

## Follow-up of colon cancer : detection of liver metastases : benefit and periodicity

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### Abstract

The aim of a follow-up programme in patients with cancer is to detect relapse or metastases in an early asymptomatic stage. This is only useful if the diagnosis of recurrence has implications for treatment and if early treatment of recurrence leads to an improved prognosis. This is certainly the case for liver metastases of colon cancer. Surgical resection of localised liver metastases has a 25-30% 5-year survival. Early chemotherapy for non-resectable metastatic disease improves the survival and prolongs the symptom-free period in comparison with chemotherapy starting at the onset of symptoms.

Follow-up for colorectal cancer should be offered to patients with the highest risk of recurrence and should consist of clinical examination, CEA monitoring, ultrasound of the liver, chest X-ray and periodic colonoscopy. Issues for further research are the determination of a follow-up programme with the highest sensitivity, the determination of the periodicity of follow-up, the search for prognostic factors for recurrence, cost issues and the final proof of a survival benefit in a large follow-up programme.

Conclusions : Indirect evidence supports the need for a good follow-up programme for colorectal cancer focussing on the detection of liver metastases. (*Acta gastroenterol. belg.*, 1998, 61, 8-10).

Key words : colon cancer, follow-up, liver metastases, recurrence, CEA, imaging methods.

### Introduction

The search of liver metastases in patients with colorectal cancer is part of a general follow-up programme. The follow-up in these patients is directed towards the detection of liver- and lung metastases, of a local recurrence and of a metachronous colon cancer and/or adenomas.

Several controversial questions have to be answered on the follow-up of colorectal cancer :

- Is a follow-up programme beneficial for the patient ?
- How should follow-up be done ?
- Is a follow-up programme cost-effective ?

### Clinical evolution of colon cancer

Colorectal cancer is one of the most frequent cancers in Belgium. More than 4200 new cases are diagnosed every year in Belgium. Fourty to 50% of these patients will develop recurrence. The majority of these recurrences are not curable by surgery or by any other treatment modality. The median survival of untreated recurrent colorectal cancer is extremely poor and does not exceed 6 months. A small proportion of patients with a recurrence can be offered a curative surgical reintervention, especially when recurrence is detected

in an early stage. The most frequent site of recurrence of a colorectal cancer is the liver.

The search for prognostic factors for recurrence is extremely important to try to make a follow-up more efficient. Most intensive follow-up could be directed towards patients with the highest risk of recurrence. Our knowledge of the prognostic factors for recurrence is at this moment rather limited. The prognostic factors are actually mainly based on pathological staging criteria (Dukes Staging System or Modified Dukes Staging Classification or the TNM Classification). New parameters are certainly needed. The development of the molecular biology could be of help in the future. It has indeed been suggested that factors such as thymidylate synthase concentration or the presence of p53 mutation could be of prognostic significance.

### Conditions for a follow-up programme

It is generally accepted that a follow-up for a malignant disease is only useful if several conditions are fulfilled.

1. Recurrence should be frequent. The search of an extremely rare event in an asymptomatic patient is usually not rewarding and not cost-efficient.
2. The diagnosis of an asymptomatic recurrence should have an impact for the treatment. The resection of liver metastases or lung metastases of colon cancer can be curative. A five-year survival of approximately 25-30% is reported in most series (1). It is also known that the majority of the patients with resectable liver- or lung metastases are asymptomatic. If a surgical resection is not considered, a chemotherapeutic treatment can be proposed. Once symptoms occur, the disease is often more widespread. In a large randomised trial the benefit of chemotherapy was shown in asymptomatic patients with metastatic colon cancer. In this study patients with asymptomatic metastatic colon cancer were randomised between chemotherapy at the moment of diagnosis and chemotherapy at the moment of the occurrence of symptoms. The survival, the

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symptom-free survival and the quality of life were significantly better in the group that received early chemotherapy (2).

3. A sensitive and specific method of follow-up that is acceptable for the patient and that is cost-effective should exist. The role of CEA, ultrasound, chest X-ray and colonoscopy in the follow-up group of colon cancer will be discussed later.
4. A group of patients with the highest likelihood of recurrence can be determined so that the most intensive follow-up programme can be directed towards those patients. At present the prognostic classification of colon cancer is based on the pathologic staging (TNM).

### Benefit of follow-up

A clear survival benefit of a follow-up programme in colon cancer has not been proven in prospective randomised trials. It is very unlikely that a survival benefit will be shown in future prospective randomised trials between follow-up and no follow-up. Large numbers of patients are needed in such a trial. Moreover many clinicians and investigators think it is at present not acceptable not to follow patients who have been operated for colon cancer.

A meta-analysis of 7 non-randomized trials suggests a small survival benefit of 4% for patients when follow-up of patients with colorectal cancer is done (3). With intensive follow-up based on frequent CEA monitoring a survival benefit of 9% has been shown because frequent CEA assays can identify treatable recurrences at a relatively early stage (3). Treatment of these recurrences appears to be associated with improved 5-year survival rates. This small relative benefit is translated into a large absolute benefit since colon cancer is a frequent cancer.

Indirect arguments are also very important to take into consideration when examining the question of the possible benefit of a follow-up programme. In the follow-up studies the detection of recurrence was in an asymptomatic stage for the majority of the patients (43-83%) (4-6) and the rates of reoperation were very low when the patients were symptomatic. The occurrence of symptoms usually reflects disseminated disease.

Surgery can be curative for liver metastases. The overall 5-year survival of patients who have undergone a hepatic resection for liver metastases is 25-30% (1). In a very large follow-up study of 1718 patients with liver metastases from colorectal cancer, 434 could be operated with curative intent. The median survival was 7 months for the 1249 patients who were not operated and the 5- and 10-year survivals of the operated patients were 39 and 23% respectively (1). Among the patients with symptomatic metastases, only very few could be operated suggesting that liver metastases should be detected before they become symptomatic (1). Although solitary lung metastases or a few lung metastases limited to one lobe of the lung are more rare, the same

conclusion can probably be made for lung- than for liver metastases. The results of the resection of lung metastases are similar to those of resection of liver metastases. Therefore the follow-up should certainly focus on liver metastases, but lung metastases cannot be neglected.

It is also clear that a follow-up programme for this purpose is not indicated in patients who are not fit for reoperation.

Another indirect argument is the demonstration of the benefit of early chemotherapy when metastatic disease is still asymptomatic compared to the start of chemotherapy when symptoms are present (2). Patients remain for a longer period symptom-free and have a better quality of life when chemotherapy is started early. The survival is also significantly longer when chemotherapy was started early (2).

### Methods of follow-up

The clinical assessment (anamnesis and clinical examination) rarely produces sufficient information to allow surgery. The determination of the level of alkaline phosphatase and transaminases has a very low sensitivity for the detection of metastases in a stage at which surgical resection can be performed (7, 8).

The determination of the CEA concentration plays certainly a role in a follow-up programme of patients with colon cancer. An increased CEA concentration is often a first indication of recurrence: it is elevated in > 50% of all patients with recurrence and in  $\pm$  80% of patients with liver metastases. The diagnosis of recurrent disease may be several months earlier by investigating the first abnormal CEA-level compared to the clinical follow-up. The detection of recurrence can also be done earlier with CEA monitoring than with CAT-scan monitoring (9).

A benefit in survival with CEA is not clearly proven in randomized trials (10, 11). A meta-analysis of non-randomized trials, however, suggests a survival benefit. In this meta-analysis with 3283 patients, it is suggested that intensive follow-up based on CEA may improve the 5-year survival rate by approximately 9% compared to a less intensive follow-up (12).

Abdominal ultrasound is often used to detect liver metastases (13, 14). The detection of liver metastases is size-dependent and also operator-dependent. In most studies the sensitivity of ultrasound is lower than of CEA and recurrences are most often found earlier with CEA monitoring than by ultrasound, but ultrasound is not done so frequently in these studies. Although no data from randomized trials on the real benefit of abdominal ultrasound in the follow-up of patients with colon cancer are available, many clinicians and many investigators propose ultrasonography in the follow-up programme. Abdominal ultrasound is indeed a relatively cheap examination that is easily accepted by the patients. The sensitivity and the specificity for liver metastases are relatively high.

### Periodicity of follow-up

Only very few objective scientific data are available to answer the question of periodicity of a follow-up programme. Therefore a large variation in the periodicity of follow-up examinations is proposed in clinical trials and for clinical practice. This varies from monthly follow-up examinations to no further follow-up examinations after surgery.

It is clear however, that the most intensive follow-up has to be done during the first 2 to 3 years. An initial follow-up programme should be individualized for every patient based on the risk of recurrence.

A practical scheme could consist of determination of the CEA-level 4 times a year during the first 3 years after operation and of performing an abdominal ultrasound and a chest X-ray once to twice a year during this period. During the 4th or 5th year after the operation, the follow-up should probably be less intensive. Yearly CEA, abdominal ultrasound and chest X-ray could be advised. A total colonoscopy should be done at diagnosis to look for synchronous adenomatous polyps or cancers and thereafter at year 1, 3, 6 and further every 3 years.

### Psychological impact of follow-up

Several prospective studies have shown that an intensive follow-up after surgical intervention for colon cancer did not lead to psychological stress. Only in the subgroup of older, single and female patients, a higher level of psychological strain was found (15).

The compliance in the majority of follow-up trials was very high. In most of the trials, more than 90% of patients underwent the prescribed follow-up guidelines.

### Cost of postoperative monitoring

Intensive postoperative monitoring is certainly very expensive. No good data of the costs of a global follow-up programme are available. Most of the available data are on CEA monitoring. A general conclusion of these studies is that CEA monitoring is very expensive because the follow-up in these studies was not directed towards high risk subjects, because CEA monitoring has a relatively low sensitivity and specificity and because the survival benefit was compared with the total amount of the generated costs. No data are available on the cost of other methods such as abdominal ultrasound.

### Conclusions

The postoperative follow-up of liver metastases of colorectal cancer is controversial. Follow-up is only useful if the diagnosis of a recurrence has therapeutic implications. This is true for colorectal cancer.

There is at this moment no direct proof of benefit of a systematic follow-up programme, but there is indirect evidence of the usefulness of a follow-up programme. This indirect evidence is based mainly on the possibility to resect liver metastases with curative intention. It is also shown that early chemotherapy in asymptomatic patients can be of benefit.

The follow-up of patients with colon cancer should, however, be individualized according to the risk of recurrence and should be most intensive during the first 3 years after the surgical intervention.

Many unanswered questions remain and several issues for further research can therefore be proposed: the determination of the optimal follow-up programme, with the highest sensitivity and specificity; the determination of the best periodicity of a follow-up programme; the search for better predictive factors for recurrence; cost-efficiency, and the final proof of a survival benefit of a follow-up programme.

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