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Transarterial Chemoembolisation for Colorectal Liver Metastases with the use of Microspheres - A Literature Review

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Abstract

Classic arterial chemoembolization (conventional TACE or cTACE) and the combination of TACE with the administration of microspheres (drug-eluding beads-DEB or degradable starch microspheres-DSM) are therapeutic options for patients with colorectal liver metastases. Drug eluding beads form bonds with the chemotherapeutic drug if combined and promote a controlled release into the target vessel. Embolizing agents such as lipiodol or spheres (like Embocept) promote occlusion in the arteries supplying the tumor, thus enhancing the chemotherapeutic effect of the administered drugs and limiting the possible systemic toxic complications. TACE is currently used as palliation or as a preparation stage for surgery in colorectal cancer. Patients eligible are the ones with hepatic tumors non-responding to chemotherapy or recurring. The use of microspheres is effective in controlled diffusion of the chemotherapeutic drug in the targeted area, while limiting systemic complications. The use of TACE (DEB-TACE/ DSM-TACE) is promising for patients not responding in the first or second-line cancer treatments. Its application, however, should be individualized. Further results might arise from the implementation of TACE techniques in clinical trials.

Keywords: TACE; Chemoembolization; Spheres; Colorectal liver metastases

Abbreviations:

TACE: Transarterial Chemoembolization

cTACE: conventional transarterial chemoembolization

TAE: transarterial embolization

DEB: drug eluding beads

DSM: degradable starch microspheres

RCT: randomized clinical trial

ESMO: European Society of Medical Oncology

ASCO: American Society of Cancer Oncology

5FU: 5- Fluorouracil

Introduction

Colorectal cancer is the second most common malignancy in Europe [1-3] and the third globally [4] with an estimated mortality of more than 3 million cases by 2040 [5]. Approximately 1 in 3 patients with colorectal

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cancer will present with hepatic metastases at some point during the disease [4,5]. Surgical resection remains the only definite treatment modality [3,4] but only a small percentage of patients are eligible for it (20-30%) [3,4,6].

For non-surgical candidates with hepatic metastases there are systemic or locoregional treatment options. Systemic alternatives include chemotherapy iv or per os (5FU, irinotecan etc.) and monoclonal antibodies. Locoregional treatment includes liver-targeted therapies, such as Transarterial Chemoembolization (TACE), with or without drug eluding beads (DEB-TACE) or degradable starch microspheres (DSM-TACE), local tumor thermal ablation or local radiation [5,6]. The focus of this paper is a comprehensive review of current bibliography concerning patients with colorectal liver metastases treated with DSM-TACE or DEB-TACE (Table 1).

While normal liver tissue is supplied both byportal vein and hepatic artery branches, liver metastases receive their blood supply primarily from hepatic artery branches. Transarterial therapies for hepatic metastases take advantage of this vascular approach. The efficacy of transarterial therapies lies in the targeted local drug administration. The addition of embolic agents results in occluding the tumor feeding vessels. This procedure leads to selective ischemic effect and localized cytotoxicity, thus sparing the remaining healthy tissues [5].

The transarterial administration of drugs and embolic agents is called "transarterial chemoembolization" or "TACE". Degradable microspheres or drug-eluding beads can be used as embolic agents, thus increasing the chemotherapeutic drug effect while limiting systemic complications. The combination of TACE with these agents is known as "DSM-TACE" or "DEB-TACE" [7].

Selective administration of chemotherapeutic drugs in hepatic artery branches is already used in the setting of hepatocellular carcinoma. This targeted approach is often rendered more effective than systemic chemotherapy with limited adverse effects [7-9]. The use of many different chemotherapeutic drugs has been achieved since then. Among them, adriamycin, mitomycin and commonly irinotecan were transarterially injected to reach the hepatic artery branches that supply the hepatic tumor [10].

The same rationale applies when treating secondary hepatic metastases. The goal is to achieve better tumor response, in terms of reducing or stabilizing tumor volume [11]. Although TACE is not a first line option for metastatic colorectal cancer, it is still used for palliative purposes (after other treatment's failure) or as a preparation for hepatic resection and further locoregional treatment. According to guidelines, TACE is indicated for patients with a greater than 3-month life expectancy and a good performance status [12].

TACE for colorectal liver metastases is currently being used as DEBIRI-TACE, with irinotecan and microspheres to induce maximum local administration. The advantage of its use versus systemic only chemotherapy is already proven, as far as tumor response rate and tumor downsizing are concerned [13].

Conventional TACE

Transarterial embolization without the use of microspheres is known as "conventional TACE" or "cTACE". There are several studies on cTACE using different drugs and embolic agents, such as lipiodol [7].

A 2019 retrospective study compared the median overall survival between patients receiving TACE with different drug combinations and lipiodol. The patients in the study had unresectable colorectal liver metastases and were unresponsive to systemic treatment. Raltitrexed- or floxuridine (FUDR)-based TACE was given to patients, in more than one rounds. Overall survival and adverse effects between the two groups were comparable (13 months in the FUDR group vs 14 months in the raltitrexed group, p value= 0.556), leading the authors to conclude that raltritrexed or floxuridine-based TACE is an efficient alternative in patients with unresectable liver metastases from colorectal cancer [14].

The combination of TACE with raltitrexed and oxaliplatin was already studied in a Chinese study by Shao et al. They found the combination to be feasible and effective, with a 78.9% disease control rate and no unexpected adverse effects, yielding an overall survival of 17.8 months [15].

A study by Yun et al. tested patients undergoing TACE with oxaliplatin and 5-fluorouracil while systematically administrating cetuximab or cetuximab plus capecitabine. The authors reported comparable results between the two groups in terms of overall response and disease control rate. This study included patients with unresectable liver metastases from colorectal cancer that were expected to survive for more than 3 months [16]. Patients who failed previous systemic chemotherapy might also benefit from TACE. Ren et al. conducted a study with that patient population and had overall survival of 15 months, comparable to other studies' results. Tumor radiologic downsizing was also demonstrated, at a rate of 52.5% of a total of 53 patients [17]. Although TACE is not considered first-line therapy for colorectal liver metastases, there are studies mentioning TACE as an earlier therapeutic option. A 2015 meta-analysis with 90 studies addressing hepatic artery therapies for metastatic colorectal cancer found cases where TACE was performed as a first-line treatment. More specifically, median overall survival (OS) was 15,2 months in patients who first received TACE. Patients who failed at least one previous systematic treatment yielded better results with second-line TACE, achieving a median OS

Table 1: Studies about TACE in metastatic colorectal cancer.

Authors/Year	Title	Study Characteristics	Number of patients	Intervention/Drug combination	Study Goals	Tumor Control	Primary Endpoints/ Survival
Gruber-Rouh et al 2014	Transarterial chemoembolization of unresectable systemic chemotherapy-refractory liver metastases from colorectal cancer: Long-term results over a 10-year period	Retrospective	564	TACE (lipiodol, DSM) with -Mitomycin C -Mitomycin C+ gemcitabine -Mitomycin C+ irinotecan -Mitomycin C+ Irinotecan+ cisplatin	- Evaluate treatment efficacy - Determine prognostic factors for success	PR 16.7% SD 48.2% PD 16.7 %	Median survival 14.3 months 1-year survival 62%
Wei et al 2019	Transarterial chemoembolization with raltitrexed-based or floxuridine-based chemotherapy for unresectable colorectal cancer liver metastasis	Retrospective	81	TACE (lipiodol) with -Raltitrexed+oxali platin+pirarubicin (raltitrexed group) -FUDR, oxaliplatin, and pirarubicin (FUDR group)	- Compare efficacy, safety between drugs	Raltitrexed group- ORR 67,2%, DCR 86,9% FUDR group- ORR 45.0%, DCRs 80.0%,	median OS was 14.0 months-raltitrexed group median OS was 13.0 months in the FUDR group (P = 0.556)
Shao et al 2018	Efficacy and safety of raltitrexed-based transarterial chemoembolization for colorectal cancer liver metastases	Prospective	90	TACE (lipiodol) with Raltitrexed+oxaliplatin	- Compare efficacy, safety between drugs	DCR 78,9%	Time to progression 9.1 months OS 17.8 months
Yun et al 2021	Efficacy of transcatheter arterial chemoembolization combined with capecitabine and cetuximab in the treatment of colorectal cancer with liver metastasis	Prospective	140	TACE with -capecitabine+ cetuximab (capecitabine group) -cetuximab (control group)	- Compare efficacy, safety between drugs	Capecitabine group: ORR 51,4%, DCR 94.3% Control group: ORR37.1%, DCR 87.4%	MS capecitabine group 18.1 months MS control group 14.7 months
Ren et al 2021	Transarterial chemoembolization of unresectable systemic chemotherapy refractory liver metastases: a retrospective single-center analysis	Retrospective	53	TACE (lipiodol)	-Evaluate efficacy of TACE in patients who failed chemotherapy	ORR 52.8% DCR 79.2 %	MS 15 months PFS 6 months
Zacharias et al 2015	Comparative Effectiveness of Hepatic Artery Based Therapies for Unresectable Colorectal Liver Metastases: A Meta-Analysis	Meta-analysis	1038 TACE	TACE, Radioembolization, Hepatic Artery Infusion TACE+5-Fluorouracil; Cisplatin; Irinotecan; Mitomycin C; Gemcitabine; Doxorubicin	- Comparative effectiveness between the treatments	RR 29% for TACE	MS 15.2 months (TACE as first line treatment) MS 21.3 months (TACE after failed chemotherapy)

Albert et al 2011	Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol	Prospective	121	TACE with: mitomycin C + doxorubicin + cisplatin	- Response and survival evaluation	PR 2% SD 41% Progression 57%	MS 9 months (from first TACE treatment)
Jarząbek et al 2011	Drug-eluting microspheres transarterial chemoembolization (DEM TACE) in patients with liver metastases.Pilot study	Prospective	3 with colorectal cancer	TACE with -hepasphere (drug eluding bead) + Doxorubicine	- TACE efficiency - Survival - - Quality of Life	No separate data for colorectal patients	MS 7.5 months for colorectal cancer patients
Aliberti et al 2006	Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results	Prospective	10	TACE with Drug eluding beads + irinotecan	- Evaluate feasibility of technique, adverse effects	ORR 70%	Most patients presented mild adverse effects (vomiting, alopecia) No results for median survival
Nishiofuku et al 2013	Transcatheter arterial chemoembolization using cisplatin powder mixed with degradable starch microspheres for colorectal liver metastases after FOLFOX failure: Results of a phase I/II study	Clinical Trial	24	TACE with DSM+ cisplatin	- Access efficacy of protocol and cisplatin dosage	RR 61.1%	OS 21.1 months High RR with high cisplatin dosage (80mg)
Ngo et al 2019	Transarterial Chemoembolisation of Colorectal Liver Metastases with Irinotecan-Loaded Beads: A Bi-institutional Analysis of 125 Treatments in 53 Patients	Retrospective	53	DEBIRI-TACE	- Safety of technique, OS, PFS	Not stated	MS 14.5 months PFS 5 months
Tanaka et al 2019	Selective TACE with irinotecan-loaded 40 μm microspheres and FOLFIRI for colorectal liver metastases: phase I dose escalation pharmacokinetic study	Clinical Trial	9	TACE with: Irinotecan + microspheres (Embozene Tandem) FOLFIRI post TACE	- Evaluation of feasibility, pharmacokinetics, tolerability of intervention	RR 55.6 %	PFS 8.1 months OS 18.2 months
Vogl et al 2012	Repeated transarterial chemoembolisation using different chemotherapeutic drug combinations followed by MR-guided laser-induced thermotherapy in patients with liver metastases of colorectal carcinoma	Prospective	224	TACE (lipiodol-Embocept microspheres) with: -irinotecan+ mitomycin -gemcitabine+ mitomycin -mitomycin	- Evaluate protocol with different TACE-drug combinations	Tumor diameter reduction 21.1% PR 31.25 % SD 68.7%	MS 23 months - MS with Irinotecan+ Mitomycin 22.5 months -MS with Gemcitabine+ Mitomycin 23 months -MS with Mitomycin only 24 months (P<0.01)
Levy et al 2018	Intra-arterial therapies for unresectable and chemorefractory colorectal cancer liver metastases: a systematic review and meta-analysis	Meta-analysis	746 cTACE 222 DEB-TACE	-Conventional TACE (c TACE) -DEB-TACE - radioembolization	- Compare survival benefit, radiologic response	RR cTACE 23% RR DEB-TACE 36%	MS cTACE 16 months MS DEB-TACE 16 months

PR: partial response, SD: stable disease, PD: progressive disease, OS: overall survival, MS: median survival, ORR: objective response rate, RR: response rate, DCR: disease control rate, PFS: progression free survival, DEB: drug eluding beads, DEBIRI: drug eluding beads with irinotecan, cTACE: conventional TACE

of 21.3 months. TACE was found to achieve better survival results compared with the other two treatments studied in the meta-analysis, hepatic artery infusion and radioembolization, if used in the second line setting [18].

In a retrospective analysis by Albert et al, 43% of the patients undergoing TACE had partial response or stable disease. TACE yielded better results if used after systemic chemotherapy. The overall survival for patients with metastatic colorectal cancer did not exceed the 27-month period. A small minority of the patients of this study were able to proceed to hepatic resection of previously unresectable or recurrent lesions, after the chemoembolization [19].

A recent systematic review for Cochrane Database Library found 1 RCT about TACE in colorectal cancer. TACE was compared to simple transarterial embolization (TAE) with no drugs. The median survival for the TACE group was 10.7 months versus 7.9 months for the TAE group, with no statistical significance between the two outcomes. The lack of conclusive results and the study bias resulted in failure to suggest beneficial outcomes for the TACE group compared with the control group [5].

Spheres and TACE

Drug- eluding beads (DEB) and degradable starch microspheres (DSM) have been used in combination with TACE in the past two decades to achieve better drug concentration and vascular occlusion in patients with hepatocellular carcinoma [7,20]. The addition of drug-eluding beads in TACE procedures has already proved its efficiency in reducing tumor volume and achieving better survival rates in those patients [21].

The benefit of microspheres lies in their embolic potential and in their ability to release the administered drug in a controlled manner [7,22,23].

The use of microspheres is also efficient in protecting normal liver parenchyma during radioembolization, as shown in the study by Meyer et al. [24]. The rationale behind this lies in the protection of the normal liver by diverting the arterial flow away from the tumor area [24].

In patients with liver metastases from colorectal cancer, the combination of TACE with drug- eluding beads containing irinotecan (DEBIRI TACE) is commonly used. Different kinds and sizes of beads can be used for loading with irinotecan or the preferred chemotherapeutic drug [7]. The combination of drug- eluding beads and irinotecan in TACE was first reported in 2006, by Aliberti et al [25].

Several studies have existed since then about the role of DEB-TACE and DSM-TACE in colorectal cancer liver metastases.

Gruber-Rouh et al conducted a single-center 10-year study of the effects of TACE and different chemotherapeutic drugs in patients with metastatic colorectal cancer. The study included patients with chemorefractory cancer, patients with severe adverse effects from the chemotherapy and patients with initially inoperable hepatic metastases. Both the patient response and the overall survival were measured. TACE was offered with or after systemic chemotherapy as a 2nd or 3rd line treatment. Patients treated with TACE had a median survival of 14.3 months, regardless of the chemotherapeutic drug combination (mitomycin C, irinotecan, gemcitabine). Partial response was measured in terms of metastases downsizing, both in size and number. These patients, 36%, were eligible for treatment with a curative intent after TACE, either surgery or ablation [8].

In the systematic review by Karanicolas et al, plentiful data confirm the advantageous use of microspheres in the TACE. Studies revealed better response in the first two-month period (for drug- eluding beads with irinotecan-DEBIRI-DEB-TACE) and similar adverse effects compared to the conventional technique as well as longer survival period for patients with DEB-TACE [3].

Nishiofuku et al conducted a single-center open label trial with 24 patients with metastatic colorectal cancer, either with inoperable liver lesions or non-responsive to chemotherapy. All patients received chemotherapy as first-line treatment and then underwent TACE procedures. This study used cisplatin powder in different dosages and degradable starch microspheres. In terms of tumor response (tumor volume decrease) the authors found that a higher cisplatin dosage (80mg) resulted in a 61.1% response versus lower(50mg) cisplatin dosage (0% tumor response). That outcome rendered two patients eligible for further treatment with a curative aim. The overall survival agreed with the results of other studies, at approximately 21 months. The authors concluded that DSM-TACE with cisplatin powder is feasible and has the potential of achieving a high tumor response rate [26].

A 2019 retrospective study of 53 patients with metastatic colorectal cancer examined the feasibility and survival advantage of DEBIRI-TACE. Patients with hepatic metastases and no other treatment option were included. After a total of 125 TACE procedures, it was apparent that the patients who benefited the most were the ones who received previous locoregional treatment (like ablation). The authors demonstrated that bilobar liver disease or extrahepatic disease lead to poorer survival outcomes. Also, patients with previous chemotherapy treatment displayed better results with DEBIRI-TACE compared to chemotherapy- naïve patients. The median survival after the first TACE was 14.5 months in this study [27].

The combination of TACE with multiple concentrations irinotecan beads and the comparison to FOLFIRI treatment in terms of drug concentration and feasibility was studied

in a single-center trial by Tanaka et al. Microspheres were loaded with irinotecan in various concentrations and systemic FOLFIRI was administered in nine patients after TACE. This study demonstrated that high doses of irinotecan was tolerable by patients (even at 100mg per mL-microspheres). The concentration of blood SN-38 (irinotecan metabolite) was measured and found to be higher after TACE with irinotecan than intravenous FOLFORI, thus achieving more efficient anti-tumor action. The authors concluded that irinotecan-based TACE, even with high irinotecan dosages, is safe and produces higher drug concentration than systematic FOLFIRI treatment. The median survival of patients was in accordance with literature, at 18.2 months [28].

A 2012 study by Vogl et al included 224 colorectal cancer patients with inoperable or recurrent liver metastases that were treated with DSM-TACE as a preparation for additional locoregional treatment. EmboCept, a degradable starch microsphere, and different chemotherapeutic drugs were administered during TACE. The drugs administered in the TACE procedures were combinations among mitomycin C, irinotecan and gemcitabine and depended on the systemic therapy that patients had already received. Patients that responded to the first TACE procedure (in terms of tumor size downsizing) could be further treated with laser-induced thermotherapy. The median survival after the conclusion of treatment was 23 months [29].

A 2018 meta-analysis compared the survival and the radiologic tumor response of cTACE, DEB-TACE and radioembolization in metastatic colorectal cancer patients. All the patients included had failed previous systematic or locoregional treatment for hepatic metastases. It appeared that DEB-TACE yielded higher survival benefit than cTACE. This result, however, was not statistically proven and both techniques offered a median survival of 16 months [30].

Guidelines for TACE in metastatic colorectal cancer

The most recent guidelines for the management of metastatic colorectal cancer belong to the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO).

The recent guidelines of ASCO state the importance of a multidisciplinary team approach on treating colorectal cancer metastases. Surgical resection remains the only possible curative option. There is no mention of transarterial chemoembolization for hepatic metastases [4]. ESMO guidelines, however, state beneficial results for tumor downsizing using TACE (commonly used as DEBIRI-TACE). Due to lack of solid evidence, it is stated that using transarterial therapies for hepatic metastases as an early therapeutic option should be reserved for patients in clinical trials. For the time being, these treatments are available for individualized setting, for patients with recurrent or unresectable disease, despite the systemic chemotherapy [13].

Conclusion

Colorectal cancer is the second leading cause of cancer-assosiated death in the world. New cases are estimated about more than one million annually [31]. One quarter of the patients are diagnosed already having metastatic disease and 2-5 out of 10 patients will probably develop a metastatic lesion. Colorectal cancer more commonly metastasizes at liver and lungs. Thus, many therapeutic options have emerged to deal with these lesions. Surgical resection remains the only possible curative option for hepatic metastases, in appropriately selected patients. Multidisciplinary team approach is necessary for treatment decision. Systemic treatment with chemotherapy and local tumor control options can be recommended, both for palliative and disease-stabilization purposes [13]. The administration of different chemotherapeutic drugs in the TACE setting is under study, as is the use of different embolizing particles [32]. The use of TACE in colorectal liver metastases is not universally adopted and should be reserved for individualized cases and clinical trials. Further studies with an appropriate number of patients are needed to reach a consensus [5,7,30].

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