Current Colorectal Cancer Reports (2019) 15:79–89
https://doi.org/10.1007/s11888-019-00433-3

SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (S HUERTA, SECTION EDITOR)

Trends in Colorectal Cancer Surveillance: Current Strategies and Future Innovations-

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Published online: 26 April 2019

Abstract

Purpose of Review This review article strives to reflect on the historic surveillance debate in colorectal cancer, outline current strategies, and guidelines, and discuss new techniques being explored in surveilling colorectal adenocarcinoma.

Recent Findings Within the past decade, major governing bodies have proposed surveillance guidelines with the goal of earlier identification of cancer recurrence, thereby possibly reducing the morbidity and mortality of necessary interventions. With the innovation of tissue-specific tumor markers and fluorescence endoscopy, the approach to surveillance may be changing. The use of these new modalities allows clinicians to provide a more risk-adjusted basis for care, which is predicted to equate to higher quality care.

Summary The current surveillance guidelines provide an evidence-based framework for physicians and surgeons to follow. However, the influence of these novel surveillance techniques in colorectal cancer is yet to be realized and they ultimately have the potential to revolutionize care.

Keywords Metachronous · Recurrence · Guidelines · Therapies · Novel

Introduction

In 2018, colorectal cancer (CRC) accounted for over 1.8 million new cancer-related cases and 881,000 deaths worldwide, ranking it third in terms of incidence (10.2%) and second in mortality (9.2%) for both sexes [1]. In the USA, CRC similarly ranks second in cancer-related mortality in both sexes (8%) following lung cancer at 25% [2]. Dating to the early 1940s, CRC was responsible for the highest cancer-related mortality in the USA, but due to evolution and implementation of screening strategies coupled with early intervention and lifestyle modifications, these mortality statistics have taken a downward trend. The 5-year survival rate after resection of CRC has substantially improved from 65 to 90% when identified at stage I (locoregional invasion only) as opposed to stage III (regional lymphatic metastasis), emphasizing the need for adequate screening [3••]. However, 30–40% of these patients will still experience recurrence in their lifetimes, making surveillance after resection of pivotal importance.

The natural history of colorectal cancer indicates that metachronous lesions peak within the first 2–3 years post-curative resection; 80% in the first 2 years and upwards of 90% in the first 3 years [4]. Common sites of recurrence include the residual colon, liver, and lungs [3••]. The prevalence of metachronous lesions increases in individuals with familial syndromes [5, 6]. Postsurgical surveillance may allow early identification of these metachronous cancers, possibly leading to more efficient interventions and reduction of the morbidity and mortality associated with therapy [3••].

The goal of this manuscript is to highlight surveillance strategies in stage I–III CRC as dictated by the American Joint Committee on Cancer (AJCC) [7] as described in Table 1 and to discuss upcoming trends currently under investigation. This article does not review follow-up after the resection of stage IV CRC or patients who have undergone

This article is part of the Topical Collection on *Surgery and Surgical Innovations in Colorectal Cancer*

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nonsurgical interventions such as endoscopic resection of their tumor or chemoradiation therapy only.

Methods

An extensive literature search was conducted using these keywords: colorectal cancer, surveillance, recurrence, guidelines, therapies, and novel. All available literature was reviewed regardless of the type of article, date of publication, language, or use of human versus animal subjects. PubMed, EBSCOhost, and Ovid were the primary databases used to find literature up to December 2018. Non-translated articles, duplications, and articles older than 5 years were excluded to ensure this review reflects the most recent relevant literature. Exceptions to the exclusion criteria included relevant hallmark papers that have influenced current practice guidelines.

Overview of Current Surveillance Techniques

In the USA, at least 500,000 patients undergo one or more of these postoperative surveillance modalities every year, thus it is important to what is being currently used [3••]. These include (1) physical exam (2) laboratory testing, (3) imaging, and (4) endoscopy which are further summarized in Table 2.

Physical Exam

No diagnostic test or imaging modality should be ordered without a good history and physical exam; the role of physical exam could not be overemphasized. Despite its low sensitivity in detecting locoregional recurrence in asymptomatic patients at 6%, it has been shown to be effective in detecting secondary malignancies, such as in breast, prostate, and thyroid cancers [3••]. It also has great utility in identifying side effects of medical therapy and is essential to the psychological aspect of cancer therapy, which has been found to be a positive factor in overall survival [3••].

Laboratory Testing

Laboratory evaluation is of great importance, especially when paired with the appropriate imaging. Serum CEA, which is currently the only laboratory test approved for CRC surveillance, is an epithelial tumor marker which is expressed in up to 70% of colorectal cancers and is one of the earliest indicators of recurrence in 38–66% of patients [3••, 8, 12]. Its sensitivity varies by the location of recurrence; for liver metastasis, its sensitivity is 78% followed by locoregional recurrence at 45% and lastly at 42% for lung metastasis [3••]. Because of its low overall sensitivity at 64%, its not commonly used as a sole indicator for recurrence [8, 12]. CEA levels of ≥ 5 ng/ml should increase a clinician's suspicion for postoperative recurrence [13]. However, a retrospective review by Litvak et al. reported alarming false positive rates of up to 40% when CEA levels of ≥ 5.1 ng/dl were used as the cutoff for recurrence detection in postoperative surveillance [13]. Furthermore, the levels of CEA may be influenced by the presence of other malignancies such as in the breast, pancreas, and lung, as well as in chronic inflammatory states as in inflammatory bowel disease or in active smokers [14]. These findings underscore the importance of monitoring CEA trends as opposed to single values and the need for levels to be confirmed using other surveillance techniques [8]. Regardless of the trend, severely elevated CEA levels > 15 ng/ml correlate with poor prognosis [14].

Although serial hemoglobin, liver function tests, and fecal occult blood testing may have some efficacy in screening, they are not recommended in surveillance due to their low sensitivity and specificity for detecting CRC recurrence [15].

Table 1 AJCC classification of colorectal cancer

Stage	TNM classification	Description
0	Tis N0 M0	Tumor limited to mucosa
I	T1 N0 M0	Tumor invading submucosa
	T2 N0 M0	Tumor invading muscularis propria
II	(A) T3 N0 M0	Tumor invading subserosa but no other adjacent organs
	(B) T4 N0 M0	Invading adjacent organs or penetrating into visceral peritoneum
III	(A)T1–2 N1 M0	Metastasis to 1–3 regional lymph nodes with tumor invading submucosa and/or muscularis propria
	(B) T3–4 N1 M0	Metastasis to 1–3 regional lymph nodes with tumor invading subserosa, visceral peritoneum or adjacent organs
	(C) Any T N2 M0	Metastasis to 4 or more lymph nodes
IV	Any T, any N, M1	Distant metastasis

AJCC, American Joint Committee on Cancer; T, tumor; N, nodes; M, metastasis

Table 2 Colorectal cancer surveillance modalities

Surveillance techniques	Sensitivity	Specificity
Physical exam [3••]	6%	Not specified
Laboratory testing [8]		
Serum CEA	64%	90%
Imaging [9, 10]		
CT	70–85%	50–92%
CEUS	80–90%	Not specified
Abdominal US	50–76%	50–60%
MRI	66–95%	76–86%
F-FDG PET-CT	22–98%	93–98%
CT colonography	96–100%	Not specified
Endoscopy [11]		
Colonoscopy (lesions ≥ 10 mm)	98%	99%

CEA, carcinoembryonic antigen; *CEUS*, contrast-enhanced ultrasonography; *US*, ultrasonography; *CT*, computed tomography; *FDG*, fluorodeoxyglucose; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography

Imaging

Imaging can identify both intraluminal and extraluminal colonic recurrences, however, the main role of surveillance imaging is for early detection of metastasis most frequently found in the lungs and liver. CT is the modality of choice and is more sensitive than ultrasound (US) or CEA alone in detecting liver metastasis (sensitivities of 0.67, 0.43, and 0.33 respectively [3••]). CT imaging paired with CEA has the highest sensitivity for recurrence detection, thus their simultaneous use is recommended. Other imaging methods such as contrast-enhanced US (CEUS) have comparable sensitivity rates to CT in detecting liver metastasis (80–90%) [16]. CEUS can detect lesions of ≥ 10 mm due to its ability to highlight vascularities. However, similar to the native US, its sensitivity can easily be affected by a lack of operator proficiency, obesity, or intestinal interposition [16]. While liver metastases are common of colonic origin, pulmonary metastasis tends to be of rectal origin and are present in up to 25% of patients; these lesions are also best detected by CT [17].

Other imaging modalities such as MRI may have higher sensitivities (66–95%) compared to CT [9], however, its limitations including higher cost, lower availability, and contraindication to multiple implantable devices (e.g., cardiac defibrillators, pacemakers, cochlear implants, metallic foreign bodies, etc.) make it less conducive as surveillance strategy. Currently, MRI and endorectal US are mainly confined to rectal cancer staging. The role of FDG PET-CT in surveillance also remains controversial; however, it gains its significance in the setting of equivocal thoracoabdominal imaging and in cases where imaging is negative but CEA levels are persistently trending up [12].

Endoscopy

Endoscopic techniques have been used over the past century; however, colonoscopy specifically gained traction in the 1960s [18]. Since its development in Japan, colonoscopy has been the gold standard for screening and surveillance due to both its diagnostic and therapeutic capabilities. CT colonography has been shown to be an acceptable alternative at lesser intervals, with sensitivities up to 96–100% [9] for patients who are unable to tolerate colonoscopy or defer endoscopic evaluation. However, a prospective study conducted by Weinberg et al. demonstrated that CT colonography was an inferior method due to its poor ability to identify flat polyps including polyps of < 5 mm, and its decreased sensitivity and specificity (85.8; 95% CI, 80.9–90.7); thus colonoscopy is still the preferred method [10]. Nonetheless, it is important to still be aware of the risks with colonoscopy including perforation (0.05%), bleeding (0.26%), and mortality (0.0029%) [19] and rarely gas explosion. Specifically, perforation and bleeding risks increase in diagnostic colonoscopy especially in the setting of interventions such as polypectomies; 0.08 and 0.98% respectively [19].

Overview of Current Guidelines

Over the past decade, multiple major organizations have offered guidelines on the use of current surveillance techniques in proper postoperative follow-up. Table 3 discusses the most recent guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Colon and Rectal Surgeons (ASCRS), American Society of Clinical Oncology (ASCO), American Cancer Society (ACS), U.S. Multi-Society Task Force (USMTF), and the European Society for Medical Oncology (ESMO). Figure 1 provides an example representative schematic based on the most recent ASCRS guidelines.

Of note, Table 3 mainly highlights surveillance strategies in locally advanced disease (stage II–III, see Table 1), as the current guidelines for resectable stage I cancer in the literature are inconclusive. So far, ASCO and NCCN both suggest that extra endoscopic surveillance is not required in addition to the colonoscopy performed 1 year after resection paired with routine follow-up colonoscopy [15, 20]. However, the NCCN still recommends that all other surveillance modalities, including clinical exam, CEA testing, and imaging be continued at the same frequency for patients with stage I disease as is conducted with patient with more advanced disease (stages II and III) [20].

The guidelines described are for average-risk individuals and must be adjusted for those in high-risk categories such as those with Lynch syndrome, familial adenomatous polyposis, MYH-associated polyposis, and hyperplastic polyposis

Table 3 Current colorectal cancer surveillance guidelines

	Stage	History and physical	Endoscopy	Imaging (CT ABD/pelvis)	CEA
NCCN [20] (2014)	II–III	•Every 3 to 6 months for 2 years for ≥ T2 tumors, then every 6 months for a total of 5 years	Colon: colonoscopy •1 year if no preoperative colonoscopy •If advanced adenoma detected, repeat in 1 year, if none, repeat in 3 years, then every 5 years Rectum: flexible sigmoidoscopy ± EUS or MRI •Trans-anal excision only: every 3 to 6 months for 2 years, then every 6 months for a total of 5 years	Colon: •Every 6 to 12 months, up to 5 years in those with high risk of recurrence[a,b] Rectum: •Every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years in those with high risk for recurrence [a]	•Every 3 to 6 months for 2 years, then every 6 months till 5 years
ASCRS [21] (2015)	I–IV	•Every 3 to 6 months for 2 years, then every 6 months till 5 years[c]	Colon: colonoscopy •1 year after preoperative colonoscopy •3–6 months after surgery if colon is not cleared preoperatively[c] •Follow-up colonoscopies every 3 to 5 years depending on findings from first post-operative colonoscopy Rectum: proctoscopy/sigmoidoscopy (± EUS) •Every 6–12 months for patients with primary anastomosis for 3–5 years •Every 6 months for local excision for 3–5 years	•Annually for 5 years[c]	•Every 3 to 6 months for 2 years, then every 6 months till 5 years[c]
ASCO [15] (2013)	II–III	•Every 3 to 6 months for 5 years[c]	Colon: colonoscopy •As soon as adjuvant chemotherapy is complete if there is no preoperative colonoscopy •In the case of preoperative colonoscopy, perform 1 year after preoperative colonoscopy or resection •Every 5 years if prior colonoscopies are normal Rectum: proctosigmoidoscopy •Every 6 months for to 5 years in the setting of no prior pelvic radiation	Colon: •Annually for 3 years •Every 6–12 months for 3 years in high-risk patients[ab] Rectum: •Annually for 3 to 5 years •Every 3–6 months in high-risk patients[a]	•Every 3–6 months for 5 years[c]
ACS [22] (2015)	II–III	•Every 3 to 6 months for 2 years, then every 6 months for 5 years	Colonoscopy: •1 year after surgery •If advanced adenoma noted, repeat in 1 year •If no advanced adenoma, repeat in 3 years •If still negative, repeat every 5 years	•Every 12 months for 5 years	•Every 3 to 6 months for 2 years, then every 6 months till 5 years
U.S. MSTF [23] (2016)			Colon: colonoscopy •1 year after surgery or 1 year after preoperative colonoscopy •3 years after 1st postsurgical colonoscopy •5 years after 2nd postsurgical colonoscopy •Every 5 years until risk outweighs benefit Rectum: •Proctoscopy/sigmoidoscopy (± ERUS) •Every 3 to 6 months for 2–3 years after surgery		
ESMO [24, 25] (2013, 2017)	II–III	Colon:	Colon: colonoscopy	Colon:	Colon

Table 3 (continued)

	Stage	History and physical	Endoscopy	Imaging (CT ABD/pelvis)	CEA
		•Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years Rectum: •Every 6 months for 2 years	•1 year after surgery, then every 3 to 5 years after Rectum: •Colonoscopy every 5 years until 75 years of age	•Every 6 to 12 months for 3 years; CEUS can substitute for abdominal CT Rectum: •Minimum of 2 CT scans for 3 years	•Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years Rectum: •Every 6 months for 3 years

[a] High-risk recurrence includes those with lymphatic or venous invasion by tumor; poorly differentiated tumor (NCCN) [20]

[b] PET-CT scan is not routinely recommended

[c] Same for colon and rectum surveillance

ACS, American Cancer Society; *ASCO*, American Society of Clinical Oncology; *ASCRS*, American Society of Colon and Rectal Surgeons; *CEA*, carcinoembryonic antigen; *CEUS*, contrast-enhanced ultrasound; *CT*, computed tomography; *ERUS*, endorectal ultrasound; *ESMO*, European Society for Medical Oncology; *NCCN*, National Comprehensive Cancer Network; *US*, ultrasound; *U.S. MSTF*, U.S. Multi-Society Task Force

syndrome, or patients with variants of inflammatory bowel disease.

The Surveillance Debate

The literature remains conflicted on the CRC-specific and overall survival benefit of a high-intensity follow-up program versus a less-intensive program [26]. From 1995 to 2018, 12 trials have compared the efficacy and survival benefit of the differing surveillance strategies, as outlined in Table 4. Multiple meta-analyses have analyzed and compared these trials as well. Most recently, a meta-analysis conducted by Pita-Fernandez concluded that there was no difference in the total cancer recurrence rate between the intervention (high-intensity program) and control arms. However, patients in the intervention arms had a higher probability of detection of asymptomatic recurrence, which increased their likelihood of curative surgery, possibly resulting in increased survival ((RR) = 2.59; 95% CI 1.66–4.06) [26].

The COLOFOL trial published in 2018 provides the latest commentary to this debate. This multicenter randomized controlled trial assessed 2555 patients post-curative resection for locoregional disease (stages II or III) after curative resection, investigating the benefits of the differing follow-up programs. Its outcomes revealed that there was no significant difference between groups that received high-intensity and low-intensity follow-up in terms of a 5-year overall mortality (13 vs. 14.1% [risk difference 1.1%; 95% CI, − 1.6 to 3.8%]; $P = 0.43$) or colorectal-specific mortality (10.6 vs. 11.4% [risk difference 0.8%; 95%CI, − 1.7 to 3.3%]; $P = 0.52$) [28]. The high-intensity group did have earlier detection of recurrence as identified by Pita-Fernandez; however, earlier detection did not correlate with a survival benefit [27, 28]. The outcomes of this trial are supported by data from other trials including the FACS trial conducted by Primrose in 2014, as seen in Table 4 [28, 30]. Interestingly, the literature infers that the main benefits of higher intensity follow-up programs are more likely due to better comorbidity management, psychological support, and overall improved health behaviors rather than curative intervention alone [41].

After the review of these trials, it is the opinion of the author that less aggressive surveillance programs have the most benefit to patients as more aggressive schedules have not been shown to improve survival but instead may increase cost burden, exposure to radiation, false positive rates, and the probability of morbid salvage surgeries that may in turn reduce the patient's overall quality of life. The advancement and innovation of CRC therapies and surveillance techniques may also support the case for less aggressive surveillance as these therapies may have better long-term efficacy and the surveillance modalities may also have improved accuracy. Overall, "individualized surveillance programs" based on patient's

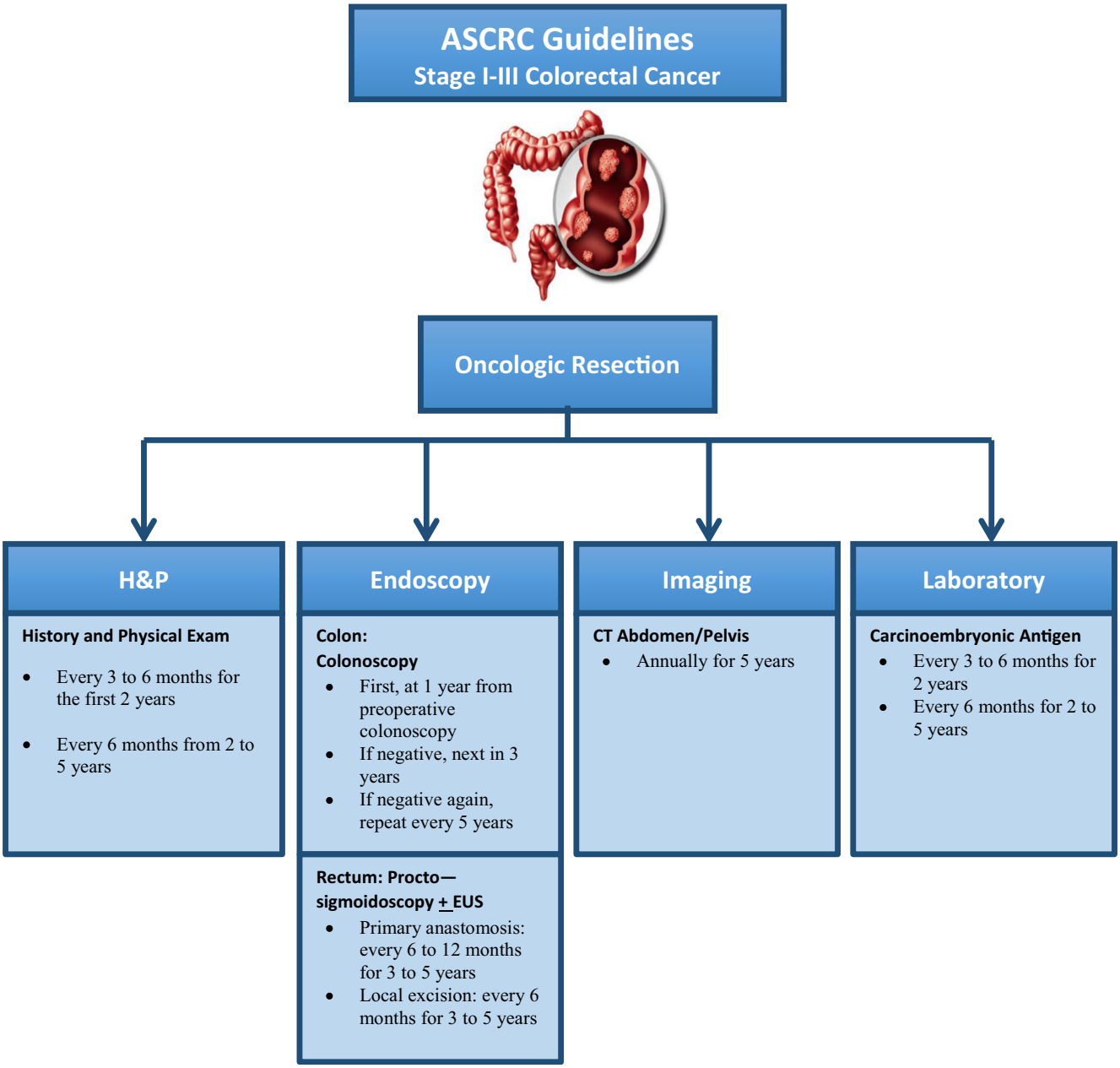

Fig. 1 Overview of colorectal surveillance guidelines [52]

stage and risks factors should have the best outcomes as it optimizes patient care and resources [42].

Novel Surveillance Techniques

As stated above, there has been a surge in the discovery of newer surveillance modalities over the past decades. These methods have the propensity to increase the accuracy of detection and reduce the time to identification of recurrence. The overall survival benefit of these individual techniques have yet to be determined; however, an overview of a few of them are outlined below and in Table 5.

Circulating Tumor DNA

Tumor DNA sequencing has identified multiple somatic mutations linked to CRC; these mutated genes are specifically known as circulating tumor DNA (ctDNA). ctDNA have short half-lives of approximately1.5 to 2 h [43, 44] with appropriate responsiveness to changes in tumor burden. They have been shown to respond to resection or chemotherapy and are sensitive even to micrometastatic disease, making them an

Table 4 Trials in colorectal cancer surveillance

Study	Description of intervention groups	Principal study outcomes
Wille-Jørgensen (2018) [27–29] COLOFOL trial $N = 2555$	•CT chest/abdomen/pelvis and CEA at 6, 12, 18, 24, and 36 months •Endoscopy at the discretion of the treating physician	•Overall mortality: no difference •CRC-specific mortality: no difference
Primrose (2014) [27, 29, 30] FACS trial $N = 603$	•CEA every 3 months for 2 years, every 6 months for 2 years •CT chest/abdomen/pelvis every 6 months for 2 years, then yearly for 3 years	•Overall mortality: insignificant benefit in the intense group •CRC-specific mortality: insignificant benefit in the intense group
Wang (2009) [27, 29, 31] $N = 326$	•Clinic visit every 3 months for the first year, every 6 months for the next 2 years and then annually •CEA, chest X-ray, CT, and colonoscopy every visit	•Overall mortality: no difference •CRC-specific mortality: N/A
Wattchow (2006) [27, 29, 32] $N = 203$	•Postoperative surveillance by surgeons as opposed to general practitioners •More frequent colonoscopy, US, and sigmoidoscopy	•Overall mortality: no difference •CRC-specific mortality: N/A
Rodriguez (2006) [27, 29, 33] $N = 259$	•CEA every 3 months for 4 years for a total of 60 months •US/CT every 6 months for 3 years and then 8 years following that for a total of 56 months •Chest X-ray and colonoscopy at 12, 24, 36, 48, and 56 months	•Overall mortality: no difference •CRC-specific mortality: N/A
Grossman (2004) [24, 27, 34] GILDA trial $N = 985$	•Clinical exam every 4 months for 2 years, then every 6 months for 3 years for a total of 5 years •Laboratory testing including CEA, LFTs, and CBC every 6 months for first 2 years and every 6 months for next 3 years for a total of 5 years •CT and US every 6 months for first 2 years, then annually for a total of 5 years •Chest X-ray and colonoscopy annually for 5 years	•Overall mortality: no difference CRC-specific mortality: N/A
Secco (2002) [27, 29, 35] $N = 337$	•Intervention group divided into high- vs. low-risk groups for recurrence High-risk group: •Clinical exam and CEA every 3 months for 2 years, every 4 months in the 3rd year, and every 6 months for the last 4th and 5th year •Proctosigmoidoscopy annually for first 5 years •Abdominal and pelvic US every 6 months in the first 3 years and yearly for the 4th and 5th year Low-risk group: •Clinical exam and CEA every 6 months for 2 years and annually in the 3rd, 4th, and 5th years •Proctosigmoidoscopy annually for 2 years and every 2 years after •Abdominal and pelvic US every 6 months for 2 years and annually after	•Overall mortality: lower in risk-adapted group •CRC-specific mortality: N/A
Schoemaker (1998) [27, 29, 36] $N = 325$	•Clinical visit, CEA, LFTs, blood counts, and FOBT every 3 months for the first 2 years, then every 6 months till 5 years •Colonoscopy, liver CT, and chest X-ray annually	•Overall mortality: no difference •CRC-specific mortality: N/A
Pietra (1998) [27, 29, 37] $N = 207$	•Clinical exam every 3 months for 2 years, then every 6 months for another 2 years, then annually	•Overall mortality: lower in intense group •CRC-specific mortality: lower in intense group
Kjeldsen (1997) [27, 29, 38] $N = 597$	•Clinical exam at 6, 12, 18, 30, 36, 48, 60, 120, 150, and 180 months after surgery	•Overall mortality: no difference •CRC-specific mortality: no difference
Makela (1995) [27, 29, 39] $N = 106$	•Patients with sigmoid or rectal tumors had a flexible sigmoidoscopy every 3 months •First postoperative colonoscopy performed at 3 months if not done preoperatively, then annually •Primary site and liver US 6 months postoperatively, then annually	•Overall mortality: no difference •CRC-specific mortality: N/A
Ohlsson (1995) [27, 29, 40] $N = 107$	•Clinical visit every 3 months for 2 years, then every 6 months for 1.5 years, then annually for a total of 60 months Clinical visit contained a clinical exam, CEA, ALP, GGT, fecal hemoglobin, CXR, and rigid proctosigmoidoscopy •Endoscopic examination of anastomosis at 9, 21, and 42 months •Colonoscopy at 3, 15, 30, and 60 months •CT pelvis at 3, 6, 12, 18, and 24 months.	•Overall mortality: no difference •CRC-specific mortality: no difference

ALP, alkaline phosphatase; *CBC*, complete blood count; *CEA*, carcinoembryonic antigen; *CRC*, colorectal cancer; *CT*, computed tomography; *CXR*, chest X-ray; *FOBT*, fecal occult blood test; *GGT*, gamma-glutamyl transferase; *LFT*, liver function test; *US*, ultrasound

effective marker. Tie et al. conducted a multicenter prospective study ($n = 250$) to determine if levels of ctDNA could be a biomarker for residual disease in patients with stage II CRC after resection and adjuvant chemotherapy [44]. Patients with elevated serial ctDNA levels after chemotherapeutic interventions were found to be at higher risk for recurrence (HR, 18;

Table 5 Overview of novel surveillance techniques

	Advantages	Limitations
Circulating tumor DNA (ctDNA) [43–45]	•Mutations are patient- specific •Responsive to resection and chemotherapy •Sensitive to micro-metastatic disease •Median lead time from detection to radiologic proof ~ 5 months	•Not all patients harbor ctDNA mutations
Vascular endothelial growth factor (VEGF) and cyclin D1 (CCND1) [46]	•Combined overexpression is linked to poor DSF and OS •Associated with increased relapse rate	•Tissue sample required—expression is detected through immunohistochemical staining of tissue and evaluation by a pathologist
Serum pentraxin-3 (PTX3) [47]	•Levels of PTX3 of ≥ 12.6 correlated with poorer 5-year survival in CRC patients	•Expressed by multiple other malignancies (lungs, pancreas, prostate) •Optimal cut-off for PTX3 levels are still to be determined
Branched-chain amino acid transaminase 1 *(BCAT1)* and Ikaros family zinc finger protein 1 *(IKZF1)* [25, 48, 49]	•These tumor markers can differentiate between benign colorectal epithelium and adenocarcinoma •Levels decline with surgical intervention and chemotherapy •Found to be more sensitive than CEA to CRC detection (67.9 vs 32.1%)	•Expression not limited to colorectal cancer •No studies have been conducted on its effects on overall survival
Recurrence scoring [50••, 51]	•Risk prediction score is obtained prior to therapeutic intervention •Involves PCR analysis of 12 genes (7 recurrence genes, 5 reference genes)	•Tissue sample required
Endoscopic techniques [50••, 51] •Chromoendoscopy: use of chemical dye to differentiate adenoma from neoplasia •Autofluorescence imaging: use of wavelength variations of light "fluorophores" to differentiate normal mucosa from neoplastic tissue •Confocal laser endomicroscopy: uses low laser power to provide in vivo imaging of cellular architecture allowing for mucosal evaluation down to cellular and subcellular resolutions	•All allow real-time analysis of tissue during endoscopy	•All listed modalities are very costly

CEA, carcinoembryonic antigen; *CRC*, colorectal cancer; *DSF*, disease-free survival; *OS*, overall survival; *PCR*, polymerase chain reaction

95% CI, 7.9 to 40; $P = 2.6 \times 10^{-12}$) as opposed to those with complete resolution of their ctDNA post-intervention. Median lead time from the detection of ctDNA to radiologic proof of recurrence was over 5 months, thus increasing the critical window of opportunity for intervention [44]. Recent studies have correlated assays from point mutations in hotspot mutated genes such as KRAS, PIK3CA, and BRAF to the total quantity of serum ctDNA in approximately 50% of CRC patients as well [43, 45]. However, according to Reinert et al., the main limitation with this technique is that ctDNAs are patient-specific and only a fraction of patients harbors such mutations [45].

Vascular Endothelial Growth Factor and Cyclin D1

Vascular endothelial growth factor (VEGF) is well known for its role in angiogenesis and endothelial cell proliferation, thereby promoting tumor growth. The expression of cyclin D1 (CCND1) has been shown to positively regulate cell cycle transition from G1 to S as well as induce the production of VEGF; which makes it a potent oncogene for multiple malignancies, including CRC [46]. In 2013, Tsai et al. conducted a study on patients with stages II–III CRC which revealed that the overexpression of VEGF and cyclin D1 had a negative synergistic effect by significantly reducing disease-free survival ($P = 0.004$) and overall survival ($P = 0.001$) of CRC patients [46]. A univariate analysis of the combined overexpression of these factors was also linked to increased relapse rates in 64% of patients ($P = 0.013$) compared to when these factors were expressed individually [46]. These results suggest that testing for VEGF and cyclin D1 overexpression postoperatively may be a key determinant in predicting relapse, thus possibly altering surveillance aggressiveness or need for chemotherapies.

Serum PENTRAXIN-3

Pentraxin 3 (PTX3), a member of the pentraxin superfamily, has also been found to be an inflammatory tumor marker often

involved in the immune regulation of cancer, similar to C-reactive proteins [47]. It is expressed in various malignancies (e.g., lung, pancreas, prostate) and additionally promotes tumor growth by increasing tumor insensitivity and angiogenesis through unknown mechanisms. According to Bin et al., this marker could also be used as an effective prognostic indicator and surveillance technique in CRC. Initially, his retrospective single-center study of 263 patients post-curative resection of CRC identified that mean serum PTX3 levels were elevated in CRC patients as opposed to their healthy controls (13.8 ∓ 3.2 ng/ml vs. 3.3 ∓ 1.2 ng/ml; $P < 0.001$) [47]. These patients were subsequently divided into two groups using a PTX3 of 12.6 ng/ml as their cutoff. A univariate analysis of their outcomes revealed that patients with a PTX3 of ≥ 12.6 had a poorer 5-year survival prognosis than their counterparts (76.6 vs. 67.8 years; $P = 0.025$) suggesting that this marker could be used as an effective prognostic tool [47]. There were obvious limitations to this study, including being a single-center study with a relatively small cohort. Additionally, the optimal cut-off for PTX3 is still subject to change and requires that an analysis of multiple studies be performed.

BCAT1 and IKZF1

Branched-chain amino acid transaminase 1 *(BCAT1)* and Ikaros family zinc finger protein 1 *(IKZF1)* are another set of genetic markers associated with CRC recurrence. These genes contain hypermethylated regions with abilities to differentiate between benign colorectal epithelium and adenocarcinoma [25]. Studies conducted by Pederson and Symonds report *BCAT1* and *IKZF1* sensitivity rates of 62–66% and specificity rates of 92–94%, making it an effective screening tool [48, 49]. In addition, these markers declined in methylation signaling after chemotherapeutic and surgical interventions, validating their importance in surveillance [25, 48, 49]. Young et al. compared the efficacy of *BCAT1/IKZF1* to CEA and found these markers to be at least two times more sensitive than CEA (67.9 vs. 32.1%) in detecting any type of CRC recurrence [25]. There were no major differences found in the specificities of these two tests (87.2% for *BCAT1/IKZF1* and 93.6% for CEA; $P = 0.210$) [25]. The outcomes of this study suggest that *BCAT1/IKZF1* could be an additional novel marker in detecting and surveilling CRC recurrence. The main limitation of this hypothesis is that *BCAT1/IKZF1* expression was not limited to CRC, which may affect its use in surveillance. In addition, this study did not assess the effects of *BCAT1/IKZF1* on overall survival.

Recurrence Score

All of the above assays are obtained after surgical resection; however, the Oncotype DX Colon Recurrence Score (Genomic Health, Inc., Redwood, CA) is a multi-gene panel calculated prior to therapeutic intervention to predict the risk of recurrence after treatment. This panel was developed after reviewing tumor expression data from over 1800 patients from four independent randomized trials [50••]. The score is calculated through a quantitative reverse transcriptase polymerase chain reaction assay that detects the expression of seven recurrence genes and five reference genes, for a total of 12 genes [50••]. Its positive correlation with recurrence has been validated by multiple prospective trials, also making it a promising tool for personalized surveillance [50••, 51].

Endoscopic Techniques

Advancements in endoscopic techniques over the standard white-light colonoscopy are also underway. The commonality among these techniques is that they employ methods that highlight neoplastic tissue from normal colonic mucosa that would otherwise not be identified by the naked eye. Chromoendoscopy uses a chemical dye to highlight different types of epithelia making it easier to differentiate adenomas from neoplasia [50••]. Similarly, autofluorescence imaging (AFI) endoscopy uses shorter wavelengths of light to stimulate substances in the tissues named "fluorophores" to emit longer fluorescent wavelengths. The quantity of fluorophores vary between normal mucosa and neoplastic tissue thus making neoplasia easily identifiable [34]. Lastly, confocal laser endomicroscopy (CLE) allows for in vivo imaging of colonic mucosa down to cellular and subcellular resolutions. This modality applies fluorescent dyes to the tissues, which produce an image of the cellular matrix when excited by a low-power laser. It allows for real-time differentiation of low-grade versus high-grade neoplasia without needing to externalize the tissue [50••, 51].

While these modalities seem promising, they are yet to show their marked superiority in recurrence detection as opposed to standard endoscopy, and the cost of these modalities remains a limiting factor for widespread use [50••].

Implications in Clinical Practice

It is clear that the burden of CRC does not stop at curative resection; thus, obtaining appropriate surveillance is imperative in dictating a patient's survival and overall wellbeing. The proposed guidelines give practicing clinicians a framework to follow when caring for their patients; however, ultimate follow-up should be determined by each patient's preoperative risks and postoperative surveillance findings.

The emergence of tumor markers other than CEA, as well as fluorescent endoscopic techniques, are strategies still under investigation to determine their specificity and efficacy for use in CRC surveillance. If found effective, they may very well revolutionize surveillance guidelines, yielding further risk-adapted care and possibly leading to less radiation exposure,

fewer incidental findings, false positives, and overall reduced cost; it is therefore essential that we continue to invest in the innovation and discovery of these techniques.

Acknowledgements The authors would like to thank Dave Primm for help in editing this article.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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