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Comparative Effectiveness of Neoadjuvant Chemotherapy in Locally Advanced Colon Cancer: Evidence from A Propensity Score–Matched Cohort

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ABSTRACT

Neoadjuvant chemotherapy (NAC) has shown value in managing locally advanced colon cancer (LACC). The National Comprehensive Cancer Network lists it as a therapeutic choice for patients with clinical T4b colon cancer. Yet, the long-term survival gains from NAC in LACC remain contested because conclusive clinical trial evidence pinpointing which patients derive the greatest benefit is lacking. The present study set out to determine the effectiveness of NAC in LACC patients, stratified by histological subtype. This retrospective analysis included 3,709 LACC patients who underwent curative resection at Harbin Medical University Cancer Hospital from 2014 through 2018. The cohort was divided into two arms: one receiving neoadjuvant chemotherapy (NAC) and the other adjuvant chemotherapy (AC). Propensity score matching (PSM) was used to balance confounding variables, and survival differences between the two arms across distinct histological subtypes were assessed using Kaplan-Meier (K-M) curves and log-rank testing. Among individuals with non-mucinous adenocarcinoma (NMAC), those managed with NAC achieved markedly superior 5-year OS (76.3% vs. 69.2%, P = .039) and DFS (67.2% vs. 60.1%, P = .041) rates compared with those who received AC. Conversely, within the mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRCC) subgroups, overall survival and disease-free survival did not differ significantly between the two treatment modalities. The prognostic utility of NAC in LACC patients was histology-dependent. NMAC may stand as a marker for enhanced long-term survival following NAC in this population.

Keywords: Colectomy, Colon cancer, Neoadjuvant chemotherapy, Survival

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Introduction

Colon cancer (CC) stands as the third most frequently diagnosed malignancy and the second highest contributor to cancer-related deaths across the globe [1]. Roughly one quarter of those diagnosed present with locally advanced colon cancer (LACC) in the absence of distant spread [1, 2]. LACC encompasses high-risk T3 lesions (extending ≥ 5 mm beyond the muscularis propria) and T4 tumors, with or without lymph node involvement. At present, complete surgical excision followed by adjuvant chemotherapy (AC) constitutes the benchmark treatment for LACC [3]. Despite deploying this aggressive, curative-intent strategy, patient outcomes remain disappointing; recurrence rates range from 20 to 30%, highlighting the relative shortfall of this approach in clearing micrometastatic tumor deposits [4]. Hence, there is a pressing demand to identify an alternative therapeutic route for the LACC population.

Over recent years, NAC has steadily gained acceptance as a standard regimen for solid tumors such as breast, esophageal, gastric, and rectal cancers [5-8]. Relative to AC, NAC—delivered preoperatively—can actively promote tumor shrinkage, downsize the lesion, and optimize resection margins, thereby raising the chance of an R0 resection [9]. A further proposed advantage of preoperative NAC is its capacity to lessen intraoperative tumor cell dissemination and to address small, subclinical metastases through earlier systemic exposure, potentially cutting recurrence risk [10]. Additionally, a subset of patients may be prevented from completing their planned adjuvant therapy due to serious postsurgical complications. Under these circumstances, a neoadjuvant strategy enables in vivo assessment of tumor chemosensitivity before surgery, thereby informing more accurate subsequent treatment planning. Consequently, the rate of patients who initiate and complete NAC is generally higher than that observed for postoperative adjuvant chemotherapy.

Although NAC is firmly entrenched and widely used across most gastrointestinal malignancies, its role in non-metastatic LACC remains debated. Several contemporary studies have reported on the practicability and effectiveness of NAC in this setting [11-14]. These works revealed substantial histological tumor regression alongside manageable toxicity and low perioperative complication rates when LACC patients are treated with NAC. That said, most investigations have centered on short-term surgical recovery metrics and resection quality in these patients. To date, evidence concerning the effect of NAC on long-term outcomes in LACC remains scarce. In a retrospective evaluation of 2,146 patients with T4 CC, de Gooyer *et al*. [9] found no meaningful difference in 5-year OS between NAC recipients and controls. Likewise, several publicly accessible randomized controlled trials, including the FOXTROT and PRODIGE22 studies, failed to demonstrate long-term oncologic benefits of NAC in LACC patients [15, 16]. The literature suggests that patients with differing phenotypic and biological profiles may exhibit varied chemotherapy sensitivities [9, 17, 18]. A rational approach to boosting NAC efficacy is to forecast drug responsiveness. Histological classification is a key parameter for assessing tumor onset, progression, and outcome. Distinct histological types differ in growth kinetics and invasive potential, and they play a critical role in tailoring individualized treatment plans across tumor streams. For instance, chemotherapy backbones are histology-specific in urinary tract cancers: carboplatin/cyclophosphamide is preferred for carcinosarcoma, paclitaxel/cisplatin for clear cell carcinoma, and paclitaxel/carboplatin for malignant stromal tumors [19-21]. Given the biological and clinicopathologic disparities among histological subtypes, examining whether histologic classification modifies the impact of NAC in LACC is a worthwhile avenue of inquiry.

Accordingly, we conducted this population-based investigation to explore how NAC influences long-term survival in LACC patients, stratified by histological type.

Materials and Methods

Cohort selection

Between January 2014 and December 2018, a total of 4,436 individuals diagnosed with locally advanced colon cancer (LACC) and treated with colectomy at Harbin Medical University Cancer Hospital were identified for retrospective data collection **(Figure 1).** Staging definitions followed the colorectal cancer TNM system issued by the American Cancer Society in its eighth edition. The Institutional Review Committee of Harbin Medical University Cancer Hospital provided ethical clearance (Ethics number: 2023–150), and every participant signed a written informed consent form.

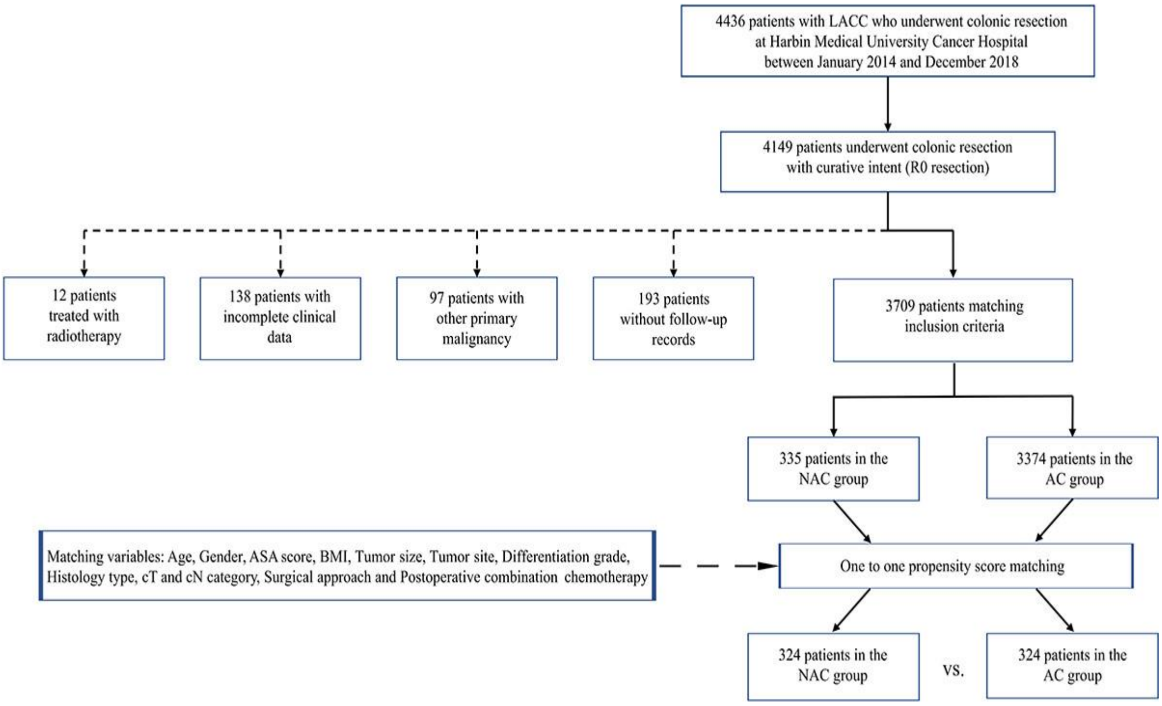


Figure 1. Flowchart of patient selection.

A set of inclusion and exclusion benchmarks governed enrollment. To qualify, patients had to be aged 18 or older, carry a pathology-verified LACC diagnosis, show no detectable distant metastasis, have undergone an R0 curative resection, and possess complete clinicopathological information alongside cancer-specific survival records. Grounds for exclusion included prior radiotherapy treatment, occurrence of major perioperative adverse events, and a background of any other primary malignancy. Based on the sequencing of chemotherapy and surgery, the cohort was divided into two arms: the NAC arm, in which chemotherapy was administered before surgery, and the AC arm, in which chemotherapy was administered after surgery.

Application of these criteria yielded 3,709 LACC patients for the retrospective analysis—335 in the NAC arm and 3,374 in the AC arm **(Figure 1).** The 727 individuals removed from consideration were excluded for the following reasons: 287 did not achieve an R0 resection, 193 had no available follow-up documentation, 97 harbored a separate primary cancer diagnosis, 138 had gaps in clinical records, and 12 had a history of radiotherapy.

Study variables

Data extraction captured the following elements: age, sex, American Society of Anesthesiologists (ASA) score, body mass index (BMI), anatomical site of the tumor, tumor size, degree of differentiation, morphological type, clinical T category (cT), clinical N category (cN), surgical modality, and postoperative chemotherapy approach.

For analysis, age was stratified into two brackets: ≤ 65 and > 65. Sex was recorded as either male or female. The ASA score was collapsed into < 3 and ≥ 3 categories. Anatomical site was designated as left colon (encompassing the colonic splenic flexure, descending colon, and sigmoid colon) or right colon (covering the ascending colon and colonic hepatic flexure). Tumor size was divided into lesions < 5 cm and those ≥ 5 cm. The grade of differentiation was grouped as "well/moderate" or "poor/undifferentiated". Morphological classification sorted cases into "non-mucinous adenocarcinoma (NMAC)", "mucinous adenocarcinoma (MAC)", and "signet ring cell carcinoma (SRCC)". Surgical modality was noted as either an "open" or "laparoscopic" technique. Postoperative chemotherapy was designated as "single-agent chemotherapy" or "combination chemotherapy".

Chemotherapeutic regimen

Participants assigned to the NAC arm received a preoperative course of at least four cycles of the XELOX protocol. In contrast, those in the AC arm received postoperative treatment with either the XELOX protocol or single-agent capecitabine. The XELOX backbone pairs capecitabine with oxaliplatin. Over each cycle, oral capecitabine was taken for 14 days, with intravenous oxaliplatin given once, on Day 1. The oxaliplatin dose was fixed at 130 mg/m² on Day 1 of each cycle; capecitabine was administered at 1,250 mg/m², split into two daily doses, taken twice daily over the 14-day cycle. When used as monotherapy, capecitabine was dosed orally at 1,250 mg/m² twice daily for five consecutive days, with a subsequent 2-day interval off treatment, together forming one full cycle. The entire treatment span was set at 6 months. Every individual included in this analysis completed the prescribed chemotherapy course.

Outcomes and follow-up

Overall survival (OS), the primary endpoint, was defined as the time from initial diagnosis to death from any cause. The secondary endpoint, disease-free survival (DFS), measured the time from diagnosis to the first occurrence of locoregional relapse, distant metastasis, a second primary tumor, or death from any cause.

Surveillance protocols mandated that all patients undergo evaluation of tumor markers (CEA, CA19–9, CA125, and CA242) in conjunction with clinical assessments. These were scheduled at 3-month intervals throughout the first 3 years and shifted to 6-month intervals during years 4 and 5. Abdominopelvic computed tomography scans were repeated biannually, while colonoscopy was performed once annually. The final follow-up milestone was reached in September 2023.

Statistical analysis

Continuous data were reported as medians with corresponding interquartile ranges (IQR); categorical data were presented as raw counts with percentages. Comparisons of baseline clinicopathological features between subgroups used the two-sample t-test, the χ^2 test, or Fisher's exact test, depending on variable type. Because treatment assignment was not randomized, propensity score matching (PSM) was applied afterward to lessen the influence of potential confounders. The matching procedure accounted for every baseline characteristic that showed a meaningful association with whether a patient received NAC or AC, as well as all baseline variables that showed imbalance. The covariates fed into PSM included: age, sex, ASA score, BMI, tumor site, tumor size, differentiation grade, morphology, clinical T category, clinical N category, surgical approach, and postoperative combination chemotherapy. A 1:1 pairing was built using the 'nearest match' algorithm and a caliper width capped at 0.01. Upon completion of matching, the groups were rechecked to confirm the elimination of any lingering significant discrepancies. Standardized mean differences (SMD) were computed both pre- and post-matching to evaluate balance quality; values greater than 0.1 were considered indicative of residual confounding. The Kaplan-Meier (K-M) method was used to generate survival plots, and between-group contrasts within each histological type (NMAC, MAC, and SRCC) were performed using the log-rank test. In parallel, a landmark analysis, anchored at 6 months post-diagnosis, was undertaken to address immortal time bias. Those who could not be followed beyond the six-month mark or who died within that window were removed from the landmark subset. Two-tailed p-values below .05 were taken as the threshold for statistical significance. All analyses were run with SPSS version 27 (Statistical Package for Social Sciences) and the R environment (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results and Discussion

Patients

Screening yielded 3,709 eligible LACC cases, of which 335 constituted the NAC arm, and 3,374 formed the AC arm **(Figure 1).** The predominant factors motivating neoadjuvant therapy were a need to reduce tumor bulk to increase the likelihood of a microscopically complete excision (cT4b: 80/335, 23.88%) and the detection of multiple involved regional nodes (168/335, 50.15%). A full summary of the baseline and tumor-related attributes of the entire study population appears in **Table 1.** Marked disparities separated the two arms across patient demographics, tumor pathology, and treatment parameters.

Table 1. Baseline and tumor characteristics of the NAC group, compared to the AC group, raw and matched data.

	SMD	**P-value**	**AC (n = 324)**	**PSM adjusted data**			**Raw data**
				NAC (n = 324)	**P-value**	**AC (n = 3374)**	**NAC (n = 335)**
Age, n (%)	0.035	0.207			< 0.001		
≤ 65			212 (65.43)	227 (70.06)		1875 (55.57)	238 (71.04)

> 65			112 (34.57)	97 (29.94)		1499 (44.43)	97 (28.96)
Gender, n (%)	0.009	0.983			0.901		
Male			193 (59.57)	200 (61.73)		2053 (60.85)	205 (61.19)
Female			131 (40.43)	124 (38.27)		1321 (39.15)	130 (38.81)
ASA, n (%)	0.048	0.233			< 0.001		
< 3			239 (73.77)	252 (77.78)		2184 (64.73)	262 (78.21)
≥ 3			85 (26.23)	72 (22.22)		1190 (35.27)	73 (21.79)
BMI (kg/m2), median [IQR]	0.007	0.592	23.73 [20.58,26.35]	23.99 [21.22,26.91]	0.097	23.99 [20.90,27.06]	23.95 [21.22,26.88]
Tumor site, n (%)	0.010	0.625			< 0.001		
Left colon			202 (62.35)	208 (64.20)		1825 (54.09)	216 (64.48)
Right colon			122 (37.65)	116 (35.80)		1549 (45.91)	119 (35.52)
Tumor size, n (%)	0.003	0.931			0.003		
<5 cm			96 (29.63)	95 (29.32)		1534 (45.47)	124 (37.01)
≥5 cm			228 (70.37)	229 (70.68)		1840 (54.53)	211 (62.99)
Differentiation grade, n (%)	0.027	0.517			0.642		
Well/moderate			251 (77.47)	244 (75.31)		2509 (74.36)	253 (75.52)
Poor/undifferentiated			73 (22.53)	80 (24.69)		865 (25.64)	82 (24.48)
Histology type, n (%)	0.026	0.404			0.021		
NMAC			287 (88.58)	290 (89.51)		3149 (93.33)	299 (89.25)
MAC			15 (4.63)	19 (5.86)		129 (3.82)	21 (6.29)
SRCC			22 (6.79)	15 (4.63)		96 (2.85)	15 (4.48)
Clinical T category, n (%)	0.019	0.207			< 0.001		
cT3b			184 (56.79)	193 (59.57)		2712 (80.38)	194 (53.91)
cT4a			79 (24.38)	61 (18.83)		492 (14.58)	61 (18.21)
cT4b			61 (18.83)	70 (21.60)		170 (5.04)	80 (23.88)
Clinical N category, n (%)	0.012	0.507			0.614		
cN0			149 (45.99)	162 (50.00)		1711 (50.71)	167 (49.85)
cN1			110 (33.95)	97 (29.94)		1041 (30.85)	99 (29.55)
cN2			65 (20.06)	65 (20.06)		622 (18.44)	69 (20.60)
Surgical approach, n (%)	0.105	0.052			< 0.001		
Open			282 (87.04)	264 (81.48)		2264 (67.10)	271 (80.90)
Laparoscopic			42 (12.96)	60 (18.52)		1110 (32.90)	64 (19.10)
Postoperative combination chemotherapy	0.038	0.529			< 0.001		
No			33 (10.19)	38 (11.73)		881 (26.11)	38 (11.34)
Yes			291 (89.81)	286 (88.27)		2493 (73.89)	297 (88.66)

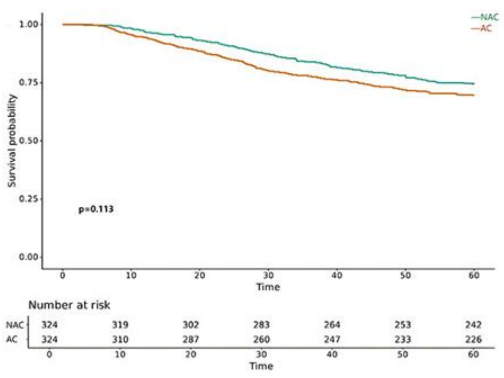
Abbreviations: ASA = American Society of Anesthesiologists physical status classification system; AD = adenocarcinoma; BMI = body mass index; IQR, interquartile range; MAC = mucinous carcinoma; PSM = propensity score-matching; SRCC = signet ring cell carcinoma.

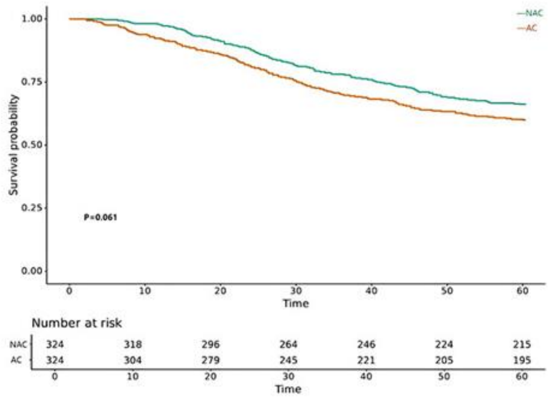
Regarding demographics, members of the NAC arm had a younger age distribution (71.04% vs. 55.57%, P < .001) and were more likely to have an ASA classification of 2 or lower (78.21% vs. 64.73%, P < .001). With respect to tumor-related variables, both cT4b status (23.88% vs. 5.04%, P < .001) and a left-colon location (64.48% vs. 54.09%, P < .001) appeared with disproportionate frequency in the NAC arm. Meanwhile, NMAC histology was encountered less often in the NAC arm than in the AC arm (89.25% vs. 93.33%, P = .021), whereas tumors of larger dimensions were more prevalent (62.99% vs. 54.53%, P = .003). The therapeutic data revealed an analogous pattern: open surgical procedures were more commonly performed in the NAC arm (80.90% vs. 67.10%, P < .001), and postoperative use of combination regimens was likewise higher (88.66% vs. 73.89%, P < .001).

After running PSM on age, sex, ASA score, BMI, tumor site, tumor size, differentiation grade, histology, cT, cN, surgical approach, and postoperative combination chemotherapy, 11 patients from the NAC side and 3,050 from the AC side were discarded due to the absence of a counterpart within the prespecified 0.01 caliper. What remained were 324 matched pairs; no statistically significant differences in baseline characteristics survived matching, and the SMD for the overwhelming majority of variables fell beneath 0.1—clear evidence of robust intergroup balance **(Table 1).**

Survival outcomes in the matched cohort

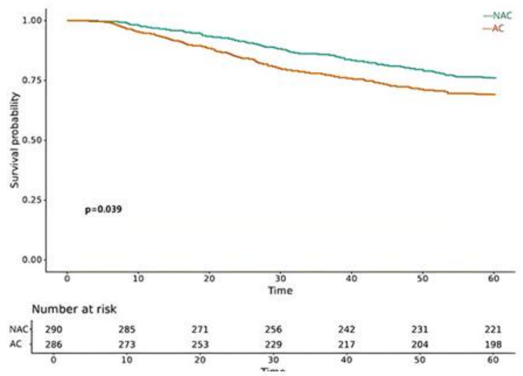
Follow-up extended for a median of 57 months (range 4–105). Across all matched subjects, the estimated 5-year OS and DFS rates were 72.2% and 63.3%, respectively. The K-M curves post-PSM are displayed in **Figure 2.** No statistically meaningful separation emerged for either OS (74.7% vs. 69.8%, P = .113) **(Figure 2a)** or DFS (66.4% vs. 60.2%, P = .061) **(Figure 2b)** when the two arms were compared in aggregate. Splitting the cohort by histological subtype, however, disclosed a divergent picture. Among NMAC patients, those exposed to NAC attained a statistically superior 5-year OS relative to AC recipients (76.3% vs. 69.2%, P = .039) **(Figure 3a),** alongside a significantly better 5-year DFS (67.2% vs. 60.1%, P = .041) **(Figure 4a).** Within the MAC/SRCC subgroup, in contrast, neither 5-year OS (61.8% vs. 73.7%, P = .320) nor 5-year DFS (58.8% vs. 60.5%, P = .822) differed to a degree that reached statistical significance **(Figures 3b and 4b).**

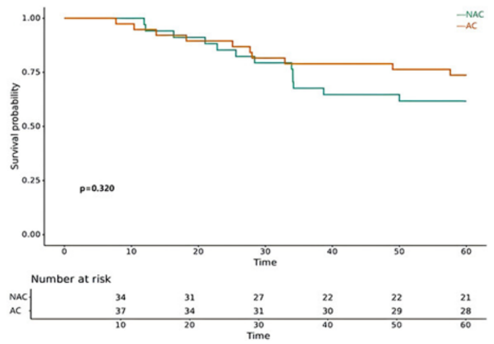




a) b)

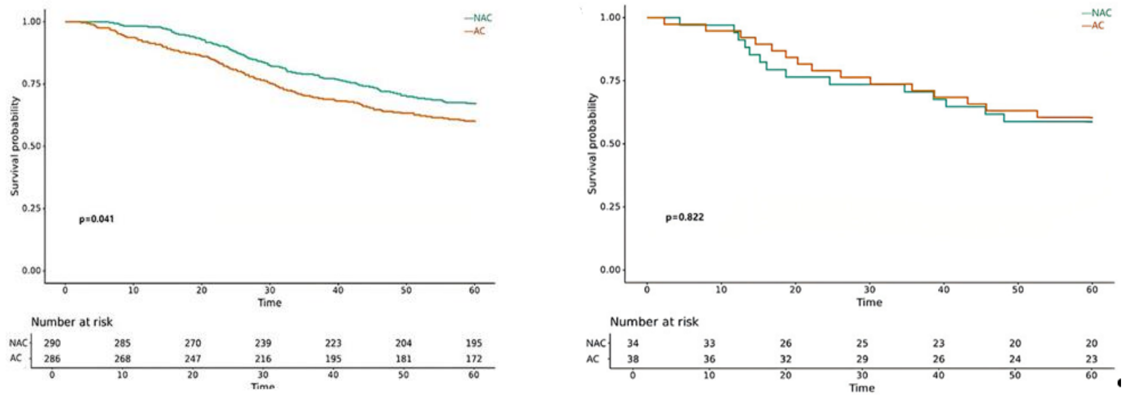
Figure 2. The OS and DFS in LACC patients with or without NAC: (a) Kaplan-Meier curve for OS stratified by NAC, and (b) Kaplan-Meier curve for disease-free survival stratified by NAC.





a) b)

Figure 3. Kaplan-Meier analysis comparing OS (p value is for 5-year OS) of the NAC group and AC group by histological types: (a) NMAC, and (b) MAC/SRCC.

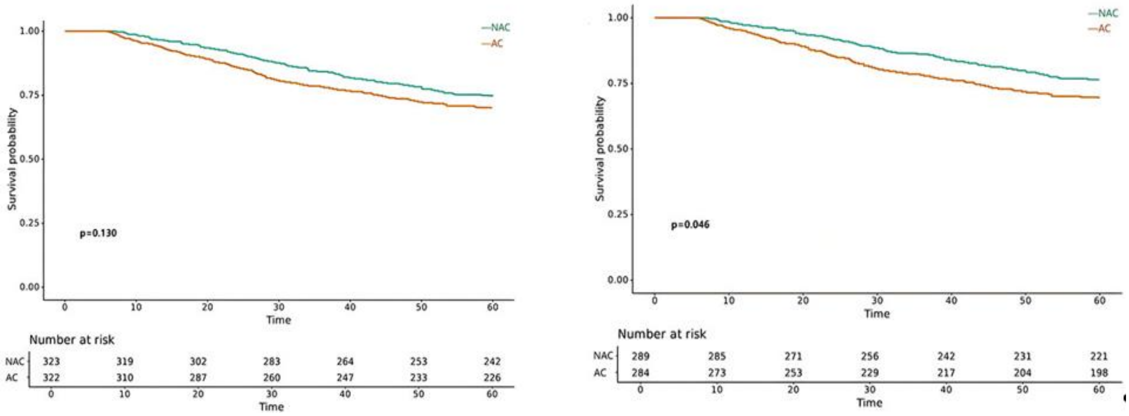


a) b)

Figure 4. Kaplan-Meier analysis comparing DFS (p value is for 5-year DFS) of the NAC group and AC group by histological types: (a) NMAC, and (b) MAC/SRCC.

Landmark analysis

Figure 5 presents the K-M–based OS comparisons from the landmark analysis. Here too, no significant intergroup difference was detected across the board (5-year OS: 74.9% vs. 70.2%, P = .130) **(Figure 5a).** Consistent with prior observations, restricting the analysis to NMAC histology revealed a survival advantage with NAC, with 5-year OS reaching 76.5% compared with 69.7% in the AC arm (P = .046) **(Figure 5b).**



a) b)

Figure 5. Kaplan-Meier analysis comparing OS (p value is for 5-year DFS) of the NAC group and AC group by histological types in the landmark cohort: (a) LACC and (b) NMAC.

To our knowledge, no prior study has examined whether the long-term consequences of NAC in LACC differ by histologic subtype. Our data show that NMAC patients who received NAC achieved statistically significant gains in both 5-year OS and DFS compared with those treated solely with AC. For the MAC and SRCC subgroups, however, the two chemotherapeutic approaches produced 5-year OS and DFS figures that were essentially superimposable, with no detectable statistical separation.

The survival-promoting properties of NAC have been convincingly shown across a spectrum of solid tumors, and the approach has been woven into the multidisciplinary care paradigm for several advanced gastrointestinal diseases—most notably esophageal, gastric, and rectal cancers [6-8]. Despite this, NAC has yet to become a standard offering for non-metastatic LACC. Earlier work has repeatedly affirmed that NAC is both safe and workable in the LACC population. Yet the existing body of evidence, including randomized controlled trials, has largely failed to demonstrate that NAC materially alters long-term oncologic endpoints in this disease [18, 22-24]. A central difficulty lies in the lack of a widely accepted framework for identifying which patient subsets stand to gain the most from this strategy.

Within the comparatively sparse literature on NAC, some signals have emerged suggesting that CCs under different molecular banners do not respond uniformly. Dehal *et al.* [18] recently reported survival divergence associated with NAC, restricted to T4b-stage disease (HR 0.77, 95% CI 0.60–0.98; p = .04), with no comparable effect observed for T3 or T4a tumors. Findings consistent with this pattern were also reported by McCahill *et al*. [25] and Smith *et al*. [26]. Their collective work advanced the view that NAC is a potentially valuable option for T4b CC, a position that aligns with the National Comprehensive Cancer Network (NCCN) guidance [27]. Adding another layer, a Danish phase II randomized controlled study and the British FOxTROT trial independently uncovered evidence that both the prevalence of BRAF alterations and microsatellite instability (MSI) status may modulate chemoresponsiveness in CC and introduce interpretative pitfalls into survival analyses [23, 24]. Given these signals, incorporating molecular subtype considerations into the NAC decision-making process for CC appears warranted.

Histologic type, widely recognized as a powerful prognostic marker, is instrumental in the construction of individualized treatment regimens for a broad array of malignancies. Within CC, however, apart from the well-characterized connection between SRCC and both an adverse prognosis and attenuated treatment response, histologic classification exerts only a modest influence on therapeutic choices. From a histopathologic standpoint, NMAC—characterized by its glandular morphology—accounts for upwards of 90% of CC cases [28]. The World Health Organization (WHO) classification scheme further categorizes CC into additional histologic variants, including mucinous, signet ring cell, spindle cell, and undifferentiated forms. MAC, a rare and biologically distinct colonic adenocarcinoma variant, is estimated to constitute between 5% and 10% of all primary CC diagnoses [29, 30]. Per WHO criteria, MAC is diagnosed when "a substantial amount of mucin (more than 50% of the tumor) is retained within the tumor" [31]. This entity is separate from SRCC, in which copious intracytoplasmic mucin crowds the nucleus to one side, with classic signet ring morphology present in over half of the neoplastic cells [32]. A robust body of work has documented that the assorted histologic subtypes of CC pursue distinct biologic courses and lead to divergent clinical outcomes. Comparative analyses have revealed that MAC, relative to NMAC, is diagnosed more often in younger women and is associated with advanced stage at detection, proximal colonic location, high-frequency microsatellite instability (MSI-H), and BRAF mutation positivity [33, 34]. MAC is also more strongly associated with lymph node involvement and peritoneal seeding [35]. SRCC, for its part, diverges sharply from NMAC on multiple clinicopathologic axes—older age at diagnosis, inferior differentiation, higher stage, and a more pronounced tendency for lymphatic and nodal permeation [32]. Because the major NAC trials in CC have not yet stratified treatment allocation by histologic subtype, whether histology should guide NAC administration remains an open question. Prompted by this knowledge gap, we conducted the largest population-based evaluation to date, specifically aimed at clarifying the long-term efficacy of NAC in LACC by histologic type.

The interplay between histology and AC effectiveness in LACC has, in fact, already drawn scientific attention. Catalano *et al*. [33], in a retrospective series of 1,025 individuals with stage II/III CC, reported that SRCC proved less susceptible to chemotherapy than NMAC [35]. A similar conclusion was reached more recently by Jiang *et al*. [32]. Moreover, investigators from Tongde Hospital of Zhejiang Province furnished evidence that MAC, too, responds less robustly to AC than NMAC among stage III CC patients [34]. Their multivariate Cox modeling revealed that, within the NMAC group, chemotherapy independently corresponded to a 46.0% drop in the hazard of colon cancer-specific death relative to no chemotherapy; for MAC, the magnitude of this reduction contracted to 37.7%. These observations align with several earlier reports [36, 37]. Our study found that NMAC was more vulnerable to NAC than MAC and SRCC in the LACC setting. K-M curves showed that NMAC patients who underwent NAC had a significantly better long-term prognosis than those who did not. By contrast, within the MAC and SRCC subsets, the OS and DFS trajectories of NAC recipients closely tracked those of NAC non-recipients, and the survival differences did not cross the threshold for statistical significance. One biologically plausible explanation for the blunted NAC responsiveness in MAC and SRCC involves a comparatively oxygen-poor microenvironment arising from diminished vascular supply. Histopathologic investigations have demonstrated that both MAC and SRCC exhibit lower microvessel density than NMAC. This feature may undermine drug sensitivity by restricting the delivery of cytotoxic agents via the tumor microcirculation [38].

Evidence from multiple investigations indicates that MAC itself is not a uniform entity but rather comprises distinct subtypes defined by underlying molecular alterations. Liu *et al*. [39] stratified MAC by MSI status. They reported that MSI-high MACs tended to present as low-stage tumors, had a favorable prognosis, and showed heightened sensitivity to chemotherapy [39]. In a related vein, recent work has tied mucinous histology to a specific CC subgroup characterized by aberrant DNA hypermethylation, designated as the CpG island methylation phenotype (CIMP) [40]. That study found no clinical benefit of 5-FU–based adjuvant chemotherapy in CIMPpositive individuals. Synthesizing these observations, we conclude that any rigorous effort to delineate the prognostic significance of NAC in MAC patients must also account for molecular features, such as MSI and CIMP status. Regrettably, the modest number of MAC/SRCC cases in the present cohort precluded meaningful subgroup dissection, underscoring the need for subsequent evaluation within a substantially expanded dataset.

Several strengths distinguish the present work. First, PSM was applied to attenuate confounding, yielding closely aligned baseline profiles between the NAC and AC arms and thereby improving comparability between the treatment and control groups. This design feature curbed confounding bias in the survival comparisons, bolstering the accuracy and trustworthiness of the estimates. Second, the population-based framework strengthens the external validity of the observations. Third, selecting OS as the primary endpoint circumvents the interpretive pitfalls that can accompany alternative outcome measures. Finally, the extended follow-up duration lends weight to the durability of our inferences.

Several limitations must also be acknowledged. First, the retrospective, observational architecture carries inherent constraints that may give rise to residual bias or unmeasured confounding. Second, by restricting the analytic sample to patients who achieved an R0 resection, we may have inadvertently introduced selection bias; future efforts would benefit from enrolling individuals across the full spectrum of resection completeness to more fully capture the long-term impact of neoadjuvant chemotherapy. Third, although age was dichotomized into ≤ 65 years and > 65 years to streamline the analysis, this simplification risks obscuring subtler age-related influences on treatment response that a more granular or continuous age treatment might reveal. Fourth, anchoring OS and DFS calculations to the date of diagnosis can, in principle, introduce immortal time bias. That said, the supplementary landmark analysis effectively mitigated this source of distortion, thereby improving the reliability and precision of the estimated treatment effect. Finally, the relatively sparse count of MAC/SRCC patients remaining after PSM constrains the breadth with which the statistical findings can be generalized.

Conclusion

Taken together, our data suggest that the prognostic utility of NAC in LACC patients depends on histological subtype. In particular, MAC and SRCC appear less chemosensitive to NAC than NMAC, and NMAC may emerge as a marker identifying LACC patients most likely to derive a long-term survival benefit from NAC. Large-scale prospective studies are warranted to determine whether histological subtype reliably predicts NAC efficacy in the LACC population.

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