other resections (all resections other than one or more enucleation(s)). Statistical analyses were undertaken using SPSS® version 25.0 (IBM, Armonk, New York, USA).

Results

A total of 159 patients with MEN1 were identified, of whom 96 met the inclusion criteria. Sixty-three patients did not meet the inclusion criteria for the following reasons: no surgery (15), liver metastases at diagnosis (6), no proper diagnosis (3), follow-up less than 1 year (34), total pancreatectomy (4) or no details on surgical procedure (1). Demographics and clinical characteristics of the cohort are shown in *Table 1*. Median age at diagnosis was 30 (range 5–81) years and 15 of the 96 patients (16 per cent) were younger than 21 years at diagnosis. There were 58 female patients (60 per cent). The insulinoma diagnosis was confirmed following a 72-h fasting test in 64 patients (67 per cent).

Table 2 Procedure-specific outcomes after insulinoma surgery in patients with multiple endocrine neoplasia type 1

	Localized			Multifocal			
	Enucleation (*n* = 17)	Whipple/ PPPD (*n* = 5)	Distal pancrea-tectomy (*n* = 41)	Distal pancrea-tectomy + enucleation head (*n* = 26)	Enucleation head + enucleation body/tail (*n* = 3)	Whipple/ PPPD + enucleation body/tail (*n* = 2)	Whipple/ PPPD + distal pancrea-tectomy (*n* = 2)
Early postoperative outcomes							
ISGPS grade B/C complications							
POPF	3 of 16	0 of 4	6 of 36	5 of 24	1 of 3	0 of 2	1 of 2
B	3	–	4	2	1	–	1
C	0	–	2	3	0	–	0
DGE	0 of 16	0 of 4	3 of 36	1 of 24	1 of 3	0 of 2	0 of 2
PPH	0 of 16	0 of 4	0 of 36	0 of 24	0 of 3	0 of 2	0 of 2
Bile leak	–	0 of 4	–	–	–	0 of 2	0 of 2
Other Clavien–Dindo grade III–IV complication	0 of 13	1 of 4	2 of 27	1 of 24	0 of 2	0 of 2	0 of 2
Death	0 of 17	0 of 5	0 of 41	0 of 26	0 of 3	0 of 2	0 of 2
Duration of hospital stay (days)* (*n* = 57)	8·5 (4–12)	19 (14–23)	9 (3–25)	15 (7–53)	–	15 (15–15)	–
Readmission	3 of 14	0 of 4	3 of 36	2 of 25	1 of 3	1 of 1	0 of 2
Long-term outcomes							
Endocrine or exocrine insufficiency	0 of 17	1 of 5	14 of 41	7 of 26	0 of 3	1 of 2	2 of 2
Exocrine insufficiency	0 of 17	1 of 5	1 of 41	2 of 26	0 of 3	1 of 2	2 of 2
New-onset diabetes	0 of 17	0 of 5	13 of 41	5 of 26	0 of 3	0 of 2	0 of 2
Development of liver metastases	0 of 17	0 of 5	3 of 41	2 of 26	1 of 3	0 of 2	0 of 2
Death	0 of 17	1 of 5	3 of 41	4 of 26	1 of 3	0 of 2	0 of 2
Follow-up (years)*	5 (1–22)	9 (7–13)	8 (1–22)	8 (1–21)	18 (10–20)	3 (1–5)	11 (8–14)

*Values are median (range). PPPD, pylorus-preserving pancreatoduodenectomy; ISGPS, International Study Group of Pancreatic Surgery; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; PPH, postpancreatectomy haemorrhage.

Preoperative imaging and type of surgery

Preoperative imaging results and surgical strategies are shown in *Table 1* and *Fig. 1*. The insulinoma was localized in 63 patients (66 per cent), and these patients underwent typical resections: single enucleation (17), distal pancreatectomy (41) or Whipple/PPPD (5). The disease was considered multifocal in 33 patients (34 per cent), leading to combined pancreatic resections, of which the majority (26 of 33) were distal pancreatectomies with enucleation of tumour in the pancreatic head. Clinical characteristics of patients undergoing one or multiple enucleations and other resections are shown in *Table S1* (supporting information). Twenty-nine of 48 patients operated before 2006 were considered to have localized insulinoma compared with 34 of 48 who had surgery from 2006 onwards (*Table S2*, supporting information).

Of 92 patients with preoperative imaging, 45 (49 per cent) had a solitary pNET on imaging. Despite having a solitary pNET on imaging, 14 of these patients underwent resection for multifocal disease, based on invasive imaging or intraoperative findings. Ten had distal pancreatectomy with enucleation, one had Whipple/PPPD with enucleation and three had multiple enucleations.

Pathology

The median number of pNETs resected was 3 (range 1–74), of which a median of 1 (0–4) was insulin-positive. Histopathological reports for four patients could not be retrieved, and detailed information regarding the exact number of insulin-positive pNETs was not available for another 17 patients. Three patients had no insulin-positive pNETs, all of whom were cured by surgery. A single insulin-positive pNET was observed in 40 of 50 patients with a localized insulinoma. Preoperative conventional imaging and outcomes of histology in patients with localized disease are summarized in *Table S3* (supporting information).

Among 25 patients with multifocal insulinomas, one, two and at least three insulin-positive pNETs were observed in 12, eight and four respectively, and one patient had no insulin-positive pNET. Eight of these patients had an insulin-positive pNET in the pancreatic head and in the

body/tail (*Table S4*, supporting information). In the remaining eight patients with multifocal disease, no detailed information regarding insulin staining was available. Among the patients with a solitary pNET on imaging but the finding of multifocal disease during surgery, five of 11 had multifocal insulin-positive pNETs.

Lymph nodes were resected in 45 patients and were tumour-positive in seven, but as insulin immunohistochemistry of metastatic lymph nodes was not undertaken routinely, the exact source could not be assessed.

Intraoperative data, postoperative complications and hospital stay

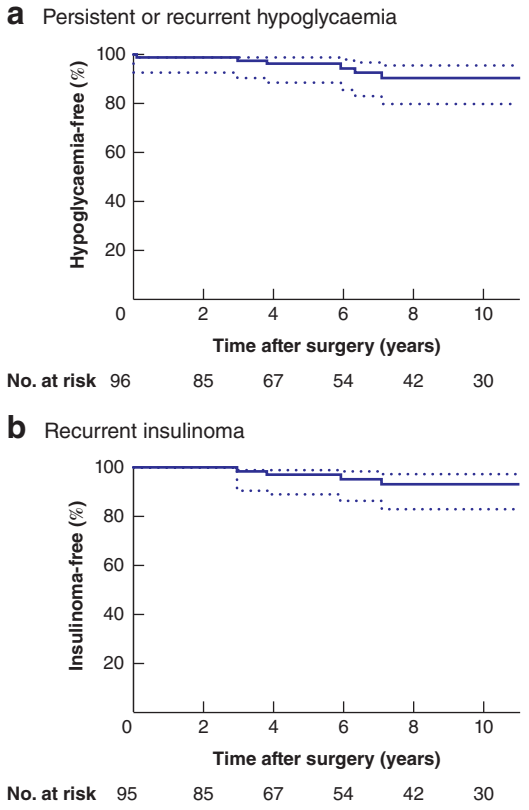
Median duration of operation was 225 (range 43–440) min, and median blood loss was 200 (0–4150) ml. Median operating time was shorter (133 *versus* 244 min) and there was less blood loss (50 *versus* 250 ml) in enucleations compared with other procedures. Postoperative outcomes are shown in *Table 2*. There was no postoperative death. ISGPS grade B/C POPF, DGE, PPH and bile leak developed in 16 of 87 (18 per cent), five of 87 (6 per cent), none of 87 and none of nine patients respectively. No relevant differences were observed between the procedures. Median hospital stay was 10 (range 3–53) days, and ten of 85 patients (12 per cent) were readmitted. Patients who underwent Whipple/PPPD alone (4) or distal pancreatectomy with enucleation (15) had a relatively long hospital stay: median 19 (14–23) and 15 (7–53) days respectively.

Recurrence of hypoglycaemia and insulinoma

The distribution of patients with postoperative hypoglycaemia is shown in *Fig. 1*. After a median follow-up of 8 (range 1–22) years, seven patients (7 per cent) had hypoglycaemia. One patient (1 per cent) had persistent hypoglycaemia and six (6 per cent) had recurrent hypoglycaemia. Of those with recurrent hypoglycaemia, four had a new insulinoma and two developed insulin-producing liver metastases. The patient with persistent disease underwent distal pancreatectomy to remove a 5-mm insulinoma with immunohistochemistry positive for insulin. Postoperative EUS showed two lesions in the pancreatic body that were resected 10 months later, resulting in biochemical cure.

Estimated 10-year hypoglycaemia-free and insulinoma-free survival rates were 91 (95 per cent c.i. 80 to 96) and 93 (83 to 97) per cent respectively (*Fig. 2*). The estimated 10-year hypoglycaemia-free survival rate was 96 (84 to 98) per cent for patients with localized insulinoma and 81 (58 to 92) per cent among those with multifocal insulinomas (*Fig. 3*). Ten patients (10 per cent) had follow-up of less than 2 years, 34 (35 per cent) less than 5 years, 63 (66 per cent) less than 10 years, 81 (84 per cent) less than 15 years, and the remaining 15 patients (16 per cent) had follow-up of 15 years or more. Five of 64 patients (8 per cent) who were diagnosed according to a 72-h fasting test developed recurrent hypoglycaemia and two of 32 who were diagnosed based on clinical criteria. Outcomes for patients who had one or more enucleations *versus* those with other resections are summarized in *Table S1* and *Fig. S1* (supporting information). Of the 15 patients aged less than 21 years at the time of surgery, two developed recurrent insulinoma.

Fig. 2 Persistent or recurrent hypoglycaemia- and recurrent insulinoma-free survival after surgery for multiple endocrine neoplasia type 1-related insulinoma

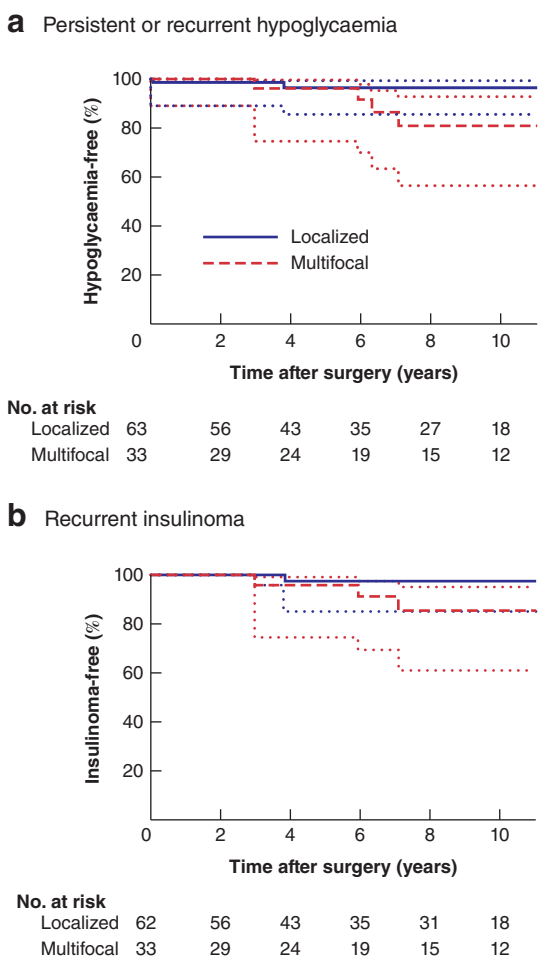


a Persistent or recurrent hypoglycaemia and **b** recurrent insulinoma. Dotted lines indicate 95 per cent confidence interval.

Pancreatic insufficiency, liver metastases and death

Twenty-five patients (26 per cent) developed pancreatic insufficiency (*Table 2*). Seven patients developed exocrine pancreatic insufficiency, and 18 had new-onset

Fig. 3 Persistent or recurrent hypoglycaemia- and recurrent insulinoma-free survival after surgery for multiple endocrine neoplasia type 1-related insulinoma, stratified by location of insulinoma



a Persistent or recurrent hypoglycaemia and **b** recurrent insulinoma. Dotted lines indicate 95 per cent confidence interval.

diabetes. None of the patients who underwent enucleation developed exocrine pancreatic insufficiency or new-onset diabetes. New-onset diabetes was only observed after distal pancreatectomy with or without enucleation, and occurred in 27 per cent of patients. Six patients developed liver metastases, of whom two had insulin-producing liver metastases. Nine patients died during follow-up but no deaths were insulinoma-related.

Discussion

These data from a large international cohort showed that surgery for MEN1-related insulinoma was effective as only one patient (1 per cent) had persistent disease. In addition, only four patients (4 per cent) developed a new insulinoma after a median follow-up of 8 years, leading to an estimated 10-year insulinoma-free survival rate of 93 per cent. Enucleation appeared to be the favourable surgical strategy for treatment of localized MEN1-related insulinoma, owing to the absence of pancreatic insufficiency and high rate of symptom resolution. In patients with multifocal disease, distal pancreatectomy combined with enucleation of tumours in the head led to cure of hypoglycaemia, but less extensive resections were also effective in some patients.

In a series[17] from the French Endocrine Tumour Study Group (GTE), 73 patients with MEN1-associated insulinomas were analysed, including a large group of patients who underwent surgery before 1990. After a median follow-up of 9 years, the rate of persistent postoperative hypoglycaemia was 4 per cent and the rate of late recurrence of hypoglycaemia was 14 per cent. Interestingly, the rate of overall persistent or recurrent hypoglycaemia (14 per cent) was much higher than that in the present study (7 per cent). This is likely explained by an improvement in perioperative imaging and operative techniques over the past three decades. More than 40 per cent of patients in the GTE cohort were treated before 1990, whereas the present study only included patients who had surgery from 1990 onwards. A more recent German publication[13] supports this as late recurrent hypoglycaemia was shown in only one of 13 patients with MEN1 who underwent surgery between 1997 and 2013, and the authors concluded that enucleation and limited resection can provide long-term cure in patients with solitary or dominant tumours.

Current ENETS guidelines advise using pancreas-sparing surgery (enucleation or limited resection) in patients with a solitary insulinoma on MRI, CT or EUS. Although this is reasonable for sporadically occurring insulinomas, patients with MEN1 are often affected by multiple concurrent NF-pNETs which might be missed on conventional imaging[26]. A solitary pNET was observed on imaging in 45 of 92 patients in the present cohort, but 14 of these patients underwent combined resections. In only five of these patients were insulin-positive pNETs found throughout the pancreas. In addition, the only patient with persistent disease underwent resection of an insulin-positive pNET, but postoperative EUS revealed multiple pNETs, which were not observed on preoperative CT. This underscores that the decision to resect a single lesion after findings on conventional imaging should be made with caution, as limited resections are performed using minimally invasive techniques without the opportunity for intraoperative bimanual palpation[27,28]. In addition, patients with a solitary lesion on conventional

imaging should be counselled about the substantial risk of a complex procedure.

For patients with equivocal preoperative imaging, ^{68}Ga-DOTA–exendin-4 PET/CT could improve preoperative insulinoma localization, facilitate minimally invasive surgery and offer better surgical outcomes[12,29]. Outcomes of arterial stimulation venous sampling, an invasive localization technique, have been reported for only a small number of patients with MEN1; this technique could not adequately localize the insulinoma in all of the patients, questioning its value in the evaluation of MEN1-related insulinoma[13,29]. Almost all insulinomas express GLP-1R, offering the opportunity to target these receptors and visualize insulinomas using PET/CT with ^{68}Ga-labelled tracer and exendin-4.

In the present study, 33 patients were deemed to have multifocal insulinomas by the operating surgeons, leading to combined resections of which the majority were distal pancreatectomy with enucleation. Patients undergoing this classical approach for MEN1-related insulinomas had a median hospital stay of 15 days. Although all patients who had combined resections were cured of hypoglycaemia, 17 of 25 patients only had an insulin-positive pNET in the head or body/tail. Some of these patients had a pNET of 2 cm or larger, which is nowadays considered as an indication for surgery, but at least a subgroup of the patients with multifocal disease might have undergone resections that were too extensive[3,30,31]. Prevention of long-term complications is important, because pancreatic insufficiency decreases quality of life in this young and otherwise unaffected population. Insulinoma is often the first manifestation of MEN1 and a common surgical indication in children and adolescents with MEN1, which underscores the importance of long-term pancreatic function[32–35]. None of the patients in this cohort who underwent enucleation developed endocrine or exocrine insufficiency, which is in line with other studies[36,37]. New-onset diabetes, on the contrary, was observed after distal pancreatectomies with or without enucleations in 26 per cent of patients. Adequate preoperative localization of the insulinoma can lead to preservation of pancreatic tissue and function.

Enucleation for patients with MEN1 and a localized insulinoma seems preferable if surgically feasible, as it is associated with a high rate of cure of hypoglycaemia, low risk of recurrent disease and absence of long-term complications. The feasibility of enucleation depends on the insulinoma size, location and relation to the main pancreatic duct. In patients with multifocal disease, a more aggressive approach seems advisable based on the present findings, but localization of the insulinoma(s) in these patients is particularly important. Surgical decision-making in patients with multiple pNETs on preoperative imaging should be tailored to the individual patient's needs and guided by the location of the insulinoma. Concurrent large NF-pNETs carry a substantial risk of malignancy and ultimately determine the life expectancy of patients with MEN1[38–40]. Furthermore, surgeons must be aware of the risk of new-onset diabetes or exocrine pancreatic insufficiency after distal pancreatectomy with or without enucleations of tumours in the head, which was 31 per cent in the present series.

Although curative resection is the recommended therapy for MEN1-related insulinoma, radiofrequency ablation (RFA) has been reported as a successful treatment[2,3]. The feasibility, efficacy and safety of percutaneous, intraoperative and EUS-guided RFA for pNETs was described in ten patients in 2014[41]. Although all patients had a complete ablation, severe complications requiring reintervention were observed in three. More recently, a retrospective study[42] from two tertiary referral centres showed that EUS-guided RFA led to complete relief of the symptoms of hypoglycaemia in all of seven patients with insulinomas, of whom one had a MEN1-related insulinoma. Another nine patients with insulinomas and symptom improvement or resolution after EUS-guided RFA were described in the literature review[43]. Complications after EUS-guided RFA have been reported in two of 18 and two of 12 patients with pNETs[42,43]. Considering the short follow-up (less than 1 year), relatively small pNET size (under 30 mm), selection of patients (those who had either refused surgery or were ineligible for surgery), and the limitations of RFA for pNETs close to surrounding structures or to the pancreatic duct, further comparative studies, ideally RCTs, are needed to clarify the role of EUS-guided RFA for MEN1-related insulinomas. For patients ineligible for surgery, EUS-guided RFA seems a viable alternative.

There are limitations to this study. The retrospective design has known disadvantages, and it was not possible to correct for possible confounding factors influencing surgical strategy, such as age, tumour size, treatment period, centre and localization of the insulinoma. A large prospective observational study or RCT comparing different surgical strategies could overcome this issue, but would be unrealistic owing to the rarity of the disease. Furthermore, identification of insulinoma on pathology is challenging because NF-pNETs might also express insulin and some insulinomas might not express insulin[44], as also observed here. Future use of enhancer signatures might differentiate more accurately between pNET subtypes in MEN1[45].

Surgery for MEN1 insulinoma is associated with higher cure rates than previously reported. Enucleation is recommended for MEN1 with a suspected solitary insulinoma if

feasible surgically. Distal pancreatectomy combined with enucleation of pancreatic head lesions seems favourable for patients with MEN1 and multiple insulinomas, but this type of resection is probably too extensive for some patients.

Collaborators

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.