

## Long-term survival of patients with carcinoid tumor and liver metastases

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### Summary

**Purpose:** To determine long-term survival and long-term stable disease in patients with atypical carcinoid tumor with liver metastases.

**Methods:** From 1993 till 2008, the records of 56 patients with atypical carcinoid were reviewed. Nine of them who had liver metastases were analysed. All patients had carcinoid tumors confirmed histologically. Treatment, including chemotherapy and somatostatin, was given as palliative therapy of short duration.

**Results:** The median survival of 9 patients was 50 months (range 12-156). Three of 9 (33.33%) patients died of disease, at 12, 48 and 50 months. The remaining 6 patients are alive after 36, 40, 108, 120, 156 and 156 months, practically without treatment and experiencing a high quality of life.

**Conclusion:** Six of 9 (66.66%) patients are alive having received almost no treatment for many years.

**Key words:** atypical carcinoid tumor, liver metastases, survival

### Introduction

Carcinoid tumor is an uncommon disease which is often cured by surgery. It is classified as a neuroendocrine tumor and is categorized into typical or atypical carcinoid [1]. Carcinoids, as other neuroendocrine tumors, may secrete hormone-like substances, such as adrenocorticotrophic hormone (ACTH), arginine and vasopressin, and in such cases paraneoplastic syndromes accompany the disease [1]. Rarely is the disease aggressive with a shortened survival. Aggressive cases are mainly classified as atypical carcinoids and about 70% metastasize to the regional lymph nodes and/or to the liver, bone and brain. In the past, carcinoid tumors were considered to be benign tumors, similar to adenomas, until metastases were observed [2]. Neuroendocrine tumors, including carcinoid tumors, may involve children and adults, males and females (ratio 1.6:1) and the treatment of choice is surgery for localized disease [3]. In advanced or metastatic disease no effective treatment exists. Chemotherapy with a cisplatin-based or a streptozotocin-based combination has

often been administered. Biotherapy, including interferon and somatostatin analogues, is also given for palliation or symptom relief [4]. Octreotide, which is one of the somatostatin analogues, may relieve pain and is administered when octreoscaning is positive [5]. In the WHO classification, typical and atypical carcinoids differ in the number of mitoses (<2 vs. 2-10 per 10 HPF, respectively), polymorphism absent vs. present, low vs. high percentage of lymph node metastasis and rare vs. common metastatic disease at presentation [6]. One of the most common sites of metastasis of the atypical carcinoid tumor is the liver. Only rare data related to patients with liver metastasis exist.

The main objective of this article was to determine the survival of patients with liver metastases from atypical carcinoid who practically received no treatment apart from palliation.

### Methods

From 1993 till 2008, the records of 56 patients

with atypical carcinoid were reviewed. Among them 9 patients who had liver metastases on presentation or developed them within 6 months confirmed by biopsy were analysed. Six out of these 9 patients were asymptomatic; all remained without treatment most of the time. The patient characteristics are presented in Table 1. Patient evaluation was performed on presentation and then every 2-6 months with clinical examination, full blood count, serum biochemistry and CT scan of the chest and abdomen. Patients with long survival underwent a CT scan of the chest and abdomen once a year or every 2 years, depending on performance status, disease stability or progression. Urinary 5-hydroxyindoloacetic acid test was done after diagnosis and in case of disease progression.

### Treatment

All 9 patients but one had their primary tumor resected on first disease presentation. Two of these 8 patients had residual disease after the operation. The single patient without surgery was not operated because no primary disease site was detected at diagnosis. The disease of this patient was located in the liver where it was either primary or more possibly, metastatic. Five patients were treated with short-term somatostatin, when symptoms such as diarrhea and flashes were present. No anticancer treatment of any kind was given during most of their survival time. Two patients never received any symptomatic or anticancer treatment. Two patients (one of whom was treated before with somatostatin) were administered chemotherapy temporarily,

and one, a middle-aged female, received tamoxifen for 30 months as a single treatment, as mentioned below. Treatment is shown in Table 2. No other specific treatment was given and 6 of the patients remained with stable disease without treatment. One female patient initially received two courses of chemotherapy without response. She had a greatly enlarged liver (15 cm from the right costal arch) and severe pain which could only be relieved by morphine. She was put on tamoxifen and within 2 weeks the pain had been completely relieved. The liver remained enlarged (13-14 cm) and her performance status was 0-1. This recovery/clinical benefit lasted for 30 months; she then had disease progression and died at the end of the 3rd year following the initiation of treatment.

### Results

Three out of 9 (33.33%) patients died of disease at 12, 48 and 50 months. All of the remaining 6 patients are alive after 36, 40, 108, 120, 156 and 156 months. Median survival was 50 months (range 12-156). The 3 patients that died had slow but steady disease progression, while the 6 alive patients remain with stable disease. These patients are more or less asymptomatic and need no treatment. In 3 out of 6 patients, CT showed an approximate 10% increase in liver deposits every 3 years, but without liver enlargement and no abnormalities of the liver enzymes. Although mitoses were > 3-10, one cannot base the difference between the 3 progressive tumors vs. the 6 with disease stability on this histological finding. Figure 1 shows patient survival.

**Table 1.** Patient characteristics

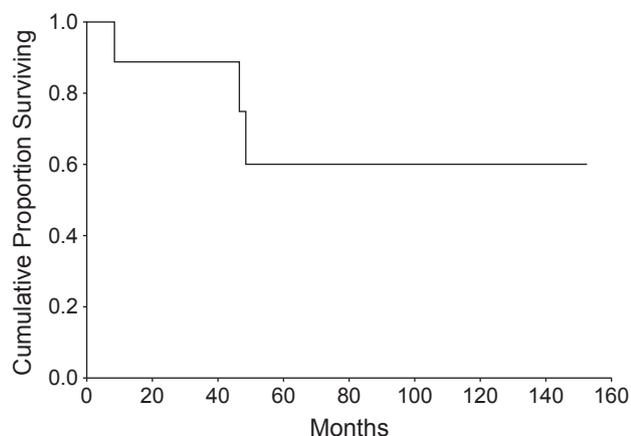
Characteristic	No. of patients
No. of patients	9
Age (years)	
Median (range)	66 (36-78)
Gender	
Male	5
Female	4
Histology	
Atypical carcinoid tumor	9
Mitosis > 3/HPF	9
Stage of disease	
IV	9
Primary site	
Intestine	4
Appendix	2
Lung	1
Stomach	1
Unknown primary	1
Total	9
Metastatic site	
Liver	9

### Discussion

The results presented in this article suggest that some carcinoid tumors may follow a malignant process

**Table 2.** Treatment administered

Treatment	No. of patients	Duration of treatment (months)
Somatostatin	4	3-8
(Octreotide)	(1)	3
Chemotherapy	2	1-2
(Somatostatin)	(1)	6
Chemotherapy	1	1
(Tamoxifen)	(1)	30
No treatment	2	
Total	9	



**Figure 1.** Long-term survival of patients with carcinoid tumor and liver metastases.

indicated by metastases in the liver. Neuroendocrine tumors are slow-growing and their natural history differs from that of other malignant tumors. The majority of neuroendocrine malignancies are resistant to chemotherapy or palliative treatment and patients often have a long survival. A good model of this behavior is the carcinoid tumor. The 3- and 5-year survival of patients with typical and atypical carcinoids is 100% and 81%, respectively for the former and 96% and 68%, respectively, for the latter. These survival data are presented in a review of carcinoid of the lung with the great majority of the patients having undergone surgery with complete tumor resection [7]. Another review reported a 5- and 10-year survival of 93.3% and 82.1%, respectively [8]; the latter study/review characterized the variety of the atypical carcinoids. This variety was also observed in our patients. The present study describes another parameter, or characteristic of the disease,

which is related to the behavior of the liver metastases. Such a parameter could be considered the long-term survival of patients with liver metastasis without anticancer treatment or surgical management. On the one hand, carcinoids with liver metastases may have a slow growth rate and lead to death after a few years and survival may be very prolonged as is shown in 6 of our patients with liver metastases. The survival of these patients ranged from 3 to 13 years with an approximate 10% liver disease progression which did not affect the quality of life. Such cases of carcinoid tumors could be classified as dormant malignancies.

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