



Chemoembolization Versus Radioembolization for Neuroendocrine Liver Metastases: A Meta-analysis Comparing Clinical Outcomes

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ABSTRACT

Background. Studies have shown intra-arterial therapies to be effective in controlling neuroendocrine liver metastases (NELMs), but the evidence supporting the selection of specific methods is limited. This meta-analysis is the first to compare survival outcomes between transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) in the treatment of NELM.

Methods. A systematic search according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in PubMed and Embase databases was conducted in February 2020 for published studies comparing survival outcomes between TACE and TARE in the treatment of NELM.

Results. Six eligible cohort studies with a total of 643 patients were identified. The TACE and TARE groups were similar in terms of age, sex, hepatic tumor burden, tumor grade, and Eastern Cooperative Oncology Group (ECOG) score. The patients treated with TACE had significantly better overall survival (odds ratio [OR], 1.92; 95% confidence interval [CI] 1.14–3.22, $p = 0.014$) than those treated with TARE. Overall survival ranged from 16.8 to 81.9 months with TACE and from 14.5 to 66.8 months with TARE. No significant differences in hepatic progression-free survival (OR, 1.01; 95% CI

0.75–1.35; $p = 0.96$) or tumor response were observed within the first 3 months (OR, 2.87; 95% CI 0.81–10.21; $p = 0.10$) or thereafter (OR, 0.98; 95% CI 0.12–7.86; $p = 0.99$). The complication rates were similar between the two groups, with 6.9% of the TACE patients versus 8.5% of TARE patients reporting major complications (OR, 1.16; 95% CI 0.54–2.48; $p = 0.71$) and respectively 44.6% and 58.8% of the TACE and TARE patients reporting minor adverse events (OR, 1.08; 95% CI 0.39–2.99; $p = 0.88$).

Conclusions. Despite similar tumor responses, an overall survival benefit was associated with TACE treatment of NELM compared with TARE treatment. Randomized controlled trials are warranted to confirm this finding and clarify whether certain subpopulations benefit from different transarterial methods.

Neuroendocrine tumors (NETs) comprise a group of neoplasms with a heterogeneous presentation and prognosis. Most of these tumors originate from the gastroenteropancreatic tract.^{1,2} Frequently, NETs are asymptomatic until they metastasize to the liver, which is a predominant site of metastatic deposits in up to 50% of cases.^{3,4}

Neuroendocrine liver metastases (NELM) can cause significant symptoms related to tumor bulk and hormonal activity. Their presence also is associated with reduced overall survival (OS).^{3,5} The 5-year survival rates range from 14 to 54% among those with distant metastases depending on the site of the primary tumor.^{3,5}

Fortunately, a variety of treatment options for treating NELM are available. These treatments are primarily aimed at improving quality of life by reducing local tumor bulk and the associated symptoms. Although surgical resection is the preferred therapy because it provides a better long-term outcome and the chance for cure, only a small percentage of patients are eligible for this therapy.^{6,7}

When surgery is not an option, intra-arterial liver-directed therapies can be used with great success. These therapies target the hypervascular nature of NELM. Specific methods include bland transarterial embolization (TAE), conventional transarterial chemoembolization (TACE), drug-eluting beads for transarterial chemoembolization (DEB-TACE), and transarterial radioembolization (TARE). The TAE approach relies purely on ischemia-induced cell damage to achieve tumor cell destruction, whereas the other approaches combine an initial dose of locally delivered chemotherapy or radiation and a following embolization.

Intra-arterial therapies have proven efficacy in controlling unresectable NELM.⁸ They also have a favorable safety profile, with the most common adverse effect being a post-embolization syndrome characterized by fever, abdominal pain, nausea, and vomiting.⁸ For these reasons, intra-arterial liver-directed therapies currently are broadly included in the treatment guidelines for neuroendocrine tumors with hepatic-predominant disease.⁹⁻¹² However, evidence to guide the selection of a specific method is limited.

To date, only a few retrospective cohort studies have directly compared the clinical outcomes and survival rates of TACE and TARE, and these studies have yielded mixed results. Most of the studies found no significant difference in survival outcomes, whereas one of the larger studies found a survival benefit associated with TACE.¹³⁻¹⁷ Singla et al.¹⁸ found that survival outcomes could be maximized with either treatment depending on the Ki67 score.

This study aimed to compare the survival and clinical outcomes between TACE and TARE in the treatment of NELM. This is the first meta-analysis on this subject and represents the largest group of patients analyzed to date.

METHODS

Study Selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic search of the PubMed and Embase databases was conducted 15 February 2020 for published studies comparing the survival outcomes between TACE and TARE in the treatment of NELM. The keywords used

in the search included chemoembolization, TACE AND radioembolization, TARE, SIRT, yttrium-90 AND neuroendocrine liver metastasis, and NELM.

The inclusion criteria specified primary research study, patients with a diagnosis of NELM, at least one distinct group of patients treated with TACE and one distinct group treated with TARE, and reported mean or median OS. There were no restrictions on the timeframe or language of publication. Studies that described treatment of primary hepatic malignancies or did not include both TACE and TARE were excluded. Systematic reviews, case reports, and abstracts also were excluded.

Data Extraction

Two independent reviewers (L.N., A.E.) extracted data into a preformed spreadsheet and resolved discrepancies by consensus. The primary outcomes of this study were median OS and hepatic progression-free survival (HPFS). The secondary outcomes were tumor response, symptom response, and major or minor adverse events. None of the studies included crossover patients but did include outcomes for patients undergoing repeat and adjunctive therapies during the follow-up period.

Quality Assessment

The Newcastle-Ottawa Scale was used to assess the quality of each included study. Each study was assigned a numeric score in eight domains designed to evaluate sample selection, comparability of cohorts, and outcomes. The scores for the included studies ranged from 5 to 9, with 9 as the maximum possible score. The most common reason for point deductions was lack of control for bias in the original analyses ($n = 4$). The risk of bias also was increased in some studies by omission of a clear description of the data source ($n = 1$) and inadequate description of a loss to follow-up evaluation ($n = 2$). The methodologic quality and risk of bias are outlined in Table 1.

Statistical Analysis

Statistical analyses were performed using Comprehensive Meta-Analysis (Biostat, Englewood, New Jersey), version 3.0, and RevMan (The Nordic Cochrane Center, Copenhagen, Denmark) version 5.3. Medians were converted to means, and interquartile ranges and confidence intervals (CIs) were converted to standard deviations where applicable. Pooled means and standard deviations were calculated according to the *Cochrane Handbook for Systematic Reviews of Interventions*. Heterogeneity of the effect sizes between studies was detected using Cochran's Q test and quantified using Higgin's I^2 test. Heterogeneity

TABLE 1 Quality assessment of included studies

First author with reference	Publication year	Selection subscore	Comparability subscore	Outcome subscore	Total Newcastle–Ottawa score
Ozkan F ¹⁵	2013	4	0	3	7
Engelman ES ¹⁶	2014	4	0	2	6
Singla S ¹⁸	2016	3	0	2	5
Chen JX ¹⁷	2017	4	2	2	8
Minh DD ¹³	2017	4	2	3	9
Egger ME ¹⁴	2020	4	0	3	7

was considered significant at p values lower than 0.1 and at an I^2 higher than 50%. A fixed-effects model was used to calculate the pooled odds ratio (OR) or standardized mean difference (SMD) for categorical data and the 95% confidence interval (CI) for quantitative data. In case of heterogeneity, a random-effects model was used.

RESULTS

Characteristics of Included Studies

The study identified 344 published titles. After review of title, abstract, and full text where indicated, six retrospective cohort studies published between 2013 and 2020 were found to meet the inclusion criteria (Fig. 1). The meta-analysis included 643 patients with NELM. Of these 643 patients, 422 were treated with TACE and 221 were treated with TARE using yttrium-90 (Table 2). The patients in the TACE group were confirmed recipients of embolization to stasis in all but the smallest study (with 14 patients), in which the description was ambiguous.

Pooled Analysis for Clinical Characteristics of Patients

The clinical characteristics of the treatment groups are summarized in Fig. 2. The treatment groups did not differ significantly by age (SMD, -0.14 ; 95% CI -0.32 to 0.03 ; $p = 0.11$) or sex (female: OR, 0.99 ; 95% CI 0.69 – 1.42 ; $p = 0.97$). The primary tumor sites were similar between the groups including the pancreas (OR, 1.71 ; 95% CI 0.77 – 1.77 ; $p = 0.32$), the lung (OR, 0.76 ; 95% CI 0.53 – 1.1 ; $p = 0.93$), and gastrointestinal sites (OR, 1.27 ; 95% CI 0.46 – 3.94 ; $p = 0.96$).

The two groups did not differ significantly in terms of hepatic tumor burden (tumor burden $>50\%$: OR, 1.71 ; 95% CI 0.96 – 3.04 ; $p = 0.07$) or tumor grade (G3: OR, 0.8 ; 95% CI 0.13 – 5.13 ; $p = 0.82$ vs G2: OR, 1.12 ; 95% CI 0.68 – 1.84 ; $p = 0.66$), although only three of the studies reported tumor grade and tumor burden. The Eastern Cooperative Oncology Group (ECOG) score, a standard

measure of patient functional status and an important predictor of survival, also was similar between the treatment groups (ECOG ≥ 1 : OR, 1.75 ; 95% CI 0.60 – 5.14 ; $p = 0.31$).

The two groups did not differ significantly regarding the presence of extrahepatic metastases (OR, 0.91 ; 95% CI 0.53 – 1.54 ; $p = 0.72$) or bilobular disease (OR, 0.82 ; 95% CI 0.48 – 1.41 ; $p = 0.47$). The history of resection or ablation of metastatic tumors was similar between the groups (OR, 1.20 ; 95% CI 0.71 – 2.02 ; $p = 0.49$). The TARE group was more likely to have received prior systemic chemotherapy (OR, 0.48 ; 95% CI 0.27 – 0.83 ; $p = 0.009$) and prior octreotide therapy (OR, 0.50 ; 95% CI 0.30 – 0.84 ; $p = 0.009$). The patients in the TACE group were significantly more likely to have undergone multiple chemoembolization treatment sessions, as is common (≥ 3 sessions: OR, 4.82 ; 95% CI 1.92 – 12.08 ; $p < 0.001$).

Pairwise Comparison of Survival

All six studies reported OS, and five studies reported hepatic progression-free survival. The median OS ranged from 16.8 to 81.9 months with TACE and from 14.5 to 66.8 months with TARE. The patients treated with TACE had significantly better OS (OR, 1.92 ; 95% CI 1.14 – 3.22 ; $p = 0.014$; Fig. 3). Surprisingly, there was no observable difference found in hepatic progression-free survival between the groups (OR, 1.01 ; 95% CI 0.75 – 1.35 ; $p = 0.96$; Fig. 3).

Pairwise Comparison of Treatment Response

Four studies reported radiographic tumor response, but only three of these studies used the standard Response Evaluation Criteria in Solid Tumours (RECIST) criteria. No significant difference between TACE and TARE in tumor response within the first 3 months was observed (OR, 2.87 ; 95% CI 0.81 – 10.2 ; $p = 0.10$) or thereafter (OR, 0.98 ; 95% CI 0.12 – 7.86 ; $p = 0.99$) (Fig. 4). Two studies reported symptom response. Among the patients who were

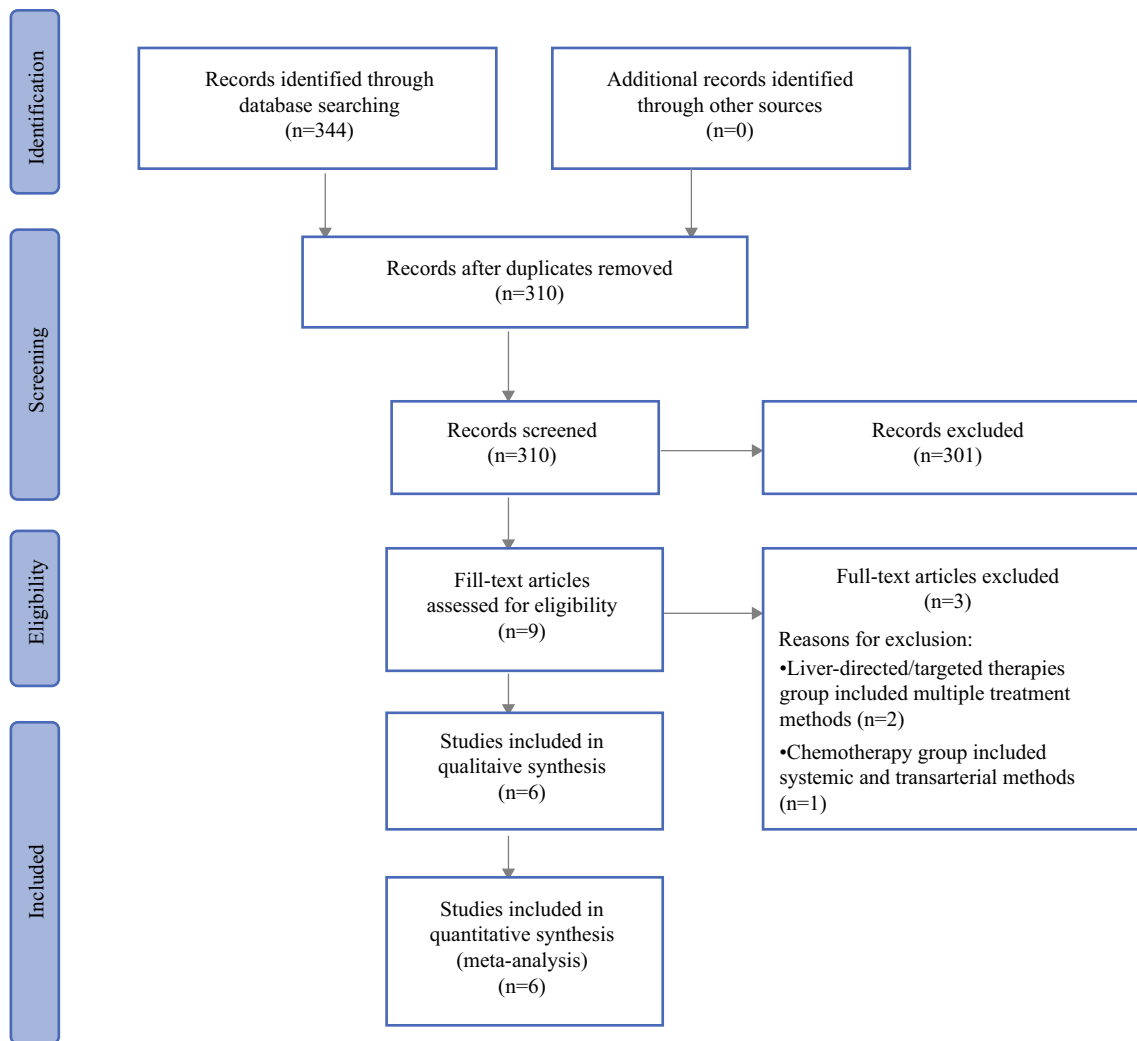


FIG. 1 PRISMA flow diagram of the study selection process

symptomatic at presentation, 52.6% of those in the TACE group and 75% of those in the TARE group reported improvement in their symptoms. The groups demonstrated no significant difference in symptom response (OR, 0.30; 95% CI 0.06–1.45; $p = 0.13$).

Pairwise Comparison of Complications

The complication rates were similar between the treatment groups (Fig. 5), with 6.9% of the TACE-treated patients reporting major adverse events compared with 8.5% of the TARE-treated patients (OR, 1.16; 95% CI 0.54–2.48; $p = 0.71$). Similarly, 44.6% of the patients treated with TACE reported minor adverse events compared with 58.8% of the patients treated with TARE (OR, 1.08; 95% CI 0.39–2.99; $p = 0.88$). The common minor adverse events included abdominal pain, nausea, vomiting, anorexia, fatigue, fever, flushing, and elevations in

aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

DISCUSSION

The number of NET patients is increasing, and these patients often present with NELM or eventually will experience NELM.^{14,18–20} Intra-arterial therapies have been proved effective in managing symptomatic and unresectable NELM, but to date, no high-quality evidence exists to support the use of a specific method.^{21–23} Although TARE is thought to have some advantages over TACE (e.g., ability to treat a complete liver lobe or miliary disease with less overall toxicity),^{14,24} the available literature comparing these treatments has yielded mixed results, leaving the choice of method largely up to institutional

TABLE 2 Characteristics of included studies

First author with reference no.	Publication year	Design	Institution	Country	Treatment groups (n)			Primary outcome measures			
					Total	TACE	TARE	Median hepatic PFS (months)		Median OS (months)	
								TACE	TARE	TACE	TARE
Ozkan F ¹⁵	2013	Retrospective cohort	Single center	Turkey	14	8	6	18.0	7.5	16.8	14.5
Engelman ES ¹⁶	2014	Retrospective cohort	Single center	USA	42	17	12	33.4	15.1	68.7	26.8
Singla S ¹⁸	2016	Retrospective cohort	Single center	USA	72	28	44	NR	NR	81.9	66.8
Chen JX ¹⁷	2017	Retrospective cohort	8 Centers	USA	155	50	64	8.1	15.7	32.9	48.2
Minh DD ¹³	2017	Retrospective cohort	Single center	China, Germany, USA	192	122	44	21.6	11.2	34.0	22.9
Egger ME ¹⁴	2020	Retrospective cohort	2 Centers	USA	248	197	51	19.9	15.9	50.1	35.9

TACE, transarterial chemoembolization; TARE, transarterial radioembolization; PFS, progression-free survival; OS, overall survival; NR, not reported

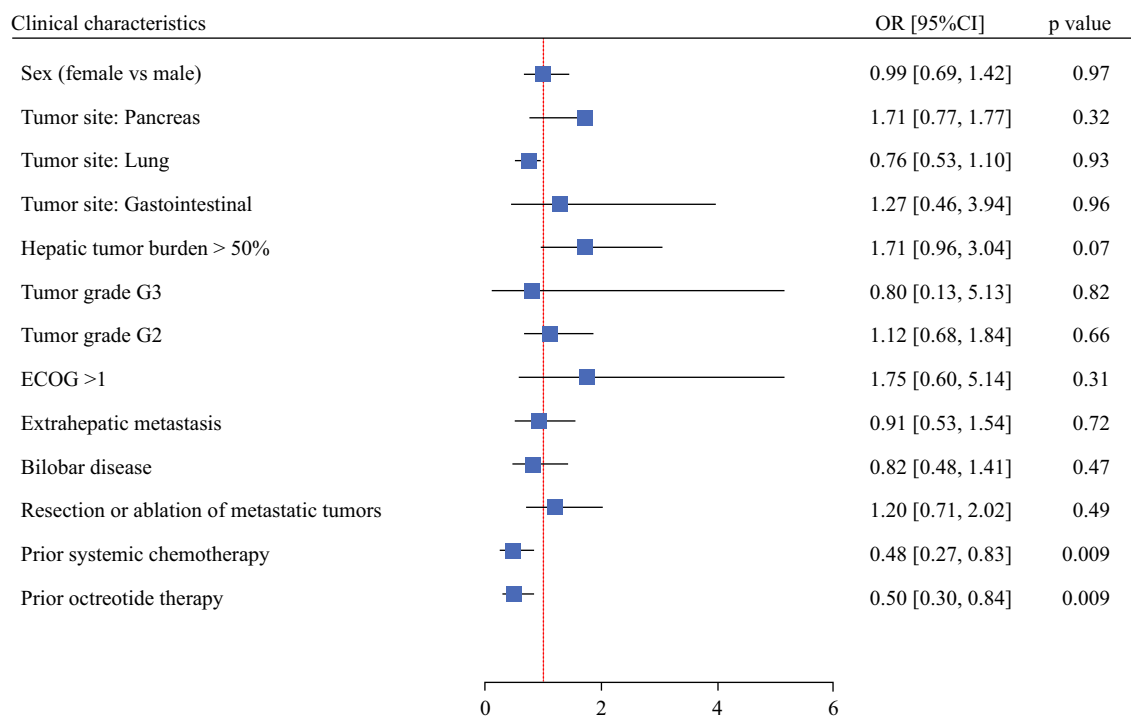


FIG. 2 Clinical characteristics of the transarterial radioembolization (TARE) group versus the transarterial chemoembolization (TACE) group

preference. This meta-analysis aimed to compare the effectiveness and survival outcomes between TACE and TARE in the management of NELM.

We found that TACE conferred a significantly longer OS than TARE. This finding is consistent with that of Minh et al.,¹³ who concluded from their propensity score analysis

of 192 patients that conventional TACE was associated with a significantly better OS than TARE. Interestingly, the HPFS did not differ between the two groups.

We also found no significant difference in hepatic tumor response rates between TACE and TARE. This is consistent with previous studies reporting uniformly high tumor

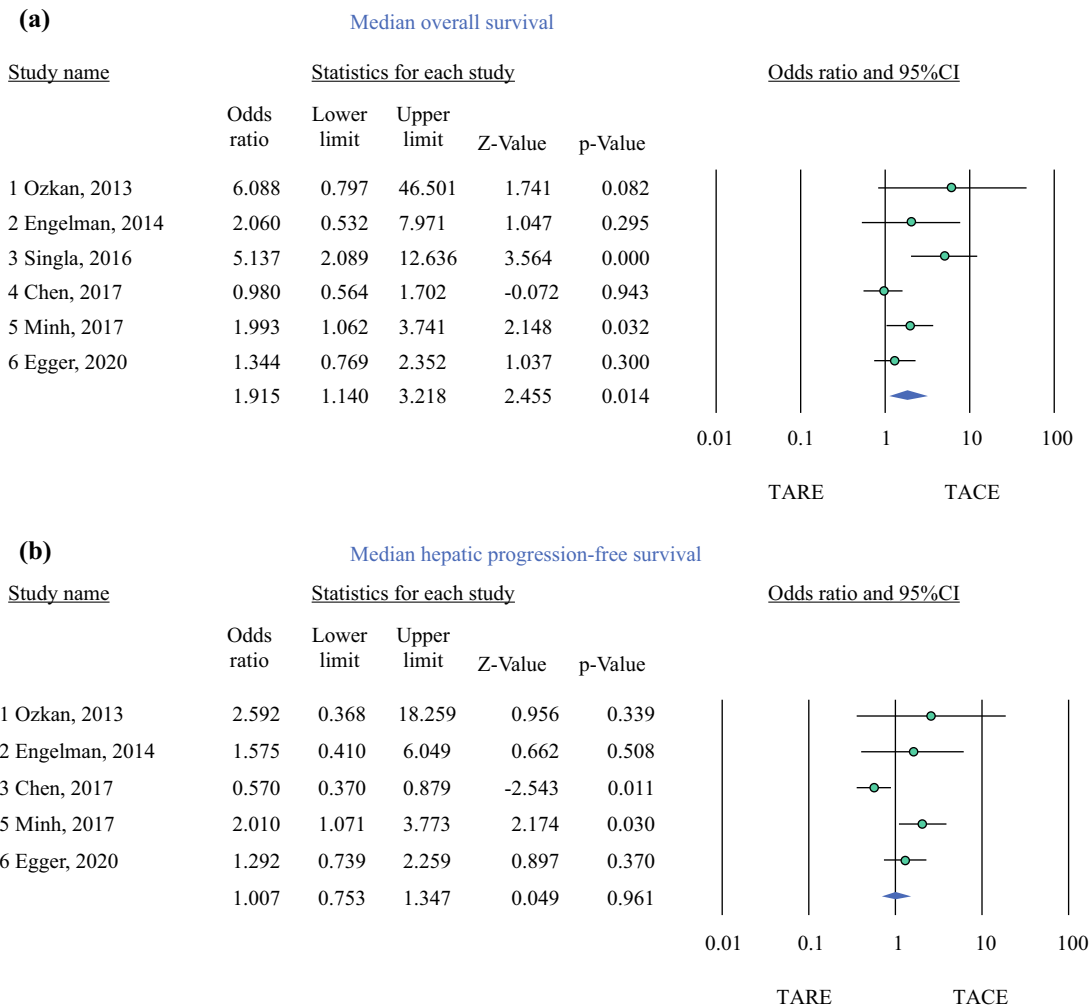


FIG. 3 Meta-analysis of survival. **a** Median overall survival (MOS). **b** Median hepatic progression-free survival (HPFS)

response rates in the form of regression or at least control of the disease in up to 95% of patients treated with TACE^{7,25,26} and up to 90% of patients treated with TARE.^{27–29}

Prior studies have similarly demonstrated that the disease control does not necessarily correlate with the OS. In their systematic review, Jia and Wang et al.⁴ reported higher disease control rates and lower median survival rates with TARE than with TACE. However, in the absence of a difference in hepatic tumor response, the mechanism underlying the observed difference in OS remains unclear.

We recognize that the treatment groups have differences in baseline characteristics that might contribute to the OS difference, but we believe this is unlikely to be explained by these factors alone. Indeed, although the TACE group showed a slight but nonsignificant trend toward more extensive hepatic disease, they also tended to undergo more treatment sessions, as is consistent with this treatment

method. Furthermore, Varker et al.³⁰ previously demonstrated that repeat TACE does not significantly prolong OS or HPFS. The TARE patients were more likely to have undergone prior systemic chemotherapy, which might have been expected to confer improved survival outcomes but perhaps instead indicated that treatment-refractory disease had developed by the time they were considered for intra-arterial therapy. Despite these differences, the groups were found to be similar in terms of several important prognostic factors including ECOG score, tumor grade, and hepatic tumor burden.

We found no significant difference in symptom response between the two treatments. Both treatments offered symptom relief for at least half of the patients, confirming the value of the treatments in improving quality of life. Furthermore, the rates of major and minor complications did not differ significantly. Overall, the rate of major complications was low in both treatment groups, which is consistent with several previous studies demonstrating the

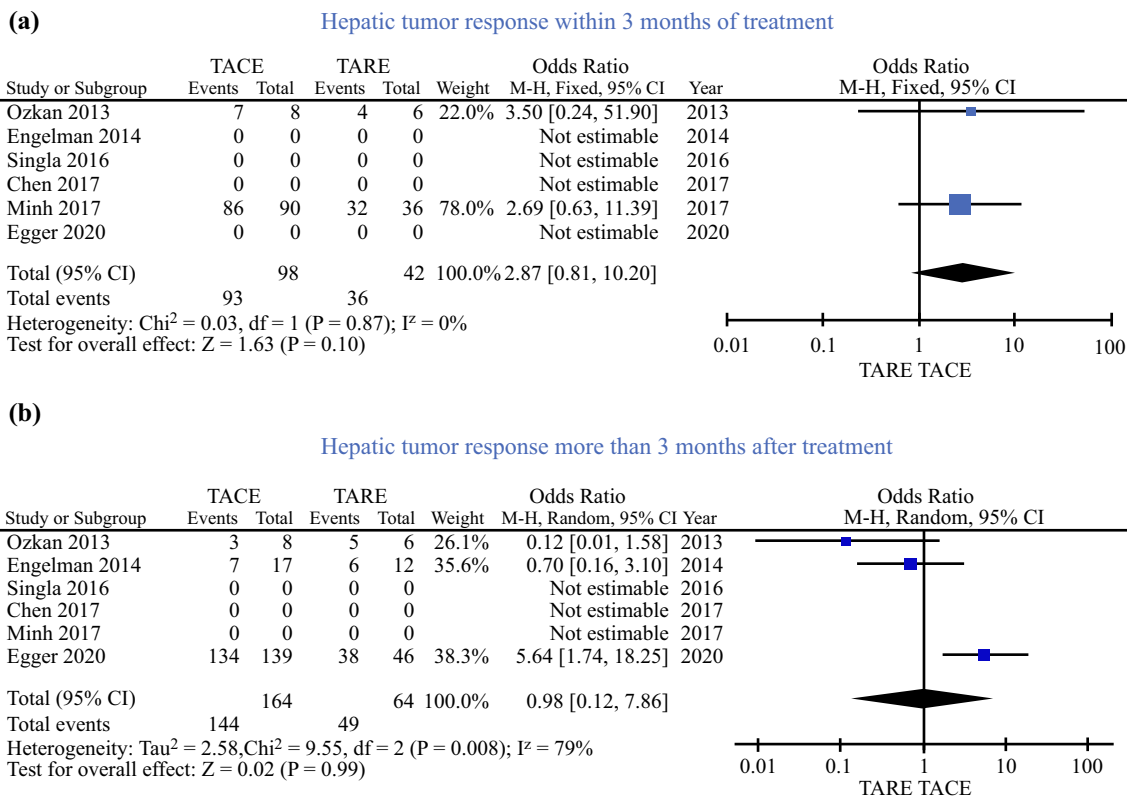


FIG. 4 Meta-analysis of hepatic tumor response. **a** Within 3 months of treatment. **b** More than 3 months after treatment

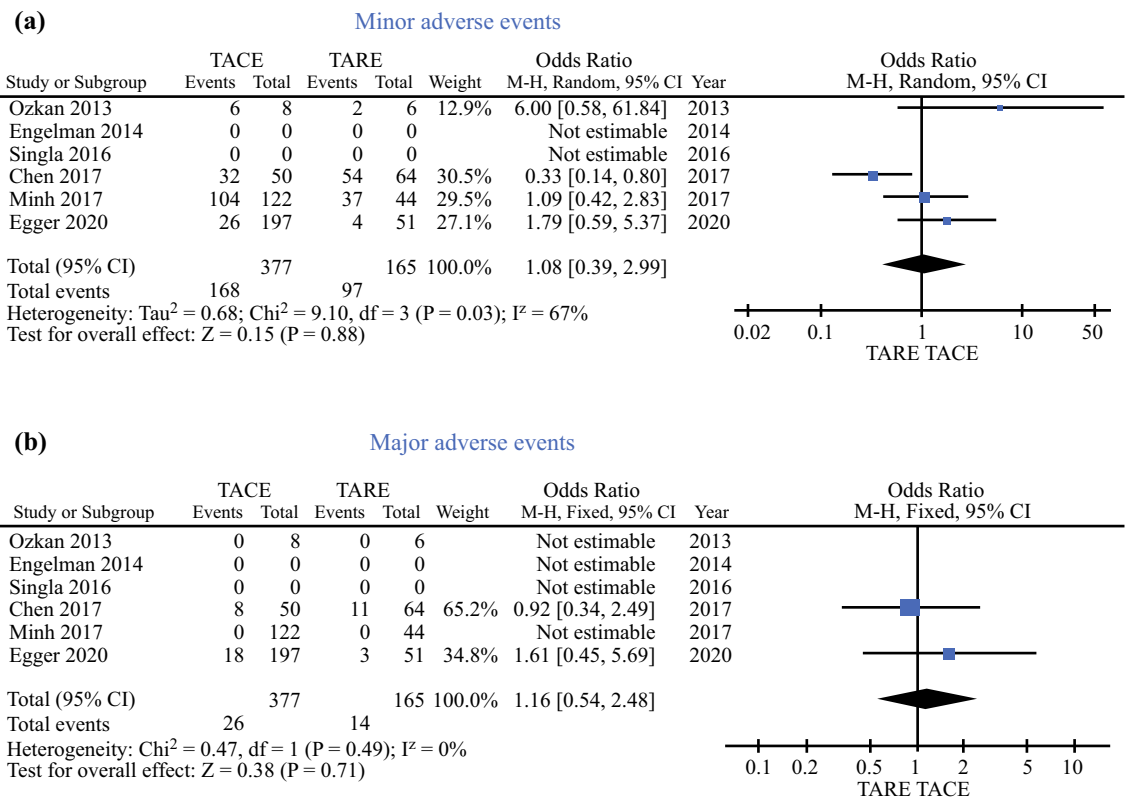


FIG. 5 Meta-analysis of adverse events. **a** Minor adverse effects. **b** Major adverse effects

safety of TACE and TARE for the treatment of NELM.^{13,14} Although laboratory markers of toxicity were not analyzed separately, we assumed that no clinically significant differences existed given the similarity of the groups in terms of adverse events.

These findings suggest that TACE may be superior to TARE in the treatment of unresectable NELM. Compared with TARE, TACE appears to offer improved OS duration, with comparable symptom response and side effects. Future prospective studies also should consider cost, number of treatments required, and quality of life.

This study had some limitations that should be acknowledged. The design of the retrospective studies that formed the basis of this meta-analysis has a relatively high level of inherent bias. We attempted to address this issue by describing how the composition of the treatment groups differed and by evaluating the degree of bias present using a standardized tool. Where possible, we attempted to focus our analyses on outcomes such as symptomatic and radiographic responses in the short period after the initial treatment. However, long-term outcomes such as survival would clearly have been affected by repeat or alternative treatments. Only one study¹⁷ differentiated the types of alternative treatments. The remaining studies included a general reference to octreotide therapy, with one study using it as an exclusion criterion. The specific type of octreotide therapy may affect OS. Evidence exists to show that peptide radionuclide therapy (PRRT) in advanced gastroenteropancreatic NET may offer a prolonged OS using 90-YDOTA₀Tyr₃ compared with other radiolabeled somatostatin analogs.³¹ Furthermore, the NETTER-1 trial showed that ¹⁷⁷Lu-Dototate PRRT had a significantly longer HPFS than octreotide long-acting repeatable therapy alone.³² Without this specific detail, it was difficult to assess and control for this source of bias. These limitations underscore the need for more highly controlled studies to compare intra-arterial therapies.

CONCLUSIONS

Despite similar hepatic tumor responses, our meta-analysis demonstrated an OS benefit associated with treating NELM with TACE instead of TARE. The TACE and TARE treatments offer comparable symptomatic relief with no significant differences in adverse effects. Randomized controlled trials are warranted to confirm these findings and clarify whether certain subpopulations might benefit from different intra-arterial methods.

DISCLOSURE There are no conflicts of interest.

FUNDING This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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