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Elevated Plasma Chromogranin A Is the First Indication of Recurrence in Radically Operated Midgut Carcinoid Tumors

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Key Words
Midgut carcinoid tumor · Chromogranin A · Tumor recurrences

Abstract
Background: Patients with malignant midgut carcinoids are occasionally diagnosed with limited tumor spread, and surgery with radical intention is performed. Despite curative intent, recurrences occur frequently, motivating long-term biochemical and radiological follow-up. This study aimed to compare the usefulness of various methods in detecting such recurrences. ***Methods:*** This retrospective study included 56 patients with radically operated midgut carcinoids referred to our University Hospital for evaluation and follow-up between 1985 and 2004. Patients were monitored 1–3 times per year using plasma-chromogranin A (P-CgA), urinary 5-hydroxyindoleacetic acid (U-5HIAA) concentrations as well as radiological examinations, including ultrasonography, computerized tomography or magnetic resonance investigation. In a subset of cases, somatostatin receptor scintigraphy and/or positron emission tomography with 5-hydroxytryptophan was performed. Time from operation until established recurrence was recorded. ***Results:*** Tumor recurrence was established in 33 of 56 patients after a median of 32 months (range 6–217). Elevated P-CgA was the first marker to become pathologically elevated in 28 of these 33 patients (85%). In 3 of these 28 patients, radiology was simultaneously positive for a recurrence. ***Conclusion:*** P-CgA was the first marker to indicate tumor recurrence in the majority of radically operated midgut carcinoid patients. To avoid unnecessary and costly examinations in asymptomatic patients, we suggest that follow-up should comprise measurements of P-CgA twice a year and annual ultrasonography until P-CgA is elevated or clinical symptoms occur, at which time all efforts should be made to identify recurrent tumor lesions in order to give the patient the best possible treatment which, if possible, should be surgical removal of the recurrence.

Introduction

The midgut carcinoid tumor is a slowly growing malignant tumor originating from enterochromaffin (EC) cells of the small bowel. Common sites for metastases include the liver together with local and mesenteric lymph nodes, and often, patients have developed metastases when diagnosed [1]. The tumor cells produce and secrete

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hormones such as serotonin, tachykinins and chromogranin A (CgA), the general marker for neuroendocrine cells [2]. In patients with metastases, hormones secreted from the tumor may induce the carcinoid syndrome which includes flush, diarrhea, right-sided heart failure and bronchial constriction [3]. Some patients develop severe abdominal pain due to intestinal obstruction caused by the primary tumor or mesenteric lymph node metastases before the occurrence of liver metastases [4]. When tumor spread is limited, radical surgery aims to remove all visible tumors. However, it is well known that most patients relapse after a period of remission that varies considerably. In 1987, Moertel [5] presented a paper including 72 patients with localized midgut carcinoid tumors who underwent curative surgery. Seventy-seven percent were eventually diagnosed with recurrent disease after a median of 16 years. No information was available on whether the recurrences were established because of continuous monitoring or whether patients sought medical care when new symptoms had developed. In another study by Wangberg et al. [6], 14 patients with intentional radical surgery had a 5-year survival of 100%. However, when investigated by somatostatin receptor scintigraphy, 7 patients (50%) were diagnosed with a recurrence. To our knowledge, there are no other previous studies in which patients have been followed after radical surgery with the intention to diagnose relapse of the tumor at an early stage.

In similar tumor entities, such as gastrinomas and patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome, which were previously regarded as fairly benign conditions that do not interfere with survival, it has been shown that an active screening and surgical treatment prolonged survival compared to untreated controls [7, 8].

We studied patients who were radically operated for their midgut carcinoid tumors and referred to our center for follow-up. They have traditionally been investigated with measurements of plasma chromogranin A (P-CgA), collection of urinary 5-hydroxyindoleacetic acid (U-5HIAA), computerized tomography (CT) and/or ultrasonography (US), at least every 6–12 months. During later years, somatostatin receptor scintigraphy has been performed at the first visit after operation and ^{11}C-5-hydroxytryptophane positron emission tomography (^{11}C-5-HTP PET) has been performed in selected cases. We present here our experiences of these different methods used in the follow-up of radically operated patients with midgut carcinoid tumors.

Materials and Methods

Patients

All patients referred to our center between 1985 and 2004 with radically operated midgut carcinoid tumors, except those with tumors located in the appendix, were included in this retrospective study. The 56 patients, 31 men and 26 women, had a median age of 59 years (range 26–84). All patients had tumors that were CgA- and serotonin-immunoreactive and/or argyrophil and argentaffin reactions. Ki-67 was calculated in 24 patients and was <2% in all specimens investigated. All patients had lymph node metastases at operation. In 2 patients, single liver metastases were removed during surgery. In 38 patients (68%), an acute operation had been performed at the local hospital whereas 18 (32%) underwent elective surgery by an experienced carcinoid surgeon at the University Hospital in Uppsala. Both the surgical report and the pathology report had to agree on the radicality of the operation before the patient could be included in the study.

Follow-Up

All patients were evaluated at our clinic 1–3 times per year with measurements of P-CgA and U-5HIAA. P-CgA was analyzed as described previously with an upper reference limit of <4 nmol/l. The reference limit was calculated as the median level +2 SD in a healthy population [9]. With regard to normal fluctuation in P-CgA [10], pathologically elevated P-CgA was defined as 3 consecutive measurements with values above the upper reference limit. U-5HIAA was calculated as the mean of two 24-hour urine collections with an upper reference limit of 50 μmol/24 h. CT or US was performed and reviewed by an experienced radiologist every 6 months. Somatostatin receptor scintigraphy and/or ^{11}C-5-HTP PET was performed at the first visit and later only if the patient presented with clinical symptoms or US/CT indicated recurrent disease. Somatostatin receptor scintigraphy was generally performed at the first visit from 1992 and onwards, while ^{11}C-5-HTP PET examinations were available from 1993 and only performed in selected cases.

Other conditions known to influence the circulating P-CgA levels, such as the use of proton pump inhibitors, presence of chronic atrophic gastritis and renal failure, were documented.

Definition of Recurrent Disease

Our current clinical praxis and this study define recurrent disease as one of the following events: (1) tumor cells detected in a new tissue specimen obtained by surgery or biopsy; (2) a tumor lesion visualized by two radiological methods (US, CT, MRI, somatostatin receptor scintigraphy or ^{11}C-5-HTP PET), or (3) a tumor lesion shown by one radiological method in combination with at least one biochemical tumor marker increased above the upper reference level.

Ethics

This study was performed according to the Declaration of Helsinki and all patients consented to the data collection and management.

Table 1. Summary of patients with radically operated midgut carcinoid tumors where one or more markers were first to indicate recurrence

First method that indicated recurrence	Patients n	Median time until first indication of a recurrence	Median time until radiologically confirmed recurrence
P-CgA	22	6 months (2–148)	37 months (6–217)
P-CgA+radiology	2	53 months (10–96)	53 months (10–96)
P-CgA+U-5HIAA	3	5 months (3–8)	18 months (10–33)
P-CgA+radiology+U-5HIAA	1	21 months	21 months
U-5HIAA	2	37 months (2–72)	58 months (25–91)
Radiology	3	20 months (8–76)	35 months (20–80)

Table 2. Results from radiological methods

	CT	US	^{11}C-5-HTP PET	SRS
Total positive	14	12	14	8
Confirmed using an additional method within 3 months	11/14	8/12	6/14	5/8
Total false negatives[1]	15	13	0	6

CT = Computer tomography; US = ultrasonography; SRS = somatostatin receptor scintigraphy; ^{11}C-5-HTP PET = carbon 11 marked 5-hydroxytryptophan positron emission tomography.

[1] Negative result 3 months prior to or at any occasion following tumor identification with another radiological method.

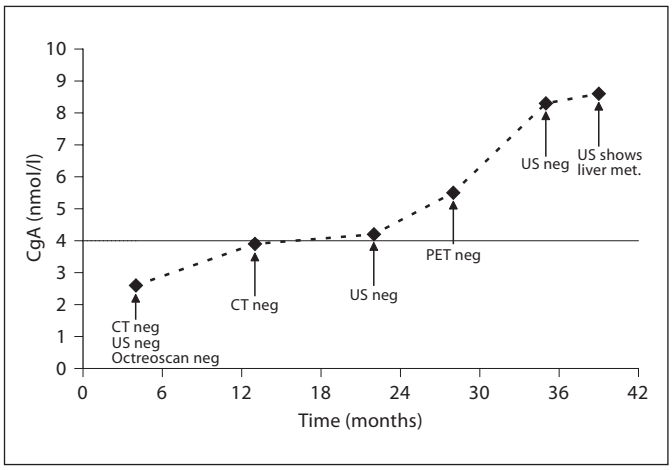

Fig. 1. Results from P-CgA measurements and radiological investigations in a patient operated with resection of the primary midgut carcinoid tumor and lymph node metastases (time 0). Adjuvant interferon treatment was initiated after 4 months and continued for 24 months. Before the interferon treatment was interrupted, an US and ^{11}C-5-HTP PET was performed to exclude recurrence of the tumor. However, already after 22 months, P-CgA had increased and reached the upper reference level. P-CgA continued to increase after the interferon treatment was withdrawn and 12 months later, carcinoid tumor metastases could be suspected with an US after 39 months and confirmed with somatostatin receptor scintigraphy and a biopsy of the tumor after 42 months.

Statistical Methods

Patient survival was calculated with the Kaplan-Meier method, causes of death other than the carcinoid disease were censored. Time until recurrence is reported in the text as median time in months with the range in parentheses.

Results

The median duration of follow-up was 90 months (15–270). Thirty-three patients (59%) demonstrated recurrence of their midgut carcinoid tumor. The results are summarized in tables 1 and 2.

The time from operation until radiological recurrence established in the 33 patients was 32 months (6–217). The first indication of recurrence, however, was observed after a median of 8 months (2–148). P-CgA was the first marker to be elevated in 28 (85%) of these patients. Radiology was simultaneously positive in only 3 patients and U-5HIAA was elevated in 4, whereas P-CgA was initially elevated without radiological or other biochemical signs of recurrence in 22 patients. P-CgA continued to be elevated for a median of 30 months before the recurrence was confirmed either by radiology or in 1 patient by surgery due to adherences. There was no difference in time until recurrence for the 2 patients with liver metastases when compared to those without liver metastases (30 and 51 months). The time course of a typical patient in this group is illustrated in figure 1.

In only 3 patients, radiology was the first method to indicate the recurrence (1 with ^{11}C-5-HTP PET, 1 with CT and 1 with somatostatin receptor scintigraphy) after 8, 20 and 76 months. An increase in U-5HIAA was the first indication of recurrent disease in 2 patients after 2 and 72 months. In these patients, the recurrence was confirmed with radiology (^{11}C-5-HTP PET and CT) 23 and 19 months later. In 4 of these 5 patients, P-CgA became pathological after some time; the fifth patient was lost to follow-up.

Twenty-three patients, with a present median time from surgery of 36 months (15–270), are still by definition tumor-free. However, among these, 10 patients have had increased P-CgA for a median of 32 months (16–119), but radiological investigations have failed to show any sign of recurrent tumor. None of these 23 patients has increased levels of U-5HIAA.

The 5-year survival for the whole group was 96% while the 10- and 15-year survival was 92%. No differences were recorded between patients operated at a local hospital or at the University Hospital in the frequency of or time until recurrence. To date, 59 and 61%, respectively, have recurrences and the time until relapse is similar in the two groups.

Factors Influencing CgA Levels

In 5 patients with recurrence of the carcinoid tumor and elevated CgA, confounding factors which might contribute to the increased CgA levels could be identified. Two patients were treated with proton pump inhibitors at a stable dose throughout the follow-up period (P-CgA varied between 4.5 and 7 nmol/l in 1 patient and between 6 and 11 nmol/l in the other), 1 patient had chronic atrophic gastritis (with P-CgA levels varying between 4 and 9.8 nmol/l during follow-up) and 2 demonstrated a minor renal failure with slightly increased but stable P-creatinine. The confounding factors were constant during follow-up while P-CgA increased.

Discussion

In this retrospective study, 33 of 56 patients who had been radically operated for a malignant midgut carcinoid tumor had recurrence of their disease after a median of 35 months. In 22 of these 33 patients, P-CgA was the earliest marker to indicate a recurrence and radiology or surgery confirmed recurrence after a median delay of almost 3 years. In an additional 3 patients, elevated P-CgA was recorded simultaneous to positive radiological findings. This is, to our knowledge, the first study comparing the usefulness of P-CgA, U-5HIAA and radiological investigations to detect midgut carcinoid tumor recurrence early.

P-CgA is a widely used marker for neuroendocrine cells. It is produced and stored together with peptide hormones in the large dense-core vesicles of the cells. When released from secretory granules, it is cleaved in different ways depending on the organ involved. Diagnostic methods using antibodies that target different parts of the CgA molecule can, therefore, vary in their sensitivity [11]. In our analysis, polyclonal antibodies which recognize the whole CgA molecule optimize CgA detection. P-CgA has previously been shown to correlate with tumor burden both in animal studies [12] and in patients with midgut carcinoid tumors [1]. It has also been shown to be a better biochemical marker than U-5HIAA in patients with limited midgut carcinoid tumor disease [13]. Furthermore, patients with recurrent endocrine tumors have higher P-CgA values than those without recurrent diseases [14].

In most of our patients, P-CgA increased slowly over time. Since P-CgA levels are correlated to tumor burden in carcinoid tumors, this slow increase in P-CgA may reflect tumor growth. In this material, 10 patients with elevated P-CgA still have no signs of tumor using radiological methods despite an increased P-CgA for a median of 32 months (16–119) and a follow-up time of a median of 47 months (18–119). We expect that a prolonged follow-up will lead to the confirmation of recurrence in some of these patients.

An increase of P-CgA can be seen in several benign conditions, including renal insufficiency [15], chronic atrophic gastritis [16] and medication with proton pump inhibitors [17]. In 5 patients, such factors were identified. These factors remained unchanged while the levels of P-CgA increased over time and eventually a tumor recurrence could be diagnosed. Our results suggest that increasing P-CgA levels should not be disregarded in patients with a known history of a carcinoid tumor, despite the presence of other factors that may induce P-CgA elevation.

Moertel [5] reported that after 25 years, 77% of 72 midgut carcinoid tumor patients had recurrent disease. The median time until recurrence was 16 years in their material. This is a much longer duration of remission than in our patients. Since the patient follow-up was not described in the Moertel material, only speculations can be made regarding these differences. It is possible that patients were not followed on a regular basis but diagnosed when recurrence of symptoms demanded medical care.

Furthermore, the improvement of biochemical markers (P-CgA and U-5HIAA) and radiology (CT) as well as the development of new techniques (somatostatin receptor scintigraphy and ^{11}C-5-HTP PET) makes it possible to detect smaller lesions today. Perhaps, with these investigations, recurrences are found earlier.

Wangberg et al. [6] had a 5-year survival of 100% in their study of 14 patients which corresponds to our study where the 15-year survival was 92%, indicating that these patients have a good prognosis. However, most patients with recurrences have received medical or interventional treatments, and this has of course an impact on their survival.

Three of the radiological methods (CT, US and ^{11}C-5-HTP PET) were comparably good at visualizing recurrences. ^{11}C-5-HTP PET is probably superior in detecting recurrences but was, in contrast to CT and US, not performed in all patients and not repeatedly. ^{11}C-5-HTP PET has previously been shown to be superior to CT and somatostatin receptor scintigraphy in detecting lesions in endocrine tumors [18]. However, very few centers have the possibility to perform ^{11}C-5-HTP PET due to technical difficulties in the synthesis of the tracer. Additionally, the cost is too high to perform ^{11}C-5-HTP PET repeatedly during standard follow-up. Therefore, ^{11}C-5-HTP PET is an investigation that should be restricted to selected cases where there is a suspicion of recurrent disease and other methods fail to verify the recurrence. Somatostatin receptor scintigraphy was done in all but 4 patients, however, not repeatedly during follow-up. This retrospective analysis may therefore underestimate its value. The comparative value of radiological methods should be verified in prospective studies.

Our results confirm that a majority of midgut carcinoid patients who are operated for locally advanced disease eventually develop metastases. Prolonged follow-up for this group of patients can, therefore, be justified even though they are asymptomatic. As pointed out in the Introduction, several other neuroendocrine tumor entities such as gastrinomas and MEN-1 patients that can be without symptoms for several years have been shown to have an impaired survival without medical care [7, 8]. It is therefore recommended to follow up these patients with radiological and biochemical screening.

We conclude that P-CgA is the most sensitive method to identify recurrent disease in patients with radically operated malignant midgut carcinoid tumors. Until now, our work-up schedules has included U-5HIAA, US, CT, MRI, somatostatin receptor scintigraphy and occasionally ^{11}C-5-HTP PET for imaging in addition to P-CgA. With the knowledge that P-CgA is the first marker to signal recurrence in a majority of cases, we suggest that asymptomatic patients with radically operated malignant midgut carcinoid tumors should be monitored by P-CgA measurements twice per year and, in suitable patients, US or CT annually. Patients who show elevated P-CgA or report symptoms of a carcinoid tumor (carcinoid syndrome or abdominal pain) should be examined by available imaging methods (US, CT or MRI, somatostatin receptor scintigraphy or ^{11}C-5-HTP PET) in order to localize the tumor and subsequently give the patient the best possible treatment which, if possible, should be surgical removal of the recurrence. Using this approach, recurrences can be diagnosed without clinically significant delay and costly and unnecessary examinations are avoided.

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