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*TOPIC HIGHLIGHT*

**Ignacio Gil-Bazo, MD, PhD,** *Series Editor*

# Rectal cancer treatment: Improving the picture

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## Abstract

Multidisciplinary approach for rectal cancer treatment is currently well defined. Nevertheless, new and promising advances are enriching the portrait. Since the US NIH Consensus in the early 90's some new characters have been added. A bird's-eye view along the last decade shows the main milestones in the development of rectal cancer treatment protocols. New drugs, in combination with radiotherapy are being tested to increase response and tumor control outcomes. However, therapeutic intensity is often associated with toxicity. Thus, innovative strategies are needed to create a better-balanced therapeutic ratio. Molecular targeted therapies and improved technology for delivering radiotherapy respond to the need for accuracy and precision in rectal cancer treatment.



**Key words:** Rectal cancer; Chemoradiotherapy; Intensity-modulated radiation therapy; Molecular targeted therapy

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## WHERE WE ARE: INTRODUCING THE CHARACTERS

Since the early 90's, radical surgery and fluoropirimidine-based chemoradiotherapy (CHRT) are the gold standards of treatment for locally advanced rectal cancer. Studies conducted by the Gastrointestinal Tumor Study Group[1,2] and the North Central Cancer Treatment Group[3] concluded that the combination of postoperative chemotherapy with radiotherapy improved local tumor control and survival in stage Ⅱ and Ⅲ rectal cancer relative to surgery alone.

Although currently the big picture mostly remains, some of the characters of the puzzle have changed. The main milestones in this development began with the improvement of the surgical technique, total mesorectal excision (TME). TME became the choice surgical procedure, with a relevant increase in local control. Actually, at some point it was thought that TME could make radiotherapy (RT) unnecessary. Nevertheless, a randomized study soon followed showing the maintained benefit of RT despite an excellent surgery, at least in terms of local control[4], outcomes that even are improving with longer follow-up.

The second landmark was to move the CHRT segment before the surgery. Initially, preoperative radiotherapy was found to improve overall survival as compared with surgery alone[5,6]. In the last decade, the dominant tendency in the therapeutic development of rectal cancer, both in Europe and North America, has been the use of preoperative radiotherapy with conventional protracted fractionation (45-50 Gy in daily fractions of 1.8-2 Gy during 5-6 wk) with concurrent chemotherapy followed by surgery at 4-8 wk. Extensive experience with preoperative CHRT showed feasibility and promising results in terms of down staging, sphincter preservation and disease control and survival parameters as interesting elements of analysis, with an acceptable toxicity profile. The most frequently used chemotherapy agent in this clinical context is 5-fluorouracil (5-FU, i.v.)[7-13]. More recently, the only phase Ⅲ trial concluded comparing pre- *vs* post-operative CHRT, demonstrated better tolerance, sphincter-saving surgical procedures and local control with preoperative CHRT[14].

Preoperative radiotherapy alone (no chemotherapy) and delayed surgery reported down staging rates of 18%[15,16]. However, the prolonged administration of CH-RT achieves down staging figures of around 65%[7-11,17]. Additionally, induction of tumor down staging improves the probability of a complete resection and sphincter-preserving surgery[11,13,18-20].

Complete pathologic response (pCR) rates range from 8% to 27% using i.v. 5-FU with preoperative irradiation[7,10,11,14,21]. In studies of postoperative 5-FU-based CHRT, severe acute toxicity ranges from 24%-40%[1,14,22,23]. However, in Phase Ⅱ studies of preoperative CH-RT, Grade 3-4 acute toxicity occurs in 15%-28% of patients[7,11,13,14,20].

Regarding tumor control and survival, published series

**Table 1 Novel chemoradiation combinations**

| | Chemotherapy | | RT (Gy) | GI grade 3-4 toxicity (%) | DS (%) | pCR (%) |
|---|---|---|---|---|---|---|
| | Capecitabine ($mg/m^2$ bid) | | | | | |
| Kim *et al* | 825 d 1-14 and 22 - 35 | | 50.4 | - | 84 | 31 |
| De Paoli *et al* | 825 bid continuous | | 50.4 | - | 57 | 24 |
| | 5-FU ($mg/m^2$ CI) | CPT-11 ($mg/m^2$ weekly) | | | | |
| Mehta *et al* | 200 | 50 | 50.4 | 28 | 71 | 37 |
| Klautke *et al* | 250 | 40 | 50.4 | 32 | 76 | 24 |
| Mohiuddin *et al* | Arm 1: 225 | Arm 1: - | HART: 55.2-60 | 27 | 78 | 26 |
| | Arm 2: 225 | Arm 2: 50 | 50-54 | 37 | 78 | 26 |
| Navarro *et al* | 225 | 50 | 45 | 14 | 49 | 14 |
| | 5-FU ($mg/m^2$ CI) | Oxaliplatin ($mg/m^2$) | | | | |
| Ryan *et al* | 200 | MTD: 60 weekly | 50.4 | 38 | - | 25 |
| Aschele *et al* | 200-225 | MTD: 60 weekly | 50.4 | 16 | 84 | 28 |
| Turrito *et al* | 300 | 80 wk 1, 3, 5 | 45 | - | 65 | 15 |
| | Capecitabine ($mg/m^2$ bid) | Oxaliplatin ($mg/m^2$) | | | | |
| Rodel *et al* | 825 d 1-14 and 22 - 35 | 50 d 1, 8, 22 | 50.4 | 6 | 55 | 19 |
| Machiels *et al* | 825 bid continuous | 50 weekly | 45 | 30 | - | 14 |

RT: Radiotherapy; DS: Downstaging; bid:Twice daily; CI: Continuous infusion; HART: Hyperfractionated accelerated radiotherapy; MTD: Maximun-tolerated-dose; GI: Gastrointestinal.

vary in follow-up. Preoperative CHRT in rectal cancer assumes ranges for 5-year local recurrence from 2% to 15%, disease-free survival from 70% to 86%, and overall survival from 60% to 85%[7,9,10,14,18,21,24-26].

In summary, incorporation of TME surgical procedure and 5-FU-based preoperative CHRT have been translated to an improvement in local control, with the additional advantage of more tolerable treatments in terms of acute toxicity and saving-sphincter surgical procedures.

## MOVING FORWARD: IMPROVING THE PORTRAIT

The picture is drawn. What is next, more characters or better colors?

Therapeutic intensity is often linked to better response and outcomes. But in oncology more is not always better. Increases in doses or number of therapeutic agents combined together lead to higher rates of toxicity. This situation is especially true in rectal cancer. Moreover, the risk of over-treatment in some patients with rectal cancer is present. One treatment approach for all rectal adjuvant patients may not be warranted. We already know that not every stage Ⅱ-Ⅲ rectal cancer is the same[27]. Prognostic factors have been studyed, both at clinical and at molecular and genetic level. In the near future these signatures should be taken into account. An adequate therapeutic index should be found, with a well-balanced ratio of benefit/toxicity.

Where can we find additional benefit in rectal cancer treatment? On the one hand, despite the improvement in local control with multimodality approaches, the rate of distant metastasis is still high, around 19%-36%[10,14]. On the other hand, growing data demonstrates a relationship between response to preoperative CHRT and survival. A higher grade of tumor regression in the surgical specimen has been associated with increased disease-free survival and overall survival after preoperative CHRT in rectal cancer[10,24,17,28-31]. Thus, achieving higher rates of complete pathologic response, but also major tumor regression, is one of the current goals in the protocols of preoperative CHRT in rectal cancer. Both effects, reduction of distant metastasis and higher tumor regression grade, require the use of more active and effective chemotherapeutics agents, with adequate toxicity profiles when administered with radiotherapy.

### *Exploring novel CHRT combinations*

**Oral fluoropyrimidines:** Oral fluoropyrimidines have been developed as a therapeutic alternative to i.v., continuous infusion of 5-FU, and have been shown to deliver similar efficacy and tolerability with the additional advantage of offering the convenience of oral chemotherapy (Table 1).

Few studies have investigated the safety and efficacy of tegafur with or without uracile (5-FU pro-drugs) and radiotherapy[32-35]. Down staging rates (54%-68%), pCR (8%-15%), and grade 3-4 toxicity (12%-43%) match quite well with those with i.v. 5-FU. Although follow-up is not as long as in the 5-FU series, outcomes in terms of local control, distant metastasis rate, disease-free survival and overall survival seem to be similar.

Capecitabine is a fluoropyrimidine carbamate active

in several solid tumors. A recent phase Ⅲ trial (X-ACT trial) has demonstrated the equivalence of capecitabine to bolus 5-FU/leucovorin in the adjuvant treatment of colon cancer[36]. Thymidine phosphorylase (TP) is a key enzyme for the metabolism of capecitabine to 5-FU. Some data suggest that tumor tissue shows higher concentrations of TP than normal tissue[37]. This phenomenon would lead to a preferential activation of capecitabine in the tumor tissue, providing a favorable ratio for toxicity and radiosensitization. Preclinical studies have shown that RT might up-regulate the TP expression in tumor cells, resulting in a selective and synergistic effect between RT and capecitabine[38]. Phase I studies have been conducted to determine the maximun-tolerated-dose (MTD) of capecitabine in combination with radiotherapy. The recommended dose for this combination was 825 mg/m$^2$ bid without break during radiotherapy period (5-6 wk)[39,40]. Two published phase Ⅱ studies have shown that preoperative CHRT with capecitabine appears to be effective in locally advanced, resectable rectal cancer. Encouraging rates of down staging (up to 84%) and pCR (24%-31%) with a favorable safety profile of the combination might warrant the use of capecitabine and RT with other effective new drugs[40-42].

**Irinotecan (CPT-11):** Irinotecan is an active chemotherapeutic agent in colorectal cancer. The combination of Irinotecan and 5-FU has been approved as first line chemotherapy for patients with metastatic colorectal cancer[41,43,44]. Phase I studies have demonstrated that CPT-11 can be safely administered concomitantly with radiotherapy (MTD: 10 mg/m$^2$ daily or 50 mg/m$^2$ weekly)[45]. Several phase Ⅱ studies have determined the efficacy and feasibility of the irinotecan and 5-FU combined-therapy plus radiotherapy in the neo-adjuvant management of rectal cancer. The rates of tumor down staging (49%-78%) and pCR are high (14%-37%) with an acceptable rate of acute severe toxicity (14%-37%)[46-49].

The combination of CPT-11 and Capecitabine with radiotherapy has been studied in recent phase Ⅰ-Ⅱ trials[50,51]. The MTD dose of Capecitabine was 500 mg/m$^2$ while combining with CPT-11 50 mg/m$^2$ weekly and 750 mg/m$^2$ while combining whit CPT-11 40 mg/m$^2$ weekly. The rate of tumor down staging and pCR were similar with the two schedules (72%-75% and 14%-21%, respectively) and similar with the combination of 5-FU, CPT-11 and radiotherapy.

**Oxaliplatin:** Oxaliplatin is a novel anti-neoplastic platinum. When combined with 5-FU, oxaliplatin improves overall survival for patients with metastatic colorectal cancer and the rate of progression-free survival for patients with completely resected stage Ⅱ and Ⅲ colon cancer[52,53]. These data encourage combining oxaliplatin and 5-FU in the preoperative setting of rectal cancer management for an improved response. Moreover, oxaliplatin has radiation sensitization properties[54].

Several phase Ⅱ studies have evaluated weekly administration schedules of oxaliplatin and 5-FU and radiotherapy. They have demonstrated that this regimen is feasible with moderate toxicity. The addition of oxaliplatin to standard 5-FU-RT seems to be associated with a promising down staging (65%-84%) and pCR rates (15%-28%)[55-57].

Oxaliplatin has been combined with Capecitabine in metastatic colorectal disease[58-60]. The combination has been adapted to preoperative CHRT and phase Ⅰ-Ⅱ trials have been published. The studies show that this regimen is active and feasible, with attractive down staging (55%-72%) and pCR rates (14%-28%)[61-63].

## RAISING THE BAR: THERAPEUTIC MODULATION

One of the paradigms for loco regional treatment of cancer is anatomic precision. Technical advances in radiation oncology including functional and molecular imaging and intensity-modulated radiation therapy (IMRT) delivery techniques are allowing greater treatment precision and dose escalation. Moreover, cancer is a biologic entity. Treating cancer requires understanding cancer biology which is changing the approach in cancer therapeutics. A number of genetic signatures and molecular pathways involved in cancer have been discovered. Parallel molecular therapeutic development is emerging. Molecular targeted treatments have being combined with conventional anticancer drugs, accordingly with specific tumor biology.

Coming back to loco regional treatment of rectal cancer, IMRT might provide anatomical specificity. Molecular therapies will complement anatomical specificity by targeting biological pathways that are deregulated in individual tumors. Precision is technologically based while accuracy is biologically based[64].

### *New biological agents: biological modulation*

Epidermal growth factor receptor (EGFR) and angiogenesis-related pathways are perhaps the molecular mechanisms best explored in colorectal cancer. Both mechanisms are involved either in colorectal carcinogenesis and tumor growth[65,66], and in radioresistence[67-69]. Thus, novel targeted biologic agents including angiogenesis and EGFR inhibitors hold tremendous promise as RT sensitizers and as systemic therapy in rectal cancer[69-71].

Preliminary reports show feasibility and promising activity combining Bevacizumab with 5-FU and RT. The MTD was determined for Bevacizumad at 5 mg/kg[72]. Additionally, surrogate markers are being investigated suggesting the ability of Bevacizumab to specifically target tumor angiogenesis[72,73].

A recent phase I study combining capecitabine, oxaliplatin and bevacizumab with preoperative RT establishes the MTD to be capecitabine 625 mg/m$^2$ BID, Oxaliplatin 50 mg/m$^2$ per week and Bevacizumab 15 mg/kg d 1 and 10 mg/kg d 8 and 22. Down staging was observed in 9/11 patients (82%) and 2/11 (18%) patients achieved pCR and in 2 of 11 only microscopic disease was found in the surgical specimen[74].

C225 (Cetuximab) is a chimeric monoclonal antibody that targets the extracellular domain of epidermal growth

factor receptor (EGFR) with high specificity and affinity[75]. Cetuximab has demonstrated increased responses combined with chemotherapy in metastasic colorectal cancer[76]. The radiosensitization activity of Cetuximab has been broadly explored[77]. Thus, the combination of chemotherapy and RT with C225 is an attractive strategy to be explored.

A pilot study has explored the addition of Cetuximab (250 mg/m$^2$ per week) to conventional i.v., continuous infusion of 5-FU and RT. Grade 3-4 diarrhea was detected in 10% and acneiform rash in 15%. Pathological complete response was achieved in 12% of patients[78].

Cetuximab has been combined with Capecitabine and RT in rectal cancer. The dose suggested is Capecitabine 825 mg/m$^2$ bid without interruption during the duration of RT and Cetuximab 250 mg/m$^2$ weekly. Grade 3 diarrhea was 10%, rectal pain 20%. Ten percent of the evaluated patients achieved pCR[79].

A phase I trail has recently evaluated the combination of Capecitabine, Oxaliplatin and C225 with RT. Doses suggested were for Cetuximab 400 mg/m$^2$ on d-7, then 6 weekly doses of 250 mg/m$^2$, for oxaliplatin 50 mg/m$^2$ d 1, 8, 22 and 29 in combination with capecitabine 1650 mg/m$^2$ bid d 1-14 and 22-35. Grade 3-4 diarrhea was 15% and grade 3-4 toxicity as skin reaction 7%[80]. The results of the phase Ⅱ study with 31 patients enrolled are coming soon.

### *Intensity Modulated Radiotherapy in rectal cancer: Rational and preliminary experience*

New drugs and biological treatments may enhance global radiotherapy effects improving therapeutic outcomes but acute effects may also be increased. Moreover, a dose-volume relationship has been established between the severity of diarrhea toxicity and the volume of irradiated small bowel at all dose levels in patients treated with preoperative chemoradiation for rectal cancer[81]. The volume of irradiated small bowel thresholds to predict acute gastrointestinal toxicity is unknown although a strong correlation exists between the volume of small bowel receiving 15 Gy (V15) and the degree of acute small bowel toxicity[82].

The development of novel and sophisticated irradiation techniques as intensity modulated radiation therapy (IMRT) represents a spectacular progress in planning and delivering external beam radiation therapy. IMRT generates highly conformal and irregularly shaped dose distribution while reducing dose to adjacent normal tissue structures. IMRT has demonstrated dosimetric superiority over 3D-conformal radiation therapy (3D-CRT) in the majority of tumor sites, including pelvic tumors where the irradiated bowel can be significantly reduced[83].

Researchers at the Royal Marsden Hospital have reported a dosimetric study comparing IMRT *vs* 3D-CRT in five rectal cancer patients. The irradiated bowel volume at 45 Gy and 50 Gy can be reduced with IMRT techniques, which could potentially resulted in marked reductions in acute and chronic bowel toxicity[84]. Tho and colleagues[81] evaluated the role of IMRT in 41 patients with locally advanced rectal cancer treated with preoperative 5FU CHRT. The results showed that IMRT provided dosimetric and radiobiological modeling benefits by reducing the dose to the small bowel, and the likelihood of late normal tissue complications. A dosimetric comparison of 3D-CRT using pelvic anatomical references, 3D-CRT with more restrictive volumes, and IMRT was explored by our institution in nine patients diagnosed with locally advanced rectal cancer. A number of parameters, such as conformity index in the planning target volume, different dose levels at the planning target volume and organs at risk were calculated and compared between the three plans. Target coverage was similar, but the conformity index was better using IMRT. Irradiation doses at small bowel and bladder were significantly reduced with IMRT planning.

Dosimetric parameters in rectal cancer with IMRT are encouraging. Clinical research looking for acute and late toxicity, tumor response, tumor control and survival is warranted. The rationale for the use of chemo-IMRT in locally advanced rectal cancer is based on the potential decrease of gastrointestinal toxicity while maintaining conventional dose to the primary tumor, draining lymph node regions and presacral region. This capacity to change the gastrointestinal toxicity profile may also allow reducing the number of fractions by increasing fraction size, which ultimately may improve the rate of pCR and cost-effectiveness.

Our institution has carried out a prospective study of preoperative chemo-IMRT in rectal cancer. The treatment protocol includes simultaneous combination of capecitabine and oxaliplatin with three escalating dose levels of IMRT, 37.5 Gy 42.5 Gy and 47.5 Gy in 15, 17 and 19 fractions, respectively[85] Chemotherapy consisted on capecitabine 825 mg/m$^2$ bid during radiation therapy (resting over the weekend) and oxaliplatin 60 mg/m$^2$ d 1, 8 and 15. Resection was scheduled 6 wk after termination of chemo-IMRT. Simulation was made with the patient positioned prone and immobilized using a combination of prone head cushion and shell with a mixed foam bag. The patient was CT scanned from the L2 vertebral body to the entire perineum with a slice thickness of 5 mm. The slices were transferred through local network to the treatment planning system. The target volumes and organs at risk (OARs) were delineated on axial CT slices in the Helax-TMS treatment planning system (Nucletron Scandinavia, Uppsala, Sweden) as seen in Figure 1. The gross tumor volume (GTV) was defined as the primary tumor and the suspicious metastasic lymph nodes visualized on the CT scan. The clinical target volume (CTV) included the GTV, the presacral region and the common and internal iliac lymph nodes. Adding a margin of 0.5-1 cm around the CTV generated the planning target volume (PTV). The OARs outlined were the bladder and the small bowel. After the GTV, CTV, PTV and OARs were contoured the edited CT slices were transferred from the Helax-TMS treatment planning system to the inverse planning system (KonRad version 2, Siemens Oncology Care Systems, Heidelberg, Germany). Inverse planning for step-and-shoot treatment was performed using 15 MV photons generated on a Mevatron Primus linear accelerator (Siemens Oncology Care Systems, Concord, USA). Seven coplanar equally spaced fields (gantry angles 0°, 51°, 103°,

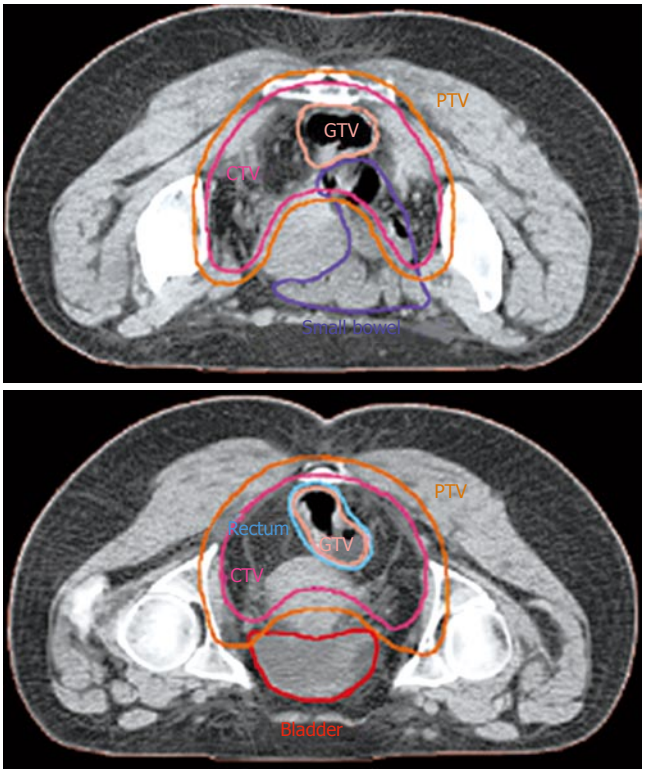


**Figure 1** The GTV, PTV and organ at risk (small bowel and bladder) countered on the axial CT slices.

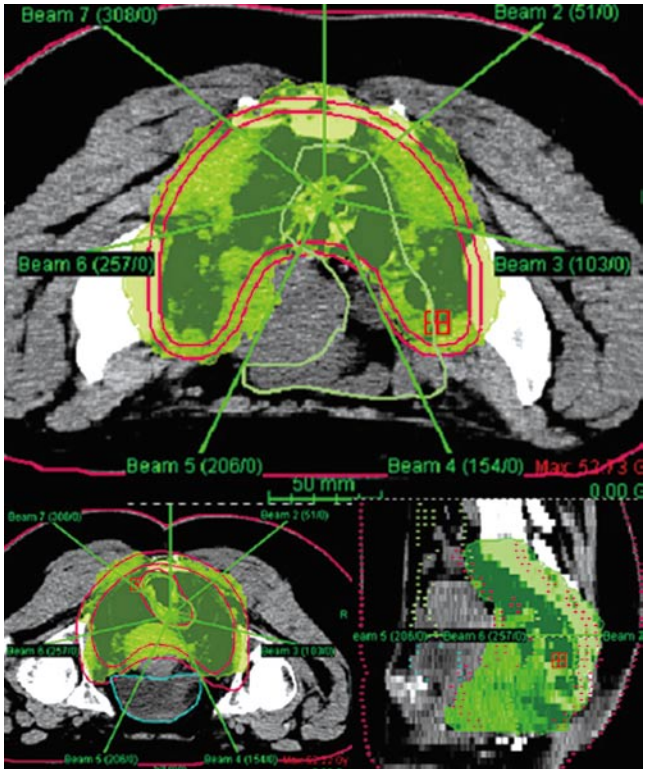


**Figure 2** Axial and sagital CT scan images with dose distributions. The 45 Gy isodose surface (green) encompass the GTV and PTV.

154°, 206°, 257° and 308°) were used and the isocenter was placed in the geometric center of the PTV. Figure 2 displays the clinical dosimetry over the patient CT scans.

The first three patients received 37.5 Gy and there were no dose-limiting toxicity (DLT) defined as any grade 3 or 4 gastrointestinal toxicities or grade 4 hematological toxicity. The next three patients received 42.5 Gy without observed DLT and the remaining patients received 47.5 Gy in 19 fractions. Preliminary data show that treatment compliance was 80%, grade 3 adverse events were seen in 21% of the cases, down staging was observed in 52% of patients and pathological response grade 3+ or 4 according to the scale established by Ruo *et al*[86] occurred in 45% of patients.

The use of preoperative IMRT combined with more active systemic chemotherapy provides a major challenge to improve treatment-related toxicity observed with more conventional radiation techniques. Furthermore, the promising favorable pathological response observed with these strategies has the potential to be associated with better loco regional control of disease and may predict better survival.

## CONCLUSIONS

Preoperative CHRT followed by TME surgery is the current framework for rectal cancer treatment picture. Further advances with better agents (chemotherapy and molecular targeted therapies) and technology (IMRT) will be translated to improved shapes and colors, enhanced contrast and brightness: response intensity with balanced toxicity.

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