Carcinoembryonic Antigen (CEA) in colorectal cancer follow-up

Verberne, Charlotte

8

Psychological effects of the intensified follow-up of the CEAwatch trial after treatment for colorectal cancer

Zhuozhao Zhan, Charlotte Verberne, Edwin van den Heuvel, Irene Grossmann, Adelita Ranchor, Theo Wiggers and Geertruida de Bock

Submitted

Abstract

Objective The aim of the present study was to evaluate psychological effects of the state-of-art intensified follow-up protocol for colorectal cancer patients in the CEA Watch trial.

Materials and Method At two time points during the CEA Watch trial questionnaires regarding patients' attitude towards the follow-up, patients' psychological functioning and patients' experiences and expectations of the follow-up were sent to participants by post. Linear mixed models were fitted to assess the influences and secular trends of the intensified follow-up on patient's attitude towards the follow-up and psychological functioning. Odds ratios were calculated using ordinal logistic mixed model to compare patients' experiences to their expectations, as well as their experiences at two different time points.

Results No statistical significant effects of the intensified follow-up were found on patients' attitude towards the follow-up and psychological functioning variables. For secular trends, negative slopes were observed for nervous anticipation subscale (Estimate: -0.50, 95%CL: [-0.90, -0.09], p-value: 0.02) and Hospital Anxiety and Depression Scale (HADS) Anxiety score (Estimate: -0.4346, 95%CL: [-0.80, -0.07], p-value: 0.02), respectively. Patients had high expectations of the intensified follow-up and their experiences at the second time point were more positive compared to the scores at the first time point.

Conclusion The intensified follow-up protocol posed no adverse effects on patients' attitude towards the follow-up and psychological functioning. In general, patients were more nervous and anxious at the start of the new follow-up protocol and had high expectations of it. As they spent more time in the follow-up and became more adapted to it, the nervousness and anxiety decreased and the preference for the frequent blood test became high.

Introduction

Recent studies investigating follow-up strategies for colorectal cancer (CRC) patients after treatment have provided favourable evidence for more intensive follow-up protocols using the measurement of serum carcinoembryonic antigen (CEA). It has been shown that intensive follow-up protocols are associated with higher detection rate of curative recurrences and shorter detection time compared to a minimal follow-up strategies or less intensive ones [1–4]. In addition, ranging from non-significant to modest survival benefits have been reported by some studies as well [4–6]. Nowadays, such intense follow-up scheme has become guidelines for routine practice [7,8].

The CEAwatch trial (Netherlands Trial Register 2182) [9] is a multicentre randomized controlled trial conducted in the Netherlands between year 2010 and 2012. In this trial, the intensified follow-up protocol adheres bimonthly CEA measurements in the first three years and trimonthly CEA measurements during the fourth and fifth years combined with CT imaging. The control follow-up protocol is the Dutch care as usual follow-up guideline of which consists every 3–6 months CEA measurement and outpatient clinic visit every six months for the first three years and yearly CEA measurement and outpatient visit during the fourth and fifth year. Compared to the care as usual follow-up, the trial showed that the recurrences are detected earlier by the intensified follow-up protocol such that higher proportion of recurrences can be treated with curative intent [9].

There is however no information with regards to the influences of the intensified follow-up protocol on the psychological aspects of patients and patients acceptance. Concerns have risen on the effects of high frequent CEA measurements and with that frequent reminders of the past disease, and the protocol that includes less frequent outpatient clinic visits and partial communication of results by letter. Considering the medical benefits, the psychological outcomes should be at least comparable with the care as usual follow-up protocol.

The aim of this study was to evaluate the psychological effects of the intervention follow-up protocol in the CEAwatch trial. The null hypothesis was that the intensified follow-up has no effects on patients' attitude towards follow-up and psychological functioning. The primary outcomes of this psychological evaluation study were patients' attitude towards the follow-up and their psychological functioning including anxiety and depression, fear of recurrences and cancer worries. The secondary outcomes were patients' experiences and expectations of the intensified follow-up.

Materials and Methods

Study design

The assessments of patients' psychological variables were performed alongside the CEA Watch trial. A detailed description of the trial has previously been published [9]. The CEAwatch trial is a multicenter stepped wedge cluster randomized trial (SW-CRT) conducted between 1st October, 2010 and 1st October, 2012 with eleven participating hospitals from the Netherlands. SW-CRT is a unidirectional design that allows the intervention to roll-out sequentially for all clusters of hospitals at different time periods of the trial [10–12]. In the CEAwatch trial, hospitals were randomly grouped into five clusters and all clusters started with the care as usual follow-up protocol. Every three months, one randomly selected cluster switched from care as usual to intensified follow-up protocol (Table 1). During the trial, patients with AJCC stage I – III CRC after curative treatment were included. Patients who received adjuvant chemotherapy were eligible after cessation of the adjuvant therapy.

Table 1. Follow-up schedule over time, according to the stepped wedge cluster-randomized design.

Cluster	Oct, 2010	Jan, 2011	Apr, 2011	Jul, 2011		Oct, 2011	Jan, 2012	
1	CAU	CEA	CEA	CEA		CEA	CEA	
2	CAU	CAU	CEA	CEA		CEA	CEA	
3	CAU	CAU	CAU	CEA	1	CEA	CEA	2
4	CAU	CAU	CAU	CAU		CEA	CEA	
5	CAU	CAU	CAU	CAU		CAU	CEA	

At day 1 of every three-monthly period a new cluster switches from the care as usual protocol (CAU) to the intensified follow-up protocol (CEA). Grey periods 1 and 2 represent the times questionnaires were sent (1st round September 2011, 2nd round June 2012)

The intensified follow-up protocol used in the CEA Watch trial adhered to bimonthly CEA measurements in the first three years and trimonthly CEA measurements during

the fourth and fifth years of the follow-up. Assessment of the rise in CEA was performed and an additional blood sample was drawn in case of CEA rise above 20% compared to the latest value, with minimum lower threshold CEA value 2.5 ng/mL. Outpatient clinic visits with imaging of thorax and abdomen were performed annually during the first three years of the follow-up. Blood test results (CEA value) including a laboratory form for the next appointment were sent to patients by automatically generated letters from a computer supporting system [13]. The care as usual follow-up followed the recommendation in the national guidelines of the Netherlands. This includes an outpatient clinic visit every six months for the first three years and annual visit during the fourth and fifth year, liver ultrasound and chest X-ray at each clinic visit, CEA measurements every 3–6 months for the first three years and once a year measurements during the fourth and fifth year.

Data collection and questionnaires

The psychological effects of the follow-up protocol were evaluated by questionnaires sent by post. At two time points during the trial, patients were asked to fill in the questionnaires. The first time points was September 2011, after three of the five clusters (6 of the 11 hospitals) had already switched to the intensified follow-up and the other two clusters were still in the care as usual follow-up. The second time point was June 2012, when all clusters had crossed over to the intensified follow-up and all patients had experienced the intensified follow-up (see Table 1). This had consequences of having different time between adopting intensified follow-up protocol and the psychological assessment. The durations of experiencing the new intensified follow-up protocols for patients from different clusters varied.

The questionnaires consisted of four sections: attitude towards follow-up, psychological functioning, experiences and expectations and sociodemographic data. Other disease-specific information, such as primary tumor stage, was retrieved from the CEA Watch trial.

Attitude towards follow-up: Patients' attitude towards the follow-up was measured by a validated 16-item questionnaire previously developed to assess routine follow-up of colorectal cancer [14]. The questionnaire consisted of four subscales: reassurance, nervous anticipation, perceived disadvantages of the follow-up and communication (with physicians). Multiple items with Likert scales were combined to derive the sum scores for each subscale. For reassurance and communication, higher scores corresponded to more positive responses, while higher score corresponded to more negative responses for nervous anticipation and perceived disadvantages.

Psychological functioning: The fear of recurrence was assessed by a 6-item questionnaire. From the original 3-item questionnaire used by several former studies [14, 15], this instrument was extended so that it is more tailored to the trial. The English translation of the added three items can be found in Table 2. Outcomes were measured

with the sum scores of the 6 items ranging from 6 to 24. A higher score indicates stronger fear. The reliability of this questionnaire was high (Cronbach's alpha: 0.80). In addition, cancer worries were examined using the Dutch version of the validated Cancer Worry Scale [16–18], with each item using a 4-point Likert scale ranging from "never" to "almost always". General anxiety and depression were examined by the Dutch version of the Hospital Anxiety and Depression Scale (HADS) [19]. It consisted of 14 items with 7 items for anxiety (ranging from 0 to 21) and 7 items for depression (ranging from 0 to 21). Within the HADS, a higher score meant more anxiety and depression respectively.

Experiences and expectations: For this part, a self-developed questionnaire was used. Patients were asked to complete 15 questions about their experiences during the intensified follow-up. If patients were still in the care as usual follow-up and had no experiences about the intensified follow-up, they were asked to answer the same 15 questions about the intensified follow-up to compare their expectations to the experiences. A 5-point Likert scale ranging from 1 to 5 was used for these items. These 15 questions are listed in Table 3.

Statistical analyses

The aforementioned SW-CRT design required special attention of the secular trends in the analysis of the questionnaire data. Considering the nested structure of the design, a linear mixed model was used to assess the effects of the intensified follow-up on patients' attitude towards the follow-up and their psychological function corrected for the secular trends. To be more specific, for each outcome, three types of effects were assumed, namely the time effects, the treatment effects and the differences between patients who switched from control to intervention and those who experienced intervention only for both measurement rounds. Time effect was estimated by contrasting second time measurements to the first time measurements within the group of patients who only had intervention for both rounds. The treatment effect was estimated by contrasting two treatment groups at the first time but correcting for the differences between patients, that is the third type of effects mentioned above. The psychological effects of the follow-up protocol were also corrected for age, gender and tumor stage. Outcomes from two measurement time points were modeled as bivariate normal and hospital was considered as a random effect. Since patients' scores were not normally distributed within the attitude and psychological functioning dimensions, sensitivity analysis was conducted. These outcomes were reanalyzed with proper transformation of the outcome. To keep the interpretation of the results simple and straightforward, the results of the linear mixed model were reported unless the sensitivity analysis would demonstrate an contradiction in conclusions. In that case, the results of the sensitivity analysis were reported instead.

Table 2. Questionnaires regarding patients' experiences of the intensified follow-up protocol

	← More Positive			More Negative →	
1) I am satisfied with the current follow-up	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
2) I am afraid of blood tests§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree
3) I find bimonthly blood tests§:	Not stressful at all	Not stressful	I don't know	Somewhat stressful	Very stressful
4) Bimonthly check of my blood reassures me	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
5) I would like my blood checked every two months	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
6) Transportation for intensified follow-up is a problem for me§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree
7) I hate to wait to turn in my blood sample§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree
8) I find results send by letters very pleasant	Very pleasant	Pleasant	I don't know	Somewhat annoying	Very annoying
9) Knowing the dates of the blood testing results is of **little** importance to me§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree
10) I think waiting a week for the blood test results is long§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree
11) I think having a conversation with the doctor during visit is:	Very important	Important	I don't know	Somewhat unimportant	Completely unimportant
12) I think frequent testing for early detection of metastases is more important than a conversation with the doctor	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
13) Having a conversation with the doctor once a year would be enough for me	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
14) I would like to know if I have a metastasis , even though I'm aware this cannot be treated for months and I have no complaints	Totally agree	Agree	I don't know	Somewhat disagree	Completely disagree
15) I find it hard to cope with the uncertainty that the follow-up cannot guarantee the detection of the metastases§	Completely disagree	Somewhat disagree	I don't know	Agree	Totally agree

§ The order of the options were deliberately reversed compared to the original questionnaire sent to patients so that OR > 1 always indicates higher probability of being more positive.

Table 3. Patient characteristics and summary of primary outcome scores for the first round and second round evaluations

	Round 1 (n = 1591)	Round 2 (n = 1556)
Age: median (range)	68 (26–94)	68 (29–93)
AJCC stage		
I	397 (27.49%)	412 (29.92%)
II	570 (39.47%)	550 (39.94%)
III	477 (33.03%)	415 (30.14%)
Gender		
Female	685 (43.11%)	621 (40.01%)
Male	904 (56.89%)	931 (59.99%)
CEA follow-up		
Intervention	770 (48.43%)	1554 (100.00%)
Control	820 (51.57%)	0 (0.00%)
Attitude towards follow-up		
Reassurance	13 (4–16)	13 (4–16)
Nervous anticipation	7 (5–20)	7 (5–18)
Perceived disadvantages	4 (3–11)	4 (3–11)
Communication	13 (4–16)	13 (4–16)
Psychological functioning		
Fear of recurrence	12 (6–23)	12 (5–22)
HADS: Anxiety	3 (0–21)	3 (0–21)
HADS: Depression	2 (0–20)	1 (0–20)
Cancer worries	13 (8–31)	13 (8–31)

To evaluate patients' experiences and expectations of the intensified follow-up, an ordinal logistical mixed model with cumulative logit link function was applied and odds ratios were calculated for two comparisons. The first comparison is between patients' experiences and their expectations corrected for the temporal effects. The second one is between patients' experiences measured at the 2nd time point and the experiences measured at the 1st time point. The model was also adjusted for patients' age, gender and the tumor stage. Principal components analysis and correlation analysis suggested no satisfying structural relationships among these 15 items. Thus, the analysis was done item by item. The p-value and confidence limits of the odds ratio (OR) were adjusted by Bonferroni correction. Only the odds ratios between experiences and expectations, as well as the odds ratios of experiences between the two time points, were presented in the result section.

If patients did not complete at least 80% of the items within certain subscales or dimensions, the score of this subscale/dimension was considered missing. Statistical analyses were performed with SAS® statistical software, version 9.4.

Results

Patient characteristics and response rate

On November 1st, 2011, total of 2,016 patients participated in the CEAwatch trial, and received the questionnaires. A total of 1,591 patients (78.9%) returned the questionnaires. On May 1st, 2012, total of 1,848 patients participated in the CEAwatch trial, 1556 (84.2%) of them returned the questionnaires. Patient characteristics of the two rounds are given in Table 4. During the first round, 820 (51.6%) of them participated in the care as usual follow-up and 720 (48.4%) were in the intensified follow-up (1 missing). At second round, all patients (2 missing) were in the intensified follow-up (Table 4). Among all patients, 1162 of them participated in both rounds of questionnaires.

Table 4. Estimates and 95% confidence limits of follow-up protocol effects and secular trends from linear mixed model for patients' attitude towards the follow-up and psychological functioning

	Intensified follow-up vs. care as usual				**Time trends**			
	Estimates	*95% CL*		*p-value*	*Estimates*	*95% CL*		*p-value*
Reassurance	0.1135	-0.4221	0.6491	0.64	-0.2258	-0.5062	0.0546	0.10
Nervous anticipation	0.5113	-0.2867	1.3092	0.18	-0.4961	-0.9019	-0.0904	**0.02***
Perceived disadvantage	0.2097	-0.3316	0.7511	0.40	-0.1890	-0.4645	0.0865	0.16
Communication	0.2438	-0.5788	1.0664	0.52	-0.3178	-0.7392	0.1036	0.13
HADS: Anxiety	0.5876	-0.0922	1.2674	0.09	-0.4346	-0.8014	-0.0678	**0.02***
HADS: Depression	0.3379	-0.4100	1.0858	0.33	-0.1552	-0.5431	0.2327	0.40
Cancer worries	0.2404	-0.6637	1.1136	0.55	-0.2117	-0.6637	0.2404	0.33
Fear of recurrence	0.1983	-0.7522	1.1487	0.65	-0.1879	-0.6728	0.2971	0.41

Primary outcomes

The estimations for the psychological effects on patients' attitude towards follow-up and psychological functioning of the intensified follow-up protocol and time periods differences are shown in Table 5. No statistical significant effects of the intensified follow-up were found on patients' attitude towards the follow-up. Furthermore, there were no significant differences on anxiety and depression, fear of recurrences and cancer worries between the intensified follow-up protocol and care as usual follow-up. Comparing between two time points, statistically significant lower score were observed at the second time points for nervous anticipation subscale (Estimate: -0.50, 95%CL: [-0.90, -0.09], p-value: 0.02) and HADS Anxiety score (Estimate: -0.4346, 95%CL: [-0.80, -0.07], p-value: 0.02), respectively, suggesting that patients were more nervous and anxious at the start of the trial and gradually adapted to the new protocol. No temporal differences were found for other subscales.

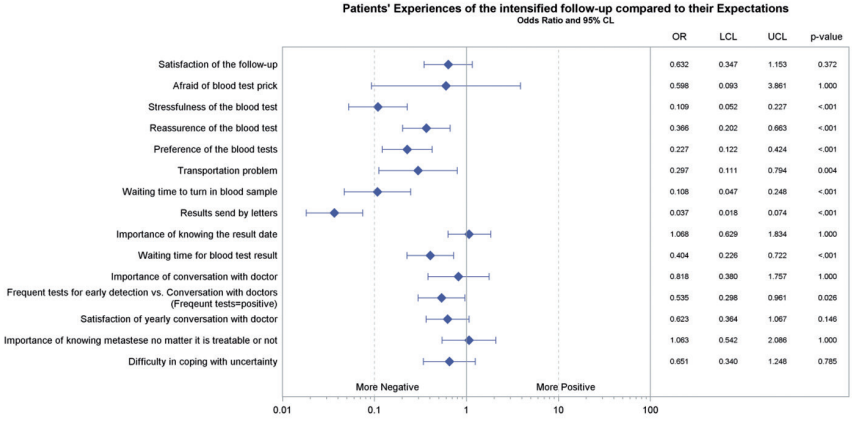
Table 5. Estimates and 95% confidence limits of follow-up protocol effects and secular trends from linear mixed model for patients' attitude towards the follow-up and psychological functioning

	Intensified follow-up vs. care as usual				Time trends			
	Estimates	*95% CL*		*p-value*	*Estimates*	*95% CL*		*p-value*
Reassurance	0.1135	-0.4221	0.6491	0.64	-0.2258	-0.5062	0.0546	0.10
Nervous anticipation	0.5113	-0.2867	1.3092	0.18	-0.4961	-0.9019	-0.0904	0.02*
Perceived disadvantage	0.2097	-0.3316	0.7511	0.40	-0.1890	-0.4645	0.0865	0.16
Communication	0.2438	-0.5788	1.0664	0.52	-0.3178	-0.7392	0.1036	0.13
HADS: Anxiety	0.5876	-0.0922	1.2674	0.09	-0.4346	-0.8014	-0.0678	0.02*
HADS: Depression	0.3379	-0.4100	1.0858	0.33	-0.1552	-0.5431	0.2327	0.40
Cancer worries	0.2404	-0.6637	1.1136	0.55	-0.2117	-0.6637	0.2404	0.33
Fear of recurrence	0.1983	-0.7522	1.1487	0.65	-0.1879	-0.6728	0.2971	0.41

Secondary outcomes

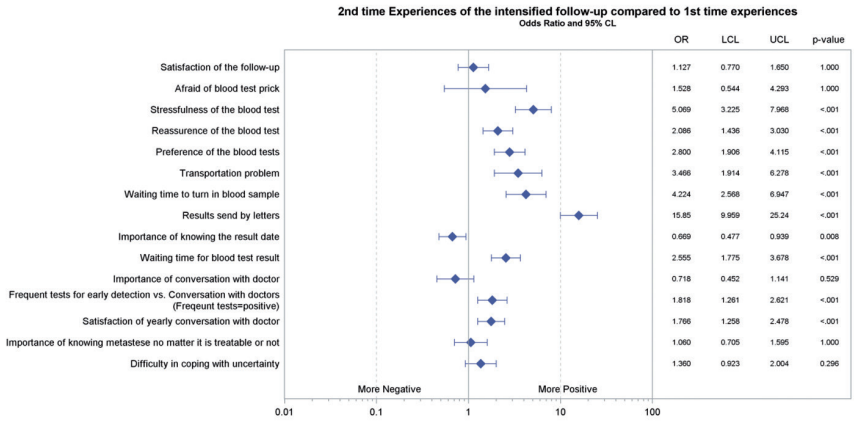
The comparisons between patients' experiences and expectations are shown in Figure 1. In general, comparing patients' experiences in the intensified follow-up to their expectations, the responses were towards the negative end of the spectrum. Particularly, patients expressed that the stress of the blood test was higher than they expected (OR: 0.11, 95% CL: [0.05, 0.23], p-value: < 0.001) while they were less reassured by it (OR: 0.37, 95% CL: [0.20, 0.66], p-value: < 0.001) and the preferences of the blood tests were not in favour of the intensified follow-up (OR: 0.23, 95% CL: [0.12, 0.42], p-value: < 0.001). In addition, the inconveniences of the blood tests like waiting time to turn in a blood sample (OR: 0.11, 95% CL: [0.05, 0.25], p-value: < 0.001) and results sent by letters (OR: 0.04, 95% CL: [0.02, 0.07], p-value: < 0.001) were less appreciated.

Figure 1. Patients experiences of the intensified follow-up compared to their expectations



In the comparisons between patients' second experiences and their first time experiences, the responses at the second time were more positive than the one at the first time as shown in Figure 2. At the second time points, patients had statistically significant higher probability to give a more positive response. Specifically, patients were more positive about all the items that did not meet with expectations in the previous comparison. Blood tests were less stressful (OR: 5.07, 95% CL: [3.23, 7.97], p-value: < 0.001) and provided more reassurance (OR: 2.09, 95% CL: [1.44, 3.03], p-value: < 0.001) at the second time point compared to their first time experiences. Preferences of the blood test became higher (OR: 2.80, 95% CL: [1.91, 4.12], p-value: < 0.001) and the frequent tests were more preferred in replacement of having conversation with the doctors (OR: 1.82, 95% CL: [1.26, 2.62], p-value: < 0.001).

Figure 2. Patients' 2nd time experiences of the intensified follow-up compared to their 1st time experiences Sensitivity analysis



The hypothesis tests of the linear mixed model could be affected by the skewed residual of the data. For reassurance subscale, the conditional residual was negatively skewed and was first converted to positive skewness and then logarithm-transformed. The estimations after the transformation (both treatment effect and time effect) were more towards the null and were consistent with the estimations of the linear mixed model. For nervous anticipation and cancer worry subscale, direct logarithm transformations were applied respectively. The treatment effect remained non-significant and the time effect remained significant for nervous anticipation. Both effects were shifted towards the null for cancer worry subscale. For both HADS subscales, square root transformations were used and

the results remained the same. The rest of the subscales were normally distributed. To conclude, the results of the sensitivity analysis agreed with the linear mixed model and the estimations presented were accurate enough to be clinically meaningful.

Discussion

In the CEAwatch trial, an intensified follow-up protocol was compared to the Dutch care as usual follow-up guideline. The major differences in the intensified follow-up protocol relevant to the discussion of the present study was that the frequency of outpatient clinic visit during the first three years of the follow-up were reduced and in replacement was a more intensive CEA measurements scheme.

The effects of the intensified follow-up protocol for CRC patients after surgery in the CEAwatch trial were evaluated with regards to patients' psychological variables. No statistical significant effects were found on patients' attitude towards the follow-up and psychological functioning. Furthermore, patients' nervous anticipation scores and HADS anxiety scores were both significantly lower in the second time points suggesting that patients became less nervous and anxious with more time spent in the new follow-up protocol. For patients' psychological functioning, no proof of increased burden or improvement was observed comparing the intensified follow-up protocol to the care as usual follow-up protocol.

Comparisons between patient's experiences and expectations resulted in more negative responses for patient's experiences which indicate that the expectations of the new follow-up protocols were high. On the other hand, by analysing the experiences at two different time points, we found that the responses became more positive later in time. Especially, patients responded more positively to blood test including reassurance, stressfulness and preference. This is in accordance with the results from the primary outcome that no decrease in reassurance were observed since it has been shown that patients are reassured by outpatient clinic visits and having conversation with the doctors [14]. From the present study, one may deduce that the frequent blood test compensated for less frequent clinic visit in the intensified follow-up protocol in terms of reassurance. In addition, patients' responses to the inconveniences of the blood tests were improved with time as well.

It has been mentioned that follow-up may remind patients of their cancers and possible relapsing of malignant disease [14]. However, even with more frequent blood tests, patients' cancer worries and fear of recurrences did not increase, nor did the HADS anxiety scores. On the contrary, patients' HADS anxiety scores decreased with time suggesting patients became less anxious once they spent more time in the follow-up. Furthermore, it is expected that patients were more nervous and anxious about the new follow-up protocol as they were inexperienced with this new strategy. And once they spent more time in it, the nervousness and anxiety decreased.

Currently, limited information is available regarding the impact of follow-up protocols on patients' quality of life and psychological functioning [14, 20] from the literature. The FACS study also planned to investigate the quality of life and satisfaction of care of the colorectal cancer follow-up and the results have not been published yet. The presented study with large sample size and high response rate provided such information for the state-of-art post-treatment follow-up protocol. Meanwhile, the results of the secondary outcome should be interpreted with caution since for this study relevant questions were formulated and these were analyzed item by item. The purpose was to provide a qualitative insight in patient's expectations and experience, tailored to the features of the intensified follow-up protocols used in the CEAwatch trial. In our opinion, it is sufficient enough to provide indirect evidence on the general trends of patients experiences with regards to the intensified follow-up and is in agreement with the primary outcomes. In addition, doubts have been raised as to the validity of the HADS. It is recommended not to use this instrument anymore for future study. However, the questionnaires were already used by then.

In conclusion, the intensified follow-up protocol posed no adverse effects on patients' attitude towards the follow-up and psychological functioning. In general, patients were more nervous and anxious at the start of the new follow-up protocol and had high expectations of it. As they spent more time in the follow-up and became more adapted to it, the nervousness and anxiety decreased and the preference for the frequent blood test became high.

References

1. Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis. Colon Rectum 2007; 50(11):1783–99.
2. Figueredo A, Rumble RB, Maroun J et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 2003; 3:26.
3. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C et al. Intensive follow-up strategies improve outcomes in non-metastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann. Oncol. 2014:941–950.
4. Primrose JN, Perera R, Gray A et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA 2014; 311(3):263–70.
5. Jeffery M, Hickey B, Hider P. Follow up strategies for patients treated for non-metastatic colorectal cancer (Review). Cochrane Database Syst Rev 2007.
6. Renehan A, Egger M. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ Br. Med. J. 2002; 324(April):1–8.
7. Duffy MJ, Lamerz R, Haglund C et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int. J. Cancer 2014; 134(11):2513–2522.
8. Locker GY, Hamilton S, Harris J et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J. Clin. Oncol. 2006; 24(33):5313–5327.
9. Verberne CJ, Zhan Z, van den Heuvel E et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomized "CEAwatch" trial. Eur. J. Surg. Oncol. 2015; 41(9):1188–1196.
10. Hemming K, Haines TP, Chilton PJ et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. Bmj 2015; 350:h391–h391.
11. Hemming K, Lilford R, Girling AJ. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Stat. Med. 2015; 34(August 2013):181–196.
12. Zhan Z, Van den Heuvel ER, Doornbos PM et al. Strengths and weaknesses of a stepped wedge cluster randomized design: its application in a colorectal cancer follow-up study. J. Clin. Epidemiol. 2014. doi:10.1016/j.jclinepi.2013.10.018.
13. Verberne CJ, Nijboer CH, de Bock GH et al. Evaluation of the use of decision-support software in carcino-embryonic antigen (CEA)-based follow-up of patients with colorectal cancer. BMC Med. Inform. Decis. Mak. 2012; 12(1):14.
14. Stiggelbout A, Haes J De. Follow-up of colorectal cancer patients: quality of life and attitudes towards follow-up. … J. cancer 1997; 75(6):914–20.

15. De Bock GH, Bonnema J, Zwaan RE et al. Patient's needs and preferences in routine follow-up after treatment for breast cancer. Br. J. Cancer 2004; 90(6):1144–50.
16. Bleiker EM a. 19th Annual Conference of the International Society for Quality of Life Research. Qual. Life Res. 2008; 21(S1):1–132.
17. Watson M, Duvivier V, Wade Walsh M et al. Family history of breast cancer: what do women understand and recall about their genetic risk? J. Med. Genet. 1998; 35(9):731–738.
18. Custers J a E, van den Berg SW, van Laarhoven HWM et al. The Cancer Worry Scale: Detecting Fear of Recurrence in Breast Cancer Survivors. Cancer Nurs. 2013; 00(0):1–7.
19. Spinhoven P, Ormel J, Sloekers PP et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol. Med. 1997; 27(2):363–70.
20. Kjeldsen BJ, Thorsen H, Whalley D, Kronborg O. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. Scand. J. Gastroenterol. 1999; 34(5):509–15.


Green Peas
究極のパチスロ店
Green Peas
Green Peas
Green Peas
5~20


喜多方ラーメン蔵
新宿南口店
カラオケ&パーティ
5F
RentNavi
アース
4F
新宿国際劇場
採みの気
3F
3F
30

September 2013
Electric City, Tokyo, Japan
met Pieter Laurens