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History of neoadjuvant therapy for rectal cancer

Tiffany Chan, MD, MHSc, FRCSC, Radhika K. Smith, MD*

Section of Colon and Rectal Surgery, Division of General Surgery, Department of Surgery, Washington University School of Medicine in St. Louis, Campus Box 8109, 660 S. Euclid Ave., St. Louis, MO 63110, USA

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ABSTRACT

Management of rectal cancer has evolved extensively over the last 30 years. Treatment of locally advanced rectal cancer currently incorporates surgery, chemotherapy, and radiation. Radiation was initially utilized as a salvage method as historic surgical practices were associated with high morbidity rates. In present day, multiple studies have demonstrated that the use of radiation as an adjunct to surgery decreases local recurrence rates. The now routine practice of total mesorectal excision during rectal cancer surgery has further improved outcomes. Numerous studies have evaluated the chemotherapeutic regimens as adjuncts to radiation therapy. Currently, fluorouracil-based regimens are commonly incorporated into neoadjuvant therapy for locally advanced rectal cancer, whereas oxaliplatin has not been incorporated due to more recent studies demonstrating increased toxicity and no clear oncologic benefit. Presently, trials are underway that aim to tailor therapies to specific patterns of disease, in hopes of allowing clinicians to selectively omit components of therapy to limit toxicity and morbidity while maintaining or improving oncologic outcomes. Thus, rectal cancer treatment continues to evolve, and decision-making surround treatment remains highly individualized and nuanced.

Introduction

Treatment of rectal cancer has evolved over the last 30 years. The standard of care in the management of locally advanced rectal cancer (LARC), defined as clinical stage II or stage III disease, includes administration of external beam radiation and chemotherapy followed by surgery and consideration of adjuvant chemotherapy. However, the current climate of rectal cancer treatment is nuanced and individualized. Therapy can be associated with morbidity, and treatment regimens have evolved with the aim of decreasing toxicity and improving outcomes. Additionally, the response to neoadjuvant therapy provides important prognostic information and potentially opens doors for alternative treatment strategies including nonoperative management, sphincter preservation, and local excision.

Radiation as a complement to surgical resection

The first introduction to neoadjuvant radiation therapy for rectal cancer was in 1917 by Janeway and Quick.[1] They noted that when radon beads were placed directly into rectal cancers, a significant tumor response was achieved. Surgery was considered a salvage procedure during this time period as the technical and anesthetic requirements to perform surgery were prohibitive.[2]

As modern surgery became safer, multiple trials in the 1980's began to detail the risks of radiation and explore the additive benefit of surgery to radiation. These trials were variable in their timing of radiation administration (neoadjuvant versus adjuvant), total radiation doses, fractionation schemas, and target volumes. However, they did show that surgery alone had high local recurrence rates up to 25–30%,[3–5] and the addition of radiation generally resulted in a significant decrease in this rate. As such, the role of radiation became established as an important component of the multimodality management of rectal cancer with respect to local control.

A number of studies demonstrated that surgery followed by radiation in the adjuvant setting delivered in 180–200 cGy a day for a total dose of 40–50 Gy, was more effective than surgery alone in decreasing local recurrence. This was demonstrated in the UK-based Medical Research Council Rectal Cancer Working Party, where the hazard ratio of local recurrence was 0.54 (95%CI 0.38–077, $p = 0.001$) significantly in favor of adjuvant radiation, with no difference in overall survival (HR 0.91, CI 0.73–1.13, $p = 0.40$) after an average of four years of follow up.[6] Similarly, the Gastrointestinal Tumor Study Group trial (1985) provided evidence that the use of adjuvant radiation and chemotherapy following curative resection of rectal cancers involving the perirectal fat, regional nodes, or both, led to significantly prolonged time to tumor recurrence compared to resection alone.[5]

Concurrently, the European Organization for Research and Treatment of Cancer Gastrointestinal Cancer Cooperative Group (1988) evaluated the addition of neoadjuvant radiation to resection and

* Corresponding author.
E-mail address: radhikasmith@wustl.edu (R.K. Smith).

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found that local recurrence rates were halved from 30% in the control group to 15% in the neoadjuvant radiotherapy group ($p = 0.003$) with no significant difference in five year overall survival (59.1% versus 69.1%, $p = 0.08$).[4] With this growing body of evidence in the 1990s, the National Institutes of Health began to recommend adjuvant chemotherapy and radiation for patients with LARC.[7–9]

Evaluation of radiation as neoadjuvant therapy

Shortly after the 1990s, a series of trials was published that looked at the use of neoadjuvant short course radiation (SC-RT) in addition to surgery. The Swedish Rectal Cancer Trial (1997) aimed to examine the role of SC-RT on overall survival. The authors randomized 1168 patients with resectable rectal cancer to SC-RT followed by surgery in one week versus surgery alone. By delivering SC-RT of 5 Gy in five fractions, the overall survival was significantly improved from 30% to 38% ($p = 0.008$), and the local recurrence rate decreased from 26% to 9% ($p < 0.001$). The Swedish trial is the only one to demonstrate a survival benefit from radiation around this time.[3] However, a criticism of this study was that the surgery was not standardized, and the rate of local recurrence in the surgery-only arm was considered higher than the standard of care for that time period. Surgical quality was also improving dramatically with the adoption of total mesorectal excision (TME), resulting in significantly lower recurrence rates. This questioned the need for preoperative radiation when applied in the post-TME setting to achieve the decrease in local recurrence.[10]

The Stockholm series, starting with the Stockholm I published in 1995, helped establish SC-RT as an effective therapy and also helped refine the optimal radiation dose to limit toxicity. Patients in Stockholm I were given 25 Gy in 5 Gy daily increments five to seven days before surgery and were compared to those who underwent surgery alone. Pelvic recurrence was 28% in the surgery only group versus 14% in the radiation plus surgery group ($p < 0.01$). Radiation however was associated with a higher rate of postoperative morbidity (8% versus 2%, $p = 0.01$) within 30 days, mainly in elderly patients.[11] Stockholm II then aimed to reduce postoperative complications while maintaining the reduction in local recurrences by reducing the irradiated volume but maintaining the total dose of 25 Gy. At long term follow up of a median of 8.8 years, pelvic recurrence was 12% in the radiotherapy and surgery group versus 25% in the surgery alone group ($p < 0.001$). The authors also noted a higher mortality within 6 months of surgery of 5% compared to 1% in the irradiated group ($p = 0.02$) attributed mainly to cardiovascular causes amongst elderly patients.[12] Most recently, Stockholm III (2017) assessed the non-inferiority of three radiation fractionation regimens and time to surgery. Patients were randomized to either SC-RT followed by surgery within 1 week, SC-RT followed by surgery in 4–8 weeks, or long course (25×2 Gy) radiation with surgery after 4–8 weeks. The study schema allowed patients to either be enrolled in two-arm randomization between the two SC-RT regimens or three-arm randomization depending on the treatment capabilities of the participating hospital. Notably, in the three-arm randomization cohort there were no differences seen in the rates of postoperative complications between groups (50% in SC-RT group, 38% in SC-RT with delay group, 39% in long course group, $p = 0.075$). However, in a pooled analysis comparing the SC-RT regimens, the risk of postoperative complications was significantly lower after SC-RT with delay than after SC-RT (53% versus 41%, $p = 0.001$). This trial concluded that SC-RT with delay to surgery is a useful alternative to conventional SC-RT with immediate surgery, while long course showed no added advantage and prolonged treatment time significantly.[13]

Role of radiation in the era of total mesorectal excision

While adjunctive therapies were becoming increasingly utilized, surgeons began to realize that the oncologic outcomes for rectal cancer surgery were highly dependent on surgical technique. Heald's initial prospective case series of 116 patients published in 1986 highlighted the concept of total mesorectal excision (TME) during low anterior resection. Emphasis was placed on sharp dissection under direct vision, excision of the entire mesorectal envelope, avoidance of blunt manual extraction, and centralizing rectal cancer operations to surgeons familiar with the TME technique. Radiotherapy was reserved only for patients who were deemed inoperable. This approach resulted in a 5 year local recurrence rate of only 3.7%.[14] In follow up, his expanded series of 519 patients with 405 curative resections had a local recurrence rate of 3% at five years and 4% and 10 years. Disease free survival was 80% at five years and 78% at 10 years.[15] These initial pure surgical series established TME as the surgical procedure of choice and called into question the need for radiation therapy to obtain local control.

Consequently, the trials that followed aimed to assess whether the decrease in local recurrence that was attributed to radiation were compensating for suboptimal surgery. The Dutch TME trial (2001) was the first trial to demonstrate that preoperative radiation reduced the risk of local recurrence even in patients who had optimal TME. It randomized 1861 patients with resectable rectal cancer to SC-RT followed by TME or to TME alone. Surgical quality was improved compared to the Swedish trial as trial surgeons were taught standardized surgical technique prior to enrolment and the first five procedures were proctored by an experienced instructor. The addition of preoperative SC-RT to TME surgery improved local recurrence from 10.9% to 5.6% ($p < 0.0001$), but did not result in improved overall survival (49% versus 48%, $p = 0.86$).[16] A critique of this study is that almost 30% of the patients in both treatment arms were stage I on final pathology. The local recurrence rate in the surgery alone group, however, was still lower than those seen in previous trials, and the addition of radiation conferred an additional reduction in local recurrence. The 10-year local recurrence was 5% in the radiotherapy and surgery group versus 11% in the surgery alone group ($p < 0.0001$), again with no difference in overall survival. Of note, on subgroup analyses, preoperative SC-RT significantly improved 10-year survival in patients with stage III cancers even with a negative circumferential resection margin (50% versus 40%, $p = 0.032$).[17] This trial established the additive benefit of preoperative radiation to high quality surgery.

Pre- versus post-operative radiation

Once established by multiple studies that surgery in combination with radiation was more effective than surgery alone for the treatment of LARC,[18] timing of the radiataion therapy came into question. Postoperative administration of chemoradiation seemed to be poorly tolerated with higher toxicity, presumably due to irradiation of poorly oxygenated tissues as well as radiation of the neorectum, which carries implications on function. As such, neoadjuvant therapy began to gain acceptance due to better patient tolerance.

The German Rectal Cancer Trial (CAO/ARO/AIO-94) (2004) established preoperative chemoradiotherapy (CRT) to be better than postoperative treatment. The authors randomized 823 patients with LARC to receive either preoperative or postoperative CRT consisting of 50.4 Gy and infusional 5-fluorouracil (5-FU). While there was no difference in the primary endpoint of overall survival (76% versus 74%, $p = 0.80$), preoperative therapy was associated with decreased rate of local recurrence (6% versus 13%, $p = 0.0006$). Preoperative CRT was also associated with greater treatment compliance, less gastrointestinal toxicity, and increased sphincter preservation for low-lying tumors.[19] At a median of 11 years of follow up, the improved local control rate with neoadjuvant CRT persisted, with a 10 year local recurrence of 7.1% for preoperative CRT versus 10.1% for postoperative treatment. No difference was detected in the 10-year incidence of distant recurrence, disease free survival, or overall survival.[20]

NSABP R-03 (2009) was also designed to determine the best setting to administer radiation and chemotherapy. This trial randomized

267 patients with LARC to pre- or postoperative CRT consisting of 5-FU, leucovorin and 45 Gy of radiation. The authors found a benefit for preoperative therapy, with higher five-year disease free survival of 64.7% versus 53.4% (HR 0.629, $p = 0.011$). There was no difference in local recurrence at 5 years with both arms recurring at 10.7% ($p = 0.693$).[21]

While postoperative radiation began to fall out of favor, the question remained whether preoperative radiation should be used routinely, or whether some patients would benefit from selective postoperative CRT for high-risk features once their final pathologic stage is known. MRC—CR07 (2009) demonstrated that postoperative radiation reduced the risk of local recurrence in Dukes B and C tumors without increased risk of serious GI complications, and no effect on distant recurrence or overall survival. This trial enrolled 80 centers across four countries and randomized 1350 patients to preoperative SC-RT followed by surgery within one week or selective postoperative CRT (45 Gy in 25 fractions with concurrent 5-FU or 5-FU/leucovorin) for patients with tumor 1 mm or less from the radial margin. Total mesorectal excision was encouraged though not mandated in the trial protocol. The overall negative circumferential radial margin rate was 89%, which compared favorably with the Dutch TME trial in which 77% of patients in the intention to treat analysis had tumor-free margins. At three years, there was a significantly lower risk of local recurrence for patients receiving preoperative radiotherapy (4.4% versus 10.6%, $p < 0.0001$) and better disease free survival (77.5% versus 71.5%, $p = 0.013$). There was no difference in overall survival.[22]

Optimal time to surgery following neoadjuvant chemoradiation

Once preoperative CRT was found to be superior to postoperative therapy, the next question to be answered was the optimal time interval between the completion of neoadjuvant CRT to surgery. The Lyon R90-01 (1999) study compared a period of less than two weeks with six to eight weeks and found improved downstaging with the longer interval.[23] The GRECCAR6 trial (2016) randomized patients to either a seven or 11 week interval from CRT (45–50 Gy with fluorouracil or capecitabine) to surgery and found no difference in the rates of pathologic complete response (15.0% versus 17.4%; $p = 0.598$), while the 11-week interval group had a worse quality of mesorectal excision (90% versus 78.7%, $p = 0.015$).[24] Similarly, a 2009 review from Cleveland Clinic demonstrated that the largest incremental increase in rate of pathologic complete response occurred after waiting at least 8 weeks until surgery, with a plateau in patient achieving a pathologic complete response beyond 12 weeks.[25]

Comparison of short course radiation versus long course chemoradiation

Two prospective randomized trials have demonstrated no oncologic differences between neoadjuvant CRT and neoadjuvant SC-RT. The Polish trial (2006) set out to evaluate these two neoadjuvant regimens directly. A total of 312 patients were randomized to either SC-RT and surgery within seven days or CRT (50 Gy in 28 fractions with bolus 5-FU and leucovorin) followed by surgery four to six weeks later. Early radiation toxicity was higher in the CRT group (18.2% versus 3.2%, $p < 0.001$). However, no difference was observed in late toxicity (10.1% versus 7.1%, $p = 0.36$), local recurrence (9% versus 14.2%, $p = 0.17$) and overall survival (47.2% versus 66.2%, $p = 0.96$). While higher rates of complete tumor response and negative circumferential margin were seen after CRT, this was attributed to the longer interval between the beginning of radiation therapy and surgery, and did not translate to a difference in oncologic outcomes.[26]

Similarly, the TROG 01.04 Trial (2012) compared patients with clinical stage T3, N0–2, M0 tumors treated with SC-RT followed by six cycles of adjuvant chemotherapy to long course CRT with infusional 5-FU and four cycles of chemotherapy. Similar conclusions were found with the Polish trial, with was no difference between the groups for three-year local recurrence, distant recurrence, overall survival, or late toxicity.[27]

While most of Europe had already adopted SC-RT, the findings of these studies generally did not alter practice in North America and practice patterns remained relatively unchanged. Both short and long course RT regimens are considered acceptable in neoadjuvant radiation treatment of LARC.

Optimal chemotherapy regimens in the neoadjuvant setting

Following establishment of preoperative treatment as standard therapy, attention then shifted to trying to determine the optimal combination of sensitizing chemotherapy and radiation in order to achieve the best response while limiting toxicity.

FFCD9203 (2006) was a French trial that aimed to assess the role of adding concurrent chemotherapy consisting of 5-FU and leucovorin to 45 Gy of radiation, followed by adjuvant 5-FU and leucovorin in the treatment of locally advanced middle and distal rectal cancers. The addition of chemotherapy to the radiation regimen decreased rate of local recurrence (8.1% versus 16.5%, p-0.004) but no difference was found in overall survival. Of note, there were higher rates of grade three or four toxicity seen with the addition of chemotherapy to radiation.

5-FU based chemoradiation protocols eventually came to be regarded as standard in the treatment of LARC. The substitution of 5-FU with the oral prodrug capecitabine was evaluated in Germany from 2002–2007 as a phase three non-inferiority trial. The five-year survival in the capecitabine group was equal to that of the 5-FU group, and there were similar rates of local recurrence (6% versus 7%, $p = 0.67$). Patients in the capecitabine group had more diarrhea, hand-foot skin reactions, and proctitis while leucopenia was more common with fluorouracil.

While the use of 5-FU or capecitabine is generally seen as a radiosensitizing agent for radiation administration, multiple trials then assessed the addition of systemic oxaliplatin as an adjunct to fluoropyrimidine-sensitized radiation. STAR-01 (2011) assessed the addition of oxaliplatin to a 5-FU based CRT regimen, which did not appear to decrease recurrences after surgery or significantly reduce mortality.[28] NSABPR-04 (2011) had two aims—to determine whether capecitabine could be substituted for continuous infusional 5-FU, and whether the addition of oxaliplatin would enhance the activity of fluropyrimidine sensitized radiation. This study further established capecitabine as an acceptable alternative. The addition of oxaliplatin was associated with significantly more toxicity, mainly diarrhea, without significant benefit in local recurrence and five year disease free and overall survival.[29] ACCORD12/0405 PRODIGE 2 (2012) also found no difference in local recurrence, disease free or overall survival at three years. There was also no difference in the primary endpoint of pathologic complete response with the addition of oxaliplatin to capecitabine (13.9% versus 19.2%, $p = 0.09$).[30]

The German CAO/ARO/AIO-04 study (2015) was performed as a follow up to the German Rectal Cancer Trial (CAO/ARO/AIO-94), and added oxaliplatin to both preoperative CRT and postoperative CRT. A total of 1256 patients were enrolled. The control group underwent standard 5-FU based CRT with 5 Gy in 28 fractions with infusional 5-FU, while the experimental arm underwent the standard therapy plus neoadjuvant oxaliplatin, as well as eight cycles of adjuvant leucovorin, 5-FU, and oxaliplatin (FOLFOX). In contrast to STAR-01, NSABPR-04 and ACCORD12, the oxaliplatin arm in this trial demonstrated higher rates of pathologic complete response (17% versus 13%, $P = 0.038$), improved disease free survival at three years (75.9% versus 71.2%, $p = 0{\cdot}03$), and similar rates of grade three or four toxicity.[31] Of note, the 5-FU schedule differed between the treatment arms, and oxaliplatin was administered in both the neoadjuvant and

adjuvant setting. This confounds the ability to accurately attribute the improvement in oncologic outcomes to neoadjuvant oxalipaltin. Given that multiple other studies suggested no oncologic benefit and worse toxicity, the addition of oxaliplatin to neoadjuvant chemoradiation is currently not recommended.

A follow up study published in 2016 from the Polish Colorectal Study Group also expanded on their 2006 study comparing short versus long course radiation by adding additional chemotherapy.[26] This more recent trial compared SC-RT followed by three cycles of FOLFOX versus long course radiation and FOLFOX. At three years, there was no difference in local recurrence (22% versus 21%, $p = 0.82$) or disease free survival (53% versus 52%, $p = 0.85$). There was higher overall survival and lower toxicity seen in the SC-RT and FOLFOX arm (73% versus 65%, $p = 0.046$).[32]

Saving radiation in the era of TME and staging MRI

While preoperative radiotherapy had been established to reduce the risk of local recurrence and potentially downstage tumors to increase the rate of sphincter preservation, radiation therapy is also associated with significant side effects. Up to 50% of patient report short term toxicity and long term side effects including autonomic nerve injury, bowel and bladder dysfunction.[33] As preoperative staging quality improved with the development of high resolution MRI, there has been increasing interest in defining a subset of patients in whom TME alone may be adequate locoregional treatment.

The MERCURY trial (2011) was a prospective multicenter multidisciplinary study that evaluated 374 patients for good prognostic MRI features predicting clear circumferential margins that could be adequately managed with surgery alone. Good features on MRI were defined as tumor >1 mm to mesorectal fascia, no extramural venous invasion, early MRI T-stage (T1-2, T3a, T3b with spread less than 5 mm from bowel wall), regardless of N stage. For low rectal tumors <5 cm from verge, good prognosis was additionally defined as MRI stage I or II, without invasion into intersphincteric plane or levators. Adjuvant chemotherapy, usually single agent fluropyrimidine regimen, was given postoperatively for node positive disease, and no patients received postoperative CRT. Patients with stage II cancers and good prognostic features had a local recurrence of 2.3%, overall survival of 65.7% and disease free survival of 76%. A total of 22 patients had stage III cancers (T2N1, T3a/bN1, T3bN2) with good prognostic features had a local recurrence rate of 0%, 95% disease free survival, and an 81% overall survival at five years.[34] Similar findings regarding the accuracy of MRI for evaluating the circumferential radial margin as a predictor of complete TME have been supported by the German OCUM trial.[35] It should be noted, however, that these treatment approach guided by MRI risk stratification is based on a prospective observational study with expertise in rectal cancer and has not been evaluated in the setting of a randomized trial.

A phase II pilot trial at Memorial Sloan Kettering Cancer Center evaluated patients with LARC 5–12 cm from anal verge with no threatened radial margin. Patients received induction FOLFOX and bevacizumab followed by restaging. Those with progressive disease proceeded to CRT with 5-FU and pelvic radiation, while patients who had clinical response or sTable disease proceeded directly to TME. Both groups received adjuvant chemotherapy. Induction chemotherapy alone was successfully utilized in 30 of the 32 patients enrolled. The complete pathologic response rate was 25% and R0 resections were achieved without the need for preoperative CRT. The remaining two patients were intolerant of FOLFOX and bevacizumab and received preoperative CRT. This study formed the basis of the currently enrolling phase III PROSPECT trial, in which patients with LARC are randomized to neoadjuvant FOLFOX followed by selective use of 5-FU or standard long course CRT to see if select patients can be spared the morbidity of pelvic radiation based on a favorable response to chemotherapy.[36]

The Chinese FOWARC trial randomized patients with LARC to fluorouracil based long course CRT, FOLFOX and CRT, or FOLFOX alone pre- and post-surgery without radiation. The authors determined that FOLFOX and CRT resulted in the highest pathologic complete response rates (14.0%, 27.5%, and 6.6% respectively). However, it also found that FOLFOX alone led to similar downstaging compared to 5-FU based CRT (37.1 versus 35.5%, respectively) with fewer postoperative complications and toxicities attribuTable to radiation administration.[37]

Evolving treatment paradigms

It has been noted that delays in initiation of adjuvant chemotherapy is associated with decreased overall and disease free survival.[38] Each four week delay in adjuvant systemic treatment has been correlated with a 14% decrease in overall survival.[39] As distant metastases represent the greatest cause of mortality for rectal cancer patients, greater emphasis has been placed on incorporating systemic therapy earlier in the treatment course.

A concept currently being explored is the role of using neoadjuvant systemic chemotherapy as a way to increase the rate of clinical complete response in patients, and increasing the possibility of nonoperative management or a “watch and wait” approach. Promising results from phase II trials Performed at Memorial Sloan Kettering Cancer Center have suggested that CRT followed by addition of FOLFOX chemotherapy prior to surgery increases the rate of complete pathologic response in LARC proportionate to the amount of cycles given.[40] Pathologic complete response rates for CRT alone were 18%, versus 25% for CRT plus two additional cycles, 30% for CRT plus four additional cycles, and 38% for CRT plus six additional cycles ($p = 0.0036$).[41] The odds of achieving pathologic complete response was 3.49 times higher for CRT plus six additional cycles compared to CRT alone ($p = 0.011$). Toxicity has been shown to be similar between the groups.

Similar results have also been seen with the use of SC-RT followed by four cycles of FOLFOX administered to a cohort of 76 patients with clinical stage T3-4, any N, any M rectal cancers. In this study performed at Washington University-St. Louis, pathologic complete response was seen in 25% of the overall cohort. Notably, this observational study included patients who were concurrently enrolled in the PROSPECT trial.[36] When sub-analyses were performed of only patients who were PROSPECT-eligible (T2N1, T3N0, or T3N1 cancers), complete pathologic response rate was seen in 39%.[42]

The RAPIDO trial aims to evaluate the role of neoadjuvant chemotherapy with six cycles of capecitabine and oxaliplatin as an adjunct to SC-RT, compared to standard long course chemoradiation with capecitabine and selective adjuvant chemotherapy. The hypothesis is that SC-RT with neoadjuvant systemic chemotherapy will increase disease free and overall survival without compromising local control.[43] This study is ongoing and aims to be done accruing in 2020.

Summary

Shifts in the rectal cancer treatment paradigm aim to provide a more tailored approach to patient care, and current studies look to refine the various treatment modalities that have been proposed in the past to optimize outcomes of pathologic and clinical complete response while attempting to limit treatment related toxicity and morbidity. The precise combination of radiation regimens, systemic therapy dosing, and surveillance schedules are still in evolution and are areas of active exploration. As such, the discussion regarding optimal rectal cancer care remains nuanced, dynamic, and complex.

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