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Follow-up of patients treated by cytoreduction and chemotherapy for peritoneal carcinomatosis of colorectal origin

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Summary *Aim*. The aim of this study was to determine the value of medical history and physical examination, tumour marker testing, and CT-scanning in the follow-up of patients treated for peritoneal carcinomatosis of colorectal origin.

Methods. Between November 1995 and June 2003, 107 patients were treated by cytoreduction and hyperthermic intra-peritoneal chemotherapy. The treatment was considered effective if residual tumour after cytoreduction was no thicker than 2.5 mm. The follow-up consisted of history, physical examination, serum CEA and CA 19.9 testing three-monthly, and CT-scanning of the abdomen six-monthly. Location of the recurrence was categorized into intra-abdominal, hepatic, thoracic, and both intra-abdominal and systemic. The investigation that led to the detection of a recurrence was ranked according to its invasiveness and costs. The simplest investigation that could have led to the detection was marked.

Results. A recurrence developed in 63 patients of the 74 patients effective initial treatment during the study period. Physical examination revealed the recurrence in 38 patients, at least one of the markers was raised above normal value in 39 patients and in 37 patients the CT-scan showed the recurrence. History and physical examination could have triggered the finding of a recurrence in 38 patients, tumour markers in 21 patients and CT-scanning in only three of the 74 recurrences.

Conclusion. Physical examination and tumour marker testing detect most recurrences. CT-scanning is not an effective tool in the follow-up, and should be reserved for on-demand use.

Introduction

Peritoneal carcinomatosis is commonly seen in colorectal cancer and it is second to metastatic disease in the liver as cause of death. In some 25% of patients, no other tumour sites can be found.[1–3] The poor survival rate is improved by the introduction of new therapies, and more peritoneal carcinomatosis patients are now in follow-up.

The aim of follow-up is to assess the initial results of the therapy and to deal with treatment-related problems, including the early detection of

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recurrent disease. Early detection may provide a renewed chance of long-term survival in selected patients. The effectiveness of follow up investigations is difficult to assess.[4]

Our patients affected by peritoneal carcinomatosis have been treated in various study protocols.[5–7] The present study examines the value of this follow-up approach.

Patients and methods

Patients

Between November 1995 and July 2003, 107 patients treated by cytoreduction followed by hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis of colorectal origin were studied. There were 47 females and 60 males. The median age was 53 years (range 24–75). The primary carcinoma was located in the appendix in 15 patients, in the colon in 87 patients, and in five in the rectum. All these patients were treated in study protocols and their data were prospectively collected. Patients with histologically proven peritoneal carcinomatosis but without evidence of liver or lung metastases, up to 70 years of age and fit to undergo major surgery were eligible for this protocol. Both synchronic and metachronic carcinomatosis were allowed.

Treatment

The treatment consisted of cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) in all patients. The first 36 patients were entered in phase I and II studies. The following 47 patients were entered in a randomised phase III study and the remaining 24 patients were treated after finishing this randomised study. All patients were treated in accordance to the phase III study protocol. The treatment is described in detail elsewhere.[7] In summary, it consisted of aggressive surgical cytoreduction and HIPEC. Mitomycin C was used for intraperitoneal chemotherapy at a temperature of 40–41 °C for 90 min.

Classification of outcomes

The result of this treatment was rated as R-1 if there was no macroscopic tumour left behind; as R-2a if the residual tumour was not thicker than 2.5 mm and as R-2b in patients in which more tumour was left behind. Patients with R-1 and R-2a were seen as patient with complete response, as 2.5 mm is the penetration depth of Mitomycin C when intraperitoneal used.

After discharge and recovery, 5-fluorouracil/leucovorin was given as adjuvant therapy in a weekly, slightly-modified 'Laufman' regimen for 26 weeks.[8] Irinotecan was used with three-week intervals,[9,10] if 5-fluorouracil/leucovorin had been given within 1 year prior to HIPEC treatment.

Follow-up

The protocols required visits at the outpatient clinic every three months for two years and at six-monthly intervals thereafter. The follow-up protocol was as follows: history, physical examination and serum CEA and CA 19.9 at each visit, and a CT-scan of the abdomen six-monthly. If symptoms arose, a CT-scan or endoscopy was performed as required to determine their cause. A PET scan was obtained in case of a tumour marker rise and inconclusive CT-scan findings.

A local recurrence was defined as any new lesion revealed by physical examination or CT-scan compared to the first examination after the HIPEC procedure. When a lesion was found on endoscopy, a recurrence was diagnosed only if histological proof was obtained. In case of rising of at least one of the tumour markers above normal value, attempts were made to confirm the presence of a recurrence. If the tumour marker value kept rising, the patient was considered to have recurrent disease even if this could not be demonstrated despite an extensive search. Systemic metastases were defined as any lesion on CT-scan or chest radiography that was not seen at a previous examination. The location of a recurrence was classified into one of five groups: intra-abdominal, hepatic, thoracic, both intra-abdominal and systemic, or unknown.

For analysis of follow-up the patients were divided into those who had an effective cytoreduction and hyperthermic intraperitoneal chemotherapy (R-1 and R-2a) and those had failed treatment (R-2b). Of each recurrence, the least invasive test was determined that could have triggered further diagnostic work-up to reveal its presence. The following order was used to rank invasiveness: (1) medical history and physical examination (2) CEA and CA19.9 tests (3) CT-scan. Endoscopy and PET-scan were left out of this ranking because these investigations were only performed on demand.

Results

The 107 patients were followed for a median of 51

months (range 5.5–91.3 months). The cytoreduction resulted in a macroscopically complete (R-1) resection in 55 patients, in a resection with minimal residual disease (R-2a; maximum thickness of residual tumour 2.5 mm) in 37 patients, and in a gross incomplete resection (R-2b) in 15 patients.

Seventy-four patients developed recurrent disease within the study period. Sixty-three of the 74 patients with recurrence had effective initial treatment (R-1 and R-2a), while 11 of those patients failed that treatment. Most recurrences occurred intra-abdominally. The recurrence sites are summarized in Table 1. Details of the location of the recurrence were missing in four patients.

Twenty-four patients with an effective initial treatment had neither symptoms nor positive findings on physical examination at the time of recurrence. Table 2 summarizes the results of the initial effective treated patients of routinely done investigations at the moment of a recurrence and their relation with its location. A number of diagnostic tests were not performed at the moment of the recurrence and were classified as 'not done' in the table. The most common symptom of recurrence was bowel obstruction. The patients with a 'thoracic' recurrence had a palpable supraclavicular mass that was found on physical examination.

The tumour markers were raised above normal value in 39 of the 63 patients at the time of recurrence. CEA was raised in 20, CA19.9 in seven patients and both were raised in 12 patients. In 37 patients, CT-scan findings were positive for recurrence. Most liver metastases were asymptomatic and were found on CT-scans. Two patients had liver metastases that were missed on the routinely done CT-scan. These patients had rising tumour markers and a PET-scan eventually identified the location of the recurrence.

Nineteen patients underwent endoscopy at the time of recurrence. Seven endoscopies were done because of rise of tumour markers without clinical symptoms in the presence of normal CT-scan findings. Only one of these endoscopies indeed revealed a recurrence. A PET-scan was done in seven patients. In two patients this was done because of a tumour marker rise without any other positive finding, the other five scans were obtained as work-up for resection of recurrent disease.

Table 3 lists the ranking of the diagnostic tests that could trigger further investigations that would have led to the finding of a recurrence. This table shows that following up on positive clinical or laboratory findings could have identified 95% of all recurrences.

In patients who had a gross incomplete cytoreduction (R-2b) the progression was found in all cases by either physical examination or laboratory tests. One patient who progressed in the liver, one patient with effusion and in one patient the location of progression stayed undetected, all other patients progressed locally.

Discussion

The present study demonstrates that medical history and physical examination together with routine serum testing of CEA and CA19.9 identify 95% of the recurrences of peritoneal carcinomatosis after an effective treatment by cytoreduction followed by hyperthermic intra-peritoneal chemotherapy. These diagnostic tests provide neither location nor proof of the presence of recurrent disease in the majority of the cases, but they trigger further investigations to reach these goals. These results concur with other publications on follow-up of colorectal cancer patients.[11,12]

Until now, most patients affected by peritoneal carcinomatosis have been treated in study protocols. As cytoreduction with HIPEC was an experimental treatment, follow-up protocols were intensive to enable assessment of survival, disease-free survival, evaluation of toxicity and to allow medical audit. This position of HIPEC is

Table 1 Location and incidence of recurrence after HIPEC

	Number of patients (%)		
	All ($N = 107$)	R-1 and R-2a ($N = 92$)	R-2b ($N = 15$)
No recurrence	33 (31)	29 (32)	4 (27)
Intra-abdominal	47 (44)	40 (43)	7 (47)
Hepatic	13 (12)	14 (15)	1 (6.7)
Thoracic	2 (1.8)	1 (1.0)	1 (6.7)
Intra-abdominal and systemic	8 (7.5)	7 (7.6)	1 (6.7)
Unknown	4 (3.7)	3 (3.3)	1 (6.7)

Table 2 Results of investigations leading to 63 recurrences in 92 patients who had an effective treatment of peritoneal carcinomatosis of colorectal origin by cytoreduction and HIPEC

	Test results	All	Intra-abdominal	Hepatic	Thoracic	Intra-abdominal and hepatic	Unknown
Results of history and physical examination	None	24	11	11	-	-	2
	Obstruction	23	21	-	-	2	-
	Pain	6	2	1	-	3	-
	Mass	4	2	-	1	1	-
	Blood loss	5	4	-	-	1	-
	Unknown	1	-	-	-	-	1
CT-scanning results	None	21	16	2	-	1	2
	Mass	35	18	10	1	6	-
	Obstruction	2	2	-	-	-	-
	Not done	5	4	-	-	-	1
CEA and CA 19.9 testing	No change	18	12	3	1	2	-
	Rise[a]	39	24	9	-	4	2
	Not done	6	4	-	-	1	1

[a] Rise of at least one of the markers above normal value.

currently changing. Now that there is growing evidence of its benefit, HIPEC is becoming more or less 'standard' treatment. For this reason, follow-up schedules demand increasing resources in terms of personnel, facilities and finances.[13]

The efficacy of follow-up is often questioned. Steele concluded that most standard follow-up regimens are empirical and not based on cost-effectiveness or patient benefit.[4] This idea is supported by other studies that did not find a survival benefit.[12,14] There are no data available on the efficacy of follow-up in peritoneal carcinomatosis. Therefore, it is only possible to look at the analogy with the follow-up of colorectal cancer in general. CEA testing has been studied extensively in the follow-up of colorectal cancer patients. Serial testing of CEA proved to be of benefit in detecting recurrence.[15–17] In measuring CEA level it must be taken into account that 30% of the colorectal tumours do not produce tumour markers.[18] The use of CT-scans in the follow-up has been subject of many studies. In most of these studies and in the present study, a positive CT-scan concurs with an increase in CEA levels.[11,12,17] For these reasons, CT-scan-based follow-up is not recommended in the ASCO guidelines for follow-up of colorectal cancer patients.[19] CT-scanning, however, maybe useful to find liver metastases and in the follow-up of patients with tumours that do not produce CEA.[20] The most aggressive follow-up approach is a routine second-look operation. This approach is advocated by some groups dealing with pseudomyxoma peritonei,[21,22] peritoneal carcinomatosis of colorectal cancer,[23,24] or gastric cancer.[25]

Sugarbaker et al.[17] suggest that physical examination and serial CEA testing are the most useful modalities in finding recurrence of colorectal cancer. Still, there is not much evidence of the effectiveness of physical examination in finding a recurrence, despite its traditional routine application.[20] Data from the largest study on this subject showed that approximately 80% of recurrences were found by CEA testing, and only 20% was found by history and physical examination.[26]

The effectiveness of follow-up depends mainly on the possibilities to treat recurrent disease.[27] Only selected patients are expected to benefit from treatment of a recurrence of carcinomatosis of colorectal origin. After an incomplete cytoreduction, treatment of a recurrence is unlikely to be successful. Follow-up of these patients will never be effective in terms of renewed chances of survival. However, following these patients during their final state of disease will be useful to provide palliative care and moral support. Like in primary colorectal cancer, follow-up should be tailored to the stage of the disease, to the results of earlier treatment and to the potential of second-line treatment.[28–30]

Little has been published on follow-up after

Table 3 Least invasive investigation that could have led to the finding of 63 recurrences after successful cytoreduction and HIPEC

	Number patients	Percentage
History and physical examination	38	61
CEA and CA 19.9 testing	21	34
CT-scan	3	4.8

Data of one patient missing.

cytoreduction and HIPEC. To the knowledge of the authors there is only one study on this subject.[24] The approach in this study is aggressive, as it entails standard second-look procedures. The present study demonstrates that most recurrences can be found after relatively simple and inexpensive initial diagnostic tests. A reasonable follow-up schedule could be: baseline CT-scan with CEA and CA 19.9 testing, followed by standard physical examination and tumour marker testing at regular intervals. Abnormal physical examination or elevated tumour markers are the only indications for more invasive and costly tests.

One should appreciate the role of surgical expertise in the management of complications and recurrent disease after a major surgical procedure such as HIPEC. The generalist, the medical oncologist and the gastroenterologist typically take care of the patients' follow-up and must appreciate the curative potential and low risk of salvage surgery.[31]

In conclusion, physical examination and tumour marker testing are the most appropriate investigations in the follow-up after cytoreduction and HIPEC. CT-scan, PET-scan and endoscopy are useful 'on demand' tools for locating the suggested recurrence.

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