Neoadjuvant Chemotherapy for Locally Advanced T4 Colon Cancer: A Nationwide Propensity-Score Matched Cohort Analysis

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Abstract

Introduction: Neoadjuvant chemotherapy (CT) for locally advanced colon cancer (LACC) could potentially lead to tumor shrinkage, eradication of micrometastases, and prevention of tumor cell shedding during surgery. This retrospective study investigates the surgical and oncological outcomes of preoperative CT for LACC. *Methods:* Using the Netherlands Cancer Registry, data of patients with stage II or III colon cancer, diagnosed between 2008 and 2016 was collected. A propensity score matching (PSM; 1:2) was performed and compared patients with clinical tumor (cT) 4 colon cancer who were treated with neoadjuvant CT to patients with cT4 colon cancer treated with adjuvant CT (Fig. 1). *Results:* A total of 192 patients treated with neoadjuvant CT were compared to 1,954 patients that received adjuvant CT. After PSM, 149 patients in the neoadjuvant group were compared to 298 patients in the control group. No significant differences were found in baseline characteristics after PSM. After neoadjuvant CT, a significant response was observed in 13 (9%) patients with 5 (4%) patients showing a complete response. Complete resection margins (R0) were achieved in 77% in the neoadjuvant group versus 86% in the adjuvant treated group (*p* = 0.037). Significantly less tumor positive lymph nodes were found in the neoadjuvant group (median 0 vs. 2, *p* < 0.001). Major complication rates and 5-year overall survival did not differ between both groups (67–65%, *p* = 0.87). *Conclusion:* Neoadjuvant CT seems safe and feasible with similar long-term survival compared to patients who are treated with adjuvant CT.

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Introduction

Colorectal cancer is the third most common type of cancer worldwide [1]. With >14,000 novel cases annually in the Netherlands, colorectal cancer can be held accountable for approximately 5,000 cancer deaths a year. About

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two-thirds of these patients present with colon cancer and approximately 15% of these patients present with locally advanced disease (i.e., T3 with ≥5 mm invasion beyond the muscularis propria or T4) without signs of distant metastases [2]. Current European guidelines recommend surgical resection of the primary tumor, followed by postoperative chemotherapy (CT) in case of high-risk stage II or III tumors [3]. This recommendation has been demonstrated to be effective in adenocarcinoma, but similar improved survival has recently been demonstrated in both mucinous and signet ring cell tumors [4, 5].

For locally advanced tumors located in the rectum, neoadjuvant chemoradiation is already well and widely established as the standard treatment protocol. Neoadjuvant CT is thought to enhance tumor regression and downsizing of the tumor, which improves tumor resectability and promotes higher rates of local control hence, achieve more R0 resections [6–9]. These benefits of neoadjuvant chemo (radio) therapy have also been proven for locally advanced breast cancer [10], gastric cancer [11], and esophageal cancer [12]. Another possible advantage of neoadjuvant therapy is the early eradication of systemic micrometastases, approximately 12 weeks earlier compared to CT administered postoperatively [13]. This could possibly prevent the occurrence of distant relapse and thus increase survival, particularly because resection of the primary tumor has shown to induce growth factor activity, which enhances growth of micrometastases [14–18]. Moreover, in case of neoadjuvant treatment, patients do not run the risk of suffering from postoperative complications which could lead to postponing or even omitting adjuvant CT. On the contrary, neoadjuvant CT does not always result in a response, and disease progression could occur during treatment. Progression could lead to obstruction and the need for emergency surgery, which is associated with worse oncological outcomes with higher morbidity and mortality [19]. In a worst case scenario, patients cannot be treated with a resection of the primary tumor because of treatment-related toxicity or disease progression and inoperability.

There have been small series describing the feasibility of neoadjuvant CT or chemoradiation in colon cancer. These studies demonstrated safety, high percentages of R0 resections, and excellent local control rates [20–23]. The most striking evidence so far has been published by the foxtrot collaboration group. They published results from a pilot phase randomized clinical study comparing neo-adjuvant to adjuvant CT [21]. The preliminary outcomes are promising but long-term outcomes are to be awaited and until now there is limited experience with this neo-adjuvant treatment strategy.

The purpose of this population-based propensity-score matched cohort study was to investigate the surgical and oncological outcomes of neoadjuvant CT for patients with locally advanced colon cancer (LACC). Surgical complications and pathological response to CT expressed as downstaging, mortality, and overall survival was compared to patients with similar disease stage who received surgery followed by adjuvant CT.

Methods

Data Acquisition
Nationwide population-based data were acquired from the Netherlands Cancer Registry (NCR). This database contains every cancer diagnosis in the Netherlands since 1989 and has an estimated completeness of at least 95%. The database is based on notification by the nationwide automated pathology registry and the National Registry of Hospital Discharge Diagnosis. Trained data managers of the Netherlands Comprehensive Cancer Organization obtain all data directly from patient medical files. Classification of tumor characteristics was done according to the TNM Classification of Malignant Tumors [24] and International Classification of Diseases for Oncology (ICD-O) [25]. To retrieve follow-up on vital status, the NCR is linked to the Municipal Personal Records database annually. At the time of data extraction, follow-up had been completed up to February 1, 2019.

Patient Selection
The database contained all patients who presented with either clinical or pathological stage II or III colon cancer (C18–C19) and who were treated with CT between 2008 and 2016. Follow-up data were available from the time of diagnosis until February 1, 2019. All patients with clinically CT-staged T4 colon cancer were selected. Patients who received radiotherapy were excluded since these were mainly rectosigmoid tumors treated with neoadjuvant chemoradiation according to rectal cancer treatment protocols. Patients with tumor location coded as rectosigmoid were also excluded because it is not possible to determine if they were treated as rectal or sigmoid cancer based on the available information. Patients who were not treated with surgical resection of the primary tumor were also excluded. LACC is defined as T4 or T3 with ≥5 mm invasion beyond the muscularis propria but since the latter is not accurately distinguishable on CT, only patients with clinically diagnosed clinical tumor (cT) 4 colon cancer were selected to represent locally advanced disease. Patients treated with neoadjuvant CT followed by surgery (with or without adjuvant CT) were selected and compared to patients who underwent surgery followed by adjuvant CT without any form of preoperative treatment (Fig. 1).

Data Selection
The extracted data included the following variables: age, sex, localization of the tumor, differentiation grade, morphology, clinical and pathological T and N stage, type of surgery, resection mar-
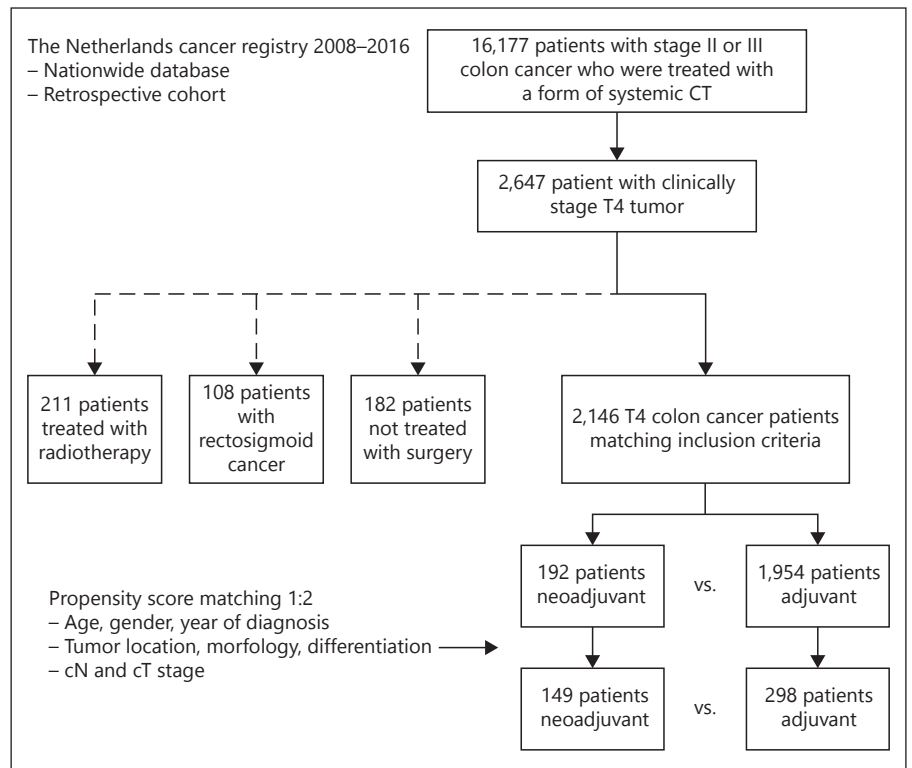
Fig. 1. Flowchart of patient selection. CT, chemotherapy; cT, clinical tumor.

gins, postoperative complications, length of follow-up, and vital status. Location of the tumor was coded according to the ICD-O (C18.0-C19.9) [8]. Morphology was divided into 3 subtypes: mucinous (ICD-O 8480, 8481), signet ring cell (8490) and non-mucinous, non-signet ring cell adenocarcinoma (8000, 8010, 8020, 8021, 8140, 8141, 8143, 8144, 8210, 8211, 8220, 8221, 8260, 8261, 8262, 8263). Date of diagnosis was defined as the date of first histological confirmation of malignancy, most often the day of endoscopic biopsy. After resection the pathologist performed final staging. Pathological tumor (ypT) and nodal staging was compared to clinical staging in both groups to assess downstaging effects of neoadjuvant CT and to highlight differences between clinical and ypT staging in the control group. R0 resections were achieved if the resection margins were microscopically free of tumor. In case of irradical resections, the resection was either labeled R1 (microscopic involvement of the resection margins) or R2 (macroscopic involvement). Major postoperative complications were recorded (abscesses and/or anastomotic leakage). Thirty-day postoperative mortality was calculated for patients whose date of resection was known in the neoadjuvant group. Thirty-day mortality was not calculated in the adjuvant group because the control group only contains patients that were treated with adjuvant CT.

Data Analysis

First, patient and tumor characteristics were compared using the χ^2 test. The Fisher's exact test was used in case one or more if the expected outcomes were <5. Continuous variables were depicted as mean + 95% CI or median + range and compared using independent sample t tests. p values <0.05 were considered significant. To assess the possibility of bias by baseline characteristics

for neoadjuvant treatment, χ^2 was performed. A propensity score matching (PSM) analysis including all baseline characteristics that were significantly associated with neoadjuvant CT treatment and all unbalanced baseline covariables was performed to adjust for confounding. Variables used in matching were: age, gender, year of diagnosis, tumor location, morphology, differentiation grade, clinical T-stage, and clinical N-stage. Patients were matched in a ratio of 1:2 between the neoadjuvant and the control groups since this results in improved precision without an increase in bias [26]. All patients without a matching counterpart were excluded from the analyses. After PSM, baseline characteristics were compared to assure that no major differences persisted between the groups. After PSM, OS curves were rendered according to the Kaplan-Meier method. The equality of the distribution between both groups was compared using the log-rank test. A landmark analysis was performed to correct for immortal time bias. The landmark was set at the time point where 90% of both groups had started treatment. This cutoff point was determined to be 96 days. All patients with a follow-up of 95 days or less were excluded from the analysis. R0 resection rates, postoperative complications, pT and pN stages were compared using χ^2 tests. The number of harvested and positive lymph nodes was compared with independent sample t tests. Clinical and ypT and nodal staging were compared to evaluate the downstaging effects of neoadjuvant CT. Significant tumor downstaging was defined as downstaging from cT4 to ypT2–0 and significant nodal downstaging as cN+ to ypN0. In the control group, clinical and pathological nodal stagings were compared to assess under- and overstaging. For all statistical analyses, IBM SPSS Statistics software, version 25.0 (IBM Corporation, Armonk, NY, USA) was used.
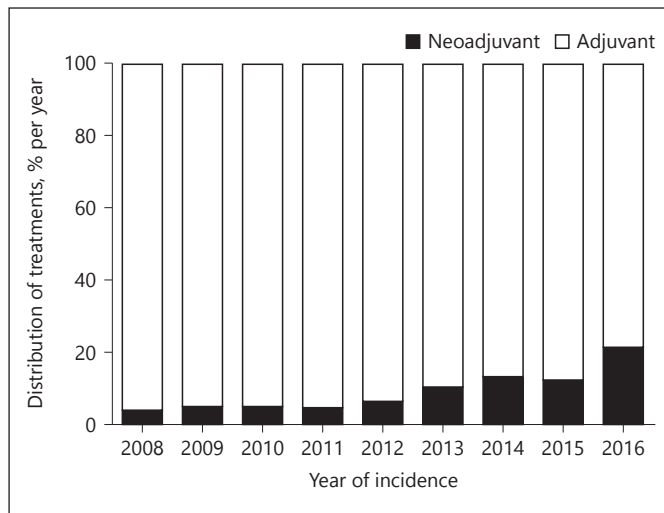
Fig. 2. Distribution of treatment regimen per year in percentage.

Results

Baseline Characteristics before Matching

From 2008 until 2016, 16,177 patients were diagnosed with stage II or III colon cancer and treated with CT. Only 2,146 of these patients were diagnosed with cT4 colon cancer and matched the inclusion criteria. The majority of these (1,954 patients [91%]) were treated with surgery and adjuvant CT and 192 (9%) received neoadjuvant CT followed by surgery. The use of neoadjuvant CT treatment increased significantly over time ($p < 0.001$; Fig. 2). In 2008, 4% of all patients diagnosed with a cT4 tumor were treated with neoadjuvant therapy compared to 21.4% in 2016. Age was not significantly different between both groups, median age in the neoadjuvant group was 64 (range 29–84) vs. 64 years (range 25–88) in the control group, $p = 0.9$ (Table 1). Patients in the neoadjuvant group had significantly more tumors located in the sigmoid colon (42 vs. 34%, $p = 0.007$) and significantly more T4b tumors (74 vs. 57.5%, $p = < 0.001$).

Propensity Score Matching

A propensity score was calculated to adjust for biases caused by differences in baseline characteristics between the 2 groups. The propensity score was calculated based on: age (categories 0–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76–80, 80–>80), gender, year of diagnosis, tumor location, differentiation grade, morphology, clinical-T stage, and clinical-N stage. The PSM excluded 43 patients in the neoadjuvant group and 1,656 patients in the control group because no matching counterpart was found (with a match tolerance of 0.01). After matching there were no significant differences in baseline characteristics between both groups (Table 1).

Staging Accuracy in the Control Group

Comparison between clinical T stage and pathological stage shows that 105 (35%) patients with a T3 tumor and 1 patient with a T2 tumor were overstaged as T4. Clinical nodal staging with CT detected lymph node metastases in 119 (52%) of all 228 patients that were node-positive after pathological analysis. Seventy seven (34%) of these 228 patients were understaged as cN0 and nodal status based on imaging was lacking in 32 (14%) of these 228 patients. Overstaging based on clinical imaging occurred in 16 (23%) of all 68 patients that showed no evidence of nodal involvement after pathological assessment (Table 2b).

Downstaging

In patients treated with neoadjuvant CT, cT stage was compared to the ypT stage to investigate the effect of neoadjuvant CT on tumor load.

In all patients, cT stage was reported before start of neoadjuvant CT. A total of 13 patients suggested significant downstaging of the primary tumor after systemic therapy (cT4 to pT0–2, 8.7%). Five of these patients showed a complete pathological response (pT0; Table 3).

In the control group, only 1 clinically T4 staged tumor was overstaged as a pathological T2 stage (0.3%). This downstaging effect was statistically significant ($p < 0.001$).

Nodal downstaging was suggested in 34 of 65 patients who were clinically node-positive (52%; Table 2a). Nodal overstaging in the control group occurred only in 16 (23%) patients that were diagnosed with cN+ even though they had pN0 disease. There were significantly less pathologically positive lymph nodes (median 0, range [0–23]) in the neoadjuvant group compared to the control group median 2 (0–23), ($p = 0.01$) The number of sampled lymph nodes was more than adequate in both groups, with a median of 17 (4–53) sampled nodes in the neoadjuvant group and 20 (0–71) in the control group.

Surgical Outcomes

After matching the difference in incomplete resection, rates in favor of the adjuvant group remained significant. In 77.2% of patients ($n = 115$) in the neoadjuvant group, a complete resection (R0) was achieved. In 19 patients (12.8%), the resection margins were macroscopically free of disease but microscopically positive for tumor invasion (R1). In 6 patients (4%) it was not possible to achieve complete resection of the tumor and there was macro-

Table 1. Baseline and tumor characteristics of neoadjuvant CT, compared to the locally advanced control group, raw and matched data

	Raw data			Propensity matched data		
	neoadjuvant CT + surgery (*n* = 192)	surgery + adjuvant CT (*n* = 1,954)	*p* value	neoadjuvant CT + surgery (*n* = 149)	surgery + adjuvant CT (*n* = 298)	*p* value
Age, years, median (range)	64 (29–84)	64 (25–88)	0.905	66.0	66.0	0.662
Gender, *n* (%)						
Male	101 (52.6)	993 (50.8)	0.651	74 (49.7)	155 (52.0)	0.640
Female	91 (47.4)	961 (49.2)		75 (50.3)	143 (48.0)	
Localization, *n* (%)						
Coecum	31 (16.1)	503 (25.7)	**0.007**	28 (18.8)	63 (21.1)	0.808
Colon	80 (41.7)	772 (39.5)		64 (43.3)	129 (43.3)	
Sigmoid	81 (42.2)	679 (34.7)		57 (38.8)	106 (35.6)	
Differentiation grade, *n* (%)						
Well/moderate	72 (37.5)	1,231 (63.0)	0.432	71 (47.7)	141 (47.3)	0.945
Poorl/undifferentiated	26 (13.5)	540 (27.6)		26 (17.4)	49 (16.4)	
Unknown	94 (49.0)	183 (9.4)		52 (34.9)	108 (36.2)	
Morphology, *n* (%)						
Adenocarcinoma	159 (82.8)	1,554 (79.5)	0.222	120 (80.5)	228 (76.5)	0.730
Mucinous carcinoma	31 (16.1)	332 (17.0)		27 (18.1)	66 (22.1)	
Signet ring cell carcinoma	0 (0)	37 (1.9)		0 (0)	1 (0.3)	
Other/unknown	2 (1.0)	31 (1.6)		2 (1.3)	3 (1.0)	
Clinical T-stage, *n* (%)						
T4	19 (9.9)	397 (20.3)	**<0.001**	13 (8.7)	25 (8.4)	0.941
T4a	31 (16.1)	433 (22.2)		24 (16.1)	52 (17.4)	
T4b	142 (74.0)	1,124 (57.5)		112 (75.2)	221 (74.2)	
Clinical N-stage, *n* (%)						
N0	81 (42.2)	721 (36.9)	0.061	65 (43.6)	120 (40.3)	0.483
N1	63 (32.8)	633 (32.4)		47 (31.5)	84 (28.2)	
N2	23 (12.0)	193 (9.9)		18 (12.1)	51 (17.1)	
Nx/unknown	25 (13.0)	407 (20.8)		19 (12.8)	43 (14.4)	

Bold *p* values indicate statistical significance.
CT, chemotherapy; T-stage, tumor stage; N-stage, nodal stage.

scopically visible residual disease (R2). In the control group, an R0 resection rate of 86.2% (*n* = 225) was achieved. There were 6% (*n* = 18) R1 resections and 1.7% (*n* = 5) R2 resections. Data regarding complications was available in 92% of the patients (*n* = 137) in the neoadjuvant group and in 93% (*n* = 275) of the control group (Table 3). There were no significant differences in surgical complications such as anastomotic leakage and abscess formation between the 2 groups (*p* = 0.854).

Survival

The median follow-up was 44 (4–133) months in the neoadjuvant group and 44 (0–133) months in the control group. The 5-year overall survival was 67% in the neoadjuvant group and 65% in the control group. However, this difference was not statistically significant (*p* = 0.867; Fig. 3). Thirty day mortality after surgery was 0% in the neoadjuvant group. This could not be compared to the control group because of immortal time bias. Multivari-

able Cox regression was not calculated since the Kaplan-Meier curves crossed, and therefore the assumption of proportional hazards is violated.

Discussion

Neoadjuvant CT for LACC is infrequently used and current research is inconclusive regarding its potential benefit. With only a few studies published, it not surprising that neoadjuvant CT for LACCs is not considered a common practice in the Netherlands yet [21–23]. This nationwide database study illustrates that preoperative CT is safe, results in significant tumor and nodal downstaging and yields excellent long-term outcomes in a selected group of patients with clinically locally advanced (cT4) colon cancer.

Preoperative systemic therapy is shown to be non-inferior in terms of safety and does not increase surgical morbidity or mortality when compared to standard sur-

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Table 2.

a Nodal downstaging in patients who received neoadjuvant CT

Pathological N-score				
	pN0	pN+	pNx	Total
Clinical N-score				
cN0	47	17	1	65
cN+	34	31	0	65
cNx	11	8	0	19
Total	92	56	1	149

b Comparison of clinical and pathological nodal staging in patients treated with adjuvant CT

Clinical N-score				
cN0	42	77	1	120
cN+	16	119	0	135
cNx	10	32	1	43
Total	68	228	2	298

CT, chemotherapy.

gery. The occurrence of major complications such as anastomotic leakage and abscess formation was equal between both the groups. Patients in the neoadjuvant group were more likely to receive a stent or stoma prior to surgery (8.7 vs. 1.0%) but far less likely to undergo emergency surgery compared to the control group (2.6 vs. 10.4%). These are encouraging results because they do not show evidence of tumor progression, warranting emergency resection during neoadjuvant treatment. This is in accordance with the preliminary results of the Foxtrot trial where no differences in postoperative morbidity and mortality were observed between the 2 groups [21]. Regrettably, this dataset only contains patients that were treated with neoadjuvant treatment and surgery. Data regarding patients that received CT with neoadjuvant intent but who were deemed inoperable because of tumor progression are lacking. On the contrary, in the Foxtrot trial all patients who were treated with neo-adjuvant CT underwent surgery and no mortality or progression leading to irresectable disease occurred in the pilot phase [21].

Another potential benefit of preoperative CT that was shown is significant downsizing of the primary tumor and downstaging of lymph nodes metastases. Evidence of significant downstaging was demonstrated in 13% of the patients and a complete pathological response was observed in 5 patients. Also, an 18% reduction of lymph node involvement after preoperative treatment was observed. These numbers might still be an underestimation

of the effect since a significant number of patients were understaged in the control group. Neoadjuvant treatment has been proposed as a risk factor for inadequate lymph node sampling in rectal cancer and more recently in colon cancer [27, 28]. This was not observed in the present study as the median number of sampled lymph nodes was significantly higher than the recommended minimum of 12 in both groups.

Pathological and clinical staging were compared in the control group because there it is debated whether CT staging is an accurate tool to distinguish high-risk tumors suitable for neoadjuvant treatment. Significant tumor downsizing was defined as a reduction from cT4 to ypT2–0 because distinction between T3 and T4 is difficult on CT, especially distinction between low-risk T1-T3ab and high-risk T3cd-T4 [29, 30]. This choice seems justified by the data that shows 35% of all clinically diagnosed T4 tumors in the control group having a T3 tumor after pathological assessment, suggesting significant overstaging. Conversely, the comparison of clinical and pathological nodal staging shows that the problem mostly lies in understaging with 35% of pN+ cases being diagnosed as clinically node-negative disease. This is in line with the recent literature on nodal staging in colorectal cancer [31]. This remains an important disadvantage of the neoadjuvant strategy because a significant number of patients could potentially receive neoadjuvant CT without appropriate indication. However, these data were collected over a longer period of time (2008–2016) and advances have been made in radiological staging T of colon cancer [32].

One of the hypothetical advantages of tumor downsizing and staging is a reduction of the amount of multivisceral resections performed and a higher R0 resection rate. In this study this could not be demonstrated, since multivisceral resections were performed more often in the neoadjuvant group (9.4 vs. 5.0%) even though this difference was not significant. The rate and absolute number of patients who underwent a multivisceral resection is much lower compared to 33% multivisceral resections reported by Govindarajan et al. [33] in patients with LACC based on data retrieved from the SEER registry. The significantly lower rate of R0 resections in the neoadjuvant group is a cause for concern since R0 resection strongly correlates with recurrence and survival in colorectal cancer [34, 35]. Nevertheless, this dataset contains no data regarding the presumed indication for neoadjuvant CT, rendering it highly difficult to determine if there is a causal relationship between neoadjuvant treatment and the higher number of incomplete resections. There might be unknown

Table 3. Surgical outcomes in patients treated with neoadjuvant CT, compared to the locally advanced control group, raw and matched data

	Raw data			Propensity matched data		
	neoadjuvant CT ($n = 192$)	adjuvant CT ($n = 1,954$)	p value	neoadjuvant CT ($n = 149$)	adjuvant CT ($n = 298$)	p value
Number of harvested lymph nodes, mean (95% CI)	20.2 (18.8–21.6)	19.9 (19.5–20.4)	0.523	19.6 (18.1–21.2)	22.5 (21.2–22.0)	**0.01**
Number of positive lymph nodes, mean (95% CI)	1.3 (0.9–1.7)	3.1 (3.0–3.3)	**<0.001**	1.3 (0.8–1.8)	3.6 (3.1–4.1)	**<0.001**
Pathological T-stages, n (%)						
T0	8 (4.2)	0 (0)	**<0.001**	5 (3.4)	0 (0)	**<0.001**
T1	2 (1.0)	0 (0)		2 (1.3)	0 (0)	
T2	8 (4.2)	12 (0.6)		6 (4.0)	1 (0.3)	
T3	70 (36.5)	734 (37.6)		52 (34.9)	105 (35.2)	
T4	104 (54.2)	1,207 (61.8)		84 (56.4)	192 (64.4)	
Tx	0 (0)	1 (0.1)		0	0	
Pathological N-stages, n (%)						
N0	117 (60.9)	532 (27.2)	**<0.001**	92 (61.7)	68 (22.8)	**<0.001**
N1	52 (27.1)	829 (42.4)		38 (25.5)	121 (40.6)	
N2	22 (11.5)	588 (30.1)		18 (12.1)	107 (35.9)	
Nx	1 (0.5)	5 (0.3)		1 (0.7)	2 (0.7)	
Resection margins, n (%)						
R0	150 (78.1)	1,681 (86.0)	**0.001**	115 (77.2)	225 (85.6)	**0.037**
R1	24 (12.5)	100 (5.1)		19 (12.8)	18 (6.0)	
R2	7 (3.6)	55 (2.8)		6 (4.0)	5 (1.7)	
Unknown	11 (5.7)	118 (6.0)		9 (6.0)	20 (6.7)	
Type of surgery, n (%)						
Colon	100 (52.1)	1,175 (60.1)	0.187	82 (55.0)	172 (57.7)	0.485
Sigmoid	66 (34.4)	592 (30.3)		47 (31.5)	95 (31.9)	
(Sub)total colon	7 (3.6)	55 (2.8)		5 (3.4)	14 (4.7)	
Multivisceral resection	18 (9.4)	120 (6.1)		14 (9.4)	15 (5.0)	
Unknown	1 (0.5)	12 (0.6)		1 (0.7)	2 (0.7)	
Type of surgery, n (%)						
Elective	171 (89.1)	1,727 (88,4)	**<0.001**	132 (88.6)	263 (88.3)	**<0.001**
Emergency	5 (2.6)	203 (10.4)		2 (2.6)	31 (10.4)	
Previous stoma/stent	16 (8.3)	17 (0.9)		13 (8.7)	3 (1.0)	
Unknown	0 (0)	7 (0.4)		0	1 (0.3)	
Complication, n (%)						
No anastomotic leakage or abscess	152 (79.2)	1,707 (87.4)	0.64	124 (83.2)	257 (86.2)	0.854
Anastomotic leakage	11 (5.7)	58 (3.0)		8 (5.4)	9 (3.0)	
Abscess	9 (4.7)	36 (1.8)		4 (2.7)	7 (2.3)	
Both	1 (0.5)	17 (0.9)		1 (0.7)	2 (0.7)	
Unknown	19 (9.9)	136 (7.0)		12 (8.1)	23 (7.7)	
Targeted therapy, n (%)						
Yes	54 (28.1)	33 (1.7)	**<0.001**	47 (31.5)	4 (1.3)	**<0.001**
No	138 (71.9)	1,921 (98.3)		102 (68.5)	294 (98.7)	

Bold p values indicate statistical significance.
CT, chemotherapy; T-stage, tumor stage; N-stage, nodal stage.

bias influencing the choice of neoadjuvant treatment. Since national guidelines recommend surgery in case of resectable tumors, presumably a significant percentage of patients treated with neoadjuvant CT had tumors with unfavorable characteristics and/or clinically unresectable tumors. This is supported by the finding that 28% of patients in the neoadjuvant group were treated with targeted therapy while treatment with the VEGF-A inhibitor Bevacizumab is normally reserved for palliative treatment and not recommended in resectable disease [36].
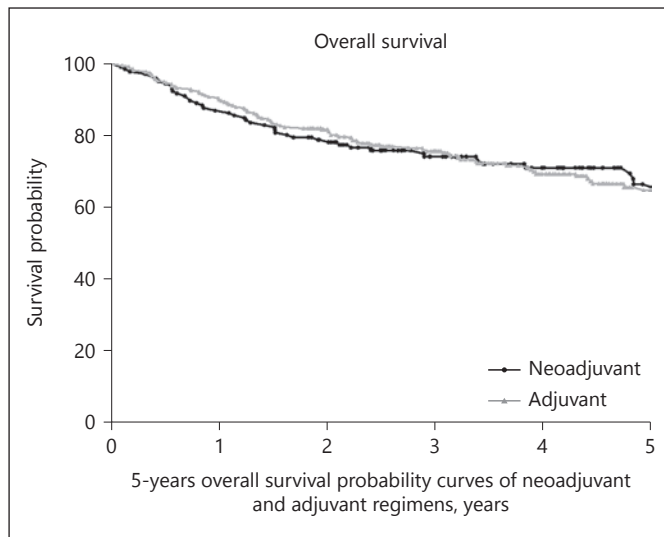
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Fig. 3. Landmarked overall survival after propensity matching.

The difference in R0 resections is, therefore, more likely a result of persisting bias based on unfavorable tumor characteristics and primary irresectability and not of the neoadjuvant treatment itself. This is supported by the preliminary data from the Foxtrot trial where in a randomized setting the percentage of margin involvement is significantly lower in the neoadjuvant group (4 vs. 20%). An encouraging finding of this study is that despite the higher R0 resection rate, an excellent 5-year overall survival rate of 67% was demonstrated in the neoadjuvant group. This is similar to the survival in the control group (65%) and comparable to recent literature [37–39]. Most importantly, these results are in accordance with the first results of the randomized phase FOxTROT trial that were presented at the ASCO annual meeting 2019. The authors reported that there was no significant difference observed in the 2-year failure rate between both groups. Five-year overall survival results are required to confirm the long-term benefits but the concordance with the results in this cohort is encouraging.

This study has some limitations; some degree of selection bias is inevitable, owing to the observational nature of the study. However, PSM was performed to balance the cohorts and differences in baseline characteristics between the groups were no longer significant. Moreover, selection bias could have occurred in the control group since only patients who were able to undergo adjuvant CT were included and as such patients who died postoperatively or suffered from severe complications were excluded. Nevertheless, including these

patients would introduce a form of bias benefitting the neoadjuvant group, since patients treated with neoadjuvant intent but found to be not eligible for surgery are also not included in this study. It is encouraging that survival is still comparable between both groups, underlining the potential value of neoadjuvant treatment in this select group of patients. Unfortunately, the NCR does not contain data on disease recurrence and thus disease-free survival cannot be calculated. The overall survival percentages in both groups are comparable since tumor recurrence is significantly associated with overall survival [40]. Pathological data on tumor regression after neoadjuvant treatment are also absent and could be of interest since this is known to correlate with recurrence-free survival in other gastrointestinal malignancies [41, 42]. Finally, the NCR does not contain specific data on the type of CT and whether patients suffered treatment-related toxicity. However, the standard adjuvant treatment regimen for colon cancer in the Netherlands consists of a fluoropyrimidine and oxaliplatin combination and it is highly likely that neoadjuvant treatment also consists of this combination.

In conclusion, this is the first nationwide population-based analysis which shows that neoadjuvant CT for locally advanced cT4 colon cancer seems safe and yields similar overall survival compared to adjuvant CT. A lower R0 resection rate was observed in the neoadjuvant group but there is no significant increase in postoperative complications or mortality. Moreover, it leads to significant downstaging of tumor and lymph node stage. The long-term survival benefit of this treatment is to be established in a large randomized trial, but it already seems to be a useful and safe modality in patients with locally advanced and possibly unresectable primary tumors.

Statement of Ethics

Disclosure Statement

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Author Contributions

S.A.R., C.V., J.M.J.S., and J.H.W.W.: study concepts. J.M.J.S. and J.H.W.W.: study design. J.-M.G., M.G.V., R.H.A.V., and J.L.-B.: data acquisition. J.-M.G., M.G.V., J.L.-B., and J.M.J.S.: quality control of data and algorithms. J.-M.G., M.G.V., J.L.-B., R.H.A.V., and J.M.J.S.: data analysis and interpretation. J.-M.G., M.G.V., J.L.-B., and R.H.A.V.: statistical analysis. J.-M.G., M.G.V., and J.L.-B.: manuscript preparation. All authors: manuscript editing. All authors: manuscript review.

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