Searching for metastases in colorectal cancer

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Table of Contents

Introduction and outline of the thesis

Colorectal cancer (CRC) is a common disease, with a life time risk of ± 10% in the Western population and an incidence of 10.000 new patients each year in the Netherlands. In approximately half of these patients metastases are found, either at diagnosis or during follow-up. These metastases are usually localized in the liver, peritoneal cavity or the lung. In the past, metastatic CRC was frequently regarded as incurable and suitable for palliative treatment only. At present, various new and developing multi-modality treatment options for liver and lung metastases and peritoneal carcinomatosis offer a (second) chance on cure. This motivated renewed efforts to optimize 'searching for metastases' in CRC.

Staging before treatment

Finding metastatic disease at an early stage, is thought to increase the chances on curative treatment. The earliest possible moment is at the time of diagnosis of the primary tumor. Finding metastatic disease before treatment may also be relevant in non-curative situations; colorectal resections know a significant morbidity and mortality and it is not always necessary or helpful in reducing symptoms of the disease. The accuracy of the diagnostic method is as important as the practicality of the diagnostic trajectories in this common disease. The most accurate and widely available imaging technique is a CT scan. Staging with abdominal and chest CT as a routine procedure before treatment was introduced as part of a regional guideline on CRC in 2007. It was however unclear, which actual benefits could be expected from staging with CT before treatment. A CT scan is expensive and incidentalomas may complicate clinical decision making. Relevant questions such as the incidence of metastatic disease at diagnosis and the influence of staging on the treatment plan for the primary tumor, factually were unanswered. To address these questions, a prospective observational study was initiated in the Medical Spectrum Twente Enschede. A prospective registration of all patients that undergo colorectal surgery was designed and incorporated in daily clinical practice, starting January 2007. The outcomes of these studies, which concern the abdominal and chest CT are described in chapter 2 and 3.

Follow-up

After intended curative treatment of colorectal cancer, patients are subjected to a follow-up of 5 years. In general this consists of 3 to 6-monthly carcino-embryonic antigen (CEA) measurements and outpatient clinic visits, with an increasing habit of additional biannual ultrasound of the liver or a CT scan at regular intervals. The current Dutch guideline on follow-up does not give a clear recommendation, due to a lack of evidence on the optimal program and diagnostic tools.

With 10.000 new patients each year, follow-up has a considerable impact on the outpatient clinic and is expensive. Meanwhile, the benefits of follow-up - concerning the oncological outcome- have been highly disappointing. Often, the practice of follow-up in colorectal cancer has been questioned but nonetheless never abandoned. Despite the lack of evidence, oncological follow-up is considered important. Follow-up comprehends an effort to improve survival in cancer, it can offer support to patients that had a life threatening disease and await recurrences, and it informs on the functional outcomes after treatment. Follow-up contains a multitude of relevant medical aspects to be taken into consideration, such as recurrence patterns, diagnostic methods, therapeutic and palliative treatment options of recurrent disease. Also, not in the least, it has an important emotional side to both patients and doctors. An attempt to optimize follow-up such as has been done for this thesis, requires an approach in which all of these aspects are considered.

To study the opinion on follow-up among Dutch surgeons, a national survey on the opinion towards follow-up and its diagnostic methods was done. This study included an query on feasibility of a new national trial (chapter 4). Serum-CEA measurement has been the cornerstone of follow-up for 30 years. Advantages of CEA are the low costs and the practicality of use. Serum CEA however can only *signal* recurrent disease; its applicability as a diagnostic tool is largely determined by the ability to subsequently localize or exclude recurrent disease with imaging techniques. This has been a major problem in the past and has contributed largely to the downfall in appreciation of CEA as a valuable diagnostic tool in follow-up. With the coming of accurate, widely available and non-invasive imaging techniques, this situation may change radically. Our second aim was, to find evidence supporting or denouncing CEA as a diagnostic method in follow-up (chapter 5 and 6). The comprehensive review of the literature on CEA in follow-up that followed, resulted in a new follow-up design. This new design was tested in a non-randomized phase II trial carried out in 2008 and 2009 in the Medical Spectrum Twente and University Medical Center Groningen, on both logistic feasibility and outcome. The primary endpoint was eligibility for curative treatment of diagnosed recurrent disease. Secondary endpoints were the ability to localize recurrent disease with standard imaging techniques and estimation of the optimal threshold value. The first results from this trial were included in the hypothesis article (chapter 6). The results from a concomitant study concerning the psychological effects of this new type of follow-up on patients are described in chapter 7.

Tailoring follow-up

The population with colorectal cancer is very heterogeneous; the risks on recurrent disease during follow-up will vary to a great extent as well. Current follow-up guidelines do not

discriminate between risk groups. Adaptation of follow-up towards risk groups and expected time to recurrent disease, thus a 'tailor made' follow-up, may reduce unnecessary diagnostics in low risk groups and be a reason to (temporarily) intensify follow-up in high-risk patients. This will become relevant when intensive follow-up, as proposed for the national trial, will prove effective. The recurrence patterns however, are likely to have changed as a result of both staging before treatment, neo-adjuvant treatment in rectal cancer and adjuvant chemotherapy in colon cancer. Our hypothesis was that as a result of these changes, the average time to recurrent disease would be prolonged as compared to the 'old' situation. Data on recurrence patterns from literature were scarce and usually outdated. The recurrence pattern within one year after surgery in patients that were staged before treatment with abdominal CT and treated according to current standards, was analyzed. A limited risk group analysis on known and prospectively registered risk factors T stage, N stage and emergency presentations was done, as a first next step towards refinements in future follow-up designs. The outcomes of this study are described in chapter 8.

2

Staging with abdominal CT before treatment is an important step towards improving the (oncological) outcome in colorectal cancer

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Background. Advanced colorectal carcinoma (CRC) is present in a relevant proportion of patients. The chance on curation of metastatic CRC has been improving in the last decade. Further, less invasive procedures for incurable CRC may improve surgical mortality rates and the quality of life. Staging may optimize the outcome by changing the treatment plan.

Methods. This prospective observational study evaluates the outcome of routine staging with abdominal CT in an unselected hospital population with CRC concerning liver metastases (LM), peritoneal carcinomatosis (PC) and T-stage in colon cancer (CC).

Findings. In this cohort of 612 patients, 31% had metastatic CRC. Staging before treatment (SCT) was omitted in 16% of patients (non-SCT), mainly in patients with emergency presentations (30%). The ability to detect advanced disease was excellent for LM (99%), good for cT stage CC (86%) and poor for PC (33%). Staging changed the treatment plan concerning avoidance of resection of the primary tumor (SCT 5%, non-SCT 1%) and curative treatment of LM (SCT 24%, non-SCT 16%).

Interpretation. Staging can change the treatment plan in both curable and incurable CRC. Lead points to optimize staging routines in CRC could be identified. The relevance of staging before treatment is increasing with current developments in treatment of advanced CRC, with a probable favorable effect on the oncological outcome.

Background

Advanced colorectal carcinoma (CRC), that is either locally advanced or metastasized disease, is present in a relevant proportion of patients diagnosed with colorectal cancer. Synchronous distant metastases in CRC are usually localized in the liver, peritoneal cavity and the lung. Staging with chest CT as a routine procedure before surgery has not shown to be of clinical benefit, mainly due to the low incidence of clinically relevant lung metastases and low specificity of chest CT.[1-3] Pre-operative staging with abdominal CT might be beneficial when the accuracy of detecting metastatic CRC is high and the findings change the treatment plan. Such findings include liver metastases, peritoneal carcinomatosis and locally advanced colon carcinoma. These conditions were in the past frequently regarded as incurable and suitable for palliative measures only but nowadays various multi-modality treatments offer a chance of cure to selected patients.[4-15] For patients with incurable advanced CRC the treatment plan can be changed towards foremost the 'best palliative care', which is not necessarily a palliative resection.[16-18]

Findings in an unselected population with CRC that were routinely staged with abdominal CT, can be helpful in the debate on actual clinical relevance and preferred routing of patients with advanced disease.

Patients and methods

The data were collected in the Medical Spectrum Twente, a large community teaching hospital in the regional capital of a foremost rural area in the eastern part of the Netherlands. It functions as a regional referral center for liver and lung surgery, but has no facilities for the treatment of peritoneal carcinomatosis (PC) with hyperthermic intraperitoneal chemotherapy (HIPEC).

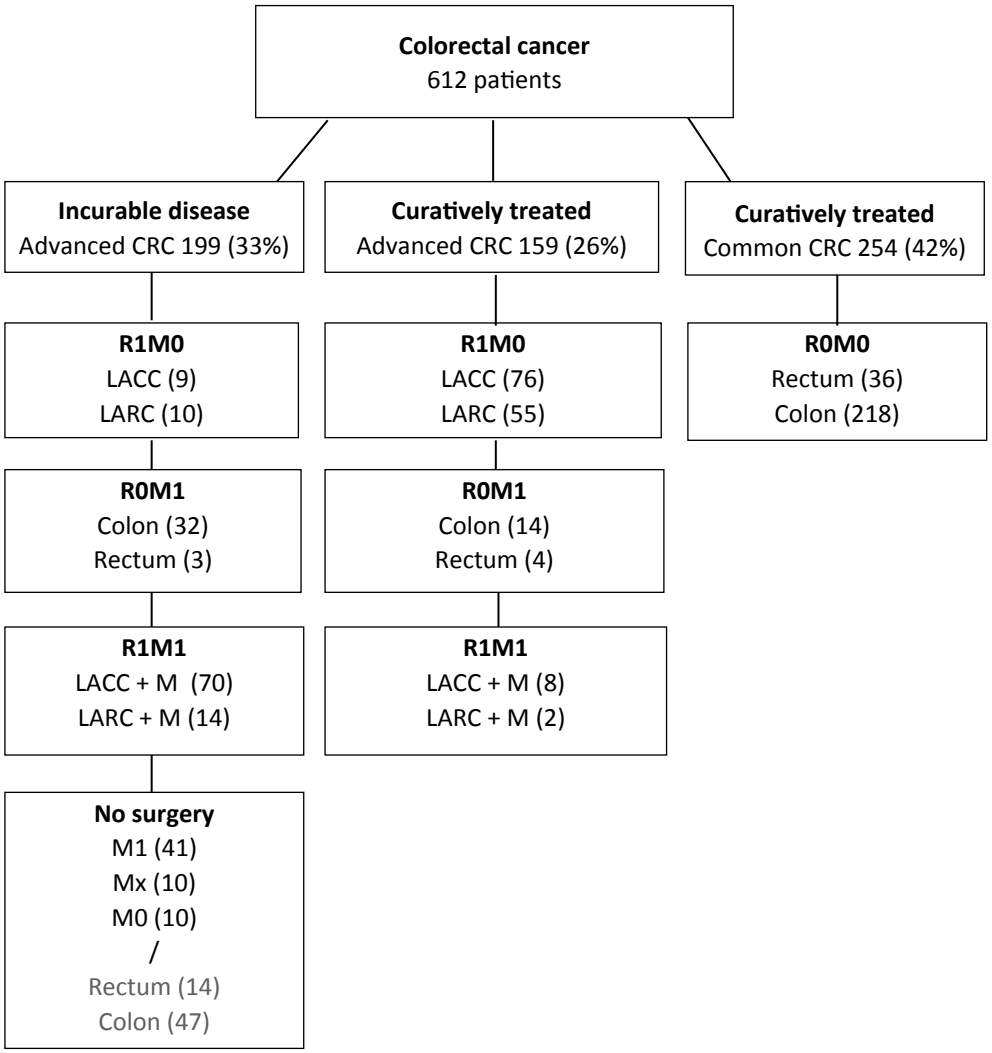
The study design is a prospective observational cohort study evaluating the outcome of routine staging with abdominal CT concerning liver metastases (LM), PC and T-stage in colon cancer (CC). Patients diagnosed with CRC from 2007 till 2009 were included in the analysis. All surgical patients with CRC in the study hospital are prospectively registered in a database designed for colorectal surgery. Patient characteristics, staging and operation procedures, the clinical M stage and pathological TNM stage, post-operative mortality, treatment of metastases and follow-up are prospectively registered. Patients with the diagnosis of CRC in the same 3 years who did not undergo surgery were identified by the regional cancer registry and retrospectively added to the database. The clinical T stage on abdominal CT was retrospectively scored based upon the original radiology reports.

Routine pre-operative staging CT of chest and abdomen for patients with CRC was introduced as a regional CRC guideline in 2007 and includes patients with emergency presentations. CT scanning was performed on a 16 and 64 slice scanner (Toshiba Aquillion 16 and 64) after intravenous contrast injection (visipaque 320, 90 ml, 3ml/s.), in the portal venous phase, with a slice thickness of 1 mm and a reconstruction of 0.8 mm. When preoperative scanning was omitted, staging with abdominal CT was intended within 3 months after surgery. Patients with rectal cancer (RC), defined as localization below the peritoneal reflection, were additionally staged with a pelvic MRI for determination of the local invasion and possible lymph node metastases (cTN stage) and treated with neo-adjuvant chemoradiation in case of locally advanced rectal cancer (LARC). From 2008, all colorectal surgery including emergency presentations is done or supervised by a specialized colorectal surgeon. Follow-up after curative treatment of non-metastatic CRC consisted of 3 monthly CEA measurements combined with biannual ultrasound of the liver.

Advanced CRC was defined as either locally advanced disease, presence of distant metastases or both. Locally advanced colon cancer (LACC) was defined by pT4 stage. Locally advanced rectal cancer (LARC) was defined as all patients that had either a T4 tumor or a T3 tumor with a threatened circumferential margin on pelvic MRI. Incurable CRC was defined as all irradical (R1 or R2) resections, when the patient had no surgery for the primary tumor, or when no curative treatment of distant metastases was done. Emergency presentation in the surgical patients was defined as all non-planned admissions to the hospital due to symptoms related to the tumor, with 'urgent' defined as surgery imperative within 5 days and 'acute' procedures within 6 hours. Pathological staging was based upon the TNM classification 2002 (6th edition) and classified according to the American Joint Committee on Cancer (AJCC) stages.

Patients that were staged with abdominal CT before treatment (SCT group) were compared to patients that were not (non-SCT group) concerning patient characteristics and influence on the treatment plan. The ability of the staging abdominal CT to detect advanced disease was analyzed in the surgical SCT group; the gold standard for PC and LACC were peroperative findings confirmed with histology. For LM the findings on CT were related to peroperative findings in case of negative outcome of the staging CT and follow-up in case of indeterminate lesions. A risk group analysis on presence of metastases and surgical mortality was done.

Figure 1. Colorectal cancer stage and treatment (2007-2009)



R1: locally advanced tumors: LACC: colon, LARC: rectum
M1: metastases

Curative treatment distant metastases in 28 patients: liver 24, peritoneal 2, lung 2.

Table 1. Characteristics all patients with CRC 2007-2009		
	All patients (n=612)	
Age		
Mean	70 yr	
Median	70 yr	
Range	33-98 yr	
Gender		
Male	349	57%
Female	263	43%
Localization primary tumor		
Colon	474	77%
Rectum	138	23%
Staging procedure		
Abdominal CT preceding treatment	513	84%
Abdominal CT < 3 months after surgery	44	7%
AJCC stage based on pTNM (2002)[a]		
Stage 0	12	2%
Stage I	75	12%
Stage II	171	28%
Stage III	143	23%
Stage IV	188	31%
Not classified[d]	23	4%
Localizations of distant metastases in cohort[b]		
Liver	101	17%
Peritoneal	27	4%
Liver and lung	24	4%
Liver and peritoneal	11	2%
Lung	7	1%
Peritoneal and lung	4	1%
More then 2 organs and/or other localisations[c]	14	2%
Localization of distant metastases per organ[b, c]		
Liver	144	24%
Peritoneal	49	8%
Lung	42	7%

[a] This includes patients with pathological downstaging after neoadjuvant chemoradiation (n=69); stage 0=a complete remission of histologically proven colorectal cancer.
[b] Staging of the lung in this cohort was done with chest CT (n=415) or chest X-ray (n=197).
[c] Other localisations were brain and skeletal metastases.
[d] Of 23 patients, 20 patients had no surgery and 3 patients had no resection resulting in an unknown TN status. Of 23 patients, 11 patients had an unknown M status and 12 patients had M0 status.

Results

Population incidences of advanced colorectal cancer (Figure 1 and Table 1)
From 2007-2009 612 patients were diagnosed with colorectal carcinoma. Metastatic CRC (mCRC) was present in 188 patients (31%). Incurable disease was present in 199 patients (33%), mainly due to mCRC (n=160). Curative treatment was achieved in 413 patients (67%). Curable advanced CRC was present in 159 patients (38%), of whom 28 patients had mCRC. Most common sites of distant metastases were the liver (n=144, 24%), peritoneal cavity (n=49, 8%) and the lung (n=42, 7%). Staging with abdominal CT before treatment was done in 513 patients (84%). Surgery, either palliative or curative, was performed in 551 patients (90%).

Detection metastatic CRC and LACC on abdominal CT (Table 2)
LM were diagnosed in the cohort of surgical patients that were staged before treatment (n=463) in 86 patients (19%). In 73 patients the LM were diagnosed on the initial staging CT (85%) and in 19 patients these were suspected (indeterminate lesions). The indeterminate lesions were identified as either LM or benign lesions with additional diagnostic testing, which were contrast-enhanced ultrasound, positron emission tomography (PET), PET/CT or MRI. In 12 patients the indeterminate lesions were diagnosed as metastases and in 7 patients as benign lesions; of these, 6 patients had a follow-up of more then one year and none was diagnosed with recurrent disease. In one patient the liver metastasis was not seen nor suspected on CT but found during surgery. The ability of the staging CT for detecting LM, summating diagnosed LM and secondary diagnosis after further analysis of indeterminate lesions, is 99%. Synchronous PC was diagnosed in 33 patients; in 11 patients prior to surgery on the staging CT (33%), in the remaining 22 patients these were found during surgery for the primary tumor (67%). Abdominal CT did accurately stage pT4 CC in 86% of patients (99 out of 115).

Table 2. Detection advanced disease on abdominal CT

SCT group (surgical patients) (n=463)

		Diagnosed	Suspected	Not seen
Liver metastases	n=86	73 85%	12 14%	1 1%
Peritoneal carcinomatosis	n=33	11 33%	6 18%	16 48%
pT4 colon carcinoma[a]	n=115	99 86%	5 4%	11 10%

	Rectum (n=115)				**Colon (n=348)**			
	cM		**pM**		**cM**		**pM**	
	n	%	n	%	n	%	n	%
Liver metastases	13	11%	16	14%	61	18%	70	20%
Peritoneal carcinomatosis	2	2%	3	3%	9	3%	30	9%
Locally advanced disease	n.a.[b]		n.a.		99	29%	123	36%

cM: metastases diagnosed before treatment on staging CT
pM: final conclusion, including additional imaging and peroperative findings
[a] In 8 patients the local invasiness was not described in the original report, leaving 115 patients for evaluation
[b] Local invasiveness (cT stage) in rectal carcinoma was determined on pelvic MRI

Comparison SCT and non-SCT patients (Table 3 and 4)

Differences in the SCT and non-SCT group were observed concerning tumor localization (proportion CC in SCT group 75% and non-SCT 90%), emergency procedures (SCT 17%, non-SCT 40%) and age (SCT mean 69 year, non-SCT mean 73 year). Staging was omitted in 30% of emergency presentations (35 of 115) versus 12% in elective surgery, and in 19% of CC (89 out of 474) versus 7% of RC.

The proportion of patients that had no surgery was equal in the SCT (11%, n=50) and the non-SCT group (10%, n=11). In patients that underwent surgery, the primary tumor was not resected in 5% in the SCT group and in 1% in the non-SCT group. When considering

Table 3. Characteristics SCT versus non-SCT patients

	SCT (n=513)		**Non-SCT (n=99)**	
Age				
Mean	69 yr		73 yr	
Median	70 yr		74 yr	
Range	33-98 yr		46-92 yr	
Gender				
Male	292	57%	57	57%
Female	221	43%	42	43%
Localization primary tumor				
Colon	385	75%	89	90%
Rectum	128	25%	10	10%
Urgency surgical procedure	*n=463*		*n=88*	
Elective	383	83%	53	60%
Urgent	61	13%	12	14%
Acute	19	4%	23	26%
AJCC stage based on pTNM (2002)[a]				
Stage 0-III	340	67%	61	62%
Stage IV	160	31%	28	28%
Not classified	13	3%	10	10%

SCT: Staged with abdominal CT before start treatment
Non-SCT: not staged with abdominal CT preceding treatment

only CC with emergency presentation to partially correct for the group differences, the primary tumor was resected in 85% in the SCT group (n=68) and in 97% in the non-SCT group (n=34). In the SCT group 3% of the colon carcinoma were irradically resected (n=13) versus 4% in the non-SCT group (n=4).

Curative treatment of synchronous LM in surgical patients was done in 21 patients (24%) in the SCT group and in 3 patients (16%) in the non-SCT group. Two patients had curative resection of LM before resection of the primary tumor and 6 patients underwent a simultaneous resection. An additional 6 patients in the SCT group were eligible for curative treatment but were found irresectable with intra-operative ultrasound (6 out of 30, 20%). Two patients with PC were treated with curative intent in the SCT group.

Table 4. Treatment outcome comparison SCT and non-SCT group

	SCT group			**non-SCT group**		
	Nt	n=	%	Nt	n=	%
Treatment primary tumor (all patients)	*513*			*99*		
Resection		438	85%		87	88%
No resection		25	5%		1	1%
No surgery		50	10%		11	11%
in emergency surgery for CC	*80*			*35*		
Resection		68	85%		34	97%
No resection		12	15%		1	3%
Resection margin (colon)	*382*			*92*		
R1 resection		8	2%		2	2%
R2 resection		5	1%		2	2%
Curative treatment liver metastases						
Elective surgery	67	20[a]	30%	6	0	-
Emergency surgery	19	1	5%	16	3[b]	19%

Nt: total number

[a] In an additional 6 patients in this group the metastases were eligible for curative treatment on CT, but turned out irresectable with intra-operative ultrasound performed during surgery for intended metastasectomy.

[b] These 3 patients were staged with abdominal CT after surgery

Risk groups on distant metastases and surgical mortality (Table 5a+b)

Risk factors for distant metastases are emergency presentation (incidence mCRC 52%), LACC (incidence mCRC 45%) and age < 70 years (incidence mCRC 36%). Risk factors for surgical mortality were emergency presentation (13% vs 3%), tumor localization in the colon (7% colon versus 2% rectum), age > 75 years (11% versus 3%) and the presence of distant metastases (9% vs 2%). The proportion of surgical patients with an emergency presentation was 21% (115/551). The proportion of surgical patients with LACC was 29% (160 out of 551).

Association pT4 stage colon cancer (LACC) and distant metastases

In LACC, PC was present in 24% (38 out of 160) and LM in 29% (46 out of 160) of surgical patients. The presence of PC is related to pT4 tumor stage; 93% of patients with PC had a pT4 tumor (38 from 41 surgical patients).

Table 5. Risk groups on metastatic CRC and surgical mortality			
Presence distant metastases	total	n=	%
Age (all patients)[a]			
< 70 years	277	100	36%
> 70 years	312	88	28%
Urgency (surgical patients)[b]			
Elective	436	88	20%
Emergency presentation	113	59	52%
Tumor localization (all patients)[a]			
Colon	457	156	34%
Rectum	132	32	24%
T-stage colon cancer (surgical patients)[b]			
pT1-3 colon cancer	266	49	18%
pT4 colon cancer	160	73	45%
Mortality risk of surgical procedure	total	n=	%
Age[c]			
< 75 years	373	11	3%
> 75 years	178	19	11%
Urgency[c]			
Elective	436	15	3%
Emergency surgery	115	15	13%
Tumor localization[c]			
Colon (all)	427	28	7%
Rectum (all)	124	2	2%
Colon (elective)	317	15	5%
Rectum (elective)	119	0	0%
Disease stage[d]			
Distant metastases	145	13	9%
No distant metastases	403	14	3%

[a] Calculated on all patients with known AJCC status (n=589)
[b] Calculated on all surgical patients with known AJCC status (n=548 all, n=426 colon)
[c] Calculated on all surgical patients (n=551)
[d] Calculated on surgical patients with known AJCC stage (n=548)

Discussion

A high percentage of metastatic CRC (31%) was found in this unselected hospital population of CRC patients. The most notable change in treatment planning was observed in performing no resection of the primary tumor in emergency surgery for colon cancer when staging was done before surgery, as a consequence of diagnosing incurable disease before surgery (15% in the SCT group versus 3% in non-SCT group). Curative treatment of LM was more often done in the group of patients that were staged (24% versus 16%) and included a change in immediate treatment planning in 8 patients. Staging did not affect the treatment plan for PC.

Does the outcome represent population based incidences?

In this hospital population a small referral bias may be present; patients with primary cT1 rectal tumors are referred for a TEM procedure in another hospital, few patients with cT4 rectal cancer were referred to another hospital for intra-operative radiotherapy and few patients were referred to the study center for both colorectal and liver surgery. The estimated referral bias is small and the incidences are expected to represent a fairly good reflection of the population incidences in this region. In a population based analysis on synchronous metastatic CRC in the southern region of the Netherlands, an incidence of 22% (RC) to 25% (CC) was found and had increased in the last decade.[19] This increase over time is probably due to changing staging routines. The incidence of metastatic CRC in the study population is higher (31%). This may be an effect of the introduction of routine staging with abdominal CT in this region that has preceded national guideline recommendations, and the prospective registration which probably increased the awareness of the surgical team. Scanning protocols may influence the results as well; existing variances in the use of intravenous contrast, slice thickness and reconstructions can all influence the accuracy of abdominal CT in detecting advanced disease. Another possible contributing factor may be regional characteristics. The study hospital is situated in a region that has a lower than average socio-economic status and subjectively more often delayed presentation to health care providers as compared to more urban regions in the Netherlands. The proportion of patients with PC in the total cohort (8%) is probably an underestimation of the real incidence, due to inclusion of patients that had no surgery (10% of total cohort); abdominal CT underestimates the presence of PC.

Change in treatment plan as an outcome of the staging abdominal CT

Advanced colorectal cancer is present in a large proportion of patients (58%). The main determinant for incurable advanced disease is metastatic CRC (80%). In incurable disease the focus of treatment is towards palliative care and can motivate a change in treatment

strategy. Staging leading to a change in surgical procedure was observed in this study, but no difference in respect to performing no surgery at all, which was unexpected. This may be due to differences in *motivation* not to perform surgery; in the non-SCT group the majority of these patients (8 out of 11) either refused further treatment or died before the diagnostic trajectory was finished, while in the SCT group the finding of incurable metastatic CRC on the staging CT was the main reason (in 41 from 61 patients). The necessity for surgery is highly dependent on the symptoms of the primary tumor, which varies from asymptomatic to obstruction, perforations and hemorrhagic complications. Also the patients vary in age and physical condition. The evidence of a potential benefit from a palliative resection versus palliative treatment without resection, remains conflicting but tends to conclude the benefit does not outweigh the risks of a resection.[16-18, 20] Alternative procedures such as an enterostomy (via a small incision guided on abdominal CT or laparoscopy) or bypass surgery in obstructive tumors, and radiotherapy in bleeding tumors can be considered on an individual basis, as an alternative to resection in incurable disease. In emergency presentations, these minimal invasive procedures may be able to serve as a 'bridge to definitive curative surgery' to achieve curation in a larger proportion of patients. Curative treatment for LM was more often done in the SCT group and included changes in timing of the respective surgical procedures for the primary tumor and LM. There is growing evidence these alternate strategies for LM are more beneficial in terms of eligibility of resection and the oncological outcome,[10, 11, 21] underlining the relevance of staging before treatment. This observational study cannot prove that the chance on curative treatment of LM is higher when staging is done before treatment, because of other differences between SCT and non-SCT group.

The present study confirms the finding of previous studies that PC is poorly visualized on a CT scan.[22] This explains the current observation that PC is most often diagnosed during surgery rather than during the pre-operative work-up. In the recent past PC was regarded as a virtually incurable condition with little treatment options and therefore accurate staging of PC was considered less important. This has changed since the introduction of HIPEC offering a chance for cure in selected patients.[6, 12, 13] Since HIPEC is performed in specialized centers only, accurate pre-operative staging of PC has become vital to improve the outcome of these patients. A high index of suspicion should be present in patients with locally advanced tumors since PC is present in a relevant proportion of these patients (24%). A promising imaging technique in this respect may be diffusion-weighted imaging (DWI) combined with MRI which is thought to be more sensitive to detect and estimate the extent of PC.[23]

LACC is present in a relevant proportion of patients (29%) with high incidence of concurrent distant metastases (46%). Extensive local disease can be a reason for referral or

palliative treatment. The finding of LACC on CT can be a reason for choosing a 'bridge to definitive surgery' in emergency surgery or when referral is considered. Such a staged treatment plan will probably enlarge chances on a radical resection and can especially in emergency surgery, avoid added morbidity and mortality. Reducing morbidity enhances the attainability of adjuvant treatment and possibly, also treatment of synchronous metastases. Perhaps more aggressive multi-modality treatment will be able to improve the oncological outcome in LACC, such as with neo-adjuvant chemotherapy[24] or radiotherapy, [25] similar to the current approaches in LARC.[7, 26-28]

Optimizing staging routines before treatment

Staging tended to be omitted in especially emergency patients, that are most at risk for metastatic disease and surgical mortality. Also specifically in this group it could have had consequences for the immediate treatment plan as was observed in the staged group. This is an important lead point for improvement. Multislice CT scanning does not need to meet logistic obstacles in both elective and emergency presentations.

Liver metastases are less often treated with curative intent than considered eligible by expert centers.[21, 29, 30] CT images, contrary to ultrasound, are reproducible and can be implemented for (external) evaluation on eligibility of curative treatment by specialized liver surgeons. Underreporting and underestimation of small liver lesions result in an apparently high radiological accuracy of abdominal CT,[31] however non-reporting of indeterminate lesions will decrease the ability to signal LM on the staging CT. Discrimination of indeterminate liver lesions with additional imaging causes no major diagnostic uncertainties and resources, as was observed with indeterminate pulmonary lesions.[1-3] The necessity of intra-operative ultrasound as the last step in the staging procedure preceding hepatic metastasectomy[21] was confirmed in this study, with cancellation of hepatic metastasectomy in 20% of patients. Abdominal MRI is an equivalent alternative to multislice CT scanning for LM,[32] however causes more logistic problems.

The focus of staging has primarily been to find distant metastases; the relevance of determining cT stage became more evident during this study, towards estimating resectability and as a sign for possible PC. Estimation of T stage on abdominal CT in this and another study seems to be reliable.[33] Standardized radiology reports may enhance the diagnostic accuracy of T-stage of CC on CT.

The absence of advanced disease identifies patients with 'common' curable CRC who do not need additional preoperative measures. These patients do not necessarily need to be discussed in a multidisciplinary oncological team before surgery; by leaving this group out of the discussion based on staging outcome, the limited available time can be reserved for discussing more complicated cases with advanced disease.

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Preoperative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure

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Ann Surg Oncol 2010; 17 (8): 2045-2050

Background. Preoperative staging of patients with colorectal carcinoma (CRC) has the potential benefit of altering treatment options when metastases are present. The clinical value of chest computed tomography (CT) in staging remains unclear.

Materials and Methods. All patients who undergo colorectal surgery in our hospital are prospectively registered, including patient, treatment, and histopathological characteristics; outcome; and follow-up. Since January 2007,
routine preoperative staging CT of chest and abdomen for patients with CRC has been performed as part of our regional guidelines. In this observational cohort study, an analysis on outcome was done after inclusion of 200 consecutive patients.

Results. Synchronous metastases were present in 60 patients (30%). Staging chest CT revealed pulmonary metastases in 6 patients, with 1 false positive finding. In 50 patients indeterminate lesions were seen on chest CT (25%). These were diagnosed during follow-up as true metastases (n=8), bronchus carcinoma (n=2), benign lesions (n=25), and remaining unknown (n=15). Ultimately, synchronous pulmonary metastases were diagnosed in 13 patients (7%), in 6 patients confined to the lung (3%). In none of the patients the treatment plan for the primary tumor was changed based on the staging chest CT.

Conclusion. The low incidence of pulmonary metastases and minimal consequences for the treatment plan limits the clinical value of routine staging chest CT before operation. It has several disadvantages such as costs, radiation exposure, and prolonged uncertainty because of the frequent finding of indeterminate lesions. Based on this study, a routine staging chest CT in CRC patients is not advocated.

Background

Preoperative staging of patients with colorectal carcinoma (CRC) has the potential benefit of altering treatment options when metastases are found. Synchronous metastases are usually detected in the liver, lung and peritoneal cavity. Staging with abdominal CT for liver metastases has resulted in various new approaches aimed at increasing the chance on curative treatment. It seems a logical next step to apply this approach on synchronous pulmonary metastases as well. Pre-operative staging with CT of chest and abdomen in a routine 'one-stop shop' setting also has a logistical advantage, saving time for both patient and physician. The clinical benefit of a staging chest CT however, has been controversial. There are few studies describing the outcome and clinical relevance of a staging chest CT. [1-5] The main problem of staging with chest CT lies in the frequent finding of indeterminate lesions (20-30%). These lesions are usually difficult to determine and seldom malignant (10-20%).[1, 3] The main advice is not to delay treatment of the primary tumor or of liver metastases when indeterminate lesions are found.[2, 3, 6] The outcome can be debated, because in most of these studies the number of patients was limited or were carried out more then 10 years ago. Accurate staging is increasingly important in the oncological multidisciplinary treatment plan of CRC. Rapid technical advancements and increasing knowledge due to histopathological correlation studies [7, 8] enhance the determination of pulmonary anomalies on chest CT. For these reasons routine staging with abdominal and chest CT was decided upon as a part of our regional guidelines for colorectal cancer. The aim of this study was to analyze the outcome and clinical benefit of routine staging with chest CT after inclusion of a consecutive series of 200 patients with colorectal cancer.

Methods

The Medical Spectrum Twente is a large teaching hospital in the Eastern part of the Netherlands that functions as a referral center for liver and lung surgery. All patients operated in our hospital for CRC are prospectively registered in a database designed for colorectal surgery, including patient -, treatment- and histopathological characteristics, outcome and follow-up. From January 2007, routine pre-operative staging CT of chest and abdomen for patients with CRC was performed as part of our regional CRC guidelines, when feasible. An analysis on benefit was intended after inclusion of 200 patients with staging CT of chest and abdomen as a prospective observational cohort study.

All patients with colon and rectal cancer presented to our department, also those with an urgent or acute presentation, were included. When due to acute circumstances a staging CT scan could not be performed before operation, this was done within 1 month after the operation. Patients with rectal cancer at 0-10 cm from the anal verge were additionally staged with a pelvic MRI for estimation of the local invasion (cTN stage). In

case of cT4 tumours or cT3 tumours with a distance < 1 mm from the mesorectal fascia, a long schedule chemoradiation consisting of 25x2 Gy combined with oral capecitabine was given, followed by surgery 6 to 8 weeks later. In case of cT3 tumours with a distance of > 1 mm from the mesorectal fascia, a short schedule radiotherapy consisting of 5x5 Gy was given, followed by surgery in the following week. Both according to the Dutch guidelines for rectal cancer. A CT scan of chest and abdomen was performed on a 16 and 64 slice scanner (Toshiba Aquillion 16 and 64) after intravenous contrast injection (visipaque 320, 90 ml, 3ml/s.), in the portal venous phase, with a slice thickness of 1 mm and a reconstruction of 0.8 mm. Lesions were evaluated on density, number of lesions, morphology, localization and size. The lesions found on chest CT were defined by the radiologists as benign, malignant or indeterminate. Indeterminate lesions are defined as lesions seen on chest CT that could not be judged by the radiologist as either benign or malignant.

Follow-up was done in all patients when feasible and consisted of 3-monthly visits with CEA measurements, according to the national guidelines. Indeterminate pulmonary lesions were re-evaluated during follow-up, with consideration of individual patients' circumstances. The definitive diagnosis of pulmonary metastases was based on imaging (aspect and growth rate on CT and/or PET scanning) or histological confirmation. Indeterminate pulmonary lesions were considered benign when there were no signs of malignant growth on repeat chest CT and no increase in CEA after at least one year of follow-up.

Results

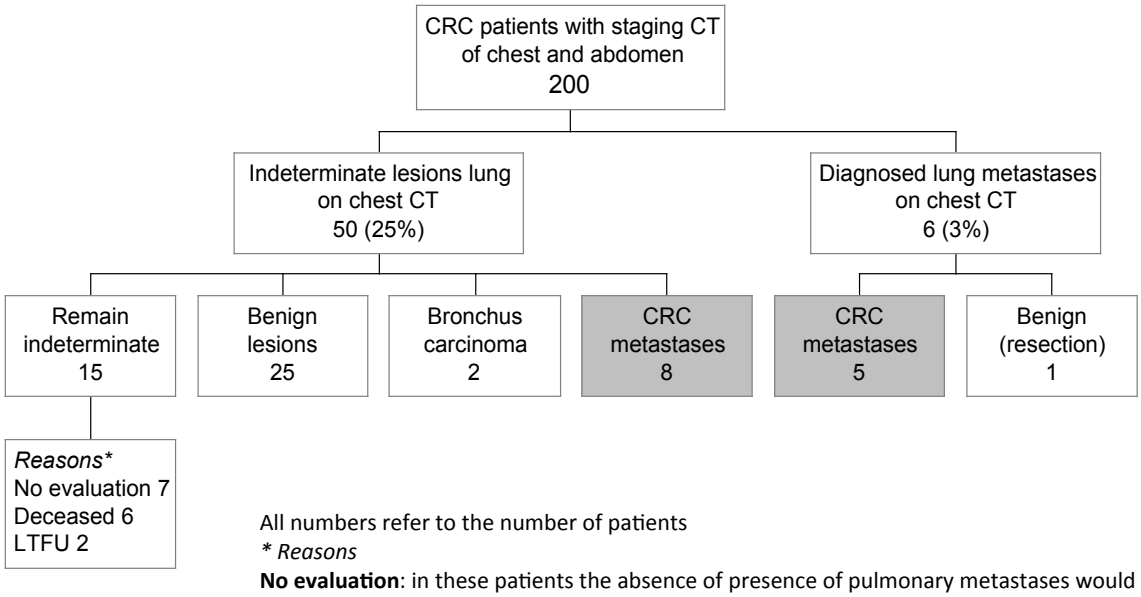
The 200 patients were included between January 2007 and August 2008 (Table 1). Elective procedures were done in 164 patients (81%). Urgent or acute procedures were done in 36 patients (19%) of whom 16 patients had a staging CT after the surgical procedure. Findings during follow-up till July 2009 were taken into the analysis.

Synchronous metastases in the liver, lung and/or peritoneal cavity were found in 60 patients of the study group (30%) (Table 2). Pulmonary metastases were diagnosed on the initial chest CT in 6 patients (3%). In one of these six patients the pulmonary lesion turned out to be benign after resection. Indeterminate lesions were seen on 50 staging chest CT's (25%) (Figure 1). Additional diagnostic procedures done during follow-up for indeterminate lesions were a repeat chest CT scan in 29 patients, a PET scan in 11 patients, and a bronchoscopy and percutaneous needle biopsy in 4 patients (Table 3). In 2 patients the percutaneous needle biopsy resulted in a small pneumothorax, in 1 of 4 patients a definite histological diagnosis could be made. In eight patients the indeterminate lesions were diagnosed as pulmonary metastases (16%), in two patients as primary bronchus carcinoma,

in 25 patients as benign lesions and in 15 patients no diagnosis was made (figure 1). The time to final diagnosis of the indeterminate lesions took three months up to one year after resection of the primary tumor.

Ultimately, 13 of the 200 study patients had synchronous pulmonary metastases (7%) (Table 2 and 4). In 6 patients the metastases were confined to the lung (3%). Four of these 6 patients had no mesenterial lymph node metastases at the primary tumor site. The prevalence of synchronous lung metastases was higher in patients with rectal cancer (0-15 cm from the anal verge) (7 out of 71, 10%) than in patients with colon cancer (6 out of 129, 5%). Three patients with rectal tumours that had neo-adjuvant treatment (radiation or chemoradiation) turned out to have lung metastases (3 out of 40, 8%) (Table 4). From the 47 patients with liver metastases, 6 patients also had lung metastases (13%). In two of six patients that had a conventional chest X-ray as well, the metastasis were visible on chest X-ray. In none of the patients with either lung metastases or indeterminate lesions the neo-adjuvant or operative plan for the primary tumor was changed. In two patients intended curative metastasectomy of true pulmonary metastases was done, both patients had widespread recurrent disease within 10 months after resection.

Figure 1. Outcome of staging chest CT in patients with CRC



All numbers refer to the number of patients

** Reasons*

No evaluation: in these patients the absence of presence of pulmonary metastases would have no consequences for (further) treatment, such as with incurable metastases on other locations or the wish of the patients to receive no further treatment.

Deceased: patients that died during hospital stay or within 3 months after discharge.

LTFU: lost to follow-up, both patients were referred to other hospitals for reasons other then the indeterminate pulmonary lesions.

TABLE 1 Patient characteristics (n=200)		
Demographics	Value	%
Age		
Mean	68	
Median	70	
Range	33-91	
Gender		
Female	83	42%
Male	117	58%
Rectal carcinoma	71	35%
Rectum 0-5 cm	16	
Rectum 5-10 cm	34	
Rectum 10-15 cm	21	
Colon carcinoma	129	65%
Resection of the primary tumor	199	99%
Neo-adjuvant treatment		
Neo-adjuvant chemoradiation rectal carcinoma	33@	
Neo-adjuvant radiotherapy (5x5Gy) rectal carcinoma	7@	
Chemotherapy	1*	
Urgency		
Elective procedure	164	81%
Urgent and acute procedures	36	19%
In hospital mortality		
Elective procedures	4	2%
Urgent en acute procedures	4	11%
AJCC stage based on pTNM (2002)		
Stage 0#	6	3%
Stage I	22	11%
Stage II	56	28%
Stage III	56	28%
Stage IV†	60	30%
Follow-up		
Mean	19 months	
Median	19 months	
Range	12-30 months	

@ Neo-adjuvant treatment was given to patients with rectal carcinoma cT3-4N1-2 on MRI, located at 0-10 cm (lowest border of the tumor) from the anal verge. From 40 patients that received neo-adjuvant radiation or chemoradiation, 11 had indeterminate lesions on chest CT.
* This patient initially received palliative chemotherapy for asymptomatic disease and incurable liver metastases. This strategy was changed when the primary tumor became symptomatic.
# Complete regression after neo-adjuvant chemoradiation for rectal carcinoma (cT3-4N1-2)
† In this table, metastases that were suspected on staging CT and confirmed during follow-up were classified as AJCC stage IV. Suspected metastases that were resected and histologically benign, were classified as stage II or III disease. This overview therefore represents the actual oncological status in the study cohort.

TABLE 2 Localization of diagnosed synchronous distant metastases (n=60)				
	Incidence		**Curative resection**	
	Value	%	Value	%
Liver metastases	47	24%	13†	28%
Lung metastases	13	7%	2#	15%
Peritoneal metastases	11	6%	1*	9%
Localization of distant metastases				
Liver	38	22%	13†	30%
Liver and lung	5	3%	0	
Liver and peritoneal	3	2%	0	
Liver / lung / peritoneal	1	0.5%	0	
Lung	6	3%	2#	
Lung / peritoneal	1	0.5%	0	
Peritoneal	6	3%	1*	

This table shows the definite classification after staging, operation and additional testing in case of indeterminate lesions.
† Only actual curative resections of liver metastases were counted
# Both patients had recurrent disease after curative resection at 5 and 10 months post-operatively
* HIPEC

TABLE 3 Additional diagnostic tests for indeterminate lesions	
	Patients
Patients with indeterminate pulmonary lesions (n=50)	n=
Regular follow-up without additional diagnostics	9
Repeat chest CT scan	29
PET scan	11
Bronchoscopy	4
Percutaneous needle biopsy	4

Multiple diagnostic procedures were usually done in a single patient.

TABLE 4 Characteristics of the 13 patients with lung metastases							
	Localization primary tumor	Neo-adjuvant treatment: cT		Localization synchronous metastases	Size & number	Urgency	pTN
Diagnosis before treatment							
1	Sigmoid	-	None	Liver / lung / PC	5 mm, M	Elective	pT4N2
2	Colon ascendens	-	None	Lung	10 mm, M	Urgent	pT4N1
3	Colon descendens	-	None	Liver / lung	80 mm, S	Elective	pT3N0
4	Rectum 10-15 cm	-	None	Lung / PC	9 mm, M	Urgent	pT4N2
5	Rectum 10-15 cm	-	None	Liver / lung	25 mm, M	Urgent	pT3N2
Delayed diagnosis							
6	Rectum 10-15 cm	-	None	Lung	7 mm, S	Elective	pT3N0
7	Rectum 10-15 cm	-	None	Liver / lung	9 mm, M	Elective	pT4N2
8	Rectum 0-5 cm	cT4	RCT	Liver / lung	4 mm, S	Elective	ypT4N0
9	Sigmoid	-	None	Lung	10 mm, M	Urgent	pT3N0
10	Coecum	-	None	Liver / lung	4 mm, S	Elective	pT4N2
11	Sigmoid	-	None	Lung	47 mm, S*	Elective	pT3N0
12	Rectum 0-5 cm	cT3	RCT	Lung	25 mm, M*	Elective	ypT0N0
13	Rectum 5-10 cm	cT3	RT	Lung	11 mm, M	Elective	pT3N1

Immediate diagnosis: diagnosed on staging CT. Delayed diagnosis: diagnosed after additional diagnostic procedures. RCT: chemoradiation, RT: short course radiotherapy (5x5 Gy). cT: cT stage on pelvic MRI. PC: peritoneal carcinomatosis

Size: *largest* pulmonary lesion on the staging CT. Number: either single (S) or multiple (M). * These lesions were primarily diagnosed as primary bronchus carcinoma, histology showed it were CRC metastases.

Discussion

Like in preceding studies, this study shows the limited clinical value of a routine preoperative staging chest CT in colorectal cancer patients. The incidence of lung metastases is low (7%), especially those that are confined to the lung (3%). Only in 5 patients lung metastases were diagnosed before treatment of the primary tumor (2.5%). Indeterminate lesions on chest CT are frequently found (in 25% of patients) and discrimination between benign and malignant lesions is often difficult. Only a minority turn out to be metastases (16%). Staging with chest CT did not result in a change of the treatment plan for the primary tumor, nor resulted in curative treatment of pulmonary metastases. It does cause diagnostic dilemmas, prolonged uncertainty and requires resources.

The clinical relevance of staging on distant metastases is highly dependent on the consequences for the treatment plan. Colorectal surgery knows a considerable morbidity and mortality, which can be reduced when the presence of incurable disease is diagnosed before the operation. For asymptomatic patients with widespread metastases, only chemotherapeutic treatment might be preferable. Also in symptomatic patients with incurable disease, treatment alternatives such as stenting for impending bowel obstruction, limited surgery with only colostomy, or radiation therapy in bleeding rectal tumors, might be better alternatives. Curable metastases found on the staging CT can result in alternative strategies such as neo-adjuvant chemotherapy, 'liver-first' approach or simultaneous resections. Intended curative resection of synchronous liver metastases can be done in an estimated 25% - 40% of patients.[9, 10] Consequently, accurate staging before resection of colorectal cancer has become a requirement for optimal oncological treatment. Abdominal CT is a very reliable diagnostic tool for liver metastases and has proven to be better than non contrast enhanced ultrasound.[9, 11, 12] However, where accurate staging of the liver has resulted in changes in treatment plans and possible favorable outcome, this does not seem to be true for pulmonary staging in this study. Several reasons were found that contribute to the suggested difference between synchronous liver and lung metastases. The incidence of lung metastases is much lower (7%) and the curative options for synchronous lung metastases are very limited or may be even non-existent.[14] This might be due to the bad prognosis of synchronous pulmonary metastases as an expression of tumor behavior, as has been suggested by other authors.[13, 14, 15] Metastases confined to the lung are rare (3%) and limits the value of a routine staging chest CT when no metastases are found on the staging abdominal CT.

Small nodules are often seen on chest CT and are usually benign, as was also found by Brent and Kronawitter.[1, 3] The difficulty with these lesions is that these are usually too small (between 0.5 and 1 cm) to evaluate on radiological characteristics such as density and

shape. Determination of the nature of these lesions has proven to be rather difficult. PET scanning has the same disadvantage of a limited discriminative capacity for small lesions. Percutaneous needle biopsies for small lesions can be technically difficult and are prone to sampling error; when the histological result doesn't show a malignancy a metastasis is still not excluded. It can however be harmful, because of the risk of pneumothorax and bleeding complications. In this study it took several months up to one year after resection of the primary tumor before the indeterminate lesions could be classified. Our definition of a benign lesion, which is no growth and no serum-CEA increase after one year, however is a mere assumption and no definitive prove the lesion is truly benign. On the other hand, the duration and absence of clinically relevant disease does imply there is no need trying to find these lesions before treatment of the primary tumor. Staging with chest CT during follow-up might be a better alternative.

The diagnostic difficulties of findings on chest CT are also reflected in literature. The reported incidence of synchronous pulmonary metastases of colorectal cancer varies largely, from 3 to 18%.[1, 3, 4, 6] This is likely influenced by the applied definition of pulmonary metastases, which is usually a derived definition due to a lack of obtainable histological proof. In this study neither the 'golden' standard for false or true metastases was available. Because of the used criteria for true metastases and study design, the real incidence might be slightly underestimated. It is however a close approximation of the number of patients with clinically relevant lung metastases in a non-selected population.

We agree with previous authors [1, 2, 3, 6] that small lesions on chest CT (< 1 cm) should be considered of limited clinical relevance and ignored in choosing the initial treatment plan. The finding of large pulmonary metastases might change the treatment plan, but these kinds of metastases are rare and often visible on chest X-ray. Few studies compared staging chest CT with chest X-ray. Two studies compared a negative chest X-ray with outcome on chest CT in pre-operative staging [1, 6] concluding that a staging chest CT had little to no additional value. One other study compared findings on staging chest X-ray with chest CT. [2] This study showed that in 4 out of 7 patients the pulmonary metastases were visible on chest X-ray. This number is comparable to the 2 out of 6 visible metastases on chest X-ray in this study.

Concerning the change of treatment plan in case of resectable liver metastases, pulmonary staging with chest CT seems the best, most sensitive option to exclude extrahepatic disease. Evaluation of consequences for hepatic metastasectomy was not the aim of this study and the patient group is too small to draw conclusions; in the 5 patients with synchronous liver- and lung metastases, the liver metastases were not resectable. Povoski [6] did study this specific patient group and concluded that chest CT had only minimally improved detection of malignant lesions of the lung over chest X-ray.

It is reasonable to argue that selected patients might benefit from a staging chest CT instead of chest X-ray. For instance patients with compromised health that are about to undergo major surgical procedures for hepatic or peritoneal carcinomatosis or patients that will receive neo-adjuvant treatment for rectal cancer. The latter group also because pulmonary metastases seem to occur more often in rectal cancer than in colon cancer and the operative procedure might be more extensive. In our study the proportion of patients with rectal cancer, especially located 0-10 cm from the anal verge, is too small to draw straightforward conclusions for this specific group but deserves further study. It is however likely the same problem with indeterminate lesions on chest CT will occur. Future studies on imaging techniques with a higher discriminative capacity for small pulmonary nodules remain required to improve staging in high-risk patient groups.

Relevant disadvantages other then the diagnostic difficulties of routine chest CT are the significant radiation exposure and costs; routine staging with CT of the chest together with CT of the abdomen is twice as expensive and induces twice as much radiation exposure. When indeterminate lesions are seen, it may further cause a prolonged period of uncertainty, unnecessary anxiety for patients and relatives and possibly lead to a delay in neo-adjuvant, surgical and adjuvant treatment. The need for additional diagnostic procedures such as repeat chest CT's with a summative radiation exposure, PET scanning or percutaneous needle biopsies, further increases costs and possible harm to the patient.

To conclude, in our opinion routine staging of colorectal cancer patients with chest CT is not advocated based on these study results. We believe that defining high-risk patient groups and predictive factors for pulmonary metastases followed by either immediate staging in selected patients or 'delayed' staging with chest CT during follow-up might be a better and less expensive alternative to identify patients with pulmonary metastases.

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4

Results of a national survey among Dutch surgeons treating patients with colorectal carcinoma. Current opinion about follow-up, treatment of metastasis, and reasons to revise follow-up practice

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Objective. Follow-up after curative resection of colorectal carcinoma (CRC) has been subjected to debate concerning its effectiveness to reduce cancer mortality. Current national and international guidelines advise CEA measurements every 3 months during 3 years after surgery. The common clinical practice and opinion about follow-up for colorectal carcinoma, was evaluated by means of a survey among Dutch general surgeons.

Methods. A web-based survey of follow-up after treatment of CRC was sent to all registered Dutch general surgeons. A reply from 246 surgeons treating patients for colorectal carcinoma in 105 out of 118 hospitals was received (response rate 91%). Questions related to actual followup protocol, opinion about serum CEA monitoring, liver and/or lung metastasectomy, and motivation to participate in a new trial concerning follow-up.

Results. For the majority of surgeons the length of follow-up was influenced by age of the patient (62%) and physical condition (76%) prohibiting hepatic metastasectomy. The generally accepted follow-up protocol consisted of CEA measurements every 3 months in the first year and six-monthly thereafter, and ultrasound examination of the liver every 6 months. Nearly all surgeons (92%) were willing to participate in a new study of follow-up protocol.

Conclusion. The adherence to national guidelines for the follow-up of colorectal carcinoma is low. The indistinctness about follow-up after curative treatment of colorectal carcinoma also affects clinical practice. Recent advancements in imaging techniques, liver and lung surgery have changed circumstances, which are not yet anticipated upon in current guidelines. Renewal of follow-up based upon scientific evidence is required.

Introduction

There is controversy regarding follow-up after curative resection of colorectal carcinoma (CRC) regarding its effectiveness in reducing cancer mortality. No clinical trial or meta-analysis has unequivocally shown a benefit on patient survival.[1–6] In the past 30 years, several attempts have been made to improve survival, either by advancements in treatment or changing the protocol of follow-up. Only serum CEA has proven to be of (limited) value, with consistent results on lead time but inconsistent results on survival.[1,7–17] Current guide-lines[18–22] therefore advise CEA measurement every 3 months over 3 years. To detect metachronous second colorectal malignancy, colonoscopy is advised every 3 years.[20] Dutch guidelines are similar to those advised by the American Society of Clinical Oncology. The lack of solid evidence on the benefit of follow-up has raised the question whether follow-up should be continued. Technical developments in imaging and increased use of liver and lung surgery for metastatic disease outdate present guidelines since they still reflect the results from studies that were done before these developments.

A survey was undertaken among Dutch general surgeons treating patients with colorectal carcinoma to assess the opinion on diagnostic methods used in follow- up, the adherence to national guidelines concerning CEA measurement, and the treatment of recurrent disease. The motivation of the respondents to participate in new studies concerning follow-up was also evaluated.

Methods

A request to complete a web-based survey was sent to all registered general surgeons in the Netherlands (n=878). A reply was received from 246 surgeons treating patients with colorectal carcinoma from 105 different hospitals out of a total of 116 hospitals in the Netherlands with a surgical department, giving a response rate of 91%. To detect possible bias through differences in response rate within hospitals, the outcome was also calculated using only one representative per hospital. In comparison with the outcome from all 246 surgeons, there were no differences. The survey included 17 questions, with a total of seven free answers that were categorized afterwards. They related to the indication for follow up, actual local follow-up practice, application of serum CEA measurement and opinion about serum CEA monitoring in follow up. The use and availability of other diagnostic methods, both for screening and evaluation of suspected metastases, and practice concerning treatment of liver and lung metastases were evaluated. Finally the opinion and feasibility for a new study, in response to a proposition in the questionnaire, was sought.

Results

Each surgeon treated approximately 30 patients with CRC per year. The length of follow up was influenced by age according to 62% (n = 153) and physical condition prohibiting hepatic metastasectomy according to 76% (n = 187). Usually after the age of 80 years follow-up

was limited. In Table 1, the percentage of surgeons who adhered to a certain follow-up test at a specific moment is given. In general CEA was measured with a lower intensity than guideline advice, especially in the second and third year, and ultrasound was used regularly. Colonoscopy was regularly done in year 1, 3 and 5 and one-third requested a yearly chest X-ray. The majority of surgeons (65%, n 1/4 161) used the thresholds for the CEA value as suggested in the questionnaire as follows: CEA < 5 ng/ml: no action, CEA > 5 < 10 ng/ml: monthly measurement, evaluation for recurrent disease when CEA is rising, CEA > 10 ng/

ml: evaluation for recurrent disease. CEA was not measured at all by 6% of respondents,

Table 1. Follow-up scheme, current practice

Year	1				2				3				4		5	
Month	3	6	9	12	3	6	9	12	3	6	9	12	6	12	6	12
Physical examination	89	78	50	78	17	72	16	74	4	49	5	47	30	55	26	66
CEA	63	78	50	83	20	69	20	78	8	47	8	74	28	60	25	67
Ultrasound liver	11	44	10	58	4	36	3	56	2	22	3	48	9	36	7	44
Chest X-ray	5	18	5	32	1	13	1	29	-	8	1	26	4	19	3	25
Colonoscopy	2	7	2	65	2	5	-	16	3	2	8	38	5	18	3	35
CT Abdomen	1	2	1	8	1	2	1	5	1	1	1	5	1	2	1	4
CT chest	-	1	1	4	1	1	1	1	1	-	1	1	1	1	1	1

All numbers are %, in whole percentages. All % > 35 are black, between 15 and 35% dark grey and < 15% in light grey

CEA-rise or doubling time was used by 14%, a lower threshold was applied by 7% and a higher threshold by 2%.

The majority (67%) chose helical computed tomography (CT) scanning of the chest and abdomen for evaluation of suspected recurrent disease, followed by positron emission tomography (PET) scanning when nothing is found on CT. Ultrasound was added by 11% of surgeons and colonoscopy by 4%. A one-third of surgeons (31%) treating colorectal

carcinoma carried out liver resections as well. Analysis of the opinion concerning the eligibility criteria for hepatic metastasectomy was done for the whole group and separately for the liver surgeons. A large majority of all surgeons (93%) concurred with liver and lung resections for metastasectomy. A minority (27%) did not consider liver resection indicated when resectable extrahepatic disease was present. There is no disagreement on these two criteria among the liver surgeons. Liver surgeons expressed a different opinion on the eligibility for hepatic metastasectomy when lymph node involvement in the hepatoduodenal ligament and bilobar disease were present. They considered these findings to be less often a contraindication for surgery (Table 2). The majority of surgeons (76%) felt that the number of metastases was not a decisive criterion for metastasectomy. When the number of metastases was considered important, a maximum of three to five was generally regarded as being amenable to surgery.

Nearly all surgeons (92%) were willing to participate in a new study concerning follow-up. When imaging was added to the proposed new follow-up scheme, ultrasound was preferred above CT scan of the abdomen by general surgeons. When the results were analysed for surgeons who also perform liver surgery, CT scanning was preferred above ultrasound. Generally imaging every 6 months in the first 2 years and every year in years three, four and five was supported by the respondents (Table 3). The most important exclusion criteria for metastasectomy included age and physical condition.

Table 2. Eligibility for hepatic metastasectomy

	All surgeons (n=246) (%)	Liver surgeons (n=76) (%)
Macroscopic resectable metastases	96,1%	98,6%
Bilobar localization	81,6%	96,1%
Lymph node metastases in hepatoduodenal ligament	17,3%	33,3%
Resectable extrahepatic disease	73,2%	68,4%
Resectable lung metastases	92,6%	88,2%
Number of metastases is a criterion	23,5%	19,7%

Table 3 and 4. Suggested imaging in follow-up																
Year	1				2				3				4		5	
Month	3	6	9	12	3	6	9	12	3	6	9	12	6	12	6	12
All surgeons																
Ultrasound	17	54	14	57	5	40	4	57	2	26	2	51	11	35	10	46
CT Abdomen	3	27	2	50	1	22	1	42	2	7	2	30	4	16	4	25
Liver surgeons																
Ultrasound	19	43	20	32	4	26	4	39	1	22	1	30	10	23	8	28
CT Abdomen	4	39	1	65	1	35	1	54	1	7	1	28	5	15	4	20
All numbers are %, in whole percentages. All % > 35 are black, between 15 and 35% dark grey and < 15% in light grey																

Discussion

The results of this survey are highly representative for the current follow-up after surgical treatment for patients with colorectal cancer in the Netherlands. The high response rate is likely due to the easy accessibility of the survey on the web, and the present interest in surgery for metastases. The results of this survey reflect the doubts and uncertainty in follow-up and treatment options for recurrent disease (Table 4). Age and poor physical condition are the main reasons which limit follow-up. At least a quarter of surgeons did not consider that age or physical condition should prohibit further surgical treatment, and a reason therefore to limit follow-up. Frequently expressed arguments for regular outpatient visits include quality control of surgical treatment and psychosocial considerations. Both arguments are controversial.[23–26] The median time after which recurrent disease is detected (disease free interval) is approximately 0.5–2 years for liver metastasis, 2–3 years for lung metastasis and 0.5–1.5 years for local recurrence.[10,11,14,17,27–29,31–34] The time after which metastasis or local recurrence are diagnosed varies with the diagnostic methods used[14,15,29–32] and the detection of local recurrence might also be dependent on the site of the primary tumour (colon or rectum). The common practice concerning CEA measurement, despite the recommendation in national guidelines, limited the three monthly measurements to the first year. After that the intensity of controls diminished to every 6 months or more. Actual measurement was often even lower and never more then 50% for CEA measurement at each moment (unpublished results). Thus the present clinical practice did not anticipate the early appearance of recurrent disease. This might lead to

missing more recurrent disease than is necessary. The logistic burden of follow-up might be another reason for the low adherence to guidelines as others have reported.[10,30,35] Finding effective logistic ways to ensure adherence to guidelines might enhance the effectiveness of follow-up. A further reason to omit CEA from follow-up that was mentioned by several surgeons in this survey was that a normal preoperative CEA would mean that it will not rise when recurrence occurs. This, however, is not valid. A normal preoperative CEA is present in approximately 50% of all patients with CRC, and 50% will rise with recurrent disease. Thus 25% will miss a chance of early detection when CEA follow-up is omitted. A majority of surgeons added ultrasound as a screening tool in their follow-up, though this was not included in the national guidelines. This may be because one regional guideline advises ultrasound when preoperative CEA is normal. Another reason might be low confidence in the value of CEA as a tumour marker, and the increasing confidence in imaging. In recent years major advances have been made in imaging. The present multislice helical CT scan can detect liver and lung metastasis when its diameter exceeds approximately 0.5 cm. It is feasible therefore to localize recurrent disease in lung and liver as soon as CEA exceeds its threshold.[15,27,36] Thus a major problem in the past has finally been solved. When CEA rises, recurrent disease can usually be localized and, where feasible, treatment can be initiated immediately. The ability of ultrasound examination to detect liver metastasis is less sensitive. Evaluation is limited to the liver, while lung metastases are also frequently curable. Considering this, the role of regular hepatic ultrasound in follow-up is questionable when helical CT scanning of thorax and abdomen is available instead. The frequency of performing a CT scan however, is limited by availability, cost and the potential health risk of radiation exposure. More patients seem eligible for surgical treatment of metastatic disease than appear to be eligible in the Netherlands. Uncertainty exists regarding the criteria for liver resection for metastasis, as also shown in another recent Dutch survey.[37] The difference of opinion between liver surgeons and general surgeons on some criteria might be an expression of this finding. In the last 10 years many criteria, that were previously considered contra-indications for metastasectomy, are now being debated. Among these criteria are age, number and localization of metastasis, presence of resectable extrahepatic disease and previous metastasectomy. The increasing safety and technical advancements have resulted in more older patients becoming candidates for metastasectomy. Furthermore, many patients with disseminated colorectal carcinoma are relatively young at 60–65 years. The number and involvement of multiple segments of both liver and lung are not contraindications, provided they are completely resectable[32,34,38–41] although the Dutch general surgeons in the survey often considered the metastasis count of liver metastasis (23.5%) and bilobar involvement (18%) to prohibit resection. Resection of synchronous or metachronous lung

metastases may result in long-term survival equal to resectable metastasis confined to only one organ.[33,34,42–44]

Among the Dutch surgeons 8–12% did not consider these patients eligible for surgery. Re-resection of metastases of both lung and liver result in near equal survival rates as after the first metastasectomy.[32,34,39–45] The differences in opinion regarding eligibility for hepatic metastasectomy indicate ongoing advances in liver surgery, which allow more patients to be a candidate for curative surgery. The same appears to be true for lung metastasis.

There is considerable controversy about follow-up after curative treatment of colorectal carcinoma because it has thus far not been proven to increase survival or quality of life. Meanwhile, recent rapid technical developments in imaging and advances in liver and lung surgery have changed the circumstances. Review of the guidelines on follow-up to reflect these changes is required. The high motivation among Dutch surgeons to participate in a new study appears to support this, making a national trial feasible.

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5

CEA measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery.

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Background. Carcinoembryonic antigen (CEA) as a marker in the follow-up after curative resection of colorectal carcinoma (CRC) is often omitted from follow-up despite guideline recommendations. One reason is the assumption that when a normal CEA value exists before curative resection of CRC, it will neither rise during follow-up. This study investigates this relationship.

Method. Data were derived from a study initiated to evaluate treatment regimes for rectal carcinoma (Dutch TME trial, n=1861) from which 954 were eligible for analysis. Recurrent disease occurred in 272 of these patients (29.5%). The pre-operative CEA value was compared to CEA values during follow-up, using threshold values of 2.5 and 5.0 ng/ml.

Results. Normal pre-operative CEA values were present in 63% (CEA < 5.0) and 39% (CEA < 2.5) of patients with recurrent disease. Patients with a normal pre-operative CEA and recurrent disease had elevated CEA values during follow-up in 41% (CEA < 5.0), 50% (CEA < 2.5) and in 60% with both threshold values when the last measurement was within 3 months before recurrent disease was diagnosed.

Conclusion. A normal pre-operative CEA is common in patients with rectal carcinoma. CEA does rise due to recurrent disease in at least 50% of patients with normal pre-operative values. Serial post-operative CEA testing cannot be discarded based on a normal pre-operative serum CEA.

Introduction

Carcinoembryonic antigen (CEA) as a marker in the follow-up of colorectal carcinoma (CRC) has been subjected to debate concerning it's effectiveness to reduce cancer mortality. CEA is known to have the ability to detect recurrent disease after curative resection of CRC at an early stage, with approximately 5 months lead time compared to clinical signs and several other tests. The effect on survival is less clear, also due to the fact that only a minority of metastasis can be treated with curative intent. Several follow-up studies have been done with contradicting results, successively reflected in meta-analyses and reviews [1-6] that conclude there is no consistent evidence that follow-up increases survival. The doubts about the value of CEA in follow-up contributes to decreasing adherence to guidelines from oncological societies,[7-10] that generally advise to measure CEA every 3 months in the first 3 years.

Other arguments than lack of evidence may influence leaving CEA out of follow-up as well. One of these is the assumed relationship between serum CEA values before and after curative surgery for colorectal carcinoma. Normal pre-operative CEA values are often considered a reason to omit serum CEA measurements from follow-up, because it is widely believed it will not rise with recurrent disease either. This belief is expressed in one regional Dutch guideline advising ultrasound instead of CEA measurement when pre-operative levels are normal, and is also reported in a recent survey.[11]

The threshold value of CEA is dependent on agreement; the industrial standard is 2.0-2.5 ng/ml dependent on the actual test. Due to frequent false-positive outcomes caused by benign gastro-intestinal disorders and smoking, the generally adhered threshold value in the follow-up for colorectal carcinoma in the Netherlands is 5.0 ng/ml.

In literature only little evidence is available about the relationship between CEA values before curative surgery and during follow-up. Staab was the first to describe the relationship between serum CEA values: he observed that in 40 patients with a normal pre-operative CEA value, none had risen during follow-up.[12] Three other authors however, published data that did demonstrate CEA elevations with recurrent disease when the serum CEA value before intended curative treatment was normal.[13-15] The goal of this study is to evaluate the relationship between serum CEA values before and after curative resection of rectal carcinoma.

Patients and methods

Patients. An analysis was carried out on data derived from a study evaluating the value of short course radiotherapy in primary resectable rectal carcinoma treated with standardized surgery (Total Mesorectal Excision or TME trial) from the Dutch ColoRectal Cancer group (DCRC-group). Results of this study were published before.[16, 17] The registration included all actual CEA values that were measured. Serial CEA testing was required every 3 months in the first three years and every 6 months in year 4 and 5, according to the study protocol that was based on national guidelines. From January 1996 until December 1999, 1861 patients were included, and follow-up data are registered until March 2006; the minimal follow-up time is therefore more then 6 years. In this study, patients with stage 0 and IV were excluded. Of the remaining eligible patients, the pre-operative CEA value and at least one post-operative CEA value were required for inclusion in this analysis.

Methods. The definition of "pre-operative CEA" is the serum CEA value measured immediately before curative resection of the primary tumour. "Post-operative CEA" is the serum CEA value after primary surgery during follow-up. To analyze the rise of CEA after curative resection in relationship to the pre-operative CEA value, we compared pre-operative values to the maximum postoperative value. This was done both for the group with and without recurrent disease. A separate analysis was performed for the group of patients with recurrent disease from whom the last post-operative CEA was determined less then 3 months before recurrent disease was diagnosed. To analyse the response of CEA after curative surgery (expected decrease) we compared the pre-operative CEA to the minimum post-operative value in both the patients with and without recurrent disease. All analyses are retrospectively done using two different threshold values, being 2.5 ng/ml and 5.0 ng/ml. No statistical analysis was applicable.

Results

Studied cohort

After exclusion of stage 0 and IV patients, 1701 patients were eligible for analysis. Stage I-II-III rectal carcinoma was diagnosed in 1665 patients, 36 patients were not classified. Both pre- and postoperative CEA values were available in 954 patients (56%). From these 954 patients, recurrent disease was diagnosed in 282 patients (29.6%). Patient demographics and tumour characteristics are described in table 1. The actual frequency of CEA measurements was much lower then required and was never above 50% at each moment (figure 1).

Relationship between pre- and postoperative CEA levels

In patients with recurrent disease (n=282), 63% (n=179) had a normal CEA value prior to primary surgery when apprehending a cut-off value of 5 ng/ml. Post-operative rise of the CEA above this threshold occurred in 41% (n=73). When a cut-off value of 2.5 ng/ml was used, 39% (n=110) had normal pre-operative CEA values. Elevated post-operative values were then found in 50% (n=55) (table 2). When the last CEA was measured within 3 months before diagnosis of local recurrence or metastasis (n=127), CEA was elevated in 59% (with a threshold of 5 ng/ml) and 61% (with a threshold of 2.5 ng/ml)(table 3).
In patients with no recurrent disease (n=672), 77% (n=519) had normal pre-operative CEA values when apprehending a cut-off value of 5 ng/ml. Post-operative rise of the CEA above this threshold during follow-up occurred in 4% (n=19). When a cut-off value of 2.5 ng/ml was used, 50% (n=337) had normal pre-operative CEA values. Elevated post-operative values were then found in 13% (n=44).

In patients with recurrent disease (n=282) and an elevated CEA value prior to primary surgery (n=172 at a threshold of 2.5 ng/ml, n=103 at a threshold of 5 ng/ml), CEA values were also elevated during follow-up in 79% (n=141 at a threshold of 2.5 ng/ml) and 82% (n=81 at a threshold of 5 ng/ml) (table 2).

CEA values were normal after curative surgery in 98% (n=658 at a threshold of 5 ng/ml) and 86% (n=578 at a threshold of 2.5 ng/ml) in all patients without recurrent disease (n=672) during follow-up. When recurrent disease was diagnosed during follow-up (n=282), CEA values were normal at the first measurement after curative surgery in 81% (n=228 at a threshold of 5 ng/ml) and 66% (n=186 at a threshold of 2.5 ng/ml).

Table 1. Patient characteristics and tumour classification			
	Eligible patients [1] (n=1701)	**Recurrent disease [2] (n=282)**	**No recurrent disease [3] (n=672)**
Age			
- median (range)	66 yr (23-92)	64 yr (23-85)	64 yr (27-88)
Sex			
- male	63 % (n=1071)	67% (n=189)	61% (n=407)
- female	37 % (n=630)	33% (n=93)	39% (n=265)
Tumour classification[4]			
- stage I	30.5 % (n=519)	8.2% (n=23)	39.9% (n=268)
- stage II	29.9% (n=508)	25.5% (n=72)	31% (n=208)
- stage III	37.5% (n=638)	65.6% (n=185)	28.3% (n=190)
- unknown	2.1% (n=36)	0.7% (n=2)	0.9% (n=6)

[1] All patients that are eligible for inclusion in this analysis (all minus stage 0 and IV patients). [2+3] Eligible patients with known pre-and postoperative CEA values, in total 954 patients. [4] Tumour classification according to the American Joint Committee on Cancer (AJCC).

Figure 1. Actual measurement of CEA during follow-up in the TME trial

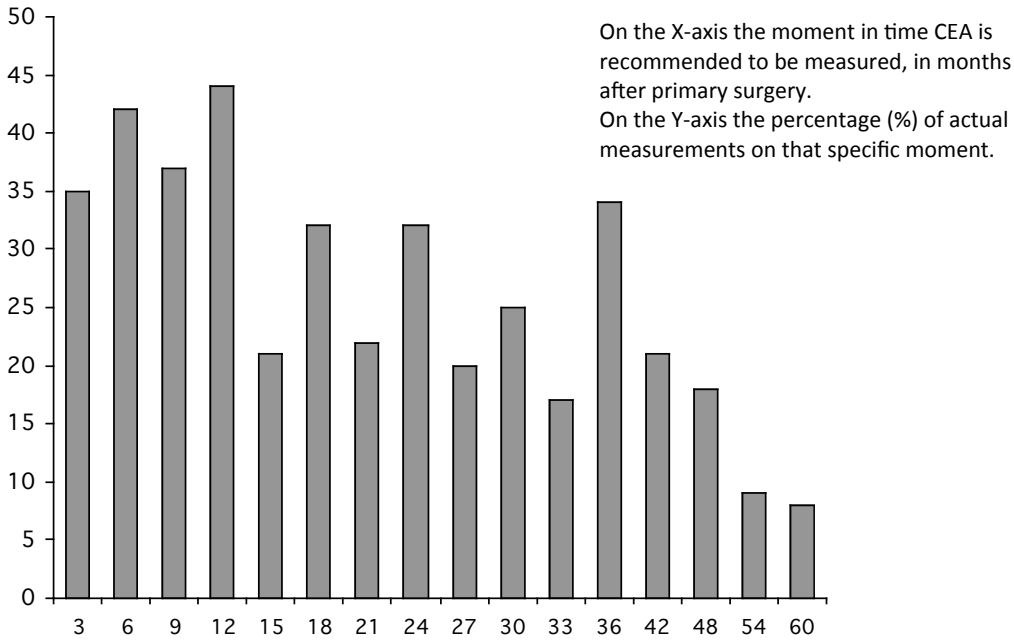

Table 2. Relationship between CEA values before and after curative surgery [1] in patients with recurrent disease		
n=282	**Postoperative value < 2.5**	**Postoperative value > 2.5**
Preoperative value < 2.5	55	55 (50%)[2]
Preoperative value > 2.5	31	141
	Postoperative value < 5.0	**Postoperative value > 5.0**
Preoperative value < 5.0	106	73
Preoperative value > 5.0	22	81

[1] The pre-operative value was compared to the highest CEA value measured during follow-up.
[2] The percentage of all patients with normal pre-operative CEA values (n=110) with elevated post-operative values (n=55)

Table 3. Relationship between CEA values before curative surgery and at diagnosis of recurrent disease[1]		
n=127	**Postoperative value < 2.5**	**Postoperative value > 2.5**
Preoperative value < 2.5	17	27 (61%)[2]
Preoperative value > 2.5	7	76
	Postoperative value < 5.0	**Postoperative value > 5.0**
Preoperative value < 5.0	28	40
Preoperative value > 5.0	10	49

[1] CEA value measured within 3 months before the diagnosis of recurrent disease was established
[2] The percentage of all patients with normal pre-operative CEA values (n=44) with elevated post-operative values (n=27)

Discussion

Summary of the results

This study suggests that a normal pre-operative CEA value does not mean it will not rise with, and due to recurrent disease during follow-up. A non-elevated CEA at primary diagnosis is common (50%), as well as a rise in CEA despite a normal pre-operative CEA (50%); this situation thus applies to a quarter of all colorectal cancer patients.

Role of false-positive postoperative CEA levels influencing study results

Incidental rises in CEA due to benign disease or smoking are known and can be the cause of 'falsely' elevated CEA levels during follow-up. This may account for a part of the elevated post-operative CEA values in this study because a comparison was made of the pre-operative CEA value with the maximum CEA value during follow-up. The proportion of these falsely elevated CEA levels was estimated by performing the same analysis in patients with no recurrent disease. This turned out to be limited (4-13%). Further the pre-operative CEA was compared with the CEA value at the time of the diagnosis of recurrent disease, assuming at least these elevated CEA values are due to recurrent disease. The percentage in this group was even higher (60%). The results of this study are in coherence with other numbers reported in literature.[13-15]

Value of CEA immediately after primary surgery

Not all CEA values return to normal after curative surgery, especially in the group of patients that are diagnosed with recurrent disease during follow-up, due to residual microscopic disease at time of intended curative surgery. A persistent abnormal post-operative CEA usually indicates synchronous metastasis or irradical resection and is applicable as a marker for the effectiveness of curative surgery. Serum CEA has a half-life of 6 to 60 days, and must be expected to return to normal within several weeks.

Considerations on the relationship between pre- and postoperative CEA levels

However it does appear that there is a relationship between pre- and postoperative CEA levels. The thought behind the assumption of the absence of rise in normal preoperative values, might not be entirely wrong. The likelihood CEA will rise with recurrent disease when pre-operative values were elevated as well is higher (78%, versus 50%) then with normal pre-operative levels. From this observation, it might be true that looking at relative CEA values, anticipating on an individual's 'normal value', would be a more effective manner of finding abnormalities then apprehending static cut-off values. The use of percentual rise or doubling time (DT) of serum CEA values might be effective. A strong prognostic value of this alternative has already been demonstrated,[12, 15, 18-20] however no

clinical trials have been initiated up until now to study the clinical benefit. Theoretically, by analysing the rise of CEA with measurement at an interval of several weeks, both sensitivity and specificity can increase. A higher sensitivity is achieved because a rise in CEA can signal recurrent disease before crossing a static threshold, especially in patients with low baseline values. A higher specificity is expected because incidental rises due to e.g. self-limiting benign disease are 'filtered' by repetitive measurements. Low specificity for malignancy has been the main problem of CEA, which has also led to the apprehension of higher threshold values then actually are normal. Use of CEA rise, there with anticipating on individual differences in CEA expression, might solve this problem. An explanation for the variances in CEA expression may be the production and shedding to the circulation or intestinal lumen by different tumour types.[21-23] Immunohistochemical staining of CEA within the cell has different cellular distribution patterns reflecting in different serum levels. This pattern of expression and successive differences in spilling to the circulation may be retained in recurrent disease.

Conclusion

The majority of patients with rectal carcinoma have normal CEA values before curative surgery and half of them will express a rise in CEA values due to recurrent disease. This means a significant number of patients will miss an opportunity on early detection of recurrent disease when CEA measurements are omitted, due a false assumption. Serial post-operative CEA testing cannot be discarded based on a normal pre-operative serum CEA.

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6

The Role of High Frequency Dynamic Threshold (HiDT) Serum Carcinoembryonic Antigen (CEA) Measurements in Colorectal Cancer Surveillance: a (revisited) hypothesis paper

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Context: Following curative treatment for primary colorectal cancer (CRC), 30 to 50% of patients will develop recurrent disease, commonly locoregional recurrence and distant metastases to the liver and lung. For CRC there are several lines of evidence supporting the hypothesis that early detection of metachronous disease offers a second opportunity for cure. The current drive in clinical trials is towards detecting metachronous disease in asymptomatic patients through more intensive imaging protocols, typically computerized tomography (CT) scanning, but this has several limitations including: high expensive and resource usage; high-rates of 'incidentaloma' incurring further costs for investigations and treatments; and neoplastic risks from cumulative radiation exposure. Against this background, an alterative strategy is a low cost 'triage' blood biomarker triggering and directing selective CT usage. This paper revisits the potential role of serum carcinoembryonic antigen (CEA), set against modern imaging techniques, changes in CRC treatment and clinically-linked decision-making software.

Limitations of past studies: A comprehensive review of the literature (1978-2008) demonstrates that the initial promise of serum CEA as an effective surveillance tool in the setting of CRC has been tarnished through perpetuation of poorly designed and underpowered studies. Specific limitations included: testing CEA as only an 'add-on' diagnostic tool; lack of standardization of threshold values; use of static thresholds; too low measurement frequency; mismatch in timing on expected time of recurrent disease. Major changes in treatment of metastatic CRC further cause a decrease of clinical applicability of past trial outcomes.

Revisited hypothesis: In 1982, Staab hypothesized that the optimal benefit of serum CEA as a surveillance tool is through high-frequency triage using a dynamic threshold (HiDT) approach. Evidence supporting this hypothesis was found in an evaluation of biochemical characteristics of serum CEA tests and retrospective studies showing the superior predictive value of a dynamic threshold value as compared to a static threshold value. A preceding pilot trial has set forth the protocol for a national randomized trial.

Future trial design: A multi-centred randomized phase III study optimizing the usage of HiDT against resectability of recurrent disease as the primary outcome measure is commencing recruitment in the Netherlands in 2010. A clinically integrated computer-assistant support system is a key component of the trial design and will concurrently be

Context

Following curative treatment for primary colorectal cancer (CRC), 30 to 50% of patients will develop recurrent disease, commonly locoregional recurrences and distant metastases to the liver and lung. Unlike most adult solid malignancies, for CRC, there are several lines of evidence supporting the hypothesis that early detection of metachronous disease offers a second opportunity for cure.[1, 3-5]

Serum CEA has been the hallmark in follow-up of colorectal carcinoma for 30 years. There has been considerable controversy concerning the benefits of serum CEA in follow-up. Five meta-analyses were carried out analyzing the evidence of the effectiveness of follow-up in colorectal cancer on survival.[1-5] Only a small survival gain was seen, predominantly when frequent serum CEA measurements were included in the follow-up.[1, 3-5] Most of the studies included in the meta-analyses however, analyzed the effect of follow-up in general, often consisting of a wide variety and combinations of diagnostic tests.[5] This limits the evidence on the diagnostic accuracy of a specific diagnostic test. The meta-analyses therefore do not necessarily reflect the diagnostic value of serum CEA in follow-up and the controversy concerning the role of serum CEA has not been solved.

The current drive in clinical trials is towards detecting metachronous disease in asymptomatic patients through more intensive imaging protocols, typically computerized tomography (CT) scanning, but this has several limitations including: high expensive and resource usage; high-rates of 'incidentaloma' incurring further costs for investigations and treatments; and neoplastic risks from cumulative radiation exposure.

Against this background, an alternative strategy is a low cost 'triage' blood biomarker triggering and directing selective CT usage. This paper revisits the potential role of serum carcinoembryonic antigen (CEA), set against modern imaging and CRC treatment and clinically-linked decision-making software, as such a surveillance tool.

Limitations of past studies

A comprehensive review of the literature (1978-2008) was performed, using search term [Carcinoembryonic antigen] AND [Colorectal neoplasm], limited to the subheadings [analysis], [diagnostic use], [blood], [standards] and limited to 'human' and 'English language'. Additional relevant references found in articles were included. Review articles were used as a reference but not included in the analysis. Selection of the abstracts was made on the available information concerning clinical use of CEA in follow-up after curative resection of CRC.

From 1978 till 2008 26 original clinical trials evaluating the outcome of follow-up after curative treatment of colorectal carcinoma which included serum CEA measurements were published (Table 1).[6-31] One publication was excluded from analysis because it concerned a double publication. The 25 clinical trials, and a few follow-up studies that did not include serum CEA measurements, have resulted in five meta-analyses on follow-up in CRC.[1-5] The 25 original articles were analyzed on actual testing the diagnostic capacity of serum-CEA, the clinically applied threshold value of serum-CEA, timing of follow-up and measurement frequency.

Most studies evaluated follow-up regimes consisting of various diagnostic tests. In only 5 from 25 clinical trials, different serum CEA regimes were compared,[6-10] from which 3 studies were randomized controlled trials.[8-10] The results of these studies show a consistent beneficial effect of serum CEA measurements on both the rate of curative resection of recurrent disease and survival (table 2). In the meta-analyses the majority of included trials did *not* compare different CEA regimes (Table 3). These meta-analyses therefore, do not reflect the diagnostic capacity of serum CEA in follow-up.

The average static normal value of serum-CEA is 2.0-2.5 ng/ml. To increase specificity and prevent the situation of inability to localize recurrent disease with imaging techniques or relaparotomy in the past, the clinically applied static threshold value has often been increased to 5 ng/ml or higher. From the 25 studies, all except one study used a static threshold value. A threshold value of ≤ 2.5 ng/ml was applied in 3 studies (13%), of ≥ 5 ng/ml in 8 studies (32%) and in 14 studies the applied threshold value was not mentioned. Applying a higher threshold value results in a decrease in sensitivity and with that, in a possible delay of diagnosis of recurrent disease.

Diagnostic tests for recurrent disease are most sensitive when the timing is aimed at the expected time to recurrence through optimizing the pre-test probability. Data from the 25 clinical studies revealed that local recurrences were found on average between 6 months and 2 years, liver metastases between 6 and 18 months and pulmonary metastases between 24 and 36 months. In the clinical trials (calculation based op 22 trials), a measurement frequency of once per ≤ 3 months was apprehended in 91% of trials in the first year, 53% in the second year and 25% in the third year. The measurement frequency actually carried out is only 46 to 62% of the reported measurement frequency, as was shown in 6 independent studies.[7, 13, 22, 46-48] This implies that the timing and measurement frequency in most studies and in clinical practice has been insufficient to expect any beneficial effect of serum-CEA in follow-up for CRC.

TABLE 1 Clinical studies on follow-up including CEA measurements					
	Year	Type trial**	N=	Recurrence rate	
				N=	%
Martin	1980	Prospective, Comparative	300	60	20%
Lim	1980	Retrospective, Non-comparative	127	20	16%
Steele	1982	Retrospective, Non-comparative	770	86	11%
Minton	1984	Prospective, Comparative	400	130	33%
Hine	1984	Prospective, Non-comparative	626	171	27%
Staab	1985	Prospective, Non-comparative	426	67	16%
Ovaska*	1990	Retrospective, Non-comparative	507	149	29%
Behbehani	1990	Prospective, Non-comparative	123	34	27%
Moertel	1993	Retrospective, Non-comparative	1216	417	34%
McCall	1993	Prospective, Non-comparative	311	98	32%
Makela	1995	Prospective, Non-comparative	106	43	41%
Ohlsson	1995	RCT, Comparative	107	35	33%
Pietra	1998	RCT, Comparative	207	46	22%
Schoemaker	1998	Prospective, Non-comparative	325	?	?
Graham	1998	Retrospective, Non-comparative	1356	421	31%
Wichmann	2000	Prospective, Non-comparative	1321	306	23%
Komborozos	2001	Retrospective, Non-comparative	113	113	100%
Bleeker	2001	Prospective, Non-comparative	496	213	43%
Glover	2002	Retrospective, Non-comparative	100	32	32%
Secco	2002	RCT, Comparative	337	184	55%
Chau	2004	Prospective, Non-comparative	530	154	29%
Bonthuis	2004	Retrospective, Non-comparative	564	149	26%
Grossmann EM	2004	RCT, Non-comparative	985	139	14%
Rodriquez	2006	RCT, Non-comparative	259	69	27%
Fernandes	2006	Prospective, Non-comparative	120	23	19%

* Results of this study were published twice, therefore only one study is taken into analysis

** Concerning CEA : all grey-marked studies were comparative concerning CEA

TABLE 2 Effect of CEA measurements in follow-up on resectability of recurrent disease and 5 year survival								
	CEA measurement frequency (months)		**Recurrence rate**		**Curative resection recurrent disease**		**5 yr survival**	
	Control	Intensive	Control	Intensive	Control	Intensive	Control	Intensive
Secco	none	3 (HR) 6 (LR)	57%	53%	16%	31%	32% (HR) 60% (LR)	50% (HR) 80% (LR)
Pietra	6	3	19%	25%	10%	65%	58%	73%
Ohlsson	none	3	33%	37%	17%	40%	67%	75%
Martin	3-6	1-2	7%	13%	27%	60%	9%	*
Minton	none	1-2 3-4 > 4	20%	28% 29% 61%	12%	54% 23% 13%	*10%***	33%

* at the time of publication the FU time ranged from 0-4 years, after which 58% of patients were still alive

** The 5 year disease free survival between FU with CEA every 1-2 months as compared to "any less frequent

TABLE 3 Summary of meta-analyses on follow-up for colorectal cancer and inclusion of trials that compared different CEA regimes				
	Year	**Studies***	**+ CEA**	**Conclusions**
Bruinvels	1994	7	3	A significant increase on survival is found only when CEA assays are included in follow-up.
Kievit**	2000	14	*3***	Overall survival gain by intensive follow-up varies between 0.5-2.0%. No sub-analysis on the role of CEA.
Renehan	2002	5	2	Intensive follow was associated with a reduction in all cause mortality (combined risk 0.81, 95% CI 0.70-0.94). The effect was most pronounced [] that used computed tomography and frequent measurements of CEA (RR 0.73 95% CI 0.6-0.89)
Jeffery	2002	5	2	There was evidence that an overall survival benefit exists for patients undergoing more intensive follow-up (OR 0.67, 95% CI 0.53-0.84). Because of wide variation in the FU programmes used [] it is not possible to infer from the data the best combination and frequency of clinic visits and additional investigations.
Tjandra	2007	8	3	Intensive follow-up after curative resection of colorectal cancer improved overall survival and reresection rate for recurrent disease. Regular surveillance with CEA (p=0.0002) and colonoscopy (p=0.04) demonstrated a significant impact on overall mortality.

* Total of randomised controlled trials and non-randomised comparative trials.

** From 4 clinical studies it could not be retrieved whether CEA regimes were different and compared, in 7 studies no different CEA regimes were compared.

Historical context: changes in clinical practice

The role of imaging techniques

Localization of recurrent disease in follow-up has been a major problem in the past, influencing the results from clinical trials carried out before 2000. Serum CEA can signal recurrent disease as a first-line screening tool, but for the definite diagnosis and treatment, the site and extent of recurrent disease must be localized. When recurrent disease is suspected but no certainty or treatment can be offered to the patient, follow-up only results in a loss of life quality and should be prevented. Up until this century, is has been very difficult to localize recurrent disease with non-invasive techniques. A second look laparotomy aimed at potentially curable liver metastases has been standard of care until the late eighties and has been the hallmark in most clinical trials included in this analysis. Because of the invasive nature of this 'diagnostic test', the demands on accuracy of the screening test have been high. Nowadays, non-invasive tests such as multislice computed tomography (CT), Magnetic reseonance imaging (MRI), contrast-enhanced ultrasound and Positron Emission Tomography (PET) can localize recurrent disease of > 1 cm in liver and lung and locoregional recurrence. This situation lowers barriers to act upon signals indicating possible recurrent disease from first-line screening with serum-CEA. The discriminative capacity of available imaging techniques however, is limited for smaller lesions. When serum CEA is used in follow-up as a first line detector of recurrent disease, the applied threshold value should be adapted to the likelihood of actual localization on imaging techniques. A threshold of at least 50% detected lesions on imaging following positive serum CEA test results should be apprehended. This to prevent recurrence of the 'old' problem of inability of localization and with that, the inability to offer treatment or support. The reverse situation that may occur is recurrent disease that does not result in an increase in serum CEA value. A significant proportion of patients have normal serum CEA values with CRC or recurrent disease. This was reviewed in three studies.[23, 39, 49] The proportion varied from 23% till 60%, depending on the clinically applied (static) threshold value. When respecting a threshold value of 2.5 ng/ml, the proportion of patients with normal CEA values will be approximately 25% at initial presentation. Because of different tumor behavior the proportion of serum CEA 'negative' disease is probably lower with recurrent disease, however this has not been described. It has been a wide believe that a normal serum CEA value at initial presentation, implies that the serum CEA value will not rise either in case of recurrent disease. Although there is indeed a tendency serum-CEA 'negative' tumors less often show an increase in serum CEA value with recurrent disease, more then 60% will show a rise with recurrent disease.[49] Serum CEA measurements can therefore not be discarded based on an initial normal CEA value. However, there will

always remain patients that have recurrent disease with normal static serum CEA values. Theoretically, applying a dynamic threshold value, might reduce the number of serum CEA 'negative' patients; also in lower ranges of serum CEA values a pattern of rise can be observed and may be more sensitive than static threshold values. Also with this approach there will always remain patients that have recurrent disease with unchanging serum CEA values. Any CEA based follow-up protocol should therefore include imaging techniques, aimed at the expected time of recurrent disease.

Patterns of recurrence.

The treatment of colorectal carcinoma has changed considerably in the past decade, changes that should be taken into account in interpreting past study results and future considerations concerning follow-up. Since the introduction of neo-adjuvant chemoradiation combined with TME surgery, the incidence of local recurrence in rectal cancer has decreased and the outcome in survival improved significantly.[50, 51] The expected time to recurrence after combined treatment for rectal cancer seems to increase.[52] Routine pre-operative staging with abdominal CT, as is now adviced in national guidelines, is likely to cause a shift from previous "early" metachronous to now synchronous liver metastases and with that, change the incidence and pattern of recurrent disease. High-risk patients with colon cancer that either have lymph node metastases or unfavorable histopathological features (such as tumor perforation, serosal infiltration or locally advanced tumors, angio-invasive or perineural growth) receive adjuvant chemotherapy up to 9 months after operation. Modern adjuvant chemotherapy consisting of 5-FU/ leucovorin combined with oxaliplatin (XELOX or FOLFOX) decreases the incidence of recurrent disease within 4 years after surgery and prolongs the time to recurrence of liver and lung metastases.[53, 54] A significant part of clinical trials analyzed in this article have been carried out before neo-adjuvant (chemo)radiation had become the standard of care. The incidence of recurrent disease after curative treatment of stage 0-III colorectal cancer will therefore probably decrease as an effect of staging and (neo)adjuvant treatment. On the other hand, synchronous liver and peritoneal metastases can more often be treated with curative intent with modern multimodality treatment options. After curative treatment, these patients have a chance on recurrent disease of approximately 50%. Recurrences in patients can often again be treated with curative intent. Inclusion of these patients in follow-up trials, which are patients that were previously not treated with curative intent and excluded from follow-up trials, will alternately increase the incidence of recurrent disease during follow-up. In an analysis on recurrence pattern in a population routinely staged with abdominal CT and treated according to current standards, the chance on early recurrence is low and limited to patients with locally advanced tumors

[Grossmann, chapter 8]. A rough estimate on the current chance on recurrent disease is 30-50%, the expected time to recurrence is between 12 and 36 months and might be prolonged to more then 5 years in defined risk groups. In the light of these changes the outcomes of follow-up trials on recurrence pattern should be taken into account in future follow-up and trial designs.

Logistic considerations

One of the reasons that may have contributed to the striking absence of clinical trials applying HiDT serum CEA measurements is the logistic burden and costs of intensive screening. Colorectal cancer is the second most common malignancy with a life time chance of approximately 10% in the Western population. Frequent outpatient clinic visits combined with serum CEA measurement for all patients treated with curative intent is not feasible, neither effective; outpatient clinic visits with physical examination do not contribute to early detection of recurrent disease [22] and it can be an unnecessary burden for the (elderly) patient. This situation may have contributed to the notable low adherence to current guideline recommendations on the measurement frequency of serum CEA as well. The solution to the logistic problems induced by HiDT is serum CEA measurement without outpatient clinic visits. This can nowadays be supported with automated processing, signalling and sharing of test results with the patient via the telephone or internet. Prototype software (CEA watch) has been designed and tested in a preceding pilot trial on the HiDT approach, with good experiences. Patients' experiences with HiDT without outpatient clinic visits was evaluated in a psychological study on patients in this preceding pilot trial and showed this approach is well tolerated and even preferred by patients above care as usual [Reijnen, chapter 7].

Conclusion

Summarizing, the diagnostic accuracy of serum CEA has been underestimated because of the methodology of clinical trials. Evidence supporting the clinical value of serum CEA on increasing the eligibility of curative resection of recurrent disease detected in asymptomatic patients and successively on survival is available. The threshold value, measurement frequency and interpretation of serum CEA values, and the timing on expected time of recurrent disease have been far from optimal in the past in both clinical trials and clinical practice. The changing clinical context limits the value of the outcomes of past clinical trials. Curative treatment options for recurrent disease have been improved considerably in the last decade, and more accurate non-invasive imaging techniques and computer support in medical care are available supporting intensive follow-up with serum CEA measurements in colorectal cancer.

Revisited hypothesis

Serum CEA reflects the expression of an embryonic protein on the cell surface, which has a function in the embryonic tissue development. This protein is expressed in the adult situation in malignancies and inflammatory disease. Serum CEA reflects the expression of the embryonic protein on the cell surface as an antigen response. There is a relation between tumor growth and serum CEA; most tumors have an exponential growth pattern followed by an exponential rise in CEA.[36, 39] Following these observations, Staab hypothesized in 1982 that the optimal benefit of serum CEA as a surveillance tool is through high-frequency measurements using a dynamic threshold.[15, 35] This hypothesis was revisited by means of a systematic review of the literature, and has acted upon changes in the clinical context of colorectal cancer. The hypothesis was tested a prospective pilot trial from which the initial results are discussed.

Biochemistry, sensitivity and specificity of serum CEA

Serum CEA measurements tests are based on monoclonal antibodies that bind CEA and as with each diagnostic test, has measurement errors. Standard measurements errors of serum tests are divided in four types. The intra-assay test variation, that is the variation in test result when using the same blood sample, is approximately 2-10%. The inter-assay variation, that is the variation in test result using the same blood sample in two different tests, is 4-12% in the lower ranges (< 15 ng/ml) and up to 20% in higher ranges.[42, 43] The differences between tests and laboratories are relatively small; meaning the accuracy of the assay is high. This allows comparison between studies and hospitals.[43] The intra-individual variation, that is the variation in serum CEA values within one person without evidence of disease, is 9.3%. The inter-individual variation, that is the difference in normal value between individuals, is approximately 55%.[44] Referencing the CEA value on the patient's previous value can eliminate this last and largest measurement error. This requires repeated measurements and interpretation of the changes in serum CEA value. Because of the other three measurement variations, the threshold value for rise should not be lower then 15%. The static threshold value as recommended by industrial standards ranges from 2.0 – 2.5 ng/ml, the optimal dynamic threshold is not formulated thus far.

The *clinically* optimal threshold value is dependent on the desired sensitivity and specificity in the target population. Sensitivity must be high in follow-up to adequately detect recurrent disease. A high specificity is of importance to minimize unnecessary diagnostic evaluation based on test results, especially when the test is applied as a screening tool. Follow-up requires both, as a screening tool in a high-risk population. The specificity increases when the pre-test probability is high; meaning the test is most accurate in a high-risk population. In four studies the sensitivity and specificity of serum

CEA on static threshold values ranging from 2.5-20 ng/ml was calculated.[13, 20, 26, 45] The pooled results show a consistent pattern of a low accuracy between 2.5 and 10 ng/ml. This is likely caused by the overlap of abnormal CEA values with benign disease in these lower ranges and the inter-individual variation. The difference between malignancies and inflammatory disease is that malignancies will continue to grow where inflammatory disease is usually self-limiting. The accuracy can be improved by using intra-individual rise, because this eliminates the inter-individual variation and shows the potentially discriminative *pattern* of rise. This requires repeated measurement and consequently a high measurement frequency. The optimal measurement frequency for this approach has been addressed in three studies.[6, 15, 33] Based on their retrospective data, all suggested a frequency in the order of every one till two months.

Summarizing, with evaluating the pattern of rise the inter-individual variation can be

TABLE 4 Quantitative rise of CEA in patients with recurrent disease

	Year	Nr pat	Nr RD	Doubling time*	Rise per 30	Absolute rise
Steele	1982	767	469		1.5% - 15.2%	
Staab	'78-85		114	10 - 231 days	-	
Boey	1984	146	51		20%	
Staab	1985	667	78	-	0.6 – 4.4 ng/ml	
Carl	1993	259	163	74 – 164 days	-	
Umehara	1993		31	60 (18–153) days	-	
Korenaga	1997		17	86 (± 18) days	-	
Yamamoto	2004		36	41-110 days	-	
Irvine	2007	139	46	-	-	> 1 ng/ml above 1st post-operative level
*Tanaka***	*2008*		*43*	*150 days*	-	

* when a differentiation per type of metastases was made, the lower and upper limits are given from all analyses on possible curable metastases (liver, lung and peritoneal metastases or local recurrence).
** In this study the threshold value of CEA-DT as a prognostic factor was calculated: no data were available on average CEA-DT in patients with recurrent disease.

eliminated and a higher discriminative capacity between malignancy and inflammatory disease is expected. This increases specificity and allows interpretation of serum CEA values in lower ranges of values, thus increasing sensitivity as well. In short; interpretation

of serum CEA values with a dynamic threshold based upon high frequency measurements (HiDT) can largely improve the accuracy.

Evidence of the hypothesis in past clinical trials

A search with [Carcinoembryonic antigen] limited to subdivisions *analysis, *diagnostic use, *blood and *standards AND 'doubling time', and a search with [Carcinoembryonic antigen] AND [Colorectal neoplasm] AND 'doubling time' or 'rise' was done, both limited to 'human' and 'English language'. Relevant references were included in the study. Abstracts were selected on information on clinical relevant information on use of a dynamic threshold value of CEA. Twelve articles were included [13, 15, 32 - 41] and analyzed on study design, clinical effectiveness and quantitative results on CEA rise found with recurrent disease. The hypothesis on using a dynamic threshold value was evaluated in a few studies. In the study of Steele, the predictive capacity of using a static versus dynamic threshold value (of > 3% rise per month) was compared in a retrospective analysis of 767 patients with CRC [13]. The proportion of patients with recurrent disease *without* rise varied from 10 - 27%, the proportion of patients with recurrent disease *with* rise varied from 33 - 84% (variation dependent on the lower limit static threshold value). The dynamic threshold value (rise) had a much stronger predictive capacity for recurrent disease than the actual height of the serum CEA value, supporting the hypothesis on HiDT. Another trial recalculated in retrospect the pattern of rise and found a median increase of 20% per month in case of recurrent disease as compared to median rise of 0.3% in recurrence free patients.[32] Only one clinical trial applying CEA-rise in follow-up has been carried out by Staab.[35] This study showed a modest survival benefit after 3 years (5 versus 25%), comparing patients that had, or refused relaparotomy induced by CEA rise. This study does not prove a better outcome when applying a dynamic threshold value in CEA as compared to other follow-up methods, however it does suggest that early detection and treatment of recurrent disease may result in a survival benefit. Further this study has been carried out in a time none-invasive imaging techniques to localize recurrent disease were not yet available. Most studies on CEA rise or doubling time evaluated the extent of rise with recurrent disease that may help the determination of the accurate threshold value (Table 4).[13, 32, 33, 37-41] None analyzed the pattern of rise and decrease with inflammatory disease or smoking.

Evidence of the hypothesis from the preceding phase II pilot trial

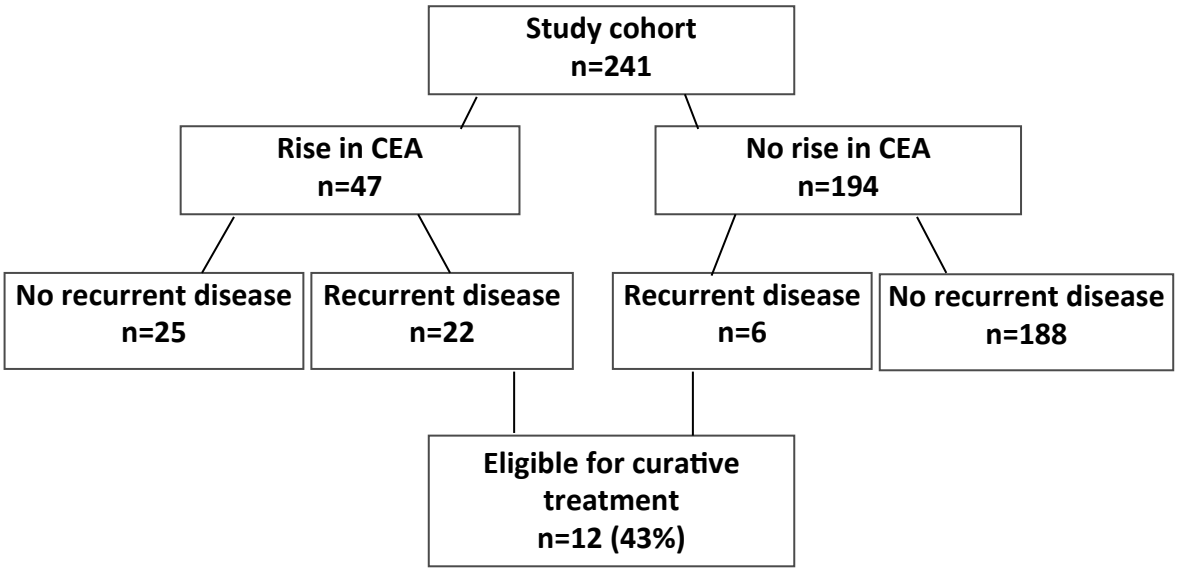
A phase II trial was started in 2007 evaluating the clinical applicability and outcomes of HiDT in follow-up after curative treatment of colorectal cancer. The primary endpoint is the eligibility of curative treatment (increase to 30%), secundary endpoints are the ability to localize recurrent disease on imaging techniques (CT, minimum 50%) and feasibility of the computer supported protocol. This study was done in two different hospitals. One hospital (n=64) applied monthly serum-CEA measurements with a dynamic threshold value of > 10% rise each month in two consecutive measurements. The other hospital (n=177) applied serum CEA measurements every 3 months, which was repeated after 6 weeks in case of a rise of > 10%. In both hospitals a routine CT of abdomen was performed at year 1 and a CT of chest and abdomen at year 2.

Recurrences up until 2 years after curative treatment, up until now, were found in 28 patients (12%) (figure 1). Of 28 patients with recurrent disease, 12 patients (43%) were eligible for curative treatment. The sensitivity of HiDT serum CEA measurements was 79% and the specificity was 88% in a mean range between 2.5 and 10 ng/ml. Mean increase factor per month was 1.48 in the recurrence group. In a subgroup analysis of patients from the first hospital who had false positive rises in CEA values (n=8), other causes such as inflammatory disease (n=3) and dysplastic polyps (n=2) were found as the cause of the rise; in these patients CEA values decreased after treatment. The mean increase factor per month in the group of patients with false positive rises in CEA was 1.25.

The dynamic threshold value applied in the study is probably too low; approximately half of the patients with a rise in CEA did not have recurrent disease. A solution for this problem -next to alteration of the threshold value- is to focus additional diagnostics on both possible recurrence, inflammatory diseases and dysplastic polyps via colonoscopy. Computer supported follow-up was feasible and positively rewarded by the treating physiocians (Verberne, unpublished results).

A subgroup analysis of the effect of smoking on base CEA values was done in one hospital (n=44). The mean base CEA value for smokers who did not show a rise in CEA (n=11) was 5.1, were the mean base value of non-smokers without rise in CEA (n=23) was 2.9 ng/mL. The non-smokers with recurrent disease (n=5) showed a mean rising factor of 1.32 per month, and the smokers (n=2) showed a mean rising factor of 1.39 per month.

These preliminary results show an improved accuracy when applying a dynamic threshold value and had an acceptable outcome concerning the primary and secundary endpoints.



Future trial design

A multi-center randomized phase III study on the usage of HiDT of serum CEA as a low cost 'triage' blood biomarker triggering and directing selective CT usage compared to care as usual is commencing recruitment in the Netherlands in 2010. All patients after curative treatment of AJCC stage II-IV colorectal cancer and fit to undergo major surgery for recurrent disease are eligible for this study. The intervention will be bi-monthly serum CEA measurements applying a dynamic threshold value of 20% rise and yearly CT of chest and abdomen at year 1, 2 and 3. The control group is care as usual. A clinically integrated computer-assisted support system is a key component of the trial design and will concurrently be evaluated. The study will be performed in 10 hospitals by the use of a stepped wedge design. Different clusters cross over at different time points in one direction – from control to intervention. The time at which the cluster may start the intervention is randomized, the baseline starting point is October 1st 2010. The primary outcome measure is the eligibility of intended curative treatment of recurrent disease. Secundary outcome measures are: overall and disease free survival; optimizing the threshold value set against attainability of localizing recurrent disease on imaging; psychological effects and logistic effectuation of high frequency serum CEA measurements.

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7

Positive psychological evaluation of an intensive follow-up trial in colorectal cancer based upon high frequency serum CEA measurements

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Objective. The aim of the study was to evaluate the psychological effects of an intensive follow-up scheme after curative treatment of colorectal cancer based upon high-frequency dynamic threshold (HiDT) serum CEA measurements and less outpatient clinic visits, as a feasibility study for a national randomized trial on follow-up.

Design and Method. In this cross-sectional study, 138 patients were sent a postal questionnaire to evaluate the effects on the patients' attitude and satisfaction, the preference for follow-up program, depression, anxiety and cancer worries. Responders in the intervention group (n=49) were compared to the care as usual group. One way ANCOVA was used for statistical analysis.

Results. Patients in the intervention group were more satisfied with their follow-up program ($p = 0.02$). Most patients (67%) preferred their current follow-up program, though the majority of the intervention patients (62%) had a second preferred option for the monthly blood tests with less contact with the physician. No significant differences were found between the intervention group and the reference group according to the attitude towards follow-up, anxiety, depression and cancer worries.

Conclusion. The positive evaluation of the follow-up based upon HiDT serum CEA measurements without concomitant outpatient clinic visits implies such approach is feasible in respect to the psychological effects of intensive screening 'from a distance'.

Introduction

Colorectal cancer is the third most-common type of cancer in the Netherlands, with an occurrence of 10.000 new patients each year. After curative resection patients are subjected to a follow-up program that consist of outpatient clinic visits each 3 to 6 months during 5 years, complemented with serum CEA measurements and imaging techniques. The main goals of follow-up are early detection of asymptomatic recurrent disease and metachronous tumors, evaluation of the functional outcome of treatment and to answer questions. [1]

The impact of follow-up on quality of life can be both positive and negative. It may offer support and confirmation but can also induce fear and worries.[2-12] In general, patients have a positive attitude towards follow-up schedules [2, 3] and the advantages are felt to outweigh the disadvantages.[3] Many patients feel reassured [13] and prefer routine follow-up [4] even if the visit leads to anxiety and there is no guarantee recurrences can be detected or treated. [4-6] Patients have high expectations of follow-up,[7] believing that an early detection of recurrence will lead to a higher chance to survive. Previous studies have shown that a higher frequency of follow-up visits does not lead to more distress but does increase confidence.[2, 14]

The efficacy of follow-up after curative treatment of colorectal cancer has been under debate; a survival benefit achieved through early detection and treatment of recurrent disease has been observed only in studies that included serum CEA measurements.[15-17] A new type of intensive follow-up regime based upon high frequency dynamic threshold (HiDT) serum CEA measurements is intended as a national randomized trial in the Netherlands. This new regime is largely carried out 'from a distance', meaning that a higher frequency of serum CEA measurements is done with a decrease of outpatient clinic visits. Patients are informed about their CEA values by postal mail. In the Medical Spectrum Twente and University Medical Center Groningen a preceding phase II trial was carried out. An evaluation of the psychological effects of intensive follow-up 'from a distance' was intended as a feasibility study for the national trial. This study evaluates the effects of the follow-up protocol on the patients' attitude and satisfaction with the follow-up program, the preferences for follow-up type, depression, anxiety and cancer worries.

Patients and methods

Patients that had curative treatment of colorectal cancer (pathological AJCC stage II and III) within one year before inclusion and were fit to undergo eventual metastasectomy, were eligible for inclusion in the phase II trial and 'marked' as eligible in their patient records. Approval of the Medical Ethical Committee was obtained in both study centers under governance of the University Medical Center Groningen (METc2007/015, NL15366.042.07). This cross-sectional survey was performed in 2009 among 60 patients who participated in the phase II clinical trial in the Medical Spectrum Twente and 80 patients that had 'care as usual'. Patients in the intervention group (n = 60) had monthly serum CEA measurements and a 6 to 12 monthly outpatient clinic visit. Patients with an increase in CEA-level in two consecutive months were invited by telephone for further examinations in the hospital. In case of a normal CEA-level patients received the result by letter. Patients had access to the hospital for intermittent appointments with a physician, in case of questions or worries. The intervention group patients were asked to take part in the study by a physician, the reference group were selected at random among the patients that were already marked as eligible for this study but were not asked to participate due to logistic reasons (no outpatient clinic visits during inclusion period). These patient had 'care as usual', consisting of an outpatient clinic visit every 3 to 6 months with concurrent serum CEA measurements. A total of 61 patients were asked to participate in the phase II trial, of whom 60 patients consented and one refused. To test the questionnaire 2 patients of this group were selected to take part in an interview. A set of 138 questionnaires was sent to the patients, of which 58 to the patients of the intervention group and 80 to respondents of the reference group. The questionnaires were analyzed anonymously.

Questionnaires

Apart from general data concerning sociodemographic status and medical history, in the postal questionnaire the following topics were covered:

Attitudes Towards follow-up. Patients were asked to fill out a validated 15-item questionnaire on attitudes towards follow-up that had been used to evaluate the follow-up of colorectal cancer.[3, 7] This questionnaire consists of four subscales: communication (with the physician), reassurance, nervous anticipation, and specific perceived disadvantages of follow-up. For the communication and the reassurance scales, a higher score meant a more positive evaluation (range 0-100). For the nervous anticipation and the disadvantages scales, a higher score meant more negative effects (range 0-100).

Anxiety and depression were examined by the Dutch version of the Hospital Anxiety and Depression Scale (HADS).[18] Within this questionnaire higher scores meant more anxiety and more depression.
Lerman developed a scale to measure cancer worries.[19] In this study we used the Dutch version of this Cancer Worry Scale. Within this questionnaire patients with higher scores had more cancer worries.
Satisfaction was measured by a questionnaire specifically designed for this study. This 5-item questionnaire (α = 0,90) was measured by a 10-point scale (Table 4). The higher the score, the more satisfied the patient was.
To measure **patients' preferred follow-up program** patients had to declare which program they preferred the most and which program they preferred the least. The patients had the choice between 4 options; (1) no follow-up, (2) visits to the physician every 3 to 6 months (the current mode of the reference group), (3) every month a blood test or (4) every month a blood test with every 6 months to every year a visit to the physician (current mode of the intervention group). A higher score meant a less preferred option for follow-up (most preferred = 1 to less preferred = 4). Additionally, patients were asked if they would like to know when they have recurrences even if they are asymptomatic but cannot be treated. The higher the score, the more the patients would like to know if they have recurrent disease. The exact questions about the satisfaction and preferences of patients are shown in the appendix.

The cross-sectional design exists of questionnaires which were sent to the patients' homes. The questionnaires were sent at a random time, not at a specific moment before or after a follow-up appointment.

Data analysis
All data were analyzed using SPSS (Statistical Package of the Social Science) for Windows. Descriptive statistics were performed for all variables. The differences in patient characteristics between the two study groups were measured by the Chi square test and the Mann Whitney U test. To asses the scale-differences in attitude towards follow-up, satisfaction and effects, the statistical procedure for one way ANCOVA was used. Associations between patients' preferred follow-up and attitudes towards follow-up, satisfaction and effects were tested using Spearman's rank-order correlation. It was decided to include gender as a covariate in all subsequent analyses because of a group difference after response in division of gender.

Results

The response rate in the intervention group was 84% (49 out of 58) and in the reference group 75% (60 out of 80). There were significantly more males than females in the intervention group (79% versus 53%). No significant differences between the groups were found on the other demographic variables (Table 1).

Table 1: Patient characteristics

	Intervention group n = 49 (%)	Reference group n= 60 (%)	p *
Average age	67	67	n.s.
Number of men	38 (79)	30 (53)	0.01
Composition of the family			n.s.
Living alone	8 (17)	7 (13)	
Living together	2 (4)	2 (6)	
Married	38 (79)	45 (82)	
Children			n.s.
None	5 (12)	12 (23)	
Yes < 20 years	4 (9)	3(6)	
Yes > 20 years	34 (79)	37(71)	
Highest education			n.s.
Primary school	10 (21)	10 (18)	
< Higher General Secondary Education	29 (62)	34 (62)	
> Pre-University Education	7 (15)	11 (20)	
Working	9(19)	8 (14)	n.s.
Co morbidity	18 (39)	32 (56)	n.s.
* Chi square and Mann Whitney U test			

Table 2: scale (and item scores) of attitude, satisfaction, preference and			
Attitude	Intervention n = 47	Reference n = 56	p*
Reassurance (scale)	**2.3**	**2.3**	n.s.
Perception of reassurance	2.4	2.3	
Reassurance after follow-up	2.3	2.3	
Advantages outweigh disadvantages	2.1	2.2	
More worries without follow-up	2.3	2.5	
Nervous Anticipation (scale)	**0.4**	**0.6**	
Nervous for follow-up	0.7	0.9	n.s.
Bad sleeping before follow-up	0.3	0.6	
Postpone plans after follow-up	0.5	0.7	
Dread follow-up	0.4	0.7	
Rather less frequently follow-up	0.3	0.2	
General Disadvantages (scale)	**0.3**	**0.5**	
Follow-up rather at General Practitioner	0.1	0.2	n.s.
Investigations burdensome	0.2	0.3	
Is follow-up a negative reminder	0.6	0.9	
Communication (scale)	**2.3**	**2.3**	
Ask about things at follow-up	2.1	2.2	n.s.
Discuss matters of concern	2.3	2.2	
Do people pay attention to you	2.5	2.5	
Do physicians have enough time	2.4	2.2	
Satisfaction (scale)	**8.8**	**8.3**	
Satisfaction with follow-up	8.8	8.4	**0.02**
Satisfaction frequency follow-up	8.9	8.1	
Satisfaction with doctor-patient contact	9.0	8.6	
Sufficient information about follow-up procedure	8.6	8.1	
Sufficient information during follow-up	8.5	8.2	
Preference			
Do patients want to know if they have recurrences?	**2.4**	**2.0**	**0.03**
Effects			
Anxiety	**0.5**	**0.7**	n.s.
Depression	**0.4**	**0.5**	n.s.
Cancer Worries	**0.7**	**1.0**	n.s.
*(p) = scale difference measured by One way ANOVA with gender as a covariate			

Attitude

No significant differences were found between the two study groups. From the outcomes in Table 2 it can be deduced that the majority of the patients in both study groups felt rather reassured by their own follow-up program, the intervention group experienced less nervous anticipation in comparison to the patients in the reference group and the reference group reported more disadvantages in the follow-up program. Patients were moderately positive about the communication with the physician. Summarizing, both study groups reported a rather positive attitude towards the follow-up program.

Satisfaction and preferences

The intervention group had significant higher scores in every separate item of the satisfaction scale in comparison to the reference group (p=0.02) (table 2). Patients in the intervention group would more often like to have the knowledge of the presence of recurrent disease in comparison to the patients in the reference group, even if there would be no curative treatment options; this difference was significant (p=0.03) (table 2).

Effects

No significant differences were found between intervention and reference group concerning anxiety, depression and cancer worries in follow-up (table 2). The majority of the patient groups reported somewhat or no anxiety. Depression was present in only a minority of the patients with a difference in occurrence favouring the intervention group. More patients in the reference group reported often, to almost always, having cancer worries, in comparison to the intervention group (P = 0,04).

Patients preferred option for follow-up

In the intervention group the majority chose for their current mode (monthly blood tests and visits to the doctor every 6 to 12 months). In the reference group about half of the respondents preferred their present mode (3-6 monthly visits to the physician). Patients had the option to point out their second preferred choice for a follow-up program. Some of the patients only declared their first choice; therefore the number of cases differed within the first and second choice. More than half of the patients in the intervention group chose the option with the monthly blood test without visits to the physician. The patients in the reference group chose very diversely for their second choice. The least attractive option was follow-up without an established follow-up program.

Associations in preference for a follow-up program

A stronger preference for the intensive follow-up was found among the patients in the reference group in case they had higher scores for nervous anticipation (table 4). Patients in the intervention group with a lower score for satisfaction preferred the follow-up program with contact with the physician. In the reference group a lower score on satisfaction meant a higher preference for their current mode. Patients in the intervention group with higher scores on depression had a higher preference for the most intensive follow-up program. Patients in the reference group with higher scores for depression and cancer worries had a stronger preference for the most intensive follow-up. Patients in the reference group with higher scores for anxiety, depression and cancer worries even had a stronger preference for the monthly blood test, without visits to the physician. They opted less for their current mode.

Table 3. Preferred options for follow-up

	Intervention group		Reference group	
	First choice n=49 (%)	Second choice n=37 (%)	First choice n=59 (%)	Second choice n=42 (%)
Most intensive follow-up	33 (67)	5 (14)	20 (34)	13 (22)
Intensive follow-up	6 (12)	23 (62)	4 (7)	14 (24)
Less intensive follow-up	8 (16)	8 (22)	32 (54)	10 (17)
No follow-up	2 (4)	1 (3)	3 (5)	5 (8)

Most intensive follow-up: monthly blood tests + 6 monthly visits to the physician
Intensive follow-up: monthly blood tests
Less intensive follow-up: 3-6 monthly visits to the physician

Table 4. Spearman's Rho correlation between preferences and attitude towards follow-up, satisfaction and effects						
	Intervention group (n = 49)			Reference Group (n = 60)		
Attitude	Most int.	Int.	Less int.	Most int.	Int.	Less int.
Reassurance	-0.28	-0.05	0.24	0.13	-0.20	0.08
Nervous anticipation	-0.18	0.06	0.28	-0.14	**-0.32***	0.26
General disadvantages	-0.05	0.09	-0.07	-0.15	-0.21	0.13
Communication	-0.12	0.21	0.12	0.18	0.28	-0.22
Satisfaction	-0.23	**0.32***	0.04	0.12	0.26	**0.31***
Anxiety	-0.08	-0.07	-0.16	-0.27	**-0.42****	**0.33***
Depression	0.13	0.10	**0.32***	**-0.35***	**-0.52****	**0.39****
Cancer Worries	-0.19	-0.08	0.05	**-0.31***	**-0.48****	**0.41****

Int.: intensive
*. Correlation is significant at the 0,05 level (2-tailed)
**. Correlation is significant at the 0,01 level (2-tailed)

Discussion and conclusion

This study was the first which measured the effects of an intensive follow-up program 'from a distance'; the main difference in follow-up between the two groups was the frequency of serum CEA measurements, from which the results were communicated by letter instead of in direct communication with the physician. Only the level of satisfaction differed significantly, favouring the intervention group ($p = 0.02$).

Patients did not experience many negative aspects of the follow-up program. As in other studies,[3, 5, 7] patients felt reassured by regular follow-up. It is however reasonable that patients have positive feelings towards the follow-up program. They are often grateful for the curative treatment and have positive beliefs in the efficacy of the follow-up program. This is even more so because all patients were treated with curative intent and the majority of the patients received a positive result of the medical tests up until now. There were few patients with suspicion on or diagnosed recurrent disease during the study period. Whether this concerned patients that returned the questionnaire is not known, because of the anonymous processing of the questionnaires. The positive feelings towards follow-up does cause difficulty in finding more optimal strategies in follow-up programs, because differences will be less pronounced.[20] However, although taking this effect into account is important in designing new follow-up strategies, finding a more optimal approach was not the aim of this study.

Patients who suffered from more anxiety, depression and cancer worries preferred a more intensive follow-up program, which is in agreement with the finding that patients who have more distress need more reassurance.[21] The level of anxiety, depression and cancer worries, and attitude towards follow up however did not differ between both groups, so this effect could not be confirmed in these study results. Intensive follow-up may lead to less instead of more distress, which may be the reason for the higher patients' satisfaction in the intervention group.

Intervention group patients more often reported a preference for knowing the presence of recurrent disease, even when no therapeutic options existed. This may have been caused by the awareness of possible recurrent disease through the study information in the intervention group. Most patients (67%) preferred their current follow-up program, reflecting their general satisfaction with their follow-up. The majority of the intervention patients (62%) had a second preferred option for the monthly blood tests with less contact with the physician. The communication with the physician was reported as moderately

positive. The outpatient clinic visit and contact with the physician seem to be less important than optimal oncological screening to the patients.

A limitation of the present study is that patients were not assigned to one of the study groups in a randomized controlled manner. However the inclusion was near random by the chance of having an outpatient clinic visit in the inclusion period (which lasted 3 months) and all but one of the asked patients agreed to participate in the trial. Patients from the experimental group might have been slightly more positive due to fact that they were invited to participate in this study (Hawthorne effect). The more positive experience of the intervention group may also have been due to the explicit reassurance that patients could contact the physician in between visits when questions or worries existed. This reassurance was not always explicitly given to the patients in the reference group, possibly causing bias.

Important issues in this new type of follow-up are adequate information on the follow-up program and the accessibility of the outpatient clinic in case of worries or questions. The possibility for intermittent appointments on the outpatient clinic for the patients in the intervention group, has barely been used during the trial and is therefore logistically feasible. Several patients expressed the importance of timely and predictable feedback on test results and direct contact with the physician by phone in case of worrisome findings of the blood tests. Signalling and processing of test results and reporting to the patient should therefore be tightly organized, preferably with an automated support system.

Follow-up programs in itself have a positive effect on reassurance and remain important for patients after curative treatment of cancer. This should obviously be based on real patients' needs and positively affect the oncological outcome. New types of follow-up should therefore be evaluated for medical effectiveness, optimal communication and patients' needs. The positive evaluation of the intervention group and the preference of the intervention group for the monthly serum CEA blood test over visits to the physician imply that an intensive follow-up program with less outpatient clinic visits as intended in the forthcoming national randomized trial, is feasible.

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Appendix

Satisfaction questions

Would you indicate through giving a report mark from 1 to 10 how satisfied you are about the follow-up program you follow?

Would you indicate through giving a report mark from 1 to 10 how satisfied you are about the number of follow-up visits you get?

Would you indicate through giving a report mark from 1 to 10 how satisfied you are about the contact you have with the physician?

Do you think you get enough information about the follow-up program after your treatment for colorectal cancer?

Would you indicate through giving a report mark from 1 to 10 how satisfied you are about the information you receive of the physician during the follow-up visit?

Patients' preferences

I would like to know when I have recurrent disease, even if I would know it can't be treated in any way and I wouldn't have complaints for months.

☒ not at all ☒ somewhat ☒ Rather ☒ Very much

Patients' preferred option for a follow-up program

What if you could choose your preferred option for a follow-up program. Which follow-up program would you prefer? Extend marks from 1 to 4:

1 for the follow-up program you mostly prefer

2 for the follow-up program you rather prefer

3 for the follow-up program you less prefer

4 for the follow-up program you least prefer

(please fill in all four different marks on the dotted lines)

….. Intensive follow-up program with visits to the physician every 6 months to once a year and every month a blood test

….. Intensive follow-up program with a blood test every month and only contact with the physician in case of question or problems

….. Less intensive follow-up program with a visit to the physician every 3 to 6 months including a blood test

….. No fixed follow-up program. I would contact the physician myself if I think it's necessary

8

Early recurrent disease after curative treatment of non-metastatic colorectal cancer found only in patients with locally advanced primary tumors; follow-up may be reduced in non-advanced cases

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Background: Over the last decade several changes in clinical practice, such as routine staging before treatment with abdominal CT and (neo) adjuvant combined treatment, are likely to influence the recurrence pattern in colorectal cancer (CRC). The efficacy and cost-effectiveness of follow-up (FU) may be enhanced with up-to-date estimates on incidence and expected time to recurrent disease (RD).

Patients and methods: A consecutive series of patients with non-metastatic CRC treated with curative intent, was analyzed on pattern of RD within one year (treatment period 2007-2008, n=190). All patients were staged with abdominal CT. Data were derived from a prospective hospital-population based registry of colorectal surgery. A post-hoc analysis on the risk factors pT, pN and urgency was done.

Results: The incidence of RD within 1 year was 6% (n=12); all these patients had locally advanced primary tumours (colon cancer 10, rectal cancer 2). The incidence of early RD was 17% in locally advanced disease and 0% in non-advanced CRC. The post-hoc multivariate analysis showed pT4 stage as main risk factor for early RD (OR 14.9, 95% CI 2.9-76.8).

Conclusion: FU aimed at the detection of RD in the first year after treatment may not be necessary in staged patients with non-advanced CRC, but cannot be postponed in patients with locally advanced primary tumors. This study is a first effort towards an individualized risk-adapted FU.

Background

Colorectal cancer (CRC) is a common disease with a life time risk of ± 10% in the Western population. Approximately half of these patients will develop liver metastases, peritoneal carcinomatosis or locoregional recurrence. In the past, metastatic CRC was frequently regarded as incurable and suitable for palliative measures only, but nowadays various multimodality treatments offer a chance for cure to selected patients.[1-6] This has set forth the routine of staging with abdominal CT on distant metastases before treatment and renewed efforts to optimize follow-up (FU).

The pattern of recurrent disease (RD) is likely to change as an effect of staging, by finding metastatic CRC at an earlier stage, i.e. before treatment. Developments in (neo) adjuvant treatment modalities in the last decade have changed recurrence patterns as well, with a decrease in incidence and a possible delay of RD as compared to historical data.[7-9] These changes in recurrence patterns are relevant in designing new FU trial strategies. Currently, the highest intensity of FU is apprehended in the first year after surgery.[10]

The aim of this study is to analyze the recurrence pattern within one year after surgery, in a consecutive series of non-metastatic CRC patients that were staged with abdominal CT and curatively treated according to current clinical practice.

Patients and methods

The data were collected in the Medical Spectrum Twente, a large community teaching hospital in the Netherlands, which functions as a referral center for liver and lung surgery. The study design is a prospective observational study in an unselected hospital patient population operated from January 2007 till December 2008. The recurrence pattern within one year after surgery ('early RD') was analyzed in a cohort of patients who were staged with abdominal CT, underwent treatment with curative intent for non-metastatic CRC and had a follow-up of at least 12 months (Figure 1). FU consisted of 3-monthly outpatient clinic visits with serum CEA measurements and biannual ultrasound of the liver. Of 190 patients included in the analysis, 64 patients participated in a phase II FU trial consisting of monthly serum CEA measurements and abdominal CT 1 and 2 years after surgery.

All surgical patients with CRC in the study hospital are prospectively registered in a database designed for colorectal surgery, which includes the staging procedures, patient -, treatment- and histopathological characteristics, outcome and FU. Patients are staged according to the TNM classification (6th edition) and classified according to the American Joint Committee on Cancer (AJCC) stages. Rectal cancer is defined as a primary adenocarcinoma located below the peritoneal reflection. Locally advanced rectal cancer (LARC) is defined as a cT4 tumor or a cT3 tumor with a threatened circumferential margin

on pelvic MRI. Locally advanced colon cancer (LACC) is defined by pT4 stage. LARC was treated with neoadjuvant chemoradiation (25 x 2 Gy and oral capecitabine) for downstaging, small cT3 rectal cancer received pre-operative 5x5 Gy radiotherapy. Adjuvant chemotherapy (5FU combined with oxaliplatin) was offered to colon cancer patients with relevant risk factors (lymph node metastases, pT4 colon cancer, angio-invasive or perineural growth). Emergency surgery is defined as all non-planned admissions to the hospital due to symptoms related to the tumor and includes both urgent (surgery imperative within 5 days) and acute surgical procedures (surgery imperative within 6 hours).

A post-hoc analysis on risk on early RD was performed concerning the prognostic factors pT, pN and urgency of surgical treatment. Statistical analysis was carried out using the Fisher Exact test and Pearson Chi-Square test where appropriate. Multivariate logistic regression analysis was performed to identify independent risk factors for recurrence. The data were analyzed using SPSS software and considered statistically significant when $p < 0.05$.

Results

Of the 354 patients operated for CRC in the analyzed period, 96 patients had synchronous metastases (27%). Twenty-five percent (88 of 354) of all patients had incurable disease, consisting of patients with either incurable distant metastases (n=72) or irradical or no resections (n=16). Staging with abdominal CT was done in 90% of the patients. (Table 1, Figure 1).

From the analyzed group of 190 patients with non-metastatic, curatively treated CRC (Figure 1), 12 patients (6%) had RD within 1 year; 2 patients had LARC (cT3-4, ypT3) and 10 patients had LACC (pT4). Locally advanced primary tumors were present in 72 patients, of whom 39 patients had LACC and 33 LARC. The incidence of RD in locally advanced CRC within one year was 17% (12 out of 72)

RD was most often localized in the peritoneal cavity (n=5) and the liver (n=5). Four of these 12 patients were treated with curative intent. The individual patient and tumor characteristics of the twelve patients with early RD are shown in table 3.

A post-hoc analysis was performed on (y)pT stage, (y)pN stage and urgency (Table 4). The strongest prognostic factors in the univariate analysis for early recurrence were T stage (pT4 , RR 17.1 (3.9-76.9), $p < 0.001$) and urgency (emergency procedures, RR 7.3 (2.6-20.8), $p = 0.001$). A strong correlation was found between urgency and pT stage. In the multivariate analysis only pT stage (pT4; OR 14.9 95% CI 2.9-76.8) was statistically significant with urgency reaching borderline significance.

Figure 1. Total cohort and selection of study patients

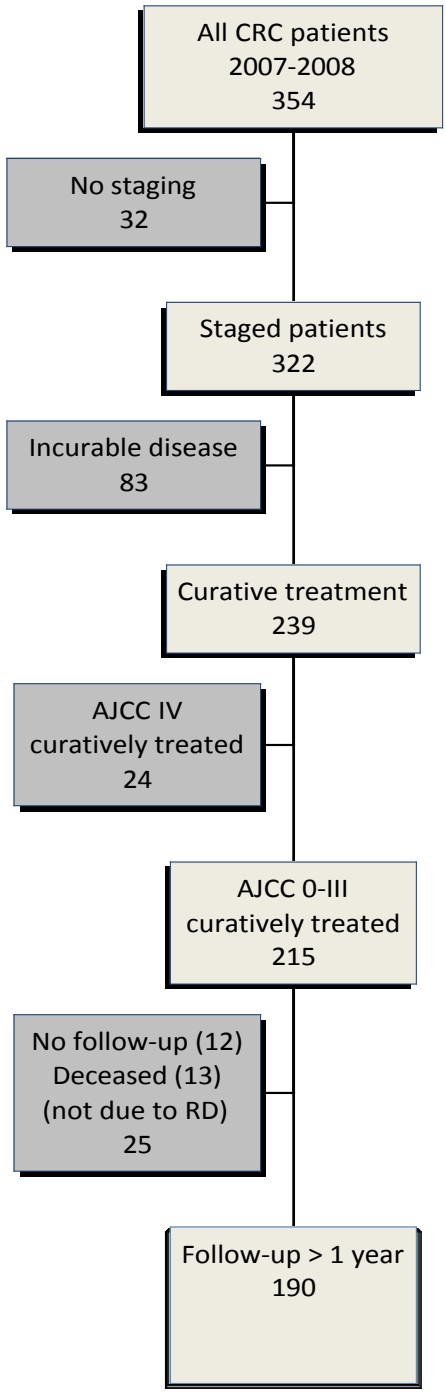

TABLE 1 Patient characteristics total cohort 2007-2008 (n=354)		
Demographics	Value	%
Age		
Mean	70 year	
Median	71 year	
Range	33-95 year	
Gender		
Female	147	42%
Male	207	58%
Localization		
Rectal carcinoma	76	21%
Colon carcinoma	278	79%
Neo-adjuvant treatment		
None	296	84%
Neo-adjuvant chemoradiation rectal carcinoma	45	13%
Neo-adjuvant radiotherapy (5x5Gy) rectal carcinoma	9	3%
Chemotherapy[a]	2	0.5%
Chemotherapy and radiotherapy[b]	2	0.5%
Urgency		
Elective procedure	276	78%
Emergency procedures	78	22%
In hospital mortality		
Elective procedures	12	4%
Emergency procedures	8	10%
AJCC stage based on pTNM (6th ed. 2002)[c]		
Stage 0	7	2%
Stage I	47	13%
Stage II	104	29%
Stage III	99	28%
Stage IV	96	27%
Treatment result		
Curable disease	266	75%
Incurable disease[d]	88	25%

[a] Both patients were treated in a palliative setting with chemotherapy. Because of local complications of the tumor during chemotherapy they underwent a palliative resection.
[b] Both patients were treated with a liver-first approach, consisting of neo-adjuvant chemotherapy followed by liver surgery, after that short-course radiotherapy (5x5 Gy) followed by rectal resection.
[c] Based on 6th ed. TNM classification, including ypTN after downstaging (n=33)
[d] Incurable disease was defined as irradical resection (R1 and R2) or distant metastases that could not be treated with curative intent.

TABLE 2 Patient characteristics analyzed cohort 2007-2008 (n=190)		
Demographics	Value	%
Age		
Mean	70	
Median	68	
Range	38-92	
Gender		
Female	147	42%
Male	207	58%
Localization		
Rectal carcinoma	40	21%
Colon carcinoma	150	79%
Neo-adjuvant treatment		
None	151	79%
Neo-adjuvant chemoradiation (rectum)	33	17%
Neo-adjuvant radiotherapy (5x5Gy) (rectum)	6	3%
Urgency		
Elective procedure	167	88%
Emergency procedures	23	12%
AJCC classification[a]		
Stage 0	7	4%
Stage I	36	19%
Stage II	75	39%
Stage III	72	38%

[a] Based on 6th ed. TNM classification, including ypTN after downstaging (n=33)

Table 3 Characteristics of patients with early recurrent disease

Nr	Sex	Age	Localization and cTN primary tumor	RCT	Urgency	pT	pN	ChT[a]	TTRD[b]	Localization RD	Treatment[c]
1	M	63	Rectum cT3N1	Yes	Elective	ypT3	ypN0	No	8	Liver	C
2	M	79	Rectum cT4N1	Yes	Elective	ypT3	ypN0	No	10	Liver	C
3	F	63	Colon	No	Acute	pT4	pN0	Yes	10	LR+PC	P
4	F	80	Colon	No	Acute	pT4	pN0	Yes	5	PC	P
5	F	72	Colon	No	Acute	pT4	pN1	No	10	PC	P
6	F	92	Colon	No	Acute	pT4	pN1	Yes	6	Incisional	P
7	F	69	Colon	No	Elective	pT4	pN1	No	9	Liver	P
8	F	84	Colon	No	Elective	pT4	pN2	Yes	9	Brain	P
9	F	65	Colon	No	Elective	pT4	pN2	Yes	3	Liver	C
10	M	61	Colon	No	Elective	pT4	pN2	Yes	10	LR	C
11	M	70	Colon	No	Acute	pT4	pN2	No	6	Liver / lung	P
12	M	64	Colon	No	Acute	pT4	pN2	Yes	11	PC	P

Abbreviations; LR: local recurrence, PC: peritoneal carcinomatosis, RCT: neo-adjuvant chemoradiation, ChT: chemotherapy, RD: recurrent disease

[a] adjuvant chemotherapy that was actually received; patients may not have received CT due to physical condition, age or individual wishes.

[b] TTRD: Time till diagnosis of recurrent disease after surgery primary tumor

[c] Treatment of recurrent disease: C: intended curative treatment, P: palliative treatment

Table 4. Risk factors for early recurrence (< 1 year)									
				Univariate analysis			Multivariate analysis		
	Total	RD	%	RR	95% CI	p-value	OR	95% CI	p-value
pT stage									
pT0-3	147	2	1.4%						
pT4	43	10	23%	17.1	3.9-76.9	<0.001	14.9	2.9-76.8	0.001
pN stage									
pN0	118	4	3%						
pN1-2	72	8	11%	3.3	1.02-10.5	0.037	n.a.	n.a.	n.a.
Urgency									
Elective	167	6	4%						
Acute	23	6	26%	7.3	2.6-20.8	0.001	3.35	0.9-13.2	0.083
Total	*190*	*12*	6%						

Abbreviations: RD: Recurrent disease, RR: relative risk OR: odds ratio, CI: confidence interval, p-value: probability value

Discussion

Recurrent disease in the first year after curative treatment of non-metastatic CRC seems to be limited to patients with locally advanced primary tumors. These results do suggest that FU in the first year after surgery aimed at detection of RD can safely be postponed in non-advanced CRC and be focused primarily on assessing the functional outcomes and psychological support adapted to the individual patient's need. The outcomes in this study question the current emphasis of FU in the first year after treatment as was reported in a national Dutch survey.[10]

An important determinant of time to recurrent disease (TTRD) is the intensity of FU.[11-13] In this study, the intensity was moderately high with 3-monthly CEA measurements and biannual imaging of the liver as part of the regular FU protocol. Also, one third of patients were included in an intensive phase II FU trial. In previous FU trials the average TTRD was already between 10 and 24 months;[11-18] early RD diagnosed in these studies most often were liver metastases found within few months after surgery. The high incidence of synchronous metastases and low incidence of early recurrences in this study as compared to previous FU studies does suggest that the majority of 'early metachronous' liver metastases are now diagnosed before treatment with abdominal CT. The outgrowth of

micrometastases further, is likely to be prevented or postponed by the more effective adjuvant chemotherapy in colon cancer patients that is usually administered up to 9-10 months after surgery.[8, 9]

To both optimize the efficacy and reduce costs of FU in future trials and protocols, assessment of 'current' recurrence patterns is essential. This study elaborates on the effects of routine staging and changed treatment on early recurrences only, and found T stage, not N stage, as the most important prognostic factor for early RD. However, since this risk factor was found in a post-hoc analysis, it will need confirmation and refinement from prospective studies that will include a more extensive risk analysis on prognostic parameters. Next to changes in early recurrences, staging and changes in treatment of CRC will probably affect the incidence and pattern of 'late' recurrences as well. In rectal cancer the effects of neo-adjuvant treatment on TTRD was already described in a systematic review.[7] The incidence was reduced and the TTRD prolonged, leading to the suggestion that an estimated 8 years of FU might be necessary for definitive assessment of therapeutic results. Adjuvant chemotherapy consisting of 5FU combined with oxaliplatin in stage III colon cancer has led to a modest improvement in disease free survival 3 to 4 years after curative treatment.[8, 9] The results from these studies suggest that the incidence of RD has decreased. Another explanation might be that the occurrence of RD has been prolonged to after 4 years since long-term results have not yet been described.

To conclude, new estimations on prevalence and expected TTRD from patient populations staged and treated according to current standards, are needed to optimize FU on both the efficacy and cost-effectiveness. The developments in treatment of metastatic CRC in the last decades have motivated new efforts to improve follow-up, as intended in a forthcoming national FU trial in the Netherlands. CRC is a common disease and intensive FU can be expensive.[16] Identification of low and high-risk groups might lead to a different policy in follow up. This can be beneficial to both groups of patients for psychological, medical and economical reasons. This study is a first effort towards such individualized risk-adapted approach.

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9

Summary / samenvatting

Staging before treatment

The outcome of the first study (chapter 2) evaluating the relevance of staging with abdominal CT before treatment, supports this as a routine procedure for all CRC patients. In the described unselected hospital population of 612 patients, a high percentage of metastatic CRC (31%) was found. The ability of abdominal CT to find metastatic CRC was good for liver metastases (LM), but poor for peritoneal carcinomatosis (PC). Estimation of T-stage of colon cancer (CC) on abdominal CT was fairly good and may, following the observed strong relation between colonic T-stage and PC, be able to serve as a surrogate indicator for PC. The most notable change in treatment planning was observed in performing no resection of the primary tumor in emergency surgery for CC, as a consequence of diagnosing incurable metastatic disease. This, and the finding of metastatic CRC in nearly half of emergency patients, underlines the relevance of staging in all urgencies. It was however observed that 'emergency staging' tended to be omitted, mainly due to logistic reasons. A heightened awareness that staging offers the opportunity to change the treatment plan to less extensive procedures may be beneficial in terms of a decrease in operative morbidity and mortality. Changes in treatment planning were observed in patients with LM as well, but not in patients with PC. This is largely due to the (failing) accuracy of the imaging technique (CT), not due the relevance of diagnosing metastatic CRC for optimal treatment. To search for metastases before treatment can improve the oncological outcome, but is as much dependent on logistics and organization as on the accuracy of the imaging technique.

Staging with chest CT before treatment was not supported by the outcomes of the second study, that evaluated the outcome in a cohort of 200 consecutive patients (chapter 3). The incidence of lung metastases was low (7%), especially those confined to the lung (3%). Due to diagnostic difficulties, only a minority of lung metastases were diagnosed before treatment (2.5%). Indeterminate lesions were frequently found (25%) and discrimination between benign and malignant lesions was difficult. Only a minority turned out to be metastases (16%). Staging with chest CT did not result in a change of the treatment plan, nor did it result in curative treatment of pulmonary metastases. It did cause diagnostic dilemmas and prolonged uncertainty. Accurate pulmonary staging was most relevant in patients that were eligible for curative treatment of metastatic CRC on other locations. Limitation of staging with chest CT to this selected patient group would significantly save resources, but still meets the same diagnostic dilemmas in respect to the indeterminate lesions. Staging with chest CT, as a conclusion, is not recommended as a routine procedure.

Follow-up

From the national survey on follow-up, we learned that renewal of follow-up based on scientific evidence is desired and a national trial feasible (chapter 4). This motivated to start a comprehensive review of literature and, if and where possible, design a new follow-up strategy (chapter 5 and 6). Follow-up, and with that serum CEA measurements, does not seem beneficial for survival; according to 5 meta-analyses, evidence is still failing. When evidence fails, beliefs can become 'facts'. One such well-known belief, that normal CEA values before treatment implies CEA will not rise in case of recurrent disease, was proven wrong (chapter 5). The review on CEA in follow-up stretching the past 30 years, showed that previous evidence failed the beneficial effects of *follow-up*, but did *not* denounce serum CEA as an effective surveillance tool. On the contrary; CEA was shown to be the only diagnostic method that has contributed to a survival benefit, albeit the effects were small. The initial promise of serum CEA has been tarnished through perpetuation of poorly designed and underpowered studies. Our conclusion was that a re-evaluation of the potential of CEA in follow-up was worthwhile (chapter 6).

At the time CEA was discovered as a tumor marker for gastrointestinal malignancies and evaluated for its clinical applicability (Staab, 1978-1982), it was suggested that bimonthly measurements and dynamic threshold interpretation would provide the optimal accuracy of serum CEA. This hypothesis was reconsidered by looking into the evidence on this approach. First, we studied how the accuracy of serum CEA would be affected when a dynamic threshold value is applied, in the context of follow-up. The clinically optimal threshold value is dependent on the desired sensitivity and specificity in the target population. Sensitivity must be high in follow-up to adequately detect recurrent disease. A high specificity is of importance to minimize unnecessary diagnostic evaluation based on test results, especially when the test is applied as a screening tool. Follow-up requires both, as a screening tool in a high-risk population. This evaluation showed that CEA has the lowest accuracy in the range from 2.5-10 ng/ml (sensitivity 70-90%, specificity 30-65%), that is likely caused by the overlap of abnormal CEA values with benign inflammatory disease and smoking in these lower ranges. At the same time, this is the preferred range in which to detect recurrent disease during follow-up, in the context of being able to offer a second chance on cure. A dynamic threshold value may overcome the interferences in these lower ranges; The difference between malignancies and inflammatory disease is that malignancies will continue to grow where inflammatory disease is usually self-limiting. The large inter-individual variation (55%) can partially be corrected by raising the lower limit static threshold value (normal 2.0-2.5 ng/ml) to 5 ng/ml and higher, as is usual nowadays. Downside of this approach is that the sensitivity will decrease. The alternative to consider intra-individual *rise* eliminates the inter-individual variation and additionally shows the

potentially discriminative *pattern* of rise. This approach does require frequent measurements. A dynamic threshold value as measure was applied in only one prospective cohort study on follow-up (Staab, 1985), but never tested in a comparative or randomized trial. The *prognostic* capacity of serum CEA-rise in comparison to a static threshold value was evaluated in several retrospective studies, all showing that CEA-rise is a far better indicator of recurrent disease than the actual value. These findings support the original hypothesis, that -in a revised format adapting to current clinical circumstances- provided the basis for a new follow-up design. This revisited approach is now referred to as high frequency dynamic threshold (HiDT) serum CEA measurements.

This 'trying again' after several previous failures, consequently met skeptical responses. Nevertheless, time and circumstances have changed and many of these changes do motivate a new effort to optimize follow-up; Improvements in treatment of metastatic CRC as mentioned before, the technical advancements in imaging techniques that facilitate accurate non-invasive localization of recurrent disease and the possibilities of automated support, all favored a new follow-up trial. In 2008, a prospective non-randomized feasibility study has started and included 241 patients in two centers (UMCG and MST). Up till now, 28 patients had recurrent disease (12%). The sensitivity of HiDT serum CEA measurements in the range between 2.5 and 10 ng/ml was 79% and the specificity 88%. The outcome concerning the eligibility for curative resection -in an interval analysis- was 43%. The trial showed that the protocol was feasible and supported the hypothesis on its theoretical grounds.

An important part of the phase II trial was to analyze the psychological effects of the new follow-up design on patients (chapter 7). To facilitate these frequent CEA measurements without causing an unworkable overload of the outpatient clinic, the monthly CEA results were processed and communicated with the patient by letter and phone, with *less* outpatient clinic visits. From this study it became clear that not only was this protocol feasible in terms of psychological impact (higher patient satisfaction, no difference on depression, cancer worries and anxiety scales), it was even preferred by patients above actual contact with the doctor. Remembering the emotional aspect of follow-up, this outcome was not expected from a doctors' point of view.

The outcomes of the phase II trial concerning the first estimates on eligibility for curative treatment of recurrent disease, and the feasibility of the protocol concerning both the automated support and psychological impact, have resulted in a forthcoming national phase III randomized trial.

Tailoring follow-up (chapter 8)

The incidence of recurrent disease within one year after curative treatment of non-metastatic CRC, provided that patients were staged before treatment with abdominal CT, turned out to be low (6%). Early recurrences were limited to patients with locally advanced primary tumors; in this selected population, the risk on recurrent disease was 17%. T stage was the most important risk factor for early recurrences. In non-advanced disease, follow-up in the first year may safely be reduced to assessment of functional outcomes and psychological support, adapted to the individual patient's need. The outcomes in this study question the current emphasis of FU in the first year after treatment that was reported in the national survey (chapter 4). This study was a first effort to describe up-to-date recurrence patterns and its relevance in enhancing the efficacy and efficiency of future tailored follow-up designs.

Stadiëren voorafgaand aan de behandeling

De relevantie van stadiëren voorafgaand aan de behandeling wordt ondersteund door de uitkomsten van het eerste onderzoek (hoofdstuk 2). In de beschreven populatie van 612 patiënten werd een hoge incidentie van gemetastaseerd colorectaal carcinoom (CRC) gevonden (31%). Met een CT van het abdomen bleek het goed mogelijk om lever metastasen te vinden, echter was de gevoeligheid voor peritoneale carcinomatosis (PC) slecht. Inschatting van het T stadium bij colon carcinomen was redelijk goed. Lokaal uitgebreide colon carcinomen en PC zijn gecorreleerd; mogelijk zou het T stadium als een alternatieve indicator voor verdenking op PC kunnen dienen. De belangrijkste verandering in het behandelplan, als een gevolg van de bevindingen bij de stadiëring, werd gezien bij patiënten met gemetastaseerd colon carcinoom met een spoedeisende presentatie. Bij deze patiënten werd er minder vaak een resectie verricht naar aanleiding van het vinden van ongenezelijke ziekte. Dit, en de aanwezigheid van afstandsmetastasen bij bijna de helft van de patiënten met een spoedeisende presentatie, onderstreept de relevantie van stadiëren bij alle urgenties. Echter bleek dat stadiëren juist bij spoedeisende presentaties vaker achterwege werd gelaten, voornamelijk om logistieke redenen. Meer alertheid op het gegeven dat vooraf stadiëren het behandelplan kan veranderen naar minder uitgebreide procedures, heeft mogelijk een gunstig effect op de operatie morbiditeit en mortaliteit. Ook bij patiënten met lever metastasen werden veranderingen in het behandelplan gezien, echter niet bij patiënten met PC. Dit is voornamelijk een gevolg van het onvermogen van de CT van het abdomen om PC af te beelden, niet vanwege het ontbreken van eventuele consequenties voor de behandeling. Het zoeken naar afstandsmetastasen kan de oncologische uitkomsten verbeteren, waarin de uiteindelijke verbetering net zo afhankelijk is van logistiek en organisatie als van de accuratesse van de beeldvormende techniek.

Stadiëring met een CT van de thorax werd *niet* ondersteund door de bevindingen van de tweede studie (hoofdstuk 3). De incidentie van longmetastasen was laag (7%), met name van metastasen die beperkt zijn tot de long (3%). Vanwege diagnostische onzekerheden werd ook slechts een kleine minderheid van de longmetastasen gediagnosticeerd vóór de behandeling van de pimaire tumor (2.5%). Indifferente afwijkingen werden vaak gezien (25%) en het maken van een onderscheid tussen goedaardige en kwaadaardige afwijkingen blijkt heel lastig. Slechts een klein deel van de indifferente afwijkingen bleek kwaadaardig (16%). Stadiëren met een CT van de thorax resulteerde niet in een verandering van het behandelplan van de primaire tumor en heeft niet geleid tot meer curatieve behandelingen. Wel gaf het aanleiding tot diagnostische dilemma's, veel aanvullend onderzoek en langdurige onzekerheid. Stadiëring van de longen was het meest relevant bij patiënten met metastasen elders die in aanmerking kwamen

voor curatieve behandeling hiervan. Het beperken van een CT van de thorax tot deze doelgroep resulteert al in een aanzienlijk besparing van kosten. Echter blijven ook in deze patiëntengroep dezelfde problememen met indifferente afwijkingen bestaan. Concluderend werd het stadiëren van de thorax met een CT scan niet geadviseerd als een routine procedure.

Follow-up

De nationale enquete over de follow-up liet zien dat een verbetering van follow-up gebaseerd op wetenschappelijk bewijs gewenst is en er voldoende draagvlak is voor een landelijke studie (hoofdstuk 4). Deze uitkomst heeft geleid tot een uitgebreide literatuurstudie met als doel indien, en waar mogelijk, een nieuwe follow-up strategie te ontwerpen (hoofdstuk 5 en 6).

Follow-up en daarmee ook het CEA, lijkt niet veel effect te hebben op de overleving, zoals werd geconcludeerd in 5 meta-analyses. Wanneer er geen bewijs is, kunnen veronderstellingen al snel verworden tot feiten. Een voorbeeld van zo'n veelgehoord 'feit', is dat als er een normale CEA waarde is voorafgaand aan resectie van de primaire tumor, het CEA ook niet zal stijgen wanneer de ziekte terug komt. Dit bleek onjuist (hoofdstuk 5). De uitgebreide literatuurstudie over het CEA in de follow-up over een periode van 30 jaar (hoofdstuk 5), toonde aan dat eerdere studies wel lieten zien dat follow-up op zichzelf een minimaal effect had, maar *niet* dat de toegevoegde waarde van het CEA als een effectieve tumormarker kon worden verworpen. Integendeel zelfs; het CEA was de enige diagnostische methode in follow-up studies met een aangetoond positief effect op de overleving, ook al waren de gemeten effecten klein. De aanvankelijke belofte van het CEA als tumormarker zijn -ten onrechte- langdurig ondermijnd door slecht opgezette en te kleine studies in het verleden. Onze conclusie was dat een herevaluatie van het potentieel van serum CEA bepalingen in de follow-up de moeite waard is (hoofdstuk 5).

In de tijd dat het serum CEA werd ontdekt als een tumor marker bij gastro-intestinale maligniteiten en de klinische toepassing werd ontwikkeld (Staab, 1978-1982), werd beredeneerd dat een tweemaandelijkse bepaling en een dynamische afkapwaarde de meest optimale accuratesse bewerkstelligen. Deze hypothese werd heroverwogen door de onderliggende bewijzen te analyseren. In de eerste plaats hebben we gekeken naar de voorspellende waarde van een dynamische afkapwaarde van het serum CEA voor recidief ziekte in de follow-up. De klinisch optimale afkapwaarde is afhankelijk van de gewenste sensitiviteit en specificteit in de beoogde populatie. De sensitiviteit moet hoog zijn om recidief ziekte adequaat te kunnen ontdekken. De specificiteit moet hoog zijn, om onnodig aanvullende onderzoek te voorkomen wanneer de test wordt gebruikt als een screenings methode. In follow-up, wat een screening in een hoog risico populatie in houdt, zijn beide

nodig. De analyse liet zien dat het serum CEA de laagste accuratesse heeft in het gebied van 2.5 tot 10 ng/ml (sensitiviteit 70-90%, specificiteit 30-65%). Dit wordt grotendeels veroorzaakt door de overlap van verhoogd serum CEA waarden door inflammatoire aandoeningen en roken in dit meetgebied. Tegelijkertijd is dit het geprefereerde meetgebied om recidief ziekte te ontdekken, met het oog op de kans een genezende behandeling te kunnen bieden. Een dynamische afkwapwaarde kan de verstoring in dit meetgebied sterk verminderen. Het verschil tussen maligniteiten en inflammatoire aandoeningen is dat maligniteiten blijven groeien waar ontstekingen meestal weer vanzelf overgaan. De aanzienlijke inter-individuele variatie (55%) kan (deels) worden gecorrigeerd door de gebruikte afkapwaarde te verhogen (normaal 2.0-2.5 ng/ml) naar 5 ng/ml, zoals dat tegenwoordig gebruikelijk is. Het nadeel van deze benadering is dat de sensitiviteit daardoor lager wordt. Het alternatief om de intra-individuele *stijging* te beoordelen, elimineert de inter-individuele variatie volledig en toont daarbij ook het potentiële onderscheidende stijgings*patroon.* Deze benadering vereist frequente metingen. Een dynamische afkapwaarde werd slechts in één prospectieve cohort studie toegepast (Staab, 1985), maar is nooit getest in een vergelijkende of gerandomiseerde studie. De voorspellende capaciteit van de CEA stijging werd wel geëvalueerd; al deze studies lieten zien dat de *stijging* van CEA een veel betere indicator is van recidief ziekte dan de *hoogte* van het CEA. Deze bevindingen ondersteunen de originele hypothese, die in een gereviseerde versie -rekening houdend met de huidige klinische context-, de basis is geworden van een nieuw follow-up ontwerp. Deze gereviseerde benadering is 'high-frequency dynamic threshold' (HiDT) [hoge frequentie dynamische afkapwaarde] serum CEA bepalingen genoemd.

Deze hernieuwde poging na verscheidene voorafgaande mislukkingen om de effectiviteit van de oncologische follow-up te verbeteren, ontmoette veel skeptische reacties. Niettemin bestonden er ook andere redenen om een nieuwe poging te doen de follow-up gericht op de detectie van recidief ziekte te verbeteren; in de aanzienlijke verbeteringen in de behandeling van gemetastaseerde ziekte, in de snelle technische vooruitgang van de beeldvormende technieken die non-invasieve localisatie van recidief ziekte mogelijk maken en in de mogelijkheden van geautomatiseerde ondersteuning. In 2008 werd een prospectieve cohort studie gestart gericht op de haalbaarheid van het protocol, waarin 241 patienten werden geincludeerd in twee centra (UMCG en MST). Tot nu toe zijn 28 patiënten gediagnosticeerd met recidief ziekte (12%). De sensitiviteit van HiDT serum CEA bepalingen in het meetgebied van 2.5-10 ng/ml was 79% en de specificiteit 88%. De uitkomsten wat betreft de mogelijkheid tot een genezende behandeling in de interim analyse was 43%. De studie toonde aan dat het protocol uitvoerbaar is en ondersteunt de hypothese op de onderliggende theoretische gronden.

Een belangrijk deel van deze fase II studie was het analyseren van de psychologische effecten van het nieuwe follow-up ontwerp (hoofdstuk 7). Om frequente serum CEA bepalingen mogelijk te maken zonder een onwerkbare overbelasting van de polikliniek te veroorzaken, werden de maandelijkse CEA bepalingen middels brieven of, bij een relevante stijging, middels telefonisch contact met de patient gecommuniceerd. Het aantal geplande polikliniek bezoeken was daarbij *minder* dan momenteel gebruikelijk. Uit deze studie werd duidelijk dat het protocol niet alleen goed uitvoerbaar was (geen verschil in depressie -, angst en kanker zorgen uitkomsten, en een hogere tevredenheid in de interventiegroep), het werd zelfs geprefereerd door de patiënten boven direct contact met de arts. De emotionele aspecten van follow-up in gedachten nemend, was deze uitkomst onverwacht vanuit het oogpunt van de medische stand.

De uitkomsten van de fase II studie wat betreft de eerste inschattingen op mogelijkheden tot een in opzet genezende behandeling, de uitvoerbaarheid van het protocol wat betreft de computer ondersteuning en de psychologische effecten, hebben geresulteerd in een aankomende nationale gerandomiseerde fase III studie.

Follow-up op maat (hoofdstuk 8)

De incidentie van recidief ziekte binnen één jaar na genezende behandeling van niet-gemetastaseerde ziekte, mits patiënten voor de behandeling goed waren gestadieerd, bleek laag (6%). Vroege recidieven waren beperkt tot de groep patiënten met locaal uitgebreide primaire tumoren; in deze geselecteerde populatie was de incidentie van recidief ziekte 17%. Het T-stadium bleek de belangrijkste risicofactor voor een *vroeg* recidief. Bij locaal beperkte ziekte kan de follow-up veilig worden gereduceerd tot de begeleiding ten aanzien van functionele uitkomsten en psychologische ondersteuning, aangepast aan de behoefte van de patiënt. Deze uitkomst stelt de huidige nadruk van de oncologische controle in het eerste jaar, zoals gerapporteerd werd in de enquete (hoofdstuk 4), ter discussie. Deze studie was een eerste stap in het beschrijven van hedendaagse recidiefpatronen en de relevantie hiervan in het verbeteren van de effectiviteit en efficiëntie van toekomstige op maat gemaakte follow-up.

10

Future perspectives

Diagnosing and localization of metastatic CRC

CRC is one of the few malignancies that can be cured in the presence of distant metastases, and current treatment strategies can offer a (second) chance on cure for metastatic or locally recurrent disease to an increasing proportion of patients. Finding and localizing metastatic disease at the earliest possible stage and also estimations on the chance on cure will only become more important. The accuracy of current widely used imaging techniques (CT) in diagnosing and localizing metastatic CRC falls short for peritoneal carcinomatosis (PC) and lung metastases; In PC because of a lack of *sensitivity* to detect this typically small nodular disease, in lung metastases because of the low *specificity* in the discrimination of small lung lesions. A step-wise staging approach that takes the strengths and limitations of CT scan into account may be practicable as a next step. For instance, a solution to the observed inaccuracy of the abdominal CT in PC can be to perform a diagnostic laparoscopy preceding surgery in case of cT4 colon carcinoma. Standardized, or automated[1] reporting of the staging CT, such as on cT stage, exact localization(s), number and size of metastases, and the index of suspicion of eventual indeterminate lesions, may contribute to the clinical judgement. Newer and developing techniques such as the PET/CT [2, 3] or diffusion-weighed MRI [4] that combine anatomical and functional characteristics may offer a better accuracy and await further study. A more experimental but nowadays promising technique is CEA-targeted radio-nuclide imaging techniques in PET and SPECT scanning.[5, 6] Additional to imaging techniques, biochemical or histological markers may contribute to both finding -or predicting the risk on- metastatic disease. Known biochemical prognostic factors are serum CEA, Ca19.9 and the CEA index of pre- and post-operative values.[7, 8, 9] Known histological markers are angio-invasive growth, [10] perineural invasion,[11] stromal-carcinoma ratio,[12, 13] T stage (chapter 2 and 8), gene expression profiles,[14] micro-metastases found with a sentinel node procedure[15, 16] and others. Current use of these prognostic parameters is mainly selecting patients for adjuvant treatment. It may be a reasonable next step to develop risk-profiles based on these parameters (with serum samples and histological biopsies) also in the context of selecting patients for *neo*-adjuvant treatment, for instance in locally advanced colon cancer (LACC). Risk profiles based on (combined) prognostic markers aimed at a differentiated follow-up may enhance both its efficacy and efficiency. Estimation on the chance of *cure* of intended metastases treatment may be another future use of prognostic parameters, and may contribute to appropriate selection of patients for high risk procedures such as treatment of PC. An important consideration in this discussion is that not only the imaging techniques' accuracy or predictive capacity of prognostic markers matter in (re)staging. New developments have to be evaluated in their clinical context and the applicability for *all* patients. Another elemental consideration in designing new strategies for staging,

registration and follow-up is that CRC is a high-volume disease, of which the impact on time spend and hospital resources should not be underestimated.

Research methods

When starting the clinical studies for this thesis in 2007, we reasoned that the best way to support our studies would be to design a prospective registration of all patients that underwent colorectal surgery. The efforts that were done to design a comprehensive but practicable database, did add significantly to the practicality of doing research and the accuracy of data. What the outcomes of this database revealed further, were relevant differences in incidences (e.g. of synchronous metastatic disease), age and outcome, as compared to trial populations. This is not surprising; relevant co-morbidity (WHO > 1, ASA 3 or higher, Karnofsky score < 90%), emergency procedures and / or advanced age are usually exclusion criteria in clinical trials.[17] However, as was observed from our registration the proportion of these patients in CRC is high and also, that specifically these patients are the most vulnerable. Emergency presentations account for 20%, the average age between trial - and unselected populations is up to 7 years; and co-morbidity frequently comes with age. Further, the outcomes of metastases treatment have been improving in the past decade(s). These outcomes however, are usually evaluated in retrospective cohort studies that consider *treated* patients. What remains unknown meanwhile, is how many patients that may have been eligible for intended curative metastases treatment, are missed in the work-up process; Either by missing the metastases at staging, follow-up or improper judgement on eligibility for treatment. To summarize, current evidence mainly reflects the outcomes of a (better) selection of the CRC population and that of the highest risk patients remains shrouded.

To gain a comprehensive insight in in this disease and put new developments in a broader context, unselected population data are needed to complement current research methods. The most reliable method of data accrual is prospective registration from the original sources. Advantages of prospective registration are not only the higher accuracy, but also up-to-date data. Time is a relevant issue in CRC; many simultaneous changes are taking place in (neo-)adjuvant treatment, curative metastases treatment, palliative treatment, staging methods and follow-up. None is unrelated to the other which increases the complexity and requires complete data. The availability of recent prospective data, that is obtained with prospective data collection, enables researchers to keep pace with the rapidly changing circumstances and put those into their appropriate context. Disadvantages may be a data collection with no predefined research goal, resulting in either too much or too little data. The availability of a well designed data set may on the

other hand result in serendipitous observations that can initiate new developments. One such finding from our registration was the adverse outcome seen in locally advanced colon cancer (LACC), that has a high incidence of synchronous metastases (chapter 2) and a high risk on early recurrences (chapter 8). Perhaps neo-adjuvant or multi-modality treatment options analogue to that for LARC, may result in better oncological outcomes.

Existing databases with population data that may be complementary to other research methods, are the oncological registry of the Comprehensive Cancer Centers (CCC) and the Dutch Surgical Colorectal Audit (DSCA). The CCC register selected oncological data; its strength is unselected population data. However, its weaknesses are the limited and retrospective data collection, that is neither adapted to specific (medical) characteristics in colorectal cancer. The DSCA is a new initiative that collects data from colorectal cancer patients with the aim of quality control and benchmarking. The strength of this database is that it considers specific circumstances in colorectal cancer surgery. Its weakness is that it is not designed for research purposes and only involves surgical patients, and that there is neither a control system to estimate the proportion of unregistered patients. When a research purpose would be aimed upon, both the data set and method of data accrual would need alterations. To prevent 'garbage in, garbage out', the database design requires limitation of data fields and unequivocal but comprehensive content options.[18] Further, it would need active involvements of other disciplines.

Our vision is that a prospective registration of selected core data for research purposes on a national scale would significantly enhance current and future research in colorectal cancer. Ideally, clinicians from all involved specialities participate in the registration with specific, limited data sets. In respect to the content, it should include selected key variables in the outcome on both medical factors (such as parameters influencing the treatment morbidity and mortality) and oncological (prognostic) parameters. In respect to the interpretation and reporting of observations, active involvement of clinical epidemiologists in the design and development, appreciating international standards,[19] can secure the scientific value. Studies concerning patients with emergency presentations or the elderly, or outcomes of metastases treatment on a population scale would become feasible. The accuracy of data will, inherently to this research method, be high and unbiased. When this database would be coupled to a biodatabank with serum and tissue samples, it can result in high quality studies on prognostic markers for individualized treatment and follow-up. When offering this data set as an (accredited) open source for researchers from various backgrounds, new or unique ideas in interdisciplinary cooperation may arise. In our opinion, such initiative will be invaluable for future progression in research for all patients.

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My Resumé

I studied medicine at the Academic Medical Center in Amsterdam from 1993 till my graduation as a medical doctor (cum laude) in July 2000. Alternating with my internships I have been teaching anatomy dissection courses and embryology to medical and biology students for 3 years. From August 2000 till December 2003, I worked as a surgical resident (non-trainee) in the Spaarne Hospital Heemstede, the AMC in Amsterdam and the UMC Utrecht (cardiothoracic surgery). Further I spent 3 months working on full-time research concerning bile duct injuries at the AMC.

On January 1st 2004 my traineeship in general surgery started in the UMC Groningen (prof dr H.J. ten Duis), and was continued in the Medical Spectrum Twente in Enschede (dr W.J.B. Mastboom) from July 1st 2006 till January 1st 2010. My fifth year was focused on vascular surgery (dr R.H. Geelkerken). In my last year of clinical surgical training I specialized in gastro-intestinal and oncological surgery, in which time I gained interest and experience in colorectal surgery, proctology, (para) thyreoid surgery and surgical oncology.

In February 2010 I started as a fellow in gastro-intestinal surgery at the Catharina hospital in Eindhoven (dr H.J.T. Rutten), with specific attention for locally advanced rectal cancer, treatment of peritoneal carcinomatosis (dr I.H.J.T. de Hingh) and liver surgery at the Máxima Medical Center Veldhoven (Dr R.M.H. Roumen).

My aim for the future is to work as a oncological surgeon, with a specific interest in in colorectal cancer and metastases treatment.

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Stellingen

Staging before treatment is an important step towards improving the (oncological) outcome in colorectal cancer
(dit proefschrift)

Renewal of follow-up for colorectal cancer based upon scientific evidence from a new trial is both required and feasible
(dit proefschrift)

The question is not **whether** to use serum CEA as a tool for early detection of recurrent disease of colorectal cancer, but **how**
(dit proefschrift)

Whether innovations in oncological care will also benefit the patient depends as much on organisation and logistics as on content
(dit proefschrift)

Voor zorgmanagers dienen dan ook gelijke wetten ten aanzien van de medische aansprakelijkheid te gelden als voor (para) medici

Patients can live without their doctor, doctors not without their patients
(dit proefschrift)

None is unrelated to the other
(dit proefschrift)

Leven en lot worden worden niet bepaald door wat je wilt; het wordt een richting gegeven door wat je doet met dat, wat je overkomt.

Make everything as simple as possible (but not simpler)
(Albert Einstein)