Systematic review

Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases

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Background: Surgery for small intestinal neuroendocrine tumours (SI-NETs) is limited by metastatic disease in most patients. However, resection of the primary lesion alone has been advocated in patients with unresectable liver metastases. The present systematic review investigated the value of surgical resection of the primary lesion in patients with unresectable metastatic disease.

Methods: MEDLINE was searched for studies reporting the outcome of patients with SI-NETs and unresectable liver metastases where there was an explicit comparison between resection of the primary lesion alone and no resection. The primary outcome was overall survival. Secondary outcomes were progression-free survival, treatment-related mortality and relief of symptoms.

Results: Meta-analysis was not possible, but six studies were analysed qualitatively to highlight useful information. Possible confounders in these studies were the inclusion of patients with other primary tumour sites, unknown primary tumour or non-metastatic disease. Bearing in mind these limitations, there was a clear trend towards longer survival in patients who underwent surgical resection in all studies; their median overall survival ranged from 75 to 139 months compared with 50–88 months in patients who did not have resection. The difference between the two groups was statistically significant in three studies. Data on symptomatic improvement were scarce and did not suggest a clear benefit of surgery. Surgery-related mortality seemed low.

Conclusion: Available data suggest a possible benefit of resection of the primary lesion in patients with unresectable liver metastases, but the studies have several limitations and the results should therefore be considered with caution.

Paper accepted 8 May 2012

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.8842

Introduction

Small intestinal neuroendocrine tumours (SI-NETs) are one of the most common forms of neuroendocrine neoplasm. The incidence and prevalence of neuroendocrine neoplasms have increased substantially in recent decades[1–4]. Tumours originating from the small bowel are often grouped together with those originating from the proximal colon, and termed 'midgut' carcinoids.

SI-NETs are considered indolent tumours with a relatively good prognosis. However, most patients present with distant metastases at the time of diagnosis; this limits the possibility of radical surgery, which is the only curative therapeutic approach[5]. Nevertheless, as the 5-year survival rate of patients with metastatic SI-NETs exceeds 60 per cent[6,7], surgical therapy in the setting of metastatic disease has been promoted[8], especially when radical resection of both the primary tumour and liver metastases is achievable[5]. However, extrahepatic metastases are present at diagnosis in 25 per cent of patients[6]. Cytoreductive surgery, also termed debulking, which involves the greatest possible reduction of tumour mass in the context of persistent metastases[8,9], is generally carried out when it is possible to remove 70–90 per cent of the disease.

In patients who are suitable neither for radical resection nor for debulking owing to extensive metastatic burden, surgical resection of the primary intestinal lesion alone has been advocated by some authors[10–12]. This approach may include either simple segmental resection to remove

the primary tumour, or a more extensive resection of the mesentery, with lymph node metastases. The rationale of such an approach resides in the potential to provide relief from hormonal and local tumour-related symptoms; to limit disease to the liver, improving the efficacy of further treatment by decreasing the overall tumour burden; and to increase survival. Although this approach is considered a standard procedure by most experts and guidelines, data in support of this are scarce, heterogeneous and difficult to evaluate. A systematic review was therefore designed to evaluate surgical resection of the primary intestinal lesion alone in patients with SI-NETs and unresectable liver metastases.

Methods

Search strategy

A computerized literature search of MEDLINE and the Cochrane database of systematic reviews for a previous systematic review of the selected topic revealed no published papers. MEDLINE was searched until November 2011 using the specific search terms as detailed in *Appendix S1* (supporting information). The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13].

To identify additional studies, the references of all the identified papers were reviewed for further relevant articles. The titles of all identified articles were screened to ascertain their relevance. Abstracts and/or full texts of selected potentially relevant papers were further evaluated.

Criteria for considering studies for the review

Studies reporting the outcome of patients with SI-NETs and liver metastases deemed not radically resectable, irrespective of the presence or absence of extrahepatic disease, tumour grade or functional status, were considered. Studies were included regardless of study type, language, publication status or sample size. Randomized controlled trials (RCTs), quasi-RCTS and non-RCTs were considered for analysis. However, given the likely paucity of high-quality data on the topic, prospective and retrospective cohort studies were also considered for the review. These studies were included whenever there was an explicit comparison between resection of the primary lesion alone in the presence of unresectable liver metastases *versus* no resection of the primary lesion. Other medical or ablative treatments were permitted. Case–control studies and case reports or case series were not included. In the event of duplicate publications, the most recent or more complete publication was used.

Two independent reviewers carried out study identification and selection, and disagreements were discussed with a third reviewer. Excluded studies and reasons for exclusion were recorded.

Outcome measures

The primary outcome evaluated was overall survival, expressed as the proportion of patients alive 1, 3, 5 or 10 years after the intervention, and/or as median survival of the group. Secondary outcomes were progression-free survival (PFS), defined as the interval between primary treatment and disease progression, for example an increase in the number or size of lesions, as determined by imaging studies. Treatment-related mortality and morbidity, and symptomatic relief were also evaluated. Finally, if feasible, potential factors associated with outcome such as hepatic tumour burden, resection of lymph nodes, histological grade (assessed by Ki-67 index), chromogranin A or 5-hydroxyindoleacetic acid (5-HIAA) values, the presence of carcinoid heart disease or other tumour features were evaluated.

Data extraction

The following data were collected: study design, location and year of publication; number of patients, accrual period and method of diagnosis; type of surgery; co-variables – sex, age, histology, biochemical markers and carcinoid heart disease; duration of follow-up; overall survival and PFS; relief of symptoms; and treatment-related mortality and morbidity.

Statistical analysis

A meta-analysis of any RCTs identified was planned using the software package MedCalc (MedCalc Software, Mariakerke, Belgium) with the following methods: calculation of the relative risk with 95 per cent confidence interval for dichotomous variables, calculation of the mean difference for continuous variables, use of a random-effects model, evaluation of heterogeneity by χ^2 test, and measure of the quantity of heterogeneity by means of the I^2 value[14–16].

Results

A total of 2399 references were identified by the MEDLINE search (*Fig. 1*). Five other potentially interesting

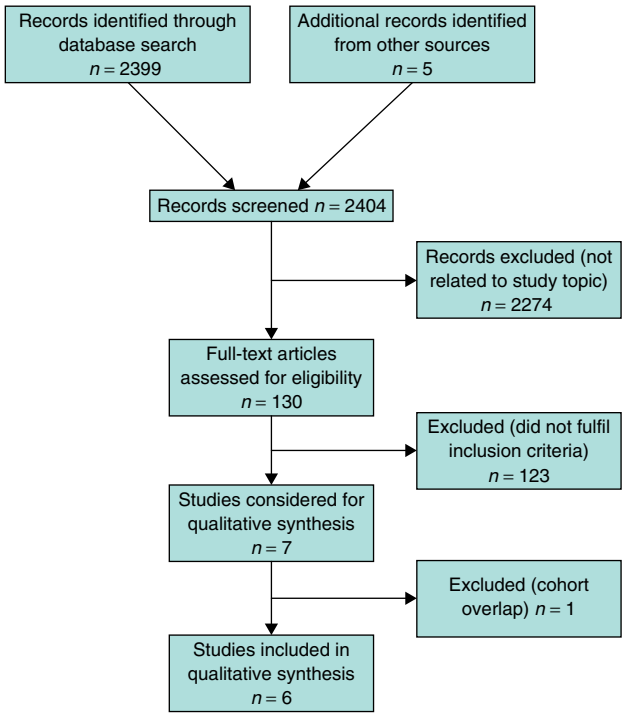

Fig. 1 PRISMA diagram showing selection of articles for review

studies were found by searching references. After evaluation, 2274 studies were excluded as they were not related to the study topic. Of 130 studies examined in more detail, seven were potentially appropriate for inclusion in the review[17–23]. However, one of these[17] investigated a population that was included in a larger cohort reported in a more recent paper[22] and was therefore excluded. Finally, six studies remained for analysis (*Table 1*)[18–23]. None of these studies met all the inclusion criteria (*Table S1*, supporting information). Nonetheless they were all analysed qualitatively for useful information, although no meta-analysis could be performed.

Study characteristics and reason for exclusion from quantitative analysis

Table 1 shows the descriptive characteristics of the six studies. All were retrospective cohort studies. Three reports provided little or no information on age or sex[18,21,23] and two did not specify the length of follow-up[19,21]. Few studies reported tumour features such as Ki-67 index, basal levels of chromogranin A or 5-HIAA, and carcinoid heart disease as co-variables for outcome.

All studies reported the outcome of patients with SI-NETs, but in two studies data regarding the outcomes of interest for patients with SI-NETs were not presented separately from those of patients with neuroendocrine neoplasms originating from other primary sites (*Table S1*, supporting information)[18,21]. Some studies also included patients in whom the primary lesion was unknown[19,20,23]. One of the studies corrected for this to overcome possible bias[20].

The six studies included 971 (range 48–366) patients with SI-NETS and liver metastases (*Table 2*). The

Table 1 Summary of the six studies considered for the review

Reference	Year	Country	Study accrual period	Setting and design	Proportion of patients with SI-NETs*	Male sex (%)	Age (years)†	Treatment(s) compared	Outcome
Givi *et al.*[18]	2006	Oregon, USA	1995–2006	Single RCS	76 of 84 (90)	51	NR	Resected *versus* unresected	PFS, median OS, 5-year survival
Strosberg *et al.*[19]	2009	Florida, USA	1999–2003	Single RCS	146 of 146 (100)	44·6	60 (14–84)	Resected *versus* unresected	Median OS, 5-year survival
Ahmed *et al.*[20]	2009	UK	1973–2007	Multicentre RCS	319 of 360 (88·6)	52·5	61·5 (16–86)	Resected *versus* unresected	Median OS, 5-year survival
Søreide *et al.*[21]	1992	Norway	1960–1989	Single RCS	65 of 75 (87)	NR	61 (18–80)	Resected *versus* unresected and resection *versus* no resection of metastases	Median OS
Norlén *et al.*[22]	2012	Sweden	1985–2010	Single RCS	603 of 603 (100)	53·9	63·1(11·3)‡	Resected *versus* unresected	5-year survival
van der Horst-Schrivers *et al.*[23]	2007	The Netherlands	1992–2003	Single RCS	47 of 76 (62)	NR	59·4‡	Resected *versus* unresected	Median OS, 5-year survival

*Values in parentheses are percentages. †Values are median (range) unless indicated otherwise; ‡values are mean(s.d.). SI-NET, small intestinal neuroendocrine tumour; RCS, retrospective cohort study; PFS, progression-free survival; OS, overall survival; NR, not reported.

Table 2 Characteristics of patients in the six studies included in the qualitative synthesis

Reference	Patients with SI-NETs and liver metastases	Patients with carcinoid syndrome	Method of diagnosis	Ki-67 index analysed	Resected primary SI-NETs	Unresected primary SI-NETs	Length of follow-up
Givi *et al.*[18]	76 of 76 (100)	29 of 84 (35)	Histology	No	56 of 76 (74)	20 of 76 (26)	Median 90 months
Strosberg *et al.*[19]	135 of 146 (92·5)	119 of 146 (81·5)	NR	No	100 of 135 (74·1)	35 of 135 (25·9)	NR
Ahmed *et al.*[20]	285 of 319 (89·3)	244 of 294 (83·0)	Histology	Yes	209 of 319 (65·5)	76 of 319 (23·8)	Mean 5·29 years
Søreide *et al.*[21]	48 of 65 (74)	18 of 52 (35)	Histology	No	53 of 65 (82)	12 of 65 (18)	NR
Norlén *et al.*[22]	366 of 601 (60·9)*	355 of 603 (58·9)	Histology	No	493 of 603 (81·8)	86 of 603 (14·3)	Mean(s.d.) 6·9(5·2) years
van der Horst-Schrivers *et al.*[23]	61 of 76† (80)	NR	Clinical charts (including histology)	No	27 of 76 (36)	49 of 76 (64)	Median 55 months

Values in parentheses are percentages. *Data not available for two patients. †Twenty-nine of these patients did not have small intestinal localization of tumour ascertained. SI-NET, small intestinal neuroendocrine tumour; NR, not reported.

Table 3 Survival and symptomatic improvement in patients who had resection of the primary tumour and those who did not in six studies included in the qualitative synthesis

Reference	No. of patients	Median overall survival (months)	5-year survival (%)	Median progression-free survival (months)
Givi *et al.*[18]*	Resected 66	108	81	54
	Unresected 18	50	21	27
Strosberg *et al.*[19]	Resected 100	110	NR	NR
	Unresected 35	88	NR	NR
Ahmed *et al.*[20]	Resected 209	119 (89, 149)	74	NR
	Unresected 76	57 (32, 81)	46	NR
Søreide *et al.*[21]	Resected 53	139	NR	NR
	Unresected 12	69	NR	NR
Norlén *et al.*[22]	Resected 493	NR	75	NR
	Unresected 86	NR	28	NR
Van der Horst-Schrivers *et al.*[23]	Resected 27	75 (44, 107)	57	NR
	Unresected 49	52 (37, 68)	44	NR

Values in parentheses are 95 per cent confidence intervals. *Patients who had unsuccessful attempts at primary tumour resection were included in the primary resected group. NR, not reported.

number of patients who underwent resection was 938 (range 27–493). However, five of the studies[19–23] also included patients without liver metastases at the time of surgery (*Table S1*, supporting information). In one study, 12 per cent of the patients undergoing resection of the primary tumour did not present with metastases at the time of surgery, but developed hepatic metastases during follow-up[19]. In another, it was not clearly stated whether all patients who underwent primary tumour resection had metastatic disease. The number of patients who had resection of the primary tumour in the presence of metastatic liver disease was not clearly indicated in the remaining studies[21–23]. In most of these series, a significant portion of patients underwent liver resection as tumour debulking, but the outcome of these patients could not be separated from that of patients who had resection of the primary tumour alone[19–22].

Survival data for patients not undergoing resection of the primary tumour also included patients who underwent exploration and/or bypass surgery without resection in two studies[20,22], whereas in another study this information was taken into account[18]. Most of the studies did not specify whether lymph node clearance was performed or not[18–21,23].

Survival analysis

Overall survival data were not provided for the two patient groups in one study[22], and were expressed as median overall survival in the remainder (*Table 3*). There was a trend towards longer overall survival in patients who had resection of the primary tumour in all of the studies;

the median ranged from 50 to 88 months in patients without resection compared with 75–139 months in those who underwent resection. The difference was statistically significant in three studies[18,20,21].

The 5-year survival rate for the two groups was provided in four studies, with a difference in favour of primary tumour resection in two studies[18,22] and no difference in one[23]. The pooled 5-year survival rate was approximately 74 per cent in patients who had primary tumour resection and 36 per cent in those who did not.

In one investigation, the survival data were corrected for patients who had unresectable primary neoplasms[18]. One study reported that macroscopically radical resection of metastatic mesenteric lymph nodes together with the primary lesion was associated with increased survival compared with no lymph node clearance[22].

Secondary outcomes

PFS was available in only one study[18], where a difference between the two groups was reported. None of the studies presented a clear and specific comparison regarding symptomatic improvement between patients with and without resection. However, in one investigation, 4·7 per cent of patients who had resection of the primary lesion and 13 per cent of those who did not died from small bowel obstruction-related cachexia[20]. On the other hand, in one study, 12 per cent of patients who had primary tumour resection suffered from bowel obstruction *versus* none with unresected primary tumours[18]. However, in this study 12 per cent of patients without resection had bowel infarction, compared with none in the resected group.

Treatment-related mortality and morbidity rates of 0·5 and 7·8 per cent were reported by Norlén and colleagues[22]. In another study the 30- and 90-day mortality rates after the first operation for SI-NETs were 2 and 9 per cent respectively, with a complication rate of 14 per cent[21]. Ahmed and co-workers[20] reported that 1 per cent of patients died within 30 days of surgery.

Discussion

Published recommendations from both the European Neuroendocrine Tumour Society (ENETS)[5] and North American Neuroendocrine Tumour Society[24] include removal of the primary intestinal tumour alone, even in patients with unresectable liver metastases. The ENETS guidelines specify that 'resection of the small intestinal primary tumour should be attempted because overall outcome is better in patients after primary tumour resection although a direct causal relationship has not been proven to date'[5]. These recommendations are based on two hypotheses: that surgical resection of the primary lesion is associated with better survival, even in the setting of unresectable liver disease; and that resection of the primary intestinal lesion can prevent intestinal obstruction or ischaemic complications. The findings of the present systematic review only partially support this view.

There were no RCTs or quasi-RCTs available for inclusion in the review. The retrospective cohort studies identified could be analysed only qualitatively as they did not meet the inclusion criteria for a meta-analysis. Some studies included patients with other primary tumour sites and/or unknown primary lesions, patients without metastatic disease, or did not present sufficient data to analyse the role of resection of the primary intestinal lesion in the presence of unresectable liver metastases. Nevertheless, the findings from six studies were summarized qualitatively[18–23].

Overall survival seemed longer in patients who had the primary tumour resected. However, a bias towards resection in patients with a better performance status, less advanced disease or less aggressive tumour biology seems likely. In one study, patients who underwent resection of the primary lesion had a lower median Ki-67 index than those who did not, although the survival advantage for patients with resected primary tumour was maintained in the multivariable analysis[20]. The other analysed studies did not report data on Ki-67, or did not adjust the results for this variable. Similarly, the association between surgical strategy and factors likely to affect the prognosis, such as the presence of carcinoid heart disease or the level of biomarkers, was generally not reported or discussed.

Pooling data from patients with NETs originating from other primary sites together with those of SI-NETs may have influenced the results as foregut and hindgut NETs are known to show different biological behaviours[24]. Moreover, some studies included patients in whom the primary lesion was 'unknown'[19,20,23]. Another confounding factor is the inclusion of patients without liver metastases at the time of surgery in five studies[19–23]. Finally, data from patients who underwent resection of the primary tumour alone were often not separated from those relating to patients who also had liver resection[19–22], and in most studies clearance of the metastatic mesenteric lymph nodes was not considered as a possible co-variable influencing the outcome. However, Norlén and colleagues[22] showed increased survival for patients who had lymph node dissection. The possibility that survival benefit was due to resection of metastatic lymph nodes cannot thus be excluded. Therefore, the clinical relevance of the survival advantage reported for patients who had

resection of the primary tumour should be considered with caution.

Data regarding symptomatic improvement are scarce and controversial. This is particularly relevant considering that a proportion of patients had the primary tumour resected as an emergency owing to intestinal obstruction[22]. Therapeutic choices in these series were often dictated by the clinical presentation, and it is doubtful whether the data could be used to justify elective procedures in asymptomatic patients. Several other treatments, including somatostatin analogues[25] and peptide receptor radiotherapy[26], are effective in patients with metastatic SI-NETs. Surgery should be considered as only one of the treatment options. However, the reported data suggest low mortality and morbidity rates after operation, which favours a more aggressive surgical approach for metastatic SI-NETs than for metastatic pancreatic endocrine tumours[27].

The paucity of available data and the heterogeneity of series are a major problem limiting the possibility of an evidence-based approach to the treatment of neuroendocrine neoplasms. However, systematic reviews such as this may prove useful because, by gathering fragmented and often heterogeneous data, it is possible to underline areas where therapeutic choices are driven by expert opinion and not by solid evidence.

Randomized trials are necessary to assess whether prognosis is truly enhanced by prophylactic resection of the primary tumour in asymptomatic patients with SI-NETs. The pooled 5-year survival rate in the present review was approximately 74 per cent in patients who had the primary tumour resected compared with 36 per cent in those who did not. A randomized trial with an α error of 0·05 and a β error of 0·10 would need to enrol at least 31 patients per group but, given the possible confounders in the analysed studies, these numbers might be an underestimation.

In the absence of other data, resection of the primary tumour for patients with SI-NETs and unresectable liver metastases should follow strict selection criteria apart from those dictated by the need to resolve life-threatening symptoms.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search strategy (Word document)

Table S1 Reasons for exclusion of studies from the quantitative analysis (Word document)

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Commentary

Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases (*Br J Surg* 2012; 99: 1480–1486)

The role of resection of small intestinal neuroendocrine tumours (NETs) in the presence of unresectable liver metastases is subject to ongoing controversial debate. Based on a systematic review, this article from Capurso and colleagues concludes that, although there is a lack of firm evidence-based results, resection of the primary tumour might be beneficial for patients in this situation. The incidence of jejunal/ileal NETs is increasing[1]. Depending on the grade of tumour differentiation, synchronous liver metastases are present in up to 60 per cent of patients at the initial diagnosis[1,2]. Tumour differentiation, disease stage and extent of liver involvement have been recognized as significant factors for survival[2,3].

These observations underline the clinical relevance of the topic of this review; at the same time, however, the results imply that not only resection of the primary tumour but also treatment of the metastatic disease need to be considered. In past analyses, 5-year overall survival rates of less than 30 per cent have been reported in patients with neuroendocrine liver metastases without liver resection. Nowadays, in contrast, a broad panel of novel, targeted, systemic, locally ablative and angiographic liver-directed therapies have the potential to yield a survival rate of approximately 50 per cent at 10 years[3]. The 'liver first' approach in terms of upfront treatment of hepatic metastases, followed by resection of the primary tumour, as adopted recently in the treatment of colorectal cancer with synchronous liver metastases, might also be an appealing strategy for NETs. This reversed approach would allow assessment of the receptiveness of hepatic tumour load to treatment and the identification of patients who might not benefit from removal of the primary tumour.

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The author declares no conflict of interest.

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what is the role of the abdominal surgeon**
Tuynman Juriaan, Amsterdam, NL

**Challenges in Surgery of Endometriosis –
always interdisciplinary?**
Peter Oppelt, Linz, AT; Andreas Shamiyeh, Linz, AT

A gaze in the crystal ball: Where is the role of virtual reality and artificial Intelligence in colorectal surgery
Müller Beat, Basel, CH

MALIGNANT COLORECTAL DISEASE

**Cytoreductive Surgery
and Intraperitoneal Chemotherapy – facts and hopes**
Michel Adamina, Winterthur, CH

Metastatic Colorectal Cancer – surgical approaches and limits
Jürgen Weitz, Dresden, DE

**Extended lymph node dissection
for rectal cancer, is it still under debate?**
Miranda Kusters, Amsterdam, NL

**Organ preservation functional outcome in rectal cancer treatment – in line with patient's needs?
(Robot – laparoscopic – open surgery?)**
Hans de Wilt, Nijmegen, NL

ROBOTICS

Advances in Robotic Surgery and what we learnt so far
Parvaiz Amjad, Portsmouth, UK

**Challenging the market:
Robotic (assistant) Devices and how to choose wisely
(Da Vinci – Hugo Ras – Distalmotion ua)**
Khan Jim, London, UK

TAMIS - Robotic Transanal Surgery, does it make it easier?
Knol Joep, Genk, BE

Live Surgery – Contonal Hospital of St.Gallen
Walter Brunner, St.Gallen, CH;
Salvadore Conde Morals, Sevilla, ES;
Friedrich Herbst, Vienna, AUT;
Amjad Parvaiz, Portsmouth, UK

Video Session

Lars Pahlmann Lecture
Markus Büchler, Lisboa, PRT

Honorary Lecture
Bill Heald, Lisboa, PRT

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