

REVIEW



Radiofrequency ablation vs radiation therapy vs transarterial chemoembolization vs yttrium 90 for local treatment of liver cancer – a systematic review and network meta-analysis of survival data

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ABSTRACT

Introduction: The comparative effectiveness of radiofrequency ablation (RFA), radiation therapy (RT), transarterial chemoembolization (TACE) and transarterial radioembolization with Yttrium-90 (Y90) relative to one another for the treatment of hepatocellular carcinoma (HCC) is unclear. The aim of this systematic review and network meta-analysis is to compare RFA to RT to TACE to Y90 in the treatment of HCC.

Methods: Pubmed, Embase and Cochrane CENTRAL were searched up until April 19, 2021. Observational analyses with propensity score matched (PSM) cohort analyses and randomized controlled trials (RCT) reporting on two or more treatments relative to one another with respect to overall survival (OS) and/or progression free survival (PFS) were included. Survival data were extracted from Kaplan-Meier survival curves, and meta-analyzed using a multivariate network meta-analysis.

Results: After exclusions, 24 RCTs or PSM observational studies reporting on 5549 patients were included. While 1-year OS was greater for Y90 than TACE (RR 0.85, 95% CI: 0.72–0.99), all other 1-year OS comparisons across the 4 modalities yielded similar OS, and there were no differences across any modalities in 2-year and 3-year OS. TACE had a modest PFS advantage relative to RFA (RR 0.81, 95% CI: 0.68–0.95) and RT (RR 0.65, 95% CI: 0.51–0.83) at 2 years.

Conclusion: All modalities assessed resulted in similar OS, which explains the current heterogeneous practice patterns. This conclusion may assist in decision making based on administrative and patient costs, and implementation of these modalities. Other factors such as toxicity rate specific to individual patients could not be assessed using network meta-analysis and may also play a role in selection of modality. Further studies, ideally using PSM cohort analyses or RCT study design, reporting on OS, PFS, local control, complete response and toxicity are needed prior to drawing definitive conclusions.

ARTICLE HISTORY

Received 8 September 2021
Accepted 17 November 2021

KEYWORDS

Hepatocellular carcinoma; radiofrequency ablation; radiation therapy; transarterial chemoembolization; transarterial radioembolization; Yttrium-90; systematic review; network meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality globally, the fifth most common cancer in men, and seventh most common cancer in women [1]. Several non-surgical local therapies exist, including radiofrequency ablation (RFA), radiation therapy (RT), transarterial chemoembolization (TACE) and transarterial radioembolization with Yttrium-90 (Y90) [2], and no one modality has emerged as the preferred treatment approach across all localized HCC patients.

The comparative efficacy/effectiveness of these treatments relative to one another is unclear [3]. There exists only few randomized controlled trials (RCTs), and these have only compared two treatment modalities at a time relative to one another [4]. Any observations and conclusions are thus drawn from studies with low statistical power and lack

of generalizability. Previous systematic reviews and meta-analyses have attempted to pool study data together for a more definitive answer, but they too have been limited in their comparisons of only two treatment modalities [5–8]. They, therefore, have only investigated a selection of treatments. This may be due to limited studies comparing each modality to one another, and thereby making certain comparisons *via* conventional systematic reviews and meta-analyses infeasible. The known costs and toxicity profile of each of these modalities differ in important ways. Yet, the likelihood that a randomized trial comparing these four different treatment modalities will be performed is unlikely.

To review all treatments relative to one another, a network meta-analysis can be employed and thereby multiple modalities can be simultaneously compared. Any limitations that would have prevented prior reviews of one treatment relative to another may be overcome through a

Table 1. Study demographics.

Study	Study Design	Sample Size	Patient Diagnosis	Age	% Male	Treatments	Adjusted Covariates
Akiwande et al. [13]	PSM	96	Unresectable HCC, without advanced liver disease	NR	76%	1. Drug-Eluting Bead TACE 2. (2) Y90	Age, gender, history of hepatitis, portal vein thrombosis, total size of target, Child Pugh status, extrahepatic disease, KPS, prior liver surgery, history of ablation, prior sorafenib, current sorafenib
Berger et al. [14]	PSM	784	Stage T1 HCC, with no evidence of metastatic disease	Mean: 68.3 ± 10.4	28%	1. RFA 2. (2) RT – External Beam	Age, sex, race, AFP, cirrhosis, tumor size
Bettinger et al. [15]	PSM	105	HCC, without extrahepatic metastases	Mean: 67.5 ± 9.4	87%	1. RT – Stereotactic Body 2. (2) TACE	ECOG, portal vein thrombosis, hepatic tumor expansion, tumor size, Child Pugh score, viral liver disease
Bush et al. [16]	RCT	69	HCC, without vascular invasion	Mean: 60.1	71%	1. RT – Proton Beam 2. (2) TACE	NA
Cheng et al. [17]	RCT	195	HCC	Mean: 63.7 ± 5.4	73%	1. RFA 2. (2) TACE	NA
Chu et al. [18]	PSM	429	HCC, without vascular invasion and without extrahepatic disease	Mean: 60.7 ± 10.7	78%	1. RFA 2. (2) TACE	Age, sex, etiology, ECOG, Child Pugh score, liver cirrhosis, tumor size, serum bilirubin level, serum albumin level, serum AFP
Hara et al. [19]	PSM	212	Unresectable HCC	NR	69%	1. RFA 2. (2) RT – Stereotactic Body or Hypofractionated	Age, number of prior treatments for HCC, tumor size, Child Pugh score, performance status
Hsu et al. [20]	PSM	202	HCC	Mean: 67 ± 11	62%	1. RFA 2. (2) TACE	Tumor size, tumor number, vascular invasion, bilirubin levels, sodium levels, BCLC, CLIP score
Ishikawa et al. [21]	PSM	128	HCC	NR	63%	1. RFA 2. (2) TACE	Age, sex, AST, bilirubin, albumin, platelet count, HBV, HCV, Child Pugh grade, tumor number, maximal tumor size, AFP
Kim et al. [23]	PSM	190	HCC	NR	86%	1. RFA 2. (2) RT – Stereotactic Body	Age, sex, viral etiology, Child Turcotte Pugh class, BCLC, platelet count, AFP level, PIVKA-II level, tumor location, tumor diameter
Kim et al. [22]	PSM	626	HCC	NR	76%	1. RFA 2. (2) RT – Stereotactic Body	Age, sex, performance status, viral etiology, Child Pugh class, AFP, des-gamma carboxyprothrombin, BCLC, tumor stage, prior liver-directed treatment
Kim et al. [24]	RCT	144	HCC, without vascular invasion and without extrahepatic metastasis	NR	83%	1. RFA 2. (2) RT – Proton Beam	NA
Kolligs et al. [25]	RCT	28	Unresectable HCC, without portal vein occlusion	Mean: 66.3 ± 7.2	86%	1. TACE 2. (2) Y90	NA
Liu et al. [26]	PSM	470	HCC	Mean: 67.8 ± 11.0	70%	1. RFA 2. (2) TACE	Age, sex, serum biochemistries, etiology of HCC, Child Turcotte Pugh score, CLIP score, tumor number, TTV
Pan et al. [27]	PSM	46	Residual HCC	Mean: 57.5	91%	1. RFA 2. (2) RT – Stereotactic Body	Platelet counts, tumor diameter, proportion of tumor abutting major vessels
Parikh et al. [28]	PSM	64	Stage I-II HCC	NR	66%	1. RFA 2. (2) RT – Stereotactic Body	Age, sex, race, stage, Charlson comorbidity index, decompensated cirrhosis, treating center, number of prior treatments
Pitton et al. [29]	RCT	24	HCC	Mean: 71.1 ± 8.0	75%	1. TACE 2. (2) Y90	NA
Rajaguru et al. [30]	PSM	796	Stage I-II HCC	NR	NR	1. RFA 2. (2) RT – Stereotactic Body	NR
Salem et al. [31] ¹	RCT	45	HCC BCLC A/B	NR	73%	1. TACE 2. (2) Y90	NA
Shen et al. [32]	PSM	102	Unresectable HCC	Mean: 62.4 ± 12.8	65%	1. TACE 2. (2) RT – Stereotactic Body	Age, sex, etiology, volume of tumor, BCLC stage, albumin, bilirubin, ECOG, number of prior treatments
Su et al. [33]	PSM	190	HCC BCLC A	NR	88%	1. TACE 2. (2) RT – Stereotactic Body	Age, gender, albumin, bilirubin, ALT, tumor size, AFP

(continued)

Table 1. Continued.

Study	Study Design	Sample Size	Patient Diagnosis	Age	% Male	Treatments	Adjusted Covariates
Wahl et al. [34]	PSM	320	HCC	NR	NR	1. RFA 2. (2) RT – Stereotactic Body	Tumor size, platelet counts, performance status, number of prior treatments
Wang et al. [35]	RCT	40	Unresectable HCC	NR	95%	1. RFA 2. (2) RT – External Beam	NA
Yun et al. [36]	PSM	244	Early-stage HCC	Mean: 68.9 ± 9.5	72%	1. RFA 2. (2) TACE	Age, sex, etiology, liver cirrhosis, platelet count, Child Pugh class, tumor size, single tumor, AFP, PIVKA-II

AFP: Alpha-fetoprotein; ECOG: European Cooperative Oncology Group performance status; HCC: Hepatocellular carcinoma; KPS: Karnofsky performance status; NA: Not Applicable; NR: Not Reported; PSM: Propensity-Score Matched Cohort Study; RCT: Randomized Controlled Trial; RFA: Radiofrequency ablation; RT: Radiotherapy; TACE: Transarterial chemoembolization; Y90: Yttrium-90 radioembolization.

network meta-analysis' ability to conduct indirect comparisons. The aim of this systematic review and network meta-analysis is to compare RFA to RT to TACE to Y90 in the treatment of HCC.

Methods

This systematic review has been registered on PROSPERO (CRD 252180). PubMed, Embase and Cochrane CENTRAL were searched up until April 19, 2021 (Appendix 1). Any systematic reviews identified through screening were subjected to backward reference screening, to identify additional references that were not captured through the search.

Inclusion criteria

Articles were screened by title and abstract (level 1) screening to identify articles comparing at least two treatment modalities to each other in a comparative study (i.e., case-control study, cohort study, or RCT). These articles subsequently underwent full-text (level 2) screening to satisfy the following inclusion criteria: a) treatment intent/primary outcome of local control of HCC; and b) comparative effectiveness studies that comprised either RCTs or observational studies with propensity-score matched (PSM) cohort analyses. These full-text articles were then assessed for quantitative synthesis and included in this review and meta-analysis if they reported on overall survival (OS) and/or progression-free survival (PFS).

Quantitative synthesis

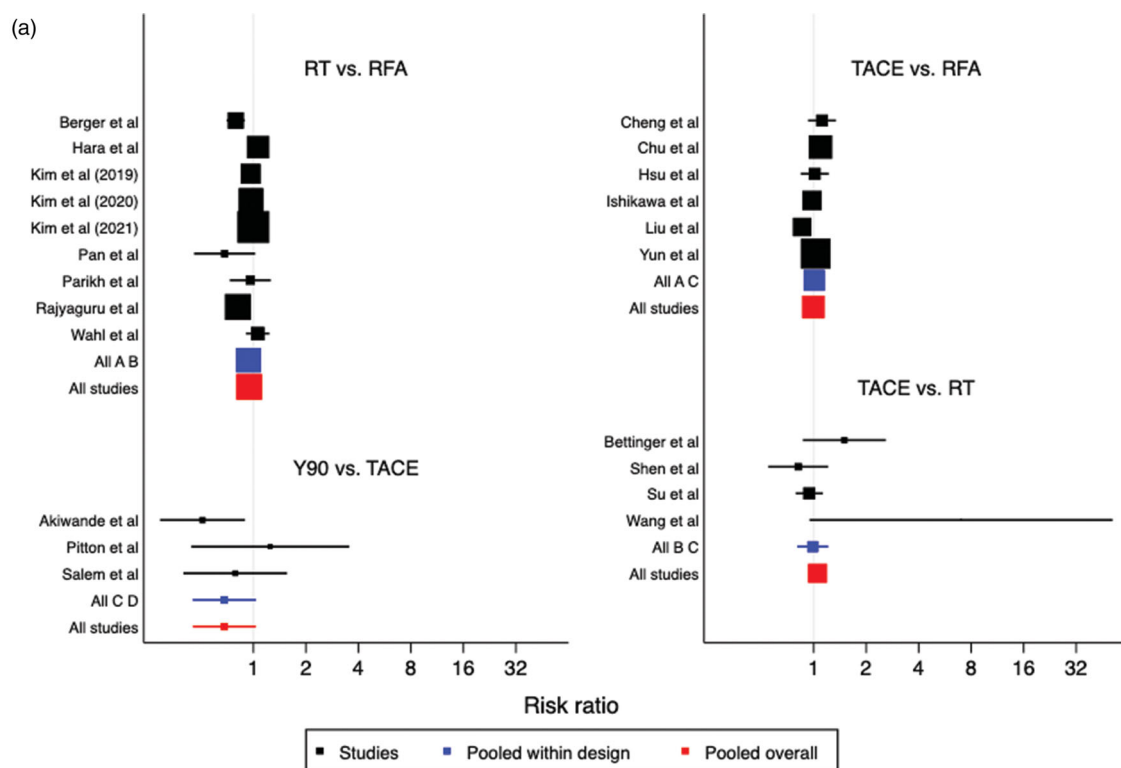
Patient demographics and treatment characteristics were recorded for each study. The recorded sample size was either the total sample size of the RCT, or the sample size of patients included in the PSM cohort analysis. OS and PFS data were extracted from Kaplan-Meier survival curves by visual estimation or in-text descriptions at the 1-year, 2-year and 3-year timepoints.

Meta-Analysis

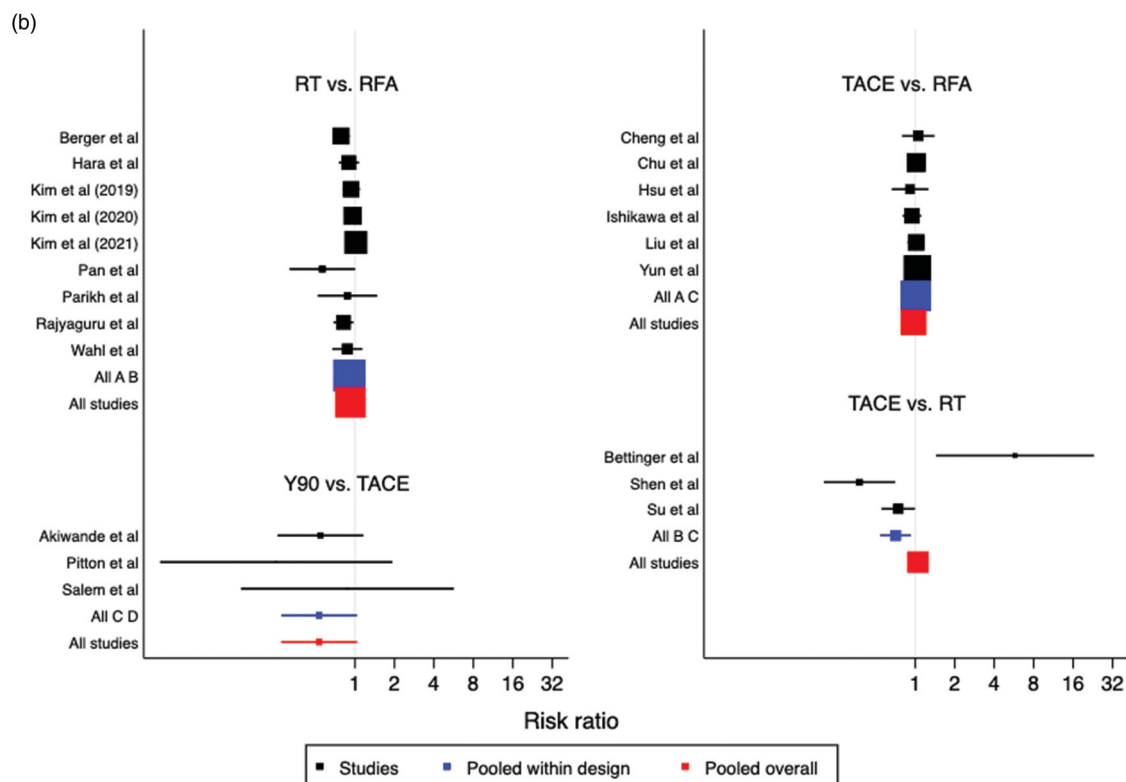
Summary relative risks and corresponding 95% confidence intervals (CI) were calculated using a multivariate network meta-analysis, with a restricted maximum likelihood model. An inconsistency model was used to assess the underlying consistency assumption of network meta-analyses [9]. P-values less than 0.05 were considered statistically significant. All analyses were conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

Quality assessment

All studies were assessed for risk of bias. RCTs were assessed using the Cochrane Risk of Bias 2 tool [10]. Observational studies were assessed using the ROBINS-I tool [11]. Summary risk of bias in the literature was visualized and is presented by the Risk-of-bias VISualization package [12].



Test of consistency: $\chi^2(1)=0.48$, $P=0.490$



Test of consistency: $\chi^2(1)=9.64$, $P=0.002$

Figure 1. Comparisons of Overall Survival. (a) 1-Year Overall Survival, (b) 2-Year Overall Survival, (c) 3-Year Overall Survival. Legend: A = RFA, B = RT, C = TACE, D = Y90. The point estimate for “pooled within design” corresponds to the effect estimate based on head-to-head comparison studies. The point estimate for “pooled overall” corresponds to the effect estimate, based on both head-to-head comparison studies and indirect comparisons.

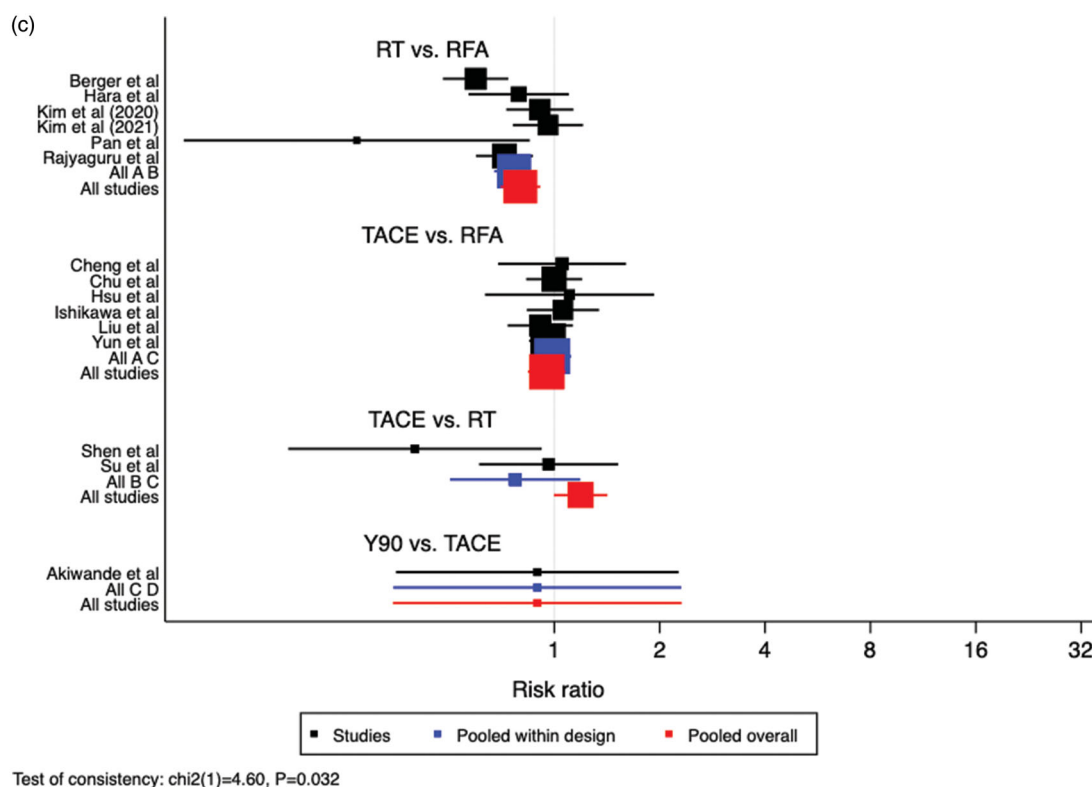


Figure 1. Continued.

Results

A total of 5003 records were identified through database search, and 33 additional records were identified through backward reference screening of systematic review articles. Of these, 84 were duplicates. The remaining 4952 records underwent level 1 screening to identify 103 full-text articles for level 2 screening. Sixty-one studies were assessed for quantitative synthesis, and 24 [13–36] RCTs or PSM observational studies were included in this review and meta-analysis (Appendix 2).

Study demographics are presented in Table 1. Six studies were RCTs, and 18 studies were observational studies with PSM cohort analysis. There were notable concerns for bias due to confounding in observational studies in the unmatched original cohorts, namely that patient demographics by compared treatment modality significantly differed. These concerns did not prevail in their analyses due to the use of propensity-score matching (Appendix 3a). Among RCTs, there was generally a low risk of bias across all assessed criteria (Appendix 3b).

Overall survival (OS)

A larger proportion of patients treated with Y90, relative to TACE, survived after one year – RR 0.85, 95% CI: 0.72–0.99. No difference was noted between Y90 and RT (RR 0.90, 95% CI: 0.77–1.05), TACE and RT (RR 1.06, 95% CI: 0.97–1.16), RT and RFA (RR 0.94, 95% CI: 0.88–1.01, and TACE and RFA (RR 1.00, 95% CI: 0.92–1.08) (Figure 1a). No difference was noted between different treatments, with respect to 2-year and 3-

year survival, aside from RT over RFA at 3-year timepoint (Figures 1b–c). RR for RT to RFA was 0.92 (95% CI: 0.86–1.00) for 2-year survival and 0.80 (95% CI: 0.70–0.91) for 3-year survival. When comparing RFA to TACE, 2-year survival had an RR of 0.96 (95% CI: 0.86–1.07) and 3-year survival had an RR of 0.95 (95% CI: 0.79–1.16). RT to TACE had an RR of 0.98 (95% CI: 0.85–1.11) for 2-year survival, and at 3-year survival had an RR of 0.98 (95% CI: 0.75–1.26). When comparing TACE to Y90, 2-year RR was 0.53 (95% CI: 0.27–1.05) and 3-year RR was 0.89 (95% CI: 0.32–2.48).

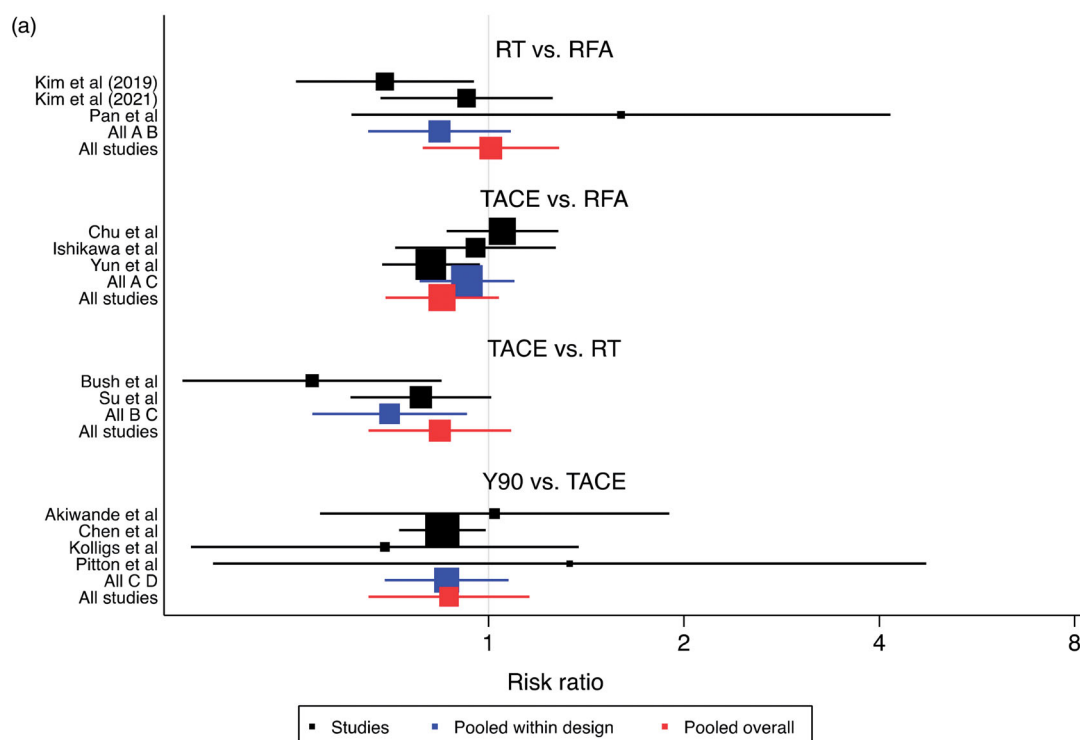
Progression-Free survival (PFS)

PFS was superior for TACE relative to RFA (RR 0.81, 95% CI: 0.68–0.95) and RT (RR 0.65, 95% CI: 0.51–0.83) at the 2-year endpoint, and to RT at the 3-year endpoint (RR 0.62, 95% CI: 0.40–0.97). Otherwise, all treatment modalities were similar (Figure 2).

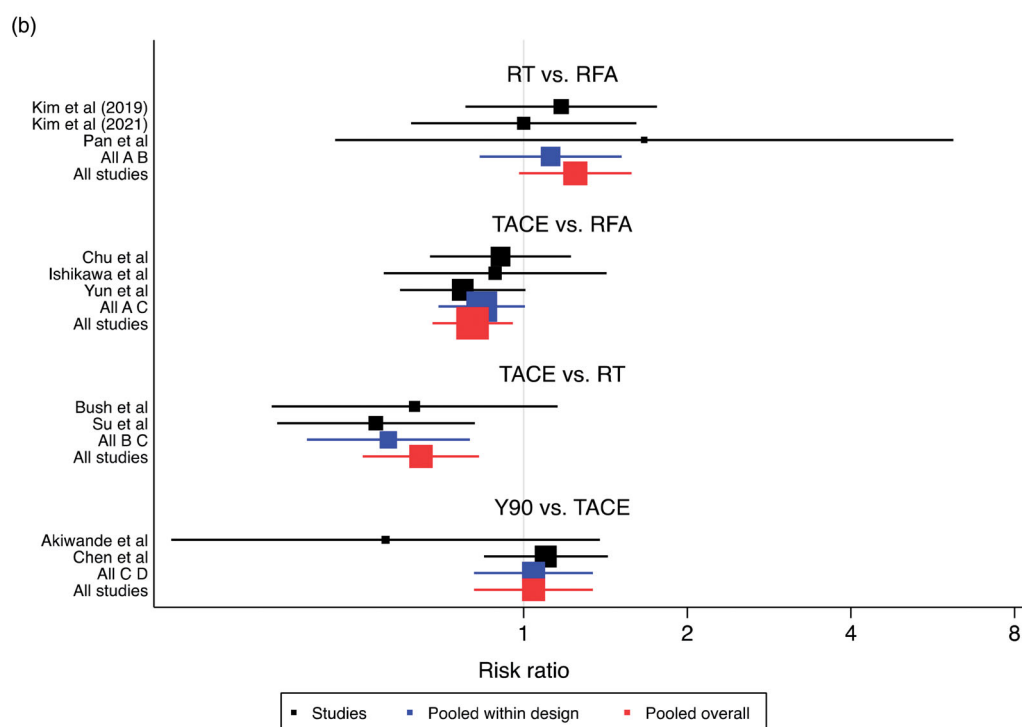
Discussion

To our knowledge, this is the first systematic review and network meta-analysis for HCC comparing RFA to RT to TACE to Y90. With 5549 patients, this is also one of the largest meta-analysis conducted to date investigating local treatment for HCC patients.

The 1-year OS was superior for patients receiving Y90 relative to TACE. However, Y90 was not found to be superior to RT in 1-year OS. This may be a result of only 1 study reporting on Y90 and RT in a head-to-head comparison. Even with



Test of consistency: $\chi^2(1)=4.68$, $P=0.030$



Test of consistency: $\chi^2(1)=1.25$, $P=0.264$

Figure 2. Comparisons of Progression Free Survival. (a) 1-Year Progression Free Survival, (b) 2-Year Progression Free Survival, (c) 3-Year Progression Free Survival. Legend: A = RFA, B = RT, C = TACE, D = Y90. The point estimate for “pooled within design” corresponds to the effect estimate based on head-to-head comparison studies. The point estimate for “pooled overall” corresponds to the effect estimate, based on both head-to-head comparison studies and indirect comparisons.

a network meta-analysis, statistical modeling can only increase precision of our summary estimate and cannot overcome the limited head-to-head data. Despite the apparent superiority of Y90 for 1-year OS, a more appropriate conclusion at this time given the paucity of data would be that all

treatment modalities yield similar OS. Further trials employing PSM cohort analysis or RCT study design are needed.

Although all treatment modalities had similar impact on OS, TACE had superior PFS. The 2- and 3-year PFS were superior for patients receiving TACE compared to both RFA

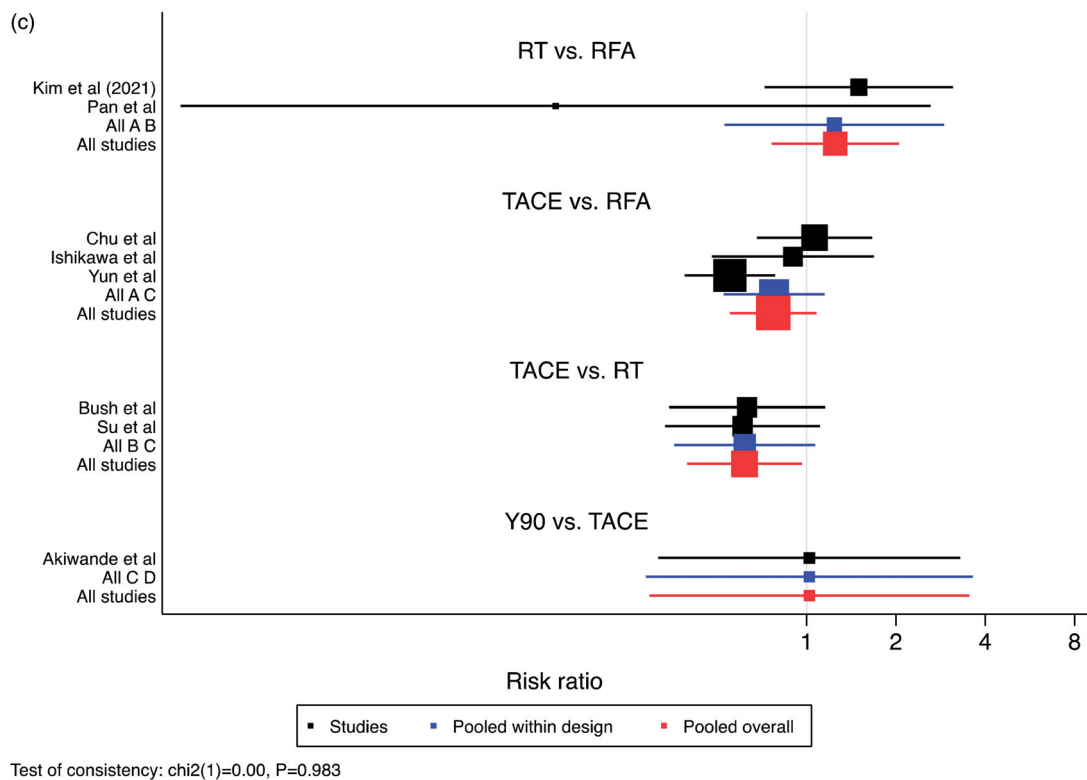


Figure 2. Continued.

and RT, and to RT, respectively. TACE may, therefore, be preferred in select patients to achieve longer time without disease progression, and analysis of subsets of patients who may benefit from this modality over other modalities is warranted. It is important to note that TACE, as noted in these studies, refers to either conventional TACE (cTACE) or drug-eluting bead TACE (DEB-TACE). Future studies should assess the comparative effectiveness/efficacy of cTACE to DEB-TACE.

Of further consideration, TACE has been reported to be superior to RT in patients with intermediate stage (Barcelona-Clinic Liver Cancer BCLC stage B) HCC [37]. Our analyses did not separate early stage and intermediate stage HCC patients due to the limited studies comparing these modalities, and thus statistical power would have been even more limited with subgroup analyses. More studies are needed on TACE in the setting of early stage and intermediate stage HCC to assess whether there exists differential effect by disease stage, as different modalities may have different strengths in treating HCC according to stage.

Given the current evidence suggesting equipoise across these commonly utilized modalities, choice of treatment modality should be based on a multitude of factors, including physician and institutional preference and experience, available resources, and individual patient and tumor characteristics.

This systematic review is not without limitations. Intrinsic in systematic review methodology, biases within individual studies are not overcome by pooled analyses of many studies. In an attempt to minimize any such bias and generate robust analyses, our review was intentionally limited only to

RCTs and PSM cohort analyses. Study quality was, therefore, generally good, with low risk of bias. Due to the paucity of studies, however, we were unable to meaningfully assess subgroup analyses by different radiation treatment modalities relative to RFA, TACE and Y90; the heterogeneous definition of RT may be the cause of heterogeneous conclusions in comparisons to RT and, therefore, nullify any true effect reported of RFA, TACE and Y90 relative to RT. This is notable given the increasing evidence that stereotactic body radiation therapy (SBRT) can lead to improved tumor control and survival compared with conventional radiotherapy techniques [38], that dose-escalated SBRT can further improve outcomes [39], and that proton therapy can reduce toxicities and may improve survival compared with photon therapy [40,41].

Additionally, we similarly were not able to make meaningful comparisons across the four modalities according to different patient subpopulations, and so it is not possible to identify which modality is best for patients with different performance levels, Child-Pugh scores, tumor locations, tumors size, multi-focality of disease, and presence/absence of vascular invasion – all factors known to influence outcomes for HCC. More trials are needed to facilitate subgroup analyses and control for any effect modification by RT modality. Furthermore, our analyses do not report on local control, overall response rates and toxicity endpoints; all important considerations when deciding on appropriate local therapy. Among the studies included in this systematic review, data on the aforementioned outcomes are inconsistent, incomplete, or not reported in the primary published

trials. Future studies should strive to report on all outcomes, inclusive of OS, local control, complete response and toxicity, so that more clinically meaningful comparisons between modalities can be made.

In conclusion, the current evidence suggests comparable OS for RFA, RT, TACE, and Y90 relative to each other in the local treatment of HCC; however, the number of studies overall are limited, and further comparative studies are needed prior to drawing definitive conclusions. In particular, additional high-quality and complete data inclusive of OS, response rates, and toxicity are needed. Such studies should use PSM cohort analyses or RCT study design with appropriate patient selection (i.e., BCLC stage stratified) and statistical power in order to inform on best practices of localized therapy for HCC.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was funded, in part, through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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Appendix 1.

Search strategy

PubMed: 3132 results

(liver neoplasms[mh] OR carcinoma, hepatocellular[mh] OR hepatoma*[tw] OR liver cancer*[tw] OR liver carcinoma*[tw] OR hepatic[tw] OR

hepatocellular[tw] OR liver cell carcinoma*[tw] OR HCC[tw] OR intra-hepatic[tw])
AND
(radiofrequency ablation[mh] OR radiation therapy[tw] OR radiotherapy[mh] OR radiotherapy[tw] OR radiotherapy[sh] OR transarterial chemoembolization[tw] OR chemoembolization, therapeutic[mh] OR embolization, therapeutic[mh] OR yttrium-90[tw] OR stereotactic[tw] OR radiosurgery[mh] OR SABR[tw] OR SBRT[tw] OR TACE[tw] OR TAE[tw] OR TRACE[tw] OR irradiat*[tw] OR proton therapy[mh] OR proton therap*[tw] OR tomotherapy*[tw])
AND
(randomized[tw] OR randomized[tw] OR randomized controlled trial[pt] OR cohort[tw] OR case-control*[tw] OR controlled clinical trial[pt])

Embase and embase classic: 1761 results

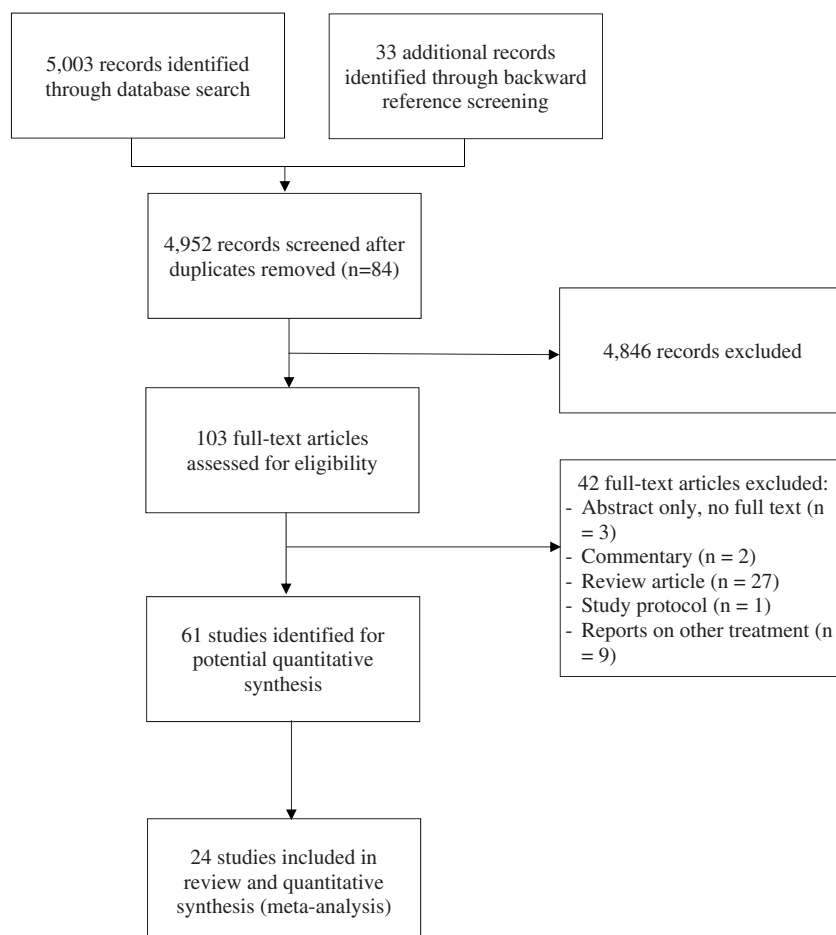
(exp liver tumor/or exp liver cell carcinoma/or hepatoma*.mp. or liver cancer*.mp. or exp liver cancer/or liver carcinoma*.mp. or hepatic.mp. or hepatocellular.mp. or liver cell carcinoma*.mp. or HCC.mp. or intra-hepatic.mp.)
and
(exp radiofrequency ablation/or radiation therapy.mp. or exp radiotherapy/or radiotherapy.mp. or transarterial chemoembolization.mp. or exp chemoembolization/or yttrium-90.mp. or exp yttrium 90/or exp stereotactic radiosurgery/or exp stereotactic body radiation therapy/or stereotactic.mp. or SABR.mp. or SBRT.mp. or TACE.mp. or TAE.mp. or TRACE.mp. or exp irradiation/or irradiat*.mp. or exp proton therapy/or proton therap*.mp. or exp tomotherapy/or tomotherapy*.mp.)
and
(exp randomized controlled trial/or randomized.mp. or randomized.mp. or exp cohort analysis/or exp controlled study/or cohort.mp. or exp case control study/or case-control*.mp. or controlled clinical trial.mp. or exp controlled clinical trial/)

Cochrane Central register of controlled trials: 110 results

(exp liver tumor/or exp liver cell carcinoma/or hepatoma*.mp. or liver cancer*.mp. or exp liver cancer/or liver carcinoma*.mp. or hepatic.mp. or hepatocellular.mp. or liver cell carcinoma*.mp. or HCC.mp. or intra-hepatic.mp.)
and
(exp radiofrequency ablation/or radiation therapy.mp. or exp radiotherapy/or radiotherapy.mp. or transarterial chemoembolization.mp. or exp chemoembolization/or yttrium-90.mp. or exp yttrium 90/or exp stereotactic radiosurgery/or exp stereotactic body radiation therapy/or stereotactic.mp. or SABR.mp. or SBRT.mp. or TACE.mp. or TAE.mp. or TRACE.mp. or exp irradiation/or irradiat*.mp. or exp proton therapy/or proton therap*.mp. or exp tomotherapy/or tomotherapy*.mp.)
and
(exp randomized controlled trial/or randomized.mp. or randomized.mp. or exp cohort analysis/or exp controlled study/or cohort.mp. or exp case control study/or case-control*.mp. or controlled clinical trial.mp. or exp controlled clinical trial/)

Appendix 2.

PRISMA flow diagram.



Appendix 3a.

Risk of bias of cohort studies 3b. Risk of bias of randomized controlled trials.

