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Surgical resection after TACE- or HAIC-based conversion therapy for initially unresectable hepatocellular carcinoma: protocol for a regimen-stratified systematic review and meta-analysis (retrospective registration with a prospectively specified update)

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ADMINISTRATIVE INFORMATION

Support - No specific funding was received for this review.

Review stage at the time of initial registration - Retrospective registration. First round (PubMed, Europe PMC, OpenAlex; 99 studies) screened, extracted and analysed in October-November 2026. Records from Embase, Scopus, Web of Science, updated searches and citation searching (23 November 2026) not yet screened. Details under Other relevant information.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2026 and was last updated on 23 November 2026.

INTRODUCTION

Review question / Objective Primary question: in adults with initially unresectable or advanced hepatocellular carcinoma (HCC), what proportion of all treated patients undergo surgical resection after a transarterial chemoembolization (TACE)-based, hepatic arterial infusion chemotherapy (HAIC)-based or combined TACE-HAIC regimen, given alone or with tyrosine kinase inhibitors or other anti-angiogenic agents (TKI) and/or immune checkpoint inhibitors (ICI), and how does this proportion differ between regimen strata?

Framework: Population, adults with initially unresectable or advanced HCC; Intervention, TACE-, HAIC- or TACE-HAIC-based regimens with or without TKI and/or ICI; Comparator, none required for the single-arm proportion, other locoregional-based regimens where compared within the same study; Outcome, surgical resection with all treated patients as the denominator.

Secondary questions: R0 resection, pathological complete response, major pathological response, objective response (mRECIST and RECIST 1.1), and overall survival of patients who underwent resection compared with those who did not.

Rationale Conversion therapy aims to make initially unresectable HCC resectable, and transarterial regimens combined with systemic agents are widely used for this purpose. Published meta-analyses report pooled conversion or resection rates from about 6% to over 40% [1, 2, 3, 4, 5, 6]. These estimates are hard to compare because reviews differ in how they define success

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(radiological resectability versus resection actually performed), in the denominator (all treated versus evaluable or responding patients), and in how regimens are grouped; several reviews pool across arterial backbones (TACE, HAIC or both) or across systemic intensity. The most recent review used an all-treated denominator but grouped regimens into three broad strategies [6]. This review estimates resection rates within strata defined jointly by the arterial backbone and the added systemic therapy, uses all treated patients as the denominator throughout, reports prediction intervals, adjusts stratum contrasts for study design and publication year, and includes studies published up to November 2026. Its findings will inform the expected yield of conversion strategies and the design of comparative trials.

Condition being studied Hepatocellular carcinoma that is initially unresectable for technical reasons (for example insufficient future liver remnant or tumour extent) or oncological reasons (for example macrovascular invasion including portal vein tumour thrombus, multifocal or advanced disease), including intermediate- and advanced-stage disease (BCLC B and C) as defined by the primary studies. Conversion therapy is treatment given to such tumours with the aim of enabling later curative-intent surgical resection.

METHODS

Search strategy Six bibliographic sources, no language limit, publication years 2015 onward. Full strategies with dates and record counts for every database will be reported in the supplementary material (PRISMA-S).

PubMed core strategy (Q1, run 28 October 2026; a further 51 PubMed, 22 Europe PMC and 6 OpenAlex strings, run 28-31 October 2026, extend it with drug, response, survival and head-to-head terms, 80 strings in total): ("Carcinoma, Hepatocellular"[MeSH] OR hepatocellular[tiab] OR HCC[tiab] OR "liver cancer"[tiab]) AND (TACE[tiab] OR DEB-TACE[tiab] OR cTACE[tiab] OR chemoembolization[tiab] OR chemoembolisation[tiab] OR "transarterial chemoembolization"[tiab] OR "transcatheter arterial chemoembolization"[tiab] OR HAIC[tiab] OR "hepatic arterial infusion"[tiab] OR "hepatic artery infusion"[tiab] OR FOLFOX[tiab] OR "TACE-HAIC"[tiab] OR "arterial infusion chemotherapy"[tiab]) AND (conversion[tiab] OR converted[tiab] OR downstag*[tiab] OR down-stag*[tiab] OR "secondary resection"[tiab] OR "salvage hepatectomy"[tiab] OR "salvage surgery"[tiab] OR "salvage resection"[tiab] OR resectability[tiab] OR "conversion surgery"[tiab] OR "conversion therapy"[tiab] OR "conversion resection"[tiab]) AND 2015:3000[dp]

Embase (Ovid), Scopus and Web of Science Core Collection: two strategies each. S1 combines HCC terms, TACE/HAIC terms (including Emtree chemoembolization) and conversion or resection terms (conversion therapy/surgery/rate, downstaging, resection rate, secondary resection, salvage hepatectomy, unresectable near resection or surgery, converted near resection). S2 replaces the conversion block with named TKI, anti-angiogenic and ICI drug terms combined with resect* OR conversion OR downstag*. Scopus S1 example: TITLE-ABS-KEY("hepatocellular carcinoma" OR "hepatocellular cancer" OR hepatoma OR "liver cancer" OR HCC) AND TITLE-ABS-KEY(TACE OR chemoemboli* OR HAIC OR (hepatic W/3 arter* W/3 infusion*) OR "transarterial infusion" OR "transcatheter arterial" OR "arterial infusion chemotherapy") AND TITLE-ABS-KEY("conversion therapy" OR "conversion surgery" OR "conversion resection" OR "conversion rate" OR "conversion hepatectomy" OR "surgical conversion" OR downstag* OR "down-stag*" OR (unresectable W/6 (resect* OR surg*)) OR "resection rate" OR "secondary resection" OR "salvage hepatectomy" OR "salvage surgery" OR (convert* W/4 resect*)) AND PUBYEAR > 2014 AND PUBYEAR < 2027.

Planned update: all PubMed, Europe PMC and OpenAlex strings will be re-run with the same wording to 23 November 2026, the closing date of the Embase, Scopus and Web of Science searches. One round of backward and forward citation searching will follow (see Information sources). The strategies were not peer reviewed by an information specialist (PRESS).

Participant or population Adults (as defined by the primary studies) with HCC judged initially unresectable or advanced at the start of the regimen. Studies of mixed populations are eligible when outcomes are reported separately for initially unresectable patients, or when all enrolled patients were treated with conversion intent. Studies restricted to resectable HCC treated with neoadjuvant intent, recurrent HCC after previous resection, or liver transplantation candidates (downstaging to transplant) are excluded.

Intervention Regimens based on TACE (conventional, drug-eluting bead or bland embolization), HAIC (for example FOLFOX-HAIC), or sequential or combined TACE-HAIC, given alone or combined with a TKI or other anti-angiogenic

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agent (for example lenvatinib, sorafenib, donafenib, apatinib, bevacizumab) and/or an ICI (anti-PD-1, anti-PD-L1 or anti-CTLA-4). Each eligible arm is assigned to one stratum defined by the arterial backbone (TACE, HAIC, TACE-HAIC, mixed) and the systemic component (none, TKI, ICI, TKI plus ICI). Regimens in which radioembolization, radiotherapy or systemic therapy without an arterial component is the backbone are excluded.

Comparator No comparator is required for the primary outcome, which is a single-group proportion. Where a study compares two eligible regimens (for example TACE plus TKI and ICI versus TACE plus TKI, or HAIC versus TACE), the within-study comparison is analysed as a head-to-head contrast. For survival, patients who underwent resection are compared with patients who did not within the same cohort.

Study designs to be included Randomized controlled trials, non-randomized prospective trials (including single-arm phase 2 trials), and prospective or retrospective cohort studies or case series with at least 10 patients in the eligible arm. All designs contribute to the stratum-specific pooled proportions; design (prospective versus retrospective) is included as a covariate in meta-regression and examined in sensitivity analyses. Case reports, case series with fewer than 10 patients per arm, reviews, editorials, letters without original data and protocols without results are excluded.

Eligibility criteria Inclusion: population, intervention and design as above; the number of patients who underwent surgical resection and the number of treated patients in the arm are reported or can be derived; published from 1 January 2015 onward; any language. The primary analysis uses studies with full text available; data available only from conference abstracts, preprints or trial registry results are used in sensitivity analyses only.

Exclusion: the denominator is restricted to responders or otherwise selected patients without the all-treated number being derivable (such arms may be analysed descriptively or in sensitivity analyses); resection numbers cannot be separated for the eligible arm; duplicate or overlapping reports.

Multiple reports and overlapping cohorts: reports of the same study are linked and the most complete report is used. Cohorts from the same centre with overlapping recruitment periods are treated as overlapping; for each stratum only one is retained in the primary analysis (the largest, or the one with the most complete outcome data) and the others are examined in sensitivity analyses. Conference abstracts are superseded by the full paper when one exists. Trial registry records do not contribute data; they are used to identify linked publications and to list ongoing studies. Uncertain eligibility is resolved by discussion between reviewers.

Information sources PubMed (MEDLINE), Europe PMC and OpenAlex (searched 28-31 October 2026, to be updated to 23 November 2026); Scopus (20 November 2026); Embase via Ovid (21 November 2026); Web of Science Core Collection (23 November 2026). Backward citation searching (reference lists) and forward citation searching (citing articles) of all included studies, studies included at abstract level, and the six earlier meta-analyses cited under Rationale will be performed once using Europe PMC (references and citations), Semantic Scholar and OpenCitations, with OpenAlex added where access allows; newly included studies will not be citation-searched again. Trial registry records retrieved by the database searches will be used to locate linked publications. Study authors will not be contacted.

Main outcome(s) Surgical resection rate: the number of patients who underwent surgical resection (hepatectomy) of the liver tumour after the regimen, divided by all patients who started the regimen in that arm (all-treated denominator). Liver transplantation, ablation and radiological resectability without surgery are not counted as events. Where a study reports both patients who became resectable and patients who actually underwent resection, the number actually resected is used. The latest reported follow-up is used.

Additional outcome(s) R0 resection rate; pathological complete response and major pathological response among resected patients; objective response rate by mRECIST and by RECIST 1.1 (all-treated denominator where available); hazard ratio for overall survival of resected versus non-resected patients within the same cohort; reasons why patients who met resectability criteria did not undergo surgery. All secondary outcomes are reported regardless of direction.

Data management Records are de-duplicated using DOI, PMID, database accession numbers and normalised titles; possible duplicates are checked manually. Screening, full-text assessment, data extraction and risk-of-bias assessment are performed first by the lead author. The lead author reads every title and abstract (keyword rules are

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used only to order records, never to exclude them), records a decision and reason code for each record, extracts each numeric value together with a verbatim quotation and its location in the source, and writes the analysis code in R (version 4.4.2; metafor 5.2.1; lme4). All extracted numbers are checked against the source reports before analysis.

Independent verification: a second reviewer, blinded to the lead author's decisions, independently screens a stratified random 20% sample of titles and abstracts (agreement reported as Cohen's kappa), re-assesses all full-text inclusion and exclusion decisions, and re-extracts the key data (number resected, denominator, stratum assignment) for all included studies, both previously and newly included. Disagreements are resolved by discussion, with the lead author making the final decision; if agreement on the title and abstract sample is low (kappa below 0.6), the second reviewer will screen all records. Decision logs, extraction tables with quotations, and analysis code will be shared with the final review.

Quality assessment / Risk of bias analysis Risk of bias of each study is assessed with the JBI critical appraisal checklist for case series (single-arm data; overall rating from the proportion of items met: at least 70% low, 50-69% moderate, below 50% high, author-defined thresholds), ROBINS-I for non-randomized comparisons, and RoB 2 for randomized comparisons. Assessments are made by the lead author and checked by the second reviewer for newly included studies. Certainty of evidence for the resection rate in each stratum and for the main contrasts is rated with GRADE adapted for single-group proportions (domains: risk of bias, inconsistency, imprecision, indirectness, publication bias). Strata with mostly high risk-of-bias studies are examined in sensitivity analyses.

Strategy of data synthesis Resection proportions are pooled within each stratum with a random-effects binomial-normal generalized linear mixed model (logit link, maximum likelihood); 95% confidence intervals and 95% prediction intervals are reported, and strata are not pooled with each other. Strata with fewer than three arms are described without pooling. Differences between strata are estimated with a logistic mixed model with stratum, study design and publication year as fixed effects and random intercepts for study and arm. Within-study comparisons are pooled as odds ratios (random effects, REML, Hartung-Knapp adjustment), and hazard ratios for overall survival are pooled on the log scale. Heterogeneity is described with tau-squared, I-squared and prediction intervals; the model is not chosen on the basis of a heterogeneity test. Small-study effects are assessed with the Peters test and funnel plots in strata with at least ten arms. Multi-arm studies contribute each eligible arm to its own stratum.

Subgroup analysis Prespecified for the update: arterial backbone and systemic component (the strata themselves); study design (prospective versus retrospective); publication year; type of TKI (lenvatinib versus other); and, within strata with enough data, the association between objective response and resection rate (meta-regression). Subgroup analyses introduced after the first-round results are labelled exploratory (see Other relevantinformation).

Sensitivity analysis Excluding arms with derived or selected denominators; excluding head-to-head cohorts restricted to advanced disease (for example portal vein tumour thrombus); restricting to studies published from 2021; excluding overlapping cohorts or replacing them with the alternative cohort; adding arms available only from conference abstracts, preprints or registry results; excluding studies at high risk of bias; restricting to prospective studies; alternative estimators (inverse-variance logit and Freeman-Tukey random-effects models, with Hartung-Knapp adjustment); and comparison of the first-round (99-study) and updatedestimates.

Language restriction No language restriction.

Country(ies) involved China.

Keywords hepatocellular carcinoma; conversion therapy; transarterial chemoembolization; hepatic arterial infusion chemotherapy; immune checkpoint inhibitors; tyrosine kinase inhibitors; hepatectomy; meta-analysis.

Dissemination plans Publication in a peer-reviewed journal and in a doctoral thesis; possible presentation at scientific meetings. The final review will cite this registration, report all deviations from it, and the registration record will be updated with the publication link. Extraction tables with source quotations, decision logs and analysis code will be made publicly available with the publication.

Contributions of each author

Author 1 - Shanru Feng - Conceived the review, ran the searches, screened records, extracted data, performed the analyses, drafted the protocol and manuscript, and made final decisions on disagreements.

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Author 2 - Xiaoying Wang - Independently screened a random 20% sample of records, verified all full-text decisions and key data, and revised the manuscript. Supervised the project, interpreted the findings and critically revised the protocol and manuscript.
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