Post-treatment surveillance in colorectal cancer patients: how to do it? A comprehensive review

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Post-treatment surveillance in colorectal cancer patients: how to do it? A comprehensive review

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Abstract

Patients who undergo a potentially curative treatment of colorectal cancer are at risk of local recurrences, distant metastases and metachronous neoplasms. Accordingly, these patients typically undergo a multimodal oncological surveillance aimed to detect relapses early, expecting a higher rate of radical re-treatments and better overall survival. Despite much research the optimal diagnostic panel and the intensity of surveillance have not been well established. Evidence indicate, however, that more intensive follow-up is unlikely to improve survival after a curative colorectal cancer surgery, chiefly due to the uncommonness of recurrences suitable for salvage treatment. A typical surveillance recommended by guidelines include regular physical examinations, computed tomography scans, serum carcinoembryonic antigen monitoring, and colonoscopies. The object of this comprehensive review is to discuss different patterns of relapses observed in colorectal cancer patients, present diagnostic options, and summarize different strategies and recommendations of the posttreatment surveillance.

Keywords: cancer, colorectal, follow-up, recurrence, surveillance.
Introduction

Colorectal cancer (CRC) with global annual incidence of 1.8 million constitutes the 3rd most common malignancy worldwide, and its incidence is expected to rise in near future [1]. 40% of CRC patients are diagnosed with localized disease (stage I or II), 35% with advanced locoregional disease (stage III), and the remainder with metastatic CRC (stage IV) upfront [2]. Owing to implementation of national screening programs number of patients diagnosed with early CRC has increased in many countries. Long-term outcomes have also improved by better diagnostic evaluation, progress in surgical and radiotherapeutic techniques, and use of adjuvant therapy. Consequently, an intent-to-cure treatment can be performed in the majority of stage I-III CRC patients, and in selected individuals with oligometastatic disease. Nevertheless, a substantial number of CRC patients develop recurrence. Recurrence rates are estimated at 10% in stage I-IIA, 36% in stage IIB-III [3, 4], and 73-78% in metastatic CRC after a curative-intent treatment [5, 6]. High incidence of recurrences warrants a long-term oncological surveillance.

The rationale behind the posttreatment follow-up is the concept that earlier detection of recurrence may provide a survival advantage. Thus, the direct aim is to capture patients with early stage, often asymptomatic recurrences, in whom a curative treatment may be performed. It estimated that up to 28-47% of patients with stage I-III CRC who underwent curative-intent treatment may be amendable for a salvage operation for a single-site recurrence [4]. Treatment of recurrences that are less advanced, smaller, involving fewer anatomical sites, associates with less extensive procedures, lower morbidity and better long-term survival [7, 8]. 5-year survival for highly selected patients who undergo a successful complete resection of single-site liver, pulmonary and peritoneal recurrences, are 34-56%, 43-71%, and 30%, respectively [7, 9, 10]. Apart from the detection of curable recurrences, surveillance may produce additional health benefits, such as detection of metachronous
neoplasms, and a better management of treatment-related toxicities or comorbidities. Yet, since not all patients develop a recurrence or have a relapse suitable for a radical handling, it is estimated that between 15 and 50 CRC patients must be surveilled to detect one case eligible for a radical re-treatment [11]. Additionally, the possible follow-up benefits may be counterbalanced by costs and institutional burden associated with frequent tests, harms related to investigations (e.g. radiation exposure, endoscopy complications), physical discomfort, and psychological stress linked to false-positive findings [12].

The aim of this article is to review strategies and controversies regarding surveillance after a modern-day CRC curative treatment (including resection, and adjuvant or neoadjuvant therapy, when applicable). It discusses different recurrence patterns that should be considered, summarizes evidence for use of particular diagnostic tests, analyzes data against intensive follow-up, and presents guidelines endorsed by oncological societies. It should be noted that the review covers sporadic CRC only, and the surveillance of patients with hereditary CRC predispositions is not discussed.

**Recurrence patterns**

CRC patients may experience diverse recurrence types (Figure 1):

i) Anastomotic: intraluminal or extramural;

ii) Locoregional other than anastomotic: involving the region of primary tumor;

iii) Metastatic.

Besides the detection of CRC recurrences, surveillance may also capture other neoplasms that impact long-term outcomes:

i) Synchronous colorectal neoplasms (adenomas and cancers);
ii) Metachronous colorectal neoplasms;

iii) Non-CRC primary malignancies.

Anastomotic recurrence

Anastomotic recurrence (AR) is defined as a recurrence involving the proximity of the bowel anastomosis. This entity shall be distinguished from other types of local relapses due to its frequent luminal character, higher resectability, and the role of endoscopy in their detection. A few mechanisms of the AR pathogenesis are postulated: incomplete resection of tumor margins, implantation of exfoliated cancer cells into the operated site, or metachronous carcinogenesis in the epithelium neighboring the primary CRC [13].

A recent meta-analysis identified a cumulative AR incidence of 2.7% (5.46% in rectal, 1.95% in colon cancer) [14]. 70.5% of AR are detected within the first 2 years, 90.8% within 3 years, and 94.5% within 5 years after treatment [14]. 5-year overall survival (OS) survival in patients experiencing AR ranges from 20.7 to 49.7% [13, 15]. Survival rates after AR are similar for colon and rectal cancers [13], and are better than in other types of recurrences [15]. Potentially curative retreatments of AR are frequent, with R0 resections attainable in 40-68% cases [8, 13, 16]. Curative resections improve 5-year survival (44% in complete resection group, and 0% in palliative resection group in one study), and are more achievable in intraluminal relapses, which associate with a better survival than extramural lesions [17].

Non-anastomotic locoregional recurrence

Since in colon cancer a large fraction of non-anastomotic locoregional recurrences (N-A LR) coincide with distant metastasis (48-80%), isolated N-A LR are rare affecting 1-3% patients [18, 19]. N-A LR may be categorized into several patterns: mesenteric/nodal, retroperitoneal, and peritoneal [8]. In a colon cancer study a radical resection could be
achieved in only 7%, 8% and 12% for each recurrence type, respectively, what contributed to worse patients’ survival than in individuals with isolated AR [8]. In colon cancer a local recurrence is observed after median 13 months after surgery (range 2-71 months) [19].

In rectal cancer N-A LR manifest as pelvic recurrences (PR), relapses originating from the tumor bed, regional lymph nodes or adjoining structures with or without pelvic invasion of the bowel wall [20]. PR affect 4-8% patients of rectal cancer patients, and median to time to pelvic recurrence is relatively long (15 to 24.7 months) [20-22]. While introduction of total mesenteric excision (TME) and preoperative (chemo)radiotherapy has reduced the incidence of locoregional recurrence, the nature and prognosis of PR has changed as well. In historical reports PR could be removed in 30-50% cases, however currently, in the age of TME and neoadjuvant radiotherapy, PR are more challenging to manage (in one report only ca. 20% were resectable) [16, 20].

**Distant metastasis**

In addition to 25% of CRC patients who are diagnosed with synchronous metastasis, one fifth develop metachronous distant spread [23, 24]. The most frequent site of metastasis is liver (60-65%), follow by lung (39-43%), extra-regional lymph nodes (16-22%), peritoneum (11-19%), bone (9%), and brain (8%) [23, 24]. Over half of patients develop metastases at more than 1 site [24]. 85% of metachronous metastases are diagnosed within 3 years, with the median time to diagnosis of 17 months [3, 23, 24]. 5-year survival of patients with a single site metachronous metastasis is ca. 15%, and less than 5% when metastases are present at two or more sites [24]. About 10% of patients with metachronous distant spread are eligible for a potentially curative metastatectomy, which may improve 5-year OS rates up to 60% in highly selected patients [24].

**Synchronous and metachronous colorectal neoplasms**
Synchronous colorectal neoplasms (adenomas and carcinomas) are present in about one-third of CRC patients: 2.2-6.2% have synchronous CRC, and 28.2-31.4% have synchronous adenomas [25-27]. Recognition of synchronous colorectal lesions prior to the treatment of the index cancer is important for several reasons. Firstly, presence of an advanced colorectal neoplasm may impact surgical approach and the extent of operation. Secondly, many synchronous neoplasms are eligible for endoscopic treatment, which is more feasible when performed prior to the surgical treatment (a prior colorectal surgery is a risk factor for inadequate bowel preparation for colonoscopy) [28]. Thirdly, meticulous detection of synchronous neoplasms may reduce the “metachronous” CRC risk, since it is estimated that 43% of the metachronous CRC are in reality carcinomas missed during the index colonoscopy [29].

Definition of metachronous colorectal neoplasm varies, but it may be defined as a neoplasm diagnosed at least 6 months after detection of the index CRC which is not a recurrence of the primary tumor [29]. In populational studies risk of metachronous colorectal neoplasms ranges from 19 to 43% [30-32], and metachronous CRC are observed in 2.2% according to a recent meta-analysis [14]. Most of these lesions (54%) are detected within 36 months of surgery, and 89% within 120 months [14]. The relative risk of second primary CRC is modest: increased 1.5-2-fold compared to the general population [33, 34]. Two-thirds of these tumors are detected in early stage (stage I-II) and in asymptomatic patients [35]. Consequently, 67-86% of patients experiencing metachronous CRC may undergo a radical treatment, and their survival is not inferior when compared to patients diagnosed with a stage-matched primary CRC [33].

Non-CRC malignancies

CRC survivors are approximately 10% more likely to experience a primary non-CRC malignancy than the age-matched general population [36]. Considering death as a competing
event, the cumulative risk of second primary malignancy at the 3-year, 5-year, and 10-year are 3.9%, 5.9%, and 10.0%, respectively [36].

Examinations

Clinical examination

Regular contact with a physician is a central element of the posttreatment care. Physical examinations and interviews offer an opportunity to detect alarming signs and symptoms requiring referral to specific diagnostic tests, adjust follow-up to the patients’ needs and preferences, take a proactive approach to treatment of comorbidities or therapy-related toxicities, and facilitate adaptation of healthier lifestyles. These may contribute to an improved physical and psychological well-being [12, 37].

Computed tomography

Computed tomography (CT) of abdomen, pelvis and chest remains a diagnostic workhorse for detection of locoregional and distal recurrences. According to reviews on accuracy of CT in CRC patients, the sensitivity and specificity of contrast-enhanced CT have been estimated at 70-85% and 50-92% for detection of local CRC recurrence, 68-85% and 90-96% for detection of liver metastasis, and 68-89% and 87-96% for detection of lung metastasis, respectively [37, 38]. In rectal cancer CT has 82% sensitivity, and 50-97% specificity in PR detection [39], but its diagnostic accuracy may be hindered by postoperative tissue scarring, altered anatomy, and artifacts.

A prospective CEA Watch trial found that CT-detected relapses associate with a longer survival from the time of surgery than self-reported recurrences [40]. Contradicting findings are reported in another prospective study, in which patients with relapses detected by CT had a longer OS from the time of relapse detection (as compared to patients with symptomatic relapses), however OS from the time of randomization did not differ (lead-time
In this trial 71% of asymptomatic patients with relapse detected by CT had a normal CEA level [41]. Value of routine CT follow-up is further questioned by two meta-

analyses which found that more frequent CTs, or even their inclusion in a surveillance protocol, did not impact OS [12, 42].

*Carcinoembryonic antigen*

Serum carcinoembryonic antigen (CEA), a glycoprotein produced by 90% of CRC, lacks accuracy necessary for the primary diagnosis of the disease [43]. However, postoperative CEA monitoring remains a cornerstone of the posttreatment surveillance. In the Clinical Outcome of Surgical Therapy (COST) trial CEA testing was the first method of recurrence detection in 29-37% of relapses [4]. CEA detection is more useful for recognition of hepatic or retroperitoneal metastasis than for detection of local or peritoneal relapses [44].

Accuracy of the CEA tests depends on the cut-off value: in a meta-analysis of 52 studies sensitivity ranges from 41% to 97%, and specificity from 52% to 100%. For threshold CEA level of 2.5 ug/L, 5 ug/L and 10 ug/L sensitivity was 82%, 71% and 68%, and specificity 80%, 88% and 97%, respectively [45]. In a study inspecting origins of CEA elevations in patients after a curative CRC treatment, a recurrence was confirmed immediately in 56% of cases, a delayed recurrence in 8.8%, a non-CRC malignancy in 3.1%, and a non-malignancy related cause of CEA abnormality (e.g. smoking) in 32% [46]. Utility of CEA as a single diagnostic test is thus questionable, especially in case of low-level (5-10 ug/L) elevations [47]. Application of a CEA threshold greater than 15 ug/L and/or observation of temporal trends (e.g. ≥25% increase from previous values) have proposed as a more appropriate strategy for the relapse detection, but only in combination with imaging techniques [48, 49]. Value of intensive CEA testing is also impugned by the CEA Watch trial and the 2019 Cochrane meta-analysis, both of which found that intensive CEA testing in surveillance protocols does not impact OS after the intent-to-cure CRC treatment [12, 40].
Colonoscopy

Colonoscopy is used in CRC patients to detect synchronous colorectal neoplasms perioperatively, and to detect metachronous neoplasms and intraluminal recurrences postoperatively. Normally the first endoscopy is performed before operation to detect and remove (or mark for a surgical removal) synchronous polyps [33]. Alternatively, if a full examination cannot be performed preoperatively (e.g. due to bowel obstruction), colonoscopy should be done early after operation (within 3-6 months) [33, 35]. Perioperative polyp ablation aims to reduce the incidence of false “metachronous” colorectal tumors observed early during surveillance, that are in reality missed synchronous lesions [29]. Hence, a full and high-quality perioperative endoscopy is warranted [29]. Subsequent follow-up endoscopies target intraluminal recurrences, metachronous cancers, and precancerous polyps.

To establish position of the surveillance colonoscopy one must take into account its diagnostic accuracy, incidence of intraluminal cancers, and their curability. According to systemic reviews, colonoscopy has a high sensitivity: 95% in detection of CRC [50], and 75-93% in detection of adenomas 6 mm or larger [51]. On the other hand, its target cancers are rare, with the cumulative incidence of 2.7% for AR and 2.2% for metachronous CRC [14]. Still, these lesions are curable, with 67-86% of metachronous CRC amenable to the intent-to-cure treatment [33]. In a prospective trial of 259 patients undergoing a multimodal surveillance, colonoscopy was responsible for detection of the highest proportion (44%) of resectable recurrences. Local relapses detected with colonoscopy were resectable in 6 out of 7 cases, and metachronous cancers in 3 out of 3 cases [52]. Similarly, in another study endoscopy detected a high fraction of curable recurrences, and 8 out of 13 (62%) of malignant lesions detected with this modality were eligible for a salvage surgery [53].

In a retrospective study of CRC patients who survived >1 year after operation, individuals receiving colonoscopies had 5-year death risk reduced by 43% as compared to
patients without colonoscopy [54], although it is possible this risk reduction was inflated by a better performance status in the group offered a colonoscopy. In another study the surveillance endoscopies did not influence colorectal cancer-specific mortality in patients over 65 year-old diagnosed with localized or regional stage colorectal cancer [55]. On the other hand, two meta-analyses that compared protocols utilizing colonoscopy with studies omitting it, found that use of colonoscopy associates with a better OS (hazard ratio, HR 0.65, 95% CI 0.53-0.81) [56, 57]. More frequent colonoscopies, however, failed to provide additional survival benefit in the meta-analyses [56, 57]. This finding is corroborated by the result of a unique randomized trial comparing intensive colonoscopy follow-up (examinations at 3-month intervals for 1 year, 6-month intervals for the next 2 years, and once a year thereafter) with less intense protocol (colonoscopy at 6, 30 and 60 months postoperatively). Although CRC patients in the intensive group had more curative operations for intraluminal recurrences (69% vs. 33%), and survived longer when the recurrence was observed (mean survival 69 vs. 24 months), the 5-year OS was not affected (77% vs. 73%). Accordingly, considering the low incidence of intraluminal recurrences and the timing of their detection (mostly the first 2-3 years [14]), reducing the number of surveillance colonoscopies appears appropriate [58].

Virtual colonography

Contrast-enhanced computed tomographic colonography (CTC) has been suggested as an alternative to conventional colonoscopy. Following a bowel inflation CTC is capable to simultaneously detect luminal and extramural local recurrences, metachronous neoplasia and metastases. Performance of CTC in the context of CRC survivors was evaluated in a meta-analysis of 7 retrospective studies, which documented 95% sensitivity and 100% specificity for the AR detection, and 100% accuracy for the metachronous CRC [59]. In a prospective study involving 202 patients examined 1 year after a curative-intent CRC resection, neither
colonoscopy, nor CTC identified any intraluminal AR, metachronous CRC, or advanced colorectal neoplasia. However, only CTC was capable to identify extramural perianastomotic relapses in two patients (1%), but also called two patients positive for diminutive anastomotic lesions later found to be non-neoplastic [60].

*Abdomen ultrasound*

While surveillance with liver ultrasound (US) is not recommended by international guidelines [61], it has been frequently employed by studies investigating multimodal follow-up [40, 52, 62-64]. In a prospective database study of 243 individuals who underwent a curative CRC resection, patients were offered imaging with abdominal US and abdominal/pelvis CT alternating every 6 months. In this protocol the interval abdomen US expedited detection of hepatic recurrences in 12 patients (32% of patients in whom liver metastases were detected), what accelerated administration of treatment in these individuals (palliative in all cases) [65]. It is, however, unclear whether these lesions could not be detected by other means, e.g. CEA testing. Indeed, in another study US was the first test to detect liver metastasis in 5 out of 230 patients, 4 of whom had elevated CEA levels. Additionally US also contributed multiple false-positive and false-negative findings [61]. In overall, this discourages follow-up with US.

US sensitivity and specificity may be enhanced via administration of intravenous contrast (contrast-enhanced US, CEUS). In a multicenter German study 290 CRC survivors (stage >IIa) were prospectively assessed with CEUS. In 26/290 patients unenhanced US detected 45 liver metastases. In contrast, CEUS detected liver metastases in 44/290 patients with a total number of 113 hepatic metastases. In all but 3 patients liver metastases were confirmed with CT (though in these 3 negative patients metastases were detected with MRI) [66]. CEUS has been suggested as a substitute of abdomen CT by the European Society Medical Oncology colon cancer guidelines [67].
**Magnetic resonance**

While pelvic magnetic resonance imaging (MRI) is widely employed preoperatively to stage rectal cancers, postoperative surveillance with MRI is rarely done. Titu et al. evaluated pelvic MRI performed at 3- to 6-month intervals (in addition to colonoscopy, clinical examination and blood tests) in 226 patients who underwent a curative surgery for rectal and left-sided colon cancers [68]. A recurrent locoregional cancer was diagnosed in MRI with 87% sensitivity (26/30 true positive recurrences; 3 out of 4 missed cases were AR) and 86% specificity. 6 patients with local recurrence (20%) were eligible for a salvage surgery, but only 2 of them had a recurrence first discovered by MRI. Accordingly, frequent pelvic MRI used to detect operable recurrences in <1% of patients, given its cost, limited accessibility, and some false-positive findings, is likely unjustified [68]. In another study, abdomen MRI performed every 3-6 months in 293 CRC survivors demonstrated 84% sensitivity and 90% specificity in the liver metastasis recognition [69]. Out of 37 patients with hepatic recurrences, 9 (24%) individuals were eligible for a curative metastatectomy, 3 of whom would have been missed without MRI (if followed by CEA, liver function tests and physical examination only). Detection of operable liver metastases in only 1% of CRC individuals offered MRI advocates against use of this scarce diagnostic resource in the surveillance [69].

**Positron emission tomography**

A prospective randomized trial of 239 patients radically operated for stage III, IV or perforated stage II CRC evaluated benefits associated with addition of a semi-annual positron emission tomography coupled with CT (FDG-PET/CT) to a 3-year surveillance protocol [70]. This intervention failed to reduce number of treatment failures (unresectable recurrences and deaths in 29% cases in the intervention group, and 24% in control) [70]. FDG-PET and PET/CT have been also studied as modalities that could assist in the interpretation of CEA elevations. A meta-analysis of 11 trials studying CRC survivors with high CEA level (cut-off
value 3-6 ng/ml) identified 90% sensitivity and 80% specificity in relapse detection with FDG-PET, and 94% sensitivity and 77% specificity for PET/CT [71]. A recent report on the use of PET/CT in patients with CEA level >5 ng/ml or with CEA level doubling, and no obvious site of CRC recurrence on clinical examination and basic imaging, documented sensitivity, specificity, positive predictive value and negative predictive value of 93%, 95%, 96% and 91%, respectively [72]. This illustrates that PET/CT may be advantageous to evaluate some cases of asymptomatic CRC survivors with unclear CEA elevations.

Other diagnostic tests

Among the most promising techniques applicable for oncological monitoring is liquid biopsy, which refers to the detection of circulating tumor cells or cell-free nucleic acids of tumor origin in bodily fluids (commonly circulating tumor DNA, ctDNA). In a study of radically operated stage I-III CRC patients, 77% (10/13) of individuals found ctDNA-positive in postoperative plasma experienced a recurrence, and a positive ctDNA preceded radiologic or clinical evidence of recurrence by a median 3 months. In contrast, none of 45 patients with negative plasma ctDNA experienced a relapse [73]. In another report, ctDNA-positive patients at postoperative day 30 were 7 times more likely to have a relapse than ctDNA-negative patients, and 17 times more likely to relapse when found ctDNA-positive after completing adjuvant chemotherapy [74]. Longitudinal serum ctDNA analyses revealed a disease recurrence on average 8.7 months ahead of the radiologic imaging (range 0.8-16.5 months) [74]. While these results are very promising, the exact position of ctDNA based liquid biopsy in CRC surveillance remains to be established.

Alternative indicators of CRC recurrence detectable in blood are epigenetic markers, (micro RNAs, methylated genes) and circulating RNA transcripts. MicroRNAs (miRNA), small RNA species responsible for the fine-tuning of gene transcript levels, are highly stable and readily detectable in bodily fluids. In CRC certain miRNAs isolated from serum have
been shown to be prognostic of the disease recurrence (e.g. miR-21, mi-31, miR-203), capable to differentiate between adenomas and CRC (miR-21), and to detect patients with distant metastasis (miR-141) [75]. Similarly, high postoperative levels of some circulating gene transcripts, Metastasis-Associated in Colon Cancer 1 (MACC1) and S100A4, have been shown to indicate elevated risk of metastasis and unfavorable survival in CRC patients [76]. Among the most interesting DNA methylation markers is methylated septin 9 (mSEPT9), a gene found to have extremely high methylation levels in CRC. Blood mSEPT9 demonstrates a higher sensitivity for diagnosing CRC than CEA, and the mSEPT9 elevation in post-operative blood samples associates with a higher metachronous metastasis rate (27.3% vs. 7.0%) and a higher 24-month mortality rate (15.2% vs. 1.2%) in surgically treated CRC patients [77]. A test based on detection of gene methylation markers, KRAS gene mutations and fecal immunochemical test (FIT) in stool samples is already a clinically applicable option for CRC screening [78], however its use in the post-treatment monitoring has not been evaluated so far. FIT alone is, however, inadequate for surveillance due its low sensitivity for detection of local recurrences (33%) and metachronous CRC (15%) [79]. Some novel protein markers indicative of CRC recurrence are serum soluble CD26 and urine collagens [80, 81]. Their clinical utility needs to be further refined and currently they have no place in the oncological practice.

**Intensive follow-up**

Multiple studies have tried to evaluate whether intensive monitoring of patients radically operated for CRC provides clinical benefits. Unfortunately, it is challenging to recap these trials collectively as definitions of intensive follow-up differ considerable between individual studies. Intensive monitoring could involve more frequent tests or use of additional diagnostic modalities. In some instances, a protocol classified as “intensive” in one study,
could be considerably less exhaustive than a “conventional” surveillance in another trial. Surveilled populations are also diverse: include patients with various CRC stages and offered different treatment types.

Despite the extreme heterogeneity in study designs, almost all randomized clinical trials (RCT) conducted in the last three decades conclude that more intense follow-up does not improve OS or cancer-specific survival (Table 1). It is observed that intensive surveillance may permit an earlier detection of relapse, and thus shorten the relapse-free survival (RFS) as observed in the Italian GILDA trial (RFS in the intensive follow-up group shorter by 5.9 months on average) [62]. In some cases, a faster diagnosis may increase the likelihood of salvage treatment. Wang et. al. utilizing frequent colonoscopies managed to increase the ratio of re-operable luminal relapses from 33% to 69%, and improve survival in patients who underwent the recurrence resection [82]. In the Follow-up After Colorectal Surgery (FACS) trial intensive CT imaging or CEA monitoring increase number of salvage surgeries when compared to a minimal follow-up (salvage surgeries performed in 8% patients monitored with CT, 6.7% with CEA, 6.6% with both CT & CEA, and 2.3% in the minimal follow-up group) [83]. More than two thirds of patients who underwent a curative-intent re-treatment were alive at a median follow-up of over 4 years from the time of relapse detection [83]. Alas, since the absolute number of operable recurrences remains low, these successes did not translate to the survival benefit for the whole population. These findings are corroborated by results of a landmark COLOFOL trial which observed 5-year mortality of 10.6% and 11.4% in the low- and high-intensity follow-up groups, respectively [84].

Some confusion on the value of intensive CRC surveillance has been caused by results of meta-analyses (Table 2). Renehan et al. analyzing data from studies delivered between 1995-1998 observed that frequent patient monitoring could reduce the all-cause mortality by 20% [85]. In 2007 Tjandra et al. using results of 8 RCT involving 2923 patients observed that
a more intensive follow-up increased the number of resectable recurrences (10.7% vs. 5.7%),
and reduced the overall mortality from 25.7% to 21.8% [57]. Similar conclusions were
reached by Pita-Fernandez, who observed that intensive surveillance could double numbers of
asymptomatic recurrences detected (relative risk, RR 2.59), curative-intent surgeries (RR
1.98), survival after recurrences (RR 2.13), and improved OS (HR 0.75; 95% CI 0.66–0.86)
[56]. Noteworthy, none of the individual RCT included in these meta-analyses except one,
reported the OS benefit. Results of large RCT published over the last 6 years altered outcomes
of meta-analyses. Among them, Mokhles et. al failed to detect benefit in OS associated with
more intensive monitoring protocols [86]. This result is reinforced by the latest iteration of the
Cochrane review that used data from 19 studies enrolling 13216 participants. While the
intensive follow-up could provide some advantages by reducing the number of symptomatic
relapses (RR 0.59) and augmented the number of intent-to-cure salvage resections (RR 1.98),
it did not impact the primary outcomes: CRC-specific survival or OS [12]. Additionally, a
more intense medical care had little influence on quality of life, depression and anxiety [12].
Consequently, a consensus has been reached that escalating follow-up provides little, if any,
assistance.

Special considerations

T1 cancers

CRC confined to submucosa (T1) can be successfully treated endoscopically,
especially in low-risk carcinomas (good/moderate histological differentiation, no tumor
budding, no deep submucosal infiltration, lymphatic or venous invasion), when the risk of
lymph node involvement is low (0-3.8%) [87]. A Dutch retrospective study reported
recurrences of T1 CRC in 6.2% and 3.4% in patients treated endoscopically and surgically,
respectively [88]. In two Japanese studies treating T1 CRC endoscopically, recurrences were observed collectively in 3/180 patients in the low-risk group (1.7%) and 18/142 (12.7%) in the high-risk group [89, 90].

McCain et al. have recently performed a cost-effectiveness analysis of surveillance in patients with locally excised T1NX rectal adenocarcinoma. Considering that 87% of these cancers are low-risk and >80% of relapses in this groups are luminal, they conclude that the most cost-effective strategy is a medium-intensity follow-up consisting of frequent luminal examinations and local imaging (pelvic MRI or endoscopic ultrasound), but refraining from distant imaging or tumor markers [91]. It may be expected that the follow-up strategy in T1 cancers could be different than in advanced CRC, but unfortunately most guidelines do not offer special recommendations.

Stage IV

No RCT has specifically evaluated the follow-up of radically operated stage IV CRC. Retrospective studies report that the majority of recurrences in intent-to-cure metastatic CRC happen early, with 63-78% patients experiencing it during the first 24 months after surgery [5, 6]. This might suggest that follow-up should be meticulous during this early period. Unfortunately, it is also observed that recurrences detected within the first 12 months are less likely to be resectable than lesions observed later, and that the prognosis is much worse with a relapse happening during the first 2 years of the follow-up [5, 6]. Consequently, it seems unlikely that an escalated early surveillance may improve survival, but evidence-based surveillance protocols remain to be established.

Guidelines
Major international clinical guidelines on the post-treatment surveillance of CRC patients are summarized in Table 3. Some recommendations refer to a specific clinical context: primary cancer site, disease stage, type of resection performed, or address use of colonoscopy only. Guidelines almost universally endorse CT scans, CEA tests and endoscopies. However, recommendations differ considerably on testing sequence, intensity, and are unfortunately not well evidence-based. In the light of results of RCT and meta-analyses, it is probable that a reduction in the testing intensity would not adversely affect the patients’ survival. It remains to be seen whether this will be reflected in future guideline updates.

Conclusions

Owing to the overall increase in CRC incidence and advancements in treatment, number of patients who undergo a potentially curative CRC therapy is rising. These individuals are at risk of different types of recurrences and new neoplasms, what advocates a multimodal surveillance to detect them early. Much research has addressed the value of particular examinations reaching a consensus on use of CT scans, CEA monitoring and colonoscopies. Studies have also tried to evaluate if particular diagnostic combinations and testing intensities could detect more potentially curable relapses and consequently increase the patients’ survival. While many questions remain unanswered, there is convincing evidence that we cannot achieve a better patients’ survival by the surveillance escalation, at least not in the whole population undergoing the follow-up. Perhaps what we require is a more risk-adapted strategy that concentrates on particular diagnostics or abstains from use of some tests basing on a particular clinical situation. While there are bits of this approach present in the current guidelines, it is certainly desirable to expand this direction much further. Novel solutions may be provided by a better understanding of tumor biology or application of new
diagnostic techniques, e.g. ctDNA testing, which by offering a very high negative predictive value could indicate patients who require limited monitoring. Certainly, more prospective and well-structured clinical trials are required to provide evidence for development of new guidelines to optimize care of CRC survivors.

**Literature**

<table>
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<th>Study name</th>
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<tr>
<td>COLOFOL 2018</td>
<td>Denmark, Sweden, Uruguay</td>
<td>2509</td>
<td>CEA at 1 month. CT (tx, abd) &amp; CEA at 6, 12, 18, 24, 36 months.</td>
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<td>CEA Watch 2017</td>
<td>Netherlands</td>
<td>3223</td>
<td>Physical, CT (tx, abd, pelv) annually for 3 years. CEA every 2 months for 3 years,</td>
<td>Physical every 6 months for 3 years, then annually for next 2 years. CEA every 3-6 months for 3 years, then annually for next 2 years. CEA at 1 month. CT (tx, abd) &amp; CEA at 12, 36 months.</td>
<td>60</td>
<td>7.5%</td>
<td>NR</td>
<td>0.78 (0.48-1.27)</td>
<td>0.73 (0.47-1.15)</td>
</tr>
<tr>
<td>Sobhani 2018</td>
<td>France</td>
<td>239</td>
<td>PET every 6 months for 3 years.</td>
<td>Physical, CEA, CA19.9, FBC every 3 months for 3 year. US, CXR at 3, 9, 25, 21, 27, 33 months. CT (tx, abd, pelv) every 6 months for 3 years. Colonoscopy at 12, 36 months.</td>
<td>36</td>
<td>35.6%</td>
<td>NR</td>
<td>1.68 (0.61-4.66)</td>
<td>1.9 (0.77-4.67)</td>
</tr>
<tr>
<td>GILDA 2016</td>
<td>Italy, Spain, US</td>
<td>1228</td>
<td>Physical, FBC, CEA, CA19.9 at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 60 months. US at 4, 8, 12, 16, 24, 36, 48, 60 months. CXR, colonoscopy annually</td>
<td>Physical, CEA at 4, 8, 12, 16, 20, 24, 30, 42, 48, 60 months US at 4, 16, months. Colonoscopy at 12, 48 month.</td>
<td>median 62</td>
<td>20.4%</td>
<td>1.24 (0.85-1.79)</td>
<td>1.16 (0.65-2.09)</td>
<td>1.13 (0.87-1.45)</td>
</tr>
</tbody>
</table>
for 5 years. 
**CT** (pelv) in **rectal cancer** at 4, 12, 24, 48 months.

**Additional in rectal cancer:**
- **Rectoscopy** at 4 months.
- **CXR** at 12 months.
- **US** at 8, 16 months.
- single **CT** (pelv) if required for baseline postadjuvant assessment.

| FACS 2014 [83] | UK | 1202 Dukes A-C | 3 options: 
1) **CEA FU** (n=300) 
**CEA** every 3 months for 2 years, then every 6 months for next 3 years. 
Single **CT** (tx, abd, pelv) at 12-18 month if requested by entry clinician. 
2) **CT FU** (n=299) 
**CT** every 6 months for 2 years, then every 12 months for next 3 years. 
**Colonoscopy** at 24 months. 
3) **CEA+CT FU** (n=302) 
**CEA** every 3 months for 2 years, then every 6 months for next 3 years. 
**CT** every 6 months for 2 years, then every 12 months for next 3 years. 
**Colonoscopy** at 24 months. |
| “Minimal” (n=301) 
Single **CT** (tx, abd, pelv) at baseline if requested by entry clinician. |
| mean 40.8 | 16.6% | **3.05** (1.42-6.59) | 1.13 (0.73-1.74) | 1.17 (0.84-1.64) |

<p>| Wang 2009 [82] | China | 326 Dukes | <strong>Colonoscopy, physical, CEA, CXR, US/CT</strong> (abd) every 3 months. |
| <strong>Colonoscopy</strong> at 6, 30, 60 months. |
| 64-79 | 9.5% | 1.10 (0.44-3.05) | 0.99 (0.60-1.64) | 0.76 (0.48-1.31) |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Stage</th>
<th>Follow-up Details</th>
<th>5-Year Interval</th>
<th>5-Year OS (%)</th>
<th>5-Year DFS (%)</th>
<th>5-Year RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sobhani 2008 [92]</td>
<td>France</td>
<td>130 stage III-IV</td>
<td>Physical, CEA, CXR, US/CT (abd) every 3 months for 1 year, then every 6 months for next 2 years, then annually.</td>
<td>24</td>
<td>35.4%</td>
<td>7.50 (1.79-31.49)</td>
<td>NR</td>
</tr>
<tr>
<td>Rodriguez-Moranta 2006 [52]</td>
<td>Spain</td>
<td>259 stage II-III</td>
<td>Physical, CEA, blood every 3 months for 5 years. US/CT every 6 months for 56 months. CXR, colonoscopy annually for 5 years.</td>
<td>48</td>
<td>26.6%</td>
<td>1.87 (0.90-3.90)</td>
<td>0.77 (0.39-1.53)</td>
</tr>
<tr>
<td>Secco 2002 [93]</td>
<td>Italy</td>
<td>192 „high recurrence risk“</td>
<td>Physical, CEA every 3 months for 2 years, then every 4 months for next 1 year, then every 6 months for next 2 years. CXR annually for 5 years. US (abd, pelv) every 6 months for 3 years, then annually for next 2 years. CXR, rigid sigmoidoscopy in rectal cancer annually for 5 years.</td>
<td>61.5</td>
<td>52.6%</td>
<td>1.80 (0.98-3.32)</td>
<td>NR</td>
</tr>
<tr>
<td>Shoe-maker 1998 [94]</td>
<td>Australia 325 Dukes A-C</td>
<td>CXR, colonoscopy, CT (abd) annually.</td>
<td>CXR, colonoscopy, CT (abd) only if clinically indicated, or at 5 year</td>
<td>60</td>
<td>36.9%</td>
<td>1.14 (0.35-3.65)</td>
<td>NR</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Number treated</td>
<td>Stage</td>
<td>Surveillance Protocols</td>
<td>Follow-up Period</td>
<td>Hazard Ratio (HR)</td>
<td>CI (95%)</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>----------------</td>
<td>-------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Pietra 1998 [63]</td>
<td>Italy</td>
<td>207 Dukes B-C</td>
<td></td>
<td>Physical, US, CEA, CXR every 3 months for 2 years, then every 6 months for next 2 years, then annually. CT (abd). <strong>Colonoscopy</strong> annually.</td>
<td>60</td>
<td>22.2%</td>
<td>3.47 (1.46-8.24)</td>
</tr>
<tr>
<td>Kjeldsen 1997 [95]</td>
<td>Denmark</td>
<td>597 Dukes A-C</td>
<td></td>
<td>Physical, DRE, colonoscopy, CXR, gynecology exam, FOB, blood tests at 6, 12, 18, 30, 36, 48, 60, 120, 150, 180 months. Physical, DRE, colonoscopy, CXR, gynecology exam, FOB, blood tests at 60, 120, 180 months.</td>
<td>NR</td>
<td>26%</td>
<td>3.18 (1.37-7.36)</td>
</tr>
<tr>
<td>Ohlsson 1995 [96]</td>
<td>Sweden</td>
<td>107 Dukes A-C</td>
<td></td>
<td>Physical, CXR, rigid proctosigmoidoscopy, CEA, FOB, GGTP, ALP every 3 months for 2 years, then every 6 months for next 2 years, then at 60 months. CT (pelv) at 3, 6, 12, 18, 24 months Colonoscopy at 3, 15, 30, 60 months. <strong>FSS/Colonoscopy</strong> to examine anastomosis at 9, 21, 42 mo. None. FOB recommended locally every 3 months for 2 years, then annually.</td>
<td>66-105.6</td>
<td>32.7%</td>
<td>1.7 (0.43-6.75)</td>
</tr>
<tr>
<td>Makela 1995 [64]</td>
<td>Finland</td>
<td>106 Dukes A-C</td>
<td></td>
<td>US at 6 months, and then annually. Colonoscopy preop or at 3 months, then annually. <strong>FSS</strong> in rectal or sigmoid cancer every 3 months. <strong>FSS and barium enema</strong> in rectal or sigmoid cancer annually.</td>
<td>60</td>
<td>40.6%</td>
<td>1.73 (0.44-6.88)</td>
</tr>
</tbody>
</table>

Table 1. Overview of prospective randomized controlled trials comparing structured surveillance protocols in patients radically treated for colorectal cancer. Hazard ratio (HR) values as provided by Jeffery et al. 2019 (Cochrane Database), significant values marked in bold. Abbreviations: abd (abdomen), ALP (alkaline phosphatase), CI (confidence interval), CXR (chest X-ray), DRE (digital rectal examination), FBC
(full blood count), FSS (flexible sigmoidoscopy), FOB (fecal occult blood), FU (follow-up), GGTP (gamma-glutamyltransferase), NR (not reported), mo (months, pelv (pelvic), tx (thorax), US (ultrasound, liver if not stated otherwise).
<table>
<thead>
<tr>
<th>Name, Year</th>
<th>Number of studies included</th>
<th>Number of patients</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renehan, 2002 [85]</td>
<td>5</td>
<td>1342</td>
<td>RR 0.81 (95% CI 0.70-0.94)</td>
</tr>
<tr>
<td>Tjanda, 2007 [57]</td>
<td>8</td>
<td>2923</td>
<td>OR 0.74 (95% CI 0.59-0.93)</td>
</tr>
<tr>
<td>Pita-Fernandez, 2014 [56]</td>
<td>11</td>
<td>4055</td>
<td>HR 0.75 (95% CI 0.66-0.86)</td>
</tr>
<tr>
<td>Mokhles, 2016 [86]</td>
<td>7</td>
<td>3325</td>
<td>HR 0.98 (95% CI 0.87-1.11)</td>
</tr>
<tr>
<td>Zhao, 2019 [42]</td>
<td>17</td>
<td>8039</td>
<td>HR 0.85 (95% CI 0.74-0.97)</td>
</tr>
<tr>
<td>Jeffery, 2019 [12]</td>
<td>19</td>
<td>13216</td>
<td>HR 0.91 (95% CI 0.80-1.04)</td>
</tr>
</tbody>
</table>

Table 2. Summary of meta-analyses analyzing impact of more intense surveillance in patients radically treated for colorectal cancer. Abbreviations: HR (hazard ratio), OR (odds ratio), RR (relative risk).
<table>
<thead>
<tr>
<th></th>
<th>Physical &amp; history</th>
<th>Computed tomography</th>
<th>CEA</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCO 2013</strong> [97]</td>
<td>every 3–6 months for 5 years.</td>
<td>thorax, abdomen, pelvic: annually for 3 years; every 6–12 months in high-risk patients. <em>(in rectal cancer pelvic CT for up to 5 years)</em></td>
<td>every 3–6 months for 5 years.</td>
<td>at 1 year, then every 5 years.</td>
</tr>
<tr>
<td><strong>ESMO 2013</strong> colon stage I-III [67]</td>
<td>every 3–6 months for 3 years, then every 6–12 months in year 4-5.</td>
<td><em>thorax, abdomen:</em> every 6–12 months for 3 years. <em>(CEUS may replace liver CT)</em></td>
<td>every 3–6 months for 3 years, then every 6–12 mo. in year 4-5.</td>
<td>at 1 year, then every 3–5 years.</td>
</tr>
<tr>
<td><strong>ESMO 2014</strong> colon st. IV [98]</td>
<td>every 3–6 months for 3 years.</td>
<td>thorax, abdomen: every 3–6 months for 3 years.</td>
<td>every 3–6 months for 3 years.</td>
<td>-</td>
</tr>
<tr>
<td><strong>ESMO 2017</strong> rectal [99]</td>
<td>every 6 months for 2 years.</td>
<td>thorax, abdomen, pelvic: minimum 2 scans in first 3 years. <em>(more active if CRM+)</em></td>
<td>at least every 6 months in first 3 years. <em>(more active if CRM+)</em></td>
<td>at 1 year if not done perioperatively; every 5 years (up to age of 75). <em>(more active follow-up for local recurrence if CRM+)</em></td>
</tr>
<tr>
<td><strong>NCCN 2020</strong> colon &amp; rectal [100]</td>
<td>every 3–6 months for 2 years, then every 6 months in year 3-5.</td>
<td>thorax, abdomen, pelvic: <em>Stage II-III:</em> every 6–12 months for 5 years. <em>Stage IV:</em> every 3–6 months for 2 years, then every 6–12 mo. in year 3-5.</td>
<td><em>Stage II-IV</em> every 3–6 months for 2 years, then every 6 mo. in year 3-5.</td>
<td><em>Stage I-IV</em> preoperatively or within 3-6 months; then at 1, 4, 9 years. <em>(if TEM performed: rectoscopy with EUS or MRI every 3–6 months for 2 years, then every 6 months in year 3-5).</em></td>
</tr>
<tr>
<td><strong>US Multi-Society Task Force 2016 (endoscopy)</strong> [35]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>preoperatively or within 3-6 months; then at 1, 4, 9 years, then every 5 years until age-justified. <em>(in rectal cancer w/o TME, after TEM or without neoadjuvant treatment: FSS/EUS every 3–6 months in year 2–3).</em></td>
</tr>
<tr>
<td>ESGE/ESDO 2019 (endoscopy) [33]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Preoperatively or within 3-6 months; then at 1, 4, 9 years. (may stop if age &gt;80 or short life-expectancy after the first negative exam).</td>
</tr>
</tbody>
</table>

Table 3. Overview of major international guidelines on post-treatment colorectal cancer surveillance. Abbreviations: ASCO: American Society of Clinical Oncology, CRM+ (positive circumferential resection margin), CT (computed tomography), CEUS (contrast-enhanced ultrasound), ESDO (European Society of Digestive Oncology), ESGE (European Society of Gastrointestinal Endoscopy), ESMO (European Society of Clinical Oncology), FSS (flexible sigmoidoscopy), NA (not applicable), NCCN (National Comprehensive Cancer Network), TEM (transanal endoscopic microsurgery).
Figure 1. Types and incidence of recurrences and malignancies observed in colorectal survivors.

- Other primary cancer: SIR 1.1
- Distant metastasis: 20%
- Synchronous CRC: 2.2-6.2%
- Metachronous CRC: 2.2%
- Anastomotic recurrence: 2.7%
- N-A local recurrence: 1-3% colon, 4-8% rectal