



Patient characteristics and clinical outcomes following initial surgical intervention for MEN1 associated pancreatic neuroendocrine tumours: A systematic review and exploratory meta-analysis of the literature[☆]



Chathura Bathiya Bandara Ratnayake^a, Benjamin PT. Loveday^{a, b}, John Albert Windsor^{a, b}, Benjamin Lawrence^{c, d}, Sanjay Pandanaboyana^{a, b, *}

^a Department of Surgery, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

^b HPB Unit, Department of General Surgery, Auckland City Hospital, Auckland, New Zealand

^c Regional Cancer and Blood Service, Auckland City Hospital, Auckland, New Zealand

^d Discipline of Oncology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

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ABSTRACT

Background: This systematic review aimed to define the outcomes of different pancreatic resection procedures for multiple endocrine neoplasia type 1 (MEN1) associated pancreatic neuroendocrine neoplasms (pNENs).

Methods: A search of PubMed, MEDLINE and SCOPUS databases were performed in accordance with PRISMA guidelines.

Results: Twenty-seven studies including 533 patients undergoing initial pancreatic resection for MEN1 associated pNENs were included in this systematic review. Three hundred and sixty-six (68.7%) distal pancreatectomies (DP), 120 (22.5%) sole enucleations (SE) and 47 (8.8%) pancreaticoduodenectomies (PD) were identified. SE was associated with a higher rate of recurrence than DP (25/67, 37% vs 40/190, 21% respectively, $P=0.008$) but a lower rate of endocrine insufficiency than PD (1/20, 5% vs 8/21, 38% respectively, $P=0.010$). A meta-analysis of major pancreatic resections (PD or DP) vs SE in 15 studies showed that SE is associated with an increased rate of recurrence (Major resection 42/184, 23% vs SE 20/53, 38% RR 0.65 CI 0.43–0.96 $P=0.032$) but reduced rate of postoperative endocrine insufficiency (Resection 37/93, 40% vs SE 0/24, 0% RR 7.37 CI 1.57–34.64 $P=0.008$). Similarly, insulinomas and functional pNENs overall had lower rates of recurrence and reoperation with major resection. There was no difference in the reoperation rates or survival outcomes after SE compared with major pancreatic resections at follow-up (pooled overall mean duration: 85 months).

Conclusion: Major pancreatic resections for MEN1 associated pNENs have a lower risk of recurrence and a higher risk of postoperative endocrine insufficiency when compared to sole enucleation, but a similar rate of reoperation and survival.

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Introduction

Multiple endocrine neoplasia type one (MEN1) is a hereditary syndrome characterised by the presence of pancreatic islet cell tumours, pituitary adenomas and hyperparathyroidism [1,2,2]. MEN1 associated pancreatic neuroendocrine neoplasms (pNEN) are observed in 40–80% of MEN1 patients and is the second most common manifestation of this disease after primary hyperparathyroidism [1]. pNENs attributed to the MEN1 syndrome comprise 10–20% of all pNENs [3]. Approximately 70–80% of patients

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* Corresponding author. HPB Unit, Department of General Surgery, Auckland City Hospital, Park Road, Grafton, Auckland, 1071, New Zealand.

E-mail address: spandanaboyana@adhb.govt.nz (S. Pandanaboyana).

diagnosed with MEN1 associated pNENs have multiple lesions [4,5,5,6,6]. Non-functioning tumours are reportedly present in approximately 55% of patients and are frequently discovered incidentally or through screening [7]. Although insulinomas are the most common sporadic functional pNENs, pancreatic gastrinomas are observed in 50% of MEN1 patients and are the most common functioning pNENs in MEN1 patients [8,9,9]. Insulinomas are found in 10–20% of MEN1 cases whereas VIPomas, somatostatinoma, GRFomas and glucagonomas are rare [10,11,11].

MEN1 is caused by a tumour suppressor gene dysfunction on chromosome 11q12–13^{10,10,12}. Numerous germline mutations have been implicated in MEN1 and historical observations have revealed the mutations have high penetrance but variable expression reflecting the genetic variability [2,2,10,10,12,13,13].

There remains controversy about the optimal surgical management of patients with MEN1 associated pNENs [14,15,15]. The genetic basis for MEN1 means that surgery is rarely curative, with tumours recurring in the remnant pancreas when the entire gland is not removed [16]. Historically, major pancreatic resections such as pancreatico-duodenectomy (PD) and total pancreatectomy were not considered because of the high morbidity and mortality compared with more conservative operations [17]. However, it is well recognised that MEN1 associated non-functioning pNENs have a significantly reduced survival due to increased frequency of metastatic disease secondary to higher pancreatic tumour burden

when compared with patients with neuroendocrine tumours that are not associated with MEN1 syndrome [11,17,18]. Therefore, some have recommended aggressive major pancreatic resections for MEN1 associated pNENs because of the increased metastatic potential and worse prognosis, even with the increased morbidity and mortality [17].

The outcomes from different surgical interventions for MEN1 associated pNENs have not been previously reviewed. The primary aim of this systematic review is to determine if there is a difference in recurrence and reoperation rates following the various initial surgical interventions for MEN1 related pNENs.

Methodology

Literature search

A literature search of major reference databases (MEDLINE, PubMed and SCOPUS) was undertaken according to the PRISMA guidelines (Fig. 1) [19] until 7th January 2018. The search terms used were the results of “Pancreas” AND the combined results of “MEN1” OR “multiple endocrine neoplasia type 1” OR “neuroendocrine tumours” AND the combined results of “surgery” OR “intervention” OR “procedure” OR “pancreatectomy” AND the combined results of “outcomes” OR “morbidity” OR “mortality.” MeSH searches were used where applicable. All non-English and non-human studies

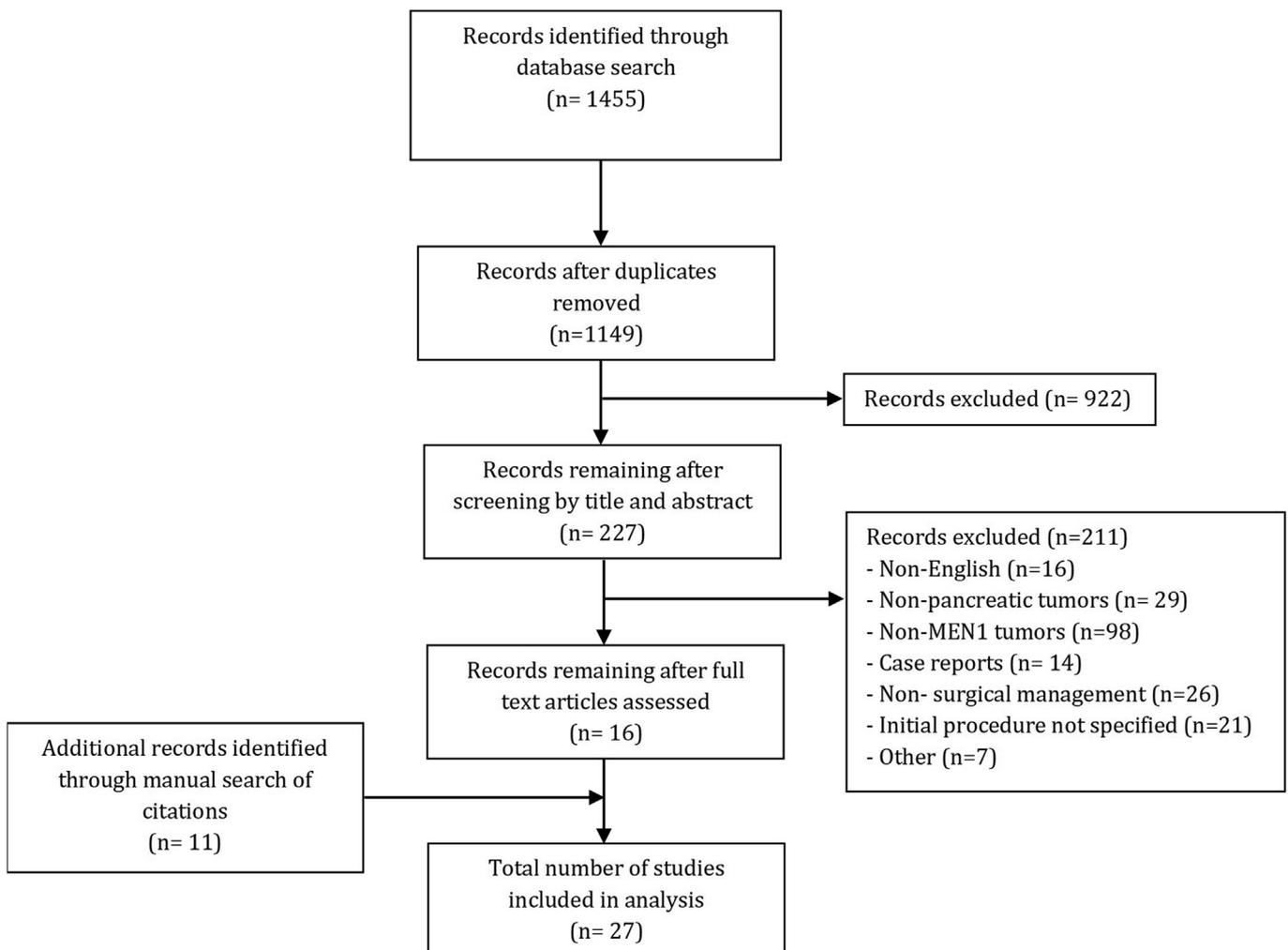


Fig. 1. PRISMA flow chart summarising the literature search.

were excluded from the search. There was no date or age restriction and a manual search of all the eligible studies was screened to identify additional studies.

Inclusion and exclusion criteria

In order to review the entire published literature on this subject, the authors employed a broad inclusion criterion to capture all relevant studies describing surgical resection for pancreatic MEN1 neuroendocrine tumours. Studies were excluded if they only focussed on non-surgical management, neuroendocrine tumours outside the pancreas, pNEN that were not associated with MEN1 syndrome, case reports, cohort studies with only one MEN1 patient, studies that failed to differentiate between initial surgical procedures and reoperations and those that failed to elaborate on surgical modality specific numbers.

Data extraction

The data was extracted from selected studies into a template developed by the authors. The data included details of the study population, study design, the methodological index for non-randomized studies (MINORS) grading score [20], the number of patients undergoing each surgical intervention, patient characteristics and clinical outcomes. Specific clinical data extracted for each surgical modality included: indication, age of patients, tumour size, tumour type, extent of disease and tumour grade when mentioned in the included studies. The following data regarding outcome measures for each surgical modality was also extracted: peri-operative mortality, peri-operative morbidity, mean follow-up time, reoperations, recurrence of disease, overall survival, disease free survival and endocrine dysfunction. Data comparing surgical vs non-surgical initial management was also retrieved from the included studies. The primary outcome measures were of recurrence of disease and reoperations following initial surgical management. The secondary outcome measures were; peri-operative mortality, peri-operative morbidity, overall survival, disease free survival and endocrine insufficiency.

Terminology and definitions

Definitions regarding the clinical characteristics and outcomes of patients were required in order to classify the data.

Pylorus preserving pancreatoduodenectomy and Whipple's procedure were considered as *pancreatoduodenectomy* (PD). *Distal pancreatectomy* (DP) included all pancreatic resections to the left of the spleno-portal junction. Corpus resection and middle pancreatectomy were included under *central pancreatectomy* (CP). PD and DP were considered together as *major pancreatic resections*. *Sole enucleation* (SE) was termed as the method of surgical management when enucleation was the initial and only pancreatic intervention of single or multiple pNENs without concurrent major pancreatic resection. *Synchronous enucleation* describes adjuvant enucleation of pNENs as part of a separate initial major resection.

All pNENs that were identified through pre-operative imaging or intra-operative examination were included. If there were no clinical symptoms of hormone excess and/or serum hormone levels were within normal limits, the tumour was described as *non-functioning* [21]. *Tumour size* included all tumours that were reported in studies identified through a combination of pre-operative imaging intraoperative measurement and histology.

Local disease was defined as disease with no evidence of nodal or distant metastases on any imaging modality. *Nodal metastasis* described the presence of at least one positive node upon imaging or biopsy and *distant metastasis* was the presence of tumour in

organs outside the pancreas other than by direct invasion [5].

Clinical outcomes were defined by *post-operative mortality* and *morbidity* within the same admission as the surgical intervention defined by the authors. *Pooled mean follow-up time* was calculated in all studies that reported long term clinical outcomes. Enucleation of single or multiple tumours alone were considered separately. Patients with reoperations limited to the enucleation of single or multiple tumours were analysed separately. The *recurrence* of disease was defined specific to the type of MEN1 tumour present. A recurrence in the setting of functioning pNENs was determined to be present if there was evidence of altered fasting serum biomarkers in the long term postoperative period that rose (hypergastrinaemia in gastrinomas) or fell (hypoglycaemia in insulinomas) from the immediate postoperative evaluation and radiographic evidence of a pancreatic mass. Solely radiographic evidence of a pancreatic mass was required to consider recurrent disease in non-functioning pNENs. *Reoperations* were only included if it involved pancreatic surgery as a resection or enucleation. *Pancreatic resection* in this context was defined as any major pancreatic resection following the initial procedure. A patient was considered *disease free*, if there was no evidence of recurrence of disease following the initial procedure.

Methodological quality

The MINORS criteria [20] and Murad et al.'s methodological quality and synthesis of case series and case reports score [22] was employed to measure the quality of study methodology. The MINORS criteria is a validated tool comprising of eight graded questions for non-comparative studies and 12 for comparative studies with a cumulative total score of 16 and 24 respectively. Murad et al. comprised of eight binary questions across four domains providing a total calculated score of eight.

Statistical analysis

There was insufficient homogenous outcome data to perform a meta-analysis of all 27 studies and compare the three different interventions. Therefore, the authors determined that a narrative systematic review of all studies that reported 'type of pancreatic resection' specific outcomes with statistical analysis of the extracted data would be more appropriate in this setting to compare PD, DP and SE. PD and DP were primarily analysed separately as to provide better guidance to surgeons regarding the clinical utility of each separate procedure in this setting. Extracted clinical characteristic and outcome comparative data was mostly nominal in nature and thus Chi squared goodness of fit test was employed with subsequent Bonferroni correction to adjust for multiple comparisons. Fisher exact test was used when categorical comparisons were required in the setting of small sample sizes. Pooled means for age, tumour diameter and follow-up interval data was calculated from individual study cohort means and sample sizes. A one-way analysis of variance (ANOVA) test with post hoc Tukey's honest significant difference (HSD) analysis was employed for all mean and derived standard deviation (SD) data. Significance was set at $P < 0.050$. Statistical analysis was computed using online ANOVA [23], Chi squared [24] and Fisher exact test calculators [25].

A subgroup meta-analysis of 15 studies was conducted using the Cochrane Collaboration Review Manager Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) [26] comparing major resections vs SE. Risk ratios (RR) was employed for comparative analysis of dichotomous data. If the data analysis revealed a low $I^2 < 50\%$ and $P > 0.100$, a fixed effects model was used, a random effects model was utilised otherwise.

Results

Literature search

The initial literature search yielded 1455 articles. Following the removal of duplicates, 1149 studies remained. Among them 227 papers were fully reviewed of which 16 met the inclusion criteria. A manual reference search of these 16 papers was conducted and 11 additional papers were identified. These 27 studies were included in the analyses (Fig. 1).

Study characteristics

All studies were published from 1994 to 2017 and were either from single (n = 19) or multiple (n = 8) centres in the United States (n = 9), Germany (n = 4), Spain (n = 3), Italy (n = 3), Japan (n = 2), United Kingdom (n = 2), Switzerland (n = 1), France (n = 1), Hong Kong (n = 1) and Sweden (n = 1). The relevant study population size ranged from 3 to 73 patients (Table 1). All articles were retrospective cohort (n = 11)^{6,21,27–35} or observational studies (n = 16)^{4,5,16,36–48} by design. Fourteen studies [4,27,29,36,37,39–46,49] did not report a specific primary or secondary outcome measure (Supplementary Table 1).

Methodological quality

The entire data set was composed of sixteen non-comparative studies [4,5,16,36–48] with a median MINORS grading score of

7.5 out of 16 (range: 3–9) and eleven [6,21,27–35] comparative studies with a median MINORS score of 14 out of 24 (range: 11–20)²⁰. All non-comparative studies failed to blind participants and to provide a prospective calculation of sample size. Major deficiencies were observed among comparative studies in the provision of adequate control groups and reporting those lost to follow-up. All studies did however clearly state aims and reported analysis through adequate statistical analysis. Murad et al. [22] was also employed to review the methodological quality with a median score was 3 out of 8 (range: 2–5) (Supplementary Table 2). Significant deficiencies were observed in the length of follow-up and outcome measures.

Patient characteristics

There was a total of 533 patients in the 27 studies who underwent pancreatic resection or sole enucleation (SE) for MEN1 associated pNENs. The pooled mean age of 157 patients reported in 9 studies [21,33–36,38,44,46,48] (Table 1) was 32.5 years, (range: 10–64 years). Patients in the SE cohort were significantly younger (pooled mean: 25.6 range: 10–63 years) than those who underwent PD (pooled mean: 38.0 range: 29–57 years, $P < 0.001$) or DP (pooled mean 33.7, range: 12–64 years, $P < 0.001$) (Table 1). No difference in age was observed between DP vs PD cohorts.

Pancreatic surgery

Of the 533 surgical interventions, DP (n = 366, 68.7%) was the

Table 1

Author, publication date, recruitment interval, number of patients undergoing each surgical modality and the number of patients with data available for analysis in each clinical characteristic or outcome category.

Reference	Year	Recruitment dates	Surgical modality				Number of patients available for analysis in each category (n)								
			PD	DP	SE	Total	Age	Tumour Diameter	Disease Spread	Peri-operative morbidity	Peri-operative mortality	Recurrence/progression	DFS	OS	Follow-up interval
Tonelli et al. [1]	2017	1992–2015	4	8		12	12	12	12	12	12	12	12	12	12
Lopez et al. [2]	2016	1977–2015		27	4	31			1			4			
Neil et al. [3]	2016	1990–2014		14	7	21									
Vezzosi et al. [4]	2015	1980–2010	9	46	18	73	73 ^a	73 ^a		73	73		73	73	73 ^a
Dy et al. [5]	2014	1994–2010	2	24		26				26					
Lopez et al. [6]	2013	1998–2011		2	2	4									
Giudici et al. [7]	2012	1992–2009	2	6		8	8	8	8	8		8	8	8	
Sakurai et al. [8]	2012	–		25	14	39									
Lopez et al. [9]	2011	1987–2009	5	24	3	32			32		32		32		
Mortellaro et al. [10]	2009	1970–2008	1	4	3	8				8		8			
Anlauf et al. [11]	2009	1975–2006	1	8	4	13	13					13			
Fernandez-Cruz et al. [12]	2008	1998–2007		3		3	3	3	3		3		3	3	3
Ruiz-Tovar et al. [13]	2008	1985–2007		4	4	8									
Sakurai et al. [14]	2007	1995–2004	2	5	2	9	9	9				9			
Teh et al. [15]	2007	1997–2005	1	5		6		6	6						
Triponez et al. [16]	2006	1997–2003	5	21	9	35				35					
Triponez et al. [17]	2006	1956–2003	1	8	5	14	14	14	14		14		14	14	14
Kouvaraki et al. [18]	2006	–	4	27	4	35					31				
Fernandez-Cruz et al. [19]	2005	1998–2003		3	7	10	10	10	10	10		10			
Bartsch et al. [20]	2005	1981–2004	2	16	6	24			24			24	24	24	
Norton et al. [21]	2001	1972–1997	2	22	14	38									
Lairmore et al. [22]	2000	1993–1999	5	11	5	21			14	21		21			
Bartsch et al. [23]	2000	1981–1999	1	9	3	13	13		13	12		13	13	13	
Lo et al. [24]	1998	1975–1996		2	1	3			3				3		
Skogseid et al. [25]	1996	–		17	1	18						18			
O'riordan et al. [26]	1994	1970–1991		15	2	17				17					
Rasbach et al. [27]	1985	1970–1983		10	2	12	12			12		12	12	12	
Total (n)			47	366	120	533	157	135	213	127	302	290	159	157	159

^a Reported as median values, PD: pancreaticoduodenectomy, DP: distal pancreatectomy, SE: sole enucleation, DFS: disease free survival, OS: overall survival.

most common followed by SE (n = 120, 22.5%), PD (n = 47, 8.8%), central pancreatectomies (CP) (n = 7, 1.3%) and total pancreatectomies (TP) (n = 7, 1.3%) (Table 1). CP and TP were excluded in the subsequent analysis as the capacity to make meaningful comparisons was limited due to the paucity of available data. DP was associated with a significantly higher rate of synchronous enucleation procedures (95/362, 26%) compared to those undergoing PD (4/47, 9%, $P = 0.008$) (Table 2).

Indications for surgical intervention

Thirteen studies stated the indication for surgical intervention and/or surgical procedure of choice. The tumour diameter threshold for surgical intervention was ≥ 10 mm in five studies [5,16,21,29,38] and ≥ 20 mm in two studies [30,38]. One study intervened in patients with 10–20 mm pancreatic tumours if there was an elevated rate of growth [30]. Four studies reported a preference for PD when patients had multiple MEN1 pNENs primarily in the head of pancreas, with or without the presence of nodal metastatic disease [4,36,43,48]. Among these studies, two reported conducting synchronous enucleations of tumours identified in the body or tail of the pancreas [4,48]. Resection of synchronous liver metastases was performed in one study [16]. This is in contrast to four studies excluded patients with diffuse liver metastases [16,21,28,33].

DP was selected when multiple [30] macroscopic lesions were present in the body and tail of the pancreas relative to the head in five studies [21,42,43,48]. Six studies reported synchronous enucleations when DP was undertaken for disease identified in the head of the pancreas [4,16,21,30,36,42]. DP was also preferred in diffuse pancreatic disease in one study [4]. Spleen preserving DP was preferred in five studies [30,35,36,43,48]. Four studies undertook SE in cases of solitary insulinomas or non-functioning pNENs [16,21,35,43].

Tumour characteristics

The imaging modalities used to diagnose and stage the MEN1 associated pNENs are summarised in supplementary table 1.

Table 2

The number of patients undergoing each surgical modality, mean age, tumour types, tumour diameter and disease spread of patients who underwent an initial surgical intervention for MEN1 pNENs in 27 studies.

	PD	DP	Sole Enucleation	p-value	Number of studies that reported findings ^a
Number of patients who underwent pancreatic surgery	47	366	120		27
synchronous enucleation^b (%)	4 (9)	95 (26)		0.008	27
Total number of patients	47	362			
Pooled mean age around the time of surgery (range) in years	38.0 (29–57)	33.7 (12–64)	25.6 (10–63)	<0.001	9
Tumour types (%)					16
- Insulinoma	17 (46)	75 (46)	41 (62)	0.070	
- Gastrinoma	9 (24)	22 (13)	10 (15)	0.251	
- Non-functional	7 (19)	60 (37)	15 (23)	0.029	
- Other ^c	4 (11)	7 (4)	0 (0)	0.030	
Total number of tumours	37	164	66		
Pooled mean tumour diameter \pm standard deviation in mm	22.7 \pm 12.3	20.1 \pm 16.2	17.8 \pm 9.8	0.496	8
Disease Spread (%)					13
- Local disease	16 (59)	117 (85)	42 (88)	0.004	
- Nodal metastasis	11 (40)	12 (9)	5 (10)	<0.001	
- Distant metastasis	0 (0)	9 (7)	1 (2)	0.213	
Total number of patients	27	138	48		

PD: Pancreatico-duodenectomy (Whipples), DP: Distal pancreatectomy, ^aThe number of studies that reported findings for each row denotes the total number of studies that had surgical modality specific information regarding the major heading of the corresponding row (i.e. Tumour types). This meant for each row, only a specified proportion of the total 533 patients were used in the analysis of each clinical detail and outcome measure. This is why the totals in each row are different. ^bIf the study did not mention a synchronous enucleation procedure during major pancreatic resection, it was assumed to not have occurred. ^cOther tumour types included: VIPoma, GRFoma, Glucagonoma and Somatostatinoma.

Although CT was the most commonly utilised imaging modality, cohort specific imaging data was not provided, and so comparisons are limited. There were no significant differences ($P = 0.496$) in the tumour diameter between the three surgical interventions: PD (pooled mean 22.7 \pm 12.3 mm SD), DP (pooled mean 20.1 \pm 16.2 mm SD) and SE (pooled mean 17.8 \pm 9.8 mm SD).

Insulinomas were the most prevalent MEN1 associated pNENs among all identified tumours across all surgical interventions in 16 studies [5,6,16,21,28,30,33–37,39,41,44,45,48] that reported specific tumour types (133/267, 49.8%) (Table 2). The proportion of insulinomas resected by SE was higher than by DP (41/66, 62% vs 75/164, 46%, $P = 0.025$) but was not different from the PD cohort (17/37, 46%, $P = 0.112$). Gastrinomas (41/267, 15.4%) were evenly distributed between the surgical interventions ($p = 0.251$). DP patients had a higher proportion of non-functioning tumours (60/164, 37%) compared to PD (7/37, 19%, $P = 0.039$) and SE (15/66, 23%, $P = 0.043$).

The majority of patients (175/213, 82%) treated by surgery for MEN1 associated pNENs had localized disease. The rate of nodal metastases was highest in those undergoing PD (11/27, 40%) compared with DP (12/138, 9%, $P < 0.001$) and SE (5/48, 10%, $P = 0.002$). A minority of patients (10/213, 5%) had initial surgical interventions in the presence of known distant metastatic disease, and there was no difference between the surgical cohorts ($P = 0.213$). Three studies [5,16,34] commented on the stage of disease in the setting of non-functioning pNENs in MEN1 patients that underwent resection (n = 39). Local disease comprised the largest proportion of non-functioning pNENs (77%, 30/39). Lymph node metastases (18%, 7/39) and distant metastasis (5%, 2/39) was seen in a small proportion of patients. One study [5] included a patient who underwent enucleation of a pancreatic pNEN in the setting of distant metastatic disease concurrently with a duodenal excision of a duodenal gastrinoma (Table 1). All included studies failed to report cohort specific tumour grade data.

Postoperative outcomes

Table 3 shows data on postoperative outcomes. Two patients died in the postoperative period (PD n = 1, DP n = 1); one from a

Table 3

Post-operative mortality and morbidity data of patients who underwent an initial surgical intervention for MEN1 pNENs in 27 studies.

	PD	DP	Sole Enucleation	p-value	Number of studies that reported findings ^a
Peri-operative mortality during admission (%)	1 (3)	1 (1)	0 (0)	0.280	15
Total number of patients	37	207	58		
Post-operative morbidity during admission (%)					8
- Pancreatic Fistula	1 (6)	7 (8)	5 (19)	0.222	
- Other morbidity ^b	6 (33)	11 (13)	4 (15)	0.113	
Total number of patients	18	83	26		

PD: Pancreatico-duodenectomy (Whipples), DP: Distal pancreatectomy. ^aThe number of studies that reported findings for each row denotes the total number of studies that had surgical modality specific information regarding the major heading of the corresponding row (i.e. Post-operative morbidity during admission). This meant for each row, only a specified proportion of the total 533 patients were used in the analysis of each clinical detail and outcome measure. This is why the totals in each row are different. ^bOther morbidity included haemorrhage, pancreatitis, collection, sepsis.

respiratory arrest following a pulmonary embolus [39] and the other from a respiratory arrest associated with severe restrictive pulmonary disease and following a prolonged intensive care unit admission [43]. There were no reports of postoperative deaths among those undergoing SE procedures.

The overall postoperative morbidity did not differ across all surgical cohorts. Pancreatic fistulae were reported following PD (1/18, 6% patients), DP in 7/83, 8% and SE in 5/26, 19%, but there was no significant difference between the cohorts (Fisher exact test $P = 0.130$). Two studies [46,50] failed to specify the number of patients with pancreatic fistulae in their cohort of MEN1 patients undergoing PD or DP thereby contributing to the limited incidence. All included articles failed to report pancreatic fistula grades according to the International study group on Pancreatic Fistula classification (ISGPF) [51]. Insulin dependent diabetes was the most commonly reported long-term complication of surgical intervention [32,33,38,46]. The prevalence of endocrine insufficiency was significantly lower in the SE cohort (1/20, 5%) compared to PD (8/21, 38%, $P = 0.021$) and DP (30/102, 29%, $P = 0.024$).

Tumour recurrence and reoperation

The pooled mean follow-up period was 67.6 months, (range 1–242 months) for the PD cohort compared with 88.6 months (range 1–230 months) for the DP cohort and 84.5 months (range 8–241 months) for the SE cohort ($P = 0.187$). The recurrence of MEN1 associated pNENs was higher in the SE cohort (25/67, 37%) compared with the DP cohort (40/190, 21%, $P = 0.008$) within each

of their respective follow-up intervals. However, no significant difference was observed between PD compared with SE. There was no significant difference between the three surgical cohorts for the reoperation rates: PD (1/9, 11%), DP (10/68, 15%) and SE (6/34, 18%) ($P = 0.867$). Reoperations were not undertaken in all patients who had recurrence of MEN1 tumours in four studies [6,16,39,46]. One study [16] re-operated on recurrence if it satisfied the original surgical indication criteria and three studies [6,39,46] failed to report reasons for this discrepancy.

Survival

The disease-free survival (DFS) and overall survival (OS) rates were reported in 8 studies [5,21,33–36,46,48] for specific surgical interventions (Table 1), during a pooled mean follow-up interval of 85 months (range 1–242 months). One study reported the DFS in two PD patients but did not mention their overall survival status at the end of the follow-up interval and were thus excluded in the PD analysis [5]. The DFS was not significantly different between the three surgical cohorts: PD (13/19, 68%), DP (78/106, 74%), and SE (20/34, 59%) ($P = 0.268$) within each of their respective pooled mean follow-up intervals (Table 4). However, the OS for PD (14/17, 82%) was significantly lower than DP (104/106, 98%, $P = 0.002$). The OS among patients who underwent PD did not differ to the SE cohort (33/34, 97%, $P = 0.066$) (Table 4). There were 6 reported deaths in the entire study population, and the reasons were pNEN malignancy ($n = 4$)^{5,34,38}, pulmonary embolism ($n = 1$)³³ and a car accident ($n = 1$)⁵ in a patient who had an SE.

Table 4

Mean follow-up period, recurrence or progression rate, reoperation rate, endocrine insufficiency rate, disease free survival and overall survival of patients who underwent an initial surgical intervention for MEN1 pNENs in 27 studies.

	PD	DP	Sole Enucleation	p-value	Number of studies that reported findings ^a
Pooled mean follow-up period (range) in months	67.6 (1–242)	88.6 (1–230)	84.5 (8–241)	0.187	8
Recurrence or progression within mean follow-up period (%)	6 (18)	40 (21)	25 (37)	0.019	17
Total number of patients	33	190	67		
Pancreatic reoperation within mean follow-up period (%)					8
- Major pancreatic resection	1 (11)	8 (12)	6 (18)	0.698	
- Enucleation	0 (0)	2 (3)	0 (0)	0.525	
Total number of patients	9	68	34		
Endocrine insufficiency within mean follow-up period (%)	8 (38)	30 (29)	1 (5)	0.039	6
Total number of patients	21	102	20		
Disease free survival at the end of mean follow-up period (%)	13 (68)	78 (74)	20 (59)	0.157	8
Total number of patients	19	106	34		
Overall survival within mean follow-up period (%)	14 (82)	104 (98)	33 (97)	0.045	8
Total number of patients	17	106	34		

PD: Pancreatico-duodenectomy (Whipples), DP: Distal pancreatectomy. ^aThe number of studies that reported findings for each row denotes the total number of studies that had surgical modality specific information regarding the major heading of the corresponding row (i.e. Endocrine insufficiency within mean follow-up period). This meant for each row, only a specified proportion of the total 533 patients were used in the analysis of each clinical detail and outcome measure. This is why the totals in each row are different.

Subgroup meta-analysis of clinical outcomes

Major pancreatic resections were associated with lower recurrence rate compared to SE (Major resection 42/184, 23% vs SE 20/53, 38% RR 0.65 CI 0.43–0.96 P = 0.032, Fig. 2A) in 10 studies [5,16,21,32–34,38,39,43,44] that reported this data. Furthermore, the incidence of postoperative endocrine insufficiency was lower in the SE group when compared to major pancreatic resections (Major Resection 37/93, 40% vs SE 0/24, 0% RR 7.37 CI 1.57–34.64 P = 0.008, Fig. 2B) [32,33,38]. However, no difference was noted in the rate of reoperations (P = 0.845)^{16,21,34,39,44}, disease free survival (P = 0.518)^{5,21,33,34,38} and overall survival (P = 0.743)^{5,21,32–34}.

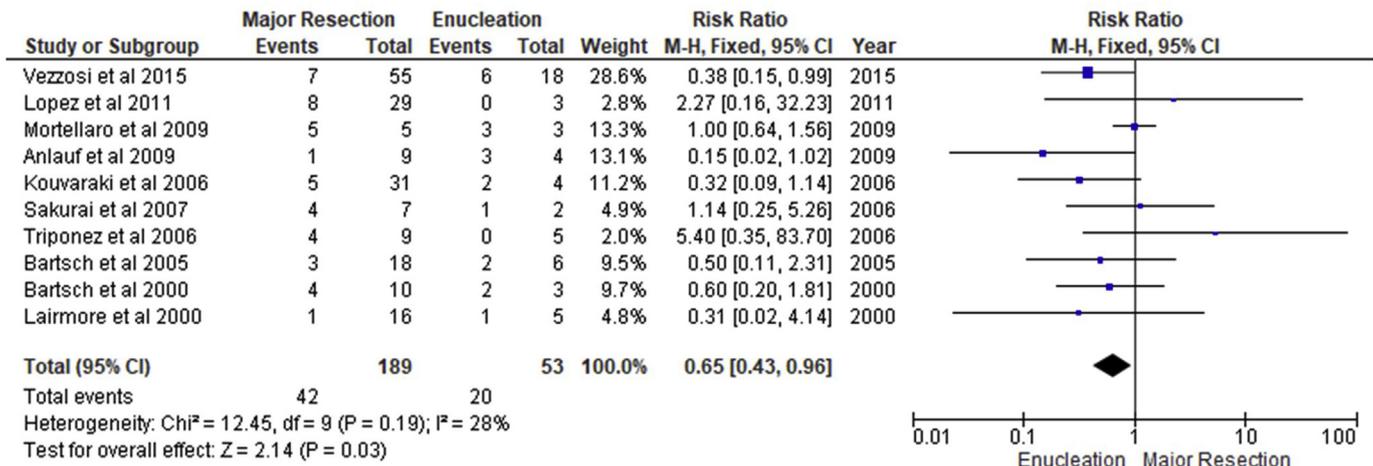
A subgroup meta-analysis was also conducted to review the rates of recurrence and reoperation in specific MEN1 related pNENs. Outcomes for non-functional pNENs were only compared in one study [34] and were therefore not analysed in the meta-analysis. A significantly higher risk of recurrence (Major resection 12/118, 10% vs SE 11/38, 29% RR 0.36 CI 0.19–0.69 P = 0.002, Supplementary Figure S1) and reoperation (Major resection 2/60, 3% vs SE 6/13, 46% RR 0.17 CI 0.06–0.51 P = 0.002, Supplementary Figure S2) was observed following SE compared to major resection among patients with insulinomas in seven [16,21,33,41,44–46] and five [16,21,41,44,46] studies respectively. Conversely, no difference in recurrence (Major resection 6/15, 40% vs SE 1/6, 17% RR 2.05 CI 0.63–6.69 P = 0.233, Supplementary Figure S1) and

resection (Major resection 2/15, 13% vs SE 1/6, 17% RR 0.78 CI 0.12–4.97 P = 0.786, Supplementary Figure S2) was observed with major resections and SE for patients with Gastrinomas in two included studies [21,39]. Upon review of all functional pNENs, a significant higher risk of recurrence (Major resection 23/123, 19% vs SE 16/41, 39% RR 0.50 CI 0.25–0.98 P = 0.042, Supplementary Figure S1) and reoperation (Major resection 7/65, 11% vs SE 7/16, 44% RR 0.34 CI 0.15–0.78 P = 0.012, Supplementary Figure S2) was noted with SE when compared to major resection in eight [16,21,39,41,44,46] and six [16,21,39,41,44,46] studies respectively.

Non-surgical management of pNENs

Among the studies included in this systematic review, six made observation regarding non-surgical management of MEN1 associated pNENs and of those six [6,16,21,32,34,38], three [6,32,34] studies made statistical comparisons with surgical management. Two studies found that there was no difference in recurrence of disease and survival when compared to resection for larger tumours [6] and tumours [34] of the same size (less than two cm) however, both reported shorter follow-up intervals in the conservative cohorts (No Surgery 3 ± 2.5 years vs Surgery 6.0 ± 4.4 years, P < 0.010⁶ and No Surgery 3.3 ± 2.6 years vs Surgery 6.7 ± 4.0 years, P = 0.001³⁴ respectively). Although Kouvaraki [32] et al. similarly found no difference in disease free survival, they reported a

A) Recurrence of Pancreatic Neuro Endocrine Neoplasms



B) Endocrine Insufficiency

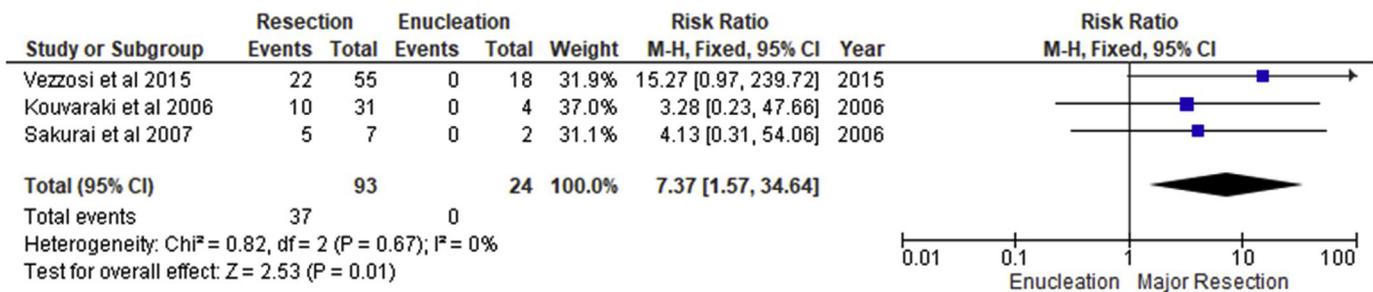


Fig. 2. Forest plots showing rates of pNEN recurrence (A) and postoperative endocrine insufficient (B) following the initial surgical intervention for MEN1 related pNEN in patients who underwent major pancreatic resection (pancreatoduodenectomy and distal pancreatectomy) vs Sole enucleation procedures. A Manel-Haenszel random effects model was used for meta-analysis of A) And a fixed effect model was used for outcome B) Risk ratios are shown with 95 percent confidence intervals.

reduced overall survival in those who underwent non-surgical management at 10 years post initial management.

Discussion

This systematic review found that SE procedures were associated with a higher rate of recurrence of pNENs compared to DP and a lower rate of endocrine insufficiency compared to PD. Similarly, upon meta-analysis of specific MEN1 related pNENs, both insulinomas and functional pNENs had higher rates of recurrence and reoperation in those with SE. Patients undergoing PD appeared to have higher rates of lymph node metastases and reduced overall survival when compared to DP group.

The surgical management of pNENs in patients with MEN1 is particularly challenging because they are more often multifocal. Furthermore, the non-functioning MEN1 associated pNENs have higher rates of tumour growth and increased need for surgical resection compared to sporadic non-functioning pNENs that are not associated with MEN1¹⁸.

Insulinomas are often symptomatic and therefore warrant surgical resection for sustained symptom control including those associated with MEN 1 syndrome. This probably contributed to the high incidence of insulinomas in this review even though no difference in tumour size was reported. There is a role for SE when insulinomas are solitary and in the absence of pancreatic or bile duct dilation to avoid major pancreatic resection while still achieving oncological clearance. Historically there was a more liberal use of distal pancreatectomy with concurrent enucleation of pancreatic head masses as the initial therapy for patients with insulinomas [49]. This has been associated with a lower rate of recurrence but a higher rate of iatrogenic endocrine insufficiency, consistent with the findings of the present study [47,52].

Pancreatic gastrinomas are more common than insulinomas in patients with MEN1 syndrome (although not in this series), and can cause challenges in management because they tend to be multiple, can be outside the pancreas ('gastrinoma triangle') and are associated with higher rates of recurrence [16]. Since only cases undergoing surgical resection were included, there is an inherent selection bias that probably accounts for the reduced proportion of gastrinoma compared with insulinoma. In the present series, gastrinomas were distributed evenly between the surgical interventions. Although PD should allow optimal local control with associated lymph node clearance, it is noted that surgical resection often does not improve survival [16]. Indeed, an aggressive extensive resection is generally considered in the setting of large (>1–2 cm) MEN1 gastrinomas due to their tendency to recur with increasing evidence reporting the futility of limited resection [53]. Unfortunately, only small numbers were available for meta-analysis of the primary outcomes in two studies. Therefore, the lack of a significant result may have resulted from the limited sample utilised in the analysis.

No study in the present series presented a surveillance strategy following surgical treatment of MEN1 associated pNENs. A systematic review of surveillance strategy for non-functioning pNENs revealed that 9% patients in the MEN1 group developed nodal or distant metastasis during follow-up period, with no such progression noted in patients with sporadic pNEN [18]. Similarly, other studies have also found 33%–55% of MEN1 associated non-functioning pNENs required subsequent surgical treatment if they were initially managed conservatively [54,55]. In this review, approximately 23% of patients with non-functioning pNENs were found to have nodal metastases or distant metastatic disease at the time of initial surgical intervention. These findings confirm the view that MEN1 associated pNENs appear to have a different disease course compared to sporadic pNENs and this suggests that

conservative strategies may not be appropriate. It is important here to note that although limited data were available to determine the efficacy of a non-surgical management of very small pNENs, individual studies have observed similar recurrence and survival outcomes suggesting there may be a role for surveillance in the management of very small MEN1 related pNENs.

Because of the multifocal nature of pNENs associated with MEN1, it has been argued that total pancreatectomy should be considered [17]. This occurred in just 1.3% of patients in this study. A PD is considered the preferred operation for gastrinoma because of the possibility of duodenal location, but there is no consensus regarding the best surgical strategy for non-functioning pNENs [8,9]. Unlike functional pNENs, major pancreatic resection has generally only been indicated for those with large, high grade tumours at risk of malignancy rather than for symptomatic relief [8,9].

The natural history of MEN1 associated pNENs indicates that a majority of patients develop new pNENs during follow up, raising concerns about a policy of major pancreatic resection at the first presentation. In addition, these patients are often high risk for postoperative pancreatic fistula because the pancreas is usually soft and the main pancreatic duct non-dilated. The perioperative and survival data from the present review suggests comparable survival outcomes for (DP or PD) compared with a parenchymal preservation procedure (SE), but this is offset by the higher rates of recurrence (but no increase in reoperation rates) and better preservation of pancreatic exocrine and endocrine function in the longer term. It also remains that the SE cohort was younger and may not be fully exposed to the chronic manifestations of the disease following surgery thereby altering survival outcomes. Furthermore, as patients are young at the time of presentation (mean age 32 years), a more conservative approach to surgery (e.g. SE) allows a better quality of life compared to major pancreatic resections in the longer term. Also, SE does not preclude a major pancreatic resection in the future. However, the relative contraindication to SE is if the pNEN is in close proximity to the main pancreatic duct, as this increases the risk of postoperative pancreatic fistulae [56].

There are several limitations to this systematic review. The relatively low MINORS scores indicate the overall relatively poor quality of the available studies [20], especially so for the non-comparative studies. The studies included in the analysis were generally underpowered and observational in nature, reflecting the relative rarity of MEN1 associated pNENs. Although the broad inclusion criteria resulted in nine of the included studies comprising of 10 or fewer patients (Table 1), the aim of this review was to review all studies pertaining to the initial surgical management of MEN1 related pNENs and this was achieved through the inclusion of these studies. Much of the data was retrospective and observational therefore this analysis is generally exploratory in nature. Articles were also recruited patients from 1956 to 2015 resulting in significant heterogeneity in the cohorts compared. Indications for specific surgical resection was not reported in all studies, further providing a potential source of heterogeneity within groups analysed. Comparative studies rarely compared patient outcomes between different surgical interventions and this data had to be manually extracted, limiting the number of studies included in this review. This meant a significant proportion of the potentially relevant data was excluded on the basis that studies failed to report patient characteristics and outcomes in relation to different surgical interventions. For instance, it was difficult to say from available data whether stage I and III patients with pNENs had the same recurrent rate and OS. Furthermore, non-English studies were excluded from this review. Another limitation of the included studies was the highly variable follow-up period resulting in significant heterogeneity in the dataset and difficulty interpreting the

results of long-term survival analyses. The pooled mean follow-up time ranged from 6 to 8 years which in the context of the patient age and long natural history of MEN1 associated pNENs is relatively short. Two surgical interventions (i.e. TP and CP) were excluded from analysis in this review because of the paucity of data available from the studies. This means that the clinical efficacy of each surgical modality must be interpreted with caution.

Another significant limitation to this systematic review was the lack of consistent reporting of the stage and grade of pNENs which is important in comparing outcomes. The grading classification by the World Health Organisation (WHO) established in 2010 recommends the Ki67 proliferative index [53] and it correlates with tumour stage [51,52]. The data retrieved from the 27 studies failed to provide patient cohort specific description regarding the Ki67 proliferation index, which limited the ability to compare the different surgical cohorts. The studies did however classify the distribution of neoplastic disease under the headings: local disease, nodal metastasis and distant metastasis. Future studies to identify genetic or molecular factors that indicate an aggressive course of MEN 1 associated pNENs may allow tailoring of surgical procedure to individual patients.

Conclusion

In a systematic review and exploratory meta-analysis of the English language literature, major pancreatic resection confers similar survival rates to sole enucleation, but the latter is associated with a lower risk of postoperative endocrine insufficiency and a higher risk of recurrence but not reoperation. However, the significant heterogeneity identified in the reporting of this data necessitates large future multicentre prospective comparative studies with long term follow-up to allow a definitive conclusion as to whether the initial surgical intervention for MEN1 associated pNENs should be enucleation or resection. The available data suggests that the former, where it can be safely performed is probably the better option.

Conflicts of interests

None to declare.

Role of funding source

Not applicable.

Ethics committee approval

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2019.03.002>.

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