

# Definitive high-dose radiotherapy with concurrent chemotherapy for locally advanced rectal cancer

## A case report and literature review

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### Abstract

**Background:** Standard management for locally advanced rectal cancer (LARC) involves preoperative chemoradiotherapy (CRT) and radical surgery. However, this level of treatment may be unnecessary for a subgroup of LARC patients. Previous reports have shown that approximately 20% of LARC patients experience a complete tumor response to preoperative CRT. Post-CRT nonoperative management of these patients may prevent morbidities associated with radical surgery. To our knowledge, this case report firstly presents the favorable long-term outcomes of a LARC patient who underwent definitive aim CRT.

**Methods:** The patient was 73 years' old, and staging workups revealed T3N2bM0 rectal adenocarcinoma. He agreed to receive CRT, but refused surgery. A radiotherapy (RT) dose of 64.8 Gy was prescribed, which was higher than conventional (50.4 Gy) preoperative aim RT. The regimen of concurrent chemotherapy was the same as that used in preoperative aim CRT: 2 cycles of 5-fluorouracil and leucovorin.

**Results:** Three months after CRT completion, a complete tumor response was identified clinically. Colonoscopic biopsy after 1 year showed no tumor cells. This patient is alive after 4 years with no evidence of recurrence or severe toxicity.

**Conclusion:** The long-term outcomes of this case indicate the feasibility of definitive high-dose RT with concurrent chemotherapy for LARC.

**Abbreviations:** CRT = chemoradiotherapy, CT = computed tomography, CTV = clinical target volume, LARC = locally advanced rectal cancer, RT = radiotherapy.

**Keywords:** nonoperative management, radiation therapy, rectal cancer, watch-and-wait

## 1. Introduction

Standard management for locally advanced rectal cancer (LARC; stage II or III) consists of preoperative (rather than postoperative) chemoradiotherapy (CRT), radical transabdominal surgery, and postoperative chemotherapy.<sup>[1]</sup> This multimodal combined treatment plan has significantly improved disease control and patient survival, but has inevitably been accompanied by an increase in morbidities and functional deterioration.<sup>[2]</sup>

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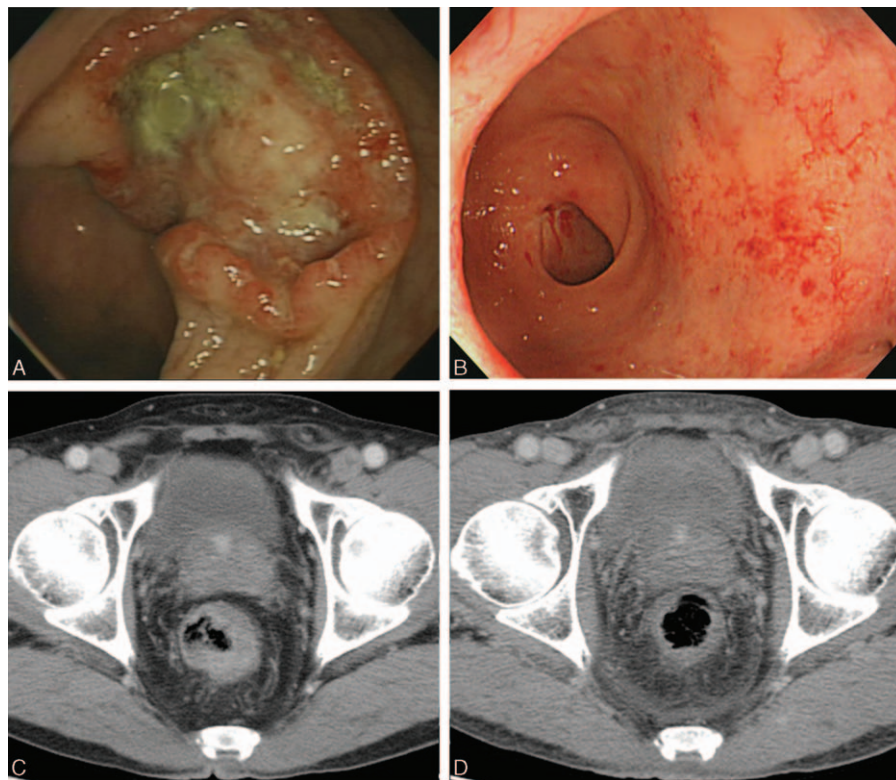
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To decrease suffering from treatment sequelae, research to individualize treatments for LARC patients is under active investigation.<sup>[2]</sup> Shifting the timing of CRT, that is, from postoperative to preoperative has allowed for the classification of LARC patients based on the tumor response to preoperative CRT.<sup>[3]</sup> Whether the tumor regresses post-CRT or not, the tumor is removed surgically; however, long-term outcomes are strongly correlated with the degree of CRT-induced tumor regression.<sup>[4]</sup> The CRT response reflects tumor behavior and has become a key factor in introducing personalized treatments for LARC. For example, conservative local excision or a nonoperative watch-and-wait approach has been investigated to avoid the morbidities associated with radical surgery in selected LARC patients whose tumors show a complete or near-complete response to CRT.<sup>[5,6]</sup>

This study presents a case of LARC in a patient who refused surgery, received definitive high-dose radiotherapy (RT) with concurrent chemotherapy, and showed a complete tumor response with long-term disease-free survival. Relevant issues are discussed with a literature review.

## 2. Case report

A 73-year-old man visited the hospital in September 2011 because of hematochezia, which had started 3 days before. Complete blood cell counts and chemistry results were within normal ranges. The serum carcinoembryonic antigen level was 6.31 ng/mL (normal range 0–5.0 ng/mL). Nothing was palpated upon digital rectal examination, but colonoscopy showed an ulcerofungating mass (Fig. 1A), with the distal end located 10 cm

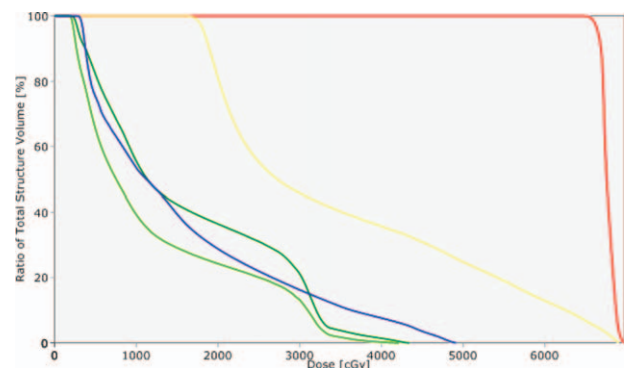


**Figure 1.** Colonoscopy before (A) and 1 year after chemoradiotherapy (B). Computed tomography before (C) and 3 months after chemoradiotherapy (D).

from the anal verge. Pathological examination revealed a well-differentiated adenocarcinoma. Pelvic computed tomography (CT) and magnetic resonance imaging indicated a 4-cm-long irregular shaped eccentric enhancing wall thickening with perirectal fat infiltration (Fig. 1C), and 7 enlarged (short-axis diameter  $\geq 5$  mm) mesorectal lymph nodes.  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography-CT revealed a hypermetabolic lesion in the rectum, with a maximum standardized uptake value of 8.3, and several perirectal lymphadenopathies with mild fluorodeoxyglucose uptake. No distant metastasis was detected. The pretreatment clinical stage was determined to be T3N2bM0 (IIIC) according to the American Joint Committee on Cancer staging, 7<sup>th</sup> ed.<sup>[7]</sup> The institutional review board (Soonchunhyang University Cheonan Hospital) waived the approval, as this is a retrospective case report. Written informed consent was obtained from the patient.

The patient refused surgery despite explanations to him that surgical resection was the standard definitive treatment. Instead, he agreed to undergo CRT. RT with a radiation dose higher than that of standard preoperative RT was prescribed as definitive treatment. For RT simulation, the patient was immobilized in the prone position using a belly board. A contrast-enhanced planning CT scan was performed using a 16-slice CT scanner (Brilliance CT Big Bore; Philips Medical Systems, Cleveland, OH). Axial CT images were obtained at 5-mm intervals and imported to the Eclipse RT planning system (Varian Medical Systems, Inc., Palo Alto, CA). Target delineation followed the recommendations of the International Commission on Radiation Units and Measurements reports No. 50 and 62.<sup>[8]</sup> The initial clinical target volume (CTV) encompassed the gross mural tumor, involved lymph nodes, mesorectum, presacral space, and the internal iliac and distal common iliac lymphatics. The planning target volume was generated by the addition of a 5-mm isotropic set-up margin to

the CTV. The small bowel, bladder, and femur head were outlined as organs at risk. Most of the small bowel was displaced from the pelvic cavity by the belly board.<sup>[9]</sup> A 3-dimensional conformal plan was developed using a 6-MV photon posterior-anterior field and 15-MV photon opposed lateral fields with 45 degree wedges. The plan was normalized such that  $\geq 95\%$  of the planning target volume received 100% of the prescription dose. A 45-Gy total dose was delivered with a 1.8-Gy fraction dose. A boost RT of 19.8 Gy was then delivered in 11 fractions. Boost CTV included the gross mural tumor, involved lymph nodes, and adjacent mesorectum. The boost plan was composed of four 15-MV photon fields: anterior/posterior right/left oblique fields. Figure 2 shows the dose-volume histogram with plan summation (initial and boost plans). RT was performed on a Novalis Tx system (Varian Medical Systems, Palo Alto, CA and BrainLab,



**Figure 2.** Dose-volume histogram: boost planning target volume (red), bladder (yellow), small bowel (blue), left (dark green), and right (green) femur head.

Feldkirchen, Germany). Patient set-up was verified weekly before treatment using an electronic portal imaging device. Chemotherapy was administered concurrently with RT, using 5-fluorouracil and leucovorin, and consisted of 2 cycles of a bolus infusion of 5-fluorouracil (450 mg/m<sup>2</sup>/d) and leucovorin (20 mg/m<sup>2</sup>/d) for 5 days during the 1–5 and 24–28 fractions of RT. The patient was admitted to the hospital during concurrent CRT, but on other days, RT alone was performed during the outpatient visits.

Follow-up evaluation for rectal cancer patients consisted of physical and digital rectal examinations, complete blood cell counts, liver function tests, and measurement of carcinoembryonic antigen levels every 3 months for the first 2 years and every 6 months thereafter. Abdominopelvic CT and chest radiography were conducted every 6 months. Colonoscopy and positron emission tomography-CT were performed every year.

Three months after CRT completion, the mass or stenosis was not palpated on digital rectal examination. Serum carcinoembryonic antigen levels decreased to 1.65 ng/mL. Follow-up serial CTs showed diminished rectal wall thickness (Fig. 1D). No intraluminal mass or ulceration was observed during colonoscopy at 1 year (Fig. 1B), and biopsy of a scar revealed no tumor cells, but revealed chronic nonspecific proctitis. Treatment toxicity involved nausea and fatigue during CRT and defecation difficulty during the early follow-ups; however, these subsided with conservative management. Urinary or sexual side effects were not observed. Four years after treatment, the patient is alive with no evidence of disease and no severe complications.

### 3. Discussion

The present LARC patient was not treated by surgery. CRT, involving a higher than conventional preoperative RT dose, eradicated all of the tumor cells. A complete response by CRT represents low biologic tumor aggressiveness, and the patient survived with no tumor relapse or serious toxicity.

Standard treatment for this patient would be a combination of preoperative CRT and radical surgery.<sup>[1]</sup> Surgical resection has played a major role in the treatment of rectal cancer, whereas CRT is considered a neoadjuvant or adjuvant therapy. However, surgical resection is also a major contributor to the morbidities induced by combined treatments.<sup>[10–12]</sup> The standard surgical technique involves total mesorectal excision as proposed by Heald et al.<sup>[13]</sup> This technique removes a circumferential envelope of perirectal tissue in its entirety and significantly reduces local recurrence rates compared with the historical blunt dissection. However, various perioperative complications are associated with this procedure, such as infection, pelvic sepsis, vascular or ureteral injury, anastomotic leak, and wound complications.<sup>[6]</sup> The mortality rate after total mesorectal excision is at least 2% even in fit patients,<sup>[6]</sup> and over one-third of patients report some degree of urologic and sexual dysfunction and fecal incontinence.<sup>[14]</sup> A permanent colostomy, inducing significant physical and psychological morbidity, is required in 10% to 30% of rectal cancer patients.<sup>[15]</sup>

RT decreases local recurrence rates compared with total mesorectal excision alone,<sup>[16]</sup> and this effect is more pronounced when given preoperatively versus postoperatively.<sup>[17,18]</sup> In addition to this long-term benefit, preoperative CRT results in the complete regression of tumors in approximately 20% of patients.<sup>[3]</sup> Such findings challenge the routine use of radical resection in all LARC patients. For selected patients showing a remarkable CRT response, investigators have explored post-CRT nonoperative management, also called a watch-and-wait approach, with surgery reserved as salvage therapy.<sup>[6,14]</sup>

Individualized strategies investigated for LARC patients also include selective use of RT to evade radiation toxicity, which exacerbates surgical morbidities.<sup>[19]</sup> However, for those patients in whom RT performs a definitive role and completely eradicates the tumor, selective use of surgery (or deferral of surgery) results in fewer morbidities because surgery is the main cause of morbidities following combined multimodal treatments. Nonoperative management of this patient was not determined after identifying a CRT response, but rather was decided before treatment due to the refusal of surgery. However long-term follow-up outcomes indicate that this nonoperative approach is feasible.

Nonoperative management or a watch-and-wait approach was pioneered by Habr-Gama and her colleagues in Brazil.<sup>[20,21]</sup> They published a series of retrospective studies including hundreds of patients with mainly T3 or N1 mid/low rectal tumors.<sup>[22]</sup> According to their latest publication,<sup>[23]</sup> this approach resulted in a 5-year rate of local recurrence that was “not amenable to salvage” as low as 6%. Early tumor regrowth (within the initial 12 months of follow-up) occurred in up to 19% of patients; however, 94% of these patients were able to undergo salvage surgery, with a 75% sphincter preservation rate. After 12 months post-CRT, an additional 11% of patients developed local recurrence, but salvage was feasible in 91%, with sphincter preservation in 35%. Systemic relapse rates were not different between patients with and without local recurrence (18% vs. 13%,  $P=0.6$ ), and the 3-year disease-free and overall survival rates were 78% and 88%, respectively, which are comparable to outcomes after standard treatments including CRT and surgical resection. These outcomes, including those from a small series prospective trial in The Netherlands,<sup>[24]</sup> were achieved after a conventional preoperative CRT regimen, with a typical RT dose of 50.4 Gy.<sup>[25]</sup> A more intensified CRT regimen may further increase the number of candidates recommended for a watch-and-wait approach and could further reduce recurrence rates. In the present study, the patient received 64.8-Gy RT.

Appelt et al showed a significant dose–response relationship for LARC regression in the range of 50.4 to 70 Gy.<sup>[26,27]</sup> In this study, an additional radiation boost was delivered using brachytherapy. Recently, the outcomes of a prospective observational study in which patients with T2–3N0–1M0 distal rectal cancer were managed with high-dose CRT and a watchful waiting strategy have been reported.<sup>[28]</sup> Sixty-five Gy RT was composed of 60 Gy external beam RT and 5 Gy endorectal brachytherapy boost. Of 51 eligible patients, 40 (78.4%) had a clinical complete response and were allocated to observation. Cumulative local recurrence rates in the observance groups after 1 and 2 years were 15.5% and 25.9%, respectively. Curative salvage surgery was feasible in all patients who developed local recurrence. No unexpected serious adverse reactions or treatment-related deaths occurred, and ultimately, more than half of all patients were managed nonsurgically. The current case used external beam RT only; however, it suggests that high-dose RT may increase the chances of a complete response and preclude surgical resection, without serious side effects. Newer technologies such as intensity-modulated RT and proton therapy may allow for a safe increase in the radiation dose for treatment of rectal cancer,<sup>[29,30]</sup> which could thereby expand the patient group suitable for nonsurgical strategies and improve the long-term outcomes of patients treated by such strategies.

Bypassing definitive surgery, which has long been the standard treatment for LARC, represents a radical change in the practice. Currently, limitations persist in terms of CRT response



evaluation and appropriate candidate selection. However, this alternative option is of particular concern in elderly or medically inoperable patients who are at higher risk of significant morbidity (including permanent stoma) and mortality associated with radical surgery. If biomolecular strategies are developed to accurately select tumors with a high susceptibility to RT, high-dose CRT may become a valid option as definitive treatment. Continuing evolution of rectal cancer treatment, especially for distal rectal cancer, may mimic that of anal cancer, for which CRT is the standard definitive treatment.

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