CDI-00743-2018.R1
Systematic Review

Consensus and controversies regarding follow-up after curative intent treatment of non-metastatic colorectal cancer: a synopsis of guidelines used in countries represented in ESCP

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Conflicts of interest

The authors declare no conflicts of interest.

Word count excluding abstract, references, tables, figures and legends: 9047 words.

Abstract

Aim

It is common clinical practice to follow patients for a period of years after curative intent treatment of non-metastatic colorectal cancer, but follow-up strategies vary widely. The aim of this systematic review was to provide an overview of recommendations in guidelines from ESCP member countries on this topic, with supporting evidence.

Methods

A systematic search of Medline, Embase and guidelines databases Tripdatabase, BMJ Best Practice and Guidelines International Network was performed. Quality assessment included usage of the AGREE-II tool. All topics with recommendations from included guidelines were identified and categorized. For each subtopic, a conclusion was made followed by the degree of consensus and the highest level of evidence.

Results

Twenty one guidelines were included. The majority recommended that structured follow-up should be offered, except for patients where treatment of recurrence would be inappropriate. It was generally agreed that clinical visits, CEA measurement, and liver imaging should be part of follow-up, based on high level of evidence, although frequency is controversial. There was also consensus on imaging of the chest and pelvis in rectal cancer, as well as endoscopy, based on lower levels of evidence and with a level of intensity that was contradictory.

Conclusion

In available guidelines, multimodality follow-up after curative intent treatment of colorectal cancer is widely recommended, but exact content and intensity is highly controversial. International agreement on the optimal follow-up schedule is unlikely to be achieved on current evidence, and further research should re-focus on individualized ‘patient-driven’ follow-up and new biomarkers.

What does this paper add to the literature?

This guidelines synopsis provides an overview of the recommendations and evidence for follow-up after curative intent treatment of non-metastatic colorectal cancer. Furthermore, it highlights recent research and recommendations for future research.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an incidence of nearly 1.4 million in 2012 (1). The last decades have shown extensive improvements in treatment of patients with CRC, illustrated by a decreasing number of recurrences and improved survival rates (2,3). After treatment with curative intent, it is common clinical practice to follow patients for a certain period of time. The purpose of follow-up is primarily to detect any curable malignancy, either local recurrence, distant metastasis or second primary cancer. Secondly, follow-up aims to identify and handle late adverse effects after treatment.

However, the ideal follow-up schedule is unclear. Recent randomized trials have compared follow-up-strategies with different intensities and combinations of methods (4-7). A Cochrane review, which included some of these trials, concluded that there was no improvement of overall survival from intensive follow-up after CRC, although intensive follow-up had a beneficial effect on the chance of having salvage surgery with curative intent (8).

Currently, recommendations for follow-up after curatively treated CRC are described in several national and international clinical practice guidelines and consensus papers. These documents cover topics ranging from diagnostic imaging, blood tests and endoscopy, to symptom management and screening for late adverse effects. In anticipation of more evidence, several topics in the guidelines remain controversial, and there is a need for clarifying the levels of evidence for each intervention and the recommendations included in the guidelines.

The European Society of Coloproctology (ESCP) Research Committee has encouraged a systematic review of current guidelines of their members' countries, resulting in a synopsis of recommendations and evidence within this field. The aim of this study was to provide an overview of the recommendations and evidence for follow-up after curative intent treatment of non-metastatic CRC, as stated in national and international guidelines used in ESCP member countries. Any controversy and lack of evidence for different aspects of the follow-up were determined. These findings were discussed in relation to ongoing research, and topics that require additional evidence were identified.

Method

A systematic search was performed to identify national and international guidelines and consensus documents regarding the follow-up after treatment with curative intent of non-metastatic CRC patients published up to 1 May 2017. With the assistance of a clinical librarian, the search was carried out using the medical databases Medline (PubMed version) and Embase (Ovid version) and guideline databases Trip-database, BMJ Best Practice and Guidelines International Network, with a time limit set for publications between 2007 and 2017 and without language restriction. The search terms included the following main themes: colorectal cancer, follow-up and guideline/consensus. Details of the search are provided in Appendix 1. Additionally, websites of national health authorities, as well as surgical and oncological societies were searched, and a letter of request for national guidelines was sent twice to all ESCP national representatives. The search results were imported into Covidence for further selection (9).

After removal of duplicates, two reviewers (VPB and IHJ) independently performed every step in the selection process. Guidelines and consensus documents were included if they presented recommendations on follow-up after curative intent treatment of non-metastatic CRC. Eligible documents should have been developed by authors considered to be an acknowledged working group and should be used in countries represented in ESCP. Papers overlapping or presenting the same guideline or consensus document were excluded. In case of disagreement, discussion took place until consensus was reached. A cross reference search was performed for all included papers. In order to identify potential updated versions of included guidelines, a restricted search was performed at 15 January 2018. The translation of non-English guidelines and consensus documents was performed with the help from native speakers.

All topics followed by recommendations in the included guidelines and consensus documents were categorized into main topics. If relevant, the main topics were specified into subtopics. Recommendations from the included documents were presented per (sub)topic. In case of difficulties with interpretation or understanding of elements in the guidelines, the authors or national ESCP representatives were consulted. Relevant exceptions or deviations for certain patient groups (e.g. tumour stage) were explicitly mentioned. A conclusion was made for each (sub)topic, followed by a statement whether consensus was reached or this was controversial. Consensus was reached when at least half of the included guidelines mentioned a topic, and at least two-thirds of these made a similar recommendation for the topic. In all other cases the conclusion was regarded controversial. Guidelines that consisted of two separate documents for colon and rectal cancer patients were referred to as one guideline in the text, but any difference related to a (sub)topic was included separately. In the classification of consensus/controversy, the two related documents always counted as one guideline.

For each conclusion, the source reference with the highest level of evidence referred to in the guidelines and consensus documents was cited. The level of evidence was classified according to the

Oxford Centre for Evidence-based Medicine Levels of Evidence 2009 (10). If not reported in this format, the evidence level was manually reassigned. A level of evidence ≥3b was regarded insufficient.

The quality assessment of the guidelines and consensus documents included the following parameters: year of publication, adequate guideline development group, type of evidence, usage of adequate grading system, and The Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument. A guideline development group was considered adequate if it consisted of at least one surgeon, one radiologist and one medical oncologist since these health professionals are the most important for the follow-up of CRC patients. Information about the professional representation in the guideline development groups is provided in Appendix 2. A grading system was considered adequate if it considered both the quality of evidence and the strength of the recommendations. The AGREE-II instrument was used to estimate the AGREE score (11). Two investigators (VPB and IHJ) independently scored the included papers according to the six domains of AGREE-II (Scope and Purpose, Stakeholder Involvement, Rigour of Development, Clarity of Presentation, Applicablity, Editorial Independence). Finally, the authors commented on the quality of the guidelines and consensus documents (Appendix 3). This was a subjective parameter based on the above mentioned components of the quality assessment.

Results

Guidelines

Search and selection

The search in medical and guidelines databases retrieved 3857 references after removal of duplicates. This search resulted in final inclusion of three references. Additionally, a total of 21 eligible references were identified from the web search and after the request addressed to ESCP-representatives. Together with the three references from the database search, the final number of included references was 24 (Figure 1).

Included guidelines

The included references covered both guidelines and consensus papers. However, in this paper, they will all be referred to as guidelines. In three cases, there were guidelines that consisted of two separate documents for colon and rectal cancer patients, and thus referred to as one guideline. The final number of guidelines were 21, including 15 national guidelines and six guidelines from professional societies. The guideline from the American National Comprehensive Cancer Network (NCCN) is utilized as national recommendations in Egypt, thus it was included as one of the national guidelines. Quality assessment of the included guidelines is summarized in Table 1.

Analysis of topics

Part 1: General aspects of follow-up

Criteria for offering patients structured follow-up

Considerations regarding the patients who should undergo structured follow-up were mentioned in twelve guidelines (57%; 2, 4, 5, 6, 7, 10, 11, 12, 15, 16, 20, 21). All of these guidelines stated that follow-up should only be offered to patients who are able to receive further treatment if recurrence is detected. This was further elaborated in five guidelines (5, 6, 12, 15, 20), which all recommended to also consider (biological) age or life expectancy, as well as the patient's general condition, in the decision whether or not to offer structured follow-up. The German guideline (6) added that the patients' willingness to undergo revisional surgery should be taken into account.

Conclusion: Structured follow-up should only be offered to patients who are able to receive further treatment if recurrence is detected.

Consensus (recommended in 12 (100%) of the 12 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Intensity of follow-up

The intensity of the follow-up program was mentioned in sixteen guidelines (76%; 1, 2, 3, 4, 6, 7, 10, 11, 12, 15, 16, 17, 18, 19, 20, 21). Four of these guidelines (2, 7, 17, 19) recommended intensive follow-up, but a uniform definition of intensive follow-up was lacking. In the ESMO (17) and SEOM (19) guidelines, this recommendation only applied to colon cancer patients and stage II-III CRC patients, respectively. The NCCN (10) and EURECCA (18) guidelines did not recommend intensive follow-up, but only suggested a more intensive follow-up for patients with advanced CRC compared to low stage CRC patients. The Danish (3) and the Swedish (15) guidelines recommended less intensive follow-up pending more solid evidence that proves a survival benefit from intensive follow-up. In the remaining eight guidelines (1, 4, 6, 11, 12, 16, 20, 21), the inconclusive evidence regarding intensive versus less intensive follow-up was discussed without giving any explicit recommendation or statement.

Conclusion: It is unclear whether (selected high risk) CRC patients should receive intensive or less intensive follow-up, and also a uniform definition of intensive or less intensive follow-up is lacking.

Controversy (intensive follow-up is recommended in four guidelines (25%), which is less than two-thirds of the guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: 1a (42,43). The evidence shows an overall survival benefit for patients undergoing more intensive follow-up.

Termination of proposed follow-up

Criteria for ceasing follow-up were mentioned in four guidelines (19%; 2, 4, 11, 16). The Dutch guideline (4) recommended that the duration of follow-up should be discussed by the physician and the patient. In the Belgian colon cancer guideline (2a), it was stated that follow-up should no longer be performed when the likely benefits no longer outweigh the disadvantages of further tests (i.e. costs, time spent for the patient, false positive results and patient distress). The NICE (11) and ACPGBI (16) guidelines combined these two criteria; in these guidelines it is recommended to cease follow-up when the patient and healthcare professional have discussed and agreed that the likely benefits no longer outweigh the disadvantages of follow-up.

Conclusion: Follow-up could be terminated if the patient and healthcare professional have discussed and agreed that there is likely no potential benefit anymore.

Controversy (only mentioned in four guidelines (19%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Coordination of follow-up

Considerations regarding the coordination of follow-up were mentioned in six guidelines (29%; 2, 3, 4, 5, 12, 20). The recommendations varied with regard to the person that should be designated to this coordinating role. The Danish guideline (3) stated that the surgeon should be the coordinator; the French guideline (5) recommended the follow-up to be performed by the general practitioner, alternating with the specialized team; the Norwegian guideline (12) stated that follow-up should be performed by the general practitioner, except for the first postoperative visit and selected rectal cancer patients; the SGG guideline recommended follow-up to be locally coordinated by one of the specialists who will regularly involve other relevant physicians (surgeon, family physician, gastroenterologist, radiologist, etc). The Belgian (2) and Dutch (4) guidelines did not specify the health professional who should coordinate the follow-up. Three of these guidelines explicitly mentioned that the follow-up plan should be communicated to the patient (2, 3, 4).

Conclusion: A health professional could be designated as the coordinator for the follow-up, depending on the local health care infrastructure.

Controversy (only mentioned in six guidelines (29%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Part 2: Clinical visits

Role

The role of clinical visits, including medical history with or without physical examination, during the follow-up of CRC patients was mentioned in eighteen guidelines (86%). Sixteen guidelines (1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 15, 17, 19, 20, 21) recommended that clinical visits should be routinely performed. In five guidelines, this recommendation did not apply to stage I CRC (6, 10, 12, 20) or stage I colon cancer (21) patients. In four guidelines (2, 5, 13, 20), digital rectal examination was recommended for rectal cancer patients. The NICE guideline (11) stated that one clinical visit at 4 to 6 weeks after curative treatment should be offered, but nothing was mentioned about clinical visits thereafter. During the EURECCA (18) consensus conference, no consensus was reached about the statement that clinical visits could be considered during follow-up.

Conclusion: Clinical visits should be part of routine follow-up after CRC. Physical examination is not routinely recommended, but digital rectal examination could be included for rectal cancer patients.

Consensus (recommended in 16 (89%) of the 18 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: 1a (42). The evidence does not support the conclusion. No effect from clinical visits on survival or time to recurrence is observed. The effect on quality of life and functional outcome has not been studied.

Time schedule

Fifteen guidelines (71%; 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 17, 19, 20, 21) mentioned a time schedule for clinical visits in their recommendations (Table 2). In all of these guidelines, a higher frequency regimen was suggested within the first two to three years postoperative compared to the years thereafter, except for the ESMO rectal cancer guideline (17b), that recommended clinical visits to be performed only during the first two years after primary surgery. Thirteen guidelines (1, 2, 4, 5, 6, 7, 9, 10, 12, 17, 19, 20, 21) recommended that clinical visits should be performed until five years after primary surgery. The time schedule of the different guidelines is displayed in Table 2.

Conclusion: Clinical visits should be performed until five years after surgery with a more frequent regimen in the first two to three years.

Consensus (recommended in 13 (87%) of the 15 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Part 3: Laboratory tests

Carcinoembryonic antigen (CEA)

Role

The role of CEA during the follow-up of CRC patients was discussed in twenty guidelines (95%; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21). The Danish (3) and SIGN (14) guidelines stated that more evidence on the role of CEA was required and, therefore, routine estimation of CEA is not recommended. According to the French (5) and TNCD (21) guidelines, CEA measurement is optional. The other sixteen guidelines recommended that CEA should routinely be measured during follow-up. In three guidelines, the recommendations did not apply to stage I CRC patients (6, 10, 12). The Dutch (4) and SGG (20) guidelines recommended not to include CEA in routine follow-up of pT1N0 CRC patients.

Conclusion: Measurement of CEA should be routinely performed during follow-up, but might be restricted to stage II and III CRC.

- Stage I CRC patients: *Controversy (recommended in 11 (T1N0) and 13 (T2N0) guidelines (55% and 65% respectively), which is less than two-thirds of the guidelines that discussed this topic).*
- Stage II and III CRC patients: *Consensus (recommended in 16 (80%) of the 20 guidelines that discussed this topic).*

Highest level of evidence referred to in the guidelines: 1a (42,43). Two systematic reviews differ in their conclusions about routine CEA measurement. No significant differences regarding mortality and recurrence were found between routine CEA and no CEA measurement in Jeffery et al., while Tjandra et al. demonstrated a significant impact of regular surveillance with CEA on mortality and curative reoperation rate.

Time schedule

All guidelines that recommended routine CEA measurement during follow-up included a time schedule in their recommendations. In thirteen guidelines (1, 2, 4, 6, 7, 8, 9, 10, 12, 13, 17, 19, 20), a higher frequency regimen was suggested within the first 2-3 years compared to the years thereafter. In all these guidelines, except for the Hungarian guideline (8), time schedules for CEA determination were within the range of every 3-6 months within the first 2-3 years and every 6-12 months until 5 years after surgery. In the ESMO guideline (17), this only applied to colon cancer patients. The time schedules of the different guidelines are displayed in Table 3.

Conclusion: CEA should be measured every 3-6 months during the first 2-3 years, and thereafter every 6-12 months until five years after surgery.

Consensus (recommended in 12 (92%) of the 13 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: 1b (4). The evidence does not support the conclusion, as it suggests a more frequent timing for CEA. In the CEAWatch trial (4), recurrences were detected earlier, and significantly more recurrences were available for curative intent treatment, when using a high frequency for CEA testing (every two months), compared to usual frequency (every 3-6 months) in the first three years.

Fecal occult blood test (FOBT)

Four guidelines (19%; 2, 6, 8, 14) discussed FOBT as part of routine follow-up, of which only the Hungarian guideline (8) recommended FOBT to be performed in the routine follow-up of CRC patients.

Conclusion: FOBT should not be routinely performed during follow-up.

Controversy (only mentioned in four guidelines (19%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3b (44). The evidence supports the conclusion. It shows that FOBT is a poor marker for colorectal neoplasia, since most cancers will be missed.

Other laboratory tests

Eight guidelines (38%; 2, 6, 8, 9, 13, 17, 18, 21) discussed other laboratory tests as part of routine follow-up. The Italian guideline (9) recommended that blood cell count should routinely be performed in contrast to the Belgian (2b), German (6) and EURECCA (18) guidelines that discouraged this. The same three guidelines, as well as the TNCD guideline (21b), advised against routine measurement of liver function tests. The Belgian (2b) guideline also discouraged the use of tumour markers, other than CEA. The Hungarian guideline (8) recommended the measurement of gamma GT, CA-50 and CA 19-9, the latter also being advised by the Russian guideline (13) if it was increased before. The ESMO guideline (17a) stated that no other laboratory tests than CEA should be part of routine follow-up.

Conclusion: Laboratory tests other than CEA should not be part of follow-up.

Controversy (only mentioned in eight guidelines (38%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Part 4: Imaging

Chest imaging

Role

The role of chest imaging during follow-up of CRC patients was mentioned in all guidelines. Nineteen guidelines (1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21) recommended that chest imaging should be routinely performed. The German (6) and EURECCA (18) guidelines stated that only rectal cancer patients should undergo routine chest imaging. In some guidelines, chest imaging is not recommended for certain patient groups: stage I and II rectal cancer (18), stage I CRC (10, 12), stage I colon cancer (20, 21), stage I rectal cancer (6), pT1N0 colon cancer (2) and pT1N0 rectal cancer after radical resection (20). The Dutch guideline (4) only stated that chest imaging may be considered for rectal cancer patients, except for patients with pT1N0 rectal cancer. Similarly, the SIGN guideline (14) stated that chest imaging may be of value, but more evidence on the optimum approach is required.

Conclusion: Chest imaging should be routinely performed during follow-up of CRC, but might be omitted in stage I colon cancer

- *Stage I colon cancer: Controversy (recommended in 12 (T1N0) and 13 (T2N0) guidelines (57% and 62% respectively), which is less than two-thirds of the guidelines that discussed this topic).*
- *Stage II-III colon cancer and stage I-III rectal cancer: Consensus (recommended in at least 14 (67%) of the guidelines that discussed this topic).*

Highest level referred to in the guidelines: 2b (45). The evidence does not support the conclusion. In the RCT of Schoemaker et al., no survival benefit was found from adding chest imaging to routine follow-up.

Modality

In sixteen guidelines (84%; 1, 2, 3, 5, 7, 9, 10, 11, 12, 15, 16, 17, 18, 19, 20, 21), it was recommended to use CT, whether or not alternating with X-ray, for the detection of lung metastases. In the German (6), Hungarian (8) and Russian (13) guidelines, radiography was the preferred modality.

Conclusion: CT, whether or not alternating with X-ray, is the preferred modality for the detection of lung metastases.

Consensus (recommended in 16 (84%) of the 19 guidelines that recommended chest imaging).

Highest level referred to in the guidelines: ≥3b. No references comparing different modalities were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing

All nineteen guidelines that recommended chest imaging also proposed a time schedule. In thirteen of these (1, 2, 5, 6, 7, 9, 10, 12, 13, 18, 19, 20, 21), a regimen within the range of every 3 to 12 months for at least five years after surgery was recommended. In four guidelines (1, 2, 17, 21), a different timing was proposed for colon and rectal cancer patients (Table 4).

Conclusion: The time schedule for chest imaging should be within the range of every 3-12 months for at least five years after surgery.

Consensus (recommended in 13 (68%) of the 19 guidelines that recommended chest imaging).

Highest level referred to in the guidelines: ≥3b. No references comparing different time schedules for chest imaging were mentioned in the guidelines, all recommendations were based on expert opinion.

Liver imaging

Role

The role of liver imaging during the follow-up of CRC patients was mentioned in all guidelines. The SIGN guideline (14) stated that liver imaging may be of value, but more evidence on the optimum approach is required. The remaining twenty guidelines recommended routine performance of liver imaging during follow-up. In the EURECCA consensus paper (18), liver imaging was only recommended for rectal cancer patients. In some guidelines, certain patient groups should be refrained from routine liver imaging: stage I and II rectal cancer (18), stage I CRC (6, 10, 12), stage I colon cancer (20, 21), pT1N0 CRC (4), pT1N0 colon cancer (2) and pT1N0 rectal cancer after radical resection (20).

Conclusion: Liver imaging should be routinely performed during follow-up, but might be omitted in pT1N0 colon cancer.

- *pT1N0 colon cancer: Controversy (recommended in 12 guidelines (57%), which is less than two-thirds of the guidelines that discussed this topic).*
- *pT2N0 and stage II-III colon cancer and stage I-III rectal cancer: Consensus (recommended in at least 14 (67%) of the 21 guidelines that discussed this topic).*

Highest level referred to in the guidelines: 1a (42). The evidence supports the conclusion, since it states that the use of liver imaging seems to be associated with improved survival.

Modality

In sixteen guidelines (84%; 1, 2, 3, 5, 7, 9, 10, 11, 12, 15, 16, 17, 18, 19, 20, 21), it was recommended that imaging of the liver should be performed with CT, whether or not alternated with ultrasound. In four guidelines (4, 6, 8, 13), ultrasound was the preferred modality to detect liver metastases, although

the Dutch guideline (4) proposed CT as an alternative for patients at high risk of recurrence due to its higher sensitivity.

Conclusion: CT, whether or not alternating with ultrasound, is the preferred modality for the detection of liver metastases.

Consensus (recommended in 16 (80%) of the 20 guidelines that recommended liver imaging).

Highest level referred to in the guidelines: ≥3b. No references comparing different modalities were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing

All twenty guidelines that recommended liver imaging also proposed a time schedule (Table 5). Ten of these (1, 2, 4, 5, 6, 7, 9, 12, 19, 21) recommended liver imaging for at least 5 years with a more frequent regimen in the first 2 to 3 years. In four guidelines (1, 2, 17, 21), a different timing was proposed for colon and rectal cancer patients.

Conclusion: Liver imaging could be performed for at least 5 years with a more frequent regimen in the first 2-3 years.

Controversy (only recommended in 10 (50%) of the 20 guidelines that recommended liver imaging).

Highest level referred to in the guidelines: ≥3b. No references comparing different time schedules for liver imaging were mentioned in the guidelines, all recommendations were based on expert opinion.

<u>Non-endoscopic pelvic imaging</u>

Role

The role of non-endoscopic pelvic imaging during follow-up was mentioned in sixteen guidelines (76%; 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17b, 18, 19, 20, 21). Although pelvic imaging aims at identifying pelvic recurrences after rectal cancer, guidelines covering colon cancer follow-up also mentioned imaging of the whole abdomen, including the pelvis, and recommended this in some cases . The Danish guideline (3) did not recommend routine performance of non-endoscopic pelvic imaging, while the SIGN guideline (14) stated that pelvic imaging may be of value, but that more evidence on the optimum approach is required. The other fourteen guidelines recommended that non-endoscopic pelvic imaging should have a role in the follow-up of CRC patients after curative intent treatment. The recommendations in the Hungarian (8), Norwegian (12), ESMO (17) and SGG (20) guidelines only applied to rectal cancer patients. In some of these guidelines, the recommendations did not apply to the following patient groups: stage I CRC (10), stage I colon cancer (21), stage I rectal cancer (2, 12), T1N0 colon cancer (2), and T1N0 rectal cancer after radical resection (20). While the Dutch (4) and EURECCA (18) guidelines recommended pelvic imaging only after local excision for rectal cancer

Conclusion: Non-endoscopic pelvic imaging should have a role in follow-up after CRC, but could be restricted to pT2N0 and stage II-III rectal cancer.

- *Stage I-III colon cancer and pT1N0 rectal cancer: Controversy (recommended in at most eight (53%) of 15 (colon) and 10 (63%) of 16 (pT1N0 rectal) guidelines that discussed this topic, which is less than two thirds of the guidelines).*
- *pT2N0 and stage II-III rectal cancer: Consensus (recommended in at least eleven (73%) of the fifteen guidelines that discussed this topic).*

Highest level referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Modality

Out of the fourteen guidelines with recommendations for pelvic imaging, eleven guidelines (2, 5, 8, 10, 11, 12, 16, 17, 19, 20, 21) stated that non-endoscopic pelvic imaging should be performed with CT, either alone or in combination with other modalities. The three remaining guidelines recommended MRI (4, 18) and ultrasound (13), rather than CT.

Conclusion: CT, whether or not in combination with other methods, is the preferred modality for the detection of pelvic recurrence.

Consensus (recommended in 11 (79%) of the 14 guidelines that discussed this topic).

Highest level referred to in the guidelines: ≥3b. No specific references for different modalities were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing

A time schedule was proposed in twelve of the fourteen guidelines that recommended pelvic imaging. There was great variation in the proposed time schedules, which are displayed in Table 6.

Conclusion: The optimum time schedule for pelvic imaging is unclear.

Controversy (No consensus on a specific time schedule)

Highest level referred to in the guidelines: ≥3b. No references comparing different time schedules for non-endoscopic pelvic imaging were mentioned in the guidelines, all recommendations were based on expert opinion.

<u>Endoscopic ultrasound</u>

Role

The use of endoscopic ultrasound in routine follow-up was mentioned in nine (43%) of the included guidelines. Seven guidelines (2, 9, 15, 18, 19, 20, 21) recommended that endoscopic ultrasound of the rectum should be part of follow-up of selected rectal cancer patients. The guidelines listed different

selection criteria for endoscopic rectal ultrasound, including: rectal cancer patients, except for pT1N0 rectal cancer patients who underwent TME (20); after local excision/TEMS or stage I rectal cancer (2, 18) or T1N0 rectal cancer (9); T1sm2–3 and T2 rectal cancers (15); rectal cancer patients with high risk (local excision of T2 or poor differentiated tumors, those with positive margins (≤1mm) and those with T4 or N2 rectal cancer) (19); and patients who did not have an abdominoperineal excision (21). The Danish (3) and the German (6) guidelines recommended not to use endoscopic ultrasound for routine follow-up.

Conclusion: Endoscopic rectal ultrasound could be considered as part of follow-up for a selected group of rectal cancer patients.

Controversy (only mentioned in nine guidelines (43%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3b (46). The evidence supports the conclusion. It showed that endoscopic ultrasound guided biopsy improved the accuracy of detecting local recurrences after rectal cancer.

Time schedule

Five of the guidelines mentioning the topic recommended a timing schedule for endoscopic ultrasound (2, 9, 15, 19, 20). All five schedules differed.

Conclusion: The optimum time schedule for endoscopic ultrasound is unclear.

Controversy (No consensus on a specific time schedule)

Highest level of evidence referred to in the guidelines: ≥3b. No references comparing different time schedules for endoscopic pelvic imaging were mentioned in the guidelines, all recommendations were based on expert opinion..

<u>Full body imaging</u>

PET-CT imaging was mentioned in fourteen guidelines (67%; 2, 3, 5, 6, 7, 8, 9, 10, 12, 15, 17, 18, 19, 21). In all of these guidelines, it was recommended that PET-CT should not be routinely performed during follow-up. Eight guidelines (2a, 5, 8, 9, 15, 17, 19, 21) stated that PET-CT can be used in case of suspicion of recurrence.

Conclusion: PET-CT should not be routinely performed during follow-up after CRC.

Consensus (recommended in 14 (100%) of the 14 guidelines that discussed this topic).

Highest level referred to in the guidelines: 1b (47). The evidence does not support the conclusion. It states that PET-CT as part of a routine follow-up strategy may lead to earlier detection of recurrent CRC.

Part 5: Endoscopy

Perioperative colonoscopy

Role

The role of perioperative colonoscopy of CRC patients was mentioned in all guidelines, except for the Hungarian (8). In all twenty guidelines, it was recommended that a complete colonoscopy should be performed after surgery, if this was not done at the time of diagnostic work-up (notably for an emergency/obstructing cancer). In the NCCN (10) and Norwegian (12) guideline, this recommendation only applied to stage II and III CRC patients. The Dutch guideline (4) stated that a complete colonoscopy should not be performed in cases where the colon segment proximal of the malignancy was also resected.

Conclusion: A complete colonoscopy should be performed after surgery, in case this was not done preoperatively.

Consensus (recommended in 18 (90%) (stage I CRC) or 20 (100%) (stage II-III CRC) of the 20 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: ≥3b. No references specifically about perioperative colonoscopy were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing

Fifteen guidelines (2, 4, 5, 6, 7, 9, 10, 12, 13, 16, 17, 18, 19, 20, 21) suggested a specific timing for the postoperative complete colonoscopy. In all of these guidelines, it was recommended to perform the colonoscopy within 3-6 months after surgery. The ESMO guideline (17) stated that in rectal cancer patients, the colonoscopy can be postponed to 1 year postoperative. In the Dutch (4), German (6), NCCN (10) and SEOM (19) guidelines, it was explicitly stated that if a complete colonoscopy has been performed postoperatively, it replaces the surveillance colonoscopy at 1 year.

Conclusion: Complete colonoscopy should be performed within 3-6 months after surgery in case this was not done at the time of diagnostic work-up.

Consensus (recommended in 15 (100%) of the 15 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: ≥3b. No references comparing different timings for the perioperative colonoscopy were mentioned in the guidelines, all recommendations were based on expert opinion.

Surveillance colonoscopy

Role

Surveillance colonoscopy was mentioned in all guidelines. All guidelines recommended that surveillance colonoscopy should be routinely performed during the follow-up of CRC patients.

Conclusion: Surveillance colonoscopy should be routinely performed during the follow-up after CRC.

Consensus (recommended in 21 (100%) of the 21 guidelines that discussed this topic).

Highest level of evidence referred to in the guidelines: 2b (48). The evidence supports the conclusion, since it shows that endoscopic surveillance is associated with improved survival.

Timing

A time schedule for surveillance colonoscopy was mentioned in all guidelines, but the proposed regimens varied widely (Table 7). Thirteen guidelines recommended that after one or two clean colonoscopies within the first five years after surgery, the interval of performing a surveillance colonoscopy should be extended to five years (2b, 4, 5, 6, 7, 9, 10, 13, 15, 16, 17, 19, 20). In six guidelines, a recommendation was made about when to cease the surveillance colonoscopy. The Danish (3) and ESMO (17) guidelines stated that surveillance colonoscopy should be performed till the age of 75, although this only applied to rectal cancer patients in the latter guideline. Other reasons to cease surveillance colonoscopy were poor general condition (4), a reasonable age (5), the presence of comorbidity (14) and a life expectancy of less than 10 years (21).

Conclusion: The optimum time schedule for surveillance colonoscopies is unclear, as well as duration of endoscopic surveillance.

Controversy (No consensus on a specific time schedule)

Highest level of evidence referred to in the guidelines: 1b (49). In a prospective randomized controlled trial published by Wang et al., it was shown that intensive colonoscopic surveillance (3-month intervals for 1 year, 6-month intervals for the next 2 years and once a year thereafter) did not improve overall survival compared to routine colonoscopic surveillance (colonoscopy at 6, 30 and 60 months postoperatively). They recommend that colonoscopy should be performed at 1 and 2 years postoperative, and the interval should be extended to 3 or 5 years thereafter.

Additional surveillance of the anastomosis after resection of rectal cancer

Role

Endoscopic inspection of the anastomosis after resection of a rectal neoplasm in addition to surveillance colonoscopy, was mentioned in eight guidelines (38%; 3, 6, 8, 9, 12, 19, 20, 21). All of

them, except for the Danish (3) and the TNCD (21), recommended endoscopy as part of routine follow-up. The German guideline (6) restricted the eligible patient group to stage II and III rectal cancer patients who had not received neoadjuvant or adjuvant radiochemotherapy. The Norwegian (12) recommendation only applied to rectal cancer patients who underwent a low anterior resection.

Conclusion: Endoscopic inspection of the anastomosis after resection of rectal cancer in addition to surveillance colonoscopy could be routinely performed during follow-up.

Controversy (only mentioned in eight guidelines (38%), which is less than half of the included papers).

Highest level of evidence referred to in the guidelines: ≥3b (50). It concludes that endoscopic surveillance of the rectum is not effective in identifying local recurrences of rectal cancer. Thus it does not support the conclusion.

Timing

Five of these guidelines (8, 9, 12, 19, 20) suggested a specific timing for endoscopic surveillance after surgical resection of rectal cancer, but no regimen was the same. In the Italian guideline (9), the proposed timing was stage dependent: a more frequent endoscopic examination was recommended for stage II and III rectal cancer patients. The SEOM recommendation (19) was risk-dependent: a more frequent endoscopic surveillance was recommended for rectal cancer patients with high-risk of local recurrence (positive circumferential resection margin, T4 or N2 cancers, and rectal cancer patients who had not received pelvic radiation).

Conclusion: The optimum timing for endoscopic surveillance of the anastomosis after rectal cancer resection is unclear.

Controversy (No consensus on a specific time schedule)

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

<u>Inspection of the scar after polypectomy and rectal preserving treatment</u>

Role

All seven guidelines that mentioned the topic also recommended that endoscopic inspection of the scar should be part of routine follow-up after polypectomy of pT1 *colon* cancer (3, 4, 6, 8, 12, 15, 20). Similarly, all ten guidelines (3, 4, 6, 8, 9, 10, 15, 18, 19, 20) that mentioned endoscopic inspection of the scar after rectal preserving treatment for *rectal* cancer, also recommended that it should be part of routine follow-up.

Conclusion: Endoscopic surveillance of the scar could play a role in follow-up after polypectomy of pT1 colon cancer and after rectal preserving treatment of rectal cancer.

- *pT1 colon cancer: Controversy (only mentioned in seven guidelines (33%), which is less than half of the included papers).*
- *Rectum preserving treatment of rectal cancer: Controversy (only mentioned in ten guidelines (48%), which is less than half of the included papers).*

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing of surveillance after polypectomy for pT1 colon cancer

Six out of seven guidelines suggested a specific timing for endoscopic surveillance. Four guidelines recommended inspection of the scar within the first 3 months after polypectomy (3, 4, 12, 20). In the German guideline (6), it was stated that the first endoscopic inspection should be performed at 6 months after polypectomy. The Hungarian guideline (8) recommended endoscopic surveillance 3 years after polypectomy. There was a substantial variation in the guidelines for timing of the endoscopic surveillance after this first inspection.

Conclusion: The first endoscopic inspection of the scar in pT1 colon cancer patients should be performed within the first 3 months after polypectomy.

Consensus (recommended in four (67%) of six guidelines).

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Timing of surveillance after rectal preserving treatment for rectal cancer

All ten guidelines suggested a specific timing for endoscopic surveillance in rectal cancer patients who underwent rectal preserving treatment. In all guidelines, except for the Hungarian (8), it was recommended to perform endoscopic inspection of the scar within the first 6 months after surgery. There was a substantial variation in the guidelines for timing of the endoscopic surveillance after this first inspection.

Conclusion: The first endoscopic inspection of the scar after rectal preserving treatment of rectal cancer should be performed within the first 6 months.

Consensus (recommended in ten (100%) of ten guidelines)

Highest level of evidence referred to in the guidelines: ≥3b. No references were mentioned in the guidelines, all recommendations were based on expert opinion.

Part 6: Survivorship after CRC -supportive care and handling of late effects

The issues of supportive care and handling of late effects were addressed in 12 guidelines (57%; 1, 3, 4, 5, 6, 10, 11, 12, 14, 15, 16, 17). Late effects mentioned in the guidelines were bowel dysfunction (low anterior resection syndrome, chronic diarrhea), stoma problems, anastomotic stenosis, adhesions, urinary and sexual problems, pain, neuropathy, fatigue, lymphedema, cognitive dysfunction, insomnia, psychosocial problems, body image issues and fear of recurrence. Five guidelines (4, 5, 6, 11, 12) had specific recommendations for the handling of late effects, whereas the ACPGBI guideline (16) had recommendations regarding supportive care in general. Proposed initiatives were structured stoma care, treatment of low anterior resection syndrome (loperamide, fiber supplement, irrigation, pelvic physiotherapy, neurostimulation), nutritional education, referral to urologist/sexologist/pelvic physiotherapist, occupational reintegration and psychosocial interventions such as treatment of fear of cancer recurrence. Five guidelines suggested that structured preventive care with health promoting initiatives should be part of supportive care to CRC survivors (5, 6, 10, 15, 16). The need for structured planning and implementation of initiatives for supportive care and handling of late effects was mentioned in all guidelines, although not explicitly stated in the German (6) and in the SIGN (14). Five guidelines proposed the utilization of a written survivorship care plan (5, 10, 15, 16, 17).
Although the topic was mentioned in half of the guidelines, there was a great variation in the extent, level of detail and focus for the mentioned recommendations and interventions within this field.

Conclusion: Handling of late effects could be part of follow-up.
Controversy (recommended in 4 (33%) of the 12 guidelines that mentioned handling of late effects).
Highest level referred to in the guidelines: 2c (51).

Discussion

This synopsis included 21 guidelines that covered follow-up after non-metastatic CRC used in countries represented in ESCP. The analysis of the recommendations showed that it is common practice to perform routine follow-up, and that several combinations of methods, modalities and time schedules are used. Consensus was reached for half of the subtopics. The evidence for approaches, methods and frequency was scarce; sufficient evidence (<3 on the OCEBM) was available for only 10 subtopics (Table 8). In the following, the results will be discussed in relation to existing and emerging evidence, and subjects for further research will be pointed out.

The main focus of this synopsis was routine follow-up with the overall purpose of improving survival after curative intent treatment of CRC. The hypothesis that routine follow-up as compared to no follow-up, improves survival is based on the assumption that surveillance leads to early detection of recurrence at a stage recurrent disease is still eligible for curative intent treatment. Colonoscopy surveillance may also detect synchronous/metachronous disease. However, whether a certain increase in intensity of follow-up still results in improvement of survival is controversial. Two meta-analyses could not demonstrate impact on survival from intensive follow-up (42,43). The first study, a Cochrane review, included eight randomized controlled trials comparing intensive follow-up to regular or minimum follow-up. A significant effect from intensive follow-up on overall survival was found, but without differences in the absolute number of recurrences or disease-specific survival (42). The same accounts for the meta-analysis performed by Tjandra et al (43). Despite a higher rate and earlier detection of asymptomatic recurrence, resulting in an increased re-resection rate for recurrent disease, no improvement of cancer-related mortality was found. The main limitations of these meta-analyses are the poor statistical power of the included trials and the clinical heterogeneity of follow-up strategies used among the different trials. Moreover, as techniques and indications to detect and treat recurrent disease have changed, and continue to change, only recent studies should be included in meta-analyses. Following this, an optimum follow-up strategy has been difficult to determine. This has led to the onset of several large randomized controlled trials comparing follow-up regimens of different intensity. Four of these have published results, and a brief overview is presented in Table 9. Results from the PRODIGE-trial are awaited (52).

The inconclusive research on the effect of intensive follow-up on survival was reflected in this synopsis, where the issue was mentioned and discussed in sixteen guidelines, without an explicit recommendation on the preferred intensity in eight of them. An updated version of the Cochrane review (2016) included fifteen studies including the FACS and GILDA trial (8). Although ten of the guidelines in this synopsis were published or updated in 2016 or 2017, none of them referred to this version. This might be explained by the lengthy development process of a guideline, and the

systematic search is likely to have taken place months or years prior to the publication date. Contrary to the previous Cochrane review, the beneficial effect of intensive follow-up on overall survival was no longer found and again no effect of intensive follow-up on disease-specific survival was reported, despite a higher rate of salvage surgery with curative intent. Similar, based on pooled data from seven randomized trials published from 1995 to 2016 comparing more intensive follow-up with contemporary follow-up, Mokhles et al. (2016) concluded that despite earlier detection of recurrence, a more intensive follow-up strategy did not result in a survival benefit (53). These findings will most certainly have its impact on the development of future guidelines. A possible explanation of this finding might be a dilution of a potential survival impact of surveillance if the majority of included patients had low-risk CRC. In addition, improved pre-operative work-up resulting in more accurate staging might have led to more metastases being detected in the pre-operative phase, rather than postoperatively during follow-up. This would implicate that future studies should focus on a more tailored approach in high risk patients, for example patients with T4 or N2 disease. On the other hand, the FACS-trial showed that although recurrence in early stage cancer was less frequent the benefit of revisional surgery was higher than in more advanced stages (6).

The components of follow-up strategies are commonly investigated in combined programs. This hampers the ability to identify and evaluate the effect of isolated aspects of follow-up on the detection of recurrence and survival. This is illustrated by the lack of sufficient evidence for more than half of the subtopics in this synopsis, especially for the preferred modality and timing.

Medical history with or without physical examination are in general considered an integrated part of routine follow-up. This was reflected in the synopsis by the substantial consensus for recommending regular clinical visits during the first five years after surgery. The highest level of evidence cited for this recommendation was the Cochrane review (42), which comprised two sub-analyses of the role and frequency of clinical visits, respectively. None of these sub-analyses showed a beneficial effect from clinical visits on recurrence or overall survival. The substantial consensus found in our synopsis suggests that there are additional purposes for the physicians to regularly see the patients in the outpatient clinics. These purposes could be to reassure and comfort the patient, and to evaluate the quality of treatment and care, besides financially related reasons depending on the local health care system. No separate analysis of clinical visits was reported in the updated version of the Cochrane review (42). A recently published non-randomized study reported that patient-initiated follow-up with no pre-scheduled visits could be an acceptable alternative to regular outpatient visits, when measured by patient satisfaction, quality of life and costs. However, survival and time to recurrence were not assessed as outcome measures (54). Emerging alternative approaches will probably add new perspectives to this issue.

The guidelines showed consensus for including CEA in routine follow-up of stage II-III patients, and consensus was also reached for a minimum range of timing for CEA measurements. However, the high-level evidence, referred to in the guidelines did not substantiate these conclusions (4,42,43,55). An association between CEA-monitoring and improved overall survival has previously been shown in two small randomized trials (56,57). More recent research with more statistical power has not been able to demonstrate this association, yet CEA seems to have a beneficial effect on time to recurrence and proportion of resectable recurrences (4,6). Another Cochrane review set out to determine the diagnostic meaning of different blood CEA levels in monitoring for CRC recurrence (55). The authors concluded that CEA is insufficiently sensitive to be used alone, even with a low threshold. The ongoing PRODIGE trial aims at evaluating the utility of CEA versus no CEA in the follow-up of resected stage II-III CRC patients. Results are expected by the end of 2018, and the primary outcome is overall survival (52).

There was no consensus for including FOBT or other laboratory tests (except CEA) in routine follow-up. Research looking into this topic is scarce, and mainly consists of old, low-evidence studies (44,58,59). Promising results have emerged from more recent research into the field of circulating tumour cells or circulating tumour DNA as biomarkers for the risk of recurrent CRC (60,61). This could yield a new method for risk-stratified surveillance of CRC in future follow-up programs, yet further research results are required.

In this synopsis, consensus was found for including chest imaging in routine follow-up for all rectal cancer patients and stage II-III colon cancer patients, with CT as preferred modality. The suggested time schedules differed, yet imaging at least annually for the first five years after surgery was recommended. Recent research supports the conclusions (62,63), even though more evidence is required in order to substantiate more firm conclusions regarding the modality and timing of chest imaging for the detection of pulmonary metastases.

Except for the SIGN guideline, all guidelines recommended to include liver imaging in routine follow-up. The evidence supporting this recommendation was the Cochrane review from Jeffery et al. (42), which found a beneficial effect from liver imaging on overall survival (OR 0.64, 95% CI 0.49 to 0.85). The updated version of the Cochrane review (8) did not report a significant difference on survival between more or less liver imaging. A limitation for conclusions regarding the independent role and timing of liver imaging is that liver imaging in these larger trials is combined with chest and pelvic imaging. The guidelines showed consensus for recommending CT as preferred modality for detecting liver metastases. Although high-level evidence for this recommendation was lacking in the guidelines, more recent research supports this conclusion (64,65).

There was consensus for recommending non-endoscopic pelvic imaging as part of routine follow-up after resection for pT2N0 and stage II-III rectal cancer. No evidence explicitly supported the recommendation in the guidelines. Research into this field does not clearly substantiate the role of routine pelvic imaging in follow-up (66). A non-systematic review looking into imaging methods for detection of locally recurrent rectal cancer suggested a more risk-stratified approach to pelvic imaging, along with more research into this topic (67).

Only few guidelines mentioned and recommended routine endoscopic rectal imaging for selected rectal cancer patients. This recommendation was supported by an observational, non-controlled study (46), and is further substantiated by evidence suggesting that endoscopic ultrasound should be offered to high-risk rectal cancer patients (68-70).

Full body imaging was mentioned in fourteen guidelines, yet none of them recommended it to be part of routine follow-up. Even although PET-CT is considered to entail high sensitivity for detecting CRC recurrence (71,72), evidence is inconclusive for incorporating the method in routine follow-up (73).

Convincing consensus for the recommendations on perioperative colonoscopy was reached, and all guidelines recommended it to be part of routine follow-up. This is presumably because of the well demonstrated benefits of adenoma removal in preventing further colorectal cancer and death from colorectal cancer (74). The specific evidence for perioperative colonoscopy is less convincing. The highest level of evidence referred to were one randomized controlled trial and one observational follow-up study (48,49). The observational study found that surveillance colonoscopy within one year after surgery was associated with improved survival (48). The RCT compared an intensive colonoscopy follow-up-timing with less intensive colonoscopy surveillance and concluded that there was minimal effect on survival from the intensive follow-up (49). Some of the more recent trials have also included colonoscopy as part of the investigated follow-up programs, although none of these concluded any beneficial effect on survival (5,6). This paucity of evidence presumably explains why there was no consensus for a specific follow-up schedule.

For the topics regarding endoscopic inspection of the scar after polypectomy and rectal preserving treatment, no consensus was reached, neither for the role or timing of such surveillance. Controversy was in all these cases due to a low number of guidelines mentioning the topic (<50%), and there were no references related to these recommendations. Even if there is extensive evidence for follow-up regimens following polypectomy in general, only few studies have looked into endoscopic surveillance after removal of malignant polyps (pT1 cancer) in the colon (75). A little more attention has been paid to the issue of follow-up after locally excised rectal cancer, due to the relatively high risk of local recurrence (70,76), and a more frequent endoscopic surveillance has been suggested (76).

The same risk of recurrence is not observed after surgical resection of rectal cancer, and the evidence supporting any value of routine rectoscopy besides routine surveillance colonoscopy is sparse. The guidelines included in this synopsis did not result in consensus for recommending routine rectoscopy, even though six guidelines did recommend it. A recent retrospective study revealed no effect from frequent rectoscopy on the detection of local recurrences from resected rectal cancer (50).

The management of late effects and delivery of supportive care as part of routine follow-up was mentioned in half of the guidelines. However, there was a great variation in the recommendations, probably reflecting that this is an emerging topic within follow-up strategies. Several studies suggest that late effects following CRC negatively impacts quality of life (77-79) and can lead to psychological distress and poor survival (80-82). This calls for implementing specific recommendations for late effects and survivorship care in the guidelines for follow-up.

This guidelines synopsis does have some limitations. There was substantial variation in the quality of the guidelines, with Agree-scores ranging from 0.08 to 0.92. Also the other quality parameters showed variation. However, none of the guidelines were excluded, as the aim of this synopsis was to display an actuarial, not a selected, view over current recommendations. Furthermore, the synopsis was challenged by the heterogeneity in the guidelines when it came to displaying and distinguishing between recommendations for colon and rectal cancer follow-up. This has possibly led to a less transparent presentation of the results than wished for.

Notwithstanding, this synopsis do present a comprehensive analysis, based on a methodology and structure known from previous guidelines synopses (83-86). Moreover, it was performed in collaboration with ESCP representatives, helping to retrieve, and in some cases translate or interpret, the content in the guidelines.

In conclusion, in currently available guidelines, consensus on the follow-up after curative intent treatment of CRC is regularly lacking and the evidence for the different methods and associated modalities and time schedules is restricted. Upcoming results from ongoing trials regarding the utility of imaging, CEA and other biomarkers might elucidate these topics further, but it is unlikely that international agreement on an optimum follow-up schedule will eventually be achieved. An overall survival impact of multimodality follow-up of a certain intensity could still not be found in most recent meta-analysis. As a consequence, this indicates the need for a more tailored and individualized approach to those patients that potentially benefit the most. Cost-effectiveness might also be optimized by reducing hospital visits with a more patient-led follow-up.

Acknowledgements

The study was endorsed by the European Society for Coloproctology Research Committee and by the Guidelines Committee. The work was funded by the European Society for Coloproctology Guidelines Committee.

List of figures and tables:

Supplementary documents:

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Table 1. Included guidelines and quality assessment

	Guideline	Institution	Year	Adequate guideline development group	Type of evidence	Adequate grading system	AGREE score
National guidelines							
1	Austrian guideline (12,13)	Österreichische Gesellschaft für Hämatologie & Onkologie	2017	No	ND	No	0.08
2	Belgian guideline	College of Oncology					
A	Colon cancer (14)		2014	Yes	SS	Yes	0.92
B	Rectal cancer (15)		2007	Yes	SS	Yes	0.67
3	Danish guideline (16)	Sundhedsstyrelsen	2015	No	ND	No	0.17
4	Dutch guideline (17)	Integraal Kankercentrum Nederland	2014	Yes	SS	Yes	0.83
5	French guideline (18)	Haute Autorité de Santé, Institut National du Cancer	2012	Yes	SS	No	0.67
6	German guideline (19)	Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft und Deutschen Krebshilfe	2017	Yes	SS	Yes	0.83
7	Greek and Cypriot guideline (20,21)	Hellenic Society of Medical Oncologists	2016	Yes	EO	Yes	0.42
8	Hungarian guideline (22)	Az Egészségügyi Minisztérium	2012	No	EO	Yes	0.42
9	Italian guideline (23)	Società Italiana di Chirurgia Colo-Rettale	2011	No	ND	No	0.17
10	NCCN guideline (24,25)	National Comprehensive Cancer Network	2017	Yes	SS	No	0.83
11	NICE guideline (26)	National Institute for Health and Care Excellence	2014	Yes	SS	Yes	0.83
12	Norwegian guideline (27)	Helsedirektoratet	2017	Yes	SS	No	0.67
13	Russian guideline (28,29)	Ассоциации онкологов России	2014	No	ND	No	0.17
14	SIGN guideline (30)	Scottish Intercollegiate Guidelines Network	2011	Yes	SS	Yes	0.83
15	Swedish guideline (31)	Regionala cancercentrum i samverkan	2016	Yes	EO	Yes	0.50
Guidelines from professional societies							
16	ACPGBI guideline (32)	Association of Coloproctology of Great Britain and Ireland	2017	Yes	SS	Yes	0.58
17	ESMO guideline	European Society for Medical Oncology working group					
a	Colon cancer (33)		2013	No	EO	Yes	0.67
b	Rectal cancer (34)		2017	Yes	EO	Yes	0.58
18	EURECCA (35,36)	European Registration of Cancer Care	2013	Yes	EO	No	0.58
19	SEOM-SERAM Consensus	Sociedad Española de Oncología Médica/Sociedad Española de Radiología	2016	No	EO	No	0.33

	Paper (37,38)	Médica					
20	SGG guideline (39)	Société Suisse de Gastro-entérologie	2014	No	EO	No	0.33
21	TNCD guideline	Thésaurus National de Cancérologie Digestive					
a	Colon cancer (40)		2016	No	SS	No	0.42
b	Rectal cancer (41)		2016	No	SS	No	0.42

EO, expert opinion; SS, systematic search; ND, not describe

Table 2. Clinical visits during the first five years after primary surgery

Guidelines	**Months after surgery**																
	<4-6 weeks	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
2. Belgian guideline																	
a. Colon cancer	x	x	x	x	x	x	x	x	x		x		x	x	x	x	x
b. Rectal cancer		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
3. Danish guideline	Not recommended																
4. Dutch guideline[1]			x		x		x		x				x		x		x
5. French guideline		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
6. German guideline			x		x		x		x				x		x		x
7. Greek and Cypriot guideline		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8 Hungarian guideline		x	x	x	x	x	x	x	x		x		x	x	x		
9. Italian guideline[2]	x	x 4mo		x_{8mo}	x	x_{16mo}		x_{20mo}	x		x		x	x	x	x	x
10.NCCN[1]			x		x		x		x		x		x	x	x	x	x
11. NICE guideline (UK)	No timing recommended except from an initial postoperative visit																
12. Norwegian guideline	x		x		x		x		x		x		x		x		x
13. Russian guideline			x		x				x				x		x		x
14. SIGN guideline (Scotland)	No recommendation for time schedule																
15. Swedish guideline	No timing recommended except from an initial postoperative visit																
16. ACPGBI guideline	No timing recommended																
17. ESMO guideline																	
a. Colon cancer[1]			x		x		x		x		x		x		x		x
b. Rectal cancer			x		x		x		x								
18. EURECCA	No recommendation for time schedule																
19. SEOM-SERAM Consensus Paper[1, 3]		x	x	x	x	x	x	x	x		x		x	x	x	x	x
20. SGG		x	x	x	x		x		x		x		x		x		x
21. TNCD guideline																	
a. Colon cancer		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
b. Rectal cancer		x	x	x	x	x	x	x	x		x		x	x	x	x	x

[1]*The least frequent timing from the recommendation is stated.*
[2]*Less frequent timing for stage 1 cancers (and other low-risk cancers). The less frequent timing does not apply after local excision for rectal cancer*
[3]*For rectum cancer patients: every 3-6 months for 3 years, then every 6 months until 5 years*

Table 3. CEA measuring during the first five years after primary surgery

Guidelines	**Months after surgery**																
	<4-6 weeks	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
2. Belgian guideline																	
c. Colon cancer	x	x	x	x	x	x	x	x	x		x		x	x	x	x	x
d. Rectal cancer		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
3. Danish guideline	Not recommended																
4. Dutch guideline[1]			x		x		x		x		x		x	x	x	x	x
5. French guideline	CEA measurement is optional, proposed timing: every 3 months for 3 years.																
6. German guideline			x		x		x		x				x		x		x
7. Greek and Cypriot guideline		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
8 Hungarian guideline		x	x	x	x	x	x	x	x		x		x	x	x		
9. Italian guideline[2]	x	x 4mo		x8mo	x	x16mo		x20mo	x		x		x	x	x	x	x
10.NCCN[1]			x		x		x		x		x		x	x	x	x	x
11. NICE guideline (UK)			x		x		x		x		x		x				
12. Norwegian guideline	x		x		x		x		x		x		x		x		x
13. Russian guideline		x	x	x	x	x	x	x	x		x		x	x	x	x	x
14. SIGN guideline (Scotland)	No recommendation for time schedule																
15. Swedish guideline	x				x								x				
16. ACPGBI guideline			x		x		x		x		x		x				
17. ESMO guideline																	
c. Colon cancer			x		x		x		x		x		x		x		x
d. Rectal cancer			x		x		x		x		x		x				
18. EURECCA	No recommendation for time schedule																
19. SEOM-SERAM Consensus Paper[1, 3]		x	x	x	x	x	x	x	x		x		x	x	x	x	x
20. SGG		x	x	x	x		x		x		x		x		x		x
21. TNCD guideline																	
c. Colon cancer	CEA measurement is optional, proposed timing: every 3 months for 3 years.																
d. Rectal cancer	CEA measurement is optional, proposed timing: every 3 months for 3 years.																

[1]*The least frequent timing from the recommendation is stated.*
[2]*Less frequent timing for stage 1 cancers (and other low-risk cancers). The less frequent timing does not apply after local excision for rectal cancer*
[3]*For rectum cancer patients: every 3-6 months for 3 years, then every 6 months until 5 years*

Table 4. Chest imaging during the first five years after primary surgery

Guidelines	**Months after surgery**																
	4-6 weeks	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline[a]			x		x		x		x		x		x		x		x
2. Belgian guideline																	
a. Colon cancer	x		x		x		x		x				x		x		x
b. Rectal cancer[b]			x		x		x		x		x		x		x		x
3. Danish guideline					x								x				
4. Dutch guideline	No timing recommended.																
5. French guideline					x				x				x		x		x
6. German guideline		x			x				x				x		x		x
7. Greek and Cypriot guideline*					x				x				x		x		x
8 Hungarian guideline			x		x		x		x				x		x		
9. Italian guideline					x				x				x		x		x
10. NCCN*					x				x				x		x		x
11. NICE guideline (UK)	At least twice during the first three years after primary surgery.																
12. Norwegian guideline					x				x				x		x		x
13. Russian guideline*					x				x				x		x		x
14. SIGN guideline (Scotland)	No timing recommended.																
15. Swedish guideline					x								x				
16. ACPGBI guideline	At least twice during the first three years after primary surgery.																
17. ESMO guideline																	
a. Colon cancer*					x				x				x				
b. Rectal cancer	At least twice during the first three years after primary surgery.																
18. EURECCA					x				x				x		x		x
19. SEOM-SERAM*					x				x				x		x		x
20. SGG					x				x				x		x		x
21. TNCD guideline																	
a. Colon cancer					x				x				x		x		x
b. Rectal cancer		x	x	x	x	x	x	x	x		x		x	x	x	x	x

**The least frequent timing from the recommendation is stated.*

[a]*Colon cancer patients: annually during the first three years after primary surgery.*

[b]*Stage I patients: every six months during the first three years after primary surgery.*

Table 5. Liver imaging during the first five years after primary surgery

Guidelines	**Months after surgery**																
	4-6 weeks	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline[a]			x		x		x		x		x		x		x		x
2. Belgian guideline																	
a. Colon cancer	x		x		x		x		x				x		x		x
b. Rectal cancer[b]			x		x		x		x		x		x		x		x
3. Danish guideline					x								x				
4. Dutch guideline*			x		x				x				x		x		x
5. French guideline*			x		x		x		x		x		x	x	x	x	x
6. German guideline		x[c]	x		x		x		x				x		x		x
7. Greek and Cypriot guideline*					x				x				x		x		x
8. Hungarian guideline			x		x		x		x				x		x		
9. Italian guideline	Every four months during the first two years, then every six months till five years after primary surgery.																
10.NCCN*					x				x				x		x		x
11. NICE guideline (UK)	At least twice during the first three years after primary surgery.																
12. Norwegian guideline			x		x		x		x		x		x		x		x
13. Russian guideline*			x		x		x		x		x		x	x	x	x	x
14. SIGN guideline (Scotland)	No timing recommended.																
15. Swedish guideline					x								x				
16. ACPGBI guideline	At least twice during the first three years after primary surgery.																
17. ESMO guideline																	
a. Colon cancer*					x				x				x				
b. Rectal cancer	At least twice during the first three years after primary surgery.																
18. EURECCA					x				x				x		x		x
19. SEOM-SERAM*					x				x				x		x		x
20. SGG					x				x				x		x		x
21. TNCD guideline					x				x				x		x		x
a. Colon cancer*			x		x		x		x		x		x	x	x	x	x
b. Rectal cancer		x	x	x	x	x	x	x	x		x		x	x	x	x	x

**The least frequent timing from the recommendation is stated.*

[a]*Colon cancer patients: annually during the first three years after primary surgery.*

[b]*Stage I patients: every six months during the first three years after primary surgery.*

[c]*Only for rectal cancer patients.*

Table 6. Pelvic imaging during the first five years after primary surgery

Guidelines	**Months after surgery**																
	4-6 weeks	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline	Not recommended.																
2. Belgian guideline																	
a. Colon cancer	x		x		x		x		x				x		x		x
b. Rectal cancer					x				x				x				
3. Danish guideline	Not recommended.																
4. Dutch guideline	Not recommended.																
5. French guideline			x		x		x		x		x		x	x	x	x	x
6. German guideline	Not recommended.																
7. Greek and Cypriot guideline	Not recommended.																
8 Hungarian guideline			x		x				x				x		x		
9. Italian guideline	Not recommended.																
10. NCCN*					x				x				x		x		x
11. NICE guideline (UK)	At least twice during the first three years after primary surgery.																
12. Norwegian guideline			x														x
13. Russian guideline*			x		x		x		x		x		x	x	x	x	x
14. SIGN guideline (Scotland)	No timing recommended.																
15. Swedish guideline	Not recommended.																
16. ACPGBI guideline	At least twice during the first three years after primary surgery.																
17. ESMO guideline																	
a. Colon cancer	Not recommended.																
b. Rectal cancer	At least twice during the first three years after primary surgery.																
18. EURECCA	No timing recommended.																
19. SEOM-SERAM Consensus Paper*					x				x				x		x		x
20. SGG					x				x				x		x		x
21. TNCD guideline																	
a. Colon cancer*			x		x		x		x		x		x	x	x	x	x
b. Rectal cancer		x	x	x	x	x	x	x	x		x		x	x	x	x	x

**The least frequent timing from the recommendation is stated.*

Table 7. Perioperative and surveillance colonoscopy during the first five years after primary surgery

Guidelines	**Months after surgery**															
	Perioperative	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
1. Austrian guideline[1]	x			x										x		
2. Belgian guideline																
e. Colon cancer	x			x												x
f. Rectal cancer	x			x										x[2]		
3. Danish guideline	x															x
4. Dutch guideline	x			x[3]								x[2]				
5. French guideline	x											x[2]				
6. German guideline	x			x[2,3]												
7. Greek and Cypriot guideline	x											x[2]				
8 Hungarian guideline				x				x				x		x		
9. Italian guideline	x			x										x[4]		
10. NCCN	x			x[3]										x[2]		
11. NICE guideline (UK)	x			x[4]												
12. Norwegian guideline	x															x
13. Russian guideline	x			x								x[2]				
14. SIGN guideline (Scotland)	x															x[2]
15. Swedish guideline	x											x[2]				
16. ACPGBI guideline	x			x[2]												
17. ESMO guideline																
e. Colon cancer[5]	x			x[2]												
f. Rectal cancer	x															x[2]
18. EURECCA[5]	x	Consider a surveillance colonoscopy[6]														
19. SEOM-SERAM Consensus Paper[5]	x													x[7]		
20. SGG	x			x										x[2]		
21. TNCD guideline																
e. Colon cancer	x											x				x
f. Rectal cancer	x											x				

[1] *Other recommendations for rectal cancer: perioperative colonoscopy at 12 and 36 months.*
[2] *If this is normal, then colonoscopy every five years*
[3] *If complete colonoscopy is performed postoperatively, the 1-year colonoscopy is skipped*
[4] *If negative then repeat after 5 years*
[5] *The least frequent timing from the recommendation is stated.*
[6] *Other recommendations for rectal cancer: colonoscopy at 3 years after resection and then, if normal, once every 5/6 years thereafter.*
[7] *Other recommendations for rectal cancer: Full colonoscopy one year after surgery. Repeat examination in 3 years for patients without adenomas.*

Table 8. Subtopics, consensus/controversy and highest level of evidence for the subtopics

Main topic	Subtopic	Consensus/Controversy	Highest level of evidence referred in the guidelines
General aspects	Criteria for offering patients structured follow-up	Consensus	≥3b (no references)
	Intensity of follow-up	Controversy	1a (12,13)
	Individual termination of follow-up	Controversy	≥3b (no references)
	Coordination of follow-up	Controversy	≥3b (no references)
Clinical visits	Should play a role in follow-up	Consensus	1a (12)
	Time schedule	Consensus	≥3b (no references)
Laboratory tests			
CEA	Role	Consensus (stage II-III CRC)	1a (12,13)
	Time schedule	Consensus	1b (4)
FOBT	Role	Controversy	≥3b (14)
Other lab-tests	Role	Controversy	≥3b (no references)
Imaging			
Chest imaging	Role	Consensus (stage II-III CC and stage I-III RC)	2b (15)
	Modality	Consensus	≥3b (no references)
	Time schedule	Consensus	≥3b (no references)
Liver imaging	Role	Consensus (stage II-III CC and stage I-III RC)	1a (12)
	Modality	Consensus	≥3b (no references)
	Time schedule	Controversy	≥3b (no references)
Pelvic imaging (non-endoscopic)	Role	Consensus (stage II-III RC)	≥3b (no references)
	Modality	Consensus	≥3b (no references)
	Time schedule	Controversy	≥3b (no references)
Pelvic imaging (endoscopic)	Role	Controversy	≥3b (16)
	Time schedule	Controversy	≥3b (no references)
Full body imaging	Role	Consensus	1b (17)
Endoscopy			
Perioperative colonoscopy	Role	Consensus	≥3b (no references)
	Time schedule	Consensus	≥3b (no references)
Surveillance colonoscopy	Role	Consensus	2b (18)
	Time schedule	Controversy	1b (19)
Inspection of the scar after polypectomy	Role	Controversy	≥3b (no references)
	Time schedule	Controversy	≥3b (no references)
Inspection of the anastomosis after rectal resection	Role	Controversy	1b (19)
	Time schedule	Controversy	≥3b (no references)
Inspection of the scar after rectal preserving treatment	Role	Controversy	≥3b (no references)
	Time schedule	Controversy	≥3b (no references)

Table 9. Overview of recent major randomized trials regarding intensive versus less intensive follow-up after curative intent treatment of CRC.

	Intervention/comparison	Main results
FACS (6) **(n=1202)**	**1. CEA follow-up:** CEA every 3 months for 2 years, then every 6 months for 3 years, with a CT scan of the chest, abdomen, and pelvis at 12-18 months if requested at study entry by hospital clinician. **2. CT follow-up:** CT scan of the chest, abdomen, and pelvis every 6 months for 2 years, then annually for 3 years, and colonoscopy at 2 years. **3. CEA and CT follow-up:** both CEA and CT follow-up as described above, and colonoscopy at 2 years. **4. Minimum follow-up:** no scheduled follow-up except a single CT scan of the chest, abdomen, and pelvis at 12-18 months if requested at study entry by the hospital clinician.	• Recurrence was detected in 199 patients (16,6%) of which 71 patients were treated with curative intent. • Surgical treatment of recurrence with curative intent was 2.3% in the minimum follow-up group. Compared with minimum follow-up, the absolute difference in the percentage of patients treated with curative intent was: o 4.4% in the CEA group (adjusted OR, 3.00; 95% CI, 1.23-7.33) o 5.7% in the CT group (adjusted OR, 3.63; 95% CI, 1.51-8.69) o 4.3% in the CEA+CT group (adjusted OR 3.10, 95% CI, 1.10-8.71) • The number of deaths was not significantly different in the more intensive follow-up groups compared with minimum follow-up.
GILDA (5) **(n=1228)**	**Intensive follow-up** • Clinical visits, FBC, CEA and CA 19-9 every 4 months for 2 years, then every 6 months for 2 years and then annually for 1 year. • Chest X-ray and colonoscopy annually for 5 years. • Liver ultrasound at 4, 8, 12, 16, 24, 36, 48 and 60 months. *Additional for RC patients:* proctoscopy at 4 and 8 months, CT-scan of the abdomen and pelvis at 4, 12, 24 and 48 months. **Minimum follow-up** • Clinical visits and CEA every 4 months for 2 years, then every 6 months for 2 years and then annually for 1 year. • Liver ultrasound at 4 (colon cancer) or 8 (rectal cancer) and 16 months. • Colonoscopy at 12 and 48 months. *Additional for RC patients*: proctoscopy at 4 months, chest X-ray at 12 months.	• Recurrence was detected in 250 patients (20.4%). • A significant difference in mean disease-free survival between the intensive and minimum follow-up groups was found (5.9 months, 95% CI, 2.71-9.11). • No significant difference in overall survival between the intensive and minimum follow-up groups was found. • Health-related quality of life scores did not differ between the groups
CEA Watch (4) **(n=3223)**	**Experimental group** • CEA every 2 months for 3 years, then every 3 months for 2 years. o Repeated at 1 month if the absolute CEA value was >2.5 ng/mL and increased by 20% since the previous measurement. o If a consecutive rise was observed, a CT scan of chest and abdomen was advised. • Outpatient clinic visit, imaging of the chest and abdomen annually for 3 years.	• Recurrence was detected in 243 patients (7.5%). • In the experimental group (compared to the control group): o A higher proportion of recurrences was detected (OR, 180, 95% CI, 1.33-2.50); o A higher proportion of recurrences that could be treated with curative intent was higher (OR, 2.84, 95% CI, 1.38-5.86); o A shorter time to detection of recurrence was shorter (HR, 1.45, 95% CI,

	Intervention/comparison	Main results
	Control group • CEA every 3-6 months for 3 years, then annually for 2 years. • Outpatient clinic visit, liver ultrasound and chest X-ray every 6 months for 3 years, then annually for 2 years.	1.08-1.95). • No significant difference in disease-specific or overall survival was found between the two groups.
COLOFOL (7) **n=2509**	**Intensive follow-up** • CT-thorax and abdomen at 6, 12, 18, 24 and 36 months after surgery • CEA at 6, 12, 18, 24 and 36 months after surgery **Minimum follow-up** • CT-thorax and abdomen at 12 and 36 months after surgery • CEA at 12 and 36 months after surgery	• No significant difference between the two groups in 5-year overall mortality rate ($p = 0.43$), 5-year colorectal cancer–specific mortality rate ($p = 0.52$) and colorectal cancer–specific recurrence rate ($p = 0.15$).

CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; FBC, full blood count; HR, hazard ratio; OR, odds ratio; RC, rectal cancer.

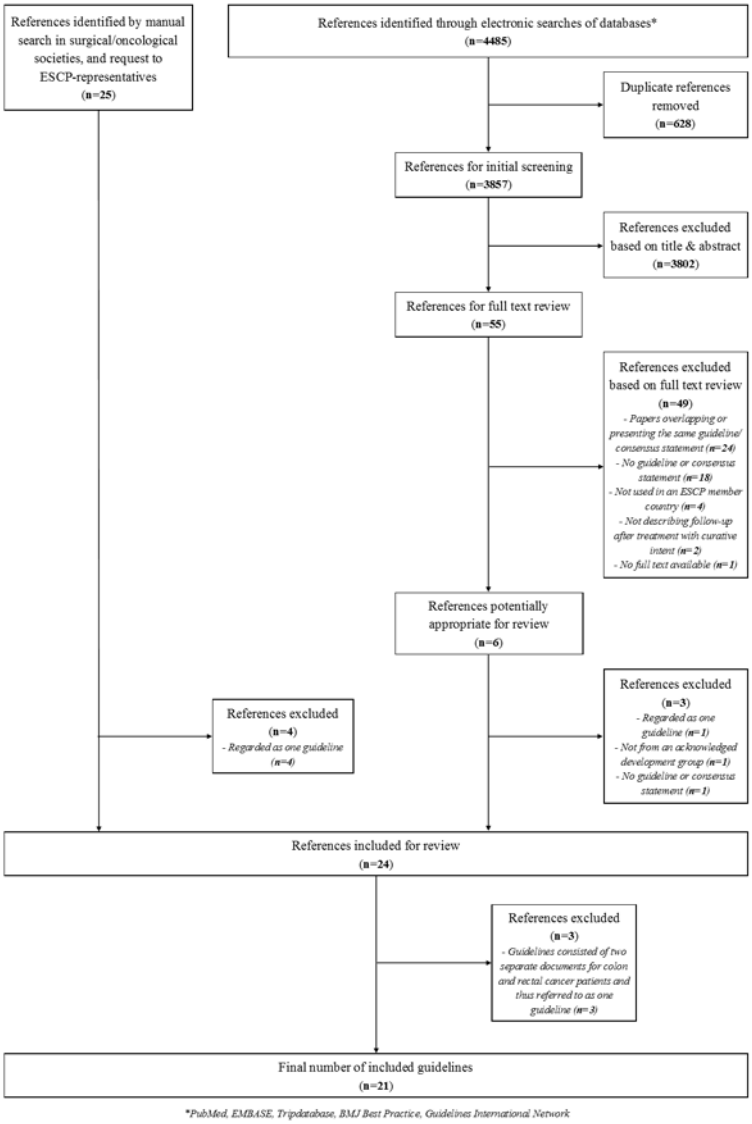

Figure 1. Selection process for guidelines for follow-up after curative intent treatment of CRC

SUPPORTING INFORMATION: APPENDIX 1

Search strategy

The search will be structured with the stated purpose as the pivot. Thus search topics will include the following main themes: *guidelines/consensus, follow-up* and *primary colorectal cancer* (see Table 1). The initial systematic search will be performed to identify regional, national and European guidelines and consensus documents regarding follow-up after rectal cancer treatment in the medical databases PubMed and Embase.

Furthermore, the search will be extended into guideline databases, including Tripdatabase, BMJ Best Practice and Guidelines International Network.

Finally, websites of national health authorities, as well as surgical and oncological societies will be searched.

The three mentioned main themes will be combined by Boolean operators: "OR" (within themes), and "AND" (between themes) (See Table 1).

The search will be limited to publication date: no older than 01.01.2007.

Table 1: Search strategy for medical and guideline databases

	Theme 1 Guidelines	**Theme 2 Follow-up**	**Theme 3 Colorectal cancer**
PubMed [Publication Type]	uideline actice Guideline Consensus Development Conference, NIH	Aftercare Case Management	Colorectal Neoplasms Rectal Neoplasms
PubMed [MeSH] The search for MeSH-terms was performed on March 16, 2017.	Guidelines as Topic Health Planning Guidelines Consensus Consensus Development Conferences, NIH as topic Evidence-Based Medicine		
PubMed Title and Abstract [tiab]	Consensus Evidence Based Medicine Guideline* Best practice*	Aftercare After Care Follow Up Care Case Management Follow up Routine control Control programme	Colorectal Neoplasm* Colorectal Tumor* Colorectal Tumour* Colorectal Carcinoma* Colorectal Cancer* Rectal Neoplasm* Rectum Neoplasm* Rectal Tumor* Rectal Tumour* Cancer of Rectum Rectum Cancer* Rectal Cancer* Cancer of the Rectum Neoplasm of the Rectum
Embase	'Practice guideline'/exp	'Aftercare'/exp	'Colorectal cancer'/exp

(Emtree) The search for terms in Emtree was performed on March 17, 2017	’Consensus’/exp ‘Consensus Development’/exp 'Evidence based medicine'/exp	’Case Management’/exp ‘Follow up’/exp	
Embase - freetext(.ti,ab,kw)	actice Guideline uideline* ealth Planning Guidelines nsensus nsensus Development idence Based Medicine Best practice*	Aftercare After Care Follow Up Care Case Management Follow up Routine control Control programme	Colorectal Cancer* Colorectal Carcinoma* Colorectal Neoplasm* Colorectal Tumor* Colorectal Tumour* Colon Tumor* Colon Carcinoma* Colon Cancer* Rectum Tumor* Rectum Carcinoma* Rectum Cancer* Rectal Neoplasm* Rectal Tumor* Rectal Tumour* Rectal Cancer* Cancer of Rectum Cancer of the Rectum Neoplasm of the Rectum
Tripdatabase	Free-text search: 'Guidelines colorectal cancer follow-up'		
BMJ Best Practice	Free-text search: 'Follow-up colorectal cancer'		
Guidelines International Network	Free-text search: 'Follow-up colorectal cancer'		

SUPPORTING INFORMATION: APPENDIX 2

Representation in the guideline development groups

		Oncologist				
	Surgeon	**Medical oncologist**	Radiation oncologist	Gastro-enterologist	**Radiologist**	Pathologist
1. Austrian	X	X	X	X		
2a. Belgian colon	X	X		X	X	X
2b. Belgian rectum	X	X	X	X	X	X
3. Danish	X	X				
4. Dutch	X	X	X	X	X	X
5. French	X	X	X	X	X	X
6. German	X	X	X	X	X	X
7. Greek & Cypriot	X	X	X	X	X	X
8. Hungarian	No authors specified					
9. Italian	X					
10. NCCN	X	X	X	X	X	X
11. NICE	X	X		X	X	X
12. Norwegian	X	X	X		X	X
13. Russian		X	X	X	X	
14. SIGN	X	X	X	X	X	X
15. Swedish	X	X	X		X	X
16. ACPGBI	X	X	X		X	X
17a. ESMO colon	X	X	X			
17b. ESMO rectum	X	X	X		X	
18. EURECCA	X	X	X		X	X
19. SEOM		X			X	
20. SGG				X		
21a. TNCD colon	X	X		X		X
21b. TNCD rectum	X	X	X	X		X

SUPPORTING INFORMATION: APPENDIX 3

Authors' comments on the quality of the included guidelines

	Guideline	Author comments
1	Austrian guideline	Brief, although a clear presentation of recommendations. No link to evidence. No description of scope and methodology.
2a	Belgian guideline, colon	Well described scope and methodology. Clear presentation of recommendations and accordingly evidence.
2b	Belgian guideline, rectum	Well described methodology, recommendations and evidence. Although lack of implementation strategy.
3	Danish guideline	Clear scope, and brief presentation of recommendations. Deficient description of the methodology.
4	Dutch guideline	Well described scope, recommendations and applicability. No specified search strategy and selection process
5	French guideline	Clear presentation of recommendations. No description of selection of literature and grading system.
6	German guideline	Well described scope and methodology. Clear presentation of recommendations and accordingly evidence.
7	Greek and Cypriot guideline	Clear presentation of recommendations. No description of search strategy and selection process.
8	Hungarian guideline	Clear scope and presentation of recommendations. Deficient description of the methodology.
9	Italian guideline	Clear presentation of recommendations. Deficient description of scope and methodology.
10	NCCN guideline	Well described methodology, recommendations and evidence. Although lack of implementation strategy.
11	NICE guideline	Well described methodology, recommendations and evidence. Although lack of implementation strategy.
12	Norwegian guideline	Clear scope and presentation of recommendations. No description of search strategy and selection process
13	Russian guideline	Clear presentation of recommendations. Deficient description of scope and methodology.
14	SIGN guideline	Clear description of scope and methodology, except for the selection process. Sufficient, but not really specified, description of recommendations.
15	Swedish guideline	Well described scope and economic evaluation. No description of search strategy and selection process, unclear presentation of recommendations.
16	ACPGBI	Clear presentation of recommendations. Adequate, but not transparent, search strategy and selection process. No implementation strategy.
17a	ESMO guideline, colon	Clear presentation of recommendations. Adequate, but not transparent methodology. No implementation strategy.
17b	ESMO guideline, rectum	Clear presentation of recommendations. Adequate, but not transparent methodology. No implementation strategy.
18	EURECCA consensus paper	Clear scope. Adequate, but not transparent presentation of recommendations. Poor description of methodology.
19	SEOM/SERAM consensus	Clear scope and presentation of recommendations. Poor description of methodology. No implementation strategy.

	paper	
20	SGG guideline	Clear scope and presentation of recommendations. Poor description of methodology. No implementation strategy.
21a	TNCD guideline, colon	Clear presentation of recommendations. Systematic search strategy, but weak description of methodology in general.
21b	TNCD guideline, rectum	Clear presentation of recommendations and grading the evidence. No clear description of search strategy and selection process.