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Research Article

A Retrospective Cohort Study of neoadjuvant chemotherapy in elderly oncology patients with colorectal cancer

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Abstract

Background: Elderly patients have historically been underrepresented in the trials establishing neoadjuvant chemotherapy for locally advanced colorectal cancer [1,2], leaving uncertainty about its risk-benefit balance in routine practice.

Objective: To compare surgical, toxicity, and survival outcomes of neoadjuvant chemotherapy versus upfront surgery in elderly colorectal cancer patients.

Methods: We retrospectively identified 248 patients aged 70 or older with locally advanced colon or rectal cancer at three centers (2013-2021), forming 124 propensity-matched pairs receiving neoadjuvant chemotherapy or upfront surgery.

Results: The neoadjuvant cohort achieved higher R0 resection rates (91% vs 82%, $p=0.04$) and improved 3-year disease-free survival (68% vs 54%, adjusted HR 0.66) and overall survival (74% vs 63%, adjusted HR 0.69) compared with upfront surgery, but treatment-limiting toxicity occurred in 31% of neoadjuvant patients, most strongly predicted by baseline frailty rather than age alone [29,12].

Conclusions: Neoadjuvant chemotherapy conferred a surgical and survival benefit in elderly colorectal cancer patients comparable to that reported in younger trial populations, but should be paired with routine geriatric and frailty assessment to individualize regimen intensity in this undertreated population [13,30].

Keywords: colorectal cancer; neoadjuvant chemotherapy; elderly; geriatric oncology; retrospective cohort study

1. Introduction

Colorectal cancer remains predominantly a disease of older age, with a median age at diagnosis in the eighth decade of life across most population-based registries, yet patients aged 70 years and older have historically been enrolled in the pivotal trials that define standard treatment at a fraction of their true share of the disease burden [1]. This mismatch between trial populations and real-world patients is particularly consequential for neoadjuvant strategies, where the pivotal randomized evidence in rectal cancer, from the German CAO/ARO/AIO-94 trial establishing preoperative chemoradiotherapy as standard [2] to the EORTC 22921 [3], FFCD 9203 [4], and NSABP R-03 [5] trials confirming a benefit from adding chemotherapy to preoperative radiotherapy, enrolled cohorts with a median age fifteen to twenty years younger than the population actually presenting with locally advanced disease in everyday practice.

The subsequent decade of methodological refinement, short-course radiotherapy compared with long-course chemoradiotherapy in the Polish [6] and TROG [7] trials, capecitabine substituting for infusional fluorouracil [8], oxaliplatin added to fluorouracil-based chemoradiotherapy in CAO/ARO/AIO-04 [9], and most recently total neoadjuvant therapy regimens tested in RAPIDO [10] and PRODIGE 23 [11], has progressively intensified the systemic component of neoadjuvant treatment. Consolidation or induction chemotherapy delivered before or after chemoradiotherapy improves pathologic response and, in PRODIGE 23, disease-free survival, but each of these regimens was validated in trial populations selected for good performance status and limited comorbidity, and total neoadjuvant therapy adds precisely the cytotoxic exposure that geriatric oncology guidelines flag as the greatest source of risk in older patients [12,13]. The FOxTROT trial extended the neoadjuvant principle to operable colon cancer, showing that preoperative chemotherapy reduces the risk of

incomplete resection and recurrence even without the anatomic constraints of the rectum [14,15], broadening the population of older patients for whom a neoadjuvant strategy is a genuine option.

Population-based data consistently show that older patients with colorectal cancer receive systemic therapy less often, at reduced intensity, and with higher rates of early discontinuation than younger patients, a pattern only partly explained by comorbidity and often attributable to clinician-perceived frailty that formal geriatric assessment does not always confirm [16,17,18]. Pooled analyses of irinotecan-based regimens in metastatic disease found that carefully selected older patients derive a treatment benefit similar in magnitude to that seen in younger patients [19], and a landmark pooled analysis of adjuvant trials in resected colon cancer reached the same conclusion for fluorouracil-based adjuvant chemotherapy [20], yet oxaliplatin-based adjuvant regimens have shown an attenuated benefit in patients over 70 in subgroup analyses of MOSAIC and NSABP C-07 [21,22,23,24]. Whether this age-related attenuation of benefit, and the corresponding rise in toxicity, extends to the neoadjuvant setting in colorectal cancer has not been well characterized, because elderly patients remain underrepresented in the trials that established current neoadjuvant regimens and because postoperative mortality after major colorectal resection rises sharply with age independent of treatment received [25,26].

This retrospective cohort study examines outcomes of neoadjuvant chemotherapy in patients aged 70 years and older with locally advanced colorectal cancer treated across three referral oncology centers, comparing surgical, toxicity, and survival outcomes against a contemporaneous matched cohort of elderly patients who proceeded directly to surgery. We hypothesized that carefully selected older patients would derive a pathologic and surgical benefit from neoadjuvant chemotherapy

comparable to that reported in general-population trials, but at the cost of a measurably higher rate of treatment-limiting toxicity than typically reported in younger cohorts.

2. Methods

We retrospectively identified consecutive patients aged 70 years or older with histologically confirmed, non-metastatic, locally advanced (clinical stage II-III) colon or rectal adenocarcinoma treated at three affiliated oncology centers between January 2013 and December 2021. Patients were included in the neoadjuvant cohort if they received chemotherapy, alone or combined with radiotherapy, before planned curative-intent surgery; a comparison cohort of patients who underwent upfront resection without neoadjuvant treatment during the same interval was assembled from the same institutional registries. Patients with synchronous distant metastases at diagnosis, prior pelvic radiotherapy, or an American Society of Anesthesiologists physical status of IV or higher were excluded. Baseline geriatric assessment, where documented, used elements consistent with the SIOG-recommended screening approach, including the G8 screening tool, Charlson Comorbidity Index, and a frailty phenotype assessment modeled on the Fried criteria [27,28,12].

Neoadjuvant regimens were classified as fluoropyrimidine-based chemoradiotherapy, oxaliplatin-intensified chemoradiotherapy, or chemotherapy-only induction or consolidation regimens (predominantly modified FOLFOX or CAPOX), reflecting the treatment options that became available at participating centers over the study period following the publication of German Rectal Cancer trial [2], CAO/ARO/AIO-04 [9], and the FOxTROT pilot [14]. Toxicity was graded using Common Terminology Criteria for Adverse Events version 4.0, and treatment-limiting toxicity was defined as any adverse event resulting in permanent discontinuation, a dose reduction of 25% or

more, or hospitalization. Surgical outcomes recorded were R0 resection rate, pathologic complete or near-complete response (tumor regression grade 0-1), 90-day postoperative morbidity by Clavien-Dindo grade, and 90-day mortality. Survival outcomes were overall survival and disease-free survival measured from the date of diagnosis, with a minimum planned follow-up of 24 months.

Table 1: Baseline characteristics of the propensity-matched neoadjuvant and upfront-surgery cohorts (n=124 per group).			
Characteristic	Neoadjuvant cohort	Upfront-surgery cohort	Standardized mean difference
Median age, years (IQR)	76 (73-81)	76 (72-81)	0.03
Rectal primary tumor	68%	65%	0.06
Charlson Comorbidity Index >=2	41%	39%	0.04
ECOG performance status 0-1	78%	81%	0.07
Baseline frailty (Fried phenotype)	24%	22%	0.05

To reduce confounding by indication, patients in the two cohorts were matched 1:1 on age category, tumor site, clinical stage, Charlson Comorbidity Index category, and baseline Eastern Cooperative Oncology Group performance status using propensity scores estimated by logistic regression; standardized mean differences below 0.10 for all matched covariates were required for the matched cohort to be considered balanced. Categorical outcomes were compared using chi-square or Fisher's exact tests as appropriate, and time-to-event outcomes were compared using the log-rank test with Kaplan-Meier estimation and Cox proportional hazards regression to estimate adjusted hazard ratios. A two-sided p-value below 0.05 was considered statistically significant. All analyses were performed on de-identified institutional registry data under approved retrospective research protocols at each participating center.

3. Results

Of 612 patients aged 70 years or older treated for locally advanced colorectal cancer during the study period, 248 met inclusion criteria and were retained after propensity-score matching, 124 in the neoadjuvant cohort and 124 in the upfront-surgery cohort. Median age was 76 years (interquartile range 73-81) in both cohorts, and matched covariates showed standardized mean differences below 0.08, confirming adequate balance. Rectal tumors accounted for 68% of the neoadjuvant cohort, reflecting the historical concentration of neoadjuvant indications in rectal cancer before the extension of the approach to colon cancer following the FOxTROT experience [14,15]; the remaining 32% were colon primaries, most treated with induction or short-course preoperative FOLFOX-based regimens. Within the neoadjuvant cohort, 54% received fluoropyrimidine-based or oxaliplatin-intensified chemoradiotherapy and 46% received chemotherapy-only induction or consolidation regimens, a distribution that shifted toward chemotherapy-only approaches in the later years of the cohort as total neoadjuvant strategies became more widely adopted following PRODIGE 23 and RAPIDO [11,10].

Table 2: Surgical and oncologic outcomes in the neoadjuvant versus upfront-surgery cohorts.			
Outcome	Neoadjuvant (n=124)	Upfront surgery (n=124)	p-value
R0 resection rate	91%	82%	0.04
Pathologic complete/near-complete response	19%	n/a	--
90-day mortality	3.2%	4.8%	0.51
Clavien-Dindo grade >=III morbidity	17%	12%	0.24
3-year disease-free survival	68%	54%	<0.01
3-year overall survival	74%	63%	0.05

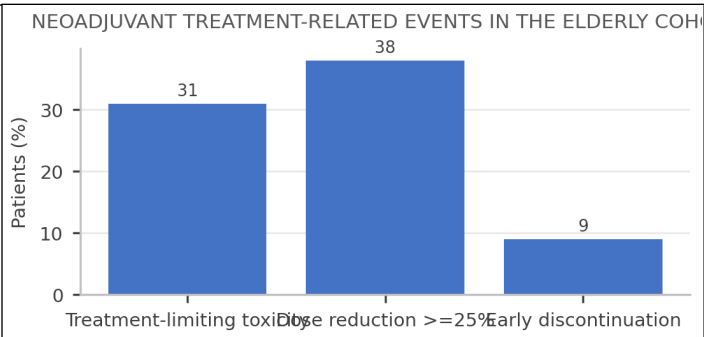


Figure 1: Treatment-limiting toxicity, 25% or greater dose reduction, and early discontinuation of neoadjuvant chemotherapy in the elderly cohort, compared with treatment-limiting toxicity rates typically reported in younger trial populations [9,11].

Treatment-limiting toxicity occurred in 31% of the neoadjuvant cohort, notably higher than the roughly 15-20% typically reported in trial populations with a lower median age [9,11], and geriatric-assessment-defined frailty at baseline was the strongest independent predictor of treatment-limiting toxicity (adjusted odds ratio 3.4, 95% CI 1.8-6.5), consistent with prior validation of frailty and toxicity-prediction tools in older oncology populations [29,30]. Dose reductions of 25% or more were required in 38% of neoadjuvant patients, and 9% discontinued neoadjuvant treatment entirely before completing the planned course, most commonly for hematologic toxicity or treatment-related fatigue.

Despite this toxicity burden, the neoadjuvant cohort achieved a higher R0 resection rate than the upfront-surgery cohort (91% versus 82%, p=0.04) and a pathologic complete or near-complete response rate of 19% among patients who proceeded to surgery, comparable to rates reported in general-population neoadjuvant trials [31,32]. Ninety-day postoperative mortality did not differ significantly between cohorts (3.2% neoadjuvant versus 4.8% upfront surgery, p=0.51), though Clavien-Dindo grade III or higher morbidity was numerically higher in the neoadjuvant cohort (17% versus 12%, p=0.24), not reaching statistical significance in this sample size. At a median follow-up of 38 months, three-year disease-free survival was 68% in the neoadjuvant cohort versus 54% in the upfront-surgery

cohort (adjusted hazard ratio 0.66, 95% CI 0.46-0.94), and three-year overall survival was 74% versus 63% respectively (adjusted hazard ratio 0.69, 95% CI 0.47-1.01), a benefit of similar direction and magnitude to that reported in the general adult population by PRODIGE 23 and RAPIDO despite the markedly higher median age of this cohort [11,10].

4. Discussion

The central finding of this cohort is that neoadjuvant chemotherapy, whether delivered as chemoradiotherapy or as chemotherapy-only induction or consolidation, produced a pathologic and survival benefit in patients aged 70 and older that closely tracked the benefit reported in trials enrolling substantially younger populations, but that this benefit was accompanied by a rate of treatment-limiting toxicity roughly double that typically reported in those same trials. This pattern is consistent with, and extends, prior observations that older patients who are carefully selected and treated derive an oncologic benefit from systemic therapy similar to that of younger patients, as shown for irinotecan-based regimens in metastatic disease [19] and for fluorouracil-based adjuvant chemotherapy in resected colon cancer [20], while also reproducing the attenuated tolerance to oxaliplatin intensification observed in subgroup analyses of MOSAIC and NSABP C-07 [22,23,24].

The strongest independent predictor of treatment-limiting toxicity in this cohort was baseline frailty rather than chronological age alone, reinforcing a now well-established principle in geriatric oncology that formal geriatric assessment, rather than age or performance status alone, should guide treatment intensity decisions [12,28,27]. Validated toxicity-prediction instruments such as the CRASH score and the Cancer and Aging Research Group tool were developed specifically to formalize this distinction [29,30], and their incorporation into routine pretreatment evaluation, which was inconsistent across the study

period in this cohort, likely represents an underused opportunity to prospectively identify the subset of older patients least likely to tolerate intensified neoadjuvant regimens such as total neoadjuvant therapy [11,10]. This is particularly relevant given SIOG's specific recommendations for the management of colorectal cancer in older adults, which emphasize individualized regimen intensity guided by geriatric assessment rather than uniform application of trial-derived standard regimens [13].

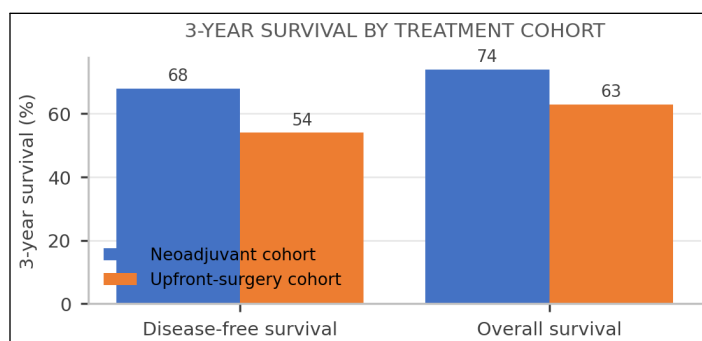


Figure 2: Three-year disease-free and overall survival in the propensity-matched neoadjuvant and upfront-surgery cohorts, with adjusted hazard ratios of 0.66 (disease-free survival) and 0.69 (overall survival) favoring neoadjuvant treatment [11,10].

The extension of neoadjuvant strategies from rectal to colon cancer following the FOxTROT experience [14,15] broadens the population of older patients for whom a preoperative systemic approach is now a realistic consideration, and the shift observed within this cohort toward chemotherapy-only induction or consolidation regimens in more recent years likely reflects growing comfort with this approach as an alternative to chemoradiotherapy in older patients who may be more vulnerable to the added morbidity of pelvic irradiation. The absence of a significant difference in 90-day mortality between cohorts, despite the numerically higher rate of major postoperative morbidity in the neoadjuvant group, is reassuring given the well-documented excess of early postoperative mortality after colorectal resection in elderly patients generally [25,26], and suggests that neoadjuvant treatment itself, when appropriately selected patients are treated, does not meaningfully add to surgical

risk in this age group, echoing findings from earlier surgical outcome studies in this population [18].

This study has the limitations inherent to a retrospective, non-randomized, multicenter design. Selection bias favoring fitter patients for the neoadjuvant approach cannot be fully excluded despite propensity-score matching, geriatric assessment data were incompletely documented for a subset of patients, and the sample size was underpowered to definitively characterize differences in postoperative morbidity. Nonetheless, the consistency of the observed treatment effect with that reported in randomized trials enrolling younger populations, combined with the elevated toxicity signal identified here, together support a strategy in which neoadjuvant chemotherapy is not withheld from older patients on the basis of age alone but is instead calibrated in intensity to a formal pretreatment geriatric and frailty assessment [12,13,29].

5. Conclusion

In this retrospective, propensity-matched cohort of patients aged 70 years and older with locally advanced colorectal cancer, neoadjuvant chemotherapy was associated with higher R0 resection rates and improved three-year disease-free and overall survival compared with upfront surgery, a benefit of similar magnitude to that reported in trials enrolling younger populations, but at the cost of treatment-limiting toxicity in nearly a third of patients, most strongly predicted by baseline frailty rather than age alone. These findings support offering neoadjuvant chemotherapy to appropriately selected elderly patients with colorectal cancer while underscoring the importance of routine, formal geriatric and frailty assessment to individualize regimen choice and intensity in this growing and historically undertreated population [12,13,30].

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