

Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis

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Accepted Manuscript

Role of Palliative Resection of the Primary Tumour in Advanced Pancreatic and Small Intestinal Neuroendocrine Tumours: A Systematic Review and Meta-analysis

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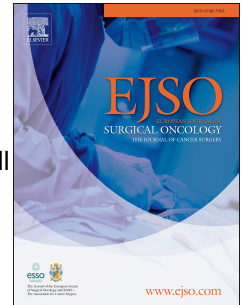
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Synopsis

The role of palliative resection of the primary tumour in small intestinal (SI-NET) and pancreatic neuroendocrine tumours (P-NET) was evaluated through systematic review and meta-analysis. Overall survival was significantly longer in patients undergoing palliative resection of both P-NETs (HR 0.43; 95% CI: 0.34 - 0.57, $p < 0.001$) and SI-NETs (HR 0.47; 95% CI: 0.35 - 0.55, $p = 0.007$).

Abstract

Purpose: This study aimed to evaluate the impact on overall survival following palliative surgery to remove the primary lesion in unresectable metastatic small intestinal (SI-NET) and pancreatic neuroendocrine tumours (P-NET).

Methods: A systematic review of the literature and meta-analysis was performed. MEDLINE and Embase databases were searched to identify articles comparing patients undergoing palliative primary tumour resection without metastatectomy vs. no resection. Relevant articles were identified in accordance with PRISMA guidelines. The primary outcome was overall survival. Included studies were evaluated for heterogeneity and publication bias.

Results: 13 studies met the inclusion criteria, of which 6 presented data suitable for meta-analysis. No randomised controlled trials were identified. Analysis of pooled multivariate hazard ratios demonstrated significantly longer overall survival in patients undergoing resection of both P-NETs (HR 0.43; 95% CI: 0.34 - 0.57, $p < 0.001$) and SI-NETs (HR 0.47; 95% CI: 0.35 - 0.55, $p = 0.007$). The increase in median survival in patients treated surgically relative to non-surgically ranged from 14 to 46 months in P-NET, and 22 to 112 months in SI-NET. The number needed to treat in order that one additional patient was alive at five years, ranged from 3.0 to 4.2, and 1.7 to 7.7 respectively.

Conclusions: Meta-analysis demonstrates that palliative resection of primary SI-NETs and P-NETs in the setting of unresectable metastatic disease can increase survival. Although these results should be interpreted with caution due to potential selection and publication bias, the data supports consideration of surgery, particularly in patients with low tumour burdens and good functional status.

Running Head: Palliative surgery in enteropancreatic NET

Introduction

Enteropancreatic neuroendocrine tumours (EP-NETs) are a heterogeneous group of neoplasms with varying malignant potential and clinical manifestations. They arise from cells of the diffuse endocrine system of the intestinal tract and pancreas and frequently develop in the jejunum, ileum, appendix, and less commonly the hindgut, pancreas and duodenum.^{1,2} The incidence of EP-NET has more than doubled in the past 15 years and they now represent the second most prevalent tumours of both the pancreas and the intestinal tract, occurring in 3.7 per 100,000 individuals per year.³ The majority of EP-NETs present with metastatic disease and their prognosis correlates closely with histological differentiation and grade as determined by mitotic rate and Ki67 index.⁴

Approximately 70% of small intestinal NETs (SI-NET) are non-functioning, with the remainder presenting with, or developing, secretory features usually due to metastatic involvement of the liver, leading to carcinoid syndrome. Carcinoid syndrome can also occur through involvement of the ovaries and retro-peritoneal lymph nodes. A higher-proportion (close to 50%) of pancreatic NETs (P-NET) are functioning lesions with very varied clinical manifestations, dependent on their hormonal activity. Functioning tumours, whether pancreatic or intestinal, are more common when associated with familial syndromes including MEN-1, vHL, and NF.

Surgery with curative intent is indicated for EP-NET with liver metastases, provided there is absence of extra-hepatic metastases, diffuse bilobar liver involvement, or compromised hepatic function.⁵ Resection of the intestinal or pancreatic primary, in conjunction with synchronous or delayed liver resection can achieve cure, particularly in low-grade tumours.^{6-9,9,10,10,11} However, the majority of EP-NETs present with unresectable stage IV disease, and the benefit of surgery to the primary lesion, particularly in asymptomatic non-secretory tumours, remains controversial.

Palliative resection of the primary lesion is recommended for functioning tumours causing intractable secretory symptoms, as well as SI-NETs with impending intestinal obstruction or persistent bleeding. European Neuroendocrine Tumour Society (ENETS) 2016 guidelines also now recognise a potential survival benefit from primary tumour resection in incurable SI-NETs and recommend consideration of palliative resection after careful assessment of patient comorbidities and functional status.¹² Palliative resection of non-functioning P-NETs requires potentially morbid surgery and is not widely recommended, despite emerging data demonstrating a similar survival benefit in this cohort.^{5,9,13,13-20}

This systematic review and meta-analysis aimed to evaluate the impact on overall survival following resection of the primary tumour in patients with stage IV SI-NET and P-NET, as compared to non-operative treatments.

Methods

Data search

A systematic review of English language articles reporting outcomes of surgery in advanced SI-NET and P-NET was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE (January 1946 to July 2016) and Embase (January 1988 to July 2016) searches were conducted using the search terms “neuroendocrine tumour”, “EP-NET”, “GEP-NET”, “pancreatic NET”, “intestinal NET”, “midgut NET”, “carcinoid tumour”, “surgery”, “resection”, “primary”, “metastases”, and/or “cytoreduction”.

The titles and abstracts of all potentially relevant studies were reviewed for eligibility. The references of each of the included studies were also screened for any additionally relevant articles.

Selection criteria

All studies that reported survival in patients undergoing surgery in advanced unresectable SI-NET and P-NET were evaluated. Studies that reported survival outcomes following a direct comparison between patients who underwent resection of their pancreatic or intestinal primary, versus those who did not undergo surgery, were included. Studies were excluded where surgery was undertaken with curative intent - both locally advanced disease where multivisceral resection or vascular reconstruction was necessary, and distant disease where metastatectomy or liver transplantation was performed.

There were no exclusions based on tumour grade, patient numbers, length of follow-up, or patients' functional status. In both the operative and non-operative groups, other therapies (including SSA, chemotherapy, PRRT, TACE, and RFA) were permitted.

In the case of duplicate or serial publications, the most recent or most complete data was included, and the other articles excluded from the analysis. In addition, abstracts that had not been published in full were excluded.

Data extraction

For each included study, the publication year, study design, type of surgery, site of primary tumour, number of included patients, median follow up and the age and gender distributions of patients were recorded, where available. Survival outcomes were extracted as hazard ratios (HRs) from univariable or multivariable Cox regression models, or as median survival times or survival rates at specific time points, as applicable. Quality of life and symptomatic outcomes were not recorded, due to a sparsity of data.

Statistical Methods

Studies that reported adjusted hazard ratios for survival in the surgical versus non-surgical groups were pooled using a Mantel-Haenszel fixed effects meta-analysis model. Subgroup analyses were then performed within the SI-NET and P-NET studies, with comparisons made between these two groups. Heterogeneity was assessed using I^2 statistics, and publication bias was reviewed graphically, using a funnel plot.

In addition, a plot was produced which included all available survival data of any form from the included studies. Where median survival or the five year survival rates were reported, ratios were calculated for the surgical versus non-surgical groups. The resulting values were

plotted alongside the reported hazard ratios, against the sample size, in order to visualise the results of all studies regardless of the type of outcome reported.

All meta-analyses were performed using the “metan” command in Stata 14 (StataCorp, 2015), with $p < 0.05$ classified as statistically significant throughout.

Results

Identification of Studies

A total of 1257 studies were identified by the initial searches, of which 13 satisfied the inclusion criteria (Figure. 1). These studies included 2619 patients who underwent palliative surgical resection of their primary tumour (1395 P-NET; 1064 SI-NET.) One study was a prospective cohort series (Bettini), with the remainder being retrospective studies, based on either single-centre (N=9), multi-centre (N=1) or national database (N=2) cohorts. No randomised controlled trials were identified.

Systematic Review and Meta-Analysis of Data

Table 1 illustrates descriptive characteristics of the included studies. The number of included patients ranged from 42 to 614, and the average age from 49 to 63 years. Where the gender distributions were reported, most studies had similar numbers of males and females (% male ranging from 45%-57%).

Of the thirteen papers that quoted survival outcomes for the surgical and non-surgical groups, six quoted an adjusted hazard ratio from a multivariable cox regression model (Table 2). Three studies (Huttner¹⁹, Du¹⁴ and van der Hort-Schrivers²³) additionally quoted hazard ratios from univariable analysis, which were consistent with the multivariable results (HR: 0.47 vs. 0.41, 0.39 vs. 0.34 and 0.58 vs. 0.61 respectively). Hence, the meta-analysis was based on the multivariable results in order to maximise the number of studies available for analysis.

The six studies included in the formal meta-analysis controlled for a range of different factors in their multivariable analyses (Table 1), with patient age the only factor to be considered in all studies. Franko et. al. only considered patient age and resection of the metastatic site in their multivariable analysis. They found the likelihood of resection to be highly dependent on tumour grade (79% of grade I/II vs. 25% of grade III/IV tumours were resected, $p < 0.001$), but this factor could not be included in the analysis due to issues with multicollinearity.²²

Of the other studies included in the meta-analysis, just one controlled for other medical therapy²¹, and two made no attempt to control for markers of disease burden.^{19,22} In addition, no studies controlled directly for patient comorbidity in their multivariate analysis.

Ahmed et. al. reported the results of the Cox regression model as relative risks, which were assumed to be incorrectly labelled hazard ratios. Givi et. al.³³ included 8 patients that did not have SI-NET but had foregut / hindgut primaries, and Van der Horst-Schrivers et. al.²³ included 22 patients with an unknown primary site and 7 with a colonic primary.

The six studies included in the meta-analysis were combined using a fixed effects model, which found survival to be significantly improved in patients receiving surgery ($p < 0.001$), with a pooled hazard ratio of 0.44 (95% CI: 0.35 – 0.55). Subgroup analysis found the benefit of surgery to be similar in the pancreas and small intestinal groups ($p = 0.793$), with pooled hazard ratios of 0.43 (95% CI: 0.34 – 0.57, $p < 0.001$) and 0.47 (95% CI: 0.27 – 0.81, $p = 0.007$) respectively. Figure 2 displays a forest plot of the studies reporting adjusted hazard ratios. No significant heterogeneity was detected across the studies ($I^2 = 0\%$, $p = 0.578$). A funnel plot was also produced (Figure 3), which gave no indication of publication bias.

Seven studies did not report a hazard ratio and so were not included in the meta-analysis model. These studies quoted five year survival and/or median survival as their primary outcome (Table 2). Figure 4 incorporates these studies with those included in the meta-analysis, and displays all reported outcomes. Across all 13 studies, patients undergoing primary tumour resection consistently had better survival outcomes than those that did not receive surgery. The single exception was the study by Bettini et al. which reported a non-significant reduction in five year survival after surgery (40% surgical group vs. 42% non-surgical group vs.; $p = 0.74$), although the median survival was longer in the surgical group (54 vs. 40 months).

The reported increases in median survival in patients treated surgically relative to non-surgically ranged from 14 - 46 months in P-NET (Solorzano et al, Franko et al.), and 22 - 112 months (Strosberg et al., Givi et al.) in SI-NET. Based on the reported five year survival data, the number needed to treat (NNT) with palliative surgery, in order that one additional patient be alive at five years, ranged from 1.7 to 7.7 (Givi et al., van der Horst-Schrivers et al.) in the SI-NET cohort. The NNT in the P-NET group ranged from 3.0 to 4.2 (Solorzano et al., Bertani et al.).

Those studies that considered additional covariates demonstrated a tendency towards worse outcomes in older patients, higher grade tumours, high tumour burden, and high Ki-67 index,^{14-16,19,22,23} although these findings were not universally reported.²¹

Discussion

The majority of patients with EP-NET have diffuse metastatic disease at presentation. In these patients, curative metastatectomy is not possible, but there remains ongoing debate on whether removal of the primary lesion confers a survival benefit.^{1,5,9,12,13,18,20,24-27} Although there have been no randomised controlled trials, the present study has identified 13 papers which report a direct comparison between patients receiving surgery to their primary tumour, and those treated without surgery. In nine studies, surgery yielded a significant improvement in survival, with the other four studies reporting a non-significant tendency to improved survival (Table 2). This study presents the first meta-analysis to evaluate the role of primary tumour resection in terms of overall survival, for both SI-NET and P-NET. The six studies that reported hazard ratios all made attempts to control for confounding factors, and returned a pooled hazard ratio of 0.44 (95% CI: 0.35 – 0.55; $p < 0.001$) for survival in the surgical, relative to the non-surgical group. Subgroup analysis demonstrated a similar benefit in both pancreatic and small intestinal primaries (Figure 2).

The incidence of EP-NET is increasing, but the heterogeneity and varying clinical presentation of patients has hindered standardisation of treatment strategies and limited

the initiation of multicentre randomized trials, particularly in the setting of unresectable disease. As a result, International and National guidelines have frequently relied on Level 3 and 4 evidence. The 2016 European Neuroendocrine Tumour Society (ENETS) consensus guidelines^{5,12}, in addition to other recent guidelines,^{9,18,26,27} strongly support the role of surgery in metastatic EP-NET where complete resection of primary and metastatic disease is deemed feasible. Resection of the primary with synchronous or delayed liver resection can achieve 5 year survival rates of up to 76% in well-differentiated (Ki67<5%) P-NETs and 74% in well-differentiated SI-NETs.⁶⁻¹¹ However, in the setting of unresectable metastatic disease, the value of surgery is less clear. ENETS guidelines recommend consideration of palliative resection of primary jejunal and ileal tumours, but do not comment specifically on the role of palliative primary tumour resection in P-NET.^{5,12,18} Previous ENETS guidance (2008 and 2012) did not recommend resection of pancreatic primaries, except where there are life-threatening intractable secretory symptoms.^{17,28}

These recommendations are based on early data, included in the present study, suggesting the potential for improved survival following resection of intestinal primaries, with the intention of avoiding intestinal obstruction and ischaemic complications. The contrary historical advice on pancreatic primaries results from concerns related to the significant morbidity and mortality associated with pancreatic resection, and fewer early studies suggesting a survival advantage.

Two recent systematic reviews reported surgical outcomes following resection of pancreatic and intestinal primaries in incurable disease.^{13,25} Formal meta-analysis was not undertaken in either study, although both reported a possible increase in overall survival following resection. Since publication of these systematic reviews, five additional papers have reported multivariable hazard ratios comparing outcomes for primary resection of P-NETs versus no primary resection.^{14,15,19,20,22} These additional data have enabled the formal meta-analysis presented here.

Three recent retrospective population based observational studies^{19,20,22} used the Surveillance, Epidemiology, and End Results database to identify patients undergoing palliative resection of primary metastatic P-NETs.^{19,20} Franko et. al. included patients treated between 1973 and 2003, and Huttner et. al. included those treated from 2004 to 2011. To prevent duplication of data, the study by Keutgen et. al., which included data across both time periods, was excluded from the present analysis.²⁰ Keutgen et. al. reported a median survival of 65 months (95% CI 60-86 months) in those who underwent primary tumour resection versus 10 months (95% CI 8-12 months) in those without resection ($p=0.0003$), and all three studies reported highly consistent multivariate hazard ratios demonstrating prolonged overall survival in the surgical group.

There are no randomised controlled trials evaluating the outcomes of palliative primary EP-NET resection in grade IV disease. The majority of included studies were retrospective cohort series, which may have therefore been subject to publication bias, although the forest plot produced from the meta-analysis gave no clear evidence that this was the case. Similarly, several studies made no attempt to control for confounding variables, leading to a likely bias towards patients who underwent resection (Table 1). In these series, resected patients were likely to have a smaller metastatic disease burden, lower grade tumours, and a better performance status. However, all those studies included in the formal meta-analysis did attempt to control for one or more covariates to account for this bias.

The present study could not control for the significant heterogeneity between tumour types, although several of the included studies did attempt to control for tumour biology and characteristics (Table 1). The meta-analysis also included both SI-NETs and P-NETs together, although separate sub-group analyses were performed. In addition, no attempt was made to subclassify the pathological types of P-NETs. This approach is consistent with 2016 ENETS guidelines on the management of metastatic NET, which largely does not subclassify recommendations based on tumour type or site of origin.⁵

The present meta-analysis did not attempt to evaluate symptom response or quality of life implications following surgery, due to insufficient studies reporting these outcomes. In addition, the value of synchronous or delayed surgical debulking of liver or peritoneal metastases, and the role of non-surgical targeted liver therapies, were not evaluated.

Surgical morbidity and mortality following SI-NET and P-NET resection were reported inconsistently. The large P-NET population-based studies acknowledged that these data were unavailable.^{19,20,22} Operative mortality where reported ranged from 0%-9% in SI-NET resection and 0%-3.5% in P-NET resection. There was also no data comparing outcomes in patients undergoing emergency surgery with those admitted via elective or semi-urgent pathways.

In addition, there was variation in the extent of surgery performed in each series and in each included patient. In the majority of studies, palliative resection of the SI-NET primary tumour included resection of the primary plus extensive mesenteric dissection, with the aim of debulking or removing mesenteric lymph node metastases, whilst preserving proximal mesenteric vasculature. One series reported the mean length of bowel resected as 43cm, (range 5 - 150cm), with 12% of patients also requiring right colonic resection.²¹ Most P-NET series did not include operative details although, where reported, procedures reflected the site and extent of disease and included total pancreatectomy, pancreaticoduodenectomy, distal pancreatectomy, and rarely, enucleation. Keutgen et. al. demonstrated that patients with body or tail tumours had a longer overall survival, although this was true in both resected and non-resected patients, and type of surgical procedure was not included in their multivariate analysis.²⁰

The authors acknowledge that medical therapy has evolved considerably over recent years and that surgeons have adopted more aggressive resection strategies with time. Therefore it is possible that non-operated patients treated at the beginning of study periods could have been disadvantaged. As a result of the wide date ranges reported by the included studies, and a lack of date specific outcomes in most series, meta-analysis of survival by year of diagnosis was not possible. A multivariate analysis of patients with P-NET treated between 1973 and 2011 showed that patients diagnosed after 2003 were more likely to undergo surgery, and had prolonged survival.²⁰ However, these trends have not been observed after 2004.¹⁹

The relatively indolent behaviour of EP-NET promotes a strategy of aggressive surgical intervention, even in the setting of metastatic disease. This is particularly true in symptomatic patients, with well-differentiated tumours (Ki67 <10%) and good functional status.^{10,29,30} The findings of the present meta-analysis, although limited by possible publication and selection bias, endorse a role for palliative primary tumour resection in small intestinal and pancreatic NETs, provided surgery can be performed with low morbidity and mortality. Since bias has likely favoured resection in less morbid patients with less extensive disease, it would seem logical that these patients in particular should be considered for

palliative surgery. Further work is necessary to evaluate any additional benefit of simultaneous hepatic and/or peritoneal debulking, cytoreductive surgery with hyperthermic intra-peritoneal chemotherapy and non-surgical targeted liver therapies in extensive hepatic involvement. Debulking surgery is currently advocated by ENETS 2016 guidelines in symptomatic patients where there is a stable disease burden, particularly where metastatic disease is localised, or where a significant proportion of the tumour burden is resectable, in order to decrease endocrine and local symptoms and to potentially amplify the response to systemic therapy.⁵ Future studies should aim to correlate survival and quality of life outcomes with patient and tumour-related factors including comorbidity, tumour site, Ki67 index, and degree of tumour burden. When considering palliative surgical intervention, the potential survival and symptomatic benefits must be balanced against the psychological impact of major surgery and the risk of significant morbidity.

References

- (1) Berardi R, Rinaldi S, Torniai M, Morgese F, Partelli S, Caramanti M, et al. Gastrointestinal neuroendocrine tumors: Searching the optimal treatment strategy--A literature review. *Crit Rev Oncol Hematol* 2016; 98: 264-274.
- (2) Massironi S, Sciola V, Spampatti MP, Peracchi M, Conte D. Gastric carcinoids: between underestimation and overtreatment. *World J Gastroenterol* 2009; 15(18): 2177-2183.
- (3) Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; 40(1): 1-18, vii.

- (4) Rindi G, Arnold R, Bosman FT et. al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds.). WHO classification of tumours of the digestive system. Lyon IARC 2010.
- (5) Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; 103(2): 172-185.
- (6) Sarmiento JM, Que FG, Grant CS, Thompson GB, Farnell MB, Nagorney DM. Concurrent resections of pancreatic islet cell cancers with synchronous hepatic metastases: outcomes of an aggressive approach. *Surgery* 2002; 132(6): 976-82; discussion 982-3.
- (7) Scigliano S, Lebtahi R, Maire F, Stievenart JL, Kianmanesh R, Sauvanet A, et al. Clinical and imaging follow-up after exhaustive liver resection of endocrine metastases: a 15-year monocentric experience. *Endocr Relat Cancer* 2009; 16(3): 977-990.
- (8) Norton JA, Warren RS, Kelly MG, Zuraek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery* 2003; 134(6): 1057-63; discussion 1063-5.
- (9) Oberg K, Knigge U, Kwekkeboom D, Perren A, ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23 Suppl 7: vii124-30.
- (10) Bacchetti S, Pasqual EM, Bertozzi S, Londero AP, Risaliti A. Curative versus palliative surgical resection of liver metastases in patients with neuroendocrine tumors: a meta-analysis of observational studies. *Gland Surg* 2014; 3(4): 243-251.
- (11) Eriksson J, Stalberg P, Nilsson A, Krause J, Lundberg C, Skogseid B, et al. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. *World J Surg* 2008; 32(5): 930-938.

- (12) Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. *Neuroendocrinology* 2016; 103(2): 125-138.
- (13) Capurso G, Bettini R, Rinzivillo M, Boninsegna L, Delle Fave G, Falconi M. Role of resection of the primary pancreatic neuroendocrine tumour only in patients with unresectable metastatic liver disease: a systematic review. *Neuroendocrinology* 2011; 93(4): 223-229.
- (14) Du S, Wang Z, Sang X, Lu X, Zheng Y, Xu H, et al. Surgical resection improves the outcome of the patients with neuroendocrine tumor liver metastases: large data from Asia. *Medicine (Baltimore)* 2015; 94(2): e388.
- (15) Bertani E, Fazio N, Botteri E, Chiappa A, Falconi M, Grana C, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. *Surgery* 2014; 155(4): 607-614.
- (16) Bettini R, Mantovani W, Boninsegna L, Crippa S, Capelli P, Bassi C, et al. Primary tumour resection in metastatic nonfunctioning pancreatic endocrine carcinomas. *Dig Liver Dis* 2009; 41(1): 49-55.
- (17) Falconi M, Bartsch DK, Eriksson B, Kloppel G, Lopes JM, O'Connor JM, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 2012; 95(2): 120-134.
- (18) Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2016; 103(2): 153-171.
- (19) Huttner FJ, Schneider L, Tarantino I, Warschkow R, Schmied BM, Hackert T, et al. Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the

pancreas: a population-based, propensity score-matched survival analysis. *Langenbecks Arch Surg* 2015; 400(6): 715-723.

(20) Keutgen XM, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ, et al. Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. *Surgery* 2016; 159(1): 311-318.

(21) Soreide O, Berstad T, Bakka A, Schruppf E, Hanssen LE, Engh V, et al. Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. *Surgery* 1992; 111(1): 48-54.

(22) Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg* 2010; 14(3): 541-548.

(23) van der Horst-Schrivers AN, Post WJ, Kema IP, Links TP, Willemse PH, Wymenga AN, et al. Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours. *Eur J Cancer* 2007; 43(18): 2651-2657.

(24) Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005; 12(4): 1083-1092.

(25) Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br J Surg* 2012; 99(11): 1480-1486.

(26) Singh S, Asa SL, Dey C, Kennecke H, Laidley D, Law C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. *Cancer Treat Rev* 2016; 47: 32-45.

- (27) Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013; 42(4): 557-577.
- (28) Steinmuller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2008; 87(1): 47-62.
- (29) Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Ann Surg* 2007; 245(2): 273-281.
- (30) Fendrich V, Langer P, Celik I, Bartsch DK, Zielke A, Ramaswamy A, et al. An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Ann Surg* 2006; 244(6): 845-51; discussion 852-3.
- (31) Solorzano CC, Lee JE, Pisters PW, Vauthey JN, Ayers GD, Jean ME, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery* 2001; 130(6): 1078-1085.
- (32) Nguyen SQ, Angel LP, Divino CM, Schluender S, Warner RR. Surgery in malignant pancreatic neuroendocrine tumors. *J Surg Oncol* 2007; 96(5): 397-403.
- (33) Givi B, Pommier SJ, Thompson AK, Diggs BS, Pommier RF. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery* 2006; 140(6): 891-7; discussion 897-8.
- (34) Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 2009; 89(4): 471-476.
- (35) Norlen O, Stalberg P, Oberg K, Eriksson J, Hedberg J, Hessman O, et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 2012; 36(6): 1419-1431.

Table 1. Summary of Study Characteristics.

Reference	Year	Total (primary resected)	Study Design	Mean Age (Years)	Sex (% Male)	Median Follow-up (Months)	Factors adjusted for in multivariable survival analyses
Pancreatic NET							
Solorzano et. al. ³¹	2001	96	SC RCS	-	-	-	Age, Resection of Metastatic Site Age, Ki67, Liver Tumour Burden Age, Weight Loss, Primary NET, Primary Size, Hepatic Metastasis Size Age, Gender, Ethnicity, Marital Status, Year of Diagnosis, Grade, T&N-stage
Nguyen et. al. ³²	2007	42	SC RCS	-	-	41	
Bettini et. al. ¹⁶	2009	51	SC PCS	51/57	-	26	
Franko et. al.²²	2010	614	RPBOS	59/59	-	-	
Bertani et. al.¹⁵	2014	43	SC RCS	-	-	-	
Du et. al.¹⁴	2015	98	SC RCS	49	53%	-	
Huttner et. al.¹⁹	2015	442	RPBOS	53/60	51%/57%	33/18**	
Small-Intestinal NET							
Soreide et. al. ²¹	1992	65	SC RCS	57	-	-	Age, Gamma-glutamyltransferase, Alkaline phosphatase, Urinary 5-HIAA Age, Ki67, Urinary HIAA, Serum Chromogranin A, Peptide Receptor Therapy, Somatostatin Analogue Therapy
Givi et. al. ³³	2006	84 ⁺	SC RCS	57/60	50%/50%	90	
Van der Horst-Schrivers et. al.²³	2007	76 [#]	SC RCS	59	-	-	
Ahmed et. al.²¹	2009	285	Mc RCS	60/61	53%	63**	
Strosberg et. al. ³⁴	2009	135	SC RCS	60*	45%	-	
Norlen et. al. ³⁵	2012	579	SC RCS	63	54%	83**	

Age, sex and duration of follow up are reported as Resected/Non-resected, or for the cohort as a whole, where separate statistics were not quoted for the two groups.

Studies included in the formal meta-analysis are highlighted in bold text.

Single-centre retrospective cohort series (SC RCS); multi-centre retrospective cohort series (Mc RCS); single-centre prospective cohort series (SC PCS); retrospective population based observational study using a national database (RPBOS).

*Median age; **Mean follow up.

⁺Includes 8 patients that did not have SI-NET but had foregut / hindgut primaries.

[#]Includes 22 patients with an unknown primary site and 7 with a colonic primary.

Table 2 – Survival outcomes

Study	Total N	Cox Regression		Kaplan-Meier				
		Adjusted HR (95% CI)	p-Value	5 Year Survival		Median Survival		p-Value
				Surgery	Non-Surgery	Surgery	Non-Surgery	
Pancreatic NET								
Solorzano et. al. ³¹ (2001)	96	-	-	49%	16%	36	21.6	0.06
Nguyen et. al. ³² (2007)	42	-	-	60%	30%	-	-	0.025
Bettini et. al. ¹⁶ (2009)	51	-	-	40.4%	41.8%	54.3	39.5	0.74
Franko et. al.²² (2010)	614	0.46 (0.31 - 0.68)	<0.001	-	-	58	12	<0.001
Bertani et. al.¹⁵ (2014)	43	0.18 (0.05 - 0.66)	0.01	82%	58%	77	50	0.027
Du et. al.¹⁴ (2015)	98	0.39 (0.22 - 0.70)	<0.001	-	-	-	-	-
Huttner et. al.¹⁹ (2015)	442	0.47 (0.31 - 0.70)	<0.001	48%	21%	-	-	<0.001
Small-Intestinal NET								
Soreide et. al. ²¹ (1992)	65	-	-	-	-	139	69	0.03
Givi et. al. ³³ (2006)	76	-	-	81%	21%	159	47	<0.001
Vd H-Schrivers et. al.²³ (2007)	47	0.58 (0.31 - 1.10)	0.097	57%	44%	75	52	0.084
Ahmed et. al.²¹ (2009)	285	0.26 (0.09 - 0.78)*	0.015	74%	46%	119	57	-
Strosberg et. al. ³⁴ (2009)	135	-	-	-	-	110	88	0.32
Norlen et. al. ³⁵ (2012)	579	-	-	75%	28%	-	-	<0.001

Studies reporting hazard ratios are highlighted and were included in the formal meta-analysis.

*This was reported as a relative risk in the manuscript, but is assumed to represent a hazard ratio.

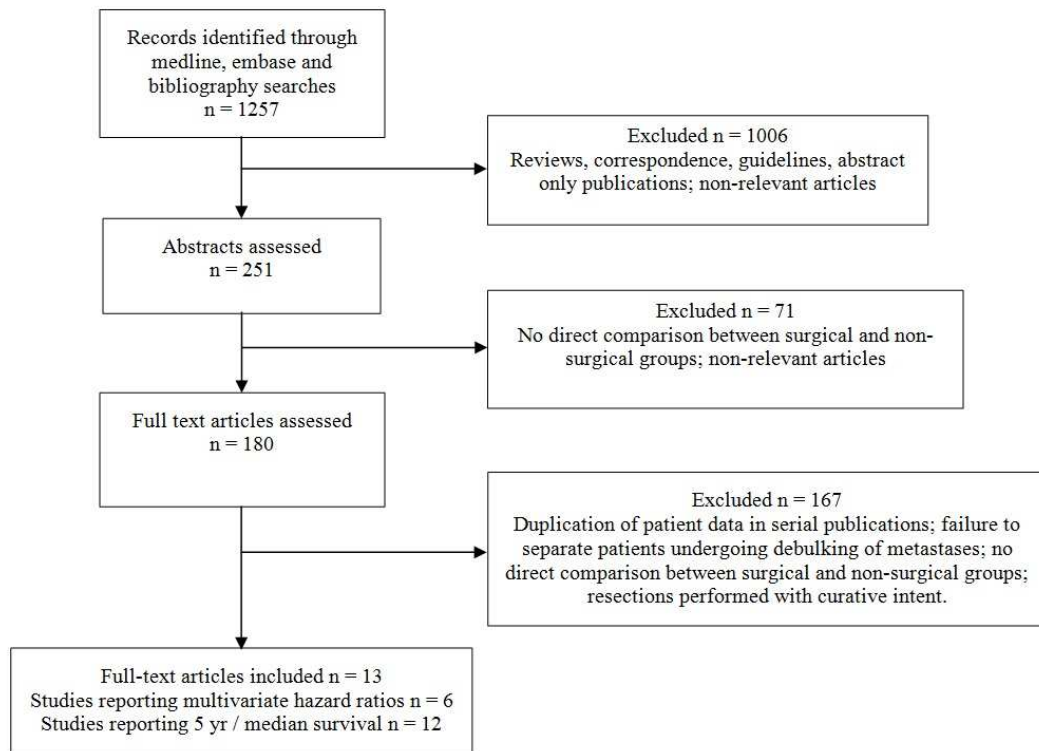
Figure 1. PRISMA flow diagram illustrating study selection.

Figure 2 – Forest plot. The six studies reporting adjusted hazard ratios are represented.

Figure 3 – Funnel Plot. Data from the six studies reporting hazard

Figure 4 – Combined plot of survival outcomes.

Ratios were produced by dividing the median survival times or five year survival rates in the non-surgical group by the surgical group. These were then plotted against the sample size in each study, with a dashed line representing the pooled hazard ratio from the meta-analysis.



Pancreatic NET

Franko et. al. (2010)

Bertani et. al. (2014)

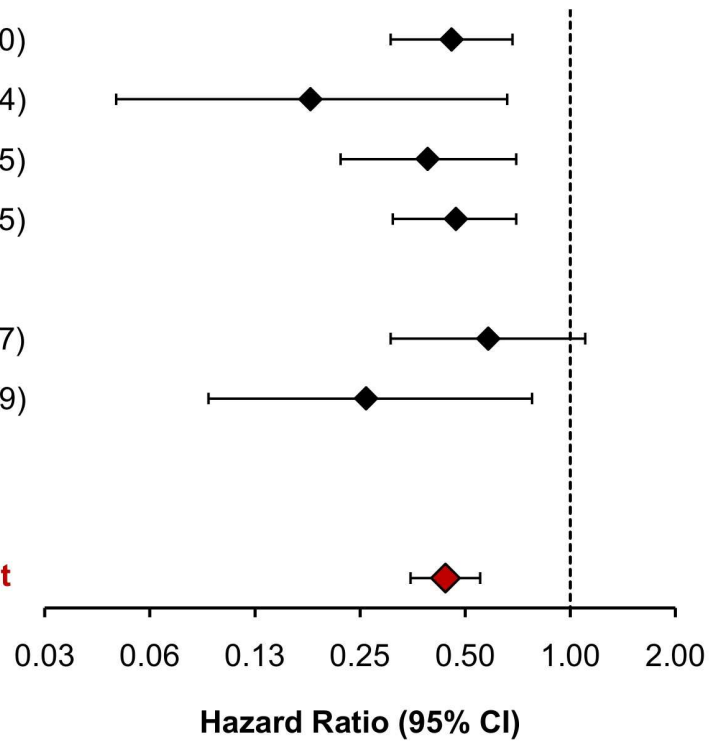
Du et. al. (2015)

Huttner et. al. (2015)

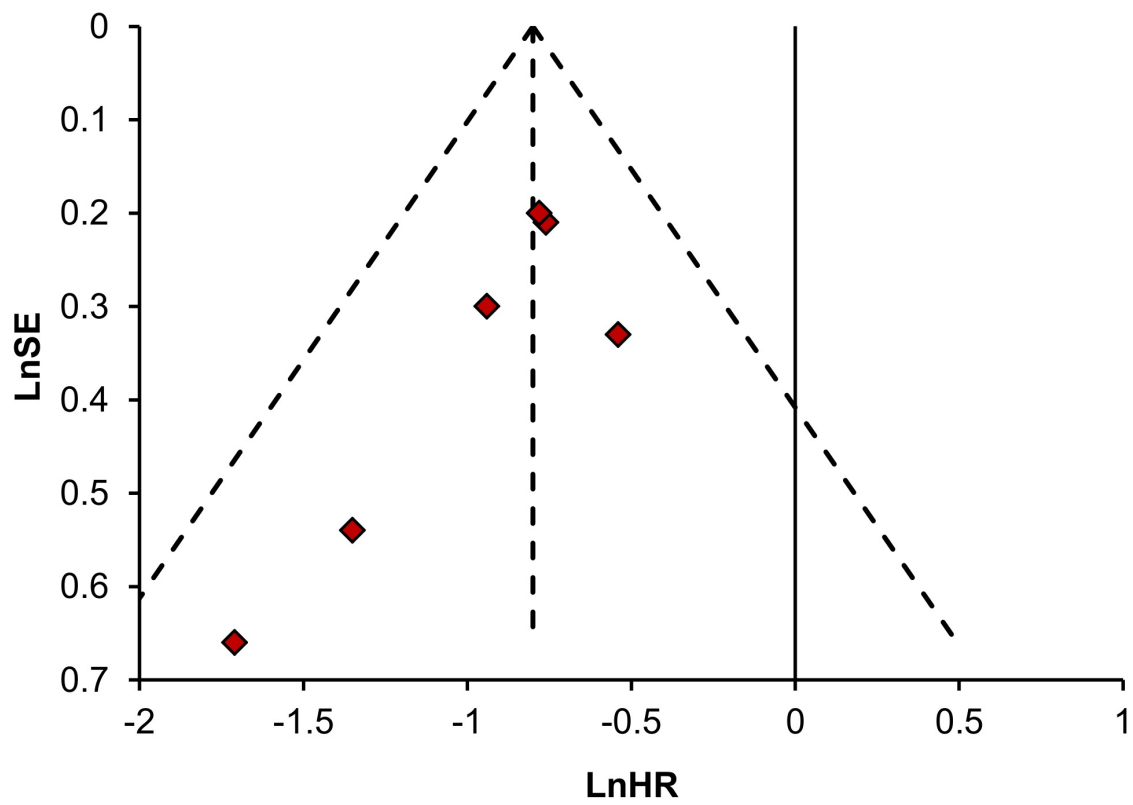
Small-Intestinal NET

Vd H-Schrivers et. al. (2007)

Ahmed et. al. (2009)

Overall EffectHeterogeneity: $\text{Chi}^2=3.80$, $\text{df}=5$, $\text{p}=0.578$ Test for Overall Effect: $Z=7.06$, $\text{p}<0.001$

ACCEPTED



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