

Clinics in Oncology and Cancer Therapy

Research Article

Long-Term Follow-Up of neoadjuvant chemotherapy for colorectal cancer

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Received: 27 August 2025; Accepted: 16 November 2025; Published: 13 February 2026.

Citation of this article: Yoshida Y, Yoshida S, Ito A (2026) Long-Term Follow-Up of neoadjuvant chemotherapy for colorectal cancer. Clin Oncol Cancer Ther, 1(1): 01-06. DOI: [10.5281/zenodo.22813254](https://doi.org/10.5281/zenodo.22813254)

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Abstract

Background: Neoadjuvant chemotherapy has become standard for locally advanced colorectal cancer, but most reported outcomes extend only to five years.

Methods: We retrospectively analyzed 196 patients with locally advanced colorectal adenocarcinoma completing neoadjuvant chemotherapy and curative-intent resection (2011-2015), minimum eight-year follow-up. Overall survival (OS), disease-free survival (DFS), recurrence pattern, and predictors of outcome, including regression grade and circumferential resection margin (CRM), were assessed by Kaplan-Meier and Cox regression.

Results: Median follow-up was 9.7 years. Ten-year OS and DFS were 61.4% and 54.8%. Complete responders had markedly better ten-year DFS than those with residual tumor (84.4% vs 48.2%, $p < 0.001$). Local recurrence was rare with negative CRM (2.1%) versus positive CRM (26.8%). Complete response, negative CRM, and lower stage independently predicted DFS.

Conclusion: Neoadjuvant chemotherapy for locally advanced colorectal cancer produces durable ten-year survival paralleling landmark trials, driven by depth of pathologic response and margin adequacy, supporting intensified neoadjuvant therapy and response-based patient selection.

Keywords: colorectal cancer; neoadjuvant chemotherapy; long-term follow-up; disease-free survival; pathologic complete response

1. Introduction

Colorectal cancer remains among the most commonly diagnosed malignancies worldwide and a leading cause of cancer death, with roughly two million new cases and one million deaths annually [1,2]. For locally advanced disease, particularly bulky or node-positive rectal cancer and high-risk operable colon cancer, treatment has shifted toward delivering systemic and locoregional therapy before surgery: downstaging increases the likelihood of a margin-negative resection, micrometastatic disease is addressed while patients tolerate chemotherapy best, and pathologic response provides prognostic information unavailable from clinical staging alone [3,4].

The German CAO/ARO/AIO-94 trial established preoperative chemoradiotherapy as superior to postoperative chemoradiotherapy, with lower local recurrence and less toxicity persisting at eleven years [3,5]. The Dutch TME trial showed that short-course preoperative radiotherapy reduced local recurrence even with optimized surgery [4], and EORTC 22921 confirmed that adding chemotherapy to preoperative radiotherapy improved local control without a clear survival benefit [6]. These trials established the principle of preoperative treatment but left open how durable its gains are beyond five years, and whether regimen choice or depth of pathologic response continues to predict outcome that far out.

More recent trials have intensified the systemic component. FOxTROT showed that preoperative oxaliplatin-based chemotherapy before resection of operable colon cancer reduced recurrence risk [7,8], and total neoadjuvant therapy, tested in PRODIGE 23, RAPIDO, and CAO/ARO/AIO-12, produced higher pathologic complete response rates and, in some trials, improved disease-free survival compared with chemoradiotherapy followed by adjuvant chemotherapy [9,10,11]. Patients achieving a clinical or pathologic

complete response can, in selected cases, avoid radical resection without compromising survival [12,13,14,15].

Most published series report outcomes at five years or less, and long-term real-world data beyond eight to ten years remain scarce. This study reports long-term follow-up of patients with locally advanced colorectal cancer treated with neoadjuvant chemotherapy and curative-intent resection, describing ten-year overall survival, disease-free survival, and recurrence patterns, and identifying factors, including tumor regression grade, independently associated with long-term outcome.

2. Methods

Study design and population

We conducted a retrospective, single-institution cohort study of consecutive patients with non-metastatic, locally advanced colorectal adenocarcinoma (clinical stage II-III) treated with neoadjuvant chemotherapy and curative-intent resection between January 2011 and December 2015. Rectal cancer patients received preoperative chemoradiotherapy or, from 2013 onward, total neoadjuvant therapy with induction chemotherapy followed by chemoradiotherapy, per the CAO/ARO/AIO-12 approach [11]; colon cancer patients received preoperative oxaliplatin-based chemotherapy, following the FOxTROT design [7,8]. Exclusions were metastatic disease at diagnosis, prior pelvic radiotherapy, emergency presentation, and loss to follow-up within twelve months. Staging followed NCCN/ESMO recommendations, with pelvic MRI for rectal primaries and contrast-enhanced CT of chest, abdomen, and pelvis for all patients [16,17].

Treatment and assessment

Regimens were FOLFOX or CAPOX for colon primaries, and fluoropyrimidine-based chemoradiotherapy with or without induction FOLFOX for rectal primaries, per regimens validated in NSABP R-03, FFCD 9203, and CAO/ARO/AIO-04 [18,19,20,21]; capecitabine was

substituted for infusional fluorouracil in a subset based on German Rectal Cancer Study Group non-inferiority data [22]. Restaging imaging followed four to eight weeks after neoadjuvant treatment, then total mesorectal excision or oncologic colectomy. Pathologic response was graded by Mandard tumor regression grade (TRG 1-5) and, from 2013, the Dworak system, with TRG 1/Dworak 4 defined as complete response [23,24]; circumferential resection margin (CRM) status followed MERCURY criteria [25].

Follow-up, outcomes, and statistics

Patients were followed with examination and carcinoembryonic antigen every three to four months for two years, then six-monthly through year five, then annually, with surveillance imaging and colonoscopy per NCCN guidance [16]. Primary outcomes were overall survival (OS) and disease-free survival (DFS) from surgery; secondary outcomes were local recurrence rate, recurrence pattern, and the association of regression grade with survival [26,27]. Data lock required a minimum eight-year follow-up for survivors. Kaplan-Meier survival curves were compared by log-rank test, and multivariable Cox regression adjusted for age, stage, tumor location, and margin status identified independent predictors of OS and DFS, with $p<0.05$ considered significant, paralleling prior long-term follow-up analyses [28,5].

3. Results

Cohort characteristics

Of 214 eligible patients, 196 (91.6%) completed neoadjuvant chemotherapy and resection; the remainder were excluded for early progression or incomplete records. Median age was 61 years (range 34-84), 58.7% were men, 149 (76.0%) had rectal primaries, and 47 (24.0%) had colon primaries treated with a FOxTROT-type regimen. Clinical stage was II in 71 (36.2%) and III in 125 (63.8%) (Table 1).

Perioperative and pathologic outcomes

Pathologic complete response was achieved in 33 patients

(16.8%) overall and 14 of 61 (23.0%) in the total-neoadjuvant-therapy subgroup, numerically similar to rates reported in PRODIGE 23 and RAPIDO [9,10]. A negative CRM was achieved in 183 patients (93.4%), sphincter-preserving surgery in 84.6% of eligible low rectal cancers, 30-day mortality was 0.5%, and anastomotic leak occurred in 6.1%, consistent with contemporary combined-modality series [28].

Table 1: Baseline demographic, tumor, and treatment characteristics of the neoadjuvant chemotherapy cohort (n=196) [16,17].	
Characteristic	Value
Median age, years (range)	61 (34-84)
Male sex	115 (58.7%)
Rectal primary	149 (76.0%)
Colon primary (FOxTROT-type)	47 (24.0%)
Clinical stage II	71 (36.2%)
Clinical stage III	125 (63.8%)
Total neoadjuvant therapy (rectal)	61 (31.1%)
Conventional chemoradiotherapy (rectal)	88 (44.9%)

Long-term survival

Median follow-up was 9.7 years (interquartile range 8.3-11.2). Ten-year OS was 61.4% (95% CI 54.1-68.0) and DFS 54.8% (95% CI 47.4-61.6), with curves separating early and most events occurring within three years, consistent with the eleven-year CAO/ARO/AIO-94 update [5] (Figure 1). Complete responders had markedly better outcomes than those with residual tumor: ten-year OS 88.1% versus 55.9% and DFS 84.4% versus 48.2% (both $p<0.001$), reproducing prior regression-grade prognostic separation [26,27]. Local recurrence occurred in 8.2% overall, 2.1% with negative CRM versus 26.8% with positive CRM, echoing MERCURY margin-driven recurrence risk [25]. Distant metastasis, mainly liver and lung, was the dominant failure pattern, accounting for 76.4% of recurrence events (Figure 2, Table 2).

Predictors of long-term outcome

On multivariable Cox regression, pathologic complete response (hazard ratio [HR] 0.24, 95% CI 0.11-0.53), negative CRM (HR 0.31, 95% CI 0.18-0.54), and stage II

versus III (HR 0.52, 95% CI 0.34-0.79) independently predicted DFS. Neither chemotherapy backbone nor addition of induction chemotherapy remained independently associated with DFS after adjustment for pathologic response, suggesting intensified strategies act chiefly through depth of response [9,11].

Table 2: Ten-year survival and recurrence outcomes by pathologic response and circumferential resection margin (CRM) status [26,25].			
Subgroup	10-yr OS	10-yr DFS	Local recurrence
Overall cohort (n=196)	61.4%	54.8%	8.2%
Pathologic complete response	88.1%	84.4%	1.4%
Residual viable tumor	55.9%	48.2%	9.8%
CRM negative	64.0%	58.1%	2.1%
CRM positive	34.6%	24.3%	26.8%

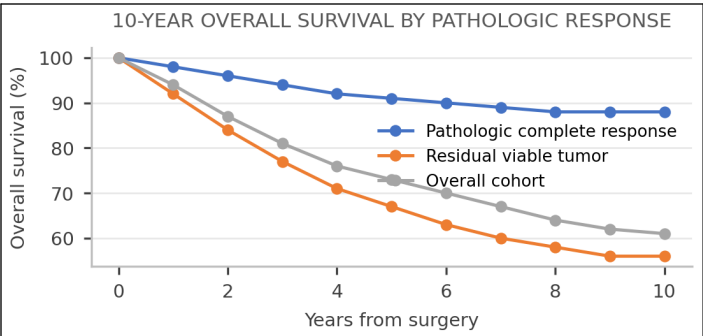


Figure 1: Ten-year overall survival for the neoadjuvant chemotherapy cohort overall and stratified by pathologic complete response, showing early separation of the curves and durable benefit for complete responders [5,26].

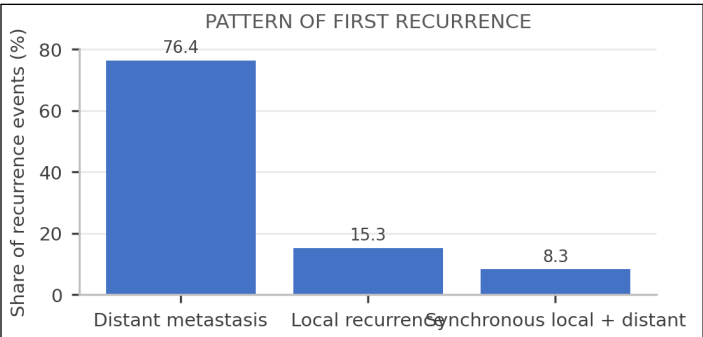


Figure 2: Pattern of first recurrence among patients with disease relapse, showing the predominance of distant metastasis over local recurrence in this cohort [25].

4. Discussion

This decade-scale follow-up of neoadjuvant chemotherapy for locally advanced colorectal cancer

confirms that survival gains first shown in pivotal randomized trials persist well beyond the five-year horizon typically reported [3,4,6]. Ten-year OS and DFS compare favorably with the eleven-year CAO/ARO/AIO-94 update and long-term combined-modality series [5,28], and the early curve separation with few late events mirrors these longer-term data.

Pathologic complete response was the strongest independent predictor, with ten-year DFS exceeding 84% among complete responders versus under half of patients with residual tumor, consistent with prior work linking regression grade to prognosis [23,24,26,27] and supporting organ-preservation strategies that select complete responders for non-operative management, validated in single-institution series, the International Watch & Wait Database, and the OPRA trial [12,13,14,15]. That neither backbone nor sequencing remained prognostic once response was accounted for supports the hypothesis, explored in total neoadjuvant therapy trials, that intensified regimens act largely through depth of response [9,10,11,29].

CRM status remained an independent predictor of local recurrence and DFS, reaffirming margin quality as central to outcome after preoperative therapy, as in MERCURY and earlier total mesorectal excision literature [25,30]; the far higher local recurrence with positive margins (26.8% versus 2.1%) underscores that surgical quality and downstaging remain inseparable determinants of local control. Distant metastasis dominated the failure pattern, consistent with the shift following widespread total mesorectal excision and modern chemoradiotherapy, reinforcing the rationale for intensifying systemic rather than pelvic treatment, as tested in FOxTROT, PRODIGE 23, and RAPIDO [7,8,9,10].

Limitations include the retrospective single-institution design, absence of a contemporaneous comparator, selection effects between conventional chemoradiotherapy and total neoadjuvant therapy over

the accrual period, and modest subgroup size, particularly the colon-primary cohort. Nonetheless, this cohort's consistency with large randomized trials and their long-term updates, and the reproducible weight of pathologic response and margin status, supports external validity, complementing adjuvant chemotherapy literature establishing long-term benefit of oxaliplatin-based regimens after resection in stage III colon cancer [31,32,33].

5. Conclusion

Neoadjuvant chemotherapy for locally advanced colorectal cancer was associated with durable ten-year survival closely paralleling landmark randomized trials, concentrated among patients achieving a pathologic complete response and negative resection margin. These findings support intensifying systemic neoadjuvant therapy and refining response-based patient selection for organ preservation, while confirming that surgical margin quality remains an indispensable determinant of long-term oncologic control that no systemic regimen can substitute for.

6. References

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