Tace To The Rescue: A Systematic Literature Review of Its Role in Battling Various Liver Metastases

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ABSTRACT

Liver metastasis, commonly originating from primary tumors such as colorectal, gastrointestinal, breast, and neuroendocrine malignancies, poses a significant treatment challenge. Patients with unresectable liver metastases are increasingly receiving transarterial chemotherapy (TACE) as a locoregional treatment. This systematic review evaluates the clinical outcomes, safety, and effectiveness of TACE in treating liver metastases across various cancer types. A systematic search of PubMed, PMC, and the Cochrane Library from January 2019 to December 2024 identified 848 articles. After removing 559 duplicates and excluding 167 abstracts, 122 full-text articles were assessed for eligibility. Exclusions included 30 case reports, 1 animal study, 3 non-English articles, 10 systematic reviews or meta-analyses, 2 pictorial reviews, 32 articles without available full text, 13 with no reported outcomes, and 2 retracted articles. The final analysis included 29 trials with 3,652 participants. Eight studies provided comparative data, while the rest were retrospective. The data suggest that TACE offers promising tumor control and may improve survival, but its effectiveness is influenced by factors like tumor burden, vascularization, and the underlying malignancy. Differences in treatment protocols, including chemotherapeutic agents and embolization materials, also affect outcomes. While TACE is generally well-tolerated, adverse effects such as liver function impairment and post-embolization syndrome have been observed. The review emphasizes the need for more randomized controlled trials and standardized treatment guidelines to better define TACE's role in managing liver metastases.

Keywords: *TACE, liver metastases, survival*

INTRODUCTION

Liver metastasis, commonly originating from primary tumors such as colorectal (CRLM), gastrointestinal (GIT LM), breast (BCLM), and neuroendocrine malignancies (NELM), poses a significant treatment challenge. Patients with unresectable liver metastases are increasingly receiving transarterial chemotherapy (TACE) as a

locoregional treatment. Transarterial chemoembolization (TACE) is one of the treatments of choice in patients with unresectable hepatocellular carcinoma (HCC), predominantly in the intermediate stage. TACE used highly concentrated chemotherapy drugs infused via selective catheterization of the arterial branch supplying the tumor. After the injection, the tumor microcirculation becomes embolized, which prolongs the cytotoxic effect and reduces the systemic toxicity of chemotherapy. There are two types of TACE techniques, conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE). (1) This systematic review evaluates the clinical outcomes, safety, and effectiveness of TACE in treating liver metastases across various cancer types.

METHOD

A systematic review was conducted to evaluate the role of transarterial chemotherapy (TACE) in managing liver metastases. The review aimed to assess clinical outcomes, safety, and effectiveness across various cancer types. A comprehensive search was performed in three major databases: PubMed, PMC, and the Cochrane Library. The search was limited to articles published from January 2019 to December 2024.

RESULT AND DISCUSSION

The final analysis included 28 trials with 3,671 participants. Eight studies provided comparative data, while the rest were retrospective.

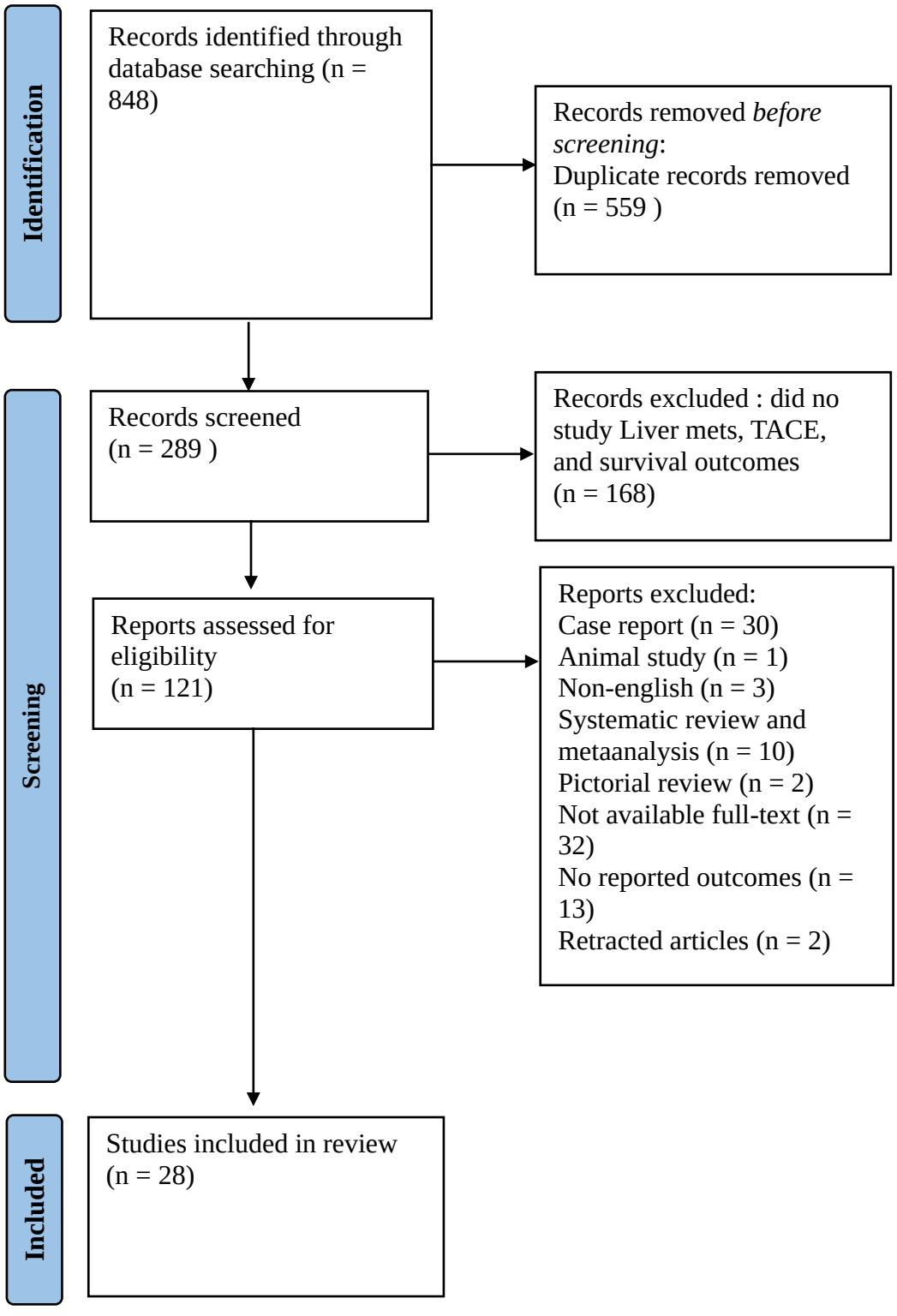
Identification
Records identified through database searching (n = 848)
Records removed *before screening*:
Duplicate records removed (n = 559)
Screening
Records screened
(n = 289)
Records excluded : did no study Liver mets, TACE, and survival outcomes
(n = 168)
Reports assessed for eligibility
(n = 121)
Reports excluded:
Case report (n = 30)
Animal study (n = 1)
Non-english (n = 3)
Systematic review and metaanalysis (n = 10)
Pictorial review (n = 2)
Not available full-text (n = 32)
No reported outcomes (n = 13)
Retracted articles (n = 2)
Included
Studies included in review
(n = 28)

Table 1. Systematic Review of TACE in Liver Metastasis (1–29)

No.	Author	Type of Cancer	Protocols	Sample size	CR (%)	PR (%)	SD (%)	PD (%)	ORR (%)	DCR (%)	OS (Mo)	PFS (Mo)
1	Ren et al, 2020	CRLM	cTACE irinotecan and oxaliplatin	53	0	55.6	44.4	0	55.6	N/A	15	6
2	Wang et al, 2019	CRLM	cTACE+lipiodol+ oxaliplatin, 5-FU, mitomycin	62	5.9	29.4	41.2	23.5	35.3	76.5	36	N/A
3	Chen et al, 2023	CRLM	DEB-TACE+ FOLFOX/FOLFOXIRI	35	0	14.3	40	37.1	14.3	N/A	47.4	6.3
4	Ngo et al, 2019	CRLM	DEB-TACE + Irinotecan	53	16.7	41.7	25	16.7	58.4	N/A	14.5	5
5	Tanaka et al, 2019	CRLM	DEB-TACE + Irinotecan	9	0	32.9	21.7	41.6	32.9	N/A	18.2	8.1
6	Sljivic et al, 2024	CRLM	DEB-TACE + Irinotecan	30	14.3	64.3	11.9	9.5	92.9	100	17.4	4.2
7	Zhao et al, 2022	CRLM	DEB-TACE (Callisphere) + Irinotecan	42	19	66.1	17.7	16.2	92.9	100	25	N/A
8	Fiorentini et al, 2022	CRLM	DEB-TACE + Irinotecan + Bevacizumab	76	1.3	54	19.6	13.1	67.2	86.9	18	13
9	Friedrich et al, 2023	CRLM	DEB-TACE + Irinotecan + Mono CT guided high-dose brachytherapy	22	10	35	35	20	45	80	N/A	5

10	Lu et al, 2022	CRLM	DEB-TACE+ (Callisphere)+ Irinotecan + Regorafenib	63	12.7	44.4	25.4	17.5	57.1	82.5	18.2	8.9
		CRLM	DEB-TACE + (Callisphere) + Irinotecan	69	5.8	27.5	34.8	31.9	33.3	68.1	11.3	5.3
11	Cao et al, 2021	CRLM	DEB-TACE + Regorafenib vs regorafenib	34	5.9	29.4	41.2	23.5	35.3	76.5	15.7	7.6
12	Li et al, 2023	CRLM	cTACE+ Irinotecan	11	0	18.2	36.3	45.5	18.2	81.8	14	4
		CRLM	DEB-TACE (Callisphere)+ Irinotecan	11	9	27.3	45.5	18.2	36.4	54.4	24	12
13	Szemitko et al, 2023	CRLM	DEB-TACE + FOLFIRI/FOLFOX/irinotecan + cetuximab	26	0	36.2	19.2	46.2	36.2	N/A	15.2	N/A
		CRLM	DEB-TACE + FOLFIRI	24	0	32.9	21.7	41.6	32.9	N/A	13.1	9.1
14	Wang et al, 2024	CRLM	DEB-TACE + FOLFIRI/ FOLFOX +/- bevacizumab/cetuximab	46	0	39.1	47.9	13	39.1	87	N/A	12.1
15	Fiorentini et al, 2020	CRLM	cTACE vs cTACE + bevacizumab	30	6 vs 31	13 vs 46	50 vs 15	31 vs 8	N/A	N/A	12	6
16	Zhang et al, 2023	CRLM	cTACE + Irinotecan	75	12.8	15.4	30.8	41	59	N/A	8.5	6
		CRLM	DEB-TACE + Irinotecan	75	16.7	41.7	25	16.7	83.3	N/A	13	10

17	Wei et al,2019	CRLM	cTACE + raltitrexed, oxaliplatin, and pirarubicin	61	13.1	54.1	19.7	13.1	67.2	86.9	14	2.1
		CRLM	cTACE + foxuridine, oxaliplatin, and pirarubicin	20	10	35	35	20	45	80	13	2.4
18	Vogl et al, 2024	CRLM	cTACE	1002	N/A	N/A	N/A	N/A	N/A	N/A	12	N/A
19	Voizard et al, 2022	CRLM	DEB-TACE + Irinotecan	36	N/A	N/A	N/A	N/A	N/A	N/A	28	14.1
20	Zhang et al, 2020	GIT LM	DEB-TACE + irinotecan, pirarubicin, oxaliplatin and mitomycin	39	1.6	34.4	54.7	9.4	36	N/A	28.7	15.3
21	Bi et al, 2022	GIT LM	DEB-TACE + gelatin sponge particle, polyvinyl alcohol, embolization microsphere + oxaliplatin, obaplatin	25	0	30	35	35	30	65	21.3	10.7
22	Vogl et al, 2023	Pancreatic Ca LM	DEB-TACE (DSM Embocept + Lipiodol)+Mytomicin C, Gemcitabine, Cisplatin	58	0	53.8	46.2	0	53.8	N/A	23	N/A
			DEB-TACE (DSM Embocept)+ Mytomicin C, Gemcitabine, Cisplatin	58	0	15.4	69.2	15.4	15.4	N/A	20	N/A
23	Yin et al, 2020	BCLM	cTACE + cyclophosphamide, epirubicin and 5-fluorouracil	19	0	47.4	21.1	31.6	47.4	N/A	75	N/A
24	Vogl et al,	BCLM	cTACE	549	N/A	N/A	N/A	N/A	N/A	N/A	16.8	N/A

	2023	BCLM	cTACE + LITT	215	N/A	N/A	N/A	N/A	N/A	N/A	36	N/A
		BCLM	cTACE + MWA	143	N/A	N/A	N/A	N/A	N/A	N/A	61.2	N/A
25	Egger et al, 2020	NELM	cTACE + doxorubicin, mitomycin, and cisplatin	197	3.6	26.6	66.2	3.6	30.2	96	50.1	19.9
26	Assouline et al, 2023	NELM	DEB-TACE or cTACE + streptozotocin	119	10	45	41	4	55		65	16
27	Luo et al, 2019	NELM	DEB-TACE and cTACE	111	N/A	N/A	N/A	N/A	N/A	N/A	40	N/A
		NELM	DEB-TACE and cTACE	84	N/A	N/A	N/A	N/A	N/A	N/A	40	16
28	Vogl et al, 2023	NELM	cTACE	89	N/A	N/A	N/A	N/A	N/A	N/A	42	N/A

The results in Table 1. show that the majority of cases involved colorectal liver metastases (CRLM), followed by breast cancer liver metastases (BCLM), neuroendocrine liver metastases (NELM), pancreatic adenocarcinoma liver metastases, and gastrointestinal tract liver metastases (GIT LM). Most studies used DEB-TACE protocols, with irinotecan being the main chemotherapy agent for CRLM. The highest median overall survival was 47.4 months, with a progression-free survival of 6.3 months, using the DEB-TACE + FOLFOX/FOLFOXIRI protocol. (4) In contrast, patients with CRLM who only received supportive care had a median survival of 7 months. (18) Some studies have added immunotherapy, such as cetuximab, which, while not significantly improving local tumor control rates (mRECIST: CR, PR, SD, PD), increased overall survival to 15.2 months compared to 13.1 months without cetuximab. (14) (13)

In BCLM, the highest median overall survival was 75 months for patients treated with cTACE using cyclophosphamide, epirubicin, and 5-fluorouracil, (30) followed by cTACE combined with microwave ablation (MWA), with a median OS of 61.2 months. (19) For NELM, the highest median overall survival was 65 months with cTACE or DEB-TACE combined with streptozotocin. (27) For GIT LM and pancreatic adenocarcinoma LM, the highest median OS was 28.7 and 23 months, respectively. (20)

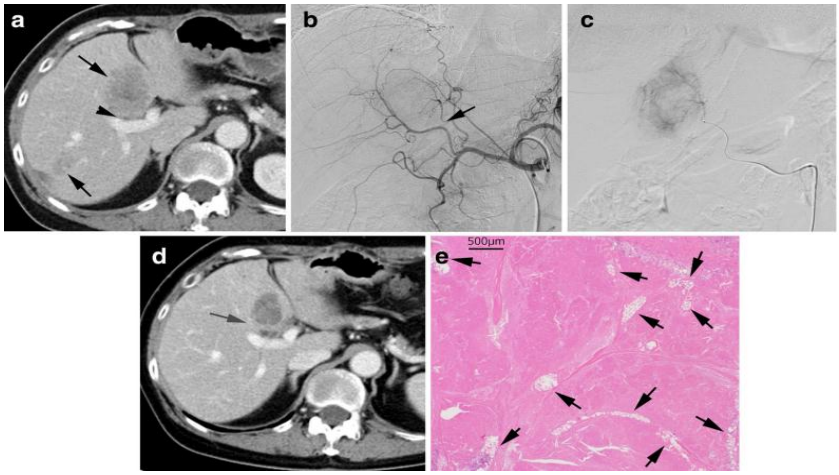

Figure 1. A case received curative surgical resection of CRLM. a)CT before TACE shows multiple liver metastases (arrows).b)Hepatic arteriography; feeding artery was detected (arrow). c)A catheter was inserted and 40 µm irinotecan loaded TANDEM was injected. d) 3 cycles of TACE and FOLFIRI showed the tumor shrunk(arrow).e)Histological findings; almost the whole area of the tumor was necrotic and numerous 40µm microspheres were seen inside the tumor (arrows) (6)

The data suggest that TACE offers promising tumor control and may improve survival, but its effectiveness depends on factors such as tumor burden, vascularization, and the underlying malignancy. Differences in treatment protocols, including the choice of chemotherapeutic agents and embolization materials, also impact outcomes.

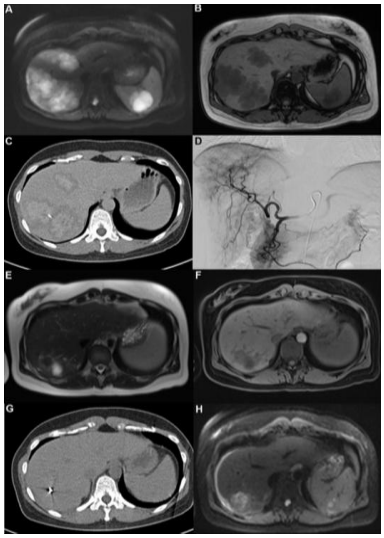

Figure 4. Treatment of the patient with BCLM with combined TACE and MWA(7)

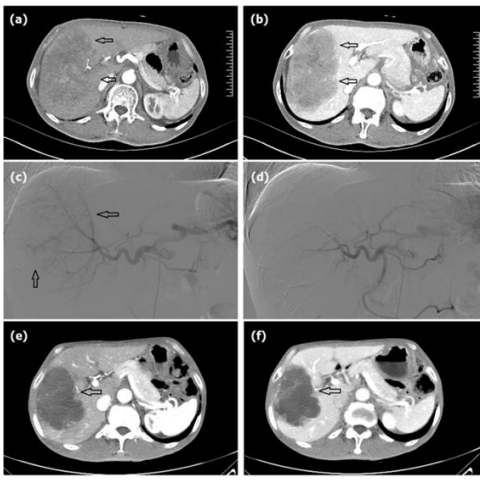

Figure 2. A 70-year maletreated by CalliSpheres® beads for gastric cancer liver metastases. a, b) Liver metastases pre-operative (arrows). c) Embolization of right hepatic artery (arrows). d) Tumor staining disappeared after embolization. e, f) Liver mets (arrows) was found to shrink after 1 month's follow-up. (11)

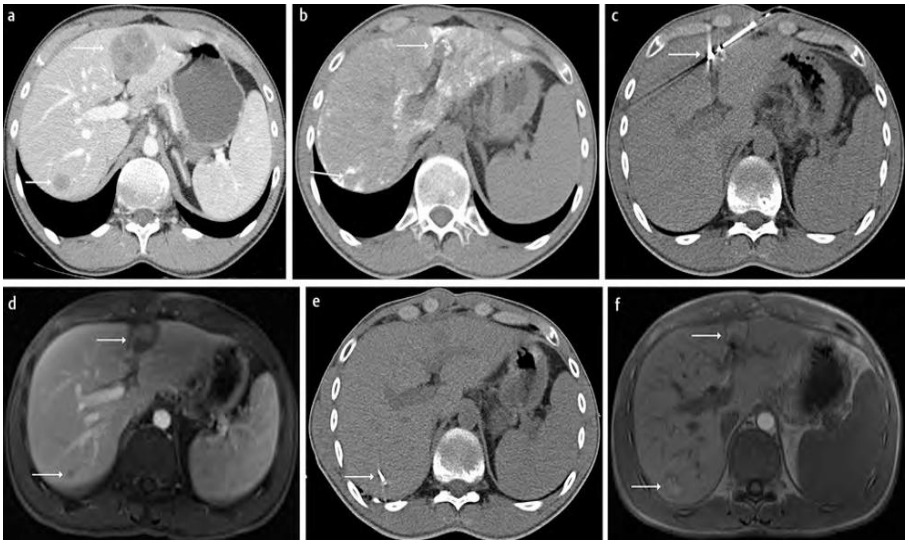

Figure 3. A 24-year-old male with two NELMs from an NET of the small intestine. The patient received 8 c-TACE and 2 MWA treatments resulting in incomplete hepatic remission. (a) Liver mets in segments 4/2 and 7. (b) After c-TACE showing a total volume reduction of 80% (upper arrow). Detection of lipiodol in the lesions (arrows). (c) The process of MWA in segment 4/2(arrow). (d)(e)(f) After MWA resulting incomplete hepatic remission. (24)

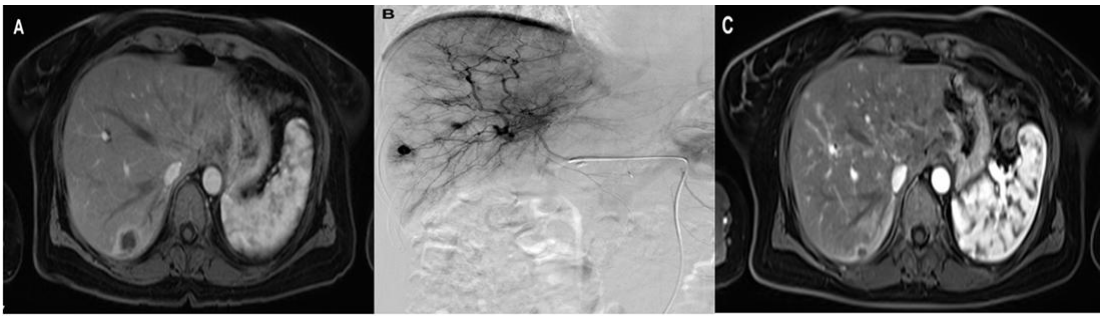

Figure 5. A 47-year-old woman with solitary liver metastasis of pancreatic adenocarcinoma was treated with 3 sessions of Lipiodol + DSM TACE with Gemcitabine, Cisplatin, and Mitomycin. (A) pre-treatment axial MRI (B) During TACE (C) post-treatment MRI shows the significant downsizing of the metastasis. (20)

Adverse effects such as liver function impairment and post-embolization syndrome have been observed. Minor adverse events reported in these 28 studies include fever, abdominal pain, nausea/vomiting, diarrhea, elevated AST and ALT, neutropenia, anemia, thrombocytopenia, and leukopenia. Major adverse events include biloma, cholecystitis, and liver abscess. Instrument-related adverse events, such as dissection of the common hepatic artery, coil migration, and occlusion of the main hepatic artery branch, were rare (<1%). (16,31)

CONCLUSION

A review of TACE for liver metastases shows potential benefits, especially in colorectal and breast cancer, but results vary. The review emphasizes the need for more randomized controlled trials and standardized treatment guidelines to better define TACE's role in managing liver metastases.

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