Description of Patients with Midgut Carcinoid Tumours: Clinical Database from a Danish Centre

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Abstract. *Background: We have initiated a clinical database of patients with neuroendocrine tumours (n= 132). Data on patients with well-differentiated endocrine carcinoma (WHO classification) previous classified as midgut carcinoid patients, are presented. Patients and Methods: Retrospectively, 56 patients with midgut carcinoid tumours were evaluated with respect to symptoms, primary tumour size, metastases, tumour markers, treatment and survival. Results: Flushing was described in 29%, diarrhoea in 52%, abdominal pain in 34%, bronchial constriction in 2% and carcinoid heart disease in 4% of the patients. Fifty-two percent had liver metastases at referral. Twenty-seven percent were considered to have had radical surgery. Patients not considered for radical surgery and patients with liver metastases had significantly higher tumour marker levels (serum chromogranin A (CgA), serum serotonin and urinary 5-hydroxyindolic acid (5-HIAA)) compared to radically-operated patients and to patients without liver metastases (p<0.05, respectively). For all the midgut carcinoid tumour patients the overall 5-year survival rate was 72%. The radically-operated patients had a 5-year survival rate of 100% (other death causes excluded). The patients with normal CgA or <5 liver metastases at referral had a 100% 5-year survival rate. The patients with <5 liver metastases had a significantly better 5-year survival rate compared to patients with multiple liver metastases (100% vs. 50%, p<0.05). Conclusion: This group of patients exhibited the same characteristic clinical features with similar survival as reported from other specialised centres. Radical surgery, normal CgA level and <5 liver metastases indicated a good prognosis and patients with <5 liver metastases had a significantly better survival compared to patients with multiple liver metastases.*

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Neuroendocrine tumours are rare tumours arising from nerve cells, endocrine glands and the diffuse endocrine system. These tumours are divided into several subgroups based on clinical, pathological and biological characteristics (1, 2). One of the most common subgroups is the so-called midgut carcinoid tumour localized in the bowel from the second part of the duodenum through the ascending colon, with an annual incidence around 0.6-1.7 per 100,000 inhabitants (3). These tumors belong to the well-differentiated endocrine carcinoma (WHO classification) group.

Midgut carcinoid tumours may present either with symptoms caused by the presence of tumour, such as abdominal discomfort, obstruction and diarrhoea or with the carcinoid syndrome which consists of diarrhoea, flushing, bronchial constriction and carcinoid heart disease (right-sided heart failure). The syndrome usually becomes overt in patients with liver metastases and is attributed to hormones and biogenic amines produced by the tumour for example serotonin and tachykinins (4).

The diagnosis and treatment of patients with carcinoid tumours requires a multidisciplinary team of clinicians, surgeons, interventional radiologists, oncologists, pathologists and clinical physiologists. The diagnosis is based on histology, biochemical markers, visualisation of the tumour by somatostatin receptor scintigraphy (SRS), ultrasound-, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning. The golden standard in visualisation to date is the SRS (5).

Patients may be treated by a combination of surgery and medical therapy with somatostatin analogues and/or interferon, with radiofrequency ablation, stereo tactic radiotherapy, hepatic arterial embolization and in patients with high mitotic activity with chemotherapy (6). Dietary prescriptions may also be given in an attempt to improve wellbeing and to avoid some of the treatment side effects.

The 5-year survival rate has been reported to be about 60% for all midgut carcinoid tumour patients in other specialised centres (3, 7, 8).

Because of the rarity and multidisciplinary requirements of handling patients with neuroendocrine tumours it is important to centralise the treatment of these patients. Department of Medicine V, Aarhus University Hospital, has functioned as a centre for diagnosis and treatment of patients with neuroendocrine/carcinoid tumours in the western part of Denmark since 1994. A clinical database including patients with carcinoid/neuroendocrine tumours (n=132) was initiated in 2003. The aim of the present study was to characterize the group of patients with midgut carcinoid tumours according to symptoms, primary tumour size, metastases, tumour markers, treatment and survival.

Patients and Methods

Patients. A total of 132 patients with neuroendocrine tumours were referred to Aarhus University Hospital for further diagnostic procedures and treatment between January 1994 and June 2003. Of these 132 patients 56 patients were diagnosed with a midgut carcinoid tumour.

The diagnosis and criterion for inclusion was histopathologically verified midgut carcinoid tumour. The tumour specimens were obtained during surgery or by ultrasound-guided biopsy and subjected to histological and immunohistochemical (chromogranin A (CgA), synaptophysin) examinations. The primary tumour (37 patients) and liver metastases (13 patients) provided the specimens for most of the pathological examinations. Two patients were diagnosed from tumour specimens originating from respectively a lymph node and a metastasis to the ovary. In four patients the tumour specimens were not obtained until later during the follow-up period. The primary tumour or metastases was detected by CT-scan, ultrasound scan, and SRS or at operation.

The gender distribution was 28 males and 28 females with a median age at diagnosis of 61.8 (range 8.0-87.7 years). The median body mass index (BMI) was 23.2 (range 15.0-33.0).

Altogether 42 patients (75%) had been operated upon at referral and 15 of them (27%) were considered to have been cured by surgery at referral.

Five patients had allready received medical therapy when referred to our department. One patient had received interferon (IntronA®), three patients a somatostatin analogue (Sandostatin®/Sandostatin LAR®) and one patient received combination therapy with Sandostatin® and IntronA®. Two patients had already received chemotherapy at referral.

At referral all routine biochemical values were within the normal range. The median value of alkaline phosphatase in serum was within the normal range even in patients with liver metastases.

Methods. The data from the first visit/referral and from follow-up after three months, six months, twelve months and then every six months were retrospectively collected from the medical records and entered into a specially designed database (carcinoid tumour database). The data comprised clinical symptoms at referral, tumour staging including metastases, surgery, histopathology, biochemistry, tumour markers, imaging and medical treatment.

Statistics. Non-parametric analyses (Kruskal-Wallis test, Mann-Whitney *U*-test) were used for comparison of hormone levels

Table I. *Liver metastases and primary tumour size.*

Primary tumour size	Liver metastases	No liver metastases	Unknown	Total
<1 cm	0	2	1	3
1-2 cm	5	7	4	16
>2 cm	10	2	2	14

between groups. Survival time from diagnosis was calculated according to the Kaplan-Meier analysis with death from any cause as the outcome. The calculations were performed using the SPSS (Chicago, Illinois, USA) computer program. The data are presented as median and range.

Results

Symptoms. The median duration of symptoms before diagnosis was 9.0 months (0.0-80.0). At referral 16 patients (29%) described flushing, 29 patients (52%) diarrhoea, 19 patients (34%) abdominal pains, one patient (2%) bronchial constriction and two patients (4%) suffered from carcinoid heart disease. The latter was detected by echocardiography, which was performed when the patients showed clinical signs indicating carcinoid heart disease.

Primary tumour and metastases including liver metastases. Of the 56 midgut carcinoid tumour patients 37 (66%) had metastases at referral which were distributed as follows: 29 patients (52%) had liver metastases; 12 patients (21%) had lymph nodes metastases; 15 patients (27%) had carcinomatosis, three patients (5%) had bone metastases and six patients (11%) had metastases at other locations.

None of the three patients with a primary tumour measuring <1 cm had liver metastases at referral. Thirty-one percent and 71% of the patients with a primary tumour measuring 1-2 cm and >2 cm respectively had liver metastases. The presence of liver metastases in relation to the primary tumour size is summarized in Table I.

Tumour markers. The tumour markers serum CgA (normal value <127 pmol/l) (2200 pmol/l [63-135, 500] *vs.* 71 pmol/l [41-287] , n=35), serum serotonin (10, 000 nmol/l [440-27, 310] *vs.* 1510 nmol/l [158-4520], n=42), and urinary 5-hydroxyindoleacetic acid (U-5-HIAA, normal value <40 µmol/d) (170 µmol/d [25-4000] *vs.* 21 µmol/d [16-69] , n=42) were determined at referral (Figure 1), and were all significantly higher in the non-radically operated patients compared to radically operated patients ($p<0.001$).

The patients with liver metastases at referral had a significantly higher tumour marker level compared to those without liver metastases ($p<0.05$) (Figure 2). At referral the
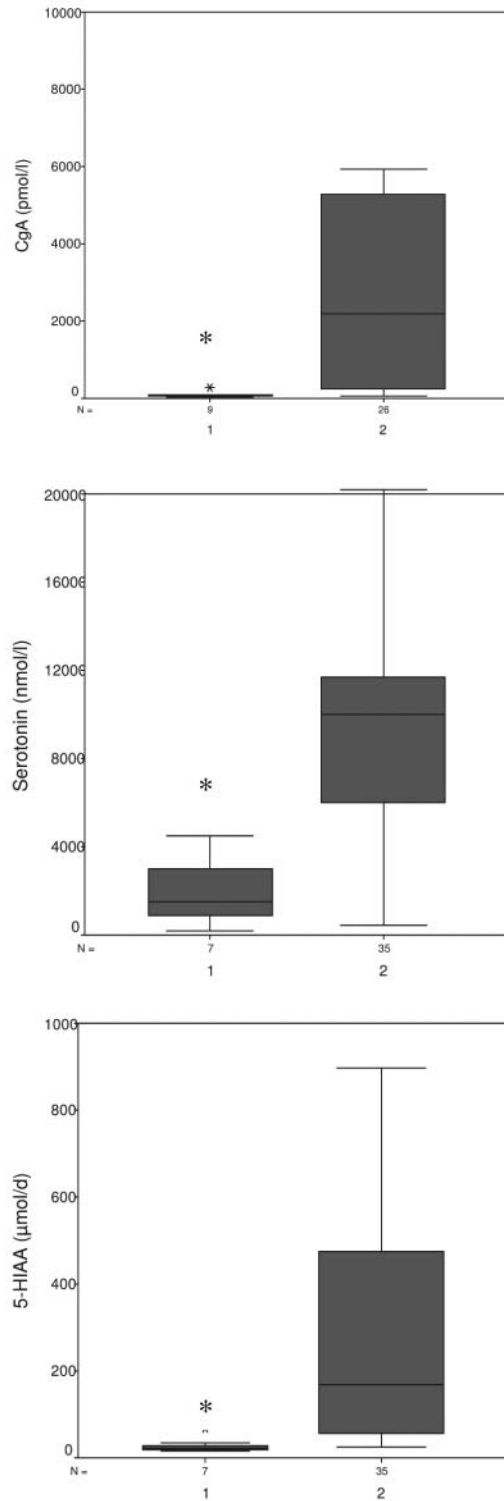
Figure 1. *Tumour markers (serum chromogranin A = CgA, n= 35, serum serotonin, n=42, urinary 5-hydroxindoleacetic acid = U-5-HIAA, n=42) in midgut carcinoid tumour patients with or without radical operation. (1= radical operation, 2= no radical operation). The box represents the interquartile range and whiskers represent highest and lowest values. *p=<0.001 radical operation vs. no radical operation.*
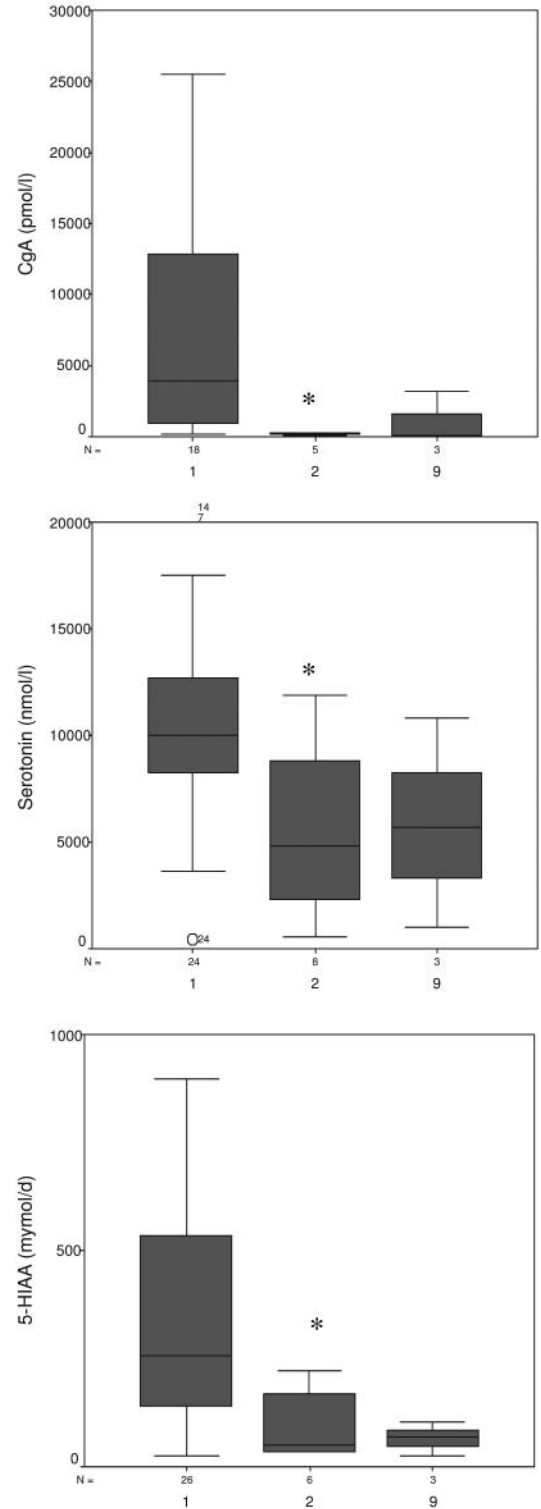
Figure 2. *Tumour markers (serum chromogranin A = CgA, n=26, serum serotonin, n=35, urinary 5-hydroxindoleacetic acid = U-5-HIAA, n=35) in 41 midgut carcinoid tumour patients without radical operation with or without liver metastases. (1= liver metastases, 2= no liver metastases, 9= unknown). The box represents the interquartile range and whiskers represent highest and lowest values. *p<0.05 no liver metastases vs. liver metastases.*

patients without liver metastases had a CgA level of 245 pmol/l [122-1300], a serotonin level of 4800 nmol/l [570-11.900] and U-5-HIAA at 50 μmol/d [33-222]. The patients with liver metastases had a CgA level of 3923 pmol/l [170-135.500], a serotonin level of 10, 000 nmol/l [440-27.310] and U-5-HIAA at 255 μmol/d [25-4000].

Treatment. First choice treatment was surgery. Forty-two patients (75%) had been operated upon and 15 patients (27%) were considered to have had radical surgery at referral.

The remaining patients were if possible treated according to Scandinavian guidelines (6) with debulking surgery (nine patients) and medical therapy including somatostatin analogues and alpha-interferon (α-IFN) usually in combination. Twenty-seven patients received combination therapy and seven patients were only treated with somatostatin analogues mainly because of unacceptable side effects to α-IFN treatment such as mental depression, aggravation of gout, muscle pain. Two patients received chemotherapy (etoposide + carboplatin) during the follow-up period.

The patients with liver metastases had if possible been treated with resection of the liver metastases (three patients before referral to our department). If resection was not possible the patients were treated with radiofrequency ablation (six patients) or stereotactic radiotherapy (two patients).

The relative changes in CgA levels, with baseline =100, in patients during treatment with combination therapy of somatostatin analogues and alpha-interferon (α-IFN) are depicted in Figure 3. The median value of the relative CgA level decreased more than 50% after initiation of combination therapy and started increasing after approximately 18-24 months suggesting tachyphylaxia and/or tumour progression.

Survival analyses. Altogether the midgut carcinoid tumour patients had a 5-year survival rate of 72%. Patients without radical surgery had a 5-year survival rate of 68% (41 patients) whereas the radically operated patients had a 5-year survival rate of 85% (15 patients) (Figure 4A). There was no significant difference between the two groups ($p=0.13$). One of the radically operated patients died from an accident (pelvic fracture) during the follow-up period and if excluded the radically operated patients had a 5-year survival rate of 100%.

Patients with an elevated (above normal) CgA level at referral had a 5-year survival rate of 70% (24 patients) whereas the patients with a normal level of chromogranin A at referral had a 5-year survival rate of 100% (11 patients) ($p=0.12$) (Figure 4B).

Patients with liver metastases at referral were divided into two groups, multiple liver metastases and less than five liver metastases. The patients with multiple liver metastases had
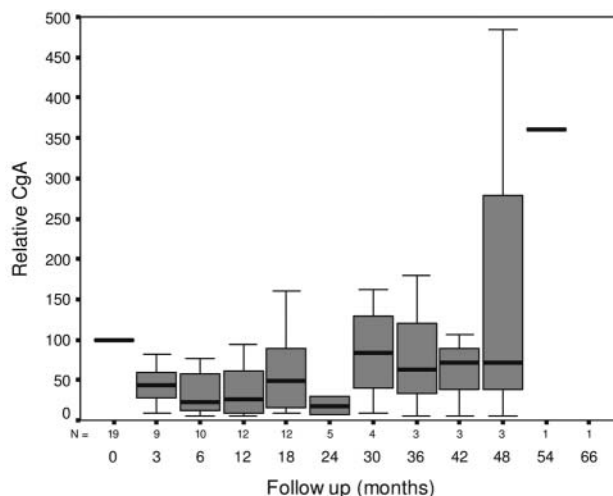

Figure 3. *Relative serum chromogranine A (CgA) levels in patients treated with combination therapy of a somatostatin analogue and interferon. The box represents the interquartile range and whiskers represent highest and lowest values. Baseline Cga level =100.*

a 5-year survival rate of 50% (15 patients) and the patients with less than five liver metastases had a 5-year survival rate of 100% (10 patients) ($p=0.014$) (Figure 4C).

Discussion

In general the clinical and biochemical parameters of the patients described in the present study were similar to those observed in other centres specialised in carcinoid tumours. Janson *et al.* (7) reported a higher frequency of the carcinoid syndrome, however, this may be explained by the fact that a larger proportion of their patients had liver metastases at referral and a smaller proportion were considered to have been radically operated compared to patients in the present study. The primary tumour size was related to the presence of metastases and the tumour burden (number of metastases) was related to levels of biochemical markers and survival.

Onaitis *et al.* (9) found that about 70% of the patients with a primary gastrointestinal carcinoid tumour measuring 1-2 cm had metastases and even 10% of patients with a primary tumour <1 cm also had metastatic disease (10%). Our limited number of patients especially in the group with smaller primary tumours brings some uncertainty to the result but our results are in line with Onaitis *et al.* and we suggest that all the patients (regardless of primary tumour size) should be examined for liver metastasis and should be followed up appropriately.

As previously demonstrated the level of circulating CgA reflects the tumour burden (7, 10) and the significantly higher levels of CgA in patients without radical surgery and in patients with liver metastases in the present study confirm these data.
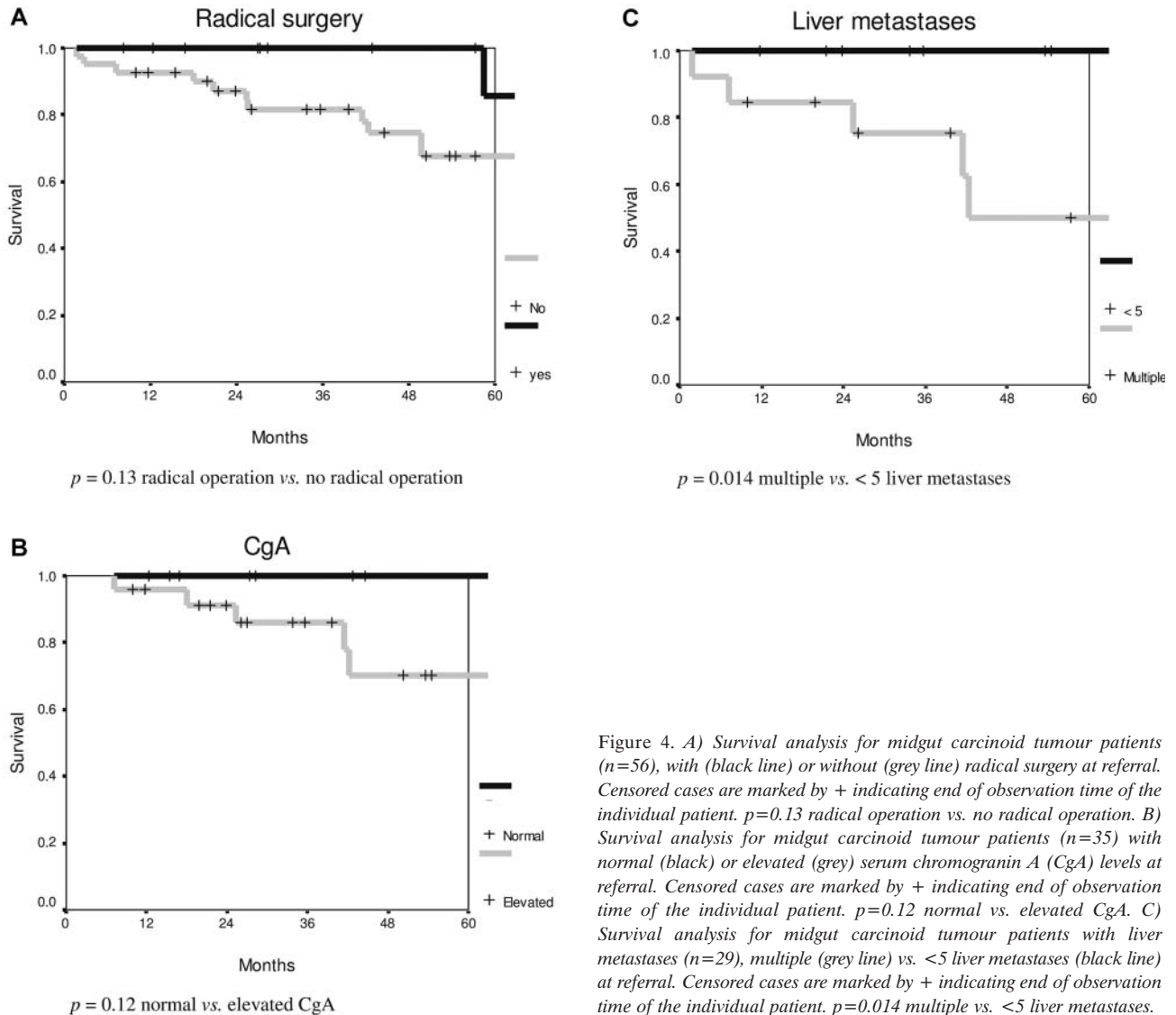
Figure 4. *A) Survival analysis for midgut carcinoid tumour patients (n=56), with (black line) or without (grey line) radical surgery at referral. Censored cases are marked by + indicating end of observation time of the individual patient. p=0.13 radical operation vs. no radical operation. B) Survival analysis for midgut carcinoid tumour patients (n=35) with normal (black) or elevated (grey) serum chromogranin A (CgA) levels at referral. Censored cases are marked by + indicating end of observation time of the individual patient. p=0.12 normal vs. elevated CgA. C) Survival analysis for midgut carcinoid tumour patients with liver metastases (n=29), multiple (grey line) vs. <5 liver metastases (black line) at referral. Censored cases are marked by + indicating end of observation time of the individual patient. p=0.014 multiple vs. <5 liver metastases.*

Surgery is essential in the treatment of midgut carcinoid tumours. As illustrated in this relatively small series, radical operations give an excellent prognosis though non-radical or debulking procedures may alleviate symptoms dramatically and improve survival (11). As the majority of the patients are diagnosed during emergency surgery for small bowel obstruction, peritonitis or appendicitis, very few of the patients receive the optimal surgical treatment at that time. Therefore, secondary surgery should be considered in every case. Such operations and the primary procedures in patients where the diagnosis is established preoperatively should be performed by a specialist unit with experience in carcinoid patients. When possible, the surgery should include clearance of mesenteric lymph nodes (12), which may be a technically difficult procedure and require the assistance of vascular surgeons (13). More extensive procedures and resection of mesenterial metastasis are seldom required in the case of appendix carcinoids. Only tumours at the base of the appendix or tumours larger than 2 cm require more than the classical appendectomy, usually a right-sided hemicolectomy. In order to prevent the carcinoid crisis during operative procedures, perioperative treatment with somatostatin analogues should be given (14).

When a radical operation is not possible the standard treatment of carcinoid tumours with low proliferation index is single or combination therapy with somatostatin analogues and α-INF (6). The CgA levels decreased after initiation of combination therapy which in some of the patients may have been due to concomitant debulking therapy by radiofrequency ablation or stereotactic radiation

therapy of liver metastases. However, in the majority of the patients the decrease of CgA level seems to be caused by the combination therapy. One recent study (15) has found a decreased level of CgA in patients with an objective response after initiation of biotherapy or chemotherapy, but the effect on CgA might have been due to inhibited synthesis and secretion after somatostatin analogue treatment (10). Increases in the CgA levels after 18-24 months of combination therapy may indicate resistance to therapy (tachyphylaxia) and/or progression of the disease.

The 5-year survival rate for all the midgut carcinoid tumour patients in this study was 72% which is in agreement with the 60 to 75% rates reported in the literature (3, 7, 8, 16). In radically operated patients 5-year survival rate rose to 100% when other causes of death were excluded, this was also the experience of Wängberg *et al.* (8).

The patients with normal CgA levels also had a 5-year survival rate of 100%. It could be argued that this was because the patients with normal CgA had been radically operated, but when the radically operated patients were excluded the 5-year survival rate was still 100% for patients with normal CgA levels.

Janson *et al.* (7) have reported that patients with five or more liver metastases had a significantly shorter median survival compared to patients without metastases or with only lymph involvement or with fewer (1-4) liver metastases. The patients with less than five liver metastases also appeared to perform better in our study which may have been related to the more aggressive treatment (debulking, radiofrequency ablation) applied.

The usually low proliferation index in these tumours gives the opportunity for any new metastases to be discovered and treated during follow-up. One patient, over a period of five years had 13 liver metastases treated by RF ablation and was without any signs of metastases at the end of follow up.

Because of the rarity of the neuroendocrine tumours and in order to improve survival and quality of life we recommend that patients with neuroendocrine tumours are treated in multidisciplinary specialised centres practising all treatment modalities.

Acknowledgements

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