REVIEW ARTICLE

A comprehensive review on posttreatment surveillance in colorectal patients

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KEY WORDS

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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, with an expectation of a higher rate of radical retreatments and better overall survival. Despite much research, the optimal diagnostic panel and the intensity of surveillance have not been well established. Evidence indicates, however, that more intensive follow-up is unlikely to improve survival after a curative colorectal cancer surgery, chiefly due to the scarcity of recurrences suitable for salvage treatment. Typical surveillance recommended by guidelines includes regular physical examinations, computed tomography scans, serum carcinoembryonic antigen monitoring, and colonoscopy. The objective 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.

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

The rationale behind the posttreatment follow-up is the assumption that earlier detection of recurrence may provide a survival advantage. Thus, the direct aim is to find patients with early-stage, often asymptomatic recurrences, in whom curative treatment may be performed. It is estimated that up to 28% to 47% of patients with stages I to 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, is associated with less extensive procedures, lower morbidity, and better long-term survival.[7,8] Five-year survival rates for highly selected patients who undergo a successful complete resection of single-site liver, pulmonary, and peritoneal recurrences, are 34% to 56%, 43% to 71%, and 30%, respectively.[7,9-11] Apart from the detection of curable recurrences, surveillance may lead to additional health benefits, such as the detection of metachronous neoplasms, and better management of treatment-related toxicities or comorbidities. Yet, since not all patients experience recurrence or have relapse suitable for a radical treatment, it is estimated that between 15 and 50 patients with CRC have to be surveilled to detect a single case eligible for radical retreatment.[12] Additionally, the possible benefits may be counterbalanced by costs and institutional burden associated with frequent tests,

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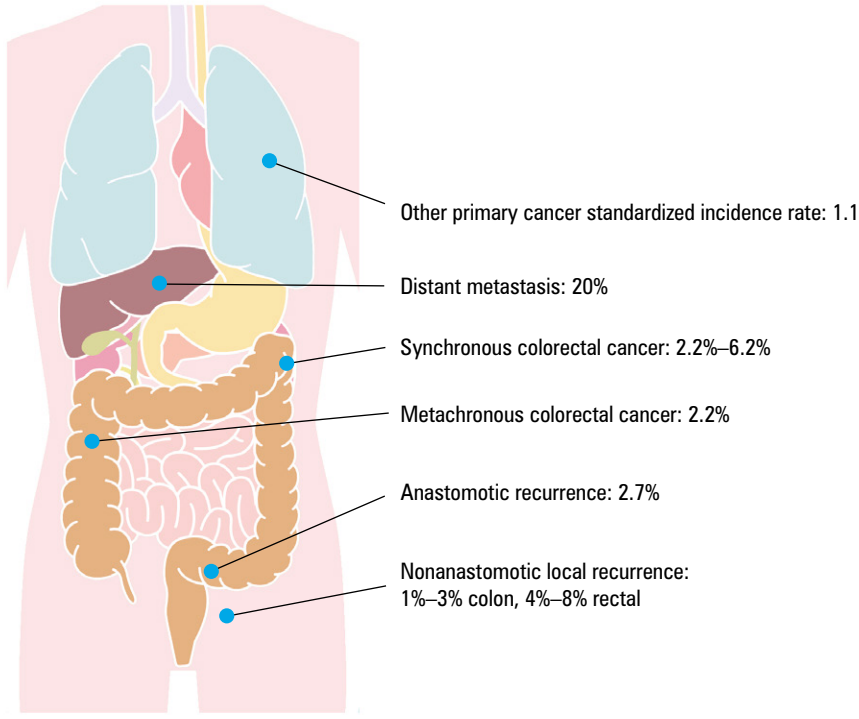

FIGURE 1 Types and incidence of recurrences and malignancies observed in colorectal survivors

harms related to investigations (eg, radiation exposure, endoscopy complications), physical discomfort, and psychological stress linked to false-positive findings.[13]

The aim of this article is to review strategies and controversies regarding the surveillance after a modern-day CRC curative treatment. It discusses various recurrence patterns that should be considered, summarizes evidence for the 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 syndromes is not discussed.

Recurrence patterns Patients with CRC may experience various recurrence types (FIGURE 1): 1) anastomotic: intraluminal or extramural; 2) locoregional other than anastomotic, involving the region of the primary tumor; and 3) metastatic. Besides the detection of CRC recurrences, other neoplasms that impact long-term outcomes may be also discovered during surveillance: 1) synchronous colorectal neoplasms (adenomas and cancers); 2) metachronous colorectal neoplasms; 3) non-CRC primary malignancies.

Anastomotic recurrence Anastomotic recurrence (AR) is defined as a recurrence involving the site of surgical intestinal anastomosis. This entity is distinguished from other types of local relapses due to its frequent intraluminal presentation, 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.[14]

A recent meta-analysis identified a cumulative AR incidence of 2.7% (5.46% in rectal, 1.95% in colon cancer).[15] A total of 70.5% of ARs are detected within the first 2 years, 90.8% within 3 years, and 94.5% within 5 years after treatment.[15] Five-year overall survival (OS) in patients experiencing AR ranges from 20.7% to 49.7%.[14,16] Survival rates after AR are similar for colon and rectal cancers,[14] and are better than in other types of recurrences.[16] Potentially curative retreatments of AR are frequent, with R0 resections attainable in 40% to 68% cases.[8,14,17] Curative resections improve 5-year survival (44% in the complete resection group, and 0% in the palliative resection group in one study), and are more achievable in intraluminal relapses, which are associated with a better survival than extramural lesions.[18]

Nonanastomotic locoregional recurrence Since in colon cancer, a large fraction of nonanastomotic locoregional recurrences (NALRs) coincide with distant metastasis (48% to 80%), isolated NALRs are rare, affecting 1% to 3% patients.[19,20] Nonanastomotic locoregional recurrences may be categorized into several patterns: mesorectal/nodal, retroperitoneal, and peritoneal.[8] In a study on patients with colon cancer, a radical resection could be achieved only in 7%, 8%, and 12% for each recurrence type, respectively, which contributed to worse survival compared with individuals with isolated AR.[8] In colon cancer, a local recurrence is observed after a median (range) of 13 (2–71) months after the surgery.[20]

In rectal cancer, NALRs manifest as pelvic recurrence, a relapse originating from the tumor bed, regional lymph nodes, or adjoining structures

with or without pelvic invasion of the bowel wall.[21] Pelvic recurrence affects 4% to 8% of rectal cancer patients, and the median time to pelvic recurrence is relatively long (15 to 24.7 months).[21-23] Since the introduction of total mesorectal excision and preoperative (chemo)radiotherapy has reduced the incidence of locoregional recurrence, the nature and prognosis of pelvic recurrence have changed as well. In historical reports, pelvic recurrence could be removed in 30% to 50% of cases; however currently, in the age of total mesorectal excision and neoadjuvant radiotherapy, pelvic recurrences are more challenging to manage (in one report, only approximately 20% were resectable).[17,21]

Distant metastasis In addition to 25% of CRC patients who are diagnosed with synchronous metastasis, one-fifth develop metachronous distant spread.[11,24] The most frequent site of metastasis is the liver (60%–65%), followed by the lung (39%–43%), extra-regional lymph nodes (16%–22%), peritoneum (11%–19%), bone (9%), and brain (8%).[11,24] Approximately half of patients develop metastases at more than 1 site.[11] A total of 85% of metachronous metastases are diagnosed within 3 years, with the median time to diagnosis of 17 months.[3,11,24] Five-year survival of patients with a single-site metachronous metastasis is approximately 15%, and less than 5% when metastases are present at 2 or more sites.[11] About 10% of patients with metachronous distant spread are eligible for a potentially curative metastasectomy, which may improve 5-year OS rates up to 60% in highly selected patients.[11] Nevertheless, the true clinical effectiveness of metastasectomy has not been well established. In a recent randomized clinical trial (RCT) investigating outcomes in CRC patients eligible for lung metastasectomy, similar OS was observed regardless of resection.[25]

Synchronous and metachronous colorectal neoplasms Synchronous colorectal neoplasms (adenomas and carcinomas) are present in about one-third of patients with CRC: 2.2% to 6.2% have synchronous CRC, and 28.2% to 31.4% have synchronous adenomas.[26-28] Recognition of synchronous colorectal lesions prior to treatment of the index cancer is important for several reasons. Firstly, an advanced colorectal neoplasm may impact the 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).[29] Thirdly, meticulous detection of synchronous neoplasms may reduce the "metachronous" CRC risk, since it is estimated that 43% of metachronous CRCs are in reality carcinomas missed at the index colonoscopy.[30]

Definition of metachronous colorectal neoplasm varies, but it may be defined as a neoplasm diagnosed at least 6 months after the detection of the index CRC which is not a recurrence of the primary tumor.[30] In populational studies, risk of metachronous colorectal neoplasms ranges from 19% to 43%,[31-33] and metachronous CRCs are observed in 2.2% according to a recent meta-analysis.[15] Most of these lesions (54%) are detected within 36 months of surgery, and 89% within 120 months.[15] The relative risk of second primary CRC is modest: increased 1.5- to 2-fold compared with the general population.[34,35] Two-thirds of these tumors are detected in early-stage (stage I–II) and in asymptomatic patients.[36] Consequently, 67% to 86% of patients experiencing metachronous CRC may undergo a radical treatment, and their survival is not inferior when compared with patients diagnosed with a stage-matched primary CRC.[34]

Non–colorectal cancer malignancies Survivors of CRC are approximately 10% more likely to experience a primary non-CRC malignancy than the age-matched general population.[37] 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%, respectively.[37]

Examinations

Clinical examination Regular contact with a physician is the core element of the posttreatment care. Physical examinations and interviews offer an opportunity to detect alarming signs and symptoms requiring referral for 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 improved physical and psychological well-being.[13,38]

Computed tomography Computed tomography (CT) of the abdomen, pelvis, and chest remains a diagnostic workhorse for the detection of locoregional and distal recurrences. According to reviews on accuracy of CT in patients with CRC, the sensitivity and specificity of contrast-enhanced CT have been estimated at 70% to 85% and 50% to 92% for the detection of local CRC recurrence, 68% to 85% and 90% to 96% for liver metastasis, and 68% to 89% and 87% to 96% for lung metastasis, respectively.[38,39] In rectal cancer, CT has 82% sensitivity, and 50% to 97% specificity in PR detection,[40] but its diagnostic accuracy may be hindered by tissue scarring, altered anatomy, and postoperative artifacts.

The prospective CEA Watch trial found that CT-detected relapses were associated with a longer survival from the time of surgery than self-reported recurrences.[41] 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 with patients with symptomatic relapses); however, OS from the time of randomization did not differ (lead-time bias).[42] In this trial,

71% of asymptomatic patients with relapse detected by CT had a normal CEA level.[42] The value of routine CT follow-up is further questioned by 2 meta-analyses which found that more frequent CTs, or even their inclusion in a surveillance protocol, did not impact OS.[13,43]

Carcinoembryonic antigen Serum carcinoembryonic antigen (CEA), a glycoprotein produced by 90% of CRCs, lacks accuracy necessary for the primary diagnosis of the disease.[44] 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% to 37% of relapses.[4] Testing for CEA is more useful to recognize hepatic or retroperitoneal metastasis than local or peritoneal relapses.[45]

Accuracy of the CEA tests depends on the cut-off value: in a meta-analysis of 52 studies, sensitivity ranged from 41% to 97%, and specificity from 52% to 100%. For threshold CEA level of 2.5 μg/l, 5 μg/l, and 10 μg/l sensitivity was 82%, 71%, and 68%, and specificity 80%, 88%, and 97%, respectively.[46] In a study inspecting origins of CEA elevations in patients after curative CRC treatment, recurrence was confirmed immediately in 56% of cases, delayed recurrence in 8.8%, non-CRC malignancy in 3.1%, and nonmalignancy-related cause of CEA abnormality (eg, smoking) in 32%.[47] The utility of CEA as a single diagnostic test is thus questionable, especially in case of low-level (5–10 μg/l) elevations.[48] A CEA threshold greater than 15 μg/l and/or observation of temporal trends (eg, ≥25% increase from previous values) have been proposed as a more appropriate strategy for the detection of relapse, but only in combination with imaging techniques.[49,50] The value of intensive CEA testing was 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 intent-to-cure CRC treatment.[13,41]

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 the operation to detect and remove (or mark for surgical removal) synchronous polyps.[34] Alternatively, if a full examination cannot be performed preoperatively (eg, due to bowel obstruction), colonoscopy should be done early after operation (within 3–6 months).[34,36] Perioperative polyp ablation aims to reduce the incidence of false "metachronous" colorectal tumors observed early during surveillance that are, in reality, missed synchronous lesions.[30] Hence, a full and high-quality perioperative endoscopy is warranted.[30] 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 as well as the incidence of intraluminal cancers and their curability. Based on systemic reviews, colonoscopy has a high sensitivity, namely, 95% in the detection of CRC,[51] and 75% to 93% in the detection of adenomas 6 mm or larger.[52] On the other hand, its target cancers are rare, with the cumulative incidence of 2.7% for AR and 2.2% for metachronous CRC.[15] Still, these lesions are curable, with 67% to 86% of metachronous CRC amenable to a curative-intent treatment.[34] In a prospective trial of 259 patients undergoing a multimodal surveillance, the highest proportion (44%) of resectable recurrences was detected by colonoscopy. Local relapses detected by colonoscopy were resectable in 6 out of 7 cases, and metachronous cancers in 3 out of 3 cases.[53] Similarly, in another study, endoscopy detected a high proportion of curable recurrences, and 8 (62%) out of 13 malignant lesions detected by this modality were eligible for a salvage surgery.[54]

In a retrospective study of CRC patients who survived more than 1 year after the operation, individuals who underwent colonoscopy had 5-year death risk reduced by 43% as compared with patients without colonoscopy,[55] although it is possible this risk reduction was inflated by a better performance status in the colonoscopy group. In another study, surveillance endoscopies did not influence the CRC-specific mortality in patients older than 65 years diagnosed with localized or regional stage CRC.[56] On the other hand, 2 meta-analyses that compared protocols utilizing colonoscopy with studies without this procedure found that colonoscopy was associated with a better OS (hazard ratio [HR], 0.65; 95% CI, 0.53–0.81).[57,58] More frequent colonoscopies, however, failed to provide any additional survival benefit in the meta-analyses.[57,58] This finding is corroborated by the results of a unique randomized trial comparing an 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), 5-year OS was not affected (77% vs 73%). Considering the uncommonness of intraluminal recurrences and their timing (mostly detected in the first 2–3 years),[15] decreasing the number of follow-up colonoscopies appears to be justified.

Virtual colonography Contrast-enhanced computed tomographic colonography (CTC) has been suggested as an alternative to conventional colonoscopy. Following a bowel inflation, CTC is capable of simultaneous detection of 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 2 patients (1%), but also called 2 patients positive for diminutive anastomotic lesions later found to be nonneoplastic.[60]

Abdomen ultrasound While surveillance utilizing the liver ultrasound is not recommended by international guidelines,[61] it has been frequently employed by studies investigating multimodal follow-up.[41,53,62-64] In a prospective database study of 243 individuals who underwent a curative CRC resection, patients were referred for imaging with abdominal ultrasound and abdominal / pelvis CT alternating every 6 months. In this protocol, the interval abdomen ultrasound expedited detection of hepatic recurrences in 12 patients (32% of patients in whom liver metastases were detected), which accelerated the 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, for example, CEA testing. Indeed, in another study, ultrasound was the first test to detect liver metastasis in 5 out of 230 patients, 4 of whom had elevated CEA levels. Additionally, ultrasound also contributed multiple false-positive and false-negative findings.[61] Overall, this discourages follow-up with ultrasound.

Ultrasound sensitivity and specificity may be enhanced via the administration of intravenous contrast (contrast-enhanced ultrasound [CEUS]). In a multicenter German study, 290 CRC survivors (stage >IIa) were prospectively assessed with CEUS. In 26 out of 290 patients, unenhanced ultrasound detected 45 liver metastases. In contrast, CEUS detected liver metastases in 44 out of 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 magnetic resonance imaging [MRI]).[66] Also, CEUS was suggested as a substitute for abdomen CT by the European Society Medical Oncology guidelines on colon cancer in 2013, however the latest version of the guidelines published in 2020 does not discuss this option.[67]

Magnetic resonance While pelvic MRI is widely employed preoperatively to stage rectal cancers, postoperative surveillance with MRI is rarely done. Titu et al[68] 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. A recurrent locoregional cancer was diagnosed on MRI with 87% sensitivity (26 out of 30 true positive recurrences; 3 out of 4 missed cases were AR) and 86% specificity. Six patients with local recurrence (20%) were eligible for a salvage surgery, but only 2 of them had a recurrence first discovered on MRI. Accordingly, frequent pelvic MRI used to detect operable recurrences in less than 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 to 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 individuals (24%) 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). The detection of operable liver metastases in only 1% of CRC individuals offered MRI advocates against the 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 the 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 the number of treatment failures (unresectable recurrences and deaths in 29% cases in the intervention group, and 24% in controls).[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 a high CEA level (cutoff 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 a CEA level greater than 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 Liquid biopsy is one of the most promising techniques applicable for oncological monitoring. It includes 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 on radically operated patients with stage I to III CRC, 10 out of 13 individuals (77%) in whom ctDNA was detected in postoperative plasma experienced a recurrence, and a positive ctDNA preceded radiologic

or clinical evidence of recurrence by a median of 3 months. In contrast, none of the 45 patients in whom ctDNA was not detected in plasma experienced relapse.[73] In another report, ctDNA-positive patients at postoperative day 30 were 7-fold more likely to have 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 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 disease recurrence (eg, miR-21, miR-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 postoperative blood samples associates with a higher metachronous metastasis rate (27.3% vs 7%) and a higher 24-month mortality rate (15.2% vs 1.8%) in surgically treated CRC patients.[77] A test based on the detection of gene methylation markers, the *KRAS* gene mutations and fecal immunochemical test 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. A fecal immunochemical test alone is, however, inadequate for surveillance due to its low sensitivity for the detection of local recurrences (33%) and metachronous CRC (15%).[79]

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 as they include patients with various CRC stages and offered diverse treatment types.

Despite the extreme heterogeneity in study designs, almost all RCTs conducted in the last 3 decades concluded that more intense follow-up does not improve OS or cancer-specific survival (TABLE 1). It was observed that intensive surveillance may permit an earlier detection of relapse, and thus shorten the relapse-free survival as observed in the Italian GILDA (Gruppo Italiano di Lavoro per la Diagnosi Anticipata) trial (relapse-free survival 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[80] used frequent colonoscopies and managed to increase the ratio of reoperable luminal relapses from 33% to 69%, and improve survival in patients who underwent the recurrence resection. In the Follow-up After Colorectal Surgery (FACS) trial, intensive CT imaging or CEA monitoring increased the number of salvage surgeries when compared with a minimal follow-up (salvage surgeries performed in 8% patients monitored with CT, 6.7% with CEA, 6.6% with both CT and CEA, and 2.3% in the minimal follow-up group).[81] More than two-thirds of patients who underwent a curative-intent retreatment were alive at a median follow-up of over 4 years from the time of relapse detection.[81] 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 were corroborated by the results of a landmark COLOFOL trial which noted 5-year mortality of 10.6% and 11.4% in the low- and high-intensity follow-up groups, respectively.[82]

Some confusion on the value of intensive CRC surveillance has been caused by results of meta-analyses (TABLE 2). Renehan et al[83] who assessed data from studies delivered between 1995 to 1998 observed that frequent patient monitoring could reduce the all-cause mortality by 20%. In 2007, Tjandra et al[58] analyzed results of 8 RCT involving 2923 patients and 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%. Similar conclusions were reached by Pita-Fernandez et al,[57] 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). Noteworthy, none of the individual RCTs included in these meta-analyses, except one, reported the OS benefit. The results of large RCTs published over the last 6 years altered outcomes of meta-analyses. Among them, Mokhles et al[84] failed to detect benefit in OS associated with more intensive monitoring protocols. This result is reinforced by the latest iteration of the Cochrane review that used data from 19 studies involving 13 216 participants. While the intensive follow-up could

TABLE 1 Overview of prospective randomized controlled trials comparing structured surveillance protocols in patients radically treated for colorectal cancer (continued on the next page)

Study, year	Country	Cases	Intensive follow-up	Standard follow-up	Duration, mo	Relapse, %	Salvage surgery, HR (95% CI)[a]	CRC-specific survival, HR (95% CI)[a]	Overall survival, HR (95% CI)[a]
COLOFOL, 2018[82]	Denmark Sweden, Uruguay	2509, stage II–III	CEA at 1 month; CT (tx, abd) and CEA at 6, 12, 18, 24, and 36 months	CEA at 1 month; CT (tx, abd) & CEA at 12 and 36 months	Median, 60	20.1	NR	0.93 (0.72–1.2)	0.92 (0.73–1.17)
CEA Watch, 2017[41]	The Netherlands	3223, stage I–III	Physical, CT (tx, abd, pelv) annually for 3 years; CEA every 2 months for 3 years, then every 3 months for next 2 years; CXR, US annually for 3 years	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 CXR, US every 6 month for 3 years, then next 2 years	60	7.5	NR	0.78 (0.48–1.27)	0.73 (0.47–1.15)
Sobhani, 2018[70]	France	239, stage III–IV and II perforated	PET every 6 months for 3 years; physical, CEA, CA19-9, and FBC every 3 months for 3 years; US and CXR at 3, 9, 25, 21, 27, and 33 months; CT (tx, abd, pelv) every 6 months for 3 years; colonoscopy at 12 and 36 months	Physical, CEA, CA19-9, and FBC every 3 months for 3 years; US and CXR at 3, 9, 25, 21, 27, and 33 months; CT (tx, abd, pelv) every 6 months for 3 years; colonoscopy at 12 and 36 months	36	35.6	NR	1.68 (0.61–4.66)	1.9 (0.77–4.67)
GILDA, 2016[62]	Italy, Spain, United States	1228, Dukes B2–C	Physical, FBC, CEA, and CA19-9 at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 60 months; US at 4, 8, 12, 16, 24, 36, 48, and 60 months; CXR and colonoscopy annually for 5 years; CT (pelv) in rectal cancer at 4, 12, 24, and 48 months	Physical and CEA at 4, 8, 12, 16, 20, 24, 30, 42, 48, and 60 months; US at 4 and 16, months; colonoscopy at 12 and 48 months; additionally in rectal cancer: rectoscopy at 4 months; CXR at 12 months; US at 8 and 16 months; single CT (pelv) if required for baseline postadjuvant assessment	Median, 62	20.4	1.24 (0.85–1.79)	1.16 (0.65–2.09)	1.13 (0.87–1.45)
FACS, 2014[81]	United Kingdom	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); CEA + CT not better than either alone	1.13 (0.73–1.74)	1.17 (0.84–1.64)
Wang, 2009[80]	China	326, Dukes A–C	Colonoscopy, physical, CEA, CXR, and US/CT (abd) every 3 months for 1 year, then every 6 months for next 2 years, then annually	Colonoscopy at 6, 30, and 60 months; physical, CEA, CXR, and US/CT (abd) every 3 months for 1 year, then every 6 months for next 2 years, then annually	64–79	9.5 by endoscopy	1.1 (0.44–2.79)	0.99 (0.6–1.61)	0.76 (0.48–1.22)
Sobhani, 2008[90]	France	130, stage III–IV	PET at 9, 15 months and "conventional FU": CEA, CA19-9, and US every 3 months (except at 9 and 15), CXR every 6 months; CT (abd) at 9 and 15 months	"Conventional FU": CEA, CA19-9, and US every 3 months (except at 9 and 15), CXR every 6 months; CT (abd) at 9 and 15 months	24	35.4	7.5 (1.79–31.49)	NR	NR
Rodriguez-Moranta, 2006[53]	Spain	259, stage II–III	Physical, CEA, and blood every 3 months for 5 years; US/CT every 6 months for 56 months; CXR, colonoscopy annually for 5 years	Physical, CEA, and blood tests every 3 months for 5 years	48	26.6	1.87 (0.9–3.9)	0.77 (0.39–1.53)	0.79 (0.45–1.4)

TABLE 1 Overview of prospective randomized controlled trials comparing structured surveillance protocols in patients radically treated for colorectal cancer (continued from the previous page)

Study, year	Country	Cases	Intensive follow-up	Standard follow-up	Duration, mo	Relapse, %	Salvage surgery, HR (95% CI)[a]	CRC-specific survival, HR (95% CI)[a]	Overall survival, HR (95% CI)[a]
Secco, 2002[91]	Italy	192, "high risk"	Physical and 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	"Minimal"	61.5	52.6	1.8 (0.98–3.32)	NR	NR
Shoemaker, 1998[92]	Australia	325, Dukes A–C	CXR, colonoscopy, and CT (abd) annually	CXR, colonoscopy, and CT (abd) only if clinically indicated, or at 5 years	60	36.9	1.14 (0.35–3.65)	NR	0.77 (0.52–1.14)
Pietra, 1998[63]	Italy	207, Dukes B–C	Physical, US, CEA, and CXR every 3 months for 2 years, then every 6 months for next 2 years, then annually; CT (abd), colonoscopy annually	Physical, US, and CEA at 6 and 12 months; CT (abd), CXR, and colonoscopy annually	60	22.2	3.47 (1.46–8.24)	0.64 (0.41–1.01)	0.57 (0.36–0.91)
Kjeldsen, 1997[93]	Denmark	597, Dukes A–C	Physical, DRE, colonoscopy, CXR, gynecology exam, FOB, and blood tests at 6, 12, 18, 30, 36, 48, 60, 120, 150, and 180 months	Physical, DRE, colonoscopy, CXR, gynecology exam, FOB, and blood tests at 60, 120, and 180 months	NR	26	3.18 (1.37–7.36)	0.98 (0.69–1.39)	0.9 (0.67–1.21)
Ohlsson, 1995[94]	Sweden	107, Dukes A–C	Physical, CXR, rigid proctosigmoidoscopy, CEA, FOB, GGTP, and 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, and 24 months; colonoscopy at 3, 15, 30, and 60 months; FSS/colonoscopy to examine anastomosis at 9, 21, 42 months	None; FOB recommended locally every 3 months for 2 years, then annually	66–105.6	32.7	1.7 (0.43–6.75)	0.73 (0.35–1.54)	0.68 (0.36–1.31)
Makela, 1995[64]	Finland	106, Dukes A–C	US at 6 months, and then annually; colonoscopy preoperatively or at 3 months, then annually; FSS in rectal or sigmoid cancer every 3 months	FSS and barium enema in rectal or sigmoid cancer annually	60	40.6	1.73 (0.44–6.88)	NR	0.86 (0.45–1.63)

a Hazard ratio (HR) values as provided by Jeffery et al[13]

Abbreviations: abd, abdomen; ALP, alkaline phosphatase; CT, computed tomography; CEA; carcinoembryonic antigen; 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; pelv, pelvic; tx, thorax; US, ultrasound (liver if not stated otherwise)

TABLE 2 Summary of meta-analyses analyzing impact of more intense surveillance in patients radically treated for colorectal cancer

Name, year	Studies included, n	Patients, n	Overall survival
Renehan, 2002[83]	5	1342	RR, 0.81 (95% CI, 0.7–0.94)
Tjanda, 2007[58]	8	2923	OR, 0.74 (95% CI, 0.59–0.93)
Pita-Fernandez, 2014[57]	11	4055	HR, 0.75 (95% CI, 0.66–0.86)
Mokhles, 2016[84]	7	3325	HR, 0.98 (95% CI, 0.87–1.11)
Zhao, 2019[43]	17	8039	HR, 0.85 (95% CI, 0.74–0.97)
Jeffery, 2019[13]	19	13 216	HR, 0.91 (95% CI, 0.8–1.04)

Abbreviations: HR, hazard ratio; OR, odds ratio; RR, relative risk

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.[13] Additionally, a more intense medical care had little influence on quality of life, depression, and anxiety.[13] Consequently, a consensus has been reached that extended follow-up provides little, if any, benefits.

Special considerations **T1 cancers** Colorectal cancer confined to the 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%).[85] A Dutch retrospective study reported recurrences of T1 CRC in 6.2% and 3.4% in patients treated endoscopically and surgically, respectively.[86] In 2 Japanese studies which reported the results of surgical treatment of T1 CRC endoscopically, recurrences were observed collectively in 3 (1.7%) out of 180 patients in the low-risk group, and 18 (12.7%) out of 142 in the high-risk group.[87,88]

McCain et al[89] 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 more than 80% of relapses in this groups are luminal, they concluded 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 imaging of other body areas or tumor markers. 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 provide special recommendations.

Stage IV No RCT has specifically evaluated the follow-up of patients with stage IV CRC who were radically operated. Retrospective studies report that the majority of recurrences in intent-to-cure metastatic CRC happen early, with 63% to 78% of patients experiencing it during the first 24 months after the 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 that occurs 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 based on good-quality evidence. In the light of results of RCTs and meta-analyses, it is probable that a reduction in the testing intensity would not adversely affect the patients' survival. It remains to be investigated whether this will be reflected in future guideline updates.

Conclusions Owing to the overall increase in CRC incidence and advancements in treatment, the number of patients who undergo a potentially curative CRC therapy is rising. These individuals are at risk of various types of recurrences and new neoplasms, which 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 whether 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 that is followed. Perhaps what we require is a more risk-adapted strategy that focuses on particular diagnostics or abstains from use of some tests based on a particular clinical situation. While there are some aspects 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, for example, ctDNA testing, which by demonstrating a 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 the development of new guidelines to optimize care of CRC survivors.

TABLE 3 Overview of major international guidelines on posttreatment colorectal cancer surveillance

Guideline, year, type of cancer	Physical and history	Computed tomography (thorax, abdomen, pelvis)	CEA	Colonoscopy
ASCO, 2019, stage I–III[95] (maximal setting)[a]	Every 6 months for 3–5 years (in high-risk cancer every 3–6 months)	Annually for 3 years (in high-risk cancer every 6–12 months)	Every 6 months for 3–5 years (in high--risk cancer every 3–6 months)	Perioperatively, at 1 year, then every 5 years or earlier as clinically indicated (up to age of 75 years); additionally, in rectal cancer treated without pelvic radiation, or without TME, or after endoscopic treatment, or if CRM+: FSS/EUS every 6 months for 2–5 years)
ASCO, 2020, stage IV[96] (maximal setting)[a]	Every 3–6 months for 2 years, then every 6 months for 5 years	Every 3–6 months for 2 years, then every 6 months in year 3–5	Every 3–6 months for 2 years, then every 6 months for 5 years	–
ESMO, 2014, colon stage IV[97]	Every 3–6 months for 3 years	Every 3–6 months for 3 years	Every 3–6 months for 3 years	–
ESMO, 2017, rectal[98]	Every 6 months for 2 years	Minimum 2 scans in the first 3 years (more active follow-up if CRM+)	At least every 6 months in the first 3 years (more active follow-up if CRM+)	At 1 year if not done perioperatively; every 5 years (up to age of 75) (more active follow-up for local recurrence if CRM+)
ESMO, 2020, colon stage I–III[67]	Every 3–6 months for 3 years, then every 6–12 months in year 4–5	Every 6–12 months for 3 years, then annually in year 4–5	Every 3–6 months for 3 years, then every 6–12 months in year 4–5	At 1 year, then every 3–5 years (or earlier as clinically indicated)
NCCN, 2020, colon and rectal[99,100]	Stage II–IV: every 3–6 months for 2 years, then every 6 months in year 3–5	Stage II–III: every 6–12 months for 5 years; Stage IV: every 3–6 months for 2 years, then every 6–12 months in year 3–5	Stage II–IV: every 3–6 months for 2 years, then every 6 months in year 3–5	Stage I–IV: preoperatively or within 3–6 months; then at 1, 4, 9 years (after transanal local excision: rectoscopy with EUS/MRI every 3–6 months for 2 years, then every 6 months in year 3–5, and colonoscopy as above)
US Multi-Society Task Force, 2016 (endoscopy)[36]	NA	NA	NA	Preoperatively or within 3–6 months; then at 1, 4, 9 years, then every 5 years (as justified by the patient's life expectancy); additionally, in rectal cancer without neoadjuvant treatment, after surgery without TME, or transanal local excision or ESD: FSS/EUS every 3–6 months for 2–3 years
ESGE/ESDO, 2019, (endoscopy)[34]	NA	NA	NA	Preoperatively or within 3–6 months; then at 1, 4, 9 years (may stop if age >80 years or short life expectancy after the first negative exam)

a The ASCO guidelines are resource stratified (maximal setting refers to availability of high-level/state-of-the art resources and services).

Abbreviations: ASCO, American Society of Clinical Oncology; CRM+, positive circumferential resection margin; CEUS, contrast-enhanced ultrasound; ESD, endoscopic submucosal dissection; ESDO, European Society of Digestive Oncology; ESGE, European Society of Gastrointestinal Endoscopy; ESMO, European Society of Clinical Oncology; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; NA, not applicable; NCCN, National Comprehensive Cancer Network; TME, total mesorectal excision; others, see **TABLE 1**

ARTICLE INFORMATION

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