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Clinical Complete Response After Neoadjuvant Therapy in Rectal Cancer: Is Surgery Needed?

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Abstract Neoadjuvant chemoradiation followed by proctectomy is the recommended treatment plan for locally advanced rectal cancer in the USA. After chemoradiation, approximately 20 % of patients experience a complete pathologic response, which is associated with improved oncological outcomes. This observation prompted questions about the necessity of surgery if the tumor has completely regressed. Using clinical complete response as a surrogate for pathologic response, the watch and wait approach was introduced as an attempt at organ preservation utilizing active surveillance protocols rather than surgery. Prospective studies have highlighted the potential benefits of this approach, with successful organ preservation and comparable oncologic outcomes. Non-operative protocols are based on thorough response assessment using clinical exam, imaging, and laboratory tests with frequent repeat examinations to detect residual or recurrent disease in a timely manner. Although a subset of patients benefit from this approach, accurate identification of appropriate patients remains challenging. Debate continues regarding use of non-operative surveillance or standard proctectomy in patients deemed to have a complete clinical response. This review discusses the current data as well as the challenges of this approach.

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Introduction

The management of rectal cancer has evolved significantly during the past few decades. Our understanding of anatomy and tumor biology coupled with improved surgical technique has led to increased rates of sphincter preservation. Removal of the rectum and mesorectum via adherence to the plane of the fascia propria of the rectum is the championed oncologic approach as total mesorectal excision (TME) improves cancer outcomes [1]. The addition of postoperative (adjuvant) radiation led to further improvements in local recurrence rates, particularly among patients with locally advanced disease [2]. Despite the improved oncologic outcomes, postoperative radiation did not affect surgical decision-making with regards to sphincter preservation. Several trials demonstrated the benefit of presurgical radiation or chemoradiation (CRT) compared to postoperative treatment, triggering a paradigm shift to the use of neoadjuvant therapy. A randomized controlled trial conducted in the Netherlands in 2001 showed that short-term preoperative radiotherapy reduces the risk of local recurrence in patients with rectal cancer who undergo TME [3]. In 2004, the German Rectal Cancer Trial reported that the use of preoperative CRT was associated with improved local control and greater sphincter preservation rates [4]. Short-course radiotherapy alone also demonstrates benefit, and the Polish rectal cancer trial demonstrated similar local recurrence outcomes to long-course neoadjuvant CRT [5], but short-course radiotherapy does not provide significant tumor downstaging. Most centers advocate the use of neoadjuvant CRT for patients with stage II and III rectal cancer [6••, 7] followed by postoperative chemotherapy [8].

Tumor response to neoadjuvant CRT varies greatly. At the favorable end of the spectrum, up to 50 % of patients have no clinically detectable tumor after completion of CRT (clinical complete response (cCR)), while 10–20 % have no pathologic evidence of residual tumor (pathologic complete response (pCR)) [4, 9–11]. Patients with pCR have a particularly favorable prognosis, with negligible risk of local recurrence and 5-year survival rates exceeding 80 % [12, 13]. With no viable tumor in their resection specimens, it is intuitive to question whether patients with pCR benefit from a procedure associated with considerable morbidity and functional consequences [14, 15]. Unfortunately, the accurate a priori determination of this subset of rectal cancer patients remains elusive. Considering the significant impact of organ preservation on functional outcomes and quality of life, some institutions have studied protocols where surgery is deferred for patients with cCR, but followed with a rigorous surveillance protocol to detect residual or recurrent disease in a timely manner. This article reviews the literature and discusses the successes and challenges of this approach.

Determining a Clinical Complete Response

Successful implementation of non-operative management protocols in rectal cancer requires reliable identification of patients with complete response to neoadjuvant CRT. This is usually achieved by a combination of clinical examination (including digital rectal exam [DRE]), endoscopy, and imaging. According to published standardized criteria, cCR is defined by the absence of all of the following: any residual deep ulceration with or without a necrotic center; any superficial ulcer or irregularity even in the presence of only mucosal ulceration; any palpable nodule even in the presence of mucosal integrity; or any significant stenosis which impedes the proctoscope from sliding through [16••]. In a recent report of 238 patients, Smith et al. reported that 16 of 22 (73 %) patients who met the aforementioned criteria had pCR in their surgical specimen [17•]. In evaluating the sensitivity of clinical criteria, among 61 patients (25 %) who were downstaged to ypT0, 45 (74 %) still had a remaining residual mucosal abnormality (most frequently ulceration) that precluded a diagnosis of cCR. In addition, in a retrospective study of 488 patients treated at a single institution, Hiotis et al. found that only 25 % of patients with cCR (defined more broadly as no detectable tumor on digital rectal exam and endoscopy) actually had pCR in the resected specimen [18]. It should be noted that in this series, surgery was performed 4–6 weeks after CRT completion, and multiple studies suggest that longer intervals may result in greater pCR rates, presumably by allowing the progression of incomplete to complete response. Another consideration is the inability to accurately assess lymph node involvement based on clinical examinations. While DRE and endoscopy allow evaluation of the mucosa, there is no accurate means of detecting residual metastatic disease in lymph nodes, with or without a mucosal response. In surgical specimens, after neoadjuvant CRT, 3.2–15 % of patients with a complete pathologic response at the mucosal surface (ypT0) still harbor metastatic cancer cells in lymph nodes [18–20].

Non-Operative Management After Clinical Complete Response

Non-operative management after cCR to neoadjuvant CRT was pioneered by Angelita Habr-Gama and colleagues in Brazil. They coined the phrase “watch and wait” in their 2006 report [21–23]. In their initial study, Habr-Gama presented 361 consecutive patients with distal rectal cancer treated with 5040 cGy and long-course 5-fluorouracil (5-FU) [22]. Eight weeks after completion of CRT, 122 patients were considered to have cCR, determined by a combination of clinical, endoscopic, and radiologic findings. The patients that were felt to achieve a complete clinical response did not undergo immediate proctectomy but rather were followed closely by physical examination, proctoscopy with biopsies as indicated, and serum carcinoembryonic antigen (CEA) levels monthly, every 2 months, every 3 months, and every 6 months for the first, second, third, and fourth years, respectively. Computed tomography (CT) scan of the abdomen and chest X-ray was performed every 6 months for the first year and yearly after this. Ninety-nine (27.4 %) patients had sustained cCR 12 months after CRT completion and were considered appropriate for non-operative management. After mean follow-up of 60 months, there were six (6 %) rectal recurrences within the lumen, one of which was combined with systemic recurrence. All five isolated luminal recurrences were salvaged, though two of these patients declined radical surgery and underwent local excision or brachytherapy. Eight (8 %) patients eventually developed metastatic disease. Interestingly, the overall and disease-free 5-year survival for the 99 patients with sustained cCR were 93 and 85 %, respectively. This was the first study to suggest that with a well-defined follow-up protocol, non-operative management of patients with rectal cancer and cCR after CRT is an option. However, it should be noted that 23 (19 %) patients with initial cCR experienced recurrence within the first 12 months and were excluded from the analyses, and there is insufficient evidence to determine whether their outcomes would have been more favorable with immediate surgery. Regardless of the exact recurrence and survival rates, this study paved the way for the watch and wait approach.

The same group reported several follow-up studies with encouraging results [24, 25, 26••, 27•]. The common features of the group’s protocol include assessment of response

8 weeks after completion of CRT by DRE, proctoscopy with biopsy of suspicious lesions, CEA levels, and imaging (endorectal ultrasound [ERUS], CT alone or combined with positron emission tomography [PET], or magnetic resonance [MRI]). In patients with initial cCR, DRE, proctoscopy, and CEA levels are repeated every 1–2 months for 12 months, with imaging repeated every 6 months. Any biopsies positive for adenocarcinoma during the first year are considered incomplete clinical response, and those patients are directed to proctectomy. After the first year, clinical surveillance examinations become less frequent (3–6 months). In their most recent update, Habr-Gama and colleagues report 31 % local recurrence rate in patients with initial cCR, the majority of which occur during the first year [27•]. Importantly, salvage surgery was possible in 93 % of tumor recurrences, and the 5-year cancer-specific survival and disease-free survival for the entire cohort, including those without cCR, were 91 and 68 %, respectively. Thirteen (14 %) of 90 patients with initial cCR developed distant recurrences, and in all but one case, these were unresectable. However, the rate of distant recurrence was similar between those with and without local recurrence (as well as with prior reports of patients with pCR in the proctectomy specimen), questioning the consequences of primary tumor management in metastatic recurrence.

Smaller reports from centers outside of Brazil have recently been published. In a prospective study from the Netherlands, Maas et al. reported the outcomes of 21 consecutive patients with rectal cancer and cCR after neoadjuvant CRT that were managed non-operatively compared to a matched cohort of patients with pCR [28••]. In this study, 5040 cGy radiation was administered with concurrent capecitabine in patients with locally advanced rectal cancer and response was assessed 6–8 weeks after completion of CRT using MRI and endoscopy with biopsies when indicated. Strict criteria were used to define cCR: no residual tumor or residual fibrosis only and no suspicious lymph nodes on MRI; no residual tumor at endoscopy or only a small residual erythematous ulcer or scar; negative biopsies from the scar, ulcer, or former tumor location; and no palpable tumor on DRE. Posttreatment surveillance was performed every 3 months during the first year and every 3–6 months thereafter and included DRE, serum CEA levels, pelvic MRI, and endoscopy, as well as CT scans for distant staging every 6 months for the first year, then yearly. Twenty-one patients that met cCR criteria were managed non-operatively and followed for an average of 25 months. One patient presented with local recurrence and underwent salvage proctectomy after 22 months of follow-up. No other disease recurrence or death was recorded in the remaining 20 patients. According to the authors, these outcomes were comparable to a similar cohort of 20 patients with pCR, where 2-year disease-free survival was 93 %. These results further highlight the potential of non-operative management in select patients with cCR and suggest that excellent results can be obtained with a strict surveillance protocol. However, they should be interpreted with caution, as the inclusion of only 21 patients with a relatively limited follow-up of 25 months may be insufficient to determine whether this approach is oncologically equivalent to radical surgery, which remains the current standard. In addition, such surveillance protocols require considerable institutional expertise and experience in order to promptly detect early recurrences and may be less applicable in centers with limited exposure.

A more recent, retrospective study from the USA reported on 32 patients with rectal cancer and cCR after neoadjuvant CRT that underwent non-operative management [29]. As this was not a prospective study, CRT regimen, cCR criteria, and follow-up were not standardized. In most cases, 5040 cGy radiation was administered and response was assessed at 4–10 weeks with a combination of DRE and endoscopy. Local recurrence occurred in six (19 %) of the patients and was salvaged in all cases with radical surgery (low anterior resection [LAR] or abdominoperineal resection [APR]). This contrasted with no local recurrence at 2 years in a group of 57 patients with pCR that underwent proctectomy. However, the 2-year distant disease-free survival and overall survival rates for the two cohorts were not statistically different. Even though the results of this study may not be generalizable, considering its retrospective nature, they still indicate the potential value of non-operative management in the setting of cCR. Of note, despite the relatively high local recurrence rate, this did not preclude salvage surgery and organ preservation was still achieved in 81 % of patients.

Investigators from Denmark recently reported a prospective observational study of 51 patients that underwent high-dose CRT followed by non-operative management for those with cCR [30••]. Patients were included if they presented with distal T2–T3 tumors that, if resected, would require either an APR and permanent stoma or a very low (coloanal) anastomosis. CRT was administered in the form of intensity-modulated radiotherapy (60 Gy in 30 fractions to the tumor, 50 Gy in 30 fractions to elective lymph node volumes), along with 5 Gy as endorectal brachytherapy and oral tegafur-uracil. Clinical response was assessed 6 weeks after completion of CRT, and cCR was defined as a small white scar or superficial erosion or ulceration without palpable tumor. Erosions and ulcerations were biopsied to confirm the absence of residual tumor. This intensified neoadjuvant protocol resulted in 40 of 51 patients (78 %) having an initial cCR, and these patients were managed non-operatively. This included clinical examinations every 2 months during the first year, every 3 months during the second year, every 6 months during the third year, then yearly. PET/CT was obtained at every other visit. After median follow-up of approximately 24 months, nine patients (22.5 %) with initial cCR developed local recurrence and all nine underwent salvage surgery with curative intent. These results suggest that aggressive CRT in combination with

non-operative management may spare a significant number of patients from the morbidity and quality of life sequelae of an APR or a coloanal anastomosis.

Not all series support watch and wait approaches. Two smaller studies, one from Brazil and one from the UK, each including 10 patients with cCR managed non-operatively, reported significantly higher local recurrence rates [31, 32]. Nakagawa and colleagues analyzed the outcomes of 52 patients with rectal adenocarcinoma who underwent 5040 cGy radiation with 5-FU [32]. Of those, 10 (19 %) had cCR on proctoscopy and were managed non-operatively. Among the 10 cases with cCR, eight (80 %) presented with local recurrence within 3–9 months. Hughes and colleagues identified 266 patients who underwent CRT for T3–T4 rectal cancer at a UK cancer center [31]. Fifty-eight patients did not proceed to surgery, ten of which were identified as having a cCR. Six of these 10 patients (60 %) subsequently developed pelvic recurrence, though none of them underwent salvage surgery. Collectively, these two studies, though both are retrospective series without standardized protocols, highlight the potential perils associated with non-operative management.

Challenges of Non-Operative Management

Non-operative management of patients with cCR after neoadjuvant CRT for rectal cancer still faces significant challenges. Arguably, the most important limitation is the accuracy of current clinical modalities to assess response at the pathologic level, which leads to a discordance between clinical and pathologic response. In addition, the relatively limited number of patients with pCR (15–20 % in most series) suggests that non-operative management is truly an option for a small subset of patients with rectal cancer, highlighting the need for improved neoadjuvant treatment regimens. Finally, in the current cost-conscious health care environment, it is necessary to fully compare the one-time cost of surgical resection against the prolonged, frequent, and thorough follow-up protocols required by non-operative approaches.

Assessment of Response

Multiple studies have investigated the accuracy of individual diagnostic tests in assessing response to CRT. Despite remaining an invaluable tool in the evaluation of rectal tumors, DRE alone has been shown to be insufficient in response assessment [33]. In a study of 94 patients by Guillem et al., clinical assessment using DRE underestimated pathologic response in 73 cases (78 %), while it identified only 3 of 14 cases (21 %) with a pCR. Similarly, endoscopy with biopsies also lacks accuracy, with concordance rates between biopsy and final pathology reported as low as 50 % [34]. Data regarding the utility of serum CEA levels, another widely used clinical parameter in rectal cancer, are also ambiguous. Even though posttreatment serum CEA levels correlates well with pathologic response in multiple independent studies, no cutoff value with adequate specificity in identifying pCR has been reported [35, 36].

The continuous improvement of imaging modalities offers additional tools to refine response assessment. As MRI is widely used for the initial staging of patients with rectal adenocarcinoma, it has significant potential in the evaluation of CRT response. Indeed, the MRI has a central role in response assessment and surveillance protocols in both the Brazilian and the Dutch studies cited above. Lambregts and colleagues reported that among the patients with cCR included in the Dutch trial, only 26 % had a normalized rectal wall on MRI, with the remaining 74 % characterized by some degree of fibrosis (full-thickness, minimal, or spicular) [37]. These findings remained consistent during long-term follow-up, with the exception of one patient that developed endoluminal recurrence. In addition, the same group showed that gadofosveset-enhanced MRI can be useful in staging lymph nodes both before and after CRT, with 80 % sensitivity and 97 % specificity for experienced readers [38]. Other reports have also suggested that MRI can be valuable in evaluating response to CRT in patients with rectal cancer [39, 40]. It is important to note that the favorable results are derived from centers with highly qualified, experienced radiologists and may not immediately be reproducible in the general population.

Additional imaging modalities that have been used in this context, with varying degrees of success, include PET/CT and ERUS. According to a study of 99 patients from Brazil, the use of PET/CT to evaluate response 12 weeks after CRT completion showed 93 % sensitivity and 53 % specificity for the detection of residual cancer, improving the accuracy of clinical assessment from 91 to 96 % [41]. However, a recent study from the Memorial Sloan Kettering Cancer Center reported less favorable results, raising doubts regarding the value of PET/CT in rectal cancer response assessment [42•]. Similarly, ERUS has been reported to be helpful in the posttreatment assessment of lymph nodes, though up to 20 % of patients may be misclassified as uN0 and its use as a sole diagnostic modality is not recommended [43].

Response assessment is further complicated by variability in the interval between CRT completion and response evaluation. Multiple studies have demonstrated that longer intervals are associated with higher rates of cCR and pCR [44, 45•]. In a study by de Campos-Lobato and colleagues, patients undergoing surgery more than 8 weeks after CRT experienced a significant improvement in pCR rate (30.8 vs. 16.5 %) [44]. Furthermore, this study and others suggest that such prolonged interval does not appear to compromise prognosis and may, in fact, improve long-term survival [46]. Unfortunately, assessment protocols in the studies evaluating non-

operative management include a wide range of treatment intervals (6–12 weeks), suggesting that their outcomes cannot be directly compared and highlighting the necessity of a standardized response evaluation protocol. Furthermore, adopting a prolonged interval between CRT and assessment may lead to the conversion of some patients with partial response into cCR, increasing the rate of patients eligible for non-operative management and shifting the risk-benefit balance of these protocols.

Overall, the clinical and radiological tests described above show varying degrees of accuracy, with no single approach offering sufficient sensitivity and specificity to identify patients with pCR. This suggests that only a combination of a thorough clinical examination, including DRE, proctoscopy, and cross-sectional imaging is a viable option in selecting patients for non-operative management. However, the persistently significant percentage of patients with residual disease misclassified as cCR, even in experienced centers practicing non-operative management, highlights the need for further research in this area, as well as for frequent and thorough follow-up of patients classified as cCR.

Response Improvement

Widespread adoption of non-operative management protocols for patients with cCR after neoadjuvant CRT is further limited by the number of patients eligible for this approach. Only 11 % of patients in the Dutch trial achieved cCR, while in their original report, Habr-Gama and colleagues reported sustained cCR rates of 27 % 12 months after CRT completion [21, 28••]. Therefore, new regimens that enhance response to CRT could significantly alter the risk/benefit balance of non-operative protocols, increasing the likelihood of complete response and, with it, the positive predictive value of current assessment modalities. Unfortunately, most clinical trials during the last decade have failed to identify an alternative regimen that is consistently superior compared to the standard combination of 5040 cGy radiation with 5-FU or capecitabine. Even though the addition of oxaliplatin resulted in a modest increase of pCR rates (17 vs. 13 %, p=0.04) in the German AIO-94 trial [47], multiple other randomized trials failed to show any benefit from oxaliplatin while reporting significantly increased toxicity rates [48–51]. Similarly, studies investigating the combination of bevacizumab with standard therapy found pCR rates between 17 and 29 %, but this was associated with an increase in toxicity and surgical complications [52, 53]. The addition of cetuximab, though well tolerated, was in fact associated with decreased pCR rates [54, 55]. More encouraging are the results of trials studying the administration of neoadjuvant consolidated chemotherapy after the completion of CRT. Garcia-Aguilar and colleagues reported that the addition of 2 cycles of modified FOLFOX-6, 4 weeks after completion of CRT and only in patients that demonstrated clinical response to CRT, resulted in a modest increase of pCR rates compared to a control cohort (18 to 25 %), though it should be noted that part of that improvement could be due to the longer interval between CRT and surgery [56]. Consistent with these results, Habr-Gama and colleagues reported that the use of additional chemotherapy cycles during CRT (5400 cGy and 5-FU/leucovorin delivered in 6 cycles every 21 days) resulted in an increase in cCR rates to 57 %, sustained 12 months after CRT completion [26••]. Intensification of the radiotherapy portion of CRT may also result in superior response rates. As reported by Appelt and colleagues at the Danish Colorectal Cancer Center South, the administration of 60 Gy to the tumor, 50 Gy to elective lymph node volumes, along with 5 Gy as endorectal brachytherapy resulted initial cCR rates of 78 %, with approximately 60 % of all patients achieving organ preservation at 2 years [30••]. This data is encouraging and needs to be further studied for reproducibility.

Finally, retrospective data indicate that concurrent treatment with HMG-CoA reductase inhibitors (statins) during CRT may result in improved response rates and more patients achieving pCR [57, 58]. Mace and colleagues reported a cohort of 407 patients in which statin use was significantly associated with improved regression scores in multivariate analysis. Of patients who were taking a statin during neoadjuvant CRT, 65.7 % achieved either pCR or moderate response (American Joint Committee on Cancer score 0 or 1, respectively) [58].

Health Care Value

Direct and indirect health care benefits and costs associated with the non-operative management of patients with cCR are difficult to estimate and present additional challenges for the widespread implementation of this approach. Patients managed non-operatively may be spared the significant morbidity associated with proctectomy [4, 59, 60]. In addition, considering that the alternative may include permanent ostomy, the deferment of surgery may lead to further improvements in quality of life. However, such benefits have to be balanced against the possibility of potentially unsalvageable recurrence that ultimately is fatal. Even though such an occurrence appears relatively uncommon (it was not reported in the Dutch trial and only occurred twice in the series by Habr-Gama and colleagues), it should be noted that the Brazilian group stated that APR was necessary in up to 50 % of the cases requiring salvage surgery [22, 28••]. Finally, both studies agree that a thorough and frequent follow-up protocol is necessary for patients managed non-operatively. This involves frequent clinic visits (up to once every 1–2 months for the first year)

along with multiple tests (including proctoscopy, biopsies, serum CEA levels, MRI, etc.). It is unclear what the total cost of such an approach may be and how it may compare with proctectomy and standard postoperative surveillance. In addition, the balance is likely to be different for each country depending on the health care system. In the current era of health care where outcomes are viewed in the light of associated costs, these considerations are particularly relevant.

Individualized Care

The complexities associated with patient and treatment selection in non-operative management protocols of cCR after neoadjuvant CRT highlight the need for individualized care. Identifying predictors of response can lead to the administration of CRT to those expected to respond favorably, while hastening surgery and sparing unnecessary radiation for those who are not. In addition, by channeling potential non-responders to surgery, greater response rates are expected among those undergoing CRT, increasing the predictive value of response assessment tools. With this goal, multiple investigators have studied predictive factors of CRT response in general and pCR specifically [61–63]. Interestingly, traditional clinicopathologic characteristics do not appear to correlate with response. Kalady and colleagues studied 306 consecutive patients and reported that age, gender, body mass index, tumor differentiation, radiation dose, and pretreatment stage were comparable between those who achieved pCR and those who did not [63]. However, molecular characteristics of pretreatment biopsies have been shown to be more predictive, as Negri and colleagues reported that higher thymidylate synthase expression was associated with favorable response, while according to a recent study by Huh and colleagues, elevated CD44 mRNA levels were predictive of poor tumor response [62]. Finally, thanks to modern high-throughput gene expression testing which allows measuring the expression levels from tens of thousands of genes in a single biopsy specimen, multiple groups have reported gene expression signatures predicting response to CRT [64–66]. Despite their tremendous potential in personalized care, however, these signatures currently require widescale validation prior to their incorporation in clinical decision-making. At the current time, genetic and molecular information has not yet translated into clinical utility.

Future Directions

In our opinion, active surveillance for rectal cancer patients who are complete clinical responders to neoadjuvant CRT will eventually become integrated into standard treatment recommendations and protocols. Two main aspects of this approach will likely evolve in the next 5–10 years. First, novel and more accurate clinical means to predict who indeed are true pathologic responders are the subject of intense studies. New imaging techniques using anatomic imaging with metabolic activity may better define tumor eradication. Also, genetic or molecular markers from tumor or serum are likely to provide insight into who has been cured by CRT alone. It is likely that multiple factors will ultimately be evaluated together to arrive at a specific individualized risk for each patient in making treatment decisions. Second, the development of new therapeutic agents, treatment modalities, or combination therapies will be targeted toward achieving a complete pathologic response as an endpoint. Experimental models will be used to determine best responses with a translation to clinical trials. All of this should lead to increasing the number of patients that will achieve a complete clinical and pathologic response, and an increased ability to appropriately recognize who these people are for selection of active surveillance.

Conclusions

There is a subset of rectal cancer patients who are cured by CRT without surgery. However, accurate selection of which patients to channel into non-operative active surveillance remains a challenge. Using clinical complete response as a surrogate for pathologic complete response is neither highly sensitive nor specific. Identifying true pathologic complete responders with improved techniques, whether imaging or genetic, are needed to limit the number of cases incorrectly chosen for non-operative management. The promising results reported from pioneering centers must be viewed in the context of seasoned expertise, and the broad application of this approach to all centers is premature. Reproducible results across several institutions, countries, and health systems are needed to provide robust support for this approach. Although non-operative management currently cannot be routinely recommended outside of clinical trials, it is an intriguing prospect for the future of rectal cancer treatment.

Compliance with Ethics Guidelines

Conflict of Interest Georgios Karagkounis and Matthew F. Kalady declare that they have no conflict of interest.

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

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