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Value of ileus-prophylactic surgery for metastatic neuroendocrine midgut tumours

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Neuroendocrine tumours of the small intestine (SINET) are a rare disease. However, a rising incidence rate and excellent long-term survival, even in the setting of metastatic disease lead to a high prevalence of SINET of up to 11/100.000. At the time of diagnosis, most patients already suffer from metastatic disease.

About one third of patients demonstrate localized or regional metastatic disease at time of presentation. For those patients the indication for curative surgery is not debated and 10-year cancer specific survival of almost 90% can be achieved. Due to major limitations of existing studies actually there is no sufficient evidence in favour of ileus-prophylactic palliative surgery for metastatic SINET. Until now the available evidence favouring an ileus-prophylactic palliative small bowel resection for stage IV SI-NET must be weighed against available high-level evidence from randomized trials that showed long-term survival under systemic therapy. Importantly, there is not a single study that indicates surgery for a symptomatic patient should be postponed. Because the majority of patients are symptomatic at the time of diagnosis, the rationale for an ileus-prophylactic palliative surgery is to operate before progression of mesenteric tumour mass and desmoplasia takes place and before intestinal obstruction and ischaemia occurs. To what extent a prophylactic palliative small bowel resection will provide a survival benefit in a situation where the mesenteric tumour mass cannot be resected radically is not clearly addressed by the current level of evidence.

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Neuroendocrine tumours of the small intestine (SINET) are a rare disease. According to population-based registries the annual incidence rate is about 1/100.000 [1–3]. However, a rising incidence rate and excellent long-term survival of 8 years and more, even in the setting of metastatic disease lead to a high prevalence of SINET [3]. While autopsy studies report a prevalence of about 1.22 per 100.000 people, some registries report a prevalence of as high as 11/100.000 [1,2,4]. Prevalence increases with age and is found four-fold higher in patients age 65 years and older compared to younger patients [1].

SINET account for over 20% of all neuroendocrine tumours and are the most common malignancy of the small intestine. Within the small bowel, NET will be found predominantly in the distal jejunum and ileum with a rising frequency from proximal to distal [2,4]. About 70% of tumours will be found in the last third of the ileum. Additionally, SINET has been shown to occur multifocally in up to 30% of patients [5].

Duo to serotonin production clinically affected patients present in the beginning with unspecific gastrointestinal discomfort and often are misdiagnosed [4]. In the further course typically they present themselves with signs of intestinal obstruction or small bowel ischaemia due to mesenteric tumour mass (Figs. 1–3) [5,6]. However, it might be difficult to differentiate the unspecific, episodic abdominal pain attributed to serotonin excess from the symptoms caused by slight intestinal ischaemia or bowel obstruction. Up to 20% of patients with SINET develop hormone excess and carcinoid syndrome. In addition to flushing (90%) and diarrhoea (80%) as being the most frequent symptoms, patient my complain of bronchial obstruction or even heart valve insufficiency known as the Hedinger syndrome [2,4,6]. However, it is not uncommon that the diagnosis will be made through biopsy of the liver metastases observed at time of diagnosis [2,4].

Neuroendocrine tumours of the gastroenteropancreatic system (GEP NET) are highly heterogeneous and display substantial variety of clinical presentation, genetic background, pattern of metastases as well as options for therapeutic intervention, that conclusive recommendations are quite difficult to be

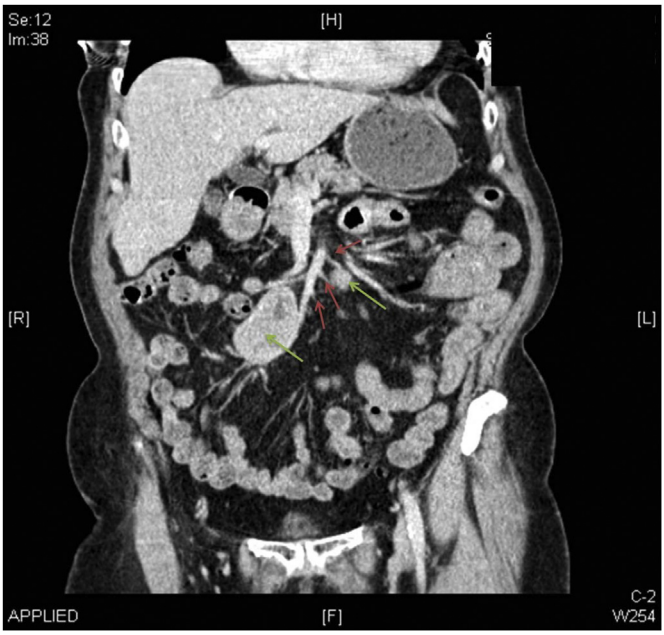

Fig. 1. Pre-operative CT-scan of a 77 years old female patient with 8 mm SINET (pT3 pN1(4/18)). Large mesenteric tumour mass (green arrow) is visible at the distal part of the superior mesenteric artery (SMA). There are small lymph node metastases at the central SMA. The first three branching of the jejunal arteries are tumour free (red arrows). Complete vascular sparing tumour resection containing 33 cm of ileum and systematic lymphadenectomy level 1 to 3 was performed. Fig is taken from Ref. [8] (own publication). Right for re-print obtained by copyright clearance center. License Number 4665931487706.

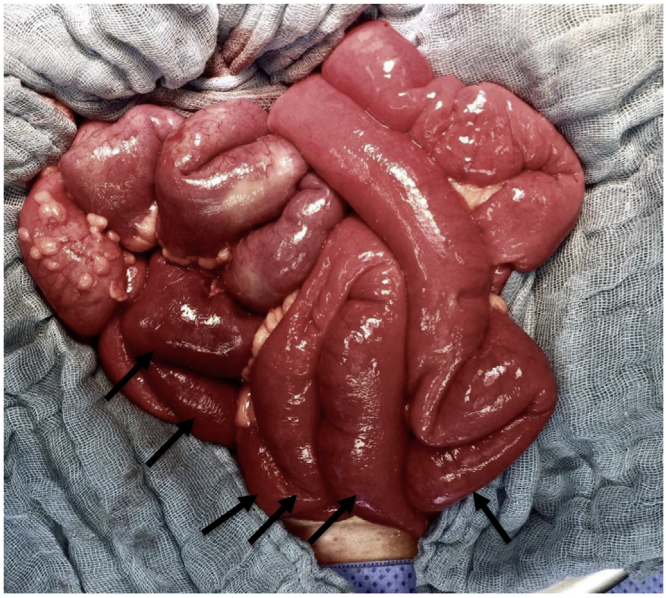

Fig. 2. Intraoperative presentation of the small bowel in a patient with stage IV, SINET and resectable mesenteric tumour deposits. The patient presented with only mild abdominal symptoms not attributed to obstruction or ischemia. Indication for surgery was ileus-prophylactic, palliative surgery. Intraoperative findings showed already present ischemia (arrows).

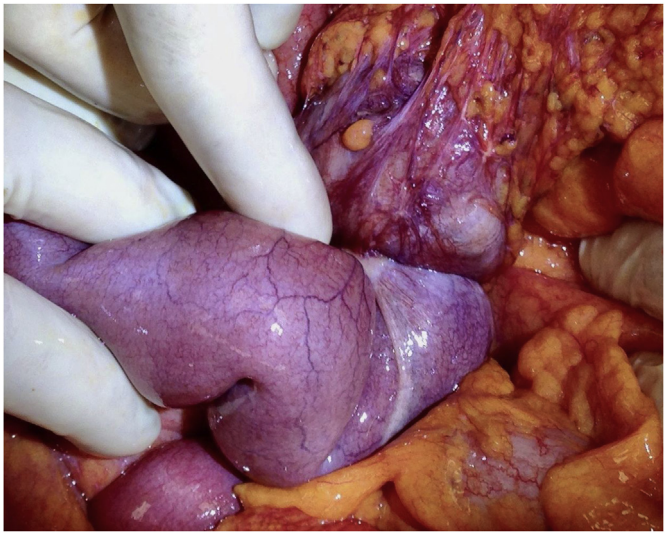

Fig. 3. Stage IV SI-NET showing primary tumour and level 1 lymph node metastases with mesenteric mass. Ileus-prophylactic, palliative surgery was performed. Fig is taken from Ref. [8] (own publication). Right for re-print obtained by copyright clearance center. License Number 4665931487706.

drawn. This review will focus on the current evidence for treatment of SI-NET and discuss the surgical strategies, in particular for stage IV SINET.

Curative surgery for localized and regional metastatic SINET

Non metastatic SINET are rare. At the time of diagnosis, most patients already suffer from metastatic disease. Distant metastases to the liver are observed in about one third of patients and more than 80% of patients present with lymph node metastases (Table 1) [5,7]. The perception, that small tumours (i.e. <10 mm) might be associated with a more indolent clinical course does not hold true for as SINET are regarded [8]. On the contrary, the risk of lymph node or distant metastases is not affected by primary tumour size. Walsh et al. showed that 71% of patients with a primary tumour <10 mm will have lymph node metastases [9]. The early metastatic potential is remarkable as the vast majority (80–90%) of tumours are low grade and low proliferating neoplasia [5,7,9]. In our series of 177 patients with SI-NET (2010–2019), there have been only 9 patients with stage pT1 and these already had lymph node metastases. There was neither a correlation between tumour stage nor between grading (Ki67 index) and lymph node involvement.

About one third of patients demonstrate localized or regional metastatic disease at time of presentation. For those patients the indication for curative surgery is not debated and 10-year cancer specific survival of almost 90% can be achieved [10]. Current ENETS as well as NANETS guidelines point out that the benefit of laparoscopic surgery must be critically weighted against the risk of an incomplete tumour resection and lymph node dissection [2,11].

About one third of patients harbour multifocal disease (Fig. 4) [5,9,12,13]. Until now there is no conclusive evidence whether or not multifocal SINET represent a more aggressive disease. Studies available showed that after complete multifocal primary tumour resection there was no difference in overall survival or rate of distant metastases compared to patients with a single primary tumour [14]. Commonly multifocal disease can only be identified by meticulous gentle palpation of the entire small bowel (Figs. 4 and 5) [5]. A study by Ethun et al. shows that by laparoscopic approach a multi focal disease was identified in only 21% of patients. In contrast, the open exploration revealed multi focal manifestation in 50% of patients [15]. In addition, the rate of primary tumours identified (n = 4.9) was twice as high for open compared to laparoscopic approach [15]. Of note, preoperative imaging substantially underrates tumour stage. Only thorough abdominal exploration provides an accurate staging [5,16].

Concerning radical surgery, a critical aspect is the recommendation to perform routine prophylactic cholecystectomy. It is well known that medical treatment with somatostatin analogues (SSA) increases the risk for gallstones. However, current ENETS guidelines are pointing out, that the evidence for doing routine cholecystectomy is low. Indeed, it is based on a retrospective study including 144 Patients of which 15% developed gall stone associated complication under SSA therapy [17]. A recent study showed that prophylactic cholecystectomy can be done safely with no significant increase in morbidity (increase of 0.4%). However, cholecystectomy was performed in only 11% of 1300 patients that underwent surgery for SINET [18]. Furthermore, it needs to be pointed out that while SSA therapy increases the risk for gall stone development, most of these will be asymptomatic [19]. Thus, the indication for prophylactic cholecystectomy should only be made on an individual but not routine basis.

Table 1
Clinical presentation of SINET.

Study	Localized	Regional	Distant metastases
Endocrine Surgery, Essen, n = 168	8/168	56/168	104/172
(unpublished data)	4,8%	33,3%	61.9%
Watzka et al., 2016	12/83	13/83	58/83
n = 83	14,5%	15,7%	69,9%
Fata et al., 2017	22/132	29/132	77/132
n = 132	16,6%	21,9%	58,3%

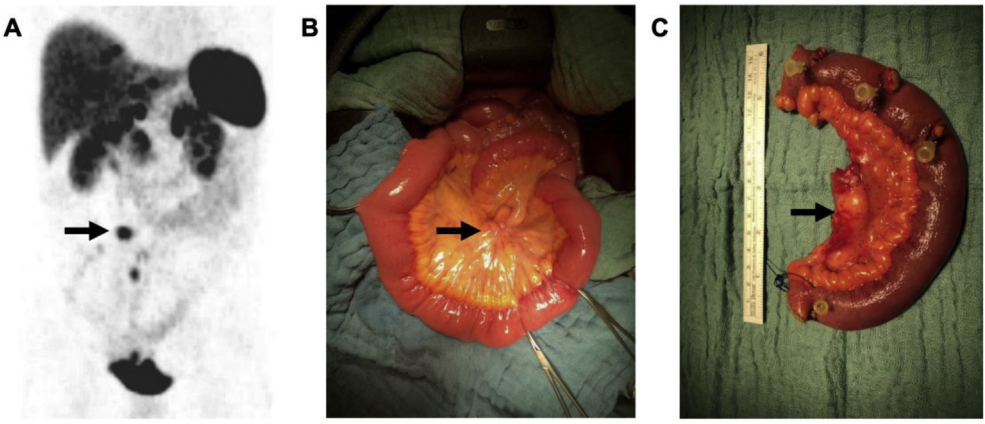

Fig. 4. Case of a 68yo patient with diagnosed and resected duodenal NET 11/2017 (other hospital) (pT2pN1, G2). A) Detection of two mesenteric/small bowel tumours and bilobar hepatic metastases on 68 Ga DOTATOC PET/MRI (5/2018). B) Indication for ileus-prophylactic palliative primary tumour resection, that identified multifocal (clamps) primary tumours and a mesenteric tumour mass (black arrow). C) Small bowel sparing resection with systematic lymphadenctomy including the mesenteric mass. Needles point to the four primary SI-NET tumours. Patient is with no signs of extrahepatic tumour residues at one year follow-up.

Pattern of lymphatic metastases and surgical strategy

Lymph node metastases are common in SI-NET and do not correlate with primary tumour size. Thus, a systematic and radical lymph node dissection is an important aspect of the surgical intervention [2,5,11]. There are numerous reports showing that systematic lymphadenectomy provides an improved survival [20]. Watzka et al. reported that patients receiving systematic lymphadenectomy showed an improved 10 year survival of 70% compared to 40% for those patients that received selective lymphadenectomy [7]. While some groups have shown that more than 6 resected lymph nodes resected can be considered as to be the cut off level for sufficient lymphadenectomy, others did not find such correlation [7]. Landry et al. identified a minimum number of 8 lymph nodes removed (HR 0.66, $p = 0{,}023$) and a ratio of >29% of prognostic relevance (HR 1.5, $p = 0{,}03$) [21]. In our series we find that a ratio over 33% is correlated with the presence of liver metastases. However, other groups could not identify this correlation [5]. A large series by Kim et al. on over 2900 patients found that the prognostic significance of high lymph node ratio only applied to early tumour stage (i.e. pT1,pT2)[20]. Until now, there is non-conclusive evidence that the total number of lymph nodes resected, or the lymph node ratio will have prognostic implications and ENETS guidelines do not provide a recommendation on a minimum number of lymph nodes resected [2].

Recently, Pasquer et al. categorized lymph node metastases into three levels according to the anatomic location [13]. Their scheme is adopted from the four region staging system proposed earlier by Akerström [22]. Pasquer et al. combined stage II and III lymph nodes into the level 2 group. Level 1 lymph nodes are located close to the bowel, level 2 lymph nodes along the large mesenteric vessels and level 3 central mesenteric and retropancreatic lymph nodes. Based on a series of 21 patients Pasquer and others showed that 60% of patients had skip lymph node involvement at level 2 and 3 while level 1 lymph nodes were tumour free [13]. This observation supports the notion, that a detailed pre- and intraoperative assessment of the extent and pattern of lymph node involvement is important to determine resectability and curation.

In this context, Lardiere-Deguelte et al. propagate a classification of lymph node involvement based on preoperative imaging (Fig. 1) [12]. This group considered the mesenteric mass at the root of the superior mesenteric arteries (SMA) that encase the first three jejunal arteries to be irresectable. To what extent this classification will have a clinical and prognostic impact, cannot be concluded based on the current evidence. It remains crucial that systematic lymphadenectomy is conducted under

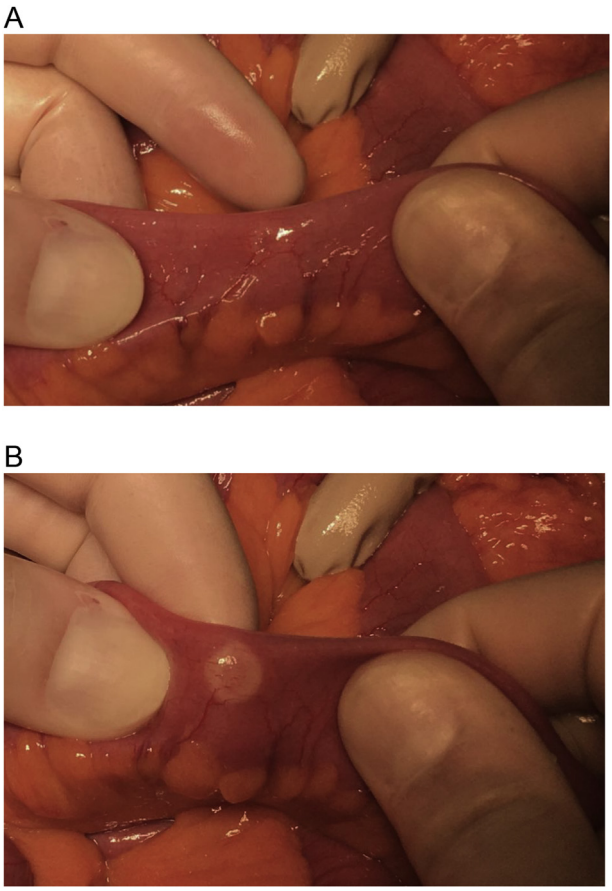

Fig. 5. Patient with small primary SI-NET. Image demonstrate the common observation that small primary tumour cannot be identified by eye (A) but reveal themselves through gentle palpation (B).

preservation of the mesenteric vessels. This allows for small bowel sparing resection without jeopardizing radical lymphadenectomy (Figs. 1 and 4) [12].

The importance of mesenteric tumour mass and desmoplasia

In SINET there is a frequent phenomenon of mesenteric tumour deposition, in which metastatic lymph nodes are completely depleted by tumour cells which then infiltrate by perinodal extension the surrounding soft tissue of the mesentery [23]. This mesenteric involvement is caused by severe desmoplastic reaction leading to fibrosis and shortening of the mesentery. While desmoplasia and mesenteric tumour mass are highly associated (96%), mesenteric fibrosis without the presence of mesenteric tumours mass is considerable more rare (44% $p < 0,01$) (Rodriguez Laval et al., 2017) [23,24]. Even small, localized SI-NET present in up to 10% of cases with mesenteric fibrosis [24,25].

The importance of mesenteric mass and mesenteric desmoplasia has not yet found its way into a prognostic classification. However, there is growing evidence that the presence of mesenteric tumour mass is of greater prognostic value than lymph node metastases. Malik et al. showed that the presence of mesenteric mass was associated with obstructive clinical symptoms as well as stage IV disease [26]. Similarly, Fata et al. showed in a cohort of 132 patients that mesenteric tumour mass was associated with reduced disease specific survival (hazard ratio 4.58), while lymph node metastases without

mesenteric involvement was not [23]. The presence of a mesenteric tumour mass was observed among 62 of 85 patients (72.9%) with liver metastases. In contrast, among 28 cases without mesenteric mass only 8 (28%) had liver metastases [23]. Thus, there is a group of patients with stage IV disease, in which early palliative surgery might prevent the development of a mesenteric tumour deposit and desmoplasia.

The role of ileus-prophylactic palliative surgery

Mesenteric fibrosis and tumour mass will lead to small bowel obstruction in about 25% [24]. Of note, Malik et al. found that patients with mesenteric tumour mass were more likely to undergo radical surgery, probably due to symptomatic clinical presentation [26]. Curiously, Blazevic et al. observed the opposite in their cohort [24]. Their patients were less likely to undergo surgery when a mesenteric mass or mesenteric fibrosis were present (OR 0.15 and 0.42, respectively. $p < 0.001$).

If the root of the superior mesenteric artery and vein (SMA and SMV) are encased the options for a curative surgery are limited. However, we hold the view that due to the impending desmoplastic reaction an ileus-prophylactic, palliative surgery is hardly avoidable. However, to what extent a prophylactic palliative small bowel resection will provide a survival benefit in a situation where the mesenteric tumour mass cannot be resected radically is not clearly addressed by the current level of evidence [2,24]. However, due to the impending bowel ischaemia we would always advocate against a loop bypass.

Until now the available evidence favouring an ileu-prophylactic palliative small bowel resection for stage IV SI-NET must be weighed against available high-level evidence from randomized trials (i.e. PROMID, CLARINET, RADIANT4 or NETTER-1) that showed long-term survival under systemic therapy (Table 2) [11]. Unfortunately, there are no randomized trials to address the question and meta-analysis are limited by the heterogeneity of the retrospective cohort studies.

In a recent meta-analysis Tsilimigras et al. concluded that surgery for midgut NET with non-respectable liver metastases was safe (<2%, 30-day mortality) and primary tumour resection was associated with an improved 5-year survival (73.1% vs 36.6%) [27]. Similarly, Guo et al. based on their recent analysis argued in favour of primary resection in stage IV SI-NET [28].

One of the first studies that showed a survival benefit of palliative surgery for stage IV SI-NET was done by Givi et al. (Table 2) [29]. This retrospective cohort study utilized the data from an institutional database. The authors reported a higher overall survival (159 months) for the group with primary tumour resection ($n = 60$), compared to the non-resected group ($n = 24$) (47 months, $p < 0.001$). However, this study did not account for confounding factors such as age or clinical symptoms. Because 26 of 60 patients (43%) had abdominal pain and signs of bowel obstruction the surgery was likely not prophylactic.

Interestingly, the authors also report on liver progression-free survival (PFS). The median PFS of the group with primary tumour resection was significantly longer (56 months) compared to the non-resected group (25 months, $p < 0.001$) [29]. However, no adjustment for confounding factors or multivariate analysis was performed. Similarly, the retrospective cohort study by Norlen et al. included over 600 patients and showed a significant survival benefit favouring primary tumour resection (Table 2). However, the study population comprised stage I to IV tumours and also this study did not analyse confounding variables [30].

There are some retrospective cohort studies that utilized adjustment for confounding factors and showed a significant survival benefit of primary resection for stage IV SINET. The study by Tierney et al. is based on the US-American National Cancer Database (NCDB) and comprised over 4000 patients with stage IV SI-NET (Table 2) [31]. The study identified a significant survival benefit for patients having received primary tumour resection (91.3 months) compared to those patients that did not (44.2 months) ($p < 0.001$). Importantly, primary resection remained a significant prognostic marker in multivariate analysis (HR 0.55, $p < 0.001$). Age <64 years was not only associated with prolonged survival but also likelihood for primary surgery. Lewis et al. utilizing the California Cancer Registry (CCR) identified over 800 patients with stage IV SI-NET (Table 2) [32]. The authors found a significant survival benefit for palliative primary resection (HR 0.5, $p < 0.001$). Major limitation of this study was that all GEP-NET have been included and only 200 of the 854 patients (23.4%) were SINET. The

Table 2
Summery of studies addressing the question of palliative surgery in SINET.

Literature	study design	patient criteria	proportion primary tumour resected	median survival surgery group	median survival no surgery group	significance univariate	significance multivariate
Givi et al., 2006	unicenter, retrospective, 1995–2006	n = 84 stage IV	n = 60 (71%)	159 months	47 months	$p < 0.001$	na
Strosberg et al., 2009	unicenter, retrospective 1999–2003	n = 146 stage IV (n = 31 CUP)	n = 100 (69%) n = 31 hepatic cytoreduction	110 months 138 months	88 months 95 months	$p = 0.32$ $p = 0.03$	na
Norlen et al., 2012	unicenter, retrospective 1985–2010	n = 603 stage I-IV	na	51% 10 years survival	6% 10-year survival	$p < 0.001$	na
Blazeviv et al., 2018	unicenter, retrospective, 1993–2016	n = 559 (425 stage IV)	n = 204 palliative surgery n = 47 curative intent	152.2 months 183.5 months	137.1 months	$p = 0.012$	not significant HR 0.62, $p = 0.1$
Daskalakis et al., 2018	unicenter, retrospective 1985–2015	n = 363[e] stage IV	n = 161 prophylactic[c] n = 89 delayed[d] n = 113 no surgery	114 months 63.6 months	– – na	– $p = 0.01$ na	Propensity score matching: OS 7.9 years vs. OS 7.6 years $p = 0.93$
Laskaratos et al., 2018	unicenter, retrospective 2000–2014	n = 387 stage IV incidental (n = 38)	44.7%[f] prophylactic	144 months[a] 145 months	72 months[a] 116 months	$p = 0.25$	HR 0.51 $p < 0.001$
Lewis et al., 2018	CCR 2005–2011	n = 854[b] (200 SINET) stage IV	n = 392 (162 SINET)	38 months	10 months	$p < 0.001$	HR 0.5 $p < 0.001$
Tierney et al., 2019	NCDB database, 2004–2014	n = 4252 stage IV	n = 2526 (59.4%)	91.3 months	44.2 months	$p < 0.001$	HR 0.55, $p < 0.001$

na, not available; HR, hazard ratio; OS, overall survival; CCR, California Cancer Registry; SEER, US-American Surveillance, Epidemiology, and End Results; NCDB, US-American National Cancer Database; CUP, cancer of unknown primary.
[a] Approximate months taken from Kaplan–Meier plot.
[b] All GEP-NET included.
[c] Prophylactic surgery within 6 months of diagnosis.
[d] Delayed surgery mean 18 months after diagnosis.
[e] Without abdominal symptoms.
[f] Of these 26% emergency surgery.

heterogeneity of study population might explain low median survival of 38 months in the primary tumour resection group and 10 months in the no-resection group.

The study by Laskaratos et al. was based on a retrospective cohort analysis including 387 patients with stage IV SINET (Table 2) [33]. After adjustment for confounding factors the authors found a significant survival benefit for palliative primary tumour surgery (HR 0.51, $p < 0.001$). 100 of 387 patients were operated electively while 45 by emergency surgery. Surgery of 48 out of 100 patients aimed to be under curative intent, while 31 out of 100 patients experienced abdominal symptoms (palliative, symptomatic). Only 13 out of 100 patients were treated with palliative, ileus-prophylactic intent (Table 3). Interestingly, a subgroup analysis showed that the survival benefit holds true only for symptomatic patients. A comparison of 38 asymptomatic patients could not show a survival benefit of ileus-prophylactic, palliative surgery (median overall survival for primary tumour removal 12.1 years vs. 9.7 years for non-surgical management). However, it is questioned, whether or not the sample size holds enough power to identify a significant difference between groups.

Both studies of Givi et al. and Tierney et al. reported a median overall survival for the no-resection group of 44.2 months and 47months, respectively [29,31]. Compared to other studies for stage IV SINET

Table 3
Indication for surgery in SI-NET.

Study	Emergency	Palliative, symptomatic	Palliative, prophylactic
Laskaratos et al., 2018 n = 387	26.0%	58.0%	3.0%
Blazevic et al., 2018 n = 559	12.5%	42.4%	28.5%
Watzka et al., 2016 n = 83	45.8%	na	na
Manguoso et al., 2018 n = 134	25.4%	na	na

this is unusually low. Other studies report median overall survival for stage IV SINET even without primary resection between 88 and 137 months [24,33,34]. Therefore, it appears to be evident that when comparing retrospective cohort studies, we have to keep in mind differing patients access to state-of-the-art multimodal therapy. Such disparities might tremendously impact timing and pattern of treatment and patient survival [35–37].

Other studies could not identify a survival benefit of palliative, ileus-prophylactic primary tumour resection for SINET. Strosberg et al. reported their retrospective data on 146 patients with stage IV disease (Table 2) [34]. Of these, 100 patients (69%) received primary tumour resection. The authors reported a non-significant difference of the median overall survival between the resection group (110 months) and the non-resection group (88 months). Interestingly, 31 cases (21%) received a hepatic tumour reduction that was correlated with an improved survival of 138 months ($p = 0.03$). While the authors state that the most patients received surgery because of clinical symptoms, the group of patients that received ileus-prophylactic, palliative surgery is not further defined. To this end, the study included 31 patients with cancer of unknown primary (CUP) in which a primary tumour resection was not performed. Thus, the most patients included in the "non-resection" group did not show a morphologic presence of SINET. Which precludes that there is sufficient evidence against a survival benefit for ileus-prophylactic palliative primary tumour surgery.

Daskalakis et al. presented an very important retrospective study based on the Uppsalla University Hospital database (Table 2) [38]. Among 820 patients with SINET the group identified 363 cases with stage IV disease but without local tumour-related symptoms. Among this cohort a group of 161 patients underwent ileus-prophylactic surgery within 6 months of diagnosis, while 202 patients did not receive surgery upfront. However, during a follow up of 5.4 years almost half of the 202 patient (89 patients, 44%) required surgery within mean 18 months after diagnosis. 32 out of 89 patients had abdominal symptoms (36%) as the reason for surgery (i.e. palliative, symptomatic surgery).

On univariate analysis, the median survival of ileus-prophylactic surgery group (9.5 years) was significantly higher compared to 5.3years for the delayed/no-surgery group ($p = 0.01$). The authors performed a propensity score matching that revealed that the overall survival was similar between both groups (prophylactic surgery 7.9 years vs. delayed surgery/no-surgery 7.7 years) ($p = 0.99$).

As this is one of the important studies that strongly argue against an ileus-prophylactic palliative surgery, a critical appraisal of the study design is warranted.

The study did not provide information on the survival rate of the 113 patients with stage IV SI-NET that never received primary tumour resection, but compared the overall survival between stage IV patients that have been operated within 6 months after diagnosis and a group of patients that have been operated in average 18 months after diagnosis. Furthermore, ill designed immortal time adjustment introduced a substantial bias. While for the primary tumour resection group follow-up starts at the time of surgery, for the entire group of 202 patients (including those 89 patients that received surgery and for which survival analysis was performed) that did not receive surgery upfront follow-up started at the time of diagnosis. Moreover, the propensity score matched cohort included 91 patients (56.5%) of the ileus-prophylactic group and 91 patients (45%) of the delayed/no surgery group. Both groups were adjusted to mean age of about 60 years. While this reflects the mean age of the unmatched ileus-prophylactic surgery group, the unmatched delayed surgery group contained 53% of

patients with age 65 and older (mean age 64.2 years). Because age is an important predictor of survival, the propensity matching lead to age reduction of the delayed surgery group. That means that the study population in the delayed/no surgery group was restricted to left extreme of the normal distribution curve and might not be representative for the whole study population. Indeed, such a patient selection represents a fundamental bias when unknown confounders like mesenteric tumour mass or desmoplasia are not included in the matching process.

Another recent cohort study advocating against an ileus-prophylactic palliative surgery comprised 425 patients with stage IV disease from the Rotterdam Cancer Center (Table 2) [24]. Primary tumour resection was performed in 68% (n = 288) out of 425 patients in total with stage IV disease. Importantly, the minority of patients received emergency surgery (12.5%) (Table 3). In addition, 122 of 425 patients showed abdominal symptoms (palliative symptomatic surgery) and in 16.3% (n = 47) surgery was under curative intent. While on unadjusted analysis ileus-prophylactic palliative surgery (n = 82) was associated with a significant survival benefit (147months vs. 99 months for non-operated patients, p = 0.019), after adjustment for confounding variables ileus-prophylactic palliative surgery did no longer translate into an improved overall survival. Unfortunately, this study does not provide detailed information on the 134 patients with stage I-III SINET that were included in the analysis. Furthermore, it does not specify if stage I-III SINET patients are part of the non-resection group.

While some authors argue against ileus-prophylactic palliative surgery, others advocate an early surgical intervention even for asymptomatic patients. Importantly, both the ENETS and NANETS guidelines outline the feasibility of ileus-prophylactic palliative primary tumour resection. In contrast, the current National Comprehensive Cancer Network Guidelines do not recommend the primary tumour resection for asymptomatic patients with stage IV disease even if disease progression occurs. However, NCCN recommend ileus-prophylactic palliative primary surgery for patients with a history of symptoms that might indicate intermitted bowel obstruction [39].

In conclusion, due to major limitations of existing studies actually there is no sufficient evidence in favour of ileus-prophylactic palliative surgery for metastatic SI-NET. But most importantly, there is not a single study that indicates surgery for a symptomatic patient should be postponed. Because the majority of patients are symptomatic at the time of diagnosis, the rationale for an ileus-prophylactic palliative surgery is to operate before progression of mesenteric tumour mass and desmoplasia takes place and before intestinal obstruction and ischaemia occurs [24,33]. (Table 3).

It was suggested that such ileus-prophylactic early surgery would prevent emergency intervention that is related to higher morbidity and mortality [40,41]. The proportion of patients that are surgically treated in an emergency setting is highly heterogeneous between studies and ranges between 12.5 and 45.8% (Table 3). Manguso et al. addressed whether elective, ileus-prophylactic surgery for SI-NET compared to surgery in an emergency setting would improve patient's outcome [42]. While the 5-year survival rate was comparable between groups (ileus-prophylactic group 72.6% vs. emergency surgery group 77.9%, p = 0,71) the analysis showed that during elective surgery 56% more lymph node have been dissected (p = 0.04). Of note, Givi et al. showed that 12% of their patients in the primary non-resected cohort died due to bowel infarction [29]. Similarly, Ahmed et al. reported that bowel obstruction was the cause of death three times more frequent in the primary not resected group (12.7%) compared to 4.7% observed in the primary resected group [43].

Until now, studies on the prognostic significance of palliative surgery for SINET only investigate overall survival as primary endpoint. Recently, it was shown for stage IV pancreatic neuroendocrine tumours (PanNET) that palliative surgery was associated with a significant survival benefit (HR 0.41, p < 0.001) [44]. This might at least in part be due to an improved response to adjuvant therapy. Bertani et al. showed that patients receiving palliative Pan-NET primary tumour resection in advance to peptide radioreceptor therapy (PRRT) showed a significantly improved tumour response or at least stabilization after PRRT [45]. Progression free survival improved from 30 to 70 months. Unfortunately, studies for stage IV SI-NET are missing that address progression free survival or response to additive treatment as primary endpoint in patients having received palliative surgery. Furthermore, despite major difficulties, prospective, randomized trials are yet to be initiated. Reasons for that might be reluctances observed both on surgeon but also patient side. In addition, until now there are no data available on the relief of symptoms or quality of life after palliative surgery. Likely collaborative efforts to implement large, multi-national registries will provide better answers to these important questions.

The debate whether ileus-prophylactic, palliative surgery will procure an overall survival benefit, cannot be settled based on the current level of evidence. Based on the current data the decision for prophylactic surgery must be made on an individual basis [2,11]. In asymptomatic stage IV SI-NET patients the risk and benefit must be carefully balanced. However, in most cases an ileus-prophylactic palliative surgery to avoid intestinal obstruction or ischaemia is hardly preventable.

Conflict of interest

None.

Practice points

- Bowel sparing resection with systematic lymphadenectomy along the superior mesenteric vessels.
- Meticulous abdominal exploration and palpation of the entire small bowel to identify multifocal disease.
- Bypass avoiding surgery whenever possible to prevent re-operation due to bowel ischemia.
- Thoughtful history of intermitted or settle abdominal symptoms indicating bowel obstruction or ischaemia.

Research agenda

- Implementation of prospective multi-institutional registries.
- Studies on the effect of primary tumour resection in stage IV SINET and the response of metastases to additive therapy.
- Prospective randomized trials to assess the effect of ileus-prophylactic, palliative surgery for SINET on progression free survival and quality of life.
- Identification of the mechanism and therapeutic options of desmoplastic reaction/mesenteric fibrosis in SINET

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