Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Verberne, C. (2016). Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up [Groningen]: University of Groningen

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Introduction and outline of the thesis
**INTRODUCTION**

**FOLLOW-UP OF PATIENTS WITH COLORECTAL CARCINOMA**

In the Netherlands, the incidence of colorectal carcinoma (CRC), cancer of the large bowel and rectum, was approximately 12,750 cases in 2010. As a result of population growth and ageing of the total population in combination with population screening for colorectal carcinoma (started January 2014), an increase in the incidence is expected. This makes CRC the second common malignancy in women and the third common malignancy in men in the Netherlands (www.cijfersoverkanker.nl). Historically, about 33–70% of patients developed metachronous recurrent disease or metastases; this percentage is mainly dependent on primary tumour stage. However, the percentage of metachronous recurrences is lowering and lies now about 20–25%. This change is considered the result of (neo)-adjuvant treatments in combination with better preoperative staging causing a shift from metachronous “recurrences” to synchronously detected metastases [1].

The treatment of non-metastasized CRC is based on radical surgical resection. Neo-adjuvant (chemo)-radiotherapy for local control of rectal cancer dependent on clinical T and N stage, and adjuvant chemotherapy for colon cancer dependent on pathological N stage have become standard of care [2–7]. After completion of treatment, patients will participate in a control program. This is called follow-up.

The main goal of follow-up is to detect recurrent disease, either local or distant, as soon as possible. The detection of recurrences in an early stage is correlated with a better overall survival than the detection of recurrent disease in later stages [8–13]. This better survival rate is considered to be the result of the increase in curative options in case of earlier detected recurrences [9,11,14] although this is not consistently found [15].

In several reviews, data have been pooled to compare survival between intensive and minimal follow-up programs [3,16,17]. Although survival is significantly better in patients following an intensive follow-up schedule in some studies [11,12], several other studies do not find different outcomes between intensive and minimal follow-up strategies [8,9,13,14]. Available studies are old and based on even older data. The main problem of these reviews is the lack of comparability between the follow-up protocols; intensive follow-up schedules in one study can even be considered minimal in other studies. The optimal filling-in of a protocol, in terms of intensity, frequency and modalities of follow-up, has been subject of discussion for decades.

The FACS trial is the first randomized study which ameliorates this comparability as a result of strict minimal and intensive protocols; the results favour intensive follow-up in terms of earlier detection of recurrences but there is no effect on survival. An important limitation is the protocol violation in the minimal follow-up group [15]. Two other trials have been conducted in recent years (COLOFOL and GILDA) but results have not yet been published [18,19].
Introduction and outline of the thesis

Follow-up modalities

From 1951 up to the late eighties, planned second-look laparotomy was ideated to control patients after curative resection. Since only a minimum of patients undergoing second-look laparotomy could be cured if recurrent disease was found in combination with high morbidity and the difficulties to organize structural second-look laparotomies, the concept was refused and abandoned in the early nineties. The search for ideal follow-up continued, and the wish for non-invasive tests continued to grow. Research on patient's sera for so-called tumor markers was developing and the techniques for imaging of the human body took an enormous flight. Nowadays, follow-up advised in guidelines contains of visits to the outpatient clinic including anamnesis and physical examination, combined with the use of follow-up “tools” including blood samples and radiological imaging.

Anamnesis and physical examination

It is known that a higher frequency of anamneses and physical examinations does not lead to an increase in the detection of recurrent disease (either local or distant). Performing more visits to the outpatient ward during follow-up is not proven to be effective for detecting recurrent disease compared to less clinic visits [8]. No effect on survival was found in an analysis for intensifying a follow-up program comparing more frequent clinic visits in follow-up to no visits at all [11]. Furthermore repetitive visits can put a strain on (already crowded) outpatient clinics.

Apart from the goal of detection recurrences, patient’s care after the treatment for cancer plays a role. It is true that communication with the medical specialist can lead to the feeling of reassurance and trust in patients [20], but on the other hand examination and communication with a doctor and can lead to anxiety and stress even in absence of physical complaints or signs [21].

Carcinoembryonic Antigen (CEA)

CEA is the most commonly used tumor marker in colorectal cancer follow-up. It was identified in 1965 by Gold in colon cancer tissues and is considered one of the first “tumor markers” [22]. CEA is a glycoprotein involved in cell adhesion and the CEA family belongs to the immunoglobulin family. Serum CEA is produced physiologically during fetal development and possibly has a function in the innate immune system, but it is unusual in the blood of healthy adults because it is shed into the intestinal tract. However CEA is expressed in adults in several solid malignancies including colorectal cancer. Thereby, CEA expression and secretion by tumor cells might promote metastatic spread by enhancing an inflammatory environment which supports tumor formation [23].
CEA measurements are cheap and available in regular laboratories and intra- and inter-assay variations are low [24]. As the tumor size increases, more CEA is observed to accumulate in the blood. CEA is therefore used as a marker to follow the activity of these malignancies. The use of CEA in follow-up is recommended in both American and European guidelines [25,26]. A complicating factor for its clinical use is that in some patients no elevations in serum CEA are observed and in specific cases, CEA is elevated in the absence of any malignancies.

Several studies have compared outcomes of follow-up using schedules containing frequent, minimal and no CEA measurements and it has become clear that follow-up schedules including frequent CEA measurements are associated with better overall survival [11,14,27,28]. Important to realize is that a general policy on what to do if CEA elevates is lacking in all mentioned studies and that the frequency of CEA testing is not uniform amongst studies. A remarkable exception is the recently published CEA second-look trial, in which patients with (predefined) CEA elevations were randomized for a diagnostic laparotomy or for a wait and see policy. The data are collected between 1982 and 1993; the trial was closed by recommendation of the Data Monitoring Committee because improvement in survival in the laparotomy group was considered highly unlikely. The trial was recovered under the Restoring Invisible and Abandoned Trials (RIAT) initiative. The final results, published in 2014, show that CEA-rise driven second look laparotomy did not lead to better survival [29].

Not only the absolute CEA value, but rather the rise in CEA per time unit has to be taken into account if CEA is used as a follow-up tool. In retrospective series, slope analysis of CEA rises was identified to correlate with the extensiveness of recurrent disease (30) and the doubling time of postoperative CEA is known to be a predictor for survival in recurrent colorectal and gastric cancer [31,32].

It is believed that a normal serum CEA value, at initial preoperative presentation, implies that the serum CEA value will also not rise in case of recurrent disease. Although there is indeed a tendency for serum-CEA negative tumours to less often show an increase in serum CEA value with recurrent disease, more than 60% of negative preoperative patients will show a rise with recurrent disease [33]. However, some patients with recurrences do not show a rise in CEA at all [31,34]. Incidence of this phenomenon differs and also depends on the threshold value used. As a result, CEA measurements can not be discarded based on an initial normal CEA value, but any follow-up protocol should include routine imaging techniques.

**Imaging**

Imaging has taken an enormous flight over the last decades. Ultrasonography (US) works by sending a pulse of ultrasound into tissue using an ultrasound transducer. The sound echoes from parts of the tissue and these echoes are recorded and displayed
as an image. US was firstly applied in the late 1940’s by obstetricians using industrial ultrasound equipment, and has expanded enormously, now including colour ultrasound, colour Doppler ultrasound and the possibility to take ultrasound-guided biopsies.

Tomography, enabling to visualize a single slice of the body using geometry, was invented already in the 1900’s but only became practical with the availability of computers (computed tomography or CT). Since the first CT scanner, technology has vastly improved in speed and quality; with the velocity of taking images in less than 1 second, availability and common use have been increased.

Positron-Emission Tomography (PET) is a form of nuclear functional imaging producing imaging of functional processes in the body. A positron-emitting tracer is introduced in the body bound to a biologically active molecule, such as fluorodeoxyglucose (FDG). The tracer can be visualized by computer analyses. FDG is a glucose analogue; the higher the concentration, the higher the metabolic activity at the site where it is visualized, resulting in the imaging of, for example, cancer metastases.

Nowadays, routine imaging techniques in CRC follow-up include multislice CT and US of the liver. CT scans can localize recurrent disease of 1 cm or larger in liver and lungs. The diagnostic sensitivity of CT-scanning for finding local recurrent disease is 85%; the sensitivity for the detection of liver metastases is 57% for ultrasound (35). In a large comprehensive literature search the sensitivity for detecting liver metastases was 64% for CT scanning. PET is applied routinely more and more with sensitivity up to 95%; however this type of imaging is costly and not available everywhere [36].

Ultrasound of the liver is the recommended imaging modality in the Dutch guidelines on follow-up. However, ultrasound has only high sensitivity rates if performed in specialist hands. Routine CT scanning is advised by the American Gastroenterology Association. CT and PET scanning have several limitations including high costs and high rates of ‘incidentaloma’ incurring further costs for investigations and treatments [37]. The best frequency and modality of routine imaging in follow-up are still to be defined.

**OUTLINE OF THIS THESIS**

The optimal follow-up regimen for patients treated for colorectal cancer has yet to be defined. This thesis aims to optimize the role of CEA in colorectal cancer follow-up.

First of all, the long-known hypothesis that the rise rather than the absolute value in CEA is valuable in signalling recurrent disease has been revised by a literature review on the topic (Chapter 2). This revisited hypothesis was then instantly tested in a pilot study, in which CEA was tested each month and additional CT scanning was performed in case of a 10% rise in CEA; both the frequency and rise of CEA are based on the litera-
ture study. The results of the pilot study define which frequency and rise of CEA are most sensitive and specific in detecting recurrent disease and can form the base of a randomized follow-up trial.

The pilot study has shown important problems of logistical nature. CEA measurements were intensified, and the concurrent appointments to the outpatient clinic put a strain on hospital logistics. Since CEA measurements can be taken in local laboratories without combining this with visit to the hospital, this led to the idea of managing the new follow-up program with software support. Software was written for this purpose, and the safety and efficacy are commented on in Chapter 3. Furthermore the literature review and pilot have led to questions on the signalling function of CEA in patients having already experienced recurrences. This issue has been investigated retrospectively in Chapter 4.

Hereafter, the randomized follow-up trial investigating the real value of the pilot results was undertaken (Chapter 5). The hypothesis was that intensified follow-up is associated with higher rates of curable recurrences, and the randomized trial aims to ameliorate the percentage of detected curable recurrences from 10% to 25%. Needing many patients in a short time frame, the design was chosen to be a stepped-wedge cluster RCT, allowing clusters of patients to cross over from the control follow-up schedule to the intervention at randomly assigned time points. The study arm made use of high-frequent CEA testing and imaging based on CEA elevations, and the current Dutch guideline acted as the control arm. In Chapter 6, the accuracy and dynamics of the new CEA regimen are further explored. Chapter 7 attends to the matter of the associated costs with the new protocol including a social analysis on associated absence from work. Chapter 8 describes patient’s experiences with the new follow-up protocol, making use of validated questionnaires.

For future work, tumor markers other than CEA, deployed either in combination with CEA or as a single marker, could be interesting. Chapter 9 gives an overview of the literature on tumor markers which could be as accurate as CEA in indicating recurrent disease in the follow-up of colorectal cancer. Since a large amount of all blood samples from the randomized trial have been stored, the review opens possibilities for future investigators and investigations. Chapters 10 and 11 are a summary and exploration of the future perspectives in both English and Dutch.


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