MINIREVIEWS

Surveillance strategies following curative resection and non-operative approach of rectal cancer: How and how long? Review of current recommendations

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Abstract

Different follow-up strategies are available for patients with rectal cancer following curative treatment. A combination of biochemical testing and imaging investigation, associated with physical examination are commonly used. However, there is currently no consensus about the types of tests to perform, the timing of the testing, and even the need for follow-up at all has been questioned. The aim of this study was to review the evidence of the impact of different follow-up tests and programs in patients with non-metastatic disease after definitive treatment of the primary. A literature review was performed of studies published on MEDLINE, EMBASE, the Cochrane Library and Web of Science up to November 2022. Current published guidelines from the most authoritative specialty societies were also reviewed. According to the follow-up strategies available, the office visit is not efficient but represents the only way to maintain direct contact with the patient and is recommended by all authoritative specialty societies. In colorectal cancer surveillance, carcinoembryonic antigen represents the only established tumor marker. Abdominal and chest computed tomography scan is recommended considering that the liver and lungs are the most common sites of recurrence. Since local relapse in rectal cancer is higher than in colon cancer, endoscopic surveillance is mandatory. Different follow-up regimens have been published but randomized comparisons and meta-analyses do not allow to determine whether intensive or less intensive follow-up had any significant influence on survival and recurrence detection rate. The available data do not allow the drawing of final conclusions on the ideal surveillance methods and the

frequency with which they should be applied. It is very useful and urgent for clinicians to identify a cost-effective strategy that allows early identification of recurrence with a special focus for high-risk patients and patients undergoing a "watch and wait" approach.

Core Tip: Follow-up programs following rectal cancer curative treatment are widely accepted as an integrated part of the therapeutic pathway, but there is still no consensus regarding which test should be performed, the time schedule, the frequency and the duration of surveillance. The impact on survival has also been questioned with recurrence detection not necessarily associated with curative surgery. The aim of this review was to provide an overview of recommendations on this topic with supporting evidence.

INTRODUCTION

Currently, the treatment of rectal cancer is based on a multimodal approach that involves not only the surgeon but other specialists such as gastroenterologists, radiotherapists, and oncologists. Due to the wide range of circumstances in the initial stage and responsivity to neoadjuvant treatments, many therapeutic pathways are available that may lead to different follow-up plans and open the door to the debate. There is currently no consensus about the types of tests to perform, the timing of the testing, and even the need for follow-up at all has been questioned. Only patients treated radically for the primary tumor with non-metastatic disease are eligible for post-operative follow-up. Although at the time of diagnosis, approximately 70% of patients affected by colorectal cancer will be treated surgically with curative intent[1], recurrence occurs in about 30% to 50% of patients undergoing curative treatments, including both local relapse and distant metastasis[2]. Therefore, surveillance programs following radical rectal cancer resection are an integral part of the therapeutic pathway. The most common sites of distant metastasis are the liver followed by the lungs; however, rectal cancer is correlated more often to local failure than colon cancer, carrying a significantly higher risk of local recurrence. Specifically, anastomotic recurrence is recorded in 5% to 15% of patients[3], although it should be noted that the recurrence more frequently grows extraluminally, generally in the pre-sacral area and less often in the anastomosis site[4]. The rate of distant metastasis in colon and rectal cancer is similar instead[5]. Treatment with curative intent of recurrence is feasible, and this increases prognosis and overall survival. Given the great risk of relapse, to improve prognosis of patients with disease recurrence, follow-up regimens should detect cancer recurrence early. The key point is to find the best surveillance programs that allow the early detection of recurrent cancer when it is still responsive to curative treatment. Follow-up programs have strategic importance only in this setting. Finally, we should consider two more aspects related to surveillance programs. Follow-up has an important psychological impact indeed: on the one hand it may provide comfort, reassuring the cancer survivor that there is no evidence of recurrence; on the other hand, it may induce negative effects such as stress and anxiety due to the intensive testing the patient is forced to go through. Finally, follow-up tests are costly and bring the inevitable risk of false positives, leading to pointless procedures and potential complications. In light of the clear benefits and potential risks of follow-up programs, it is urgent to establish a cost-effective strategy to guarantee early recognition of disease relapse and reduce potential shortcomings, narrowing surveillance to the highest-risk patients.

The aim of this study was to review the evidence of the impact of different follow-up tests and programs in patients with non-metastatic disease following surgery of the primary tumor. Current published guidelines from the most authoritative specialty societies were also reviewed and presented.

RISK ASSESSMENT

Recurrence could be local or distant and numerous risk factors have been related to cancer relapse including tumor stage, grading, circumferential margin, location, obstruction, perforation, type and adequacy of resection, lympho-vascular invasion, blood transfusions, anastomotic leak, patient constitution and sex, and last but not least, the surgeon's know-how and expertise leading to the saying "colorectal surgeons do it better"[6-9]. Nonetheless, the critical factor related to the risk of recurrence is the original histopathological cancer stage with an increased risk associated with advanced primary American Joint Committee on Cancer (AJCC) staging. Therefore, the follow-up strategy involves patients affected by early-stage disease, focusing especially on those belonging to stage II and III according to AJCC regarded as the highest risk patients. Patients affected by stage 0 neoplasia (carcinoma in situ without extension into the submucosa), patients operated with no curative intent and patients with major comorbidities that even in case of recurrence would be excluded from any active treatment, should not be followed-up. Finally, both locoregional and distant recurrences occur in most cases within 3 years of surgery, highlighting the importance of intensive early testing and suggesting a limited impact of longer follow-up[10].

FOLLOW-UP TESTS

Taking into account the different types of metastases, more than one surveillance test is usually performed to evaluate the different possible sites of recurrence. A combination of biochemical tests and imaging investigations are associated with physical examination to identify locoregional and distant metastases at an early stage. The most used tools to perform a complete surveillance include medical history and physical examinations, serial measurement of carcinoembryonic antigen (CEA), liver function tests, endoscopy, liver imaging and chest imaging and possibly, positron emission tomography (PET) scanning.

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Anamnesis and clinical examination are the first approach for any patient with rectal cancer history and are recommended by all scientific societies as an integral part of surveillance programs[4,11-15]. However, the value and role of the office visit are not still clear. The lack of specific symptoms makes diagnosis complicated and often delayed, and only 1.7% to 7% of patients with symptoms caused by recurrence have resectable disease[16-18]. Furthermore, about one-quarter of patients, even though within an intensive surveillance program, delay reporting symptoms until their next clinic visit[19]. The digital rectal examination (DRE) has progressively lost importance for the early detection of local recurrence and nowadays office evaluation remains key only for maintaining direct contact with patients, better planning surveillance tests and coordinating with different figures to avoid useless diagnostic procedures and pointless anxiety[15].

CEA

CEA is the most used tumor marker and hematic test in colorectal cancer follow-up. Its role has been extensively evaluated and it has been used in colorectal cancer for more than 40 years. CEA has not as much specificity and sensibility as a screening test, but is often the first indicator of relapse even in the case of cancers without CEA elevation prior to surgery[20]. CEA level is reported as being elevated in up to 75% of patients with colorectal cancer recurrence[21]. The reported sensitivity of CEA varies respectively from 44% to 89%, while specificity ranges from 42% to 98%[22-32]. The sensitivity and specificity of CEA for detecting recurrence depends on the cut-off value considered: a CEA cutoff of 10 µg/L is associated with sensitivity of 68% and specificity of 97%, while a cutoff of 2.5 µg/L has a sensitivity of 82% and a specificity of 80%[33]. Thus, a lower threshold level has resulted in increased sensitivity but reduced specificity. It has been reported that only 22.9% (range between 7.5% and 33%) of recurrences, identified by CEA elevation, are resectable at the time of diagnosis[10]. Recently, the follow-up after colorectal surgery (FACS) trial randomly assigned 1202 patients to four different types of follow-up. The authors report that CEA screening alone detected 6.7% of resectable metastases, compared with 8% in the computed tomography (CT) alone group and 6.6% in the group with association of CEA and CT. Thus, the rates of surgical treatment of recurrences were similar in the CEA alone group and CT alone group, without advantages in combination of CEA and CT[34]. CEA remains the most cost-effective method of identification of recurrence, although the curative rate of surgery in this scenario remains low. It should be noted that the possibility of false-positive CEA rising is real. The false-positive rate for CEA can be as high as 16%, especially in smokers[28]. For this reason, it is a

common opinion to wait for a second CEA level to confirm an elevation trend and in the case of rising CEA on sequential measurements it is suggested to embark on more specific diagnostic tools. This attitude was recently confirmed by the CEA watch trial from the Netherlands that compared usual follow-up care with an intensified follow-up schedule performed with CEA measurements every 2 months and imaging in the case of two CEA rises. Intensive CEA surveillance protocol resulted in higher recurrence detection and more recurrence suitable for curative treatment. The time of detection of recurrent disease was shorter as well[35]. Rising CEA should be managed by investigating the possible recurrence site and even the employment of a PET or PET/CT is justified if the localization of the relapse is not clear[14,36]. Finally, CEA represents the only established tumor marker in colorectal cancer follow-up programs and is strongly recommended by all major scientific societies[4,11-15].

LIVER IMAGING

The most used imaging means of studying liver parenchyma are ultrasonography (US) and CT. US is operator dependent and has lower sensitivity than CT scans, but both may detect liver recurrence early. However, the real benefit of early recurrence detection in terms of curative resection is still controversial. Mäkelä *et al*[37] reported only 6 of 22 (27%) liver metastases identified by either ultrasound (4 cases) or CT scan (2 cases), prior to elevation of CEA. This was not associated with any resection. Schoemaker *et al*[38] demonstrated a significant identification rate of asymptomatic liver metastasis by CT scan, but these figures were not associated with increased hepatic resection rates (3 resections in the intensive surveillance group and 4 in the standard arm). The tests used in the standard arm (CEA and liver function tests) allowed identification of resectable liver recurrences with CT scans not adding any substantial advantages. More recently, the results of the FACS trial were similar: liver metastases were detected both by scheduled CEA only or scheduled CT only. No advantages were reported in combining CEA and CT. CEA is evidently more cost-effective, even though CT is crucial for confirming and localizing the recurrence[34]. Only in the randomized controlled trial (RCT) from Rodríguez-Moranta *et al*[39] either abdominal CT or US were able to detect 10 (28.5%) distant metastases, 4 of which were resectable (40%). Indeed, there is an overlap between liver imaging and CEA, suggesting that isolated liver imagines in routine follow-up programs are not so useful. Nevertheless, liver imaging is recommended almost annually by all specialty societies[4,11-15].

CHEST IMAGING

Rectal cancer, more than colon cancer, frequently recurs in the lung given its particular venous drainage to the caval system, with an incidence of isolated lung metastasis of 2-10% of cases[40,41]. Unfortunately, as reported by a multicenter retrospective study, only 38% of those patients are eligible for curative metastasectomy and undergo surgical resection[42]. Mitry *et al*[43] reported even worse figures: only 4% of patients with synchronous pulmonary metastases and 14% of patients with metachronous pulmonary metastases are curatively resected. Lung recurrences may be detected by conventional chest radiography (CXR) or CT scan. The role of CXR has been evaluated, especially in the case of colon cancer follow-up, suggesting that it is not a valuable method for detecting resectable disease. Considering trials including both colon and rectal cancers, CXR was able to identify lung resectable recurrence in 1.8% to 12% of patients, which did not substantially modify survival[37,38,44]. Similarly, Rodríguez-Moranta *et al*[39] more recently reported that CXR was the first method indicating lung tumor recurrence in 3 patients (9%) in the intensive strategy group. However, only two recurrences were resectable (11%), and just one (25%) considering recurrence related to rectal cancer. These figures look similar to those published previously but highlight how the performance of CXR as a diagnostic tool is better if we consider only the patients affected by rectal cancer. However, even though CXR is not costly, a very low number of patients can benefit from scheduled CXR, and its role remains marginal in surveillance programs. Chest CT scan appears to be the only reliable method for investigating the lungs and it is suggested by all the specialty societies, at the expense of CXR[4,11-15].

ENDOSCOPY

The role of colonoscopy and rectosigmoidoscopy after curative resection is crucial and is a very important tool for identifying anastomotic recurrence and metachronous colorectal cancers. In rectal cancer, especially in patients who did not receive any neoadjuvant treatment, about 3% to 50% of cases show a locoregional recurrence, including anastomotic recurrences, that is more frequent than in colon cancers[45]. Patients affected by rectal cancer have a lifetime risk of developing a metachronous tumor in the residual viscera that ranges from 1.1% to 6.3%[20], while the risk of developing a metachronous adenoma is up to 56%[46]. Taking into account the reported figures of metachronous lesions, the role of

colonoscopy is undisputed despite the invasiveness and the risk of possible complications, such as bleeding or perforation. Two studies[38,47] reported complications related to colonoscopy surveillance in only seven cases (three perforations and four hemorrhages out of 2112 colonoscopies: 0.4%). Eight RCTs included colonoscopy and proctoscopy as a part of intensive surveillance programs, compared either with less frequent or even no endoluminal testing[16,37-39,44,47-49]. These trials, except those reported by Rodríguez-Moranta *et al*[39] and Wang *et al*[47], suggest only a marginal benefit from colonoscopy. Instead, Rodríguez-Moranta *et al*[39] and Wang *et al*[47] reported a significant identification of local relapses that can be treated with salvage surgery, leading to significantly longer survival in patients undergoing intensive colonoscopic surveillance. However, the bad results of six RCTs[16,37,38,44,48,49] adopting intensive colonoscopy programs were probably due to the short median observation period reported by each study, which was less than 5 years. The reality is that patients treated for colon and rectal cancers have a life-long and cumulative risk of developing bowel cancer again and therefore the recommendation to perform a colonoscopy over a longer period is warranted and may prove more beneficial. The major scientific societies suggest colonoscopy as a follow-up modality for removing early adenomatous polyps and detecting metachronous cancer[4,11,13,14]. The American Society of Colon and Rectal Surgeon (ASCRS)[4], The Association of Coloproctology of Great Britain and Ireland (ACPGBI)[11], The American Society of Clinical Oncology (ASCO)[13] and The National Comprehensive Cancer Network (NCCN)[14], actually suggest colonoscopy at 1 year, and subsequently according to findings. Furthermore, the ASCRS[4], ASCO[13], and NCCN[14] recommend surveillance rectosigmoidoscopy even more frequently (every 3 to 6 months for 5 years) in the presence of local recurrence risk factors and consider transanal local excision and absence of neoadjuvant radiation a risk factor *per se*. However, colonoscopy is not able to detect extra-luminal recurrent disease, which is more frequent than intraluminal recurrence in the case of rectal cancer. More often a positive circumferential margin at the time of original resection results in an extra-parietal recurrence, usually in the pre-sacral site. Endorectal ultrasound (ERUS) may overcome this limit, giving an accurate imaging of surrounding pelvic tissues. The role of ERUS for the diagnosis of local recurrence after local excision and radical surgery for rectal cancer was evaluated by de Anda *et al*[50]. The authors reported that asymptomatic local recurrences are identified by ERUS in 30% of cases and these recurrences were actually missed by digital examination or proctoscopic examination. However, only 44% of cases were amenable to salvage surgery and the impact of earlier diagnosis was not significant in terms of patient survival. Larger, multi-institutional RCTs are needed to confirm the real role and effectiveness of ERUS. Considering the lack of clear data, the ASCR and NCCN recommend surveillance endoscopy "with or without" ERUS, or alternatively magnetic resonance imaging (MRI) in surveillance programs[4,14].

PET SCANNING

PET with the use of radio-labeled glucose analogue ^{18}F-fluorodeoxyglucose (FDG) and PET associated with a CT scan (FDG PET/CT) are metabolic imaging that highlight lesions with higher glucose metabolism. Malignant lesions have higher glucose metabolism and thus a higher uptake of FDG. The use of PET/CT in colorectal cancer follow-up is currently controversial. A review and meta-analysis[51] evaluating the performance of FDG-PET or PET/CT to detect recurrences of colorectal cancer in patients with raised CEA, identifies 11 studies with a total of 510 patients. In the case of an increase in CEA, one hundred and six patients (106/510: 20.8%) had a true-negative FDG-PET/ or PET/CT. Thus, both imaging modalities ruled out 20% of false positive elevations of CEA. Moreover, the diagnostic accuracy of these techniques was 88.6% and allows a differentiation of an inflammatory process from a recurrence. PET and PET/CT had a sensitivity of 90.3% and 94.1% and a specificity of 80% and 77.2% respectively. Similarly, both modalities had good accuracy (89.03% and 92.38% respectively). Supplementary analysis showed that PET and PET/CT gave a significantly higher diagnostic performance than CT scans. Sanli *et al*[52] reported that colorectal cancer relapse was accurately detected also in the case of normal CEA rates. The NCCN[14] suggests PET/CT scans in the case of an increasing CEA, even with negative CT scans. Recently, a novel hybrid technique was introduced in the oncological field matching PET and MRI in one examination: FDG-PET/MRI. Hybrid PET/MRI combines metabolic imaging of PET with excellent soft tissue morphology of MRI[53]. The accuracy of FDG-PET/MRI is apparently superior to MRI alone in restaging after neoadjuvant chemoradiation (naCRT). The study from Crimì *et al*[54] showed that in patients with locally advanced rectal cancer undergoing restaging following preoperative chemoradiotherapy, FDG-PET/MRI was more accurate and sensitive than MRI alone both for residual cancer and regional lymph nodes (respectively ypT accuracy 92% *vs* 89%; ypN accuracy 92% *vs* 86%). Two recent studies investigated the role of FDG-PET/MRI in pelvic recurrence of rectal cancer[55,56]. The first paper from Plodeck *et al*[55] was a retrospective, single reader study, assessing the performance of FDG-PET/MRI without any comparison to MRI alone: sensitivity, specificity and accuracy were 94%. The same group published a retrospective evaluation of diagnostic performance of PET/MRI compared to MRI alone in the diagnosis of pelvic recurrence of rectal cancer: sensitivity and accuracy of PET/MRI were respectively 94% and 93% compared to 88% sensitivity and 85% accuracy of MRI in detecting recurrence. Both imaging modalities are accurate in this setting even though PET/MRI

increases confidence in diagnosis or exclusion of local recurrence and reduces the number of equivocal cases[56]. We can conclude that both PET and PET/CT provide useful information about sites of recurrence, especially extra-hepatic lesions, and possible metachronous tumors contributing substantially to patient management. Patients with a suspected recurrence, based on clinical findings or rising CEA, might benefit from a PET/CT as a first line imaging modality, since a negative CT scan does not definitively exclude a recurrence and will be followed by a PET/CT anyhow. PET/MRI is a promising imaging modality combining functional imaging and soft tissue contrast leading to more accurate evaluation of pelvic recurrence. Unfortunately, no prospective studies have evaluated the role of PET imaging in any colorectal cancer surveillance program. Indeed, the main limits of PET, PET/CT and PET/MRI are its limited availability and high cost: these drawbacks limit its use in follow-up programs and make PET imaging not realistic as a routine diagnostic method.

INTENSIVE *VS* LESS INTENSIVE FOLLOW-UP

Different follow-up regimens have been studied in RCTs and non-randomized studies, meta-analysis and systematic review, that aimed to elucidate the impact of different surveillance programs and schedule in terms of survival, recurrence detection rate and the ability to offer salvage surgery in the case of recurrence. Intensive, less intensive or even no surveillance has been proposed and the influence on cancer related outcomes has been analyzed. We identified 17 RCTs[16,34-39,44,47-49,57-63] and 8 meta-analyses[19,64-70], evaluating different follow-up strategies during surveillance programs after curative colorectal cancer surgery. Results of RCTs and meta-analyses are summarized respectively in Tables 1 and 2. Three trials[58,60,61] comparing different settings of monitoring did not show any differences in terms of recurrence detection rates and time to detection between a hospital/specialist setting and a general practice setting. Medical safety was uncompromised even if the follow-up was performed by a trained nurse. Eight trials did not show any significant differences in survival between intensive and less intensive surveillance[16,34,37,38,44,49,62,63]. The trial by Ohlsson *et al*[44] did not show any survival improvement even comparing intense follow-up with no follow-up. On the other hand, in six trials, intensive follow-up was associated with an improved overall survival, instead[35,39,47,48,57,59]. Six meta-analyses showed that, in patients with colorectal cancer followed after curative resection, an intensive follow-up program improves overall survival, detection of asymptomatic relapses and reoperation with curative intent[19,64-68]. On the other hand, there are two more recent meta-analyses that were not able to demonstrate any significant benefit from an intensification of surveillance programs[69,70]. It should be noted that the recent COLOFOL trial[63] is not included in any published meta-analyses. This trial randomized 2509 patients with stage II or III colorectal cancer to either low frequency follow-up regimens (CEA and chest/abdomen CT scan at 12 and 26 months) or high frequency follow-up regimens (CEA and CT scan at 6-12-18-24-36 months) with patients undergoing the same kind of tests. No significant advantage of the high frequency follow-up testing, both in 5-year overall mortality and colorectal cancer-specific mortality was recorded[63]. Furthermore, Renehan *et al*[64] in their meta-analysis showed that intensive surveillance leads to a 10% decrease in 5-year mortality, however only in 2% of cases salvage surgery was possible. The authors suggested that intensive follow-up programs can ameliorate psychosocial support and well-being, alter dietary and lifestyle factors and finally improve treatment of coincidental diseases leading to survival benefits. However, Baca *et al*[10] suggested that meta-analytic techniques could not be appropriate to evaluate results because of the inadequacy of sample sizes and the high heterogeneity in surveillance programs considered in the different RCTs. Finally, it has been suggested that a structured follow-up should be performed only in patients who can benefit from further treatments[15].

COST OF FOLLOW-UP

The pressure of rising health care costs has forced clinicians to review surveillance protocols to make them more effective and cheaper, trying to save unnecessary tests. Economic analysis of eleven different 5-year postoperative follow-up programs based on Medicare-allowed charges showed a wide range of costs: from $910 to $26717. Despite these significant disparities, no clear benefits were found in higher cost strategies in terms of quality of life and survival rate[71]. In the same year, Kievit *et al*[72] presented the results of a cost-effectiveness analysis comparing the results of three different policies comparing no follow-up, selective follow-up and intensive follow-up. In most cases, follow-up will only increase costs significantly without an increase in life expectancy and the author concluded that colorectal cancer follow-up is not "evidence-based medicine." A Markov model was used to simulate follow-up over a 7-year period in patients who had undergone curative resection of colorectal cancer[73]. The influence of follow-up on the quality-adjusted life expectancy of patients who had Duke's stage A and B colorectal cancer was marginal, while it ameliorated the survival in Duke's stage C patients. Graham *et al*[17] analyzed the cost of the single diagnostic method per resectable recurrence: CEA was the most cost-effective method, costing $5696 per recurrence, while CXR and colonoscopy cost $10078 and $45810 per

Table 1 Randomized controlled trials: Different surveillance strategies following curative colorectal cancer resection

Ref.	Surveillance strategy	No. of patients randomized	Significant benefit
Ohlsson *et al*[44], 1995	Total	107	No
	None (FOBT)	54	
	Intensive follow-up: examinations, FOBT, CEA, endoscopy, CXR, CT	53	
Mäkelä *et al*[37], 1995	Total	106	No
	Standard	54	
	More intensive examinations, FOBT, CEA, colonoscopy, CXR, liver US, CT	52	
Kjeldsen *et al*[16], 1997	Total	597	No
	Standard	307	
	More intensive examinations, blood tests, FOBT, CXR, colonoscopy	290	
Schoemaker *et al*[38], 1998	Total	325	No
	Standard: examinations, blood test, CEA, FOBT	158	
	Intensive: standard plus CXR, CT, colonoscopy	167	
Pietra *et al*[57], 1998	Total	207	Yes (increased curative reoperation; increased survival)
	Standard	103	
	More intensive examinations, CEA, colonoscopy, CXR, liver US, CT	104	
Secco *et al*[48], 2002	Total	358 (21 drop out)	Yes (increased curative reoperation; increased survival)
	Minimal: examinations yearly and on demand	145	
	Risk-adapted	192	
	-Low risk: less frequent examinations, CEA, rectosig-moidoscopy, CXR, US	84	
	-High risk: more frequent examinations, CEA, rectosig-moidoscopy, CXR, US	108	
Wattchow *et al*[58], 2006	Different settings no different tests	203 (46 lost fu)	No
	General Practitioner	81	
	Surgeon visit	76	
Rodríguez-Moranta *et al* [39], 2006	Total	259	Yes (increased curative reoperation, increased survival only for stage II colon tumor and rectal tumor)
	Standard: examinations, blood tests and CEA. Colonoscopy only if history of HNPCC and synchronous neoplasm	127	
	Intensive: standard plus annual colonoscopy, CXR, US and CT	132	
Sobhani *et al*[59], 2008	Total	130	Yes (increased curative reoperation; number of patients too small to evaluate survival)
	Standard: examinations, CEA, CXR, US and CT	65	
	Intensive: standard plus ^{18}FDG-PET	65	
Wang *et al*[47], 2009	Total	326	Yes (increased curative reoperation; no increased survival)
	Standard: examinations, CEA, colonoscopy, CXR, liver US and CT	161	
	Intensive: standard plus more frequent colonoscopy	165	
Strand *et al*[60], 2011	Different settings no different tests	110	No
	Nurse	54	
	Surgeon visit	56	

Augestad *et al*[61], 2013	Different settings no different tests	110	No
	General Practitioner	55	
	Surgeon visit	55	
Primrose *et al*[34] (FACS), 2014	Total	1202	No
	Minimal follow-up: no scheduled follow-up except a single CT scan at 12-18 mo	301	
	CEA follow-up: CEA every 3 mo for 2 yr, then every 6 mo for 3 yr, with a single CT scan at 12-18 mo	300	
	CT follow-up: CT scan every 6 mo for 2 yr, then annually for 3 yr	299	
	CEA and CT follow-up: combined CEA and CT imaging as above	302	
Treasure *et al*[62] (the CEA Second-Look trial), 2014	Total	Tot 216	No
	Standard: CEA monitoring with no further action even in case of CEA rising	108	
	Aggressive: CEA monitoring followed by second-look operation and possible resection in case of CEA rising	108	
Verberne *et al*[35] (CEAwatch[1], 2015	Total	3223	Yes (increased curative reoperation; no increased survival)
	Standard: CEA every 3 mo, examinations, liver US and CXR every 6 mo	1182	
	Intensive: CEA every 2 mo, examinations and CT annually. If CEA rise, repeat CEA after 1 mo. If two consecutive CEA rise, CT scan	316	
	Standard and Intensive: patients participated both in the standard protocol and in the intensive protocol	1725	
Rosati *et al*[49] (GILDA), 2016	Total	1228	No
	Standard: examinations, CEA, colonoscopy, CXR, liver imaging (US or CT scan)	613	
	Intensive: standard plus CA19-9, blood test, more frequent colonoscopy, CXR and liver imaging (US or CT), CT abdomen-pelvis	615	
Wille-Jørgensen *et al*[63] (COLOFOL), 2018	Total	2509	No
	Standard: CEA, CT chest, abdomen and pelvis at 12 and 36 mo	1256	
	Intensive: CEA, CT chest, abdomen and pelvis every 6 mo for 2 yr, then at 36 mo	1253	

[1]During the study period, hospitals changed from a standard follow-up schedule to the intensive follow-up schedule every 3 months. CEA: Carcinoembryonic antigen; CT: Computed tomography; CXR: Conventional chest radiography; FOBT: Fecal occult blood test; HNPCC: Hereditary non-polyposis colorectal cancer; mo: months; US: Ultrasonography; yr: years.

recurrence respectively. A risk adjusted follow-up policy, considering that older age and favorable cancer stage decrease cost-effectiveness, should focus solely on high-risk patients for the first 2-3 years using the most cost-effective test to increase benefits. On the other hand, a prospective, multicenter, RCT comparing a simple surveillance program including just clinical evaluation and CEA with an intensive strategy with abdominal-pelvic CT, CXR, and colonoscopy, found that, even though the overall cost of an intensive surveillance program was higher (€300315 *vs* €188630), the intensive follow-up was more cost-effective when resectability of recurrent disease was considered. In fact, the cost per resectable recurrence was €16684 in the intensive surveillance group, compared with €18863 in the simple follow-up strategy[39]. Therefore, justification of a surveillance strategy should be fundamentally based on evidence of clinical value allowing identification of recurrence at the point where a cure is still possible. Finally, the study from Augestad *et al*[61] demonstrated that a general practitioner's organized follow-up was cost-effective compared with surgeon's organized follow-up (£8233 *vs* £9889). Delegating follow-up can be effective but also safe with no harm for patients, but probably a precise algorithm of surveillance programs is the only way to help clinicians in charge for surveillance.

Table 2 Meta-analyses of follow-up studies with different surveillance strategies

Ref.	Studies included and number of patients	Benefit on survival
Bruinvels *et al*[19], 1993	7 nonrandomized	Yes
	3283 patients	
Rosen *et al*[67], 1998	2 RCTs, 3 nonrandomized	Yes
	2005 patients	
Renehan *et al*[64], 2002	5 RCTs	Yes
	1342 patients	
Figueredo *et al*[68], 2003	6 RCTs	Yes
	1679 patients	
Tjandra *et al*[65], 2007	8 RCTs	Yes
	2923 patients	
Pita-Fernández *et al*[66], 2015	11 RCTs	Yes
	4055 patients	
Mokhles *et al*[69], 2016	11 RCTs	No
	4515 patients	
Jeffery *et al*[70], 2016	15 RCTs	No
	5403 patients	

RCT: Randomized controlled trial.

CURRENT GUIDELINES AND RECOMMENDATIONS

Published guidelines from the most authoritative specialty societies indicate different protocols including medical history and physical examination, CEA levels, abdominal-pelvic and chest imaging and endoscopy. Follow-up recommendations from ASCO[13], ASCRS[4], European Society of Medical Oncology (ESMO)[12], ACPGBI[11], NCCN[14] and European Society of Coloproctology (ESCP)[15] are summarized in Table 3. In 2013, ASCO[13] endorsed the Cancer Care Ontario guidelines on follow-up care and added some statements[74]. The guidelines are primarily for patients with stage II and III disease, while stage I patients and patients resected for metastatic disease should be monitored according to the discretion of the health care provider. The suggested surveillance program considers, in the first 2-4 years, more intensive testing since 80% of recurrences occur in the first 2-2.5 years from surgery[13]. NCCN[14] and ESMO[12] guidelines actually suggest semi-annual to annual abdomen and chest CT scans for 5 years considering that up to 10% of recurrences occur after 3 years[75]. The ASCRS guidelines[4] are very similar to the previous recommendations but support the advantage of follow-up in terms of survival in patients with stage I disease. The ASCRS[4] and NCCN[14] recommend a more intensive approach for patients treated by transanal excision, while ASCO[13] suggests the same intensive approach for patients not having received radiotherapy. In NCCN guidelines[14], surveillance programs are a little more frequent than other programs. The ESMO[12] and ACPGBI[11] recommendations suggest slightly less intensive testing with a minimum of two CT scans of the chest, abdomen and pelvis associated with regular serum CEA tests in the first 3 years. The ESCP[15] recommendations are actually an overview of national and international clinical practice guidelines. Interestingly, colonoscopy and endoscopic inspection of anastomosis are recommended but the optimum time schedule and duration of surveillance are not specified since the analyzed guidelines were not all concordant[15]. A different issue is represented by the significant variation in adhesion and compliance both of members of scientific societies and patients with the recommended follow-up tests. A postal survey was mailed to active members of ASCRS in 2000 assessing the methods and frequency of follow-up. The most used tests were colonoscopy and CEA but there was wide variation in the frequency of follow-up and the diagnostic modalities employed. More interestingly, only 50% of surgeons followed the recommended guidelines of the ASCRS to whom they belonged[76]. It is clear that specialty society's recommendations differ and health care providers may find it difficult to choose the ones which are most appropriate. This may explain the low percentage of surgeons adhering to the recommended guidelines. It appears more sensible to adopt the follow-up scheme according to available manpower and local facilities.

Table 3 Summary of current surveillance guidelines from specialty societies

Guideline	MH & PE	CEA	Abdomen imaging	Chest imaging	Colonoscopy
ASCO[13]	Every 3-6 mo for 5 yr	Every 3-6 mo for 5 yr	CT of abdomen and pelvis annually for 3 yr, for high-risk patients every 6-12 mo for 3 years and then annually for 2 yr	CT of chest annually for 3 yr, for high-risk patients every 6-12 mo for 3 yr	Colonoscopy at 1 yr, subsequently according findings and every 5 yr if normal. Rectosigmoidoscopy every 6 mo for 5 yr in rectal cancer not irradiated
ASCR[4]	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr	CT of abdomen and pelvis 2 times in 5 yr, for high-risk patients annually for 5 yr	CT of chest 2 times in 5 yr, for high-risk patients annually for 5 yr	Colonoscopy at 1 yr, subsequently according findings and every 5 yr if normal. Rectosigmoidoscopy (+/- ERUS) every 6-12 mo for 3 to 5 yr for patients treated with TME; every 6 mo in patients treated with local excision
ESMO[12]	Every 6 mo for 2 yr	Every 6 mo for 3 yr	CT of abdomen and pelvis 2 times within 3 yr	CT of chest 2 times within 3 yr	Colonoscopy every 5 yr up to age 75
ACPGI [11]	No recommendation for frequency	Every 6 mo for 3 yr	CT of abdomen and pelvis 2 times within 3 yr	CT of chest 2 times within 3 yr	Colonoscopy at 1 yr subsequently according findings and every 5 yr if normal
NCCN[14]	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr for stage II or greater	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr for stage II or greater	CT of abdomen and pelvis every 3-6 mo for 2 yr, then every 6-12 mo for 3 yr	CT of chest every 3-6 mo for 2 yr, then every 6-12 mo for 3 yr	Colonoscopy at 1 yr, repeat in 3 yr then every 5 yr, Proctoscopy (with ERUS or MRI) every 3-6 mo for 2 yr, then every 6 mo for 3 yr for patients treated with transanal excision
ESCP[15]	No recommendation for frequency. Until 5 yr after surgery with a more frequent regimen in the first 2 yr to 3 yr	Every 3–6 mo for 2–3 yr, then every 6-12 mo until 5 yr after surgery	CT abdomen alternating with US for at least 5 yr with a more frequent regimen in the first 2-3 yr	CT of chest alternating with CXR every 3-12 mo for at least 5 yr after surgery	No recommendation for colonoscopy and proctoscopy

ACPGI: The association of Coloproctology of Great Britain and Ireland; ASCO: American Society of Oncology; ASCRS: American Society of Colon Rectal Surgeon; CEA: Carcinoembryonic antigen; CT: Computed tomography; CXR: Conventional chest radiography; ERUS: Endorectal ultrasound; ESMO: European Society for Medical Oncology; ESCP: European Society of Coloproctology; mo: months; MH & PE: Medical history and physical examination; MRI: Magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; TME: Total mesorectal excision; US: Ultrasonography; yr: years.

FOLLOW-UP FOLLOWING A COMPLETE RESPONSE AFTER CHEMORADIATION

Locally invasive rectal cancer is currently managed by neoadjuvant combined modality therapy (chemoradiation or even radiation alone regimens) followed by total mesorectal excision. The benefit of neoadjuvant therapy is not only the long-term local disease control, but also tumor regression. naCRT induces tumor regression (downsizing) and eventually lymph node sterilization (downstaging). After naCRT, up to 25% of patients have complete pathological tumor regression with no residual viable tumor cells at the time of surgery[77-80]. These patients have the so called "pathologic complete response (pCR)". A pCR is defined as an absence of viable tumor on histologic examination of the resection specimen and is reported as ypT0N0[81]. In a systematic review, the finding of pCR was associated with local recurrence rate and distant metastasis respectively of 0.7% and 8.7%. The 5-year overall survival rate was 90.2%, the disease-free survival (DFS) rate 87%[82]. These surprising results in patients with pCR have changed the role of standard surgery, especially considering morbidity and mortality associated with rectal surgery. Habr-Gama *et al*[83] from Brazil firstly proposed a non-operative approach for patients with significant or complete tumor regression. This alternative approach is also described as "organ-sparing treatment", "rectal preservation" or the "watch and wait" strategy. Patients with apparent clinical complete response (cCR) after naCRT are ideal candidates for conservative strategy. cCR is usually described as absence of tumor according to clinical, radiological and endoscopic investigations; however, the description cannot be as clear as pCR. Although the definition of cCR remains an active question and there is no uniform consensus, the absence of any palpable tumor at DRE and no visible lesion (flat scar, whitening of the mucosa or teleangiectasia) at endoscopy are widely accepted as main criteria to define cCR. The clinical criteria are normally complemented by the absence of residual tumor and metastatic lymph nodes on MRI[84]. The landmark paper based on this approach was firstly published in 2004 and since that time the San Paolo group has regularly updated their work[83,85]. Over 18 years, 67 (39%) patients were considered to have cCR after being reassessed following completion of radiotherapy at least 8 weeks later. At a mean follow-up of more than 5 years, overall survival reached 96% and DFS was 72% in nonoperative patients. Local recurrence (only endoluminal) and distant metastasis were observed in 11% and 10% respectively. All local recurrences were responsive to salvage therapy: 4 patients underwent radical surgery, 3 local excision and 1 additional endorectal brachytherapy[85]. Similar results have been reported by different authors in

smaller studies[86,87], but these surprising results have not been repeated by other studies with an 80% relapse rate following cCRs within 10 months of observation[88,89]. The data from the International Watch and Wait Database, including more than one-thousand patients managed by watch and wait strategy, showed a local regrowth rate of 25% and 8% distant metastasis at 3 years[90]. More recently, a total neoadjuvant therapy (TNT) has also been adopted with application of both radiation and full systemic chemotherapy before surgery leading to even better results in terms of tumor response[91]. In the prospective, randomized phase II trial from Garcia-Aguilar *et al*[91] the 3-year DFS was 76% and organ preservation was achievable in up to 53% of patients treated with TNT. Considering all these figures, the watch and wait strategy sounds promising and appealing since it avoids the significant morbidity related to surgery. Patients with a complete clinical response may achieve similar overall survival and local cancer control of patients undergoing standard surgery. The main challenge to a non-operative approach of locally advanced rectal cancer is the identification of patients with a true complete tumor regression since there is a real risk of leaving occult residual disease within the rectum or perirectal nodes. Thus, patients reported to have a cCR may bear microscopical disease with a high risk of early recurrence. These considerations are crucial for determining what kind of surveillance protocols should be adopted especially in this particular subset of patients. Again, the Brazil group[92] suggests a strict follow-up program including DRE, rigid proctoscopy with biopsy of suspicious lesions and CEA levels every 1-2 months for the first year, every 6 months in the second year and yearly thereafter. Chest X-ray and abdominal CT scans are recommended at 6 months and 12 months and yearly thereafter. The recently published RESARCH study[84] also adopts a strict follow-up strategy in patients who undergo a rectal sparing approach following neoadjuvant therapy: physical examination including digital rectal exploration, CEA levels and proctoscopy every 3 months for 2 years and subsequently every 6 months for 3 years. Chest and abdomen CT scans are recommended annually, while MRI of the pelvis is performed every 6 months for 2 years and yearly thereafter. Colonoscopy is performed at 1 year and 4 years following surgery[84]. Even though it is not suggested by the Habr-Gama *et al*[92] and the RESARCH study[84], FDG-PET and PET-CT may play an important role for surveying non-operative patients, considering that these imaging modalities are the most accurate and may help to distinguish fibrosis from viable tumor cells. Recently it has been suggested that FDG-PET/MRI may improve accuracy in restaging patients deemed to have a cCR. FDG-PET/MRI evaluating residual disease at restaging following TNT had an accuracy of 100% compared to 71% of MRI alone, adding value in restaging and surveillance programs of patients enrolled in non-operative management[93]. Finally, patients elected for this novel approach must be committed to an intensive follow-up regimen until the natural history of the non-operative approach is definitively clarified. The watch and wait strategy can only be offered to patients who will be compliant with frequent clinical and radiological evaluation. However, the key point of this novel approach remains to identify a true pCR without a resection and through targeted follow-up. Achieving the equivalence between cCR and pCR represents the crossroads to avoid either useless major resections or the risk of early local recurrence or, more correctly, tumor persistence.

CONCLUSION

Follow-up programs after rectal cancer resection are intuitively beneficial and appealing even though there is no clear evidence of benefits in terms of earlier detection of recurrence, surgical resections with curative intent and improved overall survival. The literature does not agree with the type of ideal surveillance methods and the timeframe with which they should be applied. Moreover, the cost-effectiveness of various surveillance strategies, the quality-of-life implications and the role of different surveillance techniques have not yet been clearly evaluated. In this difficult age for healthcare economies, the optimization of resources and therefore also of surveillance programs is necessary. The improvement of recurrence risk stratification, the identification of the patient population that will truly benefit from follow-up and avoid unnecessary examination in low-risk patients should be the main goal in designing a value-based follow-up strategy. The main purpose of a surveillance program must be early identification of a recurrence when curative interventions are still possible.

FOOTNOTES

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