

# Attitudes Towards Detection and Management of Hepatic Metastases in the Western World

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**Abstract**—In order to obtain insight in attitudes towards detection and management of hepatic metastases of colorectal origin, a questionnaire was sent to hospitals in 13 Western countries. Response rate was 98.0% (n = 284). In almost all hospitals (98%) some method of follow-up was employed. Carcino-embryonic antigen (CEA) determinations were performed in 84% of all hospitals: most frequently in Germany and the U.S.A., but only in 50% of the British hospitals. Hepatic resection for liver metastases was performed in 95% of all hospitals. Resectability criteria varied considerably among the countries. In the majority of German and American hospitals multiple hepatic metastases were considered resectable (including bilobar disease in 58% of German hospitals). In the majority of British and Dutch hospitals only solitary metastases were considered resectable, or liver resections were not performed at all. The mean reported number of liver resections annually per hospital, reflecting these attitudes, was 11.2 and 7.2 for German and American hospitals, and 2.1 and 1.8 for British and Dutch hospitals respectively. When irresectable hepatic metastases were diagnosed, some form of chemotherapy was applied in 74% of hospitals. Hepatic artery infusion of chemotherapeutics was performed most frequently. The mean reported number of medically treated patients annually per hospital was 34 for Germany, 18 for the U.S.A., and 12 and 9 for Great Britain and the Netherlands respectively. Adjuvant chemotherapy was performed after liver resection in 30% of all hospitals, most frequently in German and American hospitals.

Considerable disparity was observed in attitudes towards detection and in management of hepatic metastases among Western countries. On the basis of the reported 1421 liver resections and 3590 medically treated patients (annually) it is concluded that selection of the best detection and treatment policies is obviously hampered by insufficient clinical data and inconclusive evidence of purported optimal approach. To determine the optimal policy useful information can only be provided by inclusion of patients in prospective randomized trials.

## INTRODUCTION

HEPATIC METASTASES constitute an important source of morbidity and mortality from tumors arising in the gastrointestinal tract. Clinical interest in the disease is reinforced by reports on improved diagnostic procedures, such as frequent monitoring of carcino-embryonic antigen (CEA), and the extended therapeutic armamentarium. Hepatic resection for metastases is associated with low morbidity and mortality in specialized centers, and 5-year survival rates of 35% have been reported [1]. A recent impetus to continuous regional chemotherapy was the advent of the totally implantable infusion pump, and it is estimated that over 6000 pumps have been implanted over the last 5 years in

the U.S.A. Many modes of the new diagnostic and therapeutic armamentarium have not been properly evaluated yet. This has resulted in considerable controversy among the clinicians of Western countries with respect to optimal detection and treatment policy. In some countries, the more aggressive approach is adopted to offer a chance of cure or palliation for a—sometimes small—number of patients, often at a cost of considerable side-effects. In other countries the prevailing attitude is dominated by a more conservative point of view, with clinicians not being convinced of the ultimate therapeutic benefit.

This report is based on an international questionnaire with data from 284 hospitals in 13 countries, and assesses the various attitudes among Western countries with respect to this oncologic problem. The report could set the stage for discussions on reasons for the prevailing attitude in each country.

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Table 1. Number of forms received from each country

Country	Number	%
U.S.A.	105	37.0
The Netherlands	67	23.6
Great Britain	34	12.0
France	25	8.0
Germany	19	6.7
Others	34	11.6
Total 13 countries	284	100

A re-thinking of attitude seems indicated if reluctance to impose a new policy is merely based on traditionalism, or on the other hand, if a 'technology imperative' results in adopting any innovated, but unproven approach.

### MATERIALS AND METHODS

A questionnaire was initiated in 1985 among 284 hospitals in 13 Western countries. University hospitals and affiliated clinics were selected in the Netherlands. The other notified European hospitals were members of the EORTC\*-G.I. group. Major university hospitals in the U.S.A. were selected. The number of hospitals per country, from which the forms were obtained, is shown in Table 1. 'Other' countries included Belgium (9 hospitals), Italy (9), Switzerland (5), Spain (4), Sweden (4), Israel (1), Austria (1), Canada (1) and these hospitals accounted for 11.6% of all hospitals. Overall response rate was 98%. In the U.S.A. some forms were distributed further by the recipients, resulting in a 112% response rate. The questionnaire recorded information on detection, surgical and medical treatment of hepatic metastases from colorectal origin.

### RESULTS

#### 1. Detection of hepatic metastases

A method of follow-up with the aim of detecting hepatic metastases was employed in almost all hospitals (98.2%). Clinical signs and symptoms were used as exclusive indicators in 2.1% of the hospitals, combined with liver function tests in 4.6%, and with imaging techniques in 7.7%. In the majority of hospitals (83.8%) CEA was used to indicate recurrent tumor growth, including hepatic metastases. CEA and liver function tests were used during follow-up in 18.7% of all hospitals, and were combined with imaging techniques in 56.2%. The percentage of hospitals per country, in which CEA is used as follow-up parameter, is presented in Table

2. CEA was used most frequently as an indicator in German and American hospitals (100% and 97.2%, respectively), while in British hospitals this percentage amounted to 50.

#### 2. Therapeutic management

**Surgical therapy.** The criteria for resection based on hepatic involvement and the mean estimated number of liver resections per year in each hospital where surgical therapy is performed (94.7% of all hospitals) are presented by country in Table 2. The most aggressive surgical attitude was exhibited in German hospitals: in 94.7% of these hospitals multiple hepatic metastases were considered resectable, including bilobar involvement (in 57.9%). A more or less similar attitude was found in American hospitals, while in the other countries clinicians were more conservative in this respect. These attitudes were reflected in the mean reported numbers of liver resections per hospital, comprising a total number of 1421 liver resections annually in the 269 hospitals performing these procedures.

**Medical therapy.** When hepatic metastases were detected which were considered inoperable, some form of chemotherapeutic treatment was performed in the majority of hospitals (73.9%). Systemic chemotherapy was given in 13.3% of all hospitals, hepatic artery infusion of antitumor agents in 35.8% and both in 22.9%. In Table 3 the frequency of chemotherapeutic treatment and method of administration is presented per country. Again, chemotherapeutic treatment was performed more frequently using more sophisticated methods (local or a combination of systemic and local infusion) in the German and American hospitals, while in the hospitals in other countries the more conventional systemic administration was preferred, if any. The mean reported number of treatments was 17.1 per hospital per year, adding up to 3590 treated patients annually for all hospitals performing this treatment (74% of all hospitals). Although 26% of all hospitals reported that no further medical treatment was considered when inoperable hepatic metastases were diagnosed, still a total of 106 patients were treated with chemotherapeutic drugs annually in these hospitals (mean 1.4 per hospital).

Adjuvant chemotherapy after resection of hepatic metastases was administrated in 30% of all hospitals, where liver surgery was performed (distribution shown in Table 3). This mode of therapy was most frequently employed in German and American hospitals.

### DISCUSSION

Consistency was observed by country in approach towards detection of hepatic metastases, and treatment with respect to criteria for resection, number

\*European Organisation for Research and Treatment of Cancer.

Table 2. Percentage of all hospitals where CEA is used during follow-up, employed criteria for resection and mean reported number of liver resections annually per hospital performing this procedure

	Germany	U.S.A.	France	Great Britain	The Netherlands	Others	Total (%)
Screening with CEA (% of all hospitals)	100	97.2	88	50	73.1	84.8	83.8
Criteria for resection: (% of all hospitals)							
No surgery	—	—	—	5.9	17.9	3.0	5.3
One solitary metastasis	5.3	27.4	20.0	47.1	47.8	27.3	29.2
Multiple unilobar metastases	36.8	40.6	64.0	44.1	31.3	60.0	46.1
Multiple bilobar metastases	57.9	32.0	16.0	2.9	3.0	9.1	20.2
Mean number of liver resections per hospital per year	11.2	7.2	3.4	2.1	1.8	6.0	5.3

Table 3. Percentage of all hospitals, where chemotherapy for hepatic metastases is given, administration methods, mean reported number of patients treated annually per hospital performing this treatment, and percentage of hospitals where adjuvant chemotherapy after liver resection is given

	Germany	U.S.A.	France	Great Britain	The Netherlands	Others	Total (%)
Chemotherapy: (administrated by % of all hospitals)	100	97.2	52.2	44.1	47.8	84.8	73.9
Type of chemotherapy: (% of all hospitals)							
Systemic	10	15	4	15	13	12	13.3
Local	53	43	36	21	15	42	35.8
Both	37	33	8	6	16	24	22.9
Other	—	6	4	3	3	6	3.7
Number of treatments per hospital per year	34.3	18.0	15.1	12.1	9.1	14.7	17.1
Adjuvant chemotherapy: (% of all hospitals)	47	47	24	9	9	44	30

of liver resections performed and mode and frequency of chemotherapy. However, there is considerable variability in prevailing detection and treatment policies among Western countries. Conclusions from these data should be drawn with care, since the notified hospitals were not randomly selected, nor evenly distributed over the countries. Still with these drawbacks in mind, useful information could be derived.

Some form of follow-up was employed in almost all hospitals. Recent reports, mainly from the U.S.A., evaluating follow-up of colorectal carcinoma, indicated an increased resectability rate using frequent monitoring of CEA [2, 3]. This higher resectability rate resulted in a 29% 5-year survival rate in the one large study with survival results [2]. In almost all American and German hospitals CEA was used during follow-up, but in

only 50% of the British hospitals.

Hepatic resection for metastatic disease has been recognized as the only curative treatment available, with overall 5-year survival rates ranging from 25 to 35% [1, 4, 5]. Surgical therapy was not performed in 17.9% of Dutch hospitals. Bilobar hepatic involvement was considered irresectable by approx. 70–97% of all hospitals, except for the German hospitals. But bilobar hepatic involvement was found to be an important risk factor for development of hepatic recurrence after resection in a recent cumulative review of 607 patients with liver resection from 24, mainly American, institutions [1]. Hepatic resection has been shown to produce worthwhile benefit in terms of survival; however, only a small group of patients is suitable for this procedure. Clear indications for liver resection (e.g. with respect to liver involvement) cannot be derived from currently

available clinical data. Further clinical trials are needed to establish useful criteria for liver resection.

As with surgical therapy, chemotherapy was applied most frequently in German and American hospitals, and the lowest frequency was observed among British and Dutch hospitals. Chemotherapy has not been able to cure patients with metastases from colorectal origin. Based on uncontrolled studies survival benefit has been claimed, but this has not been proven in prospective randomized trials including a no-treatment control group. Furthermore, the data at this time do not provide compelling evidence of survival benefit after local infusion chemotherapy as compared to systemic administration [6]. Still, from the data it can be concluded that patients with irresectable hepatic metastases are treated in the majority of hospitals most frequently with chemotherapy administered by local infusion. Interestingly, in addition, clinicians who did not consider chemotherapy as a treatment option did treat a number of patients with irresectable hepatic metastases using chemotherapy, possibly at the patients' request. Adjuvant chemotherapy after liver resection must be considered experimental [7].

Hepatic resection of colorectal metastases has a proven curative role in those few patients having up to three metastases in the liver. For the majority

of patients with hepatic metastases there is no treatment to date that has proven to be a real break-through, resulting in the current disparity of treatment approaches. Clinicians, who are expected to and hope to help each patient with hepatic metastases who is seen, are naturally inclined to fall back upon the conventional wisdom, the lack of real wisdom and the poorly controlled wish to help all patients in some way. In fact, many of the detection and treatment methods should be considered investigational, and their routine use is probably not justified outside the setting of a clinical trial. However, the 1421 liver resections and 3590 medically treated patients (annually) reported in this study exceed by far the number of cases reported in the literature. There is an obvious need for the inclusion of patients with hepatic metastases in prospective randomized trials. Only by a cooperative approach can meaningful answers be found, which are indispensable for the design of an optimal policy in the management of this oncological problem.

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