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TOPIC HIGHLIGHT

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Colorectal cancer surveillance: What's new and what's next?

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Abstract

The accumulated evidence from two decades of randomized controlled trials has not yet resolved the question of how best to monitor colorectal cancer (CRC) survivors for early detection of recurrent and metachronous disease or even whether doing so has its intended effect. A new wave of trial data in the coming years and an evolving knowledge of relevant biomarkers may bring us closer to understanding what surveillance strategies are most effective for a given subset of patients. To best apply these insights, a number of important research questions need to be addressed, and new decision making tools must be developed. In this review, we summarize available randomized controlled trial evidence comparing alternative surveillance testing strategies, describe ongoing trials in the area, and compare professional society recommendations for surveillance. In addition, we discuss innovations relevant to CRC surveillance and outline a research agenda which will inform a more risk-stratified and personalized approach to follow-up.

Key words: Colorectal cancer; Surveillance; Follow-up; Recurrence; Relapse; Survivorship

Core tip: We summarize the current state of knowledge and recommended practice around post-treatment surveillance of colorectal cancer survivors. In addition, we describe relevant ongoing trials and the questions which they will and will not answer regarding best surveillance practices. With that background as context, we discuss related practice innovations and propose a number of research questions whose answers could inform more effective, personalized approaches to surveillance.

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INTRODUCTION

Globally, over 1 million individuals develop colorectal

cancer (CRC) each year[1]. Approximately two-thirds will be treated surgically with curative intent[2]. Among those treated curatively, around one-third will experience recurrence of the original cancer or a second primary (*i.e.*, metachronous) colorectal cancer[3]. At least 80% of these recurrences occur within the first three years following initial treatment, while nearly all will have manifested by year five[4,5]. Most patients who recur will survive less than two years[6]. Ultimately, nearly 50000 patients in the United States alone die each year from colorectal cancer[2], with mortality attributable to both advanced stage at initial diagnosis and recurrent disease.

The majority of CRC survivors undergo some form of surveillance to detect recurrence of original disease or development of metachronous CRC. The primary rationale for such surveillance is to improve outcomes by detecting recurrent or metachronous disease before onset of symptoms, at a point where curative reoperation is more likely[7]. Other reasons for conducting surveillance of survivors include psychological benefits to the patient, monitoring patients for side effects of treatment, collecting data on patient outcomes, and detecting other comorbidities.

Despite the theoretical benefits of CRC surveillance, substantial uncertainty still exists around the topic. Though surveillance has been associated with a modest overall survival benefit, improvements in cancer-specific survival have not been shown. Furthermore, the body of research in this area has not consistently pointed to a set of specific best practices for follow-up. Most recurrences detected by surveillance are not curable[8], leading to an increasing sentiment that a more customized, risk-adapted approach to follow-up is needed[9-11]. In this review, we will summarize the evidence which has been gleaned from randomized controlled trials (RCTs) of alternative surveillance testing strategies, provide updates on ongoing trials which promise additional insight, and compare professional society recommendations for surveillance. In addition, we will highlight potential innovations in surveillance-many of which will likely form the basis for a more personalized approach to surveillance in the future-and highlight areas where research is needed to address key unanswered questions. The purpose of this work is not to provide a systematic review or meta-analysis of CRC surveillance studies (others have done so superbly in recent years[10,12-14]). The purpose, rather, is to broadly describe the current state of knowledge and practice around CRC surveillance, and to higihlight the recent developments and key research questions that will shape future practice.

SEARCH STRATEGY

We identified relevant resources based on (1) PubMed searches of randomized controlled trial comparing CRC surveillance strategies; (2) ClinicalTrials.gov searches of ongoing CRC surveillance trials; (3) the authors' personal databases of related publications; (4) related scientific meeting presentations; and (5) the bibliographies of reviewed publications.

WHAT THE TRIALS TELL US

Published data from seven completed randomized controlled trials comparing alternative surveillance regimens describe the experience of some 1938 survivors of Stage Ⅰ-Ⅲ (Dukes A-C) CRC. These subjects, enrolled between 1983 and 2004, experienced 698 recurrences or instances of metachronous CRC[15-21]. Table 1 summarizes the enrollment periods, settings, stage-based inclusion criteria, and follow-up protocols examined in each of these trials. Table 2 summarizes the subject make-up and results of each trial.

Meta analyses by Tjandra *et al*[10] and Jeffery *et al*[12] have incorporated results from these trials. The primary outcome examined by both meta-analyses was overall survival (OS). Tjandra *et al*[10] included all seven available RCTs in their analysis of OS, plus preliminary results from an ongoing trial[22]. Both analyses detected statistically significant improvements in all-cause mortality with respective odds ratios (OR) of 0.74 (95%CI: 0.59-0.93)[10], and 0.73 (95%CI: 0.59-0.91)[12] for the effect of intensive follow-up relative to less intensive follow-up. However, neither meta-analysis found that cancer-specific survival was improved by intensive surveillance (although only two of the constituent RCTs reviewed[15,17] included this key endpoint as an outcome).

The two meta analyses revealed that both intensive and less intensive surveillance led to detection of a similar number of recurrences but that detection occurred between 5.91 mo (95%CI: 3.09-8.74)[12] and 6.75 mo (95%CI: 2.44-11.06)[10] earlier with intensive surveillance. Both analyses also found that curative reoperation ("salvage surgery") was significantly more likely in those subjects who were followed up intensively (OR = 2.41, 95%CI: 1.63-3.54)[10] and (OR = 2.81 95%CI: 1.65-4.79[12]). An earlier meta-analysis by Renehan *et al*[23] included six of the trials described in Tables 1 and 2, and estimated that only about one-fifth of the survival benefit of intensive surveillance was likely due to curative treatment of recurrence. The authors postulated that the remainder of the survival benefit was most likely due to some combination of increased psychological support and well-being, improved health behavior, and improved detection and management of comorbidities[13]. Thus, the increased overall survival, earlier detection of recurrence, and higher reoperation rates seen in trials provide only circumstantial evidence that intensive surveillance extends life by making cure of recurrent disease more likely.

NEXT GENERATION OF CRC SURVEILLANCE TRIALS

The body of RCT-based evidence in the area of CRC surveillance to date has a number of limitations. First, it consists of a series of small studies spanning a period of more than two decades, with no two trials having examined the same surveillance regimen in the same setting (Table 1). Beyond this heterogeneity in interventions, a series of treatment innovations over the years

Table 1 Five-year surveillance regimens tested in reviewed randomized controlled trials

	Enrollment period	Setting	Stages included	Type of regimen	Surveillance regimen
Ohlsson *et al*[15]	1983-1986	2 Swedish centers	Dukes A, B, C	Intensive	History and physical exam, rigid proctosigmoidoscopy, CEA, Alk Phos, liver function tests, fecal hemoglobin, and chest X-ray at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48 and 60 mo; endoscopic visualization of the anastomosis at 9, 21, and 42 mo; complete colonoscopy at 3, 15, 30 and 60 mo; pelvic CT (rectal cancer only) at 3, 6, 12, 18 and 24 mo
				Minimal	No structured follow-up. Advised to obtain fecal hemoglobin tests every 3 mo for 2 years, then annually. Instructed to seek care if a series of warning signs/symptoms were experienced
Mäkelä *et al*[16]	1988-1990	1 Finnish center	Dukes A, B, C	Intensive	History and physical exam CEA, CBC fecal hemoglobin at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, 54 and 60 mo; Flexible sigmoidoscopy (if rectal/sigmoid tumors) every 3 mo; Liver ultrasound every 6 mo; Colonoscopy and liver CT annually
				Minimal	History and physical exam CEA, CBC fecal hemoglobin, CXR (and rigid sigmoidoscopy if rectal cancer) at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 mo; Barium enema at 12, 24, 36 48 and 60 mo
Kjeldsen *et al*[17]	1983-1994	A single Danish county	Dukes A, B, C	Intensive	History and physical exam including digital rectal exam and gynecologic exam, hemoglobin, erythrocyte sedimentation rate, liver enzymes, fecal hemoglobin, colonoscopy, and chest X-ray at 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 120, 150 and 180 mo
				Minimal	The same investigations as above, but only at 60, 120, and 180 mo
Pietra *et al*[18]	1987-1990	1 Italian center	Dukes B, C	Intensive	History and physical exam, liver ultrasound, and CEA at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 mo; CT, Chest X-ray and colonoscopy annually
				Minimal	History and physical exam, liver ultrasound, and CEA at 6, 12, 24, 36, 48, and 60 mo; Chest X-ray and colonoscopy annually
Schoemaker *et al*[19]	1984-1990	Multiple Australian centers	Dukes A, B, C	Intensive	History and physical exam, CEA, CBC, liver function tests, and fecal hemoglobin at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 mo; Chest X-ray, liver CT, and colonoscopy annually
				Minimal	History and physical exam, CEA, CBC, liver function tests, and fecal hemoglobin at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 mo; Chest X-ray, liver CT, and colonoscopy at 60 mo
Secco *et al*[20]	1988-1996	1 Italian center	Low-risk	Intensive risk-adapted	History and physical, CEA, abdominal/pelvic ultrasound at 6, 12, 18, 24, 36, 48, and 60 mo; Chest X-ray annually; Rectal cancer only: Rigid proctosigmoidoscpy at 12, 24 and 48 mo
				Minimal	Telephone follow-up every 6 mo; History and physical exam annually
			High-risk	Intensive risk-adapted	History and physical and CEA at 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36, 42, 48, 54, and 60 mo; Abdominal/pelvic ultrasound at 6, 12, 18, 24, 30, 36, 48 and 60 mo; Rigid proctosigmoidoscopy (rectal cancer only) and chest X-ray annually
				Minimal	Telephone follow-up every 6 mo; History and physical exam annually
Rodríguez-Moranta *et al*[21]	1997-2001	3 Spanish centers	TNM Ⅱ and Ⅲ	Intensive	History and physical, CEA, CBC, and liver function tests at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 mo; Abdominal/pelvic CT (rectal cancer only) or Abdominal ultrasound (colon cancer only) at 6, 12, 18, 24, 36, 48, 60 mo; Chest X-ray and colonoscopy annually
				Minimal	History and physical, CEA, CBC, and liver function tests at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 mo; Colonoscopy at 12 and 36 mo

CEA: Carcinoembryonic antigen assay; CBC: Complete blood count; Alk phos: Alkalilne phosphatase; CT: Computed tomography.

has changed the context of the problem by making recurrence-free survival increasingly more likely (since recruitment of the trials reviewed began in 1983, CRC survival has improved by 5%-10% overall[24]). These innovations include emergence of total mesorectal excision as a standard of care for rectal cancer in many settings, widespread use of adjuvant chemotherapy in Stage Ⅲ and many Stage Ⅱ patients, and the growing practice of attempting to curatively treat oligometastatic hepatic recurrences[25,26]. Whether or not some of these innovations have changed the behavior of recurrent disease itself is difficult to know, but the possibility cannot be excluded. Importantly, improvements in imaging technology have also enabled earlier and more accurate detection of recurrent disease, while increasing the potential for false positives[27,28].

This evolution of technology and practice throws into question the relevance of much of the evidence behind current recommendations for surveillance. Fortunately, there are three large, ongoing RCTs (described below), with targeted sample sizes totaling over 8000 subjects, which will eventually shed additional light on the benefits of CRC surveillance and the comparative effectiveness of a handful of unique follow-up protocols.

FACS (Follow-up after Colorectal Surgery) Trial

The FACS trial (ClinicalTrials.gov identifier NCT00560365) opened in 2004 with a target recruitment of 4890 patients. The primary objective of this factorial trial is to examine the effect of augmenting symptomatic surveillance in primary care with two intensive methods of surveillance [frequent monitoring of carcinoembryonic antigen (CEA) in a primary care setting and intensive computed tomography (CT) imaging in a hospital setting]

Table 2 Results of reviewed randomized controlled trials of colorectal cancer surveillance strategies *n* (%)

	Type of regimen	*n*	Stages[1]	Rectal cancer	Follow-up time	Recurrences[2]	Symptoms were first sign of recurrence	Time to recurrence (mo): mean ± SD /*median*	Reoperated (% of recurrences)	Overall survival at 5 yr	Cancer-related survival at 5 yr	Survival of recurring patients 5 yr after first treated
Ohlsson *et al*[15]	Intensive	53	A/B/C: 19%/40%/41%	36%	6.8 yr median (overall)	17 (32)	8 (47)	*20*	5 (29)	75%	78%	29%
	Minimal	54	A/B/C: 17%/48%/35%	31%		18 (33)	15 (83)	*24*	3 (17)	67%	71%	22%
Mäkelä *et al*[16]	Intensive	52	A/B/C: 24%/46%/29%	31%	NR	22 (42)	3 (14)	10 ± 5	5 (22)	59%	NR	NR
	Minimal	54	A/B/C: 28%/44%/28%	28%	NR	21 (39)	4 (19)	15 ± 10	3 (14)	54%	NR	NR
Kjeldsen *et al*[17]	Intensive	290	A/B/C: 23%/51%/26%	46%	55% still followed at 5 yr (overall)	81[3] (28)	38 (47)	18	17 (21)	70%	78%[4]	NR
	Minimal	307	A/B/C: 23%/47%/30%	49%		83[3] (27)	59 (71)	27	5 (6)	68%	78%[4]	NR
Pietra *et al*[18]	Intensive	104	A/B/C: 0%/60%/40%	30%	100% still followed at 5 yr (overall)	41 (39)	10[5] (42% of local recurrences)	10.3 ± 2.7[5]	21 (51)	73%	NR	38%
	Minimal	103	A/B/C: 0%/58%/42%	36%		42[6] (41)	10[5] (83% of local recurrence)	20.2 ± 6.1[5]	6 (14)	58%	NR	0%
Schoemaker *et al*[19]	Intensive	167	A/B/C: 25%/47%/28%	28%	NR	56 (34)	NR	NR	6 (11)	77%[4]	NR	NR
	Minimal	158	A/B/C: 19%/48%/33%	26%	NR	64 (41)	NR	NR	5 (8)	70%[4]	NR	NR
Secco *et al*[20]	Low-risk–risk-adapted	84	A/B: 100%	NR	Median 42 mo	27 (32)	32%[7]	*16*	6 (22)	80%	NR	NR
	Low risk–minimal	61	A/B: 100%	NR	NR	25 (40)	75%[7]	*14*	6 (24)	60%	NR	NR
	High-risk–risk-adapted	108	A/B: 36% C: 64%	NR	Median 61.5 mo	74 (68)	32%[7]	*13.5*	25 (34)	50%	NR	NR
	High risk–minimal	84	A/B: 20% C: 80%	NR	NR	58 (69)	75%[7]	*8*	7 (12)	32%	NR	NR
Rodríguez-Moranta *et al*[21]	Intensive	127	Ⅱ: 60% Ⅲ:40%	23%	Median 49 mo	35 (27)	NR	39 ± 21	18 (51)	75%[4]	NR	NR
	Minimal	132	Ⅱ: 61% Ⅲ:39%	28%	Median 45 mo	34 (26)	NR	38 ± 19	10 (29)	73%[4]	NR	NR

[1]A, B and C refer to Dukes staging, while Ⅰ, Ⅱ and Ⅲ refer to TNM staging; [2]Includes metachronous colorectal cancers (CRCs); [3]Includes 7 cases of metachronous CRC in the intensive group and 3 in the less intensive group; [4]Estimated visually from survival curve; [5]Reported for local recurrences only; [6]Includes 1 case of metachronous CRC; [7]Reflects combined high-risk and low-risk groups. NR: Not reported; "Overall" describes all trial arms combined.

on survival of patients with stage Ⅰ, Ⅱ or Ⅲ colorectal cancer who have undergone curative resection[29]. In 2013, the FACS investigators presented interim results summarizing a mean 3.7 years of follow-up for 1,202 participants. Only 6.0% of participants had recurrence with subsequent attempted curative resection. Those followed by frequent CEA monitoring had an adjusted OR for attempted cure of recurrence of 2.7 (P = 0.035) relative to the minimal follow-up group which received only a single CT at 12-18 mo. Those followed by serial CT's had an adjusted OR of 3.4 (P = 0.007) relative to the minimum follow-up group. No additional benefit was seen in the group which received both frequent CEA and frequent CT's. In interim analyses, there were no differences seen in overall or cancer-specific mortality between any of the intensive arms and the minimum follow-up arm[30], though the final results are not yet available.

COLOFOL (Assessment of Frequency of Surveillance after Curative Resection in Patients with Stage Ⅱ and Ⅲ Colorectal Cancer)

This multicenter RCT (ClinicalTrials.gov identifier NCT00225641) is comparing two surveillance regimens involving CT-scan or MR scan of the liver, CEA, and CT scan or X-ray of the lungs at intervals of either 12 and 36 mo, or 6, 12, 18, 24 and 36 mo. The study aims to include 2500 subjects[31]. Primary outcomes will be total mortality and cancer specific mortality at five years, while secondary outcomes will include recurrence-free survival, quality of life, and cost effectiveness. Centers from Denmark (n = 15), Sweden (n = 20), Poland (n = 6), Hungary (n = 2) and The Netherlands are participating. Publication is planned for late 2014[32].

Table 3 Summary of United States and European colorectal cancer surveillance guidelines

	ASCO[33] 2005	ASCRS[34,35] 2005	NCCN[36,37] 2014	Denmark[38] 2009	Norway[39] 2012	United Kingdom[40] 2010
Stage	Ⅱ-Ⅲ	Ⅰ-Ⅲ	Ⅰ-Ⅲ	Ⅱ-Ⅲ	Ⅱ-Ⅲ	Ⅰ-Ⅲ
History and physical	q3-6 mo × 3 yr; q 6 mo in year 4-5	At least q4 mo × 2 yr	q3-6 mo × 2 yr; q6 mo in year 3-5	At 1 mo	q6 mo × 3 yr, q12 mo in year 4-5	None
CEA	q3 mo × at least 3 yr	At least q4 mo × 2 yr	q3-6 mo × 2 yr; q6 mo in year 3-5	At 1, 12 and 36 mo	q6 mo × 3 yr, q12 mo in year 4-5	None
CT chest	Annually × 3 yr if high risk	None	Annually up to 5 yr if high risk	At 12 and 36 mo	Annually × 5 yr	None
CT abdomen/ pelvis	Annually × 3 yr if high risk	None	Annually up to 5 yr if high risk	At 12 and 36 mo	At 6 mo and 5 yr	Once within first 2 yr
CEUS liver	None	None	None	None	At 12, 18, 24, 30, 36 and 48 mo	None
Colonoscopy	At 3 yr and q5 thereafter	q3 yr	At 1 and 4 yr, then q5 yr	None	At 5 yr;or CT colonography at 5 yr	q5 yr

NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; ASCRS: American Society of Colon and Rectal Cancer Surgeons; UK: United Kingdom 2010 guidelines; Nor: Norwegian 2012 guidelines; CEUS: Contrast-enhanced ultrasound; CEA: Carcinoembryonic antigen; CT: Computed tomography.

GILDA (Gruppo Italiano di Lavaro per la Diagnosi Anticipata)

Based in Italy, The GILDA group of investigators is conducting a randomized trial of intensive versus less intensive follow up in patients with Dukes B2-C CRC. Varying between study groups are the frequencies of office visits, CEA and other blood chemistries, colonoscopies, liver ultrasound, chest X-ray, and-in the case of rectal cancer survivors-proctoscopy and abdominal-pelvic CT. Outcomes of interest include overall survival, CRC mortality, quality of life and time to detection of recurrence. The GILDA investigators aim to enroll a minimum of 1500 patients across 45 centers. An interim analysis of 985 patients, published in 2004, did not demonstrate any improvement in overall survival between the two surveillance arms, though mean follow-up at the time was only 14 mo[22].

SURVEILLANCE GUIDELINES

Based on the accumulated trial evidence, a number of organizations have published surveillance recommendations[33-40]. These suggested regimens employ various combinations of carcinoembryonic antigen assays, chest CT, CT abdomen-pelvis, and contrast enhanced ultrasound of the liver. Chest X-ray and plain ultrasound of the liver are not used as a recommended test modality in any of the reviewed guidelines due to their low sensitivity and specificity. Some authors have argued for regular use of Positron Emission Tomography scanning and increased use of tumor markers, but this is not commonly accepted as a standard of practice[17,18]. Table 3 provides a summary of surveillance recommendations from the United States and Europe. There is a moderate amount of variation between the United States recommendations published by the American Society of Clinical Oncology[33], the American Society of Colon and Rectal Surgeons[34,35], and the National Comprehensive Cancer Network[36,37]. Internationally, though, the range in aggressiveness of recommended follow-up is striking, with European societies tending to prescribe much less intensive surveillance-particularly in the case of the United Kingdom's National Health Service[40]-in comparison to United States societies.

It is noteworthy that CEA assay represents the only testing modality whose increased use is associated with higher probability of detection of asymptomatic recurrence, higher curative reoperation rate, and greater mortality reduction in meta-analysis[10]. Ironically, studies of guideline adherence suggest that, across testing modalities used in surveillance, adherence to scheduled CEA testing is among the lowest[41,42]. Future research might focus on better outlining correlates and causes of this non-adherence[41].

INNOVATIONS IN SURVEILLANCE

In the last decade, a handful of investigators have reported on provider care models aimed at delivering more patient-centered, cost-effective survivorship care. These studies have explored alternatives to the conventional model of surgeon-led follow-up in a hospital-based clinic. For instance, Australian investigators randomized 203 recently-treated CRC survivors to identical follow-up regimens led by either surgeons or general practitioners. Rates of recurrence, time to detection, mortality, and quality of life were similar between the groups, but surgeons tended to initiate significantly more colonoscopies and ultrasounds, whereas general practitioners ordered more fecal hemoglobin tests[43]. Similarly, a recent Norwegian trial randomized 110 CRC survivors to either traditional hospital-based surveillance coordinated by surgeons, or community-based surveillance coordinated by general practitioners (GP's). No differences were observed in patient quality-of-life or time to detection of recurrence. Costs, however, were 16.7% lower ($P < 0.001$) in the GP-organized group[44].

Between 2002 and 2005, a Swedish trial randomized CRC survivors to post-treatment follow-up by either a surgeon or a specially-trained nurse. Surgeons and nurses

found similar numbers of recurrences with nearly identical levels of patient satisfaction. Nurses, however, spent an average of eight minutes longer with patients than did surgeons, requiring assistance from surgeons only 7% of the time[45].

Despite these results, whether or not surgeons or patients will allow generalists to direct CRC survivorship care on a large scale remains to be seen. The relationships developed during active treatment can make such handoffs difficult for providers and patients alike[46]. For those adhering to the surgeon-led follow-up model, a promising innovation might be found in the work reported by a British surgeon in the late 1990s[47]. This surgeon developed and measured the impact of a dedicated "one-stop shop" model for a CRC surveillance clinic. This model, which facilitated completion of all scheduled imaging, blood tests, and procedures in a single visit, yielded a substantial improvement in timely receipt of recommended tests compared to the period before establishment of the clinic.

Moving toward risk adapted follow-up

A series of authors over the last two decades have argued for an approach to surveillance that involves tailoring surveillance plans based on recurrence risk[9-11,20,48,49]. Though the idea is intuitively appealing as a way to spare certain patients some of the morbidity associated with surveillance and to reduce costs, little data exists on the topic. Secco and colleagues divided patients who had recently undergone curative treatment for CRC into high-risk and low-risk groups based on a number of prognostic factors. Within each of these risk groups, patients were randomized to either very minimal follow-up or a risk-adapted follow-up protocol (Table 1). Within each risk group, the risk-adapted follow-up patients showed significantly better five-year overall survival[20]. Unfortunately, there was no comparison of an overall strategy of tailoring follow-up to the risk of recurrence versus a one-size-fits-all approach of following all patients using a uniform protocol.

Any version of risk-adapted follow-up in the future will likely employ the use of molecular markers to target patients who might benefit the most form a more intensive level of surveillance. Most work on biomarkers to date has focused on prognostic markers of overall outcome or predictive markers of response to adjuvant chemotherapy. These types of markers hold great promise in informing decision making around adjuvant chemotherapy. Certain prognostic markers which may predict recurrence have the potential to inform surveillance planning after treatment. Vascular Endothelial Growth factor overexpression[50,51] and interleukin-8 overexpression[52] in tumor cells eventually may serve as such markers. Limited evidence suggests that each may signal a heightened risk of recurrence[50-52].

A "Recurrence Score" calculated based on a commercially available tumor gene expression panel (OncotypeDX - Genomic Health, Redwood City, CA, United States) has been validated as a predictor of recurrence in Stage Ⅱ CRC and is advocated as a tool for deciding whether or not to commit these patients to adjuvant chemotherapy[53-55]. Another application of this tool, and an idea which deserves further study, is the use of the recurrence score in individualized surveillance planning. Patients and their providers might opt for more aggressive surveillance if the likelihood of recurrence was high, whereas a low recurrence score might offer reassurance that minimal surveillance was a reasonable course.

The ideal set of recurrence markers would include one or more factors having low correlation with prognosis. In this way, patients could be categorized into four categories based on the two dimensions of recurrence risk and prognosis-given-recurrence. Patient with high recurrence risk but good prognosis-given-recurrence might be followed aggressively since probabilities of both detecting and successfully treating a recurrence would be high. Conversely, patients with low recurrence risk but poor prognosis-given-recurrence might opt for little or no follow-up.

OTHER AREAS FOR FUTURE RESEARCH

After decades of research on the topic, tremendous uncertainty remains concerning how to best monitor CRC survivors for recurrence or metachronous disease. The results of seven randomized controlled trials comparing alternative surveillance strategies have led to a general consensus that more intensive follow-up leads to increased curative treatment of recurrence via earlier detection and to improved overall survival. Whether or not the latter is a result of the former, or whether improved survival instead follows primarily from the benefits of increased contact with healthcare providers in general, remains unclear. In the coming years, we hope to see publication of more trial data on the topic than has been available to date thanks to three ongoing large trials. We will hopefully have a clearer picture of the cancer-specific survival benefit of intensive surveillance as well as the cost-effectiveness and quality-of-life implications of different approaches to surveillance.

Beyond the research questions highlighted above, additional areas for further study are listed below.

Need for model-based research

Even with the new trial evidence, actionable knowledge relevant for clinical practice will remain quite limited. We will still have experimental data on only a tiny fraction of the combinations and schedules of surveillance tests that are possible. Nor will we have a strong translational evidence base to guide risk-adapted follow-up. A promising possibility for leveraging the accumulated trial data may lie in computer simulation modeling. Sophisticated models could help researchers and clinicians examine the impact of virtually any surveillance regimen on patients with differing risk profiles. An example of using such modeling to synthesize what is known about testing and disease progression in such a way that allows virtual experimentation can be found in the numerous models of CRC screening strategies. These models simulate the

adenoma-carcinoma sequence by which benign polyps transform to adenocarcinomas and adenocarcinomas grow and invade healthy tissue, allowing experimentation with a practically infinite number of candidate screening strategies[56-60]. Some of these screening models have informed development of United States Preventive Services Task Force guidelines on colorectal cancer screening[56], have been applied by the Centers for Medicare and Medicaid Services to compare the effectiveness of various CRC screening strategies[57,58], and have spawned vital new research questions[59,60].

Simulating progression of recurrent CRC in such a way that allows the testing of different surveillance regimens is perhaps a more difficult problem, owing to the lack of direct observational data on unchecked recurrence progression (contrasted with the abundant data available on polyp progression and transformation). A few authors have developed recurrence models[61-65], but this line of research has not yet advanced to the point of being able to provide prescriptive recommendations for optimized surveillance regimens as has been the case for CRC screening in a healthy population. The loftiest ambition for applying simulation modeling to the problem of CRC surveillance would be to develop models which incorporate what can be inferred from RCTs about natural history of recurrence, information on test sensitivity and specificity, our best estimates of major complication risks (primarily from colonoscopy and ionizing radiation exposure), and what is known about individual risk factors for recurrence into an individualized decision aid. Such a tool could help providers and their patients reach decisions which incorporate their preferences in light of the estimated benefits and risks of specific surveillance strategies.

What role should colonoscopy play

The possible benefits of surveillance must be considered in light of the potential harms. Colonic perforation and post-procedure bleeding associated with colonoscopy represent the most concrete and serious harms arising from CRC follow-up. Endoscopic surveillance has been endorsed by all reviewed national guidelines, primarily for early detection of metachronous CRC's (which develop in 1.5%-7.7% of CRC survivors[10,66,67]) or adenomas with advanced features. The procedure has a sensitivity of 95% and a specificity of 100% for detecting high-risk polyps or tumors[68]. To date, however, no study has reported increased survival associated with routine colonoscopy after resection. Furthermore, the procedure is relatively invasive and has a major complication rate of 0.2%-1.2%[19,69,70]. This uncertain benefit and potential for harm, as well as the considerable resource demands, have led some to argue against routine endoscopic surveillance after curative CRC resection[71,72]. An area for future research might be to evaluate strategies which select for frequent colonoscopic examination only those patients at high risk for second primary cancers or advanced adenomas. Also worthy of further study is whether CT Colonography, or "virtual colonoscopy", may have the potential to provide a better balance of risks and benefits[71].

What are the quality of life implications of CRC surveillance

A longstanding, and still unresolved, question is to what extent CRC surveillance in general exacts a psychological toll on patients. Such a toll might arise from increased anxiety associated with testing or with the possibility of detection of an unresectable recurrence. Despite these theoretical harms, no negative quality of life impact has yet been demonstrated in studies comparing differing levels of follow-up. The small amount of data available on quality of life impacts of surveillance suggests a neutral or even slightly positive effect[73,74]. A 1997 Dutch study found no diminution in quality of life associated with follow-up of 130 CRC survivors at four hospitals. In fact, the average patient preferences tended to favor follow-up as opposed to no follow-up[73]. Kjeldsen and colleagues reported a slight trend toward increased quality of life among Danish CRC survivors who were followed more intensively compared to counterparts undergoing minimal follow-up[74].

The large surveillance trials underway[22,29,31] should shed further light on the quality of life impacts of CRC surveillance. An area in particular need of further study is the quality of life impact associated with false positive test results. In addition to specific focus on the effect of false positive results, an important, and as-yet-unaddressed question is the loss of quality time brought about by the pre-symptomatic diagnosis of unresectable recurrence. This represents an important concern since a substantial majority of patients whose recurrences are detected by surveillance before symptom onset will have progressed beyond the point of curative treatment[15,16,75].

For how long should crc survivors be followed

The treatment guidelines outlined in Table 3 focus primarily on the period spanning the point of initial treatment through five years post-treatment. There is no clear evidence that this timeframe is the most appropriate, however. Two opposing effects make the choice of an optimal surveillance period difficult. First-arguing for a shorter window-the majority of recurrences occur early; at least 80% of recurrences are detected by three years[4,5]. This fact would suggest that follow-up becomes much lower-yield and that false positive test results would increase drastically after three years of follow-up. On the other hand, time to recurrence appears to be an important prognostic factor for the outcome of recurrent disease[6]. Survival after curative treatment of recurrent disease may increase with later recurrences[76-79]. As such, some have suggested that longer follow-up-while detecting fewer recurrences-would detect a higher rate of curable recurrences[9,11]. The determinant of whether or not such benefit might be realized with longer follow-up is the extent to which late recurrences are treatable when they are detected based on symptoms. The proportion of

symptomatic recurrences which are considered curable is generally quite low (Table 2), but it is possible that the subset of patients whose recurrences manifest later may be an exception. Hopefully the volume of new trial data set to emerge in the coming years will permit this important subanalysis.

CONCLUSION

Optimizing colorectal cancer surveillance represents an incredibly complex medical decision making problem. A heterogeneous and far-from-completely-understood disease occurring in a population with typically advanced age and accompanying morbidity intersect with a surveillance testing framework involving numerous possible combinations of imperfect follow-up modalities. It is not surprising that the accumulation of trial data over the past decades has failed to provide a consistent answer to what strategy of surveillance-if any-most prolongs life by increasing the likelihood that recurrences will be caught early and successfully treated. Nor is it surprising that surveillance recommendations differ considerably across organizations and countries. A series of large, ongoing CRC surveillance trials will begin to produce much-anticipated results in the coming years. Not only will these results shed light on effective follow-up for CRC survivors diagnosed during a modern era of surgical and systemic treatment, but they also promise vital quality-of-life and economic findings. These trials will still have only looked at a small number of possible surveillance regimens. Additional tools, including computer simulation modeling, are needed to synthesize and leverage this new information in conjunction with knowledge of the effects of known and emerging risk factors. By so doing, we can move toward more effective, efficient, and patient-centered follow-up.

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