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REVIEW

Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review

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Abstract

Background Preoperative or neoadjuvant chemotherapy (NAC) has emerged as a novel alternative to treat locally advanced colon cancer (LACC), as in other gastrointestinal malignancies. However, evidence of its efficacy and safety has not yet been gathered in the literature. The aim of the present study was to perform an extensive review of the scientific evidence for NAC in patients with LACC.

Methods PubMed, EMBASE, MEDLINE and Cochrane Library were searched for a systematic review of the literature from 2010 to 2019. Six eligible studies were included, with a total of 27,937 patients, 1232 of them (4.4%) treated with NAC. There were only one randomized controlled trial, three phase II non-randomized single arm studies and two retrospective studies.

Results The baseline computed tomography scan showed that most of patients had a T3 tumor. The completion rate of the planned neoadjuvant treatment ranged from 52.5 to 93.8%. Between 97.2 and 100% of patients had the scheduled surgery. The median tumor volume reduction after NAC ranged from 62.5 to 63.7%. The anastomotic leak rate in the NAC group ranged from 0 to 7%, with no cases of postoperative mortality. There was major pathological tumor regression in 4–34.7% of cases. Between 84 and 100% of NAC patients had R0-surgery. Survival after NAC seems to be encouraging although significant improvement has only been proven in T4b tumours.

Conclusions According to our systematic review, the NAC may be a safe and effective emerging therapeutic alternative for treating LACC. This approach, which is still being tested, increases the reliance on accurate radiological staging.

Keywords Neoadjuvant therapy · Colonic neoplasms · Locally advanced colon cancer · Treatment outcome · Morbidity

Introduction

Colon cancer (CC) is one of the most common malignancies worldwide, being the fourth most common cause of death from cancer [1]. Current national comprehensive cancer network (NCCN) Guidelines recommend chest and abdominopelvic computed tomography (CT) scan for the initial staging of CC patients [2] although other technologies, such as magnetic resonance imaging (MRI), virtual colonoscopy, CT colonography or positron emission tomography (PET) have been proposed to improve clinical preoperative accuracy [3].

High-risk stage II CC is defined as N0/M0 patients with bowel obstruction or perforation, T4 or T3 with more than 5-mm tumor invasion beyond the muscularis propria, peritumoral or lymphovascular involvement, poorly differentiated tumors or incomplete lymphadenectomy [4–7]. High-risk stage II and stage III CC (T1-4/N1-2/M0) are commonly known as locally advanced colon cancer (LACC) and

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represent a major therapeutic challenge. Standard treatment for resectable LACC is based on complete oncologic resection followed by adjuvant chemotherapy. With the current therapy, the 5-year survival rate of LACC ranges from 73.7% in T1–T2N1a tumors, to 12.9% in T4bN2b tumors [8]. Thus, the oncological outcome remains unsatisfactory, showing a partial failure to prevent locoregional spread or eradicate micrometastases [7].

Preoperative or neoadjuvant chemotherapy (NAC) and radiotherapy are more effective than analogous postoperative treatment in rectal, esophageal and gastric cancer, being now a common standard of care [9–12]. This therapeutic sequence has resulted in better downstaging, resectability rates and improved survival in different solid tumors [13]. However, even if NAC remains still understudied in LACC, results from the available series seem promising [5, 6, 14–17].

NAC in LACC is an attractive concept with theoretical benefits. Surgery stimulates growth factors and induces immunosuppression that may promote tumor progression and spread of micrometastases in the postoperative setting [7]. Early systemic NAC could result in eradication of circulating tumor cells and lymph node metastases, shrinkage of tumor and reduction of tumor cell-shedding due to surgical trauma [6, 10, 13, 14]. Surgery after NAC could remove the tumor more radically, and minimum access might be more likely [16]. NAC is expected to have a better tolerability and could also test the chemosensitivity of the tumor, and be useful in guiding adjuvant chemotherapy [5].

On the other hand, the use of NAC has been limited by some clinical concerns. Non-sensitive patients might have distant progression or local tumor growth, requiring emergency surgery due to bowel obstruction. Furthermore, inadequate radiological tumor staging may lead to the overtreatment of low-risk patients [5].

Therefore, given this background, the main purpose of this study was to perform a systematic review of the literature to evaluate the safety and efficacy of NAC in LACC and discuss ongoing clinical trials.

Materials and methods

Search strategy

A literature search was conducted for all published studies from January 2010 to September 2019, without restrictions regarding language or country. This systematic review was performed in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) group [18]. Owing to the scarcity of studies and randomized controlled trials, non-comparative, non-randomized prospective and retrospective studies and available conference abstracts were included in the search.

Studies were identified by searching the following databases: MEDLINE (via PubMed), EMBASE (via OvidSP), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Review. Searches were adapted to each database and carried out using the specific controlled vocabulary of each database, if available (MeSH terms for MEDLINE and Emtree terms for EMBASE). Ongoing trials have been searched in the registry of clinical trials: https://clinicaltrials.gov/ and in the Spanish Registry of Clinical Studies.

Inclusion and exclusion criteria

Studies reporting data on preoperative chemotherapy in patients with LACC without metastases included the words "preoperative chemotherapy", "neoadjuvant chemotherapy" and "locally advanced colon cancer". The search terms were structured by combining one word from each group, in such a way that all possible combinations were employed. Additional manual searches in reference lists of the relevant articles were also conducted. Articles referring metastatic disease or rectal cancer, instead of colon cancer, have been excluded. When duplicate reports from the same study were identified, only the most recent publication or the one with the longest follow-up period was included. Two reviewers (JA and BI) independently assessed the titles and abstracts of articles to determine trial inclusion. Information from the full texts using a predefined data extraction sheet was extracted.

Data collection and outcomes of interest

Data regarding study design, number of patients, radiological stage, chemotherapy protocol, type of surgery, pathological findings, perioperative morbidity and oncologic outcomes were collected, if available, and were recorded. Outcomes were summed and weighted averages of the medians or means were determined. In cases of proportional data, the overall proportion was determined, censoring studies that did not report on the variable of interest.

Results

A total of 421 studies were identified through electronic searches, with 373 records with available abstracts. After reading title and abstract, 354 studies were excluded because they were not about NAC in LACC. Among the 19 remaining studies, 5 were excluded since they were case reports, 4 because of duplication of the outcomes from the same institution, 3 because of lack of information and another 1

because of combined neoadjuvant treatment with radiotherapy. Figure 1 shows the study flow diagram. A total of six studies about NAC in LACC were included. Table 1 summarizes demographic data, type of study, inclusion and exclusion criteria. There were only one randomized controlled trial, three phase II non-randomized single arm studies and two retrospective studies. The most relevant characteristics of each study are as follows:

FOxTROT, Birmingham, United Kingdom, NCT00647530

This is a multicenter clinical trial, which included 1052 patients, in 35 centers. Feasibility, reliability, tolerability and radiologic accuracy were the main objectives, and were published in the first 150 patients [5]. It evaluated three preoperative cycles of oxaliplatin, folinic acid and 5-fluorouracil (5-FU), followed by nine cycles after surgery. The control group consisted of 12 postoperative cycles. Furthermore, K-RAS wild-type patients were randomly assigned into groups getting or not panitumumab for 6 weeks. Provisional results of the entire cohort have recently been presented, and are commented on in the discussion.

ICT-XEL, Pamplona, Spain

This single-center study was conducted at the Clinica University of Navarra without a control group. A pilot study was performed with the first 22 patients [19] and later a radiological response analysis was performed in 44 patients [20]. A final analysis was conducted in 65 patients in which the primary endpoint was mid-term survival and patterns of relapse [6]. The NAC consisted of four–six cycles of oxaliplatin with capecitabine or 5-FU. Limitations are derived from the study design: retrospective, single centre and no control group.

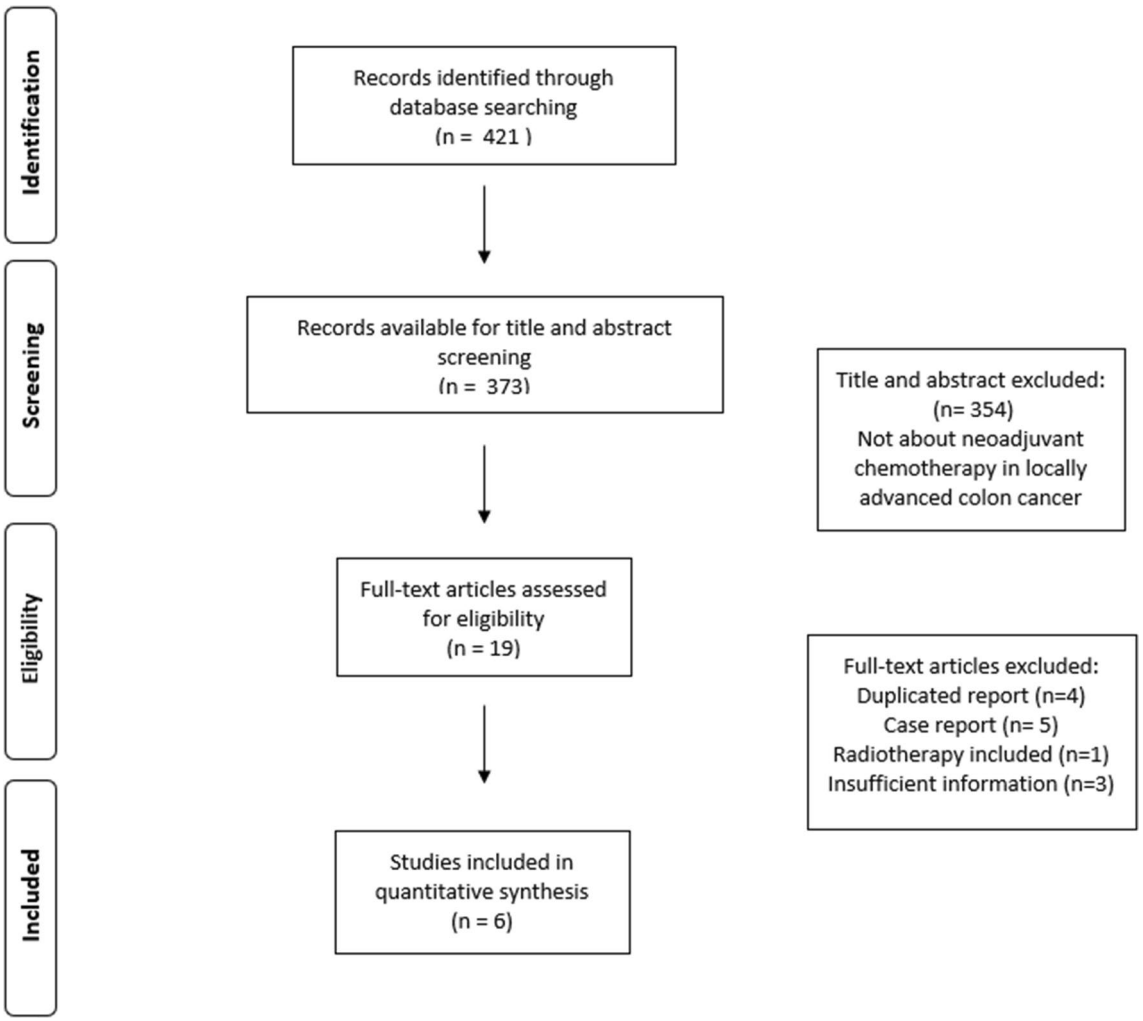

Fig. 1 Flowchart of study selection

Table 1 Demographic data

Study	Period of time	Type of study	Inclusion criteria by CT scan	Exclusion criteria	Primary endpoint	No. patients (%)			Age, years mean (range)	Female (%)	Had surgery (%)	Received AC (%)	Completed AC (%)
FOxTROT, UK [5]	2008–2010	Pilot phase of a randomized controlled trial. Three arms. Multicenter	T4 or T3 with EMI ≥ 5 mm	Radiotherapy. Distant metastases. Peritoneal carcinomatosis. Serious comorbidity. Peritonitis Colonic obstruction that has not been defunctioned. Other malignant diseases < 5y	Feasibility, safety, and efficacy of NAC	Total 150	Intervention 99	Actually received NAC 95/99 (96) Completed NAC 85/95 (89)	64 (31–82)	34 (34)	99/99 (100)	82/99 (82.8)	67/82 (81.7)
							Control 51		65 (38–78)	19 (37)	48/51 (94)	40/48 (83)	29/40 (72.5)
ICT-XEL, Spain [6]	2009–2014	Single arm. Retrospective. Single-center	Suspicious N + and/or EMI ≥ 5 mm	Rectal cancer. Distant metastases. Peritoneal carcinomatosis. Colonic obstruction	Mid-term survival and patterns of relapse	65	Actually received NAC 65 (100)	Completed NAC 61 (93,8)	64.8 (10.9)*	20 (30.8)	65 (100)	39/65 (60)	–

Table 5 (continued)

Study	Period of time	Type of study	Inclusion criteria by CT scan	Exclusion criteria	Primary endpoint	No. patients (%)			Age, years mean (range)	Female (%)	Had surgery (%)	Received AC (%)	Completed AC (%)
Vejle, Denmark [14]	2010–2013	Phase II. Single arm. Prospective. Multicenter	T4 or T3 with EMI ≥ 5 mm	Serious infection. Peripheral neuropathy. Significant cardiac disease. Other malignant diseases < 5y	Efficacy of NAC	77	Actually received NAC 73	Completed NAC 83%	69 (–)	39 (55)	71 (97.2)	–	65%
Shanghai, China [15]	2015–2016	Phase II. Single arm. Prospective. Single-center	T4 or N +	Rectal cancer. Distant metastases. Peritoneal carcinomatosis. Colonic obstruction that has not been defunctioned. Serious comorbidity	Efficacy and safety of NAC	47	Actually received NAC 47 (100)	Completed NAC 42 (89.3)	52 (25–73)	11 (23)	47 (100)	47 (100)	–
Beijing, China [16]	2014	Phase II. Single arm. Prospective. Single-center	T4N2M0	Prior malignancy. Pregnant or lactating patients. Without informed consent	Feasibility, safety and efficacy of NAC	23	Actually received NAC 23 (100)	Completed NAC 12 (52.2)	56 (29–72)	7 (30.4)	23 (100)	22 (95.6)	10 (43.5)

Table 5 (continued)

Study	Period of time	Type of study	Inclusion criteria by CT scan	Exclusion criteria	Primary endpoint	No. patients (%)		Age, years mean (range)	Female (%)	Had surgery (%)	Received AC (%)	Completed AC (%)
NCDB, USA [17]	2006–2014	Retrospective. Two arms. Multicenter	T3 and T4 M0	Metastases. No surgery. No chemotherapy. Second primary or multiple tumors. Other histology. No histological confirmation. No lymph nodes examined	Impact of NAC on survival	Total 27,575	NAC 921	58.4 (12.1)*	388 (42)	–	–	–
							Surgery + AC 26,654	61.5 (12.8)*	13,384 (50)	–	26,654 (100)	–

N+: lymph node invasion, –: data not published

CT computed tomography, *NAC* neoadjuvant chemotherapy, *AC* adjuvant chemotherapy, *EMI* extramural invasion

*Standard deviation

Vejle, Denmark, NCT01108107

The main objective of this multicenter phase II study without a control group was to evaluate the efficacy of NAC in causing regression of LACC to a tumor that would not require adjuvant chemotherapy. It also assessed tumor recurrence rate, disease-free survival (DFS), reliability and feasibility of the preoperative treatment. The NAC was based on three cycles of oxaliplatin and capecitabine (XELOX). If K-RAS, BRAF and PIK3CA were wild type, panitumumab was also administered. Adjuvant treatment entailed five cycles of XELOX to all patients that fulfilled adjuvant therapy criteria [14]. The main limitation is the short follow-up period in a phase II trial.

Shanghai, China, NCT02415829

This single-center single-arm phase II study assessed the efficacy and safety of NAC, based on three cycles of XELOX, surgery and five cycles of XELOX, for T4 or N + CC, by CT scan. Radiological response was performed after two neoadjuvant cycles [15]. Limitations are derived from being single-center and without a control group.

Beijing, China, NCT02688023

This is a prospective, open-label single-arm phase II study based on a triplet regimen of NAC in stage IIIb tumors. The main objective was the R0 resection rate. This study assessed the feasibility, safety and efficacy of folinic acid, oxaliplatin, irinotecan, followed by 5-FU ± bevacizumab (FOLFOXIRI) preoperative chemotherapy in stage IIIb patients [16]. This study is single center, limited to T4N2 tumors, and without a control group.

Santa Monica, CA, USA, National Cancer Data Base (NCDB)

This study retrospectively selected from the NCDB patients who were treated with surgery followed by adjuvant chemotherapy or NAC and surgery, from 2006 to 2014. The primary endpoint was the impact of NAC on survival. Authors included 27,575 clinically staged T3 and T4, non-metastatic, primary CC. Three percent of them (921) received NAC and surgery. There were differences in patient demographics, tumor features and treatments between standard and neoadjuvant group. Although the sample size is huge, this study has some important limitations, including being a retrospective study, with data from a national database. Furthermore, precise information on the type of surgery performed, radiological staging, or tumour recurrence is lacking because they were not available in NCDB. This means that the results should be interpreted with caution [17].

As shown in Table 1, a total of 27,937 patients were included in the 6 studies, with an age ranging from 31 to 82 years. The group receiving NAC consisted of 1232 patients. The mean completion rate of the scheduled neoadjuvant treatment ($n=311$) was 87.5% (range 52.2–93.8%). The adverse events related to NAC were well tolerated and manageable. It must be highlighted that the lowest compliance rate (52.2%) was in the study which combined a triplet regimen and for four cycles [16]. In this study, the toxicity did not affect the following surgery and did not entail greater surgical complications. In the present review, the proportion of patients who had the planned surgery after NAC was 97.2–100%.

On baseline CT scan, most of the patients had a T3 tumour (75.4%), followed by T4 tumour (24.5%) (Table 2). After NAC, the median tumor volume reduction in the two studies that evaluated it was 62.5% and 63.7%, respectively [6, 16]. In the Danish study, 48% converted to a low-grade tumor [14], and one of the Chinese studies observed a partial radiological response in 66% of patients, with a case of complete response by CT scan, according to the Response Evaluation Criteria in Solid Tumors version 1.1 guideline (RECIST version 1.1) [15]. Only 5 out of 212 patients (2.3%) showed possible metastatic or non-resectable progression after NAC [6, 14–16]. Main postoperative outcomes are shown in Table 3. The anastomotic leak rate after NAC, ranged from 0 to 7%. There were no cases of perioperative death. The postoperative stay ranged from 5 to 30 days [5, 6, 14–16]. Tumor regression grade (TRG) was evaluated in four studies, with heterogeneous results, showing a major regression that ranged from 4 to 34.7% [5, 6, 15, 16]. In the British trial and in the trial by Liu et al. the complete pathologic response was 2% [5], in the Danish trial 4.2% [14] and in the Spanish one 4.6% [6]. The post-treatment pathological report showed a lower stage than that reported in the initial radiological examination, although 4 patients had a yp-stage IV. After NAC, an R0 surgical resection was achieved in a range from 84 to 100% [5, 6, 15–17] (Table 4).

Survival outcomes were available in only four studies. In the Danish trial, after a mean follow-up period of 26.4 months, the DFS in the good-responder group, defined as patients which after NAC achieve a downstaging to a low-grade tumor that does not require more chemotherapy, was 94% versus 63% in the non-responder group, defined as patients who fulfill criteria for adjuvant chemotherapy. The 3-year overall survival (OS) of the whole cohort was 84% [14]. In the Spanish study, after a mean follow-up of 40.1 months, the 3-year DFS was 88.9% and the 5-year overall survival (OS) was 95.3% [6]. In the Beijing study, the 2-year DFS was 73.9% and the 2-year OS was 95.7% [16]. In the American retrospective study, NAC did not show a benefit for T3 and T4a tumor, but in T4b tumors, a 23% lower risk of death at 3 years (HR 0.77, 95% CI 0.6–0.98; $p=0.04$) was observed after propensity score matching, compared to patients who had adjuvant chemotherapy [17].

Discussion

The present study is, to the best of our knowledge, the first systematic review evaluating NAC in LACC. Preoperative treatment is gaining increased attention in the multidisciplinary management of LACC, as in other locally advanced tumors, like gastric, rectal, pancreatic or breast cancer [9–12]. However, very little is known about the NAC efficacy and safety as few studies are available in the literature. This could be the reason why there is a lack of a more widespread use of preoperative treatment in LACC, in spite of the theoretical advantages. This study presents a complete review of the available literature on NAC for LACC.

Safety and tolerability

Some authors may speculate that preoperative chemotherapy administration can delay surgery because of its toxicity, or has a higher probability of developing postoperative complications.

Our review shows that NAC is reliable and well tolerated, with a high proportion of patients completing the planned preoperative treatment. The proportion of patients who had apparent progression when comparing baseline CT scan and the pathological report was small. In the FOxTROT trial, the potential risk of primary tumor growth during NAC that could lead to emergency surgery was not demonstrated. There was a higher completion rate in the NAC group compared to the postoperative treatment group (68% vs. 57%) [5]. It has been observed that NAC does not delay or hamper the scheduled surgery, which is performed in almost all the cases in the review.

Imaging test accuracy

One of the most controversial aspects is the correct selection of patients with LACC. CT scan is a key tool in CC staging, having a predictive value in the prognosis [23–25]. Neoadjuvant strategies must rely upon the precision of imaging tests, as the clinical stage will be used to select high-risk patients [26]. However, difficulties in the precise tumor staging by CT scan arise, and one consequence might be overtreatment, secondary to an overstaging [25, 27].

CT scan presents limitations to identify the degree of tumor extension in the colonic wall, and its precision ranges from 33 to 82% [27, 28]. Multidetector CT scan, in combination with the use of oral and rectal contrast agents,

has improved radiologic efficiency: it is possible to collect 1-mm-thick slices which permits three-dimensional reconstruction [29, 30]. For N staging, CT scan needs to differentiate between tumor infiltration and reactive lymph nodes. Its precision widely ranges from 22 to 83% [26, 28, 31]. It could be argued that part of the promising findings published may be a result of overtreatment of the disease due to an initial overstaging rather than a real effect of the neoadjuvant treatment. However, different analyses show that CT scan can correctly identify high-risk CC, minimizing overstaging of incipient tumors [32, 33]. In the British trial, only 7% of all tumors were wrongly classified [5], and in the Spanish study, overstaging was seen in 9.1% [20]. Nowadays, there is an increasing interest in the proper radiologic selection of the patients eligible for NAC [3, 34–36].

Nørgaard et al. showed that T3 with > 5 mm extramural invasion and T4 tumors fulfill the criteria for adjuvant chemotherapy [37]. Smith and colleagues concluded that CT staging could differentiate between patients with good and poor colorectal prognosis [24]. The assessment of the radiological response after NAC might be useful in guiding the extension of preoperative treatment and the postoperative drug selection.

Pathological assessment

The good R0 resection rate and the high number of resected nodes reveals a good quality of surgery, which satisfies the oncological criteria [38]. In the British trial, a statistically significant difference was observed, favoring the NAC group in terms of apical node involvement in the resected specimens, TNM staging, resection and retroperitoneal margin involvement [5].

Tumour grade regression of the specimen is a well-known factor directly related to chemotherapy response [39, 40]. Compared with rectal cancer, where complete pathological response has been shown to range between 15 and 25%, in LACC this value seems to be lower, ranging from 2 to 4.6% [5, 6, 14, 21]. However, in this review, a moderate to complete pathological response was achieved in 29–73.8% of cases, which is encouraging indirect data of improved survival, still waiting to be confirmed after follow-up data are published. Some studies assessed the pathologic and radiologic correlation, yielding a positive but not statistically significant association, due to lack of statistical power [16, 20]. New trials like the Chinese NCT03985891 study are assessing the tumor response after neoadjuvant treatment based on chemotherapy and monoclonal antibodies. Furthermore, some trials have been developed to assess the impact of adding radiotherapy to NAC, achieving up to 38.1% of complete pathological response [41–43]. However, larger studies are needed to better understand the impact of the tumor regression grade after NAC.

Perioperative morbidity and mortality

Another interesting aspect is to evaluate is if NAC increases the postoperative complications, although no scientific

Table 2 Baseline radiological stage

Study	Radiological stage						
	Tumor volume reduction after NAC. Median % (range)	*T* (%)			*N* (%)		EMI (%)
		T2	T3	T4	−	+	
Foxtrot, UK [5]							
Intervention, *N* = 99	–	0 (0)	69 (70)	30 (30)	23 (23)	73 (74)	57/98 (58)
Control, *N* = 51	–	0(0)	35 (69)	16 (31)	12 (24)	38 (74)	31/51 (61)
ICT-XEL, Spain, *N* = 65 [6]	62.5 (39.8–79.8)	5 (7.7)	48 (73.8)	12 (18.5)	15 (23.1)	50 (76.9)	–
Vejle, Denmark, *N* = 71 [14]	–	0 (0)	60 (85%)	11 (15%)	1 (1.4)	70 (98.6)	–
Shanghai, China, *N* = 47 [15]	–	0 (0)	12 (26)	35 (74)	16 (34)	31 (66)	–
Beijing, China, *n* = 23 [16]	63.7 (1.7–82.8)	0 (0)	0 (0)	23 (100)	0 (0)	23 (100)	–
NCDB USA [17]							
NAC, *N* = 921	–	0 (0)	479 (52)	T4a 69 (7) T4b 350 (38)	450 (49)	397 (44)	–
Surgery + AC, *N* = 26,654	–	0(0)	19,999 (75)	T4a 3201 (12) T4b 2987 (11)	11,106 (42)	14,328 (54)	–

–: data not published

EMI extramural vascular invasion, *NAC* neoadjuvant chemotherapy, *AC* adjuvant chemotherapy

Table 3 Postoperative complications

Study	Stoma (%)	Postoperative complications				
		Anastomotic leak (%)	Intra-abdominal abscess (%)	Clavien–Dindo III–IV (%)	Postoperative stay., days Median (IQR)	Death (%)
Foxtrot, UK [5]						
Intervention, $N=99$	12 (12)	5 (5)	13 (13)	4 (4)	7 (5–10)	0 (0)
Control, $N=51$	5 (10)	2 (4)	4 (8)	2 (4)	6 (3–8)	1 (2)
ICT-XEL, Spain, $N=65$ [6]	–	4 (6.1)	–	5 (7.7)	6 (5–8)	0 (0)
Vejle, Denmark, $N=71$ [14]	–	7 (7)	0	–	6	0(0)
Shanghai, China, $N=47$ [15]	–	0 (0)	0(0)	0 (0)	9.4+	0(0)
Beijing, China, $n=23$ [16]	1 (4.3)	0 (0)	0 (0)	0 (0)	9 (range 7–30)	0 (0)
NCDB USA [17]						
NAC, $N=921$	–	–	–	–	–	–
Surgery + AC $N=26,654$	–	–	–	–	–	–

+: expressed in mean, –: data not published

IQR interquartile range, *NAC* neoadjuvant chemotherapy, *AC* adjuvant chemotherapy

evidence is available [44–46]. The FOxTROT trial did not observe measurable adverse effects as regards reoperation rates, stoma formation, or postoperative stay [5]. Recently, the complete results of the FOxTROT trial with 1052 patients from 85 centres in the UK, Denmark and Sweden have been presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. The authors compared 354 patients in the intervention group to 698 in the control group. NAC was safe, well tolerated and with no increase in surgical complications; in fact, there was less major surgical morbidity. Tumor regression was observed in 59% patients after NAC, including a 4% pathological complete response. Compared to the NAC group, more patients in the control group required another operation (7.1% vs. 4.3%; $p=0.05$), more often had anastomotic leak or intraabdominal abscess (7.4% vs. 4.7%; p: n.s.) and had double the number of incomplete resections (10% vs. 5%; 0.001).[47]

Oncological outcome

The current NCCN guidelines added NAC as a treatment option for patients with clinical T4b disease [48], where it has been proved to be an effective alternative [17]. A recent study assessed the role of NAC with capecitabine + oxaliplatin (CAPOX) ± bevacizumab for LACC involving the urinary bladder, concluding that this approach is an effective option improving organ preservation and oncological outcome [49].

Little exists regarding survival after NAC in the studies included in our review. In the Danish trial, after a mean follow-up period of 26.4 months, the DFS in the good response patient group was 94% versus the 63% in the non-responder group [14]. In this study, the addition of panitumumab did not show any benefit [14]. In the Spanish study, the 3-year DFS was 88.9%, after a mean follow-up of 40.1 months [6]. In the ASCO report of the FOxTROT trial, NAC showed a better 2-year failure rate (HR = 0.77), but the findings were not significant ($p=0.11$), requiring further trials to confirm the benefits [47]. The American study proved significantly better survival only in T4b tumors [17].

Currently, the optimal treatment for LACC is surgery followed by adjuvant treatment. However, LACC resection is often related to postoperative complications that reduce the possibility of administering adjuvant therapy, therefore, of a complete oncological treatment. An incomplete treatment is directly correlated with lower survival rates. Therefore, we may speculate that giving preoperative treatment to these high-risk patients may help to increase the patient's chance of having optimal oncological therapy [4, 50, 51].

If there is a good treatment response there will be a better resectability rate, and at the same time, the chance of using a laparoscopic approach is increased. Preoperative chemotherapy allows an in vivo analysis of the chemosensitivity, which targets the patient response to a specific therapeutic plan, able to tailor adjuvant postoperative treatment [4, 51].

It is well known that in LACC, there is a high risk of local progression and distant metastases. In this setting, NAC may not only provide early treatment directly to the tumor, but also to the micrometastases. The long-term results of the studies previously described, which could reveal the real impact of NAC, are awaited with great interest.

Table 4 Pathology report

Study	*R* (%)		yp *T* (%)			yp *N* (%)			Resected nodes. Median (range)	yp Stage (%)					TRG (%)			LVI (%)
	0	1–2	T0-1–2	T3	T4	N0	N1	N2		0	I	II	III	IV	Little/no	Moderate	Marked/complete	
Foxtrot UK [5]																		
Intervention *N*=99	95 (96)	4 (4)	9 (9)	60 (61)	30 (30)	59 (59)	24 (24)	15 (15)	21 (15–27)	2 (2)	6 (6)	52 (52)	38 (38)	1 (1)	65 (66)	25 (25)	4 (4)	
Control *N*=50	40 (80)	10 (20)	1 (2)	30 (60)	19 (38)	24 (48)	10 (20)	16 (32)	22 (16–30)	0 (0)	1 (2)	23 (46)	24 (48)	2 (4)	45 (90)	1 (2)	0 (0)	
ICT-XEL, Spain, *N*=65 [6]	65 (100)	0 (0)	27 (41.6)	34 (52.3)	4 (6.2)	48 (73.8)	8 (12.3)	9 (13.8)	20 (IQR: 15–29)	3 (4.6)	16 (24.6)	29 (44.6)	17 (26.2)	0 (0)	41 (63.1)	15 (23.1)	9 (13.8)	7 (10.8)
Vejle, Denmark, *N*=71 [14]	–	–	15 (21.2)	46 (64.8)	10 (14)	47 (66.2)	15 (21.1)	9 (12.7)	30 (6–97)	–	–	–	–	–	–	–	–	–
Shanghai, China, *N*=47 [15]	47 (100)	0 (0)	2 (4)	15 (32)	30 (64)	29 (62)	10 (21)	8 (17)	–	1 (2)	0 (0)	28 (60)	18 (38)	0(0)	15 (32)	29 (62)	3 (6)	10 (21)^
Beijing, China, *N*=23 [16]	20 (87)	3 (13)	2 (8.6)	10 (43.5)	11 (47.9)	12 (52.2)	6 (26.8)	5 (21.7)	–	1 (4.3)	1 (4.3)	10 (43.4)	8 (34.7)	3 (13)	6 (26.1)	9 (39.1)	8 (34.7)	–
NCDB, USA [17]																		
NAC *N*=921	776 (84)	126 (14)	–	–	–	–	–	–	≥12: 745 (81%)	–	–	–	–	–	–	–	–	
Surgery + AC *N*=26,654	23,619 (89)	2669 (10)	–	–	–	–	–	–	≥12: 23,602 (89%)	–	–	–	–	–	–	–	–	

R: Resection margins, R0: Complete, R1-2: Incomplete, *: Extramural invasion, ^: Venous invasion

NAC neoadjuvant chemotherapy, *AC* adjuvant chemotherapy, *TRG* tumor regression grade, *IQR* interquartile range, *LVI* lymphovascular invasion

Ongoing studies

As shown in Table 5, nine trials are ongoing with the main objective to assess both pathological response and survival of LACC after NAC.

- *Prodige 22–Eckinoxe, Paris, France, NCT01675999*
  This is a multicenter randomized controlled phase II trial comprising 3 arms of intervention: 4 neoadjuvant cycles of FOLFOX-4, surgical intervention and additional 8 cycles of FOLFOX-4//preoperative folinic acid, 5-FU and oxaliplatin (FOLFOX)-4 with cetuximab, surgery and 8 cycles of adjuvant FOLFOX-4 with cetuximab—arm only open for RAS wild-type patients// surgery followed by 12 adjuvant cycles of FOLFOX-4. It requires T4 or T3 with > 5 mm of extramural extension colon adenocarcinoma, and/or N2, without metastases by CT scan. Fifty-seven French centers participate in the trial. It assesses the tumor regression grade, postoperative morbidity, toxicity chemotherapy compliance, 3-year DFS, 3-year regression-free survival, quality of life and the radiological and pathological correlation [7].
- *ELECLA, León, Spain, NCT: 04,188,158*
  Conducted at the University Hospital of León, this is a multicenter randomized controlled trial, with an estimated sample size of 238 patients. The main objective is to determine if NAC increases the 2-year DFS. It will also analyses its feasibility, efficacy, toxicity, chemotherapy compliance, CT scan accuracy, and OS. It requires T3 with > 5 mm extramural invasion–T4 colon adenocarcinoma, without metastases. It consists of three cycles of XELOX, surgery and five cycles of XELOX vs. surgery followed by eight cycles of XELOX. Currently, this trial is recruiting patients and open to the incorporation of new hospitals willing to participate. The first report of complete pathologic response in this trial has been published recently [21].
- *NACSOC, Beijing, China, NCT02972541*
  This is a randomized clinical trial at Chao Yang Hospital that evaluates patients with LACC that require colon prostheses due to acute colonic obstruction. The intervention group patients, once the prostheses is implanted, will receive FOLFOX-6 or XELOX before surgery. After that, they will undergo surgery and adjuvant chemotherapy. The control group will have surgery 7–14 days after the correct implantation of the prostheses and will receive adjuvant chemotherapy. It intends to enroll 248 patients and will assess the 5-year DFS and OS, the stoma rate formation, the postoperative morbidity, the toxicity, and the rates of R0 surgery.
- Vejle, Denmark, NCT01918527
  This phase III randomized clinical trial includes hospitals in Denmark, Sweden and Norway. It assesses the 2-year DFS rate, comparing the intervention group that receives three cycles of XELOX, surgery and additional five cycles of XELOX—if the criteria are fulfilled—to the control group, which will get surgical care followed by eight cycles of XELOX. Monoclonal antibodies are not being used.
- *Optical, Guangzhou, China, NCT02572141*
  This phase III clinical trial, at Sun Yat-sen University, will evaluate the efficacy of NAC, analyzing R0 surgery rate, OS, DFS, primary tumor downstaging, NAC tolerance and perioperative complications. It attempts to include 738 patients with T3 with > 5 mm extramural invasion–T4 tumors. Treatment will be based on FOLFOX-6 or XELOX. Control group is based on colectomy followed by chemotherapy with mFOLFOX6 or CAPOX regimens.
- *Nanjing, China, NCT02882269*
  The main aim of this study proposed by The First Affiliated Hospital and Nanjing Medical University is to assess the difference in the 3-year DFS rate between adjuvant and neoadjuvant chemotherapy. It intends to enroll 400 patients, with T3–4 N0 or T1–4 N + tumors, without metastases, using FOLFOX, XELOX, folinic acid, irinotecan, and 5-FU(FOLFIRI) or capecitabine in monotherapy. In the control group, patients will receive 6 months of adjuvant chemotherapy with the same drug scheme.
- *Shanghai, China, NCT02777437*
  This is a multicenter clinical trial from the University of Fudan. It will compare the effect of NAC in laparoscopic surgical procedures of T4 tumors in 1960 patients, assessing the DFS, OS, morbidity, mortality and laparoscopic surgery proportion. NAC is based on the XELOX/FOLFOX regimen.
- *Korea, NCT03426904*
  This phase III randomized controlled trial will assess the impact on 3-year DFS of a NAC scheme based on FOLFOX in 560 patients. The control group will receive 12 cycles of postoperative FOLFOX chemotherapy.
- *Shanghai, China, NCT03125980:*

Also proposed by University of Fudan, this randomized controlled phase II trial, will assess the impact of preoperative CAPOX on 3-year DFS. This study will select 1370 T4/N + CC patients. The control group will receive conventional capecitabine plus oxaliplatin after surgery [22].

The population included in the studies seemed typical of those who might be candidates for NAC. One of the concerns is the choice of NAC regimen, mainly based on 5-FU or capecitabine, combined or not with oxaliplatin or irinotecan. Adding anti-epidermal growth factor receptor (EGFR) antibodies to NAC for KRAS wild-type patients

Table 5 Main characteristics of the ongoing trials

Study	City. Country	Type of study	Primary endpoint	Secondary endpoints	NAC scheme	Radiological inclusion criteria	Sample size
Prodige 22–Eckinoxe, [7] NCT01675999	Paris, France	Randomized clinical trial. Phase II. 3 arms. Multicenter	Histological tumor regression grade	Safety, tolerability and efficacy of NAC. 3-year DFS. 6–7-year OS. Quality of life	FOLFOX-4 ±cetuximab	T4-3(> 5 mm)/N2 M0	165
ELECLA, [21] NCT: 04,188,158	León, Spain	Randomized clinical trial. Phase II. 2 arms. Multicenter	2-Year DFS	5-Year DFS. 2-,5-year OS. Surgical morbidity	XELOX	T4-3(> 5 mm) M0	238
NACSOC NCT02972541	Beijing, China	Non-randomized clinical trial. 2 arms	5-Year DFS and OS Rate of stoma formation	Surgical complication. Rate of anastomosis. R0 resection rate. Re-operation rate. Chemotherapy completion rate. Chemotherapy related complication	FOLFOX-6/XELOX	LACC requiring colonic prostheses	248
NCT01918527	Vejle, Denmark	Randomized clinical trial. Phase III. 2 arms. Multicenter	2-Year DFS	Rate of patients fulfilling the criteria for adjuvant chemotherapy	XELOX	T4-3(> 5 mm) M0	250
Optical NCT02572141	Guangzhou, China	Randomized clinical trial. Phase III. 2 arms. Multicenter	3-Year DFS	Curative resection rate. 5-yearOS. 5-year RFS. Down-staging of primary tumors. Toxicity. Postoperative complications	FOLFOX-6/XELOX	T4-3(> 5 mm) M0	738
NCT02882269	Nanjing, China	Randomized clinical trial. Phase II–III. 2 arms	3-Year DFS	3-year OS. 3-year RFS. 3-year local recurrence rate. Length of stay. Early complication rate. Operative time. Lymphadenectomy	FOLFOX/XELOX/ FOLFIRI/ Capecitabine	T3-4N0M0/T any N + M0	400
NCT02777437	Shanghai, China	Randomized clinical trial. Phase II–III. 2 arms. Multicenter	3-Year DFS	3-year OS. Adverse events. Laparoscopic surgery rate	XELOX/FOLFOX	T4 and laparoscopic Surgical approach	1960

Table 5 (continued)

Study	City. Country	Type of study	Primary endpoint	Secondary endpoints	NAC scheme	Radiological inclusion criteria	Sample size
NCT03426904	Kyungpook, Korea	Randomized clinical trial. Phase III. 2 arms. Multicenter	3-Year RFS	3-year OS. Radiological response. Pathological response. Surgical complications. Length of stay. Quality of life. Toxicity of chemotherapy. Completion of chemotherapy. Accuracy of CT. Cycles of chemotherapy. Pathological tumor stage	FOLFOX	T3/T4 and high risk features	560
NCT03125980 [22]	Shanghai, China	Randomized clinical trial. Phase III. 2 arms. Multicenter	3-Year DFS	R0 resection rate. Tumor regression grade. 5-year OS. 5-year RFS	CapOX	T4 or N + M0	1370

The control group is based on the standard treatment of surgery followed by adjuvant chemotherapy

NAC neoadjuvant chemotherapy, *LACC* locally advanced colon cancer, *DFS* disease free survival, *RFS* relapse free survival, *OS* overall survival

remains uncertain since some studies have shown that cetuximab in addition to chemotherapy in the adjuvant setting was detrimental [52]. Furthermore, long-term toxicity of chemotherapy should not be neglected [53]. It is important to determine the microsatellite instability (MSI) status of the patients proposed for NAC because in deficient deoxyribonucleic acid (DNA) mismatch repair tumors, survival is better, and adjuvant chemotherapy may be harmful [54]. The optimal duration of NAC has not been well established, and the appropriate timing of surgery following NAC is also a question, because it should try to achieve the greatest pathological response but avoid outgrowth of the primary tumor. NAC has also been proposed as an alternative after a bridge surgery in a baseline unresectable CC [55, 56].

The current ongoing trials are being developed in different clinical scenes all around the world, and the conclusions will be perfectly complementary and with a high external validity. Some requirements are fundamental for a neoadjuvant approach: chemotherapy must be effective over the primary tumor, radiological assessment must be accurate and select high-risk patients, avoiding overtreatment, and finally, NAC should be well tolerated and given without increasing surgical morbidity [10]. Data collected from these studies will address question of what NAC regimen is best, whether NAC is safer, more effective and better tolerated that adjuvant chemotherapy, and whether the tumor response to NAC is able to guide the adjuvant treatment.

Limitations

This systematic review has some limitations. The main one is the scarcity of available studies and the small number of included patients. This fact has precluded a meta-analysis about this topic. Regarding the quality of the reviewed research, only one study was a randomized controlled trial. The remaining studies did not have a control group or were retrospective. Trying to minimize this problem, all the current and registered ongoing trials have been described.

Conclusions

According to our systematic review, NAC may be a safe and effective emerging therapeutic alternative for treating LACC. This approach, which is still being tested, increases the reliance on accurate radiological staging. Further larger scale comprehensive studies such as the ongoing trials we have summarized are warranted to shed light on the real impact of NAC in LACC, and to assess if this novel approach will change the current standard of care for these patients.

Author contributions JA, EP and CC had the idea for the article. VS, MB, MCM, IM, MN, BI and JA performed the literature search and data analysis. All authors critically revised the work and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Arredondo is the principal investigator of the ELECLA trial. The other authors declare that they have no conflict of interest.

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