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REVIEW ARTICLE

Is Resection of Primary Midgut Neuroendocrine Tumors in Patients with Unresectable Metastatic Liver Disease Justified? A Systematic Review and Meta-Analysis

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Abstract

Introduction Patients with midgut neuroendocrine tumors (MNETs) frequently present with metastatic disease at the time of diagnosis. Although combined resection of the primary MNET and liver metastases (NELM) is usually recommended for appropriate surgical candidates, primary tumor resection (PTR) in the setting of extensive, inoperable metastatic disease remains controversial.

Methods A systematic review was performed according to PRISMA guidelines utilizing Medline (PubMed), Embase, and Cochrane library—Cochrane Central Register of Controlled Trials (CENTRAL) databases until September 30, 2018.

Results Among patients with MNET and NELM, 1226 (68.4%; range, 35.5–85.1% per study) underwent PTR, whereas 567 (31.6%; range, 14.9–64.5%) patients did not. Median follow-up ranged from 55 to 90 months. Cytoreductive liver surgery was performed in approximately 15.7% (range, 0–34.8%) of patients. Pooled 5-year overall survival (OS) among the resected group was approximately 73.1% (range, 57–81%) versus 36.6% (range, 21–46%) for the non-resection group. For patients without liver debulking surgery, PTR remained associated with a decreased risk of death at 5 years compared with patients who did not have the primary tumor resected (HR 0.36, 95% CI 0.16 to 0.79, $p = 0.01$; I^2 58%, $p = 0.12$). For patients undergoing PTR, 30-day postoperative mortality ranged from 1.43 to 2%.

Conclusion PTR was safe with a low peri-operative risk of mortality and was associated with an improved OS for patients with MNET and unresectable NELM. Given the poor quality of evidence, however, strong evidenced-based recommendations cannot be made based on these retrospective single center–derived data. Future well-design randomized controlled trials will be critical in elucidating the optimal treatment strategies for patients with MNET and advanced metastatic disease.

Keywords Carcinoid · Mesenteric mass · Palliative resection · Neuroendocrine liver metastases · Survival · Small bowel resection

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Introduction

Small intestinal neuroendocrine tumors (SI-NETs) are the most common neoplasms of the small bowel and are generally associated with a relatively good prognosis.[1,2] Due to their common embryologic origin, SI-NETs are usually grouped together with neuroendocrine tumors (NETs) of the proximal colon and collectively termed midgut neuroendocrine tumors (MNET).[3] Population data from the most recent Surveillance, Epidemiology, and End Results (SEER) database revealed a steady increase in the incidence of MNET, with an adjusted annual incidence of 1.3/100.000 people in the USA as of 2008.[4]

Some patients with MNET present with an asymptomatic primary tumor and metastatic disease at the time of diagnosis.[3] The liver is the most common site of metastatic disease followed by mesenteric lymph nodes and less frequently bone.[5] In general, surgical resection of metastatic disease, when feasible, is associated with improved long-term overall survival (OS).[6] In addition, debulking of neuroendocrine liver metastases (NELM), generally with a reduction of 70–90% of overall tumor burden, has been associated with improved OS.[7] Among all patients with metastatic MNET who undergo surgical resection, the 5-year OS generally exceeds 70%.[8] As such, the European Neuroendocrine Tumor Society (ENETS) 2016 guidelines recommend combined resection of the primary MNET and liver metastases for appropriate surgical candidates.[9]

In the subset of patients with extensive, inoperable liver metastases, management of the primary MNET has, however, been more controversial.[10] Given the lack of prospective randomized trials, data to guide decision-making on resection of the primary MNET in the setting of advanced metastatic disease remain scarce and have largely been based on case series. While some studies have reported a survival benefit associated with primary tumor resection (PTR), these studies were limited by the retrospective, single-institution design, as well as heterogeneity of the study populations, and small sample sizes.[11] Therefore, the objective of the current systematic review was to summarize and critically evaluate the available evidence on PTR in the setting of inoperable metastatic disease. Specifically, we sought to quantify the impact of PTR on the survival of patients with liver metastases by performing a meta-analysis that pooled data from the multiple previous studies on this topic.

Materials and Methods

Search Sources and Data Sources

A systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[12] A study protocol was agreed upon a priori and followed by all authors. A bibliographical search was performed in Medline (PubMed), Embase, and Cochrane library—Cochrane Central Register of Controlled Trials (CENTRAL). The last search date was September 30, 2018. The following MESH terms were used in combination with Boolean operators (AND, OR, NOT): "neuroendocrine," "carcinoid," "midgut," "small bowel," "jejunum," "duodenum," "ileum," "primary tumor resection," "resecting," "surgery," "liver metastases," and "unresectable liver metastases." Two independent authors (DIT, INS) meticulously searched for potentially eligible articles retrieved by the initial search, and potential disagreements were resolved by consensus with a third reviewer (DM). References of the included studies and from previously published systematic reviews were manually assessed in order to detect any missing study.

Eligibility Criteria

Studies were considered eligible if all of the following criteria were met: (1) data reported on the outcomes of patients with MNET and associated liver metastases, irrespective of the presence or absence of extrahepatic disease, functional status or other medical or ablative treatments, (2) data on OS among patients who underwent PTR versus patients who did not, and (3) population comprised of $\geq$ 50% patients with NELM of midgut origin.

Exclusion criteria included (1) animal studies, (2) studies reporting on patients with NET originating from sites other than midgut, (3) studies reporting on MNET with non-hepatic metastases, (4) reviews and meta-analyses, (5) editorials and letters to the editors, and (6) overlapping studies. In the case of duplicate publications, only the most recent or most informative study for a single center was included in the analyses. There were no study restrictions with regard to language or study sample size. Articles that fulfilled the inclusion criteria were retrieved for full-text evaluation.

Data Extraction and Tabulation

After reviewing the full-texts of eligible studies, two independent authors (DIT, INS) performed the data extraction and crosschecked all results. Potential discrepancies in the selection of articles and the extraction of the data were resolved following consensus with a third reviewer (DM). Extracted variables included general study characteristics (e.g., author, year of publication, institution, years of enrollment, study design, number of patients, follow-up, outcomes studied), patient demographics, and clinical characteristics (e.g., age, gender, as well as number of patients with MNET, NELM, and MNET/NELM combined), treatment characteristics (e.g., number of patients undergoing PTR, debulking of NELM, chemotherapy, transarterial therapies, etc.), as well as long-

term outcomes (e.g., OS, progression-free survival (PFS) and cause of death).

Statistical Analysis

Summary statistics were reported as total and percentage for categorical variables and as median (range) or mean ± standard deviation for continuous variables, unless otherwise indicated. The meta-analysis of survival data was performed with the RevMan software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). Hazard ratio (HR) was used for the assessment of survival. Due to the anticipated study heterogeneity, the random effects model was chosen in all cases. The generic inverse variance method was chosen for survival analysis. Higgin's I^2 statistic was used for the assessment of statistical heterogeneity. Ninety-five percent confidence intervals (CI) were noted for all results. Log HR and its standard error (SE) were calculated based on the equations proposed by Parmar et al.[13] Results were considered statistically significant when the p value was less than 0.05.

Results

Identification of Eligible Studies

The successive steps of article selection process are depicted in Fig. 1. After screening 1031 records, eight studies finally met the predefined criteria and were considered eligible for inclusion in the systematic review.[14–21] Descriptive characteristics of the eligible studies are summarized in Table 1. Five studies originated from Europe and three from the USA. All studies were retrospective; seven were single-center cohorts; and one was a multicenter study incorporating data from five institutions in the UK. Patients were analyzed from 1960 to 2014. Three studies were excluded as obvious overlaps or duplications (Supplemental Table 1).[22–24] One study was excluded on the basis of comparing upfront primary MNET resection versus delayed resection.[22]

Patient Characteristics

Among the included studies, a total of 1607 patients had MNET with NELM comprising 91.2% (range, 64–100%) of the total population (Table 2). In two studies,[20,21] MNETs were mixed with NET from foregut and hindgut, while in another study,[19] 22 patients (29%) did not report the small intestinal location of the primary tumor, but the location of the NET was presumed to be MNET. Only two studies incorporated data exclusively on patients with primary MNET and associated liver metastases.[15,17] One of these studies reported separate results for patients with MNET and liver metastases and, thus, only these data were included in the analysis.[15] Mean patient age ranged from 57.0 to 63.1 years. Overall, there was a slight predominance of men (53.4%; range among studies 43.4–59.2%). All NETs were diagnosed histologically. The prevalence of reported carcinoid syndrome was 58.9% (range, 35–81.5%). The percentage of symptomatic patients undergoing PTR ranged from 63 to 90%.

Overall, 1226 (68.4%; range, 35.5– 85.1% per study) patients underwent PTR, whereas 567 (31.6%; range, 14.9– 64.5%) patients did not (Table 2). Median follow-up ranged from 55 to 90 months. Cytoreductive liver surgery was performed in approximately 15.7% (range, 0–34.8%) of patients. Most studies did not report separate results for patients undergoing liver debulking surgery and PTR versus patients who underwent PTR alone.[14,16–19,21]

Overall and Progression-Free Survival: Systematic Review

A trend toward longer OS was noted among patients who underwent PTR in all studies. Median OS ranged from 75 to 139 months among patients who underwent PTR versus 17 to 88 months for patients who did not undergo PTR. The difference was statistically significant in three studies.[17,20,21] Data on 5-year OS were reported in five studies.[15–17,19,20] Each of these studies noted a higher 5-year OS among patients who underwent PTR. Three studies demonstrated a statistically significant difference in 5-year OS among patients who underwent PTR compared with the non-PTR group.[15,16,20] Pooled 5-year OS among the resected group was approximately 73.1% (range, 57 to 81%) versus 36.6% (range, 21–46%) for the non-resection group.

Only one study reported data on 10-year OS (Table 3).[16] Specifically, Norlen et al. reported that 10-year survival was 51% among patients who underwent PTR versus 6% among patients who did not ($p < 0.001$).[16] In a separate study, Givi et al. reported data for PFS that demonstrated PTR to be associated with a longer PFS versus non-resection of the primary tumor (median PFS, 54 versus 27 months, $p = 0.005$).[20]

Subgroup Analyses on PTR Effect

To determine whether liver cytoreductive surgery may have influenced the outcomes of patients who underwent PTR, a subgroup analysis was performed. Specifically, data were pooled from the two studies that solely included patients who underwent PTR without liver debulking surgery.[15,20] Of note, among these patients, PTR remained associated with a decreased risk of death at 5 years compared with patients who did not have the primary tumor resected (HR 0.36, 95% CI 0.16 to 0.79, $p = 0.01$; I^2 58%, $p = 0.12$) (Fig. 2).[15,20] Specifically in the study by Lewis et al., 5-year OS of patients

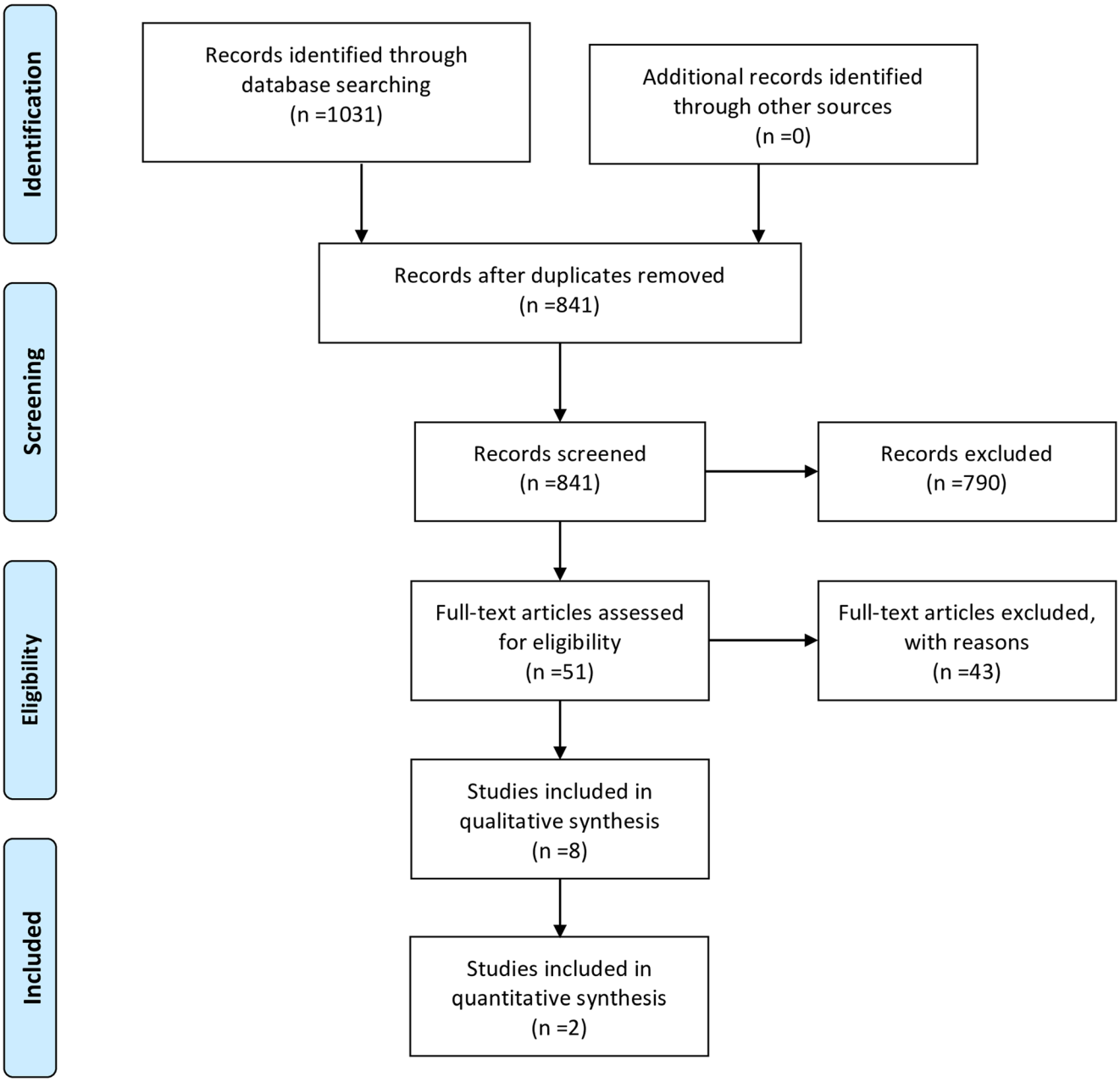

Fig. 1 Flowchart of the search strategy

with untreated liver disease who underwent PTR was higher versus patients who did not undergo primary MNET resection (62.6% versus 26.6%, $p < 0.001$).[15] Of note, the addition of liver treatment mitigated the survival difference among patients who did versus did not undergo PTR (57.2% versus 40.3%, $p = 0.08$).[15]

Two studies reported on the impact of PTR on outcomes based on presence of symptoms attributable to MNET.[14, 20] Givi et al. compared 28 patients with NELM who underwent PTR versus 18 patients who did not and reported a survival benefit among asymptomatic patients who underwent PTR ($p < 0.001$).[20] In contrast, Laskaratos et al. reported that the benefit of PTR was limited to patients who were symptomatic at presentation; in this study, PTR was not associated with an OS benefit among asymptomatic patients (median OS for PTR 12.1 years, 95% CI 9.34 to 14.9 versus no PTR 9.67 years, 95% CI 2.3 to 17.0, $p = 0.25$).[14]

In another study, Norlen et al. reported on patients undergoing PTR with or without concomitant radical metastatic mesenteric lymph node resection.[16] The authors noted that PTR combined with radical lymph node resection of all metastatic mesenteric nodes was associated with increased 5-year (radical lymph node resection; 5-year OS 77%, 95% CI 72 to 82% versus non-radical resection; 5-year OS 63%, 95 CI 56 to

Table 1 Characteristics of eligible studies

PMID	First author (year)	Institution	Years of enrollment	Study design	Inclusion criteria	Total number of patients*	Outcomes studied
29746336	Lewis (2018)	City of Hope National Medical Center, Duarte, CA	2005–2011	RCS	Patients with metastatic GI-NETs at presentation (we included only the patients with small bowel NET and liver metastases)	137**	OS (median, 5-year OS)
17188135	Givi (2006)	Oregon Health & Science University, Portland, OR, USA	1995–2006	RCS	Histologically proven carcinoid and hepatic metastases at the time of diagnosis that were not amenable; to surgical resection and/or radiofrequency ablation therapy	84	OS (median, 5-year OS), PFS, COD
30153671	Laskaratos (2018)	Royal Free London NHS Trust, UK	2000–2014	RCS	Metastatic SI-NETs (stage IV disease) at diagnosis confirmed by histology	387	OS
19174605	Strosberg (2009)	H. Lee Moffitt Cancer Center, Florida, USA	1999–2003	RCS	Metastatic NETs of the mid-gut	146	OS (median)
19458024	Ahmed (2009)	Multicenter UK/Ireland	1973–2007	Multicenter RCS	Metastatic NETs of the mid-gut only to liver	319	OS (median, RR, 5-year OS), COD
1728075	Soreide (1990)	National hospital, Oslo, Norway	1960–1989	RCS	Advanced abdominal carcinoid tumors	75	OS (median), 30-day and 90-day mortality
21984144	Norlen (2012)	Uppsala University Hospital, Sweeden	1985–2010	RCS	Histopathological diagnosis of SI-NET made through microscopy and immunohistochemical staining of either liver biopsy material or surgical specimens	603	OS (HR, 5-year and 10-year OS), 30-day mortality
17825550	Van der Horst-Schrivers (2007)	University Medical Centre Groningen, Netherlands	1992–2003	RCS	Disseminated midgut carcinoid tumors	76	OS (HR, 5-year OS)

RCS retrospective cohort study, *OS* overall survival, *PFS* progression-free survival, *SI-NET* small intestinal neuroendocrine tumor, *GI-NET* gastrointestinal neuroendocrine tumor, *COD* cause of death, *NR* not reported, *SD* standard deviation

*Refers to the whole study population, not necessarily patients with MNET and liver metastases

**We extracted data only for the patients with small bowel NET and liver meta who did not undergo liver debulking surgery

Table 2 Patient characteristics of the included studies

PMID	First author (year)	Pts w/ midgut NET/total pts	Pts w/ NELM/ total pts	Pts w/ NELM of midgut origin/total	Liver meta strictly defined as unresectable	No of pts undergoing liver debulking surgery	Other treatment	No of pts undergoing primary tumor resection (PTR)		Gender (M/F)	Age (years)	Pts w/ carcinoid syndrome
								PTR	no PTR			
29746336	Lewis (2018)	137/137 (100)*	137/137 (100)	137/137 (100)	No	0	NR	111 (81)	26 (19)	NR	NR	NR
17188135	Givi (2006)	76/84 (90.5)**	76/84 (90.5)	76/84 (90.5)	Yes	0	SSA, PTR $n = 56$ (93%) / no PTR $n = 22$ (92%), $p = 1.00$ Systemic chemo, PTR $n = 4$ / no PTR $n = 3$, $p = 0.40$ Interferon PTR $n = 2$ / no PTR $n = 0$, $p = 1.00$	60 (71.4)	24 (28.6)	43M/ 41F	57.9	NR
30153671	Laskaratos (2018)	387/387 (100)	366/387 (94.5)	366/387 (94.5)	No	13 (3.4)	SSA $n = 387$ (100%), interferon $n = 26$ (7%), PRRT $n = 153$ (40%), 131 I-MIBG $n = 37$ (10%), chemo $n = 39$ (10%), TAE $n = 41$ (11%)	173 (44.7)	214 (55.3)	208M/179F	60.3	182 (46.9)
19174605	Strosberg (2009)	146/146 (100)	135/146 (92)	135/146 (92)	No	31 (22)	SSA $n = 126$ (91%), TAE $n = 60$ (45%), systemic chemo $n = 37$ (28%), PRRT $n = 20$ (15%)	100 (69)	46 (31)	65M/81F	60§	119 (81.5)
19458024	Ahmed (2009)	319/319 (100)	319/319 (100)	319/319 (100)	No	50 (15.7)	TAE ($n = 42$), TACE ($n = 14$), PRRT($n = 120$), chemo ($n = 24$)	209 (65.5)	110 (34.5)	189M/130F	61.5§	244 (67.8)
1728075	Soreide (1990)	65/75 (86.7)***	51/75 (68)	48/75 (64)	No	25 (33)	TAE ($n = 12$), cytostatics ($n = 3$), interferon ($n = 25$)	53/65 (82)	12/65 (18)	NR	57	18/52 (35)
21984144	Norlen (2012)	603/603 (100)	465/601 (77.4) †	465/601 (77.4)	No	162/465 (34.8)	SSA ($n = 497$), interferon ($n = 477$), chemo ($n = 29$), PRRT ($n = 42$)	493 (85.1)	86 (14.9)	325M/278F	63.1	355/603 (58.9)
17825550	Van der Horst Schrivers (2007)	76/76 (100%)‡	61/76 (80.2) ‡	61/76 (80.2)	No	NR	SSA $n = 11$ (14.5%), interferon $n = 1$ (1.3%)	27 (35.5)	49 (64.5)	33M/43F	59.4	NR

PTR primary tumor resection, *NET* neuroendocrine tumors, *Pts* patients, *SSA* somatostatin analogues, *NELM* neuroendocrine liver metastases, *PRRT* peptide receptor radionuclide therapy, *chemo* chemotherapy, *TAE* transarterial embolization, *TACE* transarterial chemoembolization;

*We extracted data only for the patients with small bowel NET and liver metastases who did not undergo liver debulking surgery

**2 foregut and 2 hindgut in each of PTR and no PTR groups

***Includes also 7 foregut, 3 hindgut, and 1 unknown primary tumor

†Data for 2 pts. missing

‡22 pts. did not have small intestinal localization of tumor ascertained but presumed as midgut

§Denotes median value; age is presented as mean value unless otherwise indicated

Table 3 Overall and progression-free survival

PMID	First author (year)	Follow-up*** (months)	Liver debulking patients excluded?	Number of patients		OS (HR/ RR): PTR versus no PTR	Median OS (months)		5-year OS		10-year OS		Median PFS (months)	
				PTR	No PTR		PTR	No PTR	PTR	No PTR	PTR	No PTR	PTR	No PTR
29746336	Lewis (2018)	NR	Yes*	111 (81)	26 (19)	NR	NR	17	62.6%	26.6% ($p < 0.001$)	NR	NR	NR	NR
17188135	Givi (2006)	90	Yes**	60 (71.4)	24 (28.6)	NR	108****	50 ($p < 0.001$)	81%	21% ($p < 0.001$)	NR	NR	54****	27 ($p = 0.005$)
30153671	Laskaratos (2018)	62.9	No	173 (44.7)	214 (55.3)	HR = 0.51, (95% CI 0.37, 0.70), $p < 0.001$	NR	NR	NR	NR	NR	NR	NR	NR
19174605	Strosberg (2009)	NR	No	100 (69)	46 (31)	NR	110	88 ($p = 0.32$)	NR	NR	NR	NR	NR	NR
19458024	Ahmed (2009)	Mean 63.5	No	209 (65.5)	110 (34.5)	RR = 0.26 (95% CI 0.092–0.777), $p = 0.015$	119	57 ($p < 0.001$)	74%	46%	NR	NR	NR	NR
1728075	Soreide (1990)	NR	No	53/65 (82)	12/65 (18)	NR	139	69 ($p = 0.03$)	NR	NR	NR	NR	NR	NR
21984144	Norlen (2012)	Mean ± SD 82.8 ± 62.4	No	493 (82.8)	86 (14.3)	HR = 0.46 (95% CI 0.33–0.65), $p < 0.001$	NR	NR	75%	28% ($p < 0.001$)	51%	6% ($p < 0.001$)	NR	NR
17825550	Van der Horst Schrivers (2007)	55	No	27 (35.5)	49 (64.5)	HR = 0.58 (95% CI 0.306–1.104), $p = 0.097$	75	52	57%	44%	NR	NR	NR	NR

PTR primary tumor resected, *OS* overall survival, *PFS* progression-free survival, *HR* hazard ratio, *RR* relative risk, *NR* not reported, *CI* confidence interval

*We extracted data only for the patients with small bowel NET and liver metastases who did not undergo liver debulking surgery

**Did not include liver debulking

***Presented as median (range) unless otherwise specified

****Patients who had unsuccessful attempts at primary tumor resection were included in the primary resected group

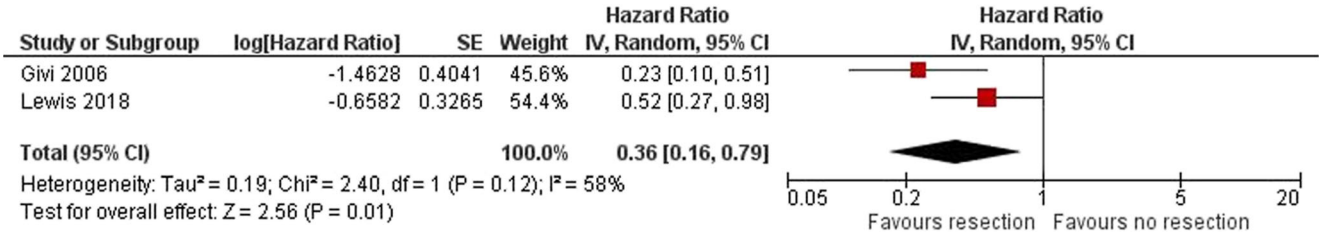

Fig. 2 Five-year overall survival of patients with neuroendocrine liver metastases of midgut origin who did or did not undergo primary tumor resection (PTR) without liver debulking surgery. PTR remained associated with a decreased risk of death at 5 years compared with patients who did not have the primary tumor resected (HR 0.36, 95% CI 0.16 to 0.79, $p = 0.01$; I^2 58%, $p = 0.12$)

71%, $p = 0.001$) and 10-year (radical resection; 10-year OS 52%, 95% CI 46 to 59% versus non-radical resection; 10-year OS 38%, 95% CI 31 to 48%, $p = 0.001$) OS versus PTR among patients who had persistent residual mesenteric lymph nodes.[16]

Cause of Death and Early Mortality

Data on cause of death and 30-day mortality were provided in four studies (Table 4).[16,17,20,21] None of these studies noted a difference in symptom improvement among patients who did and did not undergo PTR. In one study, bowel obstruction was noted in 12.5% of patients undergoing PTR versus 0% in patients without PTR; 12% of patients with no PTR suffered from bowel infarction versus 0% in the PTR group.[20] On the other hand, Ahmed et al. reported an incidence of small bowel obstruction–related cachexia of 4.8% among patients with PTR versus 12.7% in patients with no PTR.[17] Regarding concomitant liver resection, Givi et al. reported roughly the same incidence of liver failure among patients who did versus did not undergo PTR (75% and 82%, respectively).[20] Finally, 30-day postoperative mortality ranged from 1.43 to 2%.[16,17,21] While overall postoperative mortality was comparable among patients who had concomitant PTR and liver resection, one study suggested an increased risk of postoperative mortality when resection of the primary tumor was undertaken as a second operation.[16]

Discussion

Current guidelines from both the ENETS and the North American Neuroendocrine Tumor Society (NANETS) support the resection of well-differentiated SI-NET even in the presence of advanced disease.[9,25] Aggressive surgical approaches are generally accepted for SI-NET when both the primary and metastatic diseases can be completely extirpated or when the metastatic disease can be

Table 4 Causes of death and early mortality rates

PMID	First author (year)	Cause of death/early mortality rates	
		PTR	No PTR
29746336	Lewis (2018)	NR	NR
17188135	Givi (2006)	Liver failure 12 (75), bowel obstruction 2 (12.5), bowel infarction 0, other 2 (12.5), unknown 0	Liver failure 14 (82), bowel obstruction 0, bowel infarction 2 (12), other 0, unknown 1 (6)
30153,671	Laskaratos (2018)	NR	NR
19174605	Strosberg (2009)	NR	NR
19458024	Ahmed (2009)	30-day mortality 3 (1.43%), small bowel obstruction–related cachexia 10 (4.78%)	Small bowel obstruction–related cachexia 14 (12.72%)
1728075	Soreide (1990)	30-day postoperative mortality rate: 1/65 (2%), 90-day mortality rate 6/65 (9%)	Postoperative mortality rate 0%
21984144	Norlen (2012)	Overall surgery-related 30-day mortality 1.6%, 30-day mortality after first primary resection 0.5%, 30-day mortality after second primary resection 2%	Overall surgery-related 30-day mortality 0%, 30-day mortality after first primary resection 0%, 30-day mortality after second primary resection 0%
17825550	Van der Horst Schrivers (2007)	NR	NR

PTR primary tumor resected, *NR* not reported

heavily debulked.[6,26] Resection of the primary MNET in patients who clearly have unresectable/inoperable metastatic disease remains, however, controversial. The proposed rationale behind resection of primary MNET in this setting is to relieve symptoms caused by the primary tumor, prevent the future possibility of small bowel obstruction, histologically confirm the diagnosis, and potentially improve OS. Whether resection of primary MNET in patients with unresectable metastases offers a survival benefit is likely the most debated potential "benefit" of PTR. The current study was important since we performed a comprehensive systematic review of the data reported to date on patients undergoing PTR in the setting of extensive metastatic disease. Collectively, the data suggested that PTR was associated with an improved OS compared with patients who did not have PTR. Specifically, among the studies included in the systematic review, the difference in OS among patients who did and did not undergo PTR was statistically significant in six out of eight reports. In addition, pooled 5-year OS was roughly 73.1% in the PTR group versus 36.6% in the no PTR group. While the data suggested a benefit of PTR, the quality of data was poor as seven studies were single-institution case series, as well as all studies were retrospective in design and therefore selection bias and confounding by indication were likely. As such, possibly associated with a survival benefit, PTR cannot be considered standard of care for patients with MNET and unresectable metastatic disease as the level of evidence on the topic was poor.

The decision to remove an asymptomatic, incidentally discovered MNET in the setting of unresectable metastatic disease can be challenging. Not infrequently, patients will desire that the primary MNET be removed as they believe that the tumor will lead to progression of their disease and ongoing metastases. Interestingly, Laskaratos et al. noted that the survival benefit of PTR was limited to symptomatic patients, whereas patients diagnosed incidentally did not benefit from PTR.[14] These findings were consistent with a different study by Daskalakis et al. that noted no difference in overall- or cancer-specific survival comparing asymptomatic patients with stage IV SI-NET who underwent prophylactic upfront (within 6 months of diagnosis) locoregional surgery versus no/delayed surgery.[22] In contrast, Givi and colleagues reported a survival benefit among patients with asymptomatic MNET; however, the small number of patients in the study made the data difficult to interpret and problematic to generalize.[20] Despite no clear explanation as to whether PTR offers a survival benefit, a benefit has been postulated to be related to the reduction in disease burden.[20] Of note, the latest ENETS guidelines recommend palliative resection of the primary tumor and, if possible, mesenteric lymph node metastases in the setting of stage IV disease only for symptomatic patients with intestinal obstruction, ischemia, or tumor bleeding.[9,27] In addition, these recommendations suggest a multi-disciplinary discussion with careful consideration of patient performance status and comorbidities for asymptomatic patients rather than routine PTR.[9,27]

PTR in the setting of advanced unresectable metastatic disease was safe being associated with low morbidity and mortality. In particular, among the 1607 patients who had MNET with metastatic disease and underwent PTR, 30-day postoperative mortality was low ranging from only 1.4 to 2%.[16,17,21] Interestingly, Daskalakis et al. reported no difference in 30-day mortality among patients who underwent pre-emptive prophylactic PTR for asymptomatic disease versus patients who had surgery once the MNET became symptomatic; however, the former group did require more urgent operations due to intestinal obstruction than the latter group.[22] As such, while the perioperative mortality associated with PTR appeared acceptable, the decision to perform PTR, especially in asymptomatic patients with unresectable metastatic disease, still should be made on an individual basis in the setting of a multi-disciplinary evaluation.

While the current study summarized the data on PRT in a systematic manner and highlighted the current state of evidence of PRT, the relative quality of the data in the literature was poor. Most studies were retrospective and therefore were subject to significant selection bias. In addition, most series consisted only of surgical patients and it was not clear if data from non-surgical patients were adequately and completely captured to serve as the appropriate comparator. The lack of randomized controlled trials, therefore, hindered a truly evidence-based recommendation to the treatment of patients with stage IV MNETs. To our knowledge, only one trial is currently registered on Clinicaltrials.gov (NCT03442959) that is accruing patients to examine the specific issue of PTR in the setting of unresectable metastatic disease. This study is a prospective observational trial that is enrolling asymptomatic patients with SI-NET and unresectable liver metastases to compare patients with or without PTR relative to the 5-year OS as the primary outcome. Strengths of this trial include (1) homogeneous group of patients with only SI-NET, (2) a clear definition of unresectability for NELM, (3) detailed history of symptoms at presentation and previous treatments (e.g., chemotherapy, radiotherapy, somatostatin analogues), and (4) rigorous follow-up for at least 5 years after PTR. This trial will hopefully provide a better assessment of the true effect of PTR on long-term prognosis.

The current study had several limitations. Several included studies did not provide information on the extent of metastatic disease at the time of PTR or information on why the disease was necessarily unresectable.[16–19,21] Decisions on resectability can be subjective and vary from provider to provider, and

most studies did not define what factors constituted true inoperable disease. In addition, there was variation in the extent of surgery performed. In the majority of studies, palliative resection of the SI-NET included resection of the primary tumor plus extensive mesenteric dissection. However, only the Norlen et al. study performed a subgroup analysis comparing patients undergoing PTR with or without radical mesenteric lymph node resection.[16] In addition, most studies did not separate the results of patients undergoing PTR alone versus patients who underwent PTR combined with liver debulking surgery.[14,16–19,21] The role of other liver-directed therapies, such as transarterial embolization, systemic chemotherapy, somatostatin analogues, and peptide receptor radiotherapy was also implemented in different proportions of patients with metastatic MNETs and may have impacted the outcomes.[14,16–21]

Conclusion

Data from this systematic review and meta-analysis suggested that PTR was safe with a low peri-operative risk of mortality and was associated with an improved OS for patients with MNET and unresectable NELM. The quality of evidence was poor, however, and strong evidenced-based recommendations cannot be made based on these retrospective data, which were largely derived from single-institution case series. Until prospective randomized controlled trial data are available, the decision to perform resection of the primary MNET in the setting of unresectable metastatic disease needs to be made on an individualized basis as part of a multi-disciplinary evaluation. Future well-design randomized controlled trials will be critical in elucidating the optimal treatment strategies for patients with MNET and advanced metastatic disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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References

1. Hauso O, Gustafsson BI, Kidd M, et al. Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* 2008; **113**(10): 2655–64.
2. Moris D, Ntanasis-Stathopoulos I, Tsilimigras DI, et al. Update on Surgical Management of Small Bowel Neuroendocrine Tumors. *Anticancer Res* 2018; **38**(3): 1267–78.
3. Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; **17**(4): 909–18.
4. Wu L, Fu J, Wan L, et al. Survival outcomes and surgical intervention of small intestinal neuroendocrine tumors: a population based retrospective study. *Oncotarget* 2017; **8**(3): 4935–47.
5. Van Loon K, Zhang L, Keiser J, et al. Bone metastases and skeletal-related events from neuroendocrine tumors. *Endocr Connect* 2015; **4**(1): 9–17.
6. Ejaz A, Reames BN, Maithel S, et al. Cytoreductive debulking surgery among patients with neuroendocrine liver metastasis: a multi-institutional analysis. *HPB (Oxford)* 2018; **20**(3): 277–84.
7. Hodul P, Malafa M, Choi J, Kvols L. The role of cytoreductive hepatic surgery as an adjunct to the management of metastatic neuroendocrine carcinomas. *Cancer Control* 2006; **13**(1): 61–71.
8. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* 2011; **117**(15): 3332–41.
9. O'Toole D, Kianmanesh R, Caplin M. ENETS 2016 Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: An Update. *Neuroendocrinology* 2016; **103**(2): 117–8.
10. Akerstrom G, Hellman P, Hessman O, Osmak L. Management of midgut carcinoids. *J Surg Oncol* 2005; **89**(3): 161–9.
11. 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): 1480–6.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**(10): 1006–12.
13. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; **17**(24): 2815–34.
14. Laskaratos FM, Walker M, Wilkins D, et al. Evaluation of clinical prognostic factors and further delineation of the effect of mesenteric fibrosis on survival in advanced midgut neuroendocrine tumours. *Neuroendocrinology* 2018;**107**(3): 292–304
15. Lewis A, Raoof M, Ituarte PHG, et al. Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival with or without Liver Treatment. *Ann Surg* 2018
16. Norlen O, Stalberg P, Oberg K, et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 2012; **36**(6): 1419–31.
17. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer* 2009; **16**(3): 885–94.
18. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 2009; **89**(4): 471–6.
19. van der Horst-Schrivers AN, Post WJ, Kema IP, 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): 2651–7.
20. 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 7-8.
21. Soreide O, Berstad T, Bakka A, et al. Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. *Surgery* 1992; **111**(1): 48–54.
22. Daskalakis K, Karakatsanis A, Hessman O, et al. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**(2): 183–9.

23. Srirajaskanthan R, Ahmed A, Prachialias A, et al. ENETS TNM Staging Predicts Prognosis in Small Bowel Neuroendocrine Tumours. *ISRN Oncol* 2013; **2013**: 420795.
24. Hellman P, Lundstrom T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg* 2002; **26**(8): 991–7.
25. Howe JR, Cardona K, Fraker DL, et al. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 2017; **46**(6): 715–31.
26. Xiang JX, Zhang XF, Beal EW, et al. Hepatic Resection for Non-functional Neuroendocrine Liver Metastasis: Does the Presence of Unresected Primary Tumor or Extrahepatic Metastatic Disease Matter? *Ann Surg Oncol* 2018
27. Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. *Neuroendocrinology* 2016; **103**(2): 125–38.