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Systematic Review

Transarterial Chemoembolization in Locally Advanced Rectal Cancer: A Systematic Review

Hugo C. Temperley [1,*,†], Jack Bell [1,†], Tom O. Cuddihy [1], Niall J. O'Sullivan [1], Benjamin M. Mac Curtain [2], Steven Dolan [1], Niall McEniff [1], Ian Brennan [1], Kevin Sheahan [1], Martin Marshal [3], Michael E. Kelly [4,5] and Zi Q. Ng [6]

1 Department of Radiology, St. James's Hospital, D08 NHY1 Dublin, Ireland
2 Department of Surgery, Waterford University Hospital, X91 ER8E Waterford, Ireland
3 Department of Radiology, Royal Perth Hospital, Perth, WA 6000, Australia
4 Department Surgery, St. James's Hospital and Trinity College Dublin, D08 NHY1 Dublin, Ireland
5 Trinity St. James's Cancer Institute, D08 NHY1 Dublin, Ireland
6 Department of General Surgery, Royal Perth Hospital, Perth, WA 6000, Australia
* Correspondence: temperlh@tcd.ie
† These authors contributed equally to this work.

Simple Summary: Locally advanced rectal cancer presents significant treatment challenges, often requiring aggressive multimodal therapy. Transarterial chemoembolization (TACE) is an innovative approach that allows for the targeted delivery of chemotherapy directly to the tumor, minimizing systemic exposure and potentially reducing adverse effects. This systematic review aims to evaluate the current evidence on TACE in rectal cancer, focusing on its efficacy in tumor reduction, survival outcomes, and safety profile. By summarizing data from various studies, this review highlights TACE's potential role as an adjunctive therapy in managing this difficult-to-treat cancer. While initial results are promising, further research is needed to establish its optimal use in clinical practice and to better define its benefits in combination with other standard therapies.

Abstract: Background: Locally advanced rectal cancer (LARC) presents a significant treatment challenge. Transarterial chemoembolization (TACE) has emerged as a potential adjunctive treatment, offering targeted delivery of chemotherapeutic agents to the tumor site, minimizing systemic exposure. This systematic review aims to assess the current literature on this novel technique and evaluate the safety and efficacy profile of TACE in treating this complex cohort of patients. Methods: A comprehensive literature search was conducted across multiple databases, including PubMed, EMBASE, and Cochrane Library, to identify studies evaluating TACE in LARC. Inclusion criteria encompassed clinical trials, cohort studies, and case series reporting on outcomes such as tumor response rate, overall survival (OS), progression-free survival (PFS), and treatment-related adverse events. Results: A total of eight studies involving 543 patients met the inclusion criteria. The studies varied in design, with five prospective and three retrospective studies. A higher prevalence of male participants (68.7%) was noted, with a median age of 60.3 years. The studies primarily evaluated the efficacy and safety of TACE in LARC treatment. Pathological response rates, tumor reduction, and survival outcomes varied across studies, with TACE showing promise in reducing tumor size, improving survival, and controlling metastasis. Major complications were rare, reported in 6.0% of cases. Conclusions: TACE is a promising therapeutic option for patients with LARC, demonstrating favorable tumor response rates and manageable toxicity profiles. Further large-scale, randomized controlled trials are warranted to confirm these findings and better define the role of TACE in the multimodal treatment of LARC.

Keywords: rectal cancer; embolization; interventional radiology; survival; TACE; oncology

Citation: Temperley, H.C.; Bell, J.; Cuddihy, T.O.; O'Sullivan, N.J.; Mac Curtain, B.M.; Dolan, S.; McEniff, N.; Brennan, I.; Sheahan, K.; Marshal, M.; et al. Transarterial Chemoembolization in Locally Advanced Rectal Cancer: A Systematic Review. *Onco* **2024**, *4*, 412–426. https://doi.org/10.3390/onco4040029

Academic Editor: Constantin N. Baxevanis

Received: 15 September 2024
Revised: 27 October 2024
Accepted: 8 November 2024
Published: 13 November 2024

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, accounting for approximately 10% of all cancers. In 2024, the American Cancer Society estimates the diagnosis of 46,200 new rectal cancers, with one-third of cases being advanced rectal cancer (LARC) [1]. The current gold standard in clinical care regarding LARC is either neoadjuvant chemoradiation or total neoadjuvant therapy (TnT), followed by surgery and/or an adjuvant approach [2]. Those with mismatch repair (MMR)–deficient immunohistology undergo neoadjuvant immunotherapy [3,4]. LARC can pose significant challenges due to difficulties with surgery, increased rates of local recurrence, and/or distant metastases [5]. As a result of this, a more intense treatment strategy is generally employed. The shift to TnT has been proposed because it allows for better tolerance of systemic therapy, facilitates organ preservation by downstaging of the tumor, improves pathological complete response (pCR) rates, and may improve patient outcomes by reducing the risk of distant metastases and local recurrence [6–8].

Recently, transarterial chemoembolization (TACE) has been added as an alternative approach for managing LARC. TACE is a minimally invasive procedure that delivers a drug intraarterially to impede blood supply to the tumor. This can potentially be combined with chemotherapeutic agents delivered directly into the tumor [9]. TACE has long been a strategy employed in liver and gastric cancer; however, its use is scarce in rectal cancer [10,11]. The literature within the cohort is increasing, with some studies citing TACE as a viable and successful management option. New approaches of combining TACE with concurrent chemotherapy have been shown to have considerable potential [11]. In addition to this, it offers an alternative treatment that may improve oncological outcomes, even in those with advanced unresectable tumors [12]. For TACE to be feasible, detailed planning with CT angiography is essential to enable precise, super-selective embolization. This ensures targeted drug delivery to the tumor whilst minimizing damage to surrounding healthy tissues, improving the effectiveness and safety of the procedure.

This review will examine the previously published literature regarding the use of TACE as a method of treatment for LARC. To the best of the authors' knowledge, this is the first systematic review detailing studies for this treatment pathway with this cohort.

2. Methods

2.1. Study Design and Reporting Guidelines

This is a systematic review of retrospective and prospective cohort studies conducted following PRISMA reporting guidelines [13].

2.2. Search Strategy

The following databases were interrogated as part of our systematic review: PubMed, Embase, and Web of Science. The following search strategy was used: ("transarterial chemoembolization" OR "TACE" OR "chemoembolization" OR "transcatheter arterial chemoembolization") AND ("locally advanced rectal cancer" OR "rectal cancer" OR "rectal neoplasm" OR "advanced rectal cancer") up to 2 July 2024. The gray literature was also searched to identify any further ongoing works of literature.

2.3. Eligibility Criteria

Original studies investigating the use of TACE by interventional radiology (IR) in the setting of LARC. Complications were categorized using the Society of Interventional Radiology (SIR) criteria, classifying adverse events from SIR A (mild) to SIR F (severe). This standardized approach ensured consistent reporting and comparison of treatment-related complications across studies. Case reports, conference abstracts, and review articles were excluded.

2.4. Study Selection, Data Extraction, and Critical Appraisal

A database was created using the reference managing software EndNote X9™. Two researchers (JB and HCT) reviewed outputs from the searches independently of each other. Initially, duplicates were removed. Study titles were then screened and assessed for potential relevance. The abstracts of selected potential studies were then read and assessed for eligibility for inclusion based on the inclusion/exclusion criteria detailed above. Rejected reasons were recorded. The full texts of the abstracts deemed eligible for inclusion were then further analyzed using the same criteria.

To extract and store data efficiently, the Cochrane Collaboration screening and data extraction tool, Covidence, was used [14]. Data were collected by two reviewers (JB and HCT) independently, using the following headings: study details, study design, population, intervention, comparison groups, and outcomes. Conflicts between the two reviewers were resolved following an open discussion and a final decision by the senior author (ZN).

Potential biases for the non-RCT studies were assessed using the Newcastle–Ottawa scale (TH) risk of bias tool, and the results were tabulated [15]. This assessment tool grades each study as being "satisfactory" or "unsatisfactory" across various categories. We assigned stars to evaluate study quality: 7 stars "very good", 5–6 stars "good", 3–4 stars "satisfactory", and 0–2 stars "unsatisfactory". The critical appraisal was completed independently by two reviewers (JB and HCT), where, once again, a third reviewer (ZN) was asked to arbitrate in cases of discrepancies in opinion.

2.5. Statistical Analysis

Statistical analysis was performed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX, USA, StataCorp LLC). Generic inverse variance data were reported as hazard ratios (HR) and 95% confidence interval (95% CI. Outcome measures (mean + standard deviation and median + interquartile range) were recorded. If needed, outcome variables (mean and SD) were estimated from the median and range using the formula described by Hozo et al. [16]. Heterogeneity was assessed by I-squared statistics, with >50% being considered as considerable heterogeneity. Statistical significance was attributed to a p-value of <0.05. A random-effects model was applied in all cases.

2.6. Systematic Review Registration

Our systematic review was registered on PROSPERO in July 2024 (ID: CRD42024548501).

3. Results

The literature search described yielded a total of 401 results (See Figure 1). After the removal of 200 duplicates, 201 studies were then screened. Overall, 35 full texts were reviewed and assessed for eligibility following the initial screen. A total of eight studies met the eligibility criteria set and were included in our analysis [1,10,17–22]. The majority of the studies were performed in China [1,10,18–22], with one study taking place in Italy [17]. The studies varied in design; five were prospective (including phase II trials and cohort studies) [1,10,17,19,20], and three were retrospective [18,21,22]. This included a total of 543 patients with confirmed LARC. The gender distribution across the studies showed a higher prevalence of male participants, accounting for 68.7% (321/467 where gender was stated) compared to 31.3% (146/467 where gender was stated). The median age of the participants was 60.3 years. See Tables 1 and 2. Definitions of locally advanced rectal cancer (LARC) varied across the eight studies. Six out of eight studies defined LARC as tumors classified as T3-4, with or without nodal involvement [1,10,18–22]. Two of these studies further specified inclusion criteria as T3-4N0M0 or T1-4N1-2M0 [1,18]. One study defined LARC as cT3-4 N+/− M0 [19]. One study did not provide an explicit definition of LARC [17]. Six studies focused on using TACE as a neoadjuvant treatment modality [1,10,18–21]. One study assessed TACE for rectal cancer complicated by obstruction [22], and another explored its use in inoperable or recurrent rectal cancer [17] (Table 2).

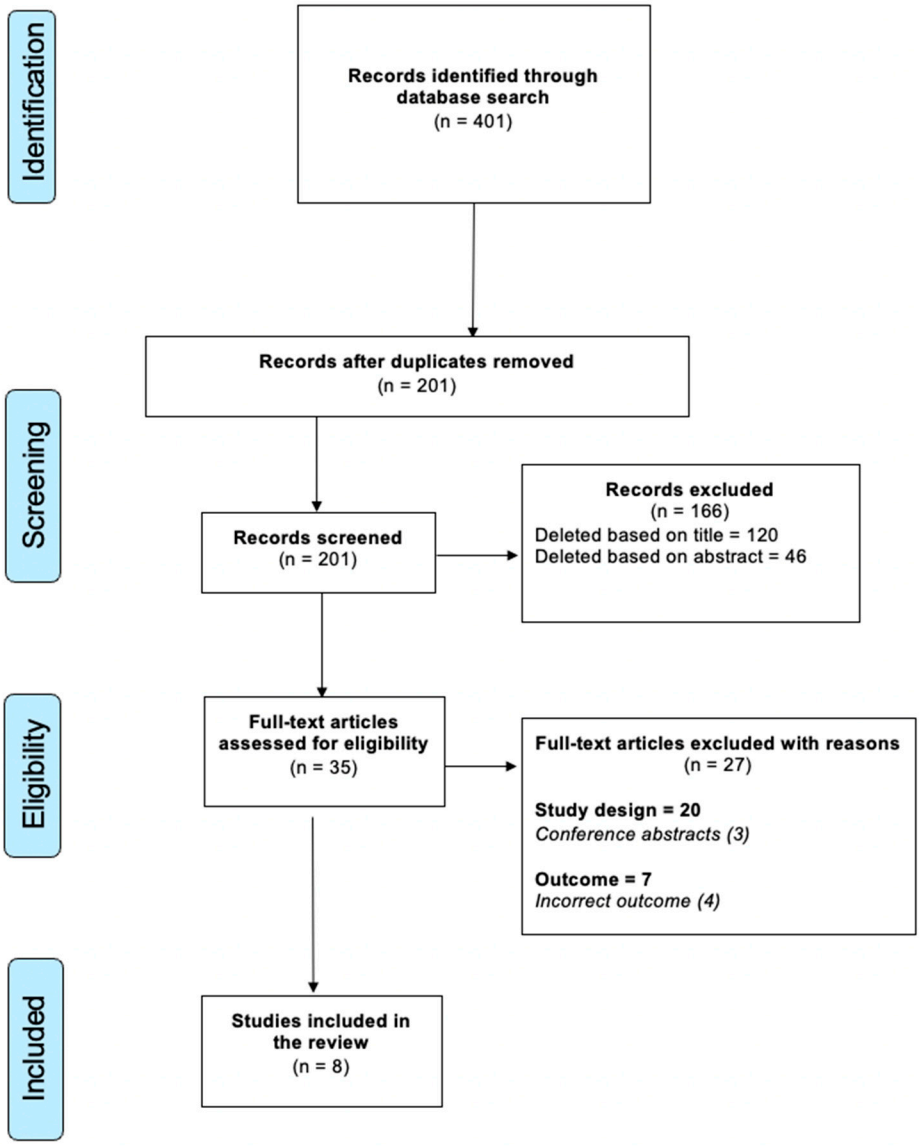

Figure 1. Study selection: a PRISMA flowchart of the selection of relevant publications included in this review.

Table 1. Study characteristics.

Author	Year	Country	Sample Size	Study Design	Male: Female	Median Age	Study Period
Bini et al.	2010	Italy	12	Prospective mono-institutional cohort study	10:2	71	Not specified
Gao et al.	2023	China	77	Retrospective study	30:10 pMMR protein group 24:13 dMMR protein group	pMMR 58.2 dMMR 59.7	2013 to 2021
Meng et al.	2021	China	118	Non-randomized prospective study	43:17 TRACE-CRT group 40:18 CRT group	TRACE-CRT: 59 CRT group: 58	2013 to 2020

Table 1. *Cont.*

Author	Year	Country	Sample Size	Study Design	Male: Female	Median Age	Study Period
Huang et al.	2023	China	32	Prospective, monocentric, open-label, single-arm phase II study	Not specified	Not Specified	Not specified
Yang et al.	2024	China	111	Single-center, prospective, phase II trial	73:38	59	Not specified
Meng et al.	2023	China	44	Retrospective cohort study	31:13	56.6	2013 to 2018
Bo Yang et al.	2020	China	95	Prospective, monocentric, non-randomized clinical study	NATRACE-CRT: 35:15 NA-CRT: 34:11	NATRACE-CRT: 62 NA-CRT: 57	Not specified
Ding et al.	2024	China	54	Retrospective analysis	33:22	58.6	Not specified

pMMR: Proficient Mismatch Repair, dMMR: Deficient Mismatch Repair, TACE: Transarterial Chemoembolization, TRACE-CRT: Transarterial Chemoembolization Combined with Chemoradiotherapy, CRT: Chemoradiotherapy, NATRACE-CRT: Neoadjuvant Transarterial Chemoembolization Combined with Chemoradiotherapy, NA-CRT: Neoadjuvant Chemoradiotherapy, and LARC: Locally Advanced Rectal Cancer.

The primary goals of the studies were to assess the efficacy, safety, and feasibility of TACE and related interventions in treating LARC. Patients were followed up on a median of 38.7 months (±14.3) (range 11.5–60 months) (Table 2).

Table 2. Overview of clinical studies on treatment approaches for rectal cancer.

Author	Study Goal	Type of Cancer	Definition of LARC	Comorbidities	Imaging Modalities in Study	Follow-Up Period
Bini et al.	Assess the feasibility, safety and efficacy of TACE with irinotecan-loaded microparticles (DEBIRI) with inoperable or recurrent rectal cancer	LARC	Not defined	COPD, CAD, essential HTN, chronic atrial fibrillation, asthma, chronic CCF, DCM	Abdominal quadriphasic CT scan, diagnostic angiography, venous phase CT, MASS, RECIST, mChoi criteria	Not specified
Gao et al.	Evaluate the effect of dMMR status on the response to neoadjuvant therapy in patients with LARC	LARC	T3-4N0M0 or T1-4N1-2M0	No serious heart, lung, liver or kidney dysfunction or immune deficiency disease were included	Digital subtraction angiography, iodixanol angiography	Follow-up time for both groups was 5 years
Meng et al. (2021)	To analyze and evaluate the impact of preoperative TACE + CRT on surgery and prognosis of LARC	LARC	cT3~4N0M0 or cT1~4N1~2M0	Not specified	MRI staging, digital subtraction angiography (DSA)	Mean follow-up time: TRACE-CRT (42.0 ± 19.7 months) vs. CRT (40.6 ± 24.7 months)

Table 2. *Cont.*

Author	Study Goal	Type of Cancer	Definition of LARC	Comorbidities	Imaging Modalities in Study	Follow-Up Period
Huang et al.	To assess the safety and efficacy of IAC plus CRT and FOLFIRINOX consolidation chemotherapy to optimize complete response and survival in distal rectal cancer	Distal rectal adenocarcinoma	cT3-4 N +/− any M0	Excludes patients with severe comorbidities such as heart failure, uncontrolled diabetes, renal failure, liver failure	Pelvic MRI, chest and abdomen CT, digital rectal examination, endoscopy	Conducted according to the OPRA trial protocol, every 3 months for the first 2 years and every 6 months for the following 3 years. All patients followed for at least 5 years
Yang et al.	To assess the efficacy and safety of preoperative TACE in patients with LARC	LARC	T3-4	Severe comorbidities were exclusion criteria	MRI, endoscopy	Median follow-up duration of 38 months
Meng et al. (2023)	To compare the effect of preoperative regional TACE + CRT versus standard CRT on preventing distant metastasis in patients with LARC	LARC	T3-4	Exclusion criteria included uncontrolled serious heart, renal, or liver failure, among others	Digital subtraction angiography	Follow-up carried out every 1–3 months during the interventional treatment period and every 3–6 months thereafter. All patients had a complete record of at least 3 years of follow-up.
Bo Yang et al.	To explore the efficacy and safety of TACE with oxaliplatin and S-1 concurrent CRT as neoadjuvant therapy for LARC	LARC	T3-4	Patients with serious complications who could not complete treatment regimen were excluded	MRI	Median 33 months for NATRACE-CRT group, median 27 months for NA-CRT group
Ding et al.	To investigate the safety, efficacy, and feasibility of TACE combined with lipiodol chemoembolization for treating advanced colorectal cancer complicated by obstruction	LARC with obstruction	T3-4	Coronary heart disease, hypertension, diabetes, cerebral infarction among others	Abdominal and pelvic enhanced computed tomography (CT) or magnetic resonance imaging (MRI)	The median follow-up time was 11.5 months

TACE: Transarterial Chemoembolization, LARC: Locally Advanced Rectal Cancer, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, HTN: Hypertension, CCF: Congestive Cardiac Failure, DCM: Dilated Cardiomyopathy, CT: Computed Tomography, MASS: Morphologic Analysis of Size and Structure, RECIST: Response Evaluation Criteria in Solid Tumors, mChoi: Modified Choi Criteria, dMMR: Deficient Mismatch Repair, CRT: Chemoradiotherapy, MRI: Magnetic Resonance Imaging, IAC: Intra-Arterial Chemotherapy, OPRA: Organ Preservation After Chemoradiotherapy Trial, DSA: Digital Subtraction Angiography, and NA-CRT: Neoadjuvant Chemoradiotherapy.

The technical aspects of the studies included are compared in Table 3. The use of femoral artery puncture as the access point was consistent across studies, with 75% of the studies targeting the superior rectal artery. A total of 37.75% of studies additionally targeted the inferior rectal artery alongside the superior rectal artery. Yang et al. [20] also targeted the internal iliac arteries bilaterally. Bini et al. [17] and Ding et al. [22] varied but were consistent in targeting arteries leading to the lesion via the superior mesenteric

artery and inferior mesenteric artery. Treatment regimens varied, with combinations of chemotherapy agents and concurrent chemoradiotherapy.

Table 3. Intervention details.

Author	Access Used	Artery Targeted	Treatment
Bini et al.	Femoral artery puncture	Arteries leading to lesion via SMA and IMA; in one case, the hypogastric artery was targeted.	TACE with irinotecan-loaded microparticles (DEBIRI)
Gao et al.	Femoral artery puncture	Superior and inferior rectal arteries	TRACE-CRT
Meng et al.	Femoral artery puncture	Superior rectal artery	TRACE-CRT vs. CRT
Huang et al.	Femoral artery puncture	Superior rectal artery and bilateral internal iliac arteries	IAC (irinotecan, raltitrexed, oxaliplatin) followed by CRT (50 Gy/25 fractions with capecitabine) and six cycles of FOLFIRINOX (leucovorin, 5-fluorouracil, oxaliplatin, irinotecan)
Yang et al.	Femoral artery puncture	Superior rectal artery and inferior rectal artery	TRACE with oxaliplatin, followed by radiotherapy (45 Gy) and oral S1 capsules, total mesorectal excision, and mFOLFOX6 or CAPOX regimens post-surgery
Meng et al. (2023)	Femoral artery puncture	Superior rectal artery	Preoperative TRACE with oxaliplatin combined with CRT (interventional group) vs. NA-CRT (control group)
Bo Yang et al.	Femoral artery puncture	Superior rectal artery and inferior rectal artery	TRACE with oxaliplatin and S-1 concurrent chemoradiotherapy (NATRACE-CRT) vs. standard fluorouracil-based chemoradiotherapy (NA-CRT)
Ding et al.	Femoral artery puncture	Tumor-supplying arterial branch via IMA and SMA	Transcatheter arterial infusion (TAI) chemotherapy combined with lipiodol chemoembolization

SMA: Superior Mesenteric Artery, IMA: Inferior Mesenteric Artery, TACE: Transarterial Chemoembolization, DEBIRI: Drug-Eluting Beads Irinotecan, TRACE-CRT: Transarterial Chemoembolization Combined with Chemoradiotherapy, CRT: Chemoradiotherapy, IAC: Intra-Arterial Chemotherapy, Gy: Gray (unit of radiation dose), FOLFIRINOX: Chemotherapy regimen consisting of Leucovorin, 5-Fluorouracil, Oxaliplatin, and Irinotecan, CAPOX: Chemotherapy regimen consisting of Capecitabine and Oxaliplatin, S-1: Oral anticancer drug (combination of Tegafur, Gimeracil, and Oteracil), NA-CRT: Neoadjuvant Chemoradiotherapy, and TAI: Transcatheter Arterial Infusion.

Adverse reactions ranged from mild to severe and were classified according to the Society of Interventional Radiology (SIR) standards. These can be seen in Tables 4–6, where complications were listed from SIR A to SIR D in the patients who received TACE. Of these patients, the most common complications were those classed as SIR A in 72.3%. The most common adverse reactions observed were leukopenia (21.4%) and nausea/vomiting (18.6%). SIR B complications were evident in 50.7% of patients. Within this group, anemia (13.6%) and radiation proctitis/enteritis (12.6%) were the most common. More serious complications accounted for a much smaller proportion, with no SIR C complications reported and only 6% of patients experiencing SIR D complications. Notably, there were zero SIR E and F complications observed. Meng et al. [1] reported no significant differences in postoperative complications between the TACE-CRT group and control. They did note a shorter mean operation time in the TACE-CRT group. In addition, Bini et al. [17] showed a decrease in ESAS scores from 3 to 2 in 100% of patients.

Table 4. Adverse reactions.

Author	Adverse Reactions
Bini et al.	Mild fever, procedure-related pain, increased WBC, LDH, AST/ALT, reactive C protein within 48 h
Gao et al.	Leukopenia, anemia, radiation enteritis, anastomotic leakage, incision infection, intestinal obstruction, incisional hernia
Meng et al.	No significant differences in postoperative complications between the groups, except for mean operation time, which was shorter in TRACE-CRT group (165.8 vs. 196.6 min, $p < 0.001$)
Huang et al.	Toxicity graded according to NCI criteria, surgical complications according to Clavien–Dindo classification, fecal incontinence according to Wexner score
Yang et al.	Grade 3–4 toxicities in 29 patients (26.13%), postoperative complication rate of 21.62%
Meng et al. (2023)	No significant differences in toxicities and complications between the two groups
Bo Yang et al.	No significant difference in incidence of preoperative toxic side effects and surgical complications between the groups

Table 5. Complications graded by the Society of Interventional Radiology (SIR) classification.

Complications	N = 397	%	SIR Classification
Leukopenia	85	21.4	A
Nausea/Vomiting	74	18.6	A
Anemia	54	13.6	B
Radiation Proctitis/Enteritis	50	12.6	B
Neutropenia	35	8.8	B
Fatigue	31	7.8	A
Loss of Appetite	31	7.8	A
Thrombocytopenia	31	7.8	A
Diarrhea	28	7.1	B
Liver Dysfunction/Deranged LFTs	28	7.1	A
Gastrointestinal Reactions	19	4.8	B
Intestinal Obstruction	12	3	D
Fever	10	2.5	B
Tenesmus	7	1.8	A
Incision Infection	6	1.5	D
Anastomotic Leakage	6	1.5	D
Hand–Foot Syndrome	5	1.3	B

In the analysis of transarterial chemoembolization (TACE), several key oncological outcomes were reported across different studies (Table 7).

Table 6. Complications graded by the Society of Interventional Radiology (SIR) classification.

Complication	N
SIR A	
Leukopenia	85
Nausea/Vomiting	74
Fatigue	31
Loss of Appetite	31
Thrombocytopenia	31
Liver Dysfunction/Deranged LFTs	28
Tenesmus	7
SIR B	
Anemia	54
Radiation Proctitis/Enteritis	50
Neutropenia	35
Fever	10
Diarrhea	28
Gastrointestinal Reactions	19
Hand–Foot Syndrome	5
SIR C	0
SIR D	
Intestinal Obstruction	12
Anastomotic Leakage	6
Incision Infection	6
SIR E	0
SIR F	0

N = number, LFT = liver function tests.

Table 7. Main oncological outcomes.

Author	Main Oncological Outcomes	Overall Survival	Disease-Free Survival
Bini et al.	• Decrease ESAS score from 3 to 2 in 100% patients • Radiological evaluation of treatment's response: (% of Tumor reduction) - RECIST 27% ± 16% - mChoi 22% ± 17% - New Volume 39% ± 26%	Median 12 Months	Not Specified
Gao et al.	• Pathological Complete Response - pMMR Group: 10% - dMMR Group: 43% • Negative Lymph Nodes - Overall: 82% - pMMR Group: 73% - dMMR Group: 92%	36 Months: 79.2% (pMMR) 5.7% (dMMR)	1 year: 89% (pMMR) vs. 92% (dMMR) 3 years: 82% (both groups)

Table 7. *Cont.*

Author	Main Oncological Outcomes	Overall Survival	Disease-Free Survival
Meng et al.	• Mean Operation Time: - TRACE-CRT group (165.8 ± 46.3 min) - CRT group (196.6 ± 46.9 min) • Reduced Incidence Distant Metastasis with TRACE-CRT	Not Specified	Not Specified
Huang et al.	• The study hypothesizes that the regimen could increase the pCR rate up to 40%, compared to approximately 15% after CRT alone.	Not Specified	Not Specified
Yang et al.	• Pathological Complete Response Rate: - 20.72%: (pCR) following TRACE and neoadjuvant chemoradiotherapy • Major Pathological Response Rate: - 48.65% defined as the sum of patients with TRG0 and TRG1	5-Year Overall Survival 74.8%	5-Year Disease-Free Survival 61.89%
Meng et al. (2023)	• Pathological T Staging Post-Treatment - TACE + CRT was significantly reduced compared to CRT alone • Significantly reduced Incidence Distant Metastasis with TRACE-CRT at 2 and 3 years	Not Specified	Not Specified
Bo Yang et al.	• Pathological Remission Rate (TRG0 + 1) - NATRACE-CRT 30% vs. NA-CRT 17.78% • Objective Response Rate - NATRACE-CRT 84% vs. NA-CRT 66.67% • Disease Control Rate (88.9%)	Not Specified	NATRACE-CRT Group 1-year 88% NA-CRT 1-year—92% NATRACE-CRT Group—3-year 76% NA-CRT 3-year 58%
Ding et al.	• Clinical Success Rate 83.3% Partial or complete relief of obstruction • Objective Response Rate (66.67%) • Disease Control Rate (88.9%)	13 Months	Not Specified

ESAS: Edmonton Symptom Assessment System, RECIST: Response Evaluation Criteria in Solid Tumors, mChoi: Modified Choi Criteria, pMMR: Proficient Mismatch Repair, dMMR: Deficient Mismatch Repair, TRACE-CRT: Transarterial Chemoembolization with Chemoradiotherapy, CRT: Chemoradiotherapy, pCR: Pathological Complete Response, TRG: Tumor Regression Grade, NATRACE-CRT: Neoadjuvant Transarterial Chemoembolization with Chemoradiotherapy, and NA-CRT: Neoadjuvant Chemoradiotherapy.

i. Pathological Response:

The pathological complete response (pCR) rates varied among the studies. Gao et al. [18] reported a higher pCR rate in the dMMR group (43%) than in the pMMR group (10%). Similarly, Yang et al. [20] reported a pCR rate of 20.72% following TACE and neoadjuvant chemoradiotherapy. Bo Yang et al. [10] found a higher pathological remission rate with NATRACE-CRT (30%) compared to NA-CRT (17.78%).

ii. Tumor Reduction and Response Rates:

Bini et al. [17] observed significant tumor reduction, with RECIST showing a reduction of 27% ± 16%, mChoi at 22% ± 17%, and New Volume at 39% ± 26%. The objective response rate (ORR) was also highlighted by Bo Yang et al. [10], with NATRACE-CRT achieving an 84% response rate compared to 66.67% in the NA-CRT group. Additionally, the disease control rate was reported as 88.9% in both Bo Yang et al. [10] and Ding et al. [22] studies.

iii. Survival Outcomes:

Overall survival (OS) varied significantly. Bini et al. [17] reported a median OS of 12 months, while Ding et al. [22] observed a median OS of 13 months. Gao et al. [18] reported a 36-month OS of 79.2% in the pMMR group and 85.7% in the dMMR group. Yang et al. [20] reported a 5-year OS of 74.8%. Disease-free survival (DFS) was reported by Gao et al. [18] with a 1-year DFS of 89% (pMMR) and 92% (dMMR) and a 3-year DFS of 82% for both groups. Bo Yang et al. [10] reported similar 1-year DFS rates of 88% in NATRACE-CRT and 92% NA-CRT, but with higher rates of 3-year DFS in the NATRACE-CRT (76% in NATRACE-CRT group compared to 58% in the NA-CRT group).

iv. Clinical Success and Metastasis Control:

Clinical success was reported by Ding et al. [22], with 83.3% of patients experiencing partial or complete relief of obstruction. Meng et al. [21] (2023) and Bo Yang et al. [10] reported a reduced incidence of distant metastasis with TRACE-CRT, further supporting the efficacy of TACE in controlling disease progression.

Quality of Studies

In regards to quality assessment, four studies were "good", four studies were "satisfactory", and no studies were "unsatisfactory" when scored using the Newcastle–Ottawa scale risk of bias tool. Supplementary Material S1 summarizes the results of our risk of bias assessment.

4. Discussion

The findings from this systematic review indicate that TACE may offer potential as a therapeutic option for LARC. The pooled data indicate a notable tumor response, with each of the studies demonstrating positive oncological outcomes, which is encouraging given the challenges associated with treating LARC through conventional methods. This discussion will explore the implications of these results, the potential mechanisms underlying the efficacy of TACE, the safety profile observed, and the future directions for research in this field.

The tumor response observed in this systematic review is significant and suggests that TACE may offer a robust alternative or adjunct to existing treatments. The targeted delivery of chemotherapeutic agents via TACE allows for higher local drug concentrations while minimizing systemic exposure, which could explain the enhanced tumor response. This localized approach can be particularly beneficial in rectal cancer, where the anatomical constraints and the proximity of the tumor to critical structures often limit the efficacy of systemic chemotherapy and radiation therapy. The study conducted by Bo Yang et al. [10] demonstrated the ORR of the treatment group, which included TACE, to be 84% compared to the conventional treatment group's ORR of 66.67%, further highlighting the potential and efficacy of TACE in the treatment of LARC. As described by the literature, the current standard of treatment for LARC, comprising preoperative neoadjuvant chemoradiotherapy, surgery, and postoperative adjuvant chemotherapy, the pCR rate is only recorded at 10–15% [20]. The higher pCR rates shown in this review and the hypothesized pCR rate of up to 40%, as reported by Huang et al. [19], highlight the need for further research to realize the true potential and efficacy of TACE.

Neoadjuvant immunotherapy has been studied across various solid tumors [23–26]; however, its effectiveness in these tumors is notably lower than in patients who have dMMR. Gao et al. [18] demonstrated that patients with MMR protein deficiency showed higher sensitivity to TACE and had an increased likelihood of achieving a pCR, further re-enforcing the potential positive benefits TACE may achieve in LARC in specific patient cohorts, ultimately improving clinical care and survival.

Neoadjuvant chemoradiotherapy, followed by surgery, has become the standard treatment for LARC. This approach helps lower the local recurrence rate and improve resection rates, sphincter preservation, and pathologic complete remission. However, it

has not substantially impacted long-term outcomes like distant metastasis rates, DFS, or OS [27–29].

The OS varied significantly between the studies. The median overall survival was found to be 12 and 13 months in the studies conducted by Bini et al. [17] and Ding et al. [22], respectively. Notably, the 5-year overall survival in the study by Yang et al. [20] was 74.8% of patients following TACE and neoadjuvant chemotherapy. These figures compare favorably with traditional treatment modalities, suggesting that TACE can effectively control tumor progression in the short term. Bo Yang et al. [10] determined that the 3-year DFS was significantly improved in the NATRACE-CRT group, further demonstrating the improved survival outcomes of TACE; however, long-term survival data were limited in the included studies. In the future, there may be potential for using TACE not only for chemotherapy but also as a delivery method for immunotherapy drugs, particularly in patients with dMMR tumors. This approach could enhance localized treatment efficacy and improve outcomes in LARC by combining immune modulation with targeted tumor reduction.

Distant metastases are the primary reason for treatment failure in rectal cancer and the leading cause of cancer-related death, significantly shortening the survival time of patients with rectal cancer [10]. Evaluation of both studies by Meng et al. [1,21] showed distant metastases were significantly reduced in the cohort of patients treated with TACE + CRT.

The safety profile of TACE, as reported in this review, indicates that the procedure is generally well-tolerated. Of the studies included, it was determined that 397 patients underwent TACE in conjunction with the standard treatment. Of this cohort of patients, common adverse events such as leukopenia 21.4%, neutropenia 18.6%, anemia 13.6%, radiation proctitis/enteritis 12.6%, fatigue 7.8%, and loss of appetite 7.8% were observed, amongst others, which are manageable with supportive care. Major complications were rare, suggesting that TACE is a relatively safe intervention when compared to the current standard treatment. This safety profile is particularly important given the already compromised health status of many patients with LARC, who may not be suitable candidates for more aggressive treatments. Although the studies demonstrate some adverse reactions, it cannot be concluded that these adverse events were a direct result of the TACE or due to the whole treatment regimen, i.e., surgery and chemoradiotherapy in combination with TACE. Major complications as graded by the SIR classification system for complications such as SIR D, anastomotic leakage, and incision infection may have still been present without TACE intervention.

Notably, both studies by Meng et al. [1,21] and the study conducted by Bo Yang et al. [10] demonstrate that there is no significant difference in toxicities and complications between patients treated with TACE versus conventional treatment.

When compared to conventional treatments such as surgery, systemic chemotherapy, and radiation therapy, TACE offers a unique advantage in terms of targeted therapy. Surgical options for LARC can be extensive and may come with significant morbidity, while systemic therapies often carry substantial side effects. Radiation therapy, although effective, can lead to complications such as radiation enteritis/proctitis and pelvic insufficiency fractures, as were observed in this review. TACE, by contrast, focuses treatment directly on the tumor site, potentially reducing the risk of systemic toxicity and improving patient tolerance. Although TACE has been widely utilized in patients with colorectal liver metastases, its application in rectal cancer has been infrequently documented. Published research has demonstrated that TACE with oxaliplatin resulted in higher pCR rates while maintaining a comparable safety profile to standard therapy [1,10].

It is estimated that 20% of rectal cancer patients present with unresectable locally advanced or metastatic cancer [30,31]. In the study by Bini et al. [17], it was shown that 33% of patients who received TACE had such a profound tumor response and a dramatic reduction in tumor size, it allowed for surgical resection of the LARC, which was previously inoperable. Furthermore, the mean operation time, as reported by Meng et al. [1], was observed to be significantly reduced in the TACE + CRT cohort when compared to standard therapy of CRT alone, again showing promise for TACE as a useful treatment adjunct.

Despite the promising results, this review highlights several limitations. The studies included varied in their design, sample size, and methodological quality, contributing to heterogeneity in the pooled analysis. Analysis of the results of each study, again, highlighted the heterogenicity of each paper with varying, albeit positive, outcomes reported, such as pCR, observed remission rate, disease control rate, etc. Additionally, most studies were observational, and there was a lack of large-scale randomized controlled trials (RCTs) to provide higher-level evidence. The short follow-up period in many studies also precludes definitive conclusions about long-term outcomes.

Future research should aim to address these limitations by conducting well-designed RCTs with larger patient cohorts and longer follow-up periods to ascertain the true treatment effect. Investigating the optimal timing and combination of TACE with other modalities, such as systemic chemotherapy or radiation therapy, could provide further insights into its role in a multimodal treatment approach. Additionally, exploring more biomarkers that predict response to TACE, such as dMMR [32], could help tailor treatments to individual patients, enhancing efficacy and minimizing unnecessary side effects.

It was not possible to conduct a meta-analysis due to the heterogenicity of follow-up times included in the studies. Further studies and research should include a standardized data collection tool/proforma, which could allow for further analysis with greater accuracy and less heterogenicity.

5. Conclusions

In summary, TACE shows considerable potential as a therapeutic option for patients with locally advanced rectal cancer, demonstrating favorable tumor response with promising long-term survival and a manageable safety profile. While the current evidence is encouraging, further rigorous studies are necessary to confirm these findings and to better define the role of TACE within the broader context of LARC treatment strategies. The integration of TACE into clinical practice could offer a valuable addition to the existing arsenal against this challenging disease, potentially improving outcomes and quality of life for many patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/onco4040029/s1, Table S1: Supplementary Material S1 summarizes the results of our risk of bias assessment.

Author Contributions: Conceptualization, H.C.T., M.M., J.B. and I.B.; methodology, M.E.K., Z.Q.N. and H.C.T.; software, N.J.O.; validation, B.M.M.C., T.O.C. and K.S.; formal analysis, N.M.; investigation, I.B.; writing—original draft preparation, H.C.T.; writing—review and editing, H.C.T., J.B. and S.D.; visualization, J.B.; supervision, Z.Q.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Data available on request from the authors.

Acknowledgments: Supported by Joly Leadership Fund, Trinity St. James Cancer Institute.

Conflicts of Interest: This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no conflicts of interest.

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