

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Monitoring for Postoperative Recurrence of Crohn's Disease



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G&H Why is monitoring for postoperative recurrence of Crohn's disease important?

NKC The risk of postoperative recurrence of Crohn's disease is incredibly high. Population-based studies have estimated that 50% to 90% of patients with Crohn's disease who underwent ileocolonic resection experience postoperative endoscopic recurrence within 1 year, increasing to almost 100% within 3 years. We have learned over the recent decades that patients' symptoms often do not correlate with disease activity, and that has led the field to move toward proactive disease monitoring. We have realized that moving away from reactive management to proactive assessment of disease activity has led to improved patient outcomes. In postoperative monitoring, asymptomatic recurrence is often found, and data show that early intervention often leads to improved outcomes, supporting a proactive monitoring approach.

G&H What are the known risk factors for recurrence?

NKC Currently, the known risk factors are cigarette smoking, penetrating disease, prior bowel surgeries (specifically 2 or more), younger age at time of surgery (<30 years), greater disease extent, longer duration of disease, and the presence of perianal disease. These risk factors typically define patients at higher risk of having disease recurrence postoperatively. The question that remains is how many of these factors are required to place someone in that category. One would think that the more risk factors, the greater the likelihood of recurrence. However, not all risk factors are equal, and one risk factor may suggest a higher risk of recurrence than another; therefore,

our ability to clearly categorize risk in many patients remains limited.

G&H What are the current recommendations for endoscopic monitoring of patients at low and high risk of postoperative recurrence of Crohn's disease?

NKC Currently, both European and American guidelines recommend endoscopic evaluation of patients at 6 to 12 months postoperatively. One of the strongest studies supporting the recommendation is the POCER trial, which evaluated proactive endoscopic postoperative monitoring with stepped-up therapy if recurrence was identified (defined as Rutgeerts score ≥ 2) compared with no endoscopic monitoring. This study demonstrated significantly lower rates of endoscopic recurrence at 18 months in the endoscopically monitored group.

In practice, based on new data, noninvasive monitoring such as fecal calprotectin (FCP) and intestinal ultrasound (IUS) is also often used at the 3-month mark. A recent publication of the Eighth Scientific Workshop of the European Crohn's and Colitis Organisation (ECCO) on diagnosing postoperative recurrence of Crohn's disease after an ileocolonic resection with ileocolonic anastomosis recommended assessing FCP levels 3 months postoperatively. This was primarily because of studies showing high sensitivity and negative predictive value when FCP was less than 100 $\mu\text{g/g}$, assisting in ruling out postoperative recurrence. That being said, the absolute level of FCP has not been an accurate predictor of postoperative recurrence; therefore, ECCO's additional recommendation was to look at the FCP trend. It is also important to note that monitoring too early comes with a risk, as FCP

earlier than 3 months postoperatively may be falsely elevated because of healing.

G&H Is there consensus on the optimal frequency of endoscopic monitoring after the initial postoperative endoscopy?

NKC There are limited data and no clear guidelines regarding the frequency of monitoring in the postoperative patient specifically past the initial endoscopy. A retrospective study looking at patients who underwent ileocolonic resection followed after initial negative postoperative endoscopic evaluation found disease recurrence

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in 40% of patients within a year. Therefore, international guidelines recommend endoscopic assessment every 1 to 3 years but ultimately leave it to the clinician's discretion. In a prospective study from Japan, video capsule endoscopy was better than standard endoscopy in predicting postoperative recurrence, so better tools are clearly needed.

Current European and American guidelines for all patients, not specifically those who underwent ileocolonic resections, recommend proactive monitoring ranging from 3- to 6-month intervals. If patients have been in deep remission, the interval may be relaxed, whereas development of clinical symptoms, elevation in FCP, or findings on IUS may warrant earlier endoscopic evaluation. In my practice, I follow patients with FCP and IUS at 3 months, endoscopic evaluation at 6 months, and IUS with or without FCP every 3 to 6 months thereafter. I choose an interval of 3 months or 6 months based on the duration of deep remission, FCP and IUS results and trends, as well as risk of recurrence.

G&H What are the sensitivity and specificity of the noninvasive tools used in this setting?

NKC The most commonly used noninvasive tools are FCP and IUS, and there have been studies on other cross-sectional imaging modalities such as computed

tomography (CT) and magnetic resonance (MR). FCP has pooled sensitivity and specificity values of approximately 0.80 and 0.60, respectively, to suspect endoscopic recurrence. IUS has also been shown to be very accurate for assessment of postoperative recurrence. The pooled sensitivity and specificity of IUS is approximately 0.89 and 0.76, respectively, which means it performs quite comparably to FCP, if not better. When evaluating these tools, it is important to remember that there are different radiographic and biochemical definitions of recurrence. Depending on which definition is used, IUS can perform even better with a sensitivity as high as 0.93 and specificity of 0.85. A number of studies have looked at CT enterography and MR enterography. These modalities appear highly comparable to one another, with a sensitivity and specificity of both being around 90% and 70%, respectively. Overall, these alternative noninvasive tools perform well and fairly similarly to one another.

G&H Could you discuss any other research on the use of IUS in these patients?

NKC IUS is a patient-centered, well-tolerated, noninvasive tool that can be used for routine postoperative monitoring. One benefit of IUS is that it can be repeated as often as providers wish with little cost or discomfort to the patient. Bowel wall thickness greater than 3 mm has been shown to have a diagnostic accuracy of nearly 90% for endoscopic recurrence. When a higher bowel wall thickness cutoff is used (≥ 5.5 mm), the specificity increases to 98%. The ideal time to monitor postoperatively using IUS has not been well studied, but in clinical practice at the University of Chicago, we often use IUS as early as 3 months after surgery. I routinely perform small intestine contrast ultrasound (SICUS) examinations in patients who have had ileocolonic resections. SICUS increases the sensitivity of IUS further by using polyethylene glycol at a relatively small volume. SICUS has been shown to have a sensitivity of 99% with a specificity of 75% and overall accuracy of 90%.

Another important issue in postoperative monitoring that confounds many studies is the presence of microscopic disease remaining at the resection margin. Current practice guidelines do not recommend routine intraoperative frozen-section analysis to assess margins, meaning that some patients may have residual microscopic disease despite an apparently complete resection. The original study by Fazio and colleagues found no difference in postoperative recurrence between patients with positive and negative microscopic margins. However, several subsequent studies have reported an increased risk of endoscopic and clinical postoperative recurrence in patients with microscopically positive margins. My colleagues and

I recently published a case report in which IUS identified residual microscopic disease immediately after surgery that was not grossly visible to the surgeon. Histologic examination of the resection specimen confirmed the suspicion of incomplete resection. While intraoperative ultrasound is well established in other surgical fields, its role in Crohn's disease margin assessment has not yet been studied and represents an exciting opportunity for future innovation.

G&H Following Crohn's disease surgery, when is pharmacologic prophylaxis recommended?

NKC In patients at high risk of recurrence, it is recommended to start pharmacologic prophylaxis early, within 1 week of surgery if using antibiotics or within 4 to 8 weeks in patients receiving immune modulators or advanced therapies. The key to treating patients at high risk of recurrence is to treat as early as possible while ensuring that postoperative healing has occurred without infectious complications prior to initiating advanced therapies.

G&H How effective are different therapies for postoperative prophylaxis?

NKC Several pharmacologic agents have been shown to have some efficacy in reducing postoperative recurrence. One is metronidazole, an antibiotic that was studied by Rutgeerts and colleagues in a randomized fashion who found that 20 mg/kg for 3 months was associated with reduced endoscopic recurrence compared with placebo at

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1 year. However, the study was limited by a high rate of adverse events and medication intolerance. A study performed at the University of Chicago showed that metronidazole at 250 mg three times a day for 3 months reduced the risk of postoperative recurrence in patients who had

undergone ileocolonic resection and was well tolerated. I therefore routinely treat my patients who have undergone ileocolonic resection with low-dose metronidazole for 3 months postoperatively.

According to guidelines from the American Gastroenterological Association, mesalamine and corticosteroids are not recommended to reduce postoperative recurrence of Crohn's disease. As for biologic and advanced therapies, most studies have been performed in anti-tumor necrosis factor (TNF) therapies. Some studies have shown endoscopic recurrence of 30% vs 60% when comparing the use of anti-TNF therapy with placebo. This has not been as well studied in other biologics, but there are limited studies using ustekinumab and vedolizumab. A large retrospective multicenter study from Europe looking at anti-TNF therapy, ustekinumab, and vedolizumab had very similar endoscopic postoperative recurrence rates at 1 year, and this was replicated in the retrospective ENEIDA registry. Thus, there is some potential utility in using ustekinumab or vedolizumab for postoperative recurrence, although the data are a bit limited. Additionally, there are very limited studies on the use of small molecules for postoperative recurrence.

G&H How can a provider decide whether to treat an individual patient proactively or according to monitoring?

NKC The aforementioned risk factors are helpful when trying to identify who is at high risk for recurrence, especially when patients have multiple risk factors or are active smokers. It is also important to remember that Crohn's disease is chronic and that the majority of patients experience postoperative recurrence at 3 years. I explain this to patients and that early treatment appears to correlate with improved outcomes. A few studies have found superior outcomes when treating patients right after surgery vs treating patients once recurrence ensued. When in doubt, I lean toward treating early rather than waiting for recurrence, especially because there are numerous advanced therapies that are well tolerated and that have an excellent safety profile. That being said, the decision to initiate treatment should involve a discussion with the patient in a shared decision-making process. Providers should discuss with their patients whether they want to take on the risk of therapy-related adverse events. In patients who are high risk with multiple risk factors, I encourage postoperative treatment with proactive monitoring and avoid just doing watchful proactive monitoring. Patients who are not as high risk should have a discussion with their provider, and if they opt for no therapy, I would recommend a multimodal monitoring strategy with objective assessment every 3 to 6 months

that would require the use of FCP and/or IUS beyond endoscopic evaluations.

G&H If you treat a patient proactively, do you monitor them differently?

NKC I do not. When deciding on a treatment option, it is important to keep in mind that, unfortunately, many of the treatments work in only a small proportion of patients. Therefore, regardless of which therapy is initiated, providers still have to ensure that it is working, and even if it does work and patients seem not to experience recurrence, we need to ensure that the patients do not lose response. That requires proactive monitoring, so I do not monitor patients differently. I continue to monitor proactively in the intervals previously mentioned.

G&H What are the research priorities in this area?

NKC Several research priorities were nicely outlined in the recent publication from the Eighth Scientific Workshop of ECCO looking at the prevention and treatment of postoperative recurrence in patients with Crohn's disease who underwent ileocolonic resection with ileocolonic anastomosis. There are still a number of unanswered questions in the field. For example, how many risk factors are needed to quantify a patient as high risk for postoperative recurrence? The publication lists the natural evolution of an i1 lesion to a Rutgeerts i2A or an i2B lesion, so when these lower-risk lesions are seen, should they be treated at that point? There are a number of areas in an anastomosis where recurrence might be seen, such as the blind end of an anastomosis or right at the inlet of an anastomosis. Is recurrence in these areas as significant as recurrence in the neoterminal ileum? There is still a need for comparative-effectiveness research looking at various biologic agents in a head-to-head prospective manner for postoperative recurrence, as well as research on small molecules that have done very well compared with other biologics in treating inflammatory bowel disease. Further research is also needed on the optimal interval subsequent to the first endoscopic evaluation and whether patients who undergo ileocolonic resection should have the same interval monitoring as patients who never had surgery. There is great interest in using diet for treating Crohn's disease,

so it is possible that diet may also play a role in preventing postoperative recurrence. Although many questions still remain unanswered, much progress has been made in this field since the original paper by Rutgeerts and colleagues. There is now a nice armamentarium of treatment options with favorable safety profiles that can be employed, along with noninvasive monitoring tools that perform very well, so we are in a much better state today for preventing recurrence and identifying early recurrence than before.

Disclosures

Dr Krugliak Cleveland is a consultant to AbbVie, Johnson & Johnson, Sanofi, GE, and NeuroLogica (subsidiary of Samsung), and is on the board of directors of iUSCAN.

Suggested Reading

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