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Review

Early Detection of Colorectal Cancer Recurrence in Patients Undergoing Surgery with Curative Intent: Current Status and Challenges

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Abstract

Despite advances in neoadjuvant and adjuvant therapy, attention to proper surgical technique, and improved pathological staging for both the primary and metastatic lesions, almost half of all colorectal cancer patients will develop recurrent disease. More concerning, this includes ~25% of patients with theoretically curable node-negative, non-metastatic Stage I and II disease. Given the annual incidence of colorectal cancer, approximately 150,000 new patients are candidates each year for follow-up surveillance. When combined with the greater population already enrolled in a surveillance protocol, this translates to a tremendous number of patients at risk for recurrence. It is therefore imperative that strategies aim for detection of recurrence as early as possible to allow initiation of treatment that may still result in cure. Yet, controversy exists regarding the optimal surveillance strategy (high-*intensity vs.* traditional), ideal testing regimen, and overall effectiveness. While benefits may involve earlier detection of recurrence, psychological welfare improvement, and greater overall survival, this must be weighed against the potential disadvantages including more invasive tests, higher rates of reoperation, and increased costs. In this review, we will examine the current options available and challenges surrounding colorectal cancer surveillance and early detection of recurrence.

Key words: colorectal cancer, colonoscopy, EUS, CEA, recurrence

Introduction

Colorectal cancer affects nearly 150,000 patients in the United States annually and is the cause of almost 50,000 deaths. (1) In those fortunate enough to be candidates for surgery with curative intent, adequate follow-up can detect early recurrence, metachronous malignancy, and metastatic disease. Multiple specialty societies have published recommendations regarding appropriate follow up of such patients (**Table 1**). (2-7) While these guidelines agree on many key points, there remain areas of controversy.

Given that ~30-50% of patients undergoing a curative resection will ultimately have recurrent dis-

ease, optimizing the surveillance strategy is paramount. (4) For such a strategy to be meaningful, however, several basic requirements must be met. First, the recurrence should be detectable in an asymptomatic phase. Otherwise, the clinician could simply wait for symptoms to occur rather than embarking on any surveillance strategy. Second, the detection of recurrent or metachronous disease should lead to effective treatment and a better clinical outcome than no surveillance. Historically, this has primarily meant additional operative intervention since surgery was the only curative option in most cases, with other modalities such as chemotherapy reserved for palliative care. More recently, advances in minimally invasive techniques (*i.e.*, chemoembolization, cryotherapy, radio frequency ablation) and highly targeted biologic agents have somewhat changed this paradigm. Nonetheless, the principle still applies that if the patient is unwilling to undergo further treatment or would not be a candidate for such, ongoing surveillance is unwarranted.

One of the difficulties clinicians face in interpreting the literature on this subject is the rapid evolution of technology. For instance, the first randomized clinical trial comparing an intensive surveillance regimen to "standard" follow up was published in 1995, with patient accrual occurring in the late 1980's. (8) Computed tomography failed to improve early detection in this study, but a CT scan performed with a 2-slice scanner 25 years ago is not the same as one performed on a 128-slice machine today. Improvements in surgical technique and postoperative management have increased the survival of those operated on for recurrences, while advances in chemotherapy and biologic agents have allowed patients who would have previously had unresectable disease to become resectable. (9) Finally, patients' treatment goals and preferences must be taken into account, as all the follow-up tests come with risks. These risks include both physical (*e.g.,* perforation, radiation exposure) and mental harms (*e.g.,* anxiety, phobic avoidance) that have potential adverse effects on the quality of the patients' remaining life. It is the hope of the authors that the information in this article will provide a starting point for a conversation with patients about the current state of the science in colorectal cancer surveillance and early detection of recurrence.

Surveillance Strategies - What is the Ideal Regimen?

Accurate staging of colorectal cancer patients not only helps to guide the proper treatment protocol, but also allows the stratification of patients into cohorts with similar prognosis for both disease-free and overall survival. Yet, it is recognized that within each AJCC Stage, certain patients live well beyond their estimated 5-year survival, while others develop recurrences or die from what, in theory, was curable disease. Tumor biology, therapeutic regimens, and the response of each individual's tumor to treatment all play a major role in eventual outcome. Beyond the requirements listed previously, in developing an ideal postoperative surveillance protocol to follow colorectal cancer patients, certain criteria are desirable: 1) wide availability; 2) high sensitivity to detect early recurrence; 3) high specificity to ensure the those without disease are correctly labeled; and 4) cost-efficiency. Yet, the success of each protocol is dependent on the strength and weaknesses inherent to its individual components. For example, a small rise in a non-specific tumor marker may have a vastly different meaning than a marked change on a PET scan in a previously unremarkable pelvis. On the other hand, while the early detection rate may improve with every 3-month history and physical, laboratory testing, CT, PET scan, endoscopic ultrasound (EUS), and colonoscopy, this is neither feasible nor cost-effective.

In evaluating the impact of an intensive versus standard surveillance strategy on outcomes for post-resection colorectal cancer patients, at least 8 randomized controlled trials, (10-18) 7 meta-analyses, (19-24) and one Cochrane update (25) have been completed in the last decade. Despite this abundance of data on which to base recommendations, problems abound. Defining what constitutes intense versus standard follow-up varies, as does the individual program. Yet, while the surveillance regimens and components differ amongst the studies, results generally suggest improved early detection, increased rates of curative resection of the recurrence, and better overall survival with more intense protocols. In the Cochrane review, (25) although the absolute number of recurrences was similar, an intensive follow-up was associated with an overall survival benefit at five years (OR=0.73; 95% CI 0.59 to 0.91). In addition, despite the heterogeneity in the studies, the authors were able to determine the time to recurrence was significantly reduced by -6.75 (95% CI -11.06 to -2.44), suggesting an earlier detection of recurrence in the high-intensity surveillance cohort. Data regarding individual components within these treatment strategies will be discussed below.

Defining and Predicting Recurrence

Once patients are on a surveillance protocol, though seemingly straightforward, the first step in managing recurrence is to accurately define its presence. In practicality, this can be much more difficult

than at first glance. Unfortunately, only ~10-20% of all recurrences for colon cancer occur local-regionally following standard oncological excision, and many of them are not visible endolumenally. Other patterns of recurrence include adjacent mesenteric nodal disease, as well as masses that involve the abdominal wall or retroperitoneum. Obstruction, perforation, and T4 lesions have been shown to be independently associated with local recurrence for colon cancer. (26) Local recurrence for rectal cancer depends largely on the stage, method of resection and adjuvant therapy. Depending on the location, tumor characteristics, and patient comorbidities (and patient desires), rectal lesions can either be removed using standard oncological techniques (*i.e.*, total mesorectal excision or abdominal-perineal resection) or transanally (local excision, transanal endoscopic microsurgery or transanal minimally invasive surgery). Following traditional transanal excision, the local recurrence rate for T1 and T2 tumors are ~10-20% and 25-50%, respectively. (27) T2 lesions are increasingly becoming more questionable for successful use of this approach, largely due to their increased recurrence. In a large study out of the University of Minnesota, the authors found a local recurrence rate of 47% in T_2 lesions. (28) You and associates evaluated 765 patients from the National Cancer Database undergoing local excision for AJCC Stage 1 disease, including 164 patients with T_2 lesions. Overall, five-year local recurrence rate was 22.1%, significantly greater than following standard resection, but less than the University of Minnesota study. (29) In part, this is likely secondary to factors such as size, dysplasia, margin status and histological predictors (*i.e.*, lymphovascular invasion, degree of differentiation, distance from the anal verge). Additionally, technical factors play a role in the rate of recurrence, with the largest adverse risk factors being inadequate resection margins. (30-32) Foremost, a transanal excision must be a full thickness biopsy with at least 1 cm margins or recurrence is almost assured.

Conversely, the risk for local recurrence after radical surgery for early stage lesions is relatively low, ranging from ~ 2 to 5%, while the risk for distant recurrence is higher at ~10-20%. (33) Other studies have demonstrated a higher overall recurrence rate at 5-years, even for early lesions, with disease-free survival of 77% for patients with Stage 1 disease following total mesorectal excision. (34) Similar to outcomes following local excision, tumor biology and technical factors such as proper TME techniques, adequate margins, and avoidance of tumor spillage all play a role. With the addition of adjuvant therapy and experienced surgeons well versed in mesorectal resection, (35) local recurrence rates < 5% have been reported with even more advanced-staged lesions. (36)

The variability in results also arises from other factors such as use of adjuvant chemo- or radiotherapy. Protocols utilize adjuvant or neo-adjuvant chemotherapy with or without radiation therapy with local excision, similar to radical excision. In fact, there has been an increasing trend for use adjuvant therapy with local excision, both in the adjuvant and neoadjuvant setting, to downstage the lesions. (37, 38) Russell and associates reported on 65 patients undergoing local excision followed by either observation or post-operative 5-FU and one of two different radiation therapy doses for high-risk lesions (T_2, T_3, positive lymphovascular invasion, size >3 cm or elevated CEA). (39) At a minimum follow-up of 5 years, 11 (17%) patients developed recurrent disease and 8 (12.3%) patients had died. Predictors of recurrent disease were higher T-stage (23% for T_3 tumors versus 4% for T_1 lesions) and larger circumference of the lesions (18% for lesions involving 21-40% of the circumference vs. 6% involving <20%). Marks and colleagues reported on a small prospective study of 14 patients with a minimum follow-up of 24 months undergoing high-dose preoperative radiation with 4500 cGy followed by LE 4-6 weeks later. (38) Three (21%) developed local recurrence and one (7%) patient died of recurrent disease. The same group subsequently reported on 48 patients stratified into three groups: those with T_3 or >3 cm in size (n=15), T_1 or T_2 lesions all < 3 cm in size (n=18), and patients with original T_3 or >3 cm lesions that following pre-operative radiation had down-staged to lower T-stage lesions or smaller than 3 cm (n=15). (40) Although the overall 5-year recurrence was 10%, patients with post-radiation stage T_3 had a 67% local recurrence rate compared to 11% for Stage T_0/T_1 lesions, calling into question it usefulness in higher T-stage cohorts.

Conversely, Perez and colleagues examined a cohort with distal rectal cancer, all of which underwent neoadjuvant chemoradiation therapy followed by radical excision. (41) Following resection, 88/289 (30%) had a pathological T_2 rectal cancer lesion, and 19% of these patients had lymph node metastases despite the chemoradiation therapy. Thus, local excision in these patients would have represented an unacceptable risk for local failure and the authors concluded that T_2 lesions should have radical surgery as the standard treatment. The same group also reported on a small cohort of patients who received neoadjuvant chemotherapy with excellent responses, and subsequent transanal endoscopic microsurgery. Despite the final pathology being ypT0-2, local failure was 15% at a median follow-up of 15 months.

Radiology and Recurrent Disease

Identifying an anastomotic recurrence via direct visualization may be fairly straightforward, and will be discussed under colonoscopy below. Yet, for extralumenal recurrence, radiology plays a major role for both early detection and differentiation of recurrent disease from benign findings such as postoperative changes. The ability of radiological tests to discriminate these lesions, while often possible within the entire clinical context, presents its own unique set of issues, and highlights some of the concerns regarding an intensive follow-up regimen. While early detection has been shown to be more prevalent with aggressive surveillance, so to have false positives that lead to more invasive tests, an increased potential for unnecessary morbidity, and higher costs. Regardless, it is important to have realistic expectations and understand the limitations of imaging studies within the framework of any given surveillance program.

CT Scan

CT remains the "workhorse" of follow-up imaging for colorectal cancer. As shown in **Table 1**, every societal recommendation uses serial CT imaging as a component of a standardized surveillance protocol. Of note, ASCO limits its guidelines for annual CT at 3 years, while NCCN recently changed their recommendation from annually for the first 3 years, now to 5 years following resection. In general, CT provides an effective means for determining the presence of new lesions (metastatic and benign) throughout the body (especially in detecting new liver and chest lesions). However, it is worse than MRI at discriminating between postoperative changes and recurrence when used alone, especially in the pelvis (CT: sensitivity of 82% and a specificity of 50% with a PPV of 69% and an NPV of 67% with an accuracy of 68%; MRI: 91% sensitivity, 100% specificity, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 89% with a 95% accuracy.) (43) While meta-analyses of randomized trials show clear benefit for CT scans performed in the first few years after surgery, the benefit in later years in unclear. In a study of 207 patients, Walter and colleagues recently examined the utility of a CT scan performed five years after curative resection of CRC. (44) Of the 34 patients who developed metastatic disease, all were discovered within 3.5 years of resection, and no cases of metastatic CRC were noted at five years. The authors rightly concluded that fifth year CT scan has no role in the surveillance of CRC.

Table 1: Societal guidelines for the surveillance of colorectal cancer treated with curative intent

Society	Year	Colonoscopy	CEA	History and Physical	Imaging
NCCN	2013	@ 1yr. If AA, repeat in 1 year. If not then 3 yrs, then 5 yrs.	q3-6 mos. X2 yrs, then q6mos. X3 yrs.	q3-6 mos. X2 yrs, then q6mos. X3 yrs.	CT C/A/P: q1yr x5 if high risk of recurrence*
ASCO	2005	Assuming "cleared" colon, 2-3 yrs. then q5 if normal.	q3 mos. x3 yrs for stage II/III disease	q3-6 mos. X3 yrs, then q6 mos. X2 yrs.	CT C/A: q 1 yr x3 yrs. Add pelvis for rectal cancer.
NICE	2011	@ 1yr. If normal, repeat in 5 yrs. If not, interval determined by findings.	@ least q6 mos. X 3 yrs.	Regular follow up starting 4-6 weeks post-operatively.	CT C/A/P: at least 2 in the first 3 yrs.
AGA	2006	@1 yr. If normal repeat in 3 then 5 yrs.	Not addressed	Not addressed	Not addressed
ESMO	2012	@ 1 yr, then q5 yrs.	q3-6 mo x3 yrs, then q6-12 months x2 yrs	q3-6 mo x3 yrs, then q6-12 months x2 yrs	CT C/A q 6-12 mo x 3 yrs if high risk. Consider q3-6 mos. Liver ultrasound.
ASCRS	2004	@ 1 yr, then q3 yrs.	Minimum of 4 months x 2 years then q 6 months x 2 years, then annually	Minimum of 4 months x 2 years then q 6 months x 2 years, then annually	Routine hepatic imaging should not be performed; Insufficient data to support or refute CXR; Consider EUS for rectal cancer

NCCN: National Cancer Care Network; yrs: years;
ASCO: American Society of Clinical Oncologists; mos: months
NICE: National Institute for Health and Care Excellence; EUS: endorectal ultrasound
AGA: American Gastroenterological Association; CXR: chest x-ray
ESMO: European Society for Medical Oncology C/A/P: chest/abdomen/pelvis
ASCRS: American Society of Colon & Rectal Surgeons
*Tumor with lymphatic or vascular invasion or poor differentiation

MRI

Magnetic resonance imaging (MRI) has a higher sensitivity (~75-90%) than CT for the detection specifically of colorectal liver metastases, (45) and is even better for determining pelvic recurrence of rectal cancer (sensitivity 91%, accuracy 62%). (46, 47) However, the higher cost of MRI and its limited value in detecting lung metastases precludes its routine use over CT for post-operative surveillance. A trial looking at the role of magnetic resonance imaging (MRI) in addition to standard surveillance found that MRI missed 13% of recurrences and 14% of positive studies were false positives. (48) There was no difference between MRI and conventional testing with regards to the detection of cases suitable for resection and the authors concluded that MRI has no role in this setting. While its utility at detecting early recurrence is debatable, (48) expert consensus panels have still recommended MRI to be used along with clinical examination and PET to determine the ability to achieve negative resection margins in pelvic rectal cancer recurrences prior to embarking on surgery. (49) Furthermore, recent innovations in MRI techniques such as the use of moving table, and T1 and STIR sequences have demonstrated whole body results for the detection of recurrent rectal cancer to be similar to PET-CT. (50)

PET Scan

Positron emission tomography with fluorodeoxyglucose (FDG-PET) provides information on the metabolic activity of a lesion, theoretically allowing better discrimination between the hypermetabolic tumor and postoperative changes. When combined via fusion imaging with CT (PET-CT), this allows both the ability to display the anatomy as well as the superimposed glucose tracer uptake. A retrospective study from the Czech Republic examined the use of PET and PET CT for the detection of recurrent colon cancer. (51) In this study, the sensitivity, specificity, and overall accuracy of F-fluorodeoxyglucose (FDG) PET/CT were 89%, 92%, and 90% correctly detecting 40 out of 45 patients with recurrent disease. Another study by Kishimoto shows CT/PET to be a sensitive method of detecting recurrent disease, but notes that its high cost made it a cost ineffective test for general use. (52) Digital fusion imaging has shown accuracy rates up to 93% for local recurrence of rectal cancer, significantly better than either study alone. (53) In addition, it is significantly more sensitive (94.6%) than CT or unenhanced magnetic resonance imaging (MRI) for the detection of liver metastases. (47) FDG-PET is also of value in the investigation of patients with raised tumor markers and negative conventional imaging, where the positive yield of tumor ranges between 38-57%, and has even correlated with overall survival. (54, 55) While cost remains an issue, it may help decrease a negative exploration rate.

In prospective data comparing MRI with PET for local recurrence of rectal cancer (using histological biopsy as the gold standard), sensitivity, specificity, positive and negative predictive value and accuracy were 86.7%, 68.9%, 48.1%, 93.9% and 73.3% for contrast-enhanced MRI and 93.3%, 68.9%, 50%, 96.9% and 75% for PET-CT. (56) Unfortunately, there were only 39 cases, and the role for early detection was debatable. Other comparisons report overall diagnostic accuracy for PET-CT at 91% (sensitivity 86%, specificity 96%) and 83% for MRI (sensitivity 72%, specificity 93%), respectively; though PET-CT appears to be better for nodal disease and both equal for organ involvement. (50) Overall, while PET and PET-CT do not appear to be overall cost beneficial for routine surveillance, it has become a primary modality for distinguishing tumor recurrence from other imaging abnormalities.

CT Colonography

Finally, CT colonography (CTC) would intuitively seem a useful surveillance modality as it provides information regarding both intra- and extra-luminal recurrences. In the U.S., this study is typically performed without IV contrast thereby limiting is ability to detect metastatic foci. In countries such as Korea, however, where IV contrast is routinely used, CTC has proven a useful surveillance tool. (57) In a study of 742 patients undergoing curative intent surgery, CTC discovered 100% of the metachronous cancers as well as 11 extracolonic recurrences, but was only 81% sensitive for the detection of advanced adenomas. Previous authors have even recommended its routine use in the setting of post-operative surveillance to allow for simultaneous evaluation of distant and local-regional recurrence, while still allowing visualization of the anastomosis. (58) However, the authors do note that inflammation and ulcers at the anastomotic site can be falsely identified as a recurrence. Other small series have reported accuracy rates of 94% (95% CI; 83-99%) for detecting local recurrence. (59, 60) While CTC has proven to be a useful tool for primary CRC screening, more studies are needed to determine if CTC provides a viable and cost effective option for CRC surveillance.

Local recurrence

The cornerstone for detecting endolumenal local recurrence, as well as metachronous cancer, is direct visualization of the colonic mucosa via colonoscopy. However, while colonoscopy remains the gold

standard for colorectal cancer detection and prevention, it is an imperfect tool even in the best hands. The miss rates for an adenocarcinoma range from 1 to 3% and do not differ substantially between standard screening examination and examinations in which a primary cancer is discovered. (61, 62) Moreover, 2-7% of patients with colorectal cancer have a synchronous colon cancer at the time of diagnosis. (63-66) Other patients may present with obstruction or perforation, where clearance of the colon is not possible at the time of an emergent operation. For these reasons, most specialty societies recommend a follow-up colonoscopy within a year after curative CRC resection, and within 6 months if visualization of the entire colon was not possible prior to surgery. (2-6, 67)

As previously noted, multiple systematic reviews have been performed comparing an intensive surveillance strategy, including colonoscopy, to either standard practice or minimal follow-up. (19-25) While the majority of these studies suggest a survival benefit for intensive surveillance (9-13%), the trials on which these meta-analyses are based were conducted prior to the current multidisciplinary approach to the care of cancer patients. As such, it is likely that the benefit of close follow-up is even more significant than was seen in these studies.

In looking specifically at the impact of colonoscopy, Wang and colleagues have since performed a randomized trial that compared intensive colonoscopic surveillance to routine colonoscopic surveillance. (68) In this study of 326 patients undergoing curative CRC resection, the intensive group received colonoscopy at 3-month intervals for one year, every 6 months for the next two years, and once a year thereafter. In the routine group, colonoscopy was performed at 6-months, 30-months, and 60-months post-operatively, in keeping with societal guidelines. The intensive surveillance group had an improved overall 5-year survival (77% vs. 73%) as well as a higher percentage of post-operative cancers, which were detected in the asymptomatic phase and more reoperations with curative intent. The rate of anastomotic recurrence in this study was between 6-8% at 2 years. A retrospective study in Japan analyzing patients from the same time frame showed a local recurrence rate of only 0.7%, which is more in line with the rates seen in studies published in the last decade, while a recent meta-analysis reported that rectal washout significantly decreases the anastomotic recurrence rate for rectal cancer (RR = 0.3; 95% CI = 0.12-0.71; P = 0.007). (69) Several investigators have calculated the cost effectiveness of colonoscopy as part of an intensive follow-up strategy. Hassan and colleagues showed colonoscopy to be cost effective, with a cost of $40,313 per life year gained. (70) Di Cristafaro *et al*. examined the cost effectiveness (*i.e.*, overall cost and percentage of recurrence detected by strategy) of the recommended multimodality surveillance protocol including colonoscopy, CEA, CT of the chest and abdomen, and physical examination. This strategy was found to be most effective for patients with stage I and II disease, who represent the vast majority of those resected with curative intent, with a cost/effectiveness ratio of € 319.24. (71) Clearly colonoscopy plays an integral role in the surveillance of colorectal cancer, as well as ruling out synchronous/metachronous disease. However, it appears unlikely, especially in light of the small percentage of intraluminal recurrences that changing the currently recommended colonoscopy intervals would dramatically impact the rates of early detection.

Role of endoscopic ultrasound

Unfortunately, not all recurrences are evident at the mucosal surface. In these cases, endoscopic ultrasound (EUS), which allows highly detailed visualization of all the bowel wall layers as well as the surrounding structures, is a useful adjunct. (72) While EUS has been widely used to detect recurrent disease of the upper GI tract, it has not been as valuable for the lower GI tract, perhaps because postoperative changes are difficult to distinguish from recurrent disease (73-77).

EUS was introduced for the evaluation of subepithelial lesions in the GI tract in the late 1980s. At the time, these devices were rigid and lacked fiberoptic visualization, thereby limiting the examination to the distal rectum and adjacent tissues. As the technology advanced, ultrasound probes allowed the examination of larger portions of the colorectum, even in cases of severe stenosis. Most early studies concluded that EUS alone was insufficient for the diagnosis alone as the sonographic findings in malignant recurrences are indistinguishable from post-operative changes, especially within the first 3-6 months. (78-81) Nakajima, *et al.* showed circumferential hypertrophy of the 3rd and 4th layers of the bowel wall was still present up to 6 months post-operatively, at which time the thickening of the 3rd layer typically resolved. (81) He suggested that localized hypertrophy of the 4th mucosal layer was a sign of recurrence that 1) would not be visible on luminal examination; and 2) would be indistinguishable from post-operative changes on CT. Recurrence was characterized by a hypoechoic area within the mucosal wall or perirectal space whereas post-surgical scarring tended to be hyperechoic. However, this has not achieved widespread adoption, and EUS alone is still highly dependent on the ability of the user, similar to its use in primary staging. (82)

EUS does have certain advantages in this setting, especially with detecting recurrent disease earlier than other convention imaging. In comparison, cross-sectional imaging has an accuracy rate in the low 80s for the post-operative detection of recurrence. One of the earliest studies to assess the accuracy of EUS for the detection of locally recurrent rectal cancer compared it to either digital rectal or sigmoidoscopic examination (73). Of the 85 patients included, 22 had endosonographic evidence of recurrence, only 19 of which were visible by other modalities. The investigators observed three patterns of recurrence: mucosal involvement similar in appearance to the primary tumor, mixed echo-density areas within the wall, and echo poor areas outside the wall. In all cases of suspected recurrence, the patient underwent a perineal biopsy for confirmation. These results supported previous studies by Hildebrandt *et al.* and Romano *et al.* demonstrating the effectiveness of EUS in the follow-up of surgically treated rectal cancer patients. (78, 83) Of the thirty recurrences noted in these studies, 6 were detected only by EUS. Based on these early studies, several investigators added EUS to other surveillance techniques as part of their standard protocol for rectal cancer. In one such study, Ramirez and colleagues performed EUS as part of their surveillance protocol beginning 3 months post-operatively. (74) A total of 66 patients were included, 13 (~20%) of whom had local recurrence. Nearly all recurrences developed within 2 years post-operatively. Of the 13 cases, 3 were diagnosed by EUS alone. Interestingly, these three cases represented 75% of the cases in which salvage surgery was possible, suggesting that EUS can detect recurrence at an early stage. Survival of the patients who underwent salvage surgery was 36 months vs. 15 months in the palliative group. While the study lacks the power to definitively prove it, the data suggest that early detection of rectal cancer by EUS may have an impact on survival. Because of this, the current US Multi-Society Task Force recommendation suggests EUS at 3-6 months for the first 2 years after resection as a reasonable option in patients with a curative resection for rectal cancer. (2)

The primary value of EUS in the evaluation for possible CRC recurrence today comes from its ability to direct fine needle aspiration (FNA) and fine needle biopsy (FNB), thus allowing the collection of specimens for histological and immunohistochemical analysis, and overcoming some of the inherent user bias. Two studies examining EUS with FNA showed it to be a highly accurate test for the diagnosis of subepithelial and extra-luminal lesions of the colon and rectum (81, 84). In both studies, the accuracy of EUS-FNA was 90-95% compared with an 82% accuracy for imaging alone (84). These studies support the findings of numerous prior investigations and case reports regarding the accuracy and/or safety of EUS-guided sampling. (72, 78-88) Taken together, these studies include a total of 1027 patients and 110 cases of recurrence with a reported accuracy ranging from 87-100%. In approximately 10% of the cases, EUS was the sole means of diagnosis. In one of the studies, EUS diagnosed 100% of the asymptomatic recurrences whereas CT only found 75% of them. (85) All six subjects were eligible to undergo curative surgery. A small study by Morken suggests that overall survival is improved in cases where recurrences were detected via EUS versus other means. (88) Similar to the Ramirez study, in 13% of cases the recurrence was detected by ERUS only, and allowed 26/39 to have an attempt at curative resection of the recurrence. While these results have been encouraging, and current recommendations/protocols for EUS use in the surveillance of rectal cancer exist, this has not been widespread. Randomized trials of EUS in this setting, perhaps with contrast enhancement, are warranted.

Distant recurrence

Limitations in Interpreting the Role of imaging

Despite advances in surgical technique and the widespread availability of neoadjuvant chemotherapy and radiation, rectal cancer recurs locally in up to one-third of cases. (89) The current rates of local colon cancer recurrence are lower than previous reports, but still occur, and can have devastating consequences not only in survival, but quality of life as well. As stated, imaging techniques are commonly employed as part of a comprehensive strategy for detecting such recurrences. Unfortunately, most studies have employed these modalities in combination with serologic tests and colonoscopy, so the direct impact of the radiographic studies themselves can be difficult to tease out. Jochmans and colleagues attempted to answer this question in a study examining the attributable detection rate of surveillance imaging in Belgium. (90) Routine imaging in this case consisted of chest x-ray and liver ultrasound every 6 months for the first year and annually for up to five years. While CEA was the most sensitive marker detecting 63% of cases, 25% were detected by imaging alone with half of those being amenable to surgical resection. However, as demonstrated by **Table 1**, most recommendations have gone away from chest radiograph and ultrasound and migrated to CT. Therefore, further data is needed to answer this question.

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) is a glycoprotein oncofetal antigen that many epithelial tumors express. (91) While CEA is typically considered a tu-

mor marker, levels may also be elevated in a variety of non-malignant conditions including pancreatitis, cigarette smoking, and inflammatory bowel disease. First described by Gold and Freedman in 1965, this relatively inexpensive blood test has been part of the majority of recommended surveillance strategies. (92) Seventy percent of patients with colorectal cancer will have an elevation in their CEA level at diagnosis, making it a useful marker for cure and surveillance of disease after surgery. (93) Despite this, some controversy still exists regarding its utility. Tan, *et al.* performed a quantitative meta-analysis of 20 studies including 4,285 patients examining the performance characteristics of CEA when used to detect CRC recurrence. (94) They found an overall sensitivity of 0.64 (95% CI 0.61-0.67) with a specificity of 0.90. Using meta-regression techniques, they calculated that the optimal balance of sensitivity and specificity occurs at 2.2 ng/ml. Even at this level, the authors concluded that CEA lacks sufficient sensitivity and specificity to be used in isolation. A recent study by Chen and colleagues in Taiwan investigated whether CEA elevation provided added value in the detection of postoperative recurrence. (91) In their study of 4,841 patients, 999 patients had elevated CEA (defined at > 5 ng/ml) and recurrence. Approximately three-quarters of these patients had their recurrence detected via other means at the same time as the first CEA elevation. The authors concluded that a more sensitive test is need for early detection of recurrence. In clinical practice, CEA is rarely used alone to determine recurrence. Rather a combination of an elevated or rising CEA in conjunction with clinical or radiographic evidence of recurrence is used. In a study by Metser and colleagues, recurrent disease was found in only 65% of patients with elevated CEA followed by multidetector CT (MDCT) and CT/PET for an average of 18 months after the CEA elevation. (95) Finally, certain tumors that expressed CEA at presentation undergo dedifferentiation and stop expressing CEA when they metastasize, rendering it useless as a surveillance tool in these cases.

EUS and distant metastasis

There are limited data on the utility of EUS in the diagnosis of distant CRC recurrence *per se*. Studies by DeWitt *et al.* and Hunerbein *et al*. looked at the accuracy of EUS for recurrent or metastatic malignancy of the GI tract in general. (76, 87) A total of 188 patients underwent EUS with FNA of suspicious lesions including lymph nodes. The size of the lesions ranged from 7-70 mm, and they were located both above and below the diaphragm. Accuracy ranged from 92-95%. In most cases, there was a clinical, radiographic, or pathological suspicion of metastatic disease. As the majority of these lesions were adenocarcinomas (including a few colon cancers), it seems reasonable to extrapolate these results to colorectal cancer. While EUS with FNA has no role in primary surveillance, it is often useful when suspicious lesions are noted on other imaging studies and has the advantage of continuous, real-time needle localization during tissue sampling. However, for the current early detection of colorectal cancer, this modality has limited use.

Adherence to guidelines

Numerous studies have revealed a high variability in adherence to published guidelines, both in the primary setting (96) and with surveillance. (96-101) The precise nature of the variance differed among the study groups and may reflect local/regional factors. For instance, in study in Manitoba, 80.4% of all subjects underwent colonoscopy within the recommended interval, whereas 47% had liver imaging and only 22% received CEA testing as recommended. (97) By contrast, in a U.S. study using the Cancer Care Outcomes Research and Surveillance (CanCORS) database, fewer than half of all subjects received a colonoscopy within 14 months of surgery. (98) Both studies noted that increased contact with one's primary care manager was associated with adherence to the guidelines.

In some studies, physicians performed more surveillance examinations than are recommended. A Norwegian study, for instance, reported that 37% of subjects received a more frequent imaging than is called for in the guidelines. (99) This was particularly true for rectal cancer patient in whom local recurrence is more of a concern. A U.S. study of four geographically distinct health care maintenance organizations showed that only 55% of CRC survivors received colonoscopy as recommended, whereas 73% received *non-recommended* tests to look for metastatic disease. (100) Moreover, patients received, on average, twice the suggested number of physical exams, indicating that lack of clinical follow-up did not explain the paucity of colonoscopic exams. While patient factors such as anxiety and fear over waiting extended intervals for repeat examinations may factor into this pattern of overuse, a physician's lack of knowledge or belief in the recommendations may also play a role into the variance with guidelines. Yet, in this era of cost-containment, additional emphasis has to be on maximizing outcomes while minimizing undue testing.

Conclusion

The 2008 Cochrane review on the detection of CRC sums up the literature on this subject well. In it, the authors state that while intensive surveillance has

been associated with improved all-cause survival, it is "not clear what constitutes the optimal follow up regimen". Various intensive surveillance strategies have been compared to either standard of care or simply less intensive regimens. The next step is to conduct trials that compare one intensive strategy to another. Furthermore, the goal is not simply the detection of recurrence, but the ability to detect recurrent disease as early as possible to facilitate intervention and cure. While advances in molecular medicine and epigenetics may provide suitable targets to allow this in the future, there is currently no single test that is adequately sensitive and specific to be used alone for the detection of CRC recurrence.

Disclaimers

The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, Department of the Navy, the Department of Defense or the U.S. Government.

Competing Interests

The authors have declared that no competing interest exists.

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