World J. Surg. 26, 991–997, 2002
DOI: 10.1007/s00268-002-6630-z

WORLD
Journal of
SURGERY

Effect of Surgery on the Outcome of Midgut Carcinoid Disease with Lymph Node and Liver Metastases

Per Hellman, M.D., Ph.D.,[1] Tobias Lundström, M.D.,[1] Ulf Öhrvall, M.D., Ph.D.,[2] Barbro Eriksson, M.D., Ph.D.,[3] Britt Skogseid, M.D., Ph.D.,[3] Kjell Öberg, M.D., Ph.D.,[3] Eva Tiensuu Janson, M.D., Ph.D.,[3] Göran Åkerström, M.D., Ph.D.[1]

[1]Department of Surgery, University Hospital, SE-751 85 Uppsala, Sweden
[2]Department of Surgery, Södersjukhuset, Ringvägen 52, S-11883 Stockholm, Sweden
[3]Department of Medicine, University Hospital, SE-751 85 Uppsala, Sweden

Published Online: May 21, 2002

Abstract. We have evaluated survival and tumor-related symptoms in the presence of mesenteric lymph node and liver metastases in relation to surgical procedures in 314 patients (148 women, mean age at diagnosis 61 years; 249 with liver metastases) treated for midgut carcinoid tumors. Of the operated patients, 46% presented with severe abdominal pain and intestinal obstruction and were operated on before the diagnosis. Medical treatment (somatostatin analogs, interferon-α) was initiated in 67% and 86%, respectively. Surgical attempts included small intestine or ileocecal/right-sided colon resection with excision of mesenteric lymph node metastases. Most of the patients ($n = 286$) had mesenteric lymph node metastases; 33% of them had unresectable mesenteric lymph node metastases and underwent surgery without mesenteric dissection. Patients who underwent resection for the primary tumor had a longer survival than those with no resection (median survival 7.4 vs. 4.0 years; $p < 0.01$). Patients who underwent successful excision of mesenteric metastases had a significantly longer survival than those with remaining lymph node metastases. Patients operated on for a primary tumor but with remaining lymph nodes but no liver metastases and who subsequently received interferon and somatostatin analog treatment had a median survival of 7.4 years. Resection of the primary tumor and the mesenteric lymph node metastases led to a significant reduction in tumor-related symptoms. Surgery to remove the primary intestinal tumor including mesenteric lymph node metastases is supported by the present results, even in the presence of liver metastases. Liver metastases and significant preoperative weight loss are identified as major negative prognostic factors for survival.

Midgut carcinoid tumors are fairly uncommon, with a clinical incidence of about 0.5 to 1.5 per 100,000 individuals [1]. This number may be an underestimation, however, as a Swedish autopsy study indicates an annual frequency of 8.4 per 100 000 inhabitants [2]. The primary tumor is often small (5–10 mm) but has most often spread to regional lymph nodes of sometimes conspicuous size and the liver at diagnosis [3]. Whereas many patients are recognized to harbor the disease during an emergency operation for acute intestinal obstruction, others may have had symptoms for even a decade before recognition of the carcinoid syndrome and the disease [4]. Many treatment modalities have been used over the years, but the presently utilized ones consist of surgery for the primary tumor including removal of regional lymph nodes, as well as resection of solitary liver lesions, liver embolization, and medical biotherapy with somatostatin analogs (octreotide) and interferon. Evaluating the results of this treatment is generally complex, and no randomized trials have been performed to clarify the role of this multimodal treatment.

The large mesenteric lymph node metastases usually cause specific problems for the patients. They may be of considerable size and are often surrounded by and involved in a fibrotic reaction [5]. The mesentery is usually shortened, and this reaction may cause obstruction or reduced flow in the mesenteric vessels, giving rise to abdominal pain, intestinal venous stasis, or even arterial occlusion with intestinal hypoxia. The diarrhea and abdominal pain often present in these patients may thus be due to many factors: the carcinoid syndrome caused by release of several peptides by the metastases, reduced intestinal oxygenation through impeded blood flow in the mesenteric vessels, or partial intestinal obstruction. Thus even though octreotide may ameliorate symptoms due to hormonal secretion, many patients still suffer from diarrhea.

The rarity of the disease and the frequent presentation at an emergency operation bears the risk of resulting in an inadequate operation with regard to the midgut carcinoid disease, even though the intestinal obstruction is solved. We have previously advocated intestinal resection including removal of the mesenteric lymph nodes as the standard operation [5]. This may not, however, have been performed during the emergency surgery.

In the present study we retrospectively analyzed the outcome of the combined medical and surgical treatment utilized at the University of Uppsala, which is a national referral center for patients with endocrine tumors. In this report we have focused on the

This International Association of Endocrine Surgeons (IAES) article was presented at the 39th World Congress of Surgery International Surgical Week (ISW01), Brussels, Belgium, August 26–30, 2001.

Correspondence to: P. Hellman, M.D., Ph.D., e-mail: per.hellman@kirurgi.uu.se

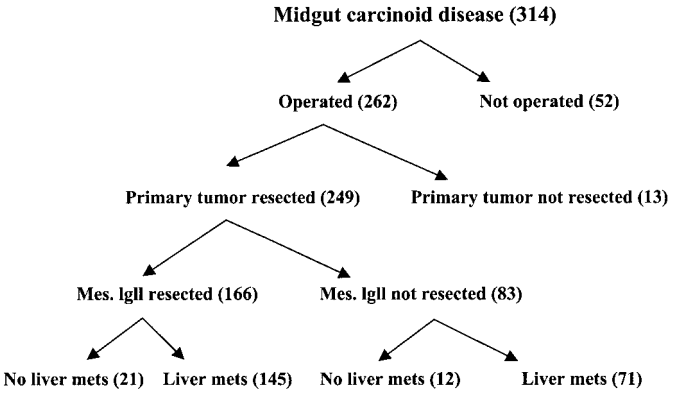


Fig. 1. Flow chart of patients. Mes. lgll: mesenteric lymph node metastases; mets: metastases.

surgical treatment and the role of removing the primary tumor and the mesenteric lymph node metastases. The results demonstrate that resection of the primary tumor and the mesenteric lymph node metastases reduce morbidity and improve survival in these patients.

Materials and Methods

Patients

During 1975–1997 a total of 314 patients (148 women, mean age 61.04 ± 0.6 years) were treated for midgut carcinoid disease at the Departments of Medicine and Surgery, University Hospital in Uppsala (Fig. 1). Altogether, 124 of these patients were referred after primary operation elsewhere. Of all 314 patients, 52 were never operated on for various reasons (e.g., cardiac or pulmonary disease, refused operation, deterioration of disease before surgery was scheduled). A total of 121 patients (46% of the operated individuals) were operated on on an emergency basis due to intestinal obstruction, and the remaining 141 underwent an elective procedure. Follow-up encompasses up to 25 years (on average 8.1 ± 3.8 years), until death or latest visit during year 2000 or 2001.

Biochemical Markers

Patients underwent measurements of 24-hour excretion of urinary 5-hydroxyindoleacetic acid (5-HIAA) and p-chromogranin A (after 1991) at the time of referral to Uppsala and then regularly during the study period. All patients had elevated 5-HIAA levels (mean 620 ± 99 μmol/24 hr; normal < 50 μmol/24 hr), and p-chromogranin A levels (mean 32 pmol/L; normal < 4 pmol/L) prior to surgery.

Radiologic and Scintigraphic Staging

Regular abdominal computed tomography (CT) scans were performed and set the standard of radiologic methods to monitor the disease. After 1992, somatostatin receptor scintigraphy using ^{111}In-DTPA-octreotide was performed to evaluate tumor distribution, although these results are not reported in the present study.

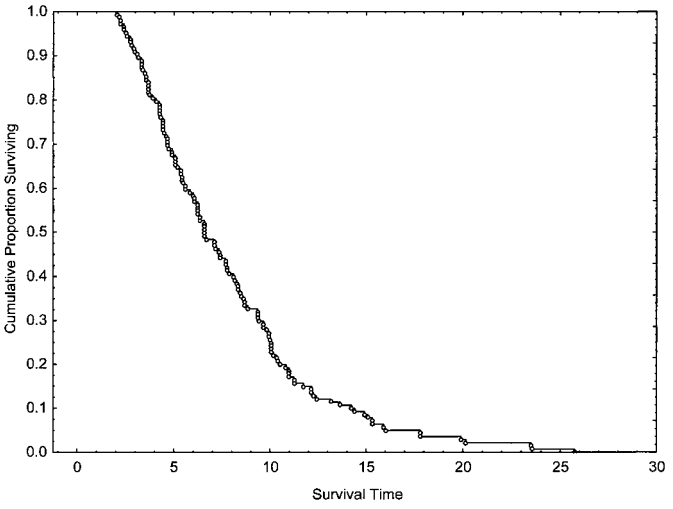


Fig. 2. Overall survival.

Nonsurgical Therapy

Most of the patients (67%) were treated with octreotide, usually in doses of 100 μg × 2 per day subcutaneously but occasionally at up to 500 μg × 3 daily. Interferon was also used in most (86%) of the patients at regular doses of 9 to 15 MIE per week. Ischemic treatment of liver metastases was used in cases of bilobar disease, by embolization with Gelfoam powder (Spongostan; Ferrosan, Copenhagen, Denmark) through the hepatic artery.

Extent of Disease

Mesenteric lymph node metastases were evident at surgery or on CT scans in 286 patients (91%), and liver metastases were seen in 253 patients (80.6%). Retroperitoneal extension of the lymph node metastases occurred in 108 patients (34.4%). The median survival of the entire patient group from onset of symptoms was 6.04 years, with a 5-year survival of 57% (Fig. 2).

Surgical Procedures

The surgical approach for the patients operated on in Uppsala was small intestine or ileocecal/right-sided hemicolectomy with mesenteric dissection and removal of mesenteric lymph node metastases; there was thorough sparing of the mesenteric vessels [5]. In 83 cases (26.4%) this was judged impossible because of retroperitoneal extension of the disease or the presence of metastase that encompassed the mesenteric vessels. Liver surgery (hemihepatectomy, left lateral resection, or atypical resections) was performed in 11 patients. Altogether, 75 patients were operated on more than once, and a total of 371 abdominal operations were performed.

Symptoms

We gathered information about the patient's symptoms before and after the surgical procedures as well as at follow-up. The symptoms were divided into: (1) presence of and daily number of diarrheal episodes, defined as watery stools; (2) abdominal pain, defined as (a) intractable, continuous pain, (b) "obstruction-like"

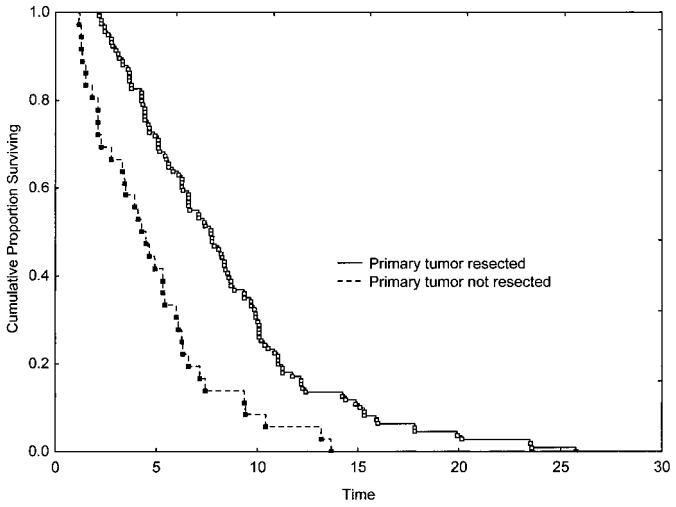


Fig. 3. Survival of patients with and without primary tumor resected.

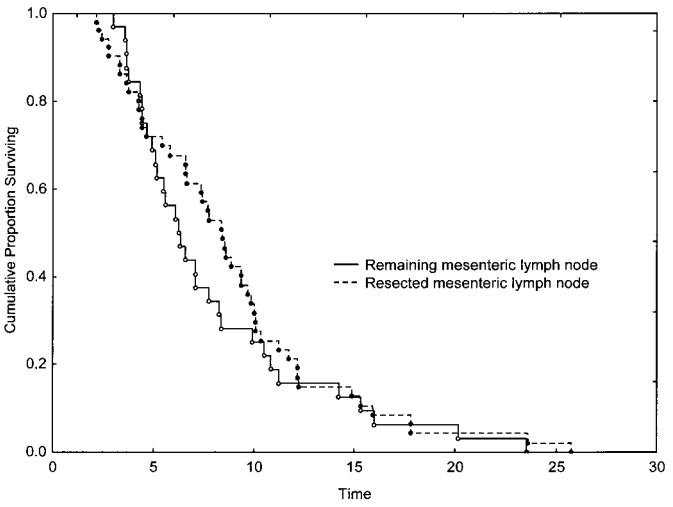


Fig. 4. Survival of patients with and without mesenteric lymph node metastases resected.

pain ("subileus"), or (c) postprandial abdominal pain, defined as regularly occurring within 30 minutes after eating; (3) significant weight loss, defined as more than 10% loss of body weight during the 6 months preceding surgery compared to patients in whom no change in body weight occurred within the 6 months preceding surgery; (4) flush, as classically occurs with the carcinoid syndrome, evident in 142 patients at the time of diagnosis.

Statistical Methods

Statistical analyses encompassed survival analyses using the Kaplan-Meier method, censoring causes of death other than those directly related to the carcinoid disease. Significance testing was performed with the log-rank test. Samples were analyzed with the two-tailed Student's *t*-test for unpaired and paired data. Numeric values are given as the mean ± SEM.

Results

Primary Tumor

Eighteen patients were primarily operated on with palliative bypass procedures only, which did not include resection of the primary tumor. All these procedures were performed at other hospitals, and the patients were later referred for follow-up medical and surgical therapy. We reoperated and removed the primary tumor in 5 of these patients; the remaining 13 did not undergo further operation. All these patients had liver metastases. These 13 patients and the nonoperated patients (altogether 65 patients) had a median survival of 4.0 years (5-year survival 42%) (Fig. 3).

The primary tumor was resected in 249 patients, with a median survival of 7.4 years (Fig. 3), significantly better than for the unoperated patients ($p < 0.01$, log-rank test). A significant difference remained when patients without liver metastases were excluded (not shown). However, the 5-year survival of patients with remaining mesenteric lymph node and liver metastases did not differ from that of the unoperated patients. In addition, there was no difference in survival or symptomatic outcome whether the operation was performed on an emergency basis or as an elective procedure.

Lymph Node and Liver Metastases

Of the patients who had their primary tumor resected, 166 (67%) also had their mesenteric lymph node metastases removed, either at the initial procedure or at reoperation within 3 years. These patients had a significantly better median survival than patients in whom the mesenteric metastases remained (7.9 vs. 6.2 years) (Fig. 4, Table 1). Although the survival curve differed significantly, it is obvious that the most gain for the patients whose mesenteric lymph node metastases were removed is an improved survival of 6 to 9 years (Fig. 4). A small number of patients ($n = 21$) without liver metastases and with resected mesenteric lymph node metastases had a median survival of 12.4 years (5-year survival 90.5%), which is significantly better than for those with resected mesenteric lymph node but with liver metastases ($p < 0.01$) (Table 1), indicating an important role for the presence of liver metastases in long-term survival. However, when patients with liver metastases are excluded, the significant difference between resected versus remaining mesenteric lymph node metastases remained ($p = 0.05$) (Fig. 5), supporting a role also for the mesenteric lymph node metastases themselves. This is further supported by the findings in patients with liver metastases: Patients with resected mesenteric lymph node metastases survived significantly longer than those with remaining mesenteric metastases (Fig. 6, Table 1). Overall, patients with liver metastases had a median survival of 4.9 years, significantly shorter than in patients not expressing liver metastases (10.1 years) ($p < 0.001$) (Fig. 7, Table 1).

Biochemical Markers

Survival was shorter in patients with high p-chromogranin A and 5-HIAA levels. Thus patients with high 5-HIAA levels (> 250 μmol/24 hr) had a significantly shorter median survival than patients with levels < 250 μmol/24 hr (4.8 vs. 7.2 years; $p < 0.01$). In general, surgery reduced both 5-HIAA and p-chromogranin A

Table 1. Characteristics of various groups of patients: univariate analysis with respect to outcome factors.

Group	No.	Age (years)[a]	Survival (years)[b]	Cumulative survival (%) 3 Years	5 Years	10 Years	*p*
All patients	314	61.04 ± 0.6	6.6	91	67	26	
Primary tumor							< 0.001
Not resected	65	63.9 ± 0.5	4.0	90	58	12	
Resected	249	59.8 ± 1.4	7.4	91	70	31	
Mesenteric lymph nodes							< 0.001
Remaining	83	60.1 ± 0.8	6.2	90	68	24	
Resected	166	58.6 ± 1.2	7.9	98	72	37	
Liver metastases	249	60.6 ± 1.1					< 0.001
Present	34	61.0 ± 1.0	4.9	65	50	17	
Not present	65	60.3 ± 1.7	10.1	95	87	65	
Present + remaining mes. lgll	13		3.8	67	42	ND	0.05
Present + resected mes. lgll	21		7.8	95	67	34	< 0.01[c]
No + remaining lgll	10		7.4	90	79	22	0.01
No + resected lgll	21		12.4	95	90.5	81	
Weight loss							< 0.001
Not significant	27	61.1 ± 0.9	9.9	85	67	45	
Significant	56	60.5 ± 0.9	4.5	73	47	15	

The group "Primary tumor, not resected" includes patients not operated on or in whom only bypass procedures were performed. No + remaining lgll: no liver metastases but remaining mesenteric lymph node metastases; No + resected lgll: no liver metastases but resected mesenteric lymph node metastases; Significant weight loss: > 10% loss of body weight within 6 months prior to surgery; Not significant weight loss: no change in weight within 6 months prior to surgery.

ND: not done.

[a]Data are presented as mean ± SEM.

[b]Data are presented as median.

[c]Versus No + resected lgll.

levels. Whereas 5-HIAA in most cases reached normal levels in patients who had undergone resection of the primary tumor or mesenteric lymph node metastases (or both), p-chromogranin A reached normal levels only in occasional patients in whom no remaining macroscopic residual tumor tissue was seen. In patients with remaining liver metastases but resected primary or mesenteric lymph node metastases (or both), the 5-HIAA and p-chromogranin A levels were significantly reduced to 7.3 μmol/24 hr and 12 pmol/L, respectively (both $p < 0.01$).

Biotherapy

In total, 12 patients had no liver metastases but did have remaining mesenteric lymph node metastases. These patients were treated with biotherapy (octreotide and interferon) for an average of 30.1 ± 10.1 and 31.4 ± 12.1 months, respectively, to stabilize the mesenteric disease; and they had a median survival (10 have died) of 7.4 years (5-year survival 79%). Two patients who initially underwent resection for their primary tumors but in whom the mesenteric metastases were found to be inoperable and were not resected were later reoperated, and the mesenteric mass was found to have undergone total remission. In addition to undergoing the primary operation, these patients had been treated with octreotide and interferon.

Patients with liver metastases and remaining mesenteric lymph node metastases were compared to evaluate the effect of biotherapy. Survival was significantly more favorable in patients treated with these agents than in those who did not receive biotherapy (median survival 5.1 vs. 3.6 years and 5-year survival 51% vs. 37%, respectively; $p < 0.05$).

Symptoms, Type of Onset

Retrospective appreciation of the onset of prodromal symptoms in electively operated patients revealed a mean time of 1.25 years (range 0–9.5 years) before diagnosis. The presence of abdominal pain or diarrhea did not affect survival compared to patients without these symptoms at diagnosis, whereas weight loss was accompanied by significantly reduced survival ($p < 0.001$) (Fig. 8).

Surgery seemed to alleviate symptoms, but especially removal of the mesenteric lymph node metastases caused a significantly higher rate of improvement compared to that of patients with remaining mesenteric metastases ($p < 0.05$, Wilcoxon). Thus the rate of diarrheal episodes was significantly lower, as were the number of watery stools in patients still suffering from diarrhea. Continuous and postprandial abdominal pain was significantly reduced, but the rate of patients with flush did not differ between those with resected and those with remaining mesenteric lymph node metastases. In toto, flush was evident in 142 patients at the time of diagnosis. Survival analyses revealed that patients in whom symptoms were diminished after surgery (57/83), regardless of the procedure performed, had a better median survival than patients with continuing symptoms after surgery (7.7 vs. 6.6 years; $p < 0.05$).

Discussion

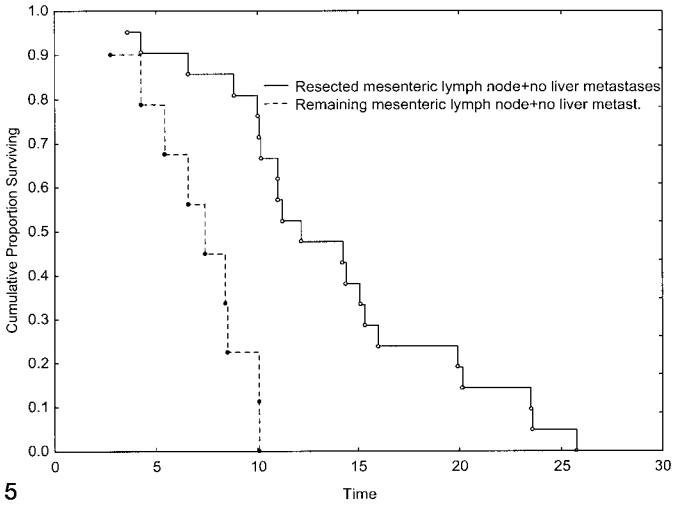
Midgut carcinoid tumors originating from the small intestine have often spread at diagnosis, usually with both mesenteric lymph node and liver metastases [3]. The regular regimen for these patients has been a combination of surgery and medical biotherapy, although there are no prospective trials clarifying the

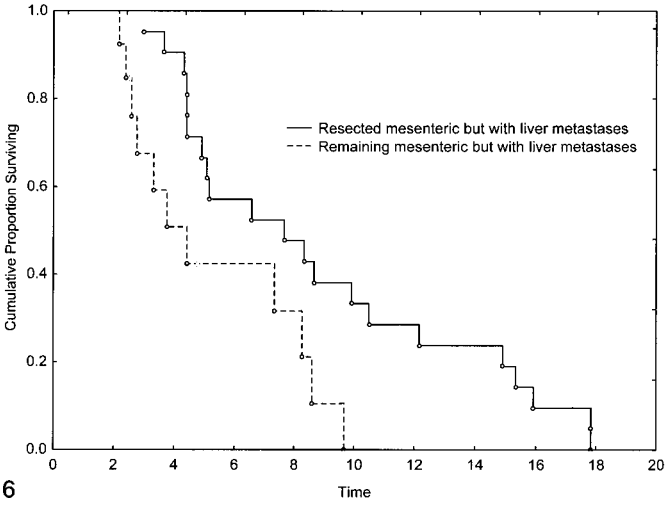
benefit of this combined treatment. Such trials would be extremely complicated and durable. Thus there are no results based on randomized trials that fulfill evidence-based criteria that clarify whether surgery for the primary tumor, the mesenteric lymph node metastases, or the liver metastases improves survival or reduces symptoms. Nevertheless, the present analysis of our patient series supports an aggressive approach to the management of these patients. The presence of liver metastases does not affect the value of resecting the primary tumor or the mesenteric lymph node metastases. Indeed, in patients with liver metastases there seems to be a lot to gain with surgery of the primary tumor and the mesenteric lymph node metastases. Moreover, it is clear that the most important variable in determining survival is the presence of liver metastases. Patients with liver and unresectable lymph node metastases benefit from continuing biotherapy.

The results demonstrate the survival advantage of resecting the primary tumor, which presumably reduces the degree of intestinal (sub)obstruction leading to abdominal pain, diarrhea, weight loss, and malnutrition. The latter was also identified as a major negative prognostic factor. No difference was seen between emergently or electively operated patients. These numbers may be obscured by the fact that 31 of the emergently operated patients underwent a second elective procedure aimed at completing the primary operation toward the one regularly used by us including mesenteric dissection and removal of lymph node metastases with sparing of the mesenteric vessels.

The complications of the midgut carcinoid disease, such as mechanical occlusion of the intestine, fibroelastosis, and adhesions causing intestinal ischemia are often associated with significant morbidity in addition to the release of peptides leading to the carcinoid syndrome. For the individual patient it may be difficult to judge the contribution from each of these causes of diarrhea and abdominal pain. Both octreotide and interferon treatment have been shown to reduce hormonal secretion and induce symptom relief, but in most cases total remission of symptoms is not achieved. In these cases additional reasons (e.g., adhesions, fibrosis, impeded arterial and venous blood flow) may be present that are not affected by biotherapy, at least not in the short-term perspective. The mesenteric lymph node metastases may themselves cause obstruction of the mesenteric vessels, usually by demonstrating a growth pattern more or less surrounding the mesenteric artery and vein. Continuous retroperitoneal extension under the horizontal part of the duodenum and pancreas usually indicates unresectability and increased risk of impeded intestinal blood flow. Indeed, the two patients treated with octreotide and interferon who were found to have total remission of the mesenteric mass at reoperation indicate that biotherapy provides increased survival compared to patients without treatment. Although these occasional findings not clearly are attributed to the biotherapy, our study shows that patients with such metastases treated with biotherapy have an increased survival compared to patients without treatment.

The present study demonstrates that surgery reduces the classic symptoms in patients with midgut carcinoid disease. Thus there is a significant reduction in diarrhea and in diffuse and postprandial abdominal pain possibly related to relative intestinal ischemia after removal of the mesenteric lymph node metastases. Patients in whom the lymph node metastases were removed within 3 years after the primary operation (either in conjunction with the primary surgery or at a reoperative procedure) had a longer survival





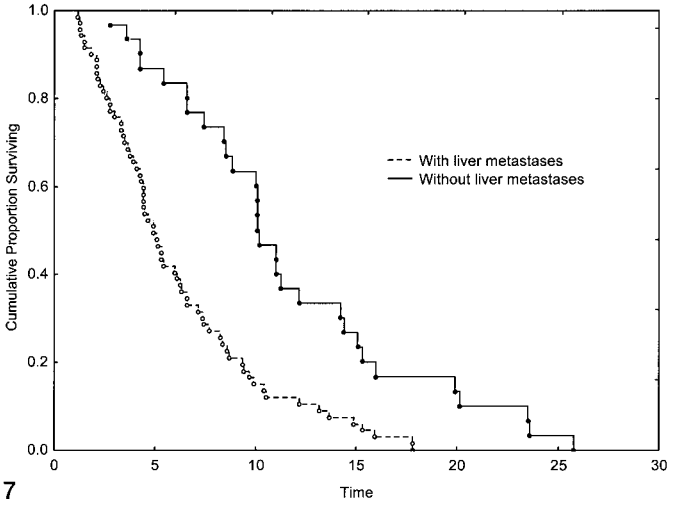


Fig. 5. Survival of patients without liver metastases (metast.) but with or without mesenteric lymph node metastases.

Fig. 6. Survival of patients with liver metastases but with and without mesenteric lymph node metastases.

Fig. 7. Survival of patients with and without liver metastases.

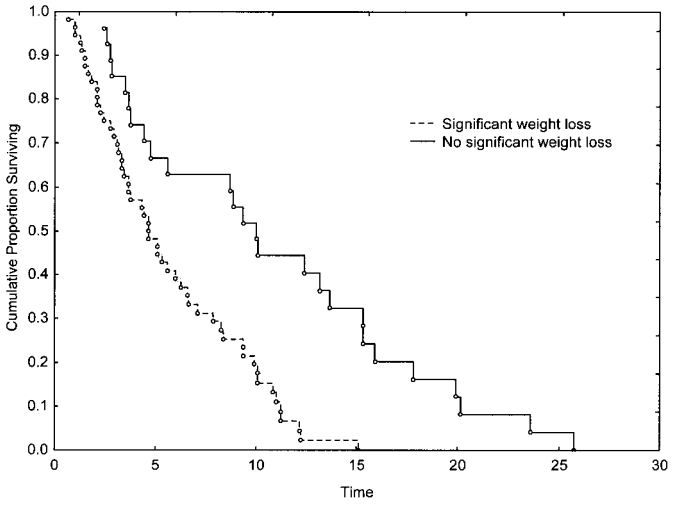


Fig. 8. Survival of patients with and without significant preoperative weight loss.

and better symptom relief than patients in whom the lymph nodes metastases were not removed. Indeed, this may indicate that the latter patient group had more extensive disease, but it nevertheless emphasizes the benefit of aggressive surgery. Significant weight loss and malnutrition before recognition of the disease demonstrated a strong correlation with reduced survival, regardless of what surgical procedure and biotherapy were given later. We may therefore intensify our treatment of this status regardless of extent of disease to increase survival.

The presence of liver metastases was identified as a major negative prognostic factor for survival, as has been noted previously [6]. Interestingly, we found that especially in these patients it seems beneficial to resect the primary tumor as well as the mesenteric lymph node metastases, supporting the notion that aggressive surgery (sometimes denoted debulking surgery) is advantageous also in the case of spread disease.

Only a small group of our patients could be regarded as being in total remission after apparently "radical" surgery. It seems, however, that these patients should be viewed as still harboring microscopic disease, which implies continuous treatment with octreotide, interferon, or both. The follow-up of all our patients includes measurements of 5-HIAA and p-chromogranin A as well as octreotide scintigraphy to detect recurrent disease and monitor progression or remission. It has previously been shown that high levels of 5-HIAA and p-chromogranin A at presentation are associated with reduced survival [6, 7], and the present study supports these findings. Our study also shows that although a reduction of these tumor marker levels is seen after surgery (whether radical surgery or debulking) it is only in selected cases that the markers return to completely normal levels, indicating the presence of residual disease in most patients.

In general it is difficult to compare our findings with others. Most reports have included mixed patient populations (with foregut, midgut, and hindgut neuroendocrine tumors), although primary tumor in the midgut has a worse prognosis than those in the lung, stomach, appendix, or rectum and a better prognosis than endocrine pancreatic tumors often classified as pancreatic carcinoids [8]. In the Mayo Clinic series patients with metastases at diagnosis at a 5-year survival of 68% [9], which was reduced to 38% and 21%, respectively, if lymph node or liver metastases were present. Ahlman has reported an overall 5-year survival among the Gothenburg patients of 57.5% [10]. A recent German survey demonstrated a 5-year survival of 86% for patients who underwent "curative" resections and 26% for those with palliative resection [11]. Our overall 5-year survivals of 67% in operated patients, 90% in "curatively" operated patients, and not lower than 42% in the worst patient groups are comparably good results, indicating not only successful surgery but also a winning strategy of medical biotherapy and most likely a profitable combination of surgery and medical care of the patients. The latter proposal is supported by a significantly higher 5-year survival rate (51% vs. 37%; $p < 0.05$) in patients with liver and mesenteric metastases who received biotherapy than in those who did not.

There are many possible comments about our results. Indeed, the disease itself may present in many ways. Some patients at diagnosis have no liver metastases and small, resectable primary tumors and mesenteric metastases, whereas others present with extensive disease including continuation of the mesenteric mass into the retroperitoneal space, massive liver metastases, and possibly carcinoid heart disease. The handling of these patients is obviously diverse, and the different outcomes are based on the prerequisites in the individual and the treatment regimen. In addition, a retrospective analysis such as the present one bears the well known disadvantage of, for example, risk of biased sampling. Nevertheless, it is important to identify a strategy that clearly guides us when we recommend surgical procedures and medical treatment to the patients.

Conclusions

Our study supports aggressive surgery in patients with midgut carcinoid disease. Specifically, resection of the primary tumor reduces symptoms and improves survival, even though inoperable mesenteric lymph node and liver metastases are present. If possible, mesenteric lymph node metastases should be resected, as this measure alleviates symptoms and improves survival. The combination of octreotide and interferon treatment seems to benefit patients additionally, although it is unclear if it helps in the few who have undergone a macroscopic "radical" surgical procedure. A lack of liver metastases is a significant factor strongly indicating a better prognosis; and weight loss, presumably due to many factors, significantly indicates a worse prognosis, regardless of the extent of disease.

Résumé. Nous avons évalué la survie et les symptômes tumeur-spécifiques après traitement chirurgical d'une tumeur carcinoïde de l'intestin moyen en présence de métastases ganglionnaires mésentériques et hépatiques chez 314 patients (148 femmes; âge moyen au moment du diagnostic 61 ans; 249 avec des métastases hépatiques). Quarante-six pourcent des patients opérés ont présenté avec une douleur abdominale sévère et une occlusion intestinale et ainsi ont été opérés avant de faire le diagnostic. Le traitement médical (analogues de la somatostatine, alpha-interféron) a été commencé dans, respectivement, 67% et 86% des cas. La chirurgie a consisté en une résection de l'intestin grêle ou iléocécale/colectomie droite avec adénolympadectomie mésentérique. La plupart de ces patients (n = 286) avaient des métastases ganglionnaires mésentériques; 33% parmi eux avaient des métastases lymphatiques mésentériques irréséquables et ainsi ont eu une chirurgie sans lymphadénectomie. La survie des patients réséqués pour tumeur primitive était plus longue comparée à celle des patients non-réséqués (survie médiane 7.4 vs 4.0 ans; $p < 0.01$). La survie des patients ayant eu une excision des métastases mésentériques a été

plus longue que celle des patients ayant eu une résection incomplète des métastases lymphatiques. La survie médiane des patients opérés pour tumeur primitive, avec métastases ganglionnaires, mais sans métastases hépatiques, traités par l'interféron et les analogues de la comatosttine a été de 7.4 ans. La résection de la tumeur primitive ainsi que des métastases ganglionnaires mésentériques entranent une réduction significative des symptômes tumeur-spécifiques. Les résultats de cette étude sont en faveur d'une chirurgie complète, enlevant la tumeur intestinale primitive et les métastases lymphatiques mésentériques, même en présence de métastaes hépatiques. La présence de métastases hépatiques et de perte importante de poids ont été identifiées comme facteurs prédicitifs négatifs significatifs de survie.

Resumen. En 314 pacientes (148 mujeres, edad media al diagnóstico 61 años, 246 con metástasis hepáticas) tratadas por tumores carcinoides del intestino medio, se evaluaron la supervivencia y los síntomas dependientes del tumor (que presentaba adenopatías metastásicas y/o metástasis hepáticas) con relación al proceder quirúrgico. El 46% de los enfermos fueron intervenidos, antes de realizarse el diagnóstico, por intenso dolor abdominal y obstrucción intestinal. Se inició un tratamiento médico con análogos de la somatostatina en el 67% o con alfa-interferon en el 86% de los casos. El tratamiento quirúrgico consistió en la resección entérica o ileocecal con hemicolectomía derecha con extirpación de las adenopatías mesentéricas metastásicas. La mayoría de los pacientes (n = 286) presentaban adenopatías mesentéricas metastásicas, que en un 33% fueron irresecables. Los pacneites, en los que el tumor primario fue extirpado, vivieron más que los no resecados (supervivencia media 7.4 vs 4.0 años; $p < 0.01$). Los pacientes a low que se pudieron extirpar las metástasis mesentéricas tuvieron mayor supervivencia. En los casos en que el tumor primario pudo ser extirpado pero no lad adenopatías metastásicas y que fueron tratados con análogos de la somatostatina a interferón, la supervivencia medai fue de 7.4 años. La resección tumoral y de las metástasis mesentéricas disminuyen significativamente la sintomatología. Los hallazgos demuestran que, aunque existan metástasis hepáticas, la resección del tumor y de las adenopatías metastásicas mesentéricas está indicada. Metástasis hepáticas y rápido adelgazamiento preoperatorio se consideran los factores pronósticos negativos más importantes por lo que a la supervivencia se refiere.

Acknowledgments

The Swedish Cancer Foundation is gratefully acknowledged for their support, making this work possible.

References

1. Godwin JD. Carcinoid tumors: an analysis of 2837 cases. Cancer 1975;36:560–569
2. Berge T, Linell F. Carcinoid tumours: frequency in a defined population during a 12-year period. Acta Pathol. Microbiol. Scand. [A] 1976;84:322–330
3. Åkerström G, Hellman P, Öhrvall U. Surgical endocrinology. In Doherty G, Skogseid B, editors, Midgut and Hindgut Carcinoid Tumors, Philadelphia, Lippincott, Williams and Wilkins, 2000;447–459
4. Makridis C, Rastad J, Oberg K, et al. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. World J. Surg. 1996;20:900–907
5. Ohrvall U, Eriksson B, Juhlin C, et al. Method for dissection of mesenteric metastases in mid-gut carcinoid tumors. World J. Surg. 2000;24:1402–1408
6. Wangberg B, Westberg G, Tylen U, et al. Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. World J. Surg. 1996;20:892–899
7. Janson ET, Holmberg L, Stridsberg M, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. Ann. Oncol. 1997;8:685–690
8. Onaitis MW, Kirshbom PM, Hayward TZ, et al. Gastrointestinal carcinoids: characterization by site of origin and hormone production. Ann. Surg. 2000;232:549–556
9. Soreide JA, van Heerden JA, Thompson GB, et al. Gastrointestinal carcinoid tumors: long-term prognosis for surgically treated patients. World J. Surg. 2000;24:1431–1436
10. Ahlman H. The role of surgery in patients with advanced midgut carcinoid tumours. Digestion 1996;57:86–87
11. Nave H, Mossinger E, Feist H, et al. Surgery as primary treatment in patients with liver metastases from carcinoid tumors: a retrospective, unicentric study over 13 years. Surgery 2001;129:170–175