AP&T Alimentary Pharmacology and Therapeutics

Systematic review: benefits and harms of transarterial embolisation for treating hepatocellular adenoma

C. Zhao*,[a], S.-L. Pei†,[a], A. Cucchetti‡, T.-J. Tong§, Y.-L. Ma*, J.-H. Zhong¶ & L.-Q. Li¶

*Department of Interventional Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China.
†Department of Anesthesia, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China.
‡Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Alma Mater Studiorum, University of Bologna, Bologna, Italy.
§Department of Mathematics, Hong Kong Baptist University, Kowloon, Hong Kong.
¶Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China.

Correspondence to:
Dr J.-H. Zhong, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd #71, Nanning 530021, China.
E-mail: zhongjianhong66@163.com
Dr Y.-L. Ma, Department of Interventional Surgery, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd #71, Nanning 530021, China.
E-mail: yilongma6@gmail.com

[a]These authors contributed equally to this work.

Publication data
Submitted 12 January 2017
First decision 5 February 2017
Resubmitted 22 February 2017
Accepted 22 February 2017

The Handling Editor for this article was Professor Stephen Harrison, and this uncommissioned review was accepted for publication after full peer-review.

SUMMARY

Background
Transarterial embolisation (TAE) is a standard treatment for bleeding hepatocellular adenoma (HCA) and, occasionally, symptomatic HCA involving large tumours. Whether TAE is similarly safe and effective as an elective treatment for bleeding and nonbleeding HCA remains unclear.

Aim
To investigate the benefits and harms of TAE for bleeding and nonbleeding HCA.

Methods
PubMed, Scopus, Embase and Cochrane Library databases were systematically searched for studies that examined post-TAE tumour reduction in patients with bleeding or nonbleeding HCA and that were published between January 2000 and January 2017.

Results
Systematic review of 21 case series involving 1468 patients with HCA in the systematic review identified 140 (9.5%) patients with 189 lesions who received TAE. Of these 140 patients, 66.4% had bleeding HCA and 33.6% had nonbleeding HCA. Intended elective TAE was performed in 27.1% of patients (38.6% of HCA lesions). Adenomatosis was observed in 6.1% of patients, and the rate of β-catenin expression was 4.5%. No malignant transformation was observed among the 189 tumours during a median follow-up time of 40 months. The complete response rate among 70 patients was 10.6%, and the partial response rate was 71.7%. No mortality or severe adverse side effects were reported during the hospitalisation period.

Conclusions
The available evidence suggests that TAE can be considered safe for elective managment of HCA as well as for management of bleeding HCA. Elective TAE can be regarded as a reasonable alternative to surgery. High-quality prospective studies with long-term follow-up are needed to corroborate and strengthen available evidence.

doi:10.1111/apt.14044

INTRODUCTION

Hepatocellular adenoma (HCA), a benign tumour composed of hepatocytes with the potential to transform into malignant hepatocellular carcinoma, is rare in Asia but prevalent in Europe.[1, 2] The etiology of the disease remains unknown, with one of the primary risk factors among women considered to be the long-term use of oral contraceptives. New HCA risk factors have emerged, such as obesity, metabolic syndrome and anabolic steroid exposure. Annual incidence of HCA is estimated to be 1 per 1 million in the general population and 3–4 per 100 000 women using oral contraceptives in the long-term.[3, 4] Symptomatic bleeding occurs in more than 14% of patients with HCA, and the risk of such bleeding increases with tumour diameter.[1] The risk of malignant transformation into hepatocellular carcinoma (HCC) is approximately 4–6% in women and up to 47% in men.[1, 5–7]

Most patients already have large tumours (>5 cm) at initial diagnosis of HCA because the condition is usually discovered accidentally based on liver function test abnormalities or based on abdominal imaging performed for other reasons. The risk of HCA haemorrhage and malignant transformation has made hepatic resection a common initial treatment for HCA, but emergent hepatic resection of ruptured HCA is associated with a mortality rate of 5–10%.[8] An alternative initial procedure is elective transarterial embolisation (TAE), which is associated with less blood loss and lower risk of postoperative complications than resection.[8] Emergency TAE is considered a standard treatment if the HCA patient is actively bleeding or if the risk of intraoperative bleeding is high.[8] In other cases, elective TAE may be superior to resection if the HCA involves large or multiple tumours, or if the tumour is difficult to reach during surgery. Both emergency and elective TAE may reduce the risk of malignant transformation of HCA.[9]

While emergency TAE is well-established, the safety and efficacy of elective TAE is less clear, such as in patients who have nonbleeding HCA or who are at low risk of intraoperative bleeding. To clarify the suitability of elective TAE for such cases, we systematically reviewed clinical studies of TAE to treat bleeding and nonbleeding HCA. We focused on the clinical presentation of HCA subsequently treated with TAE, as well as on post-TAE outcomes such as tumour size reduction, need for hepatic resection and incidence of malignant transformation.

METHODS

Literature search and selection

PubMed, Scopus, Embase and Cochrane Library databases were systematically searched for articles published between 1 January 2000 and 11 January 2017 involving TAE to treat HCA. A systematic review was carried out in accordance with the PRISMA statement for reporting systematic reviews of studies that evaluate healthcare interventions.[10] Literature searches were carried out using the medical subject headings (MeSH) "hepatocellular adenoma" and "embolisation" as well as the keywords "hepatic adenoma" and "transarterial embolisation". Results from the electronic database searches were compared to generate a list of unique articles to screen. Relevant references of all included studies were also searched manually to identify additional studies. Gray literature was not included in the present analysis.

Two authors (C.Z. and Y.-L.M.) independently screened articles for eligibility based on title, abstract and keywords. Then studies were subjected to three levels of screening. At level 1, studies were excluded if they were reviews, letters, editorials or comments, or were published in languages other than English. At level 2, abstracts of retained studies were reviewed in detail, and only those reporting clinical outcomes for series of HCA patients treated by TAE proceeded to level 3. At this final level, the full text of retained studies was read. In addition, articles questionably excluded at level 2 were read in full. The two reviewers then independently assessed the studies for relevance and methodological quality. Studies had to meet the following criteria to be included in the final analysis: (i) publication after 2000, when radiological interventional techniques became common; (ii) patient population with HCA treated by elective or emergency TAE (TAE alone, prior to surgery or after surgery); and (iii) a case series (involving at least four patients), case–control or cohort design reporting on post-TAE outcomes. When the same patients were included in multiple studies, only the largest was included in the review. Such overlap in patient populations was surmised on the basis of overlap in authorship, institutions and enrolment period. Studies reporting only nonclinical TAE outcomes, such as cost-effectiveness, were excluded. Any discrepancies in study inclusion were resolved by discussion between the reviewers and a third investigator (J.-H.Z.).

Data collection and definitions

The following data were extracted by two authors (C.Z. and Y.-L.M.) using standardised forms: family name of

the first author and publication year, country, patient enrolment period, study design, number of total patients, number of patients embolised (bleeding or nonbleeding), treatments in the remaining patients, number of patients with elective embolised, gender, patient's mean age, embolisation material, number of tumours embolised, number of adenomatoses and median follow-up. The following primary outcomes data were collected: reason for TAE, number of resections avoided (bleeding/nonbleeding), numbers and reasons for conducting or not conducting post-TAE hepatic resection, malignant transformation and TAE-related complications. Another primary outcome was tumour response rate based on RECIST guidelines,[11] according to which complete response meant disappearance of all target lesions; partial response, at least 30% decrease in the sum of the diameters of all target lesions, relative to the total diameter at baseline; progressive disease, at least a 20% increase in the sum of diameters of all target lesions; and stable disease, any change in total diameter of all target lesions, relative to the smallest total diameter of all lesions at any time during the study, that did not qualify as partial response or progressive disease.

Emergency TAE was defined as TAE conducted to treat active bleeding or to avoid intraoperative bleeding. Elective TAE was defined as TAE conducted instead of resection, such as in the case of nonbleeding HCA or for reasons other than avoiding intraoperative blood loss. Avoidance of resection was defined as no post-TAE resection as a result of tumour size reduction or involution and/or the cessation of complaints during the follow-up period. Cases in which tumour size merely remained stable or in which tumours were judged to be unresectable before and after TAE were not counted as avoidance of hepatic resection. Adenomatosis was defined as at least 10 lesions.[12] The quality of each study was assessed using a quality appraisal tool for case series studies, based on a modified Delphi technique (Table S1).[13] Study with total scores ≥14 was regarded as adequate quality.[13]

Statistical analysis

Due to the considerable heterogeneity in patient selection and data reporting, patient and outcomes data were analysed descriptively with no meta-analysis. Data were presented as numbers (with percentages) and mean or median values, as appropriate.

RESULTS

A total of 233 studies were identified using our search criteria (Figure 1), of which 27 were rejected and 206 were retained for abstract review. On the basis of the abstract, 136 studies were excluded and 47 retained and read in full. In the end, 21 studies[14–34] were included in the systematic review (Table 1). Two pairs of studies[22–25] came from the same department but involved nonoverlapping patient enrolment periods; therefore, all four studies were included in the review. In one study,[27] TAE was performed together with chemotherapy (TACE). Seven studies[14, 16, 22, 25, 29, 32, 34] followed a prospective design. Total scores in 18 (86%) studies were ≥14. These studies were regarded as adequate quality (Table S2).

The 21 studies included 1468 patients with HCA, 89.2% of whom were female and 99.5% of whom were in Western countries.[14–26, 28–34] Median age was 36 years. A total of 140 of 1468 (9.5%) patients, corresponding to 189 lesions, received TAE. Of the 140 patients who received TAE, 93 (66.4%) had bleeding HCA and 47 (33.6%) had nonbleeding HCA. Intended elective TAE was performed in 38 of 140 (27.1%) patients or on 73 of 189 (38.6%) HCA lesions. Of the remaining patients, 1252 (85.3%) received hepatic resection, 132 (9%) received conservative treatment, 3 (0.2%) received biopsy and 1 received liver transplantation. Adenomatosis was observed in 9 of 148 (6.1%) patients. The expression of β-catenin was reported in five of the included studies.[16, 22, 23, 26, 28] The rate of β-catenin expression was 4.5% (14/308). Embolisation materials used in TAE were described in five of the included studies.[21, 24, 25, 27, 32] These materials included tris-acryl gelatin microspheres, platinum coils, polyvinyl alcohol particles, absorbable gelatin sponge particles and lipiodol.

Baseline histology was not described in the studies and appears not to have been used to guide the decision whether to perform hepatic resection or not. No malignant transformation was observed among the 189 tumours during a median follow-up time of 40 months.

Time from TAE to hepatic resection was not reported in the studies. Among the 140 patients treated by TAE, resection was avoided in 64 (45.7%), of whom 29 (45.3%) were bleeding before TAE and 35 (54.7%) were not. Of the 38 patients who underwent elective TAE, 35 (92.1%) did not require further hepatic resection. In contrast, hepatic resection was avoided in only 29 of the 93 (31.2%) who experienced bleeding before acute TAE. Of the 64 cases in which resection was avoided, 59 (92%) were because of tumour regression, while the reasons for the remaining 5 (7.8%) are unknown. The detailed time

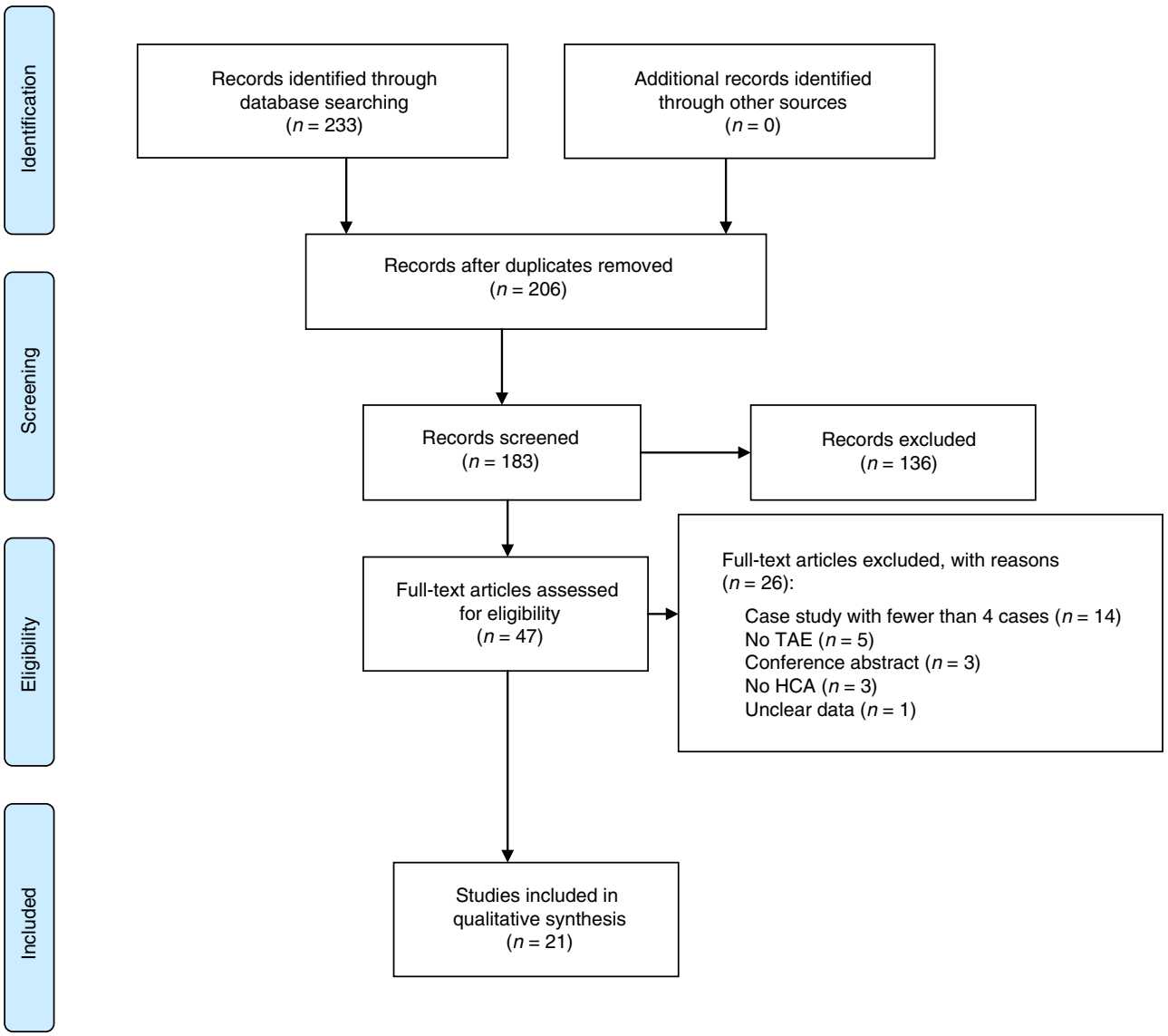

Figure 1 | PRISMA flow diagram. TAE, transarterial embolisation; HCA, hepatocellular adenoma.

of resection after TAE was not described in the studies. Of the 75 patients with resection after TAE, resection was based on protocol in 68 (90.1%), persistent tumour in 3 (4%) and intra-abdominal hematoma in 2 (2.7%) (Table 2).

Eight studies in the systematic review, involving 70 of all 140 (50%) patients who underwent TAE, reported whether or not tumour size changed after the procedure.[17, 21, 22, 25–27, 31, 32] In the study by Bunchorntavakul and coworkers,[17] only 14 of 17 patients for whom follow-up data were available showed partial imaging response. Therefore, only these 14 patients were pooled in the calculation of tumour reduction. Of the 14 patients, 11 (79%) showed tumour regression as defined by the revised RECIST guidelines.[11] In two other studies,[21, 26] the pooled calculation of tumour reduction was based on number of tumours, not the number of patients. In the end, we pooled data on 113 tumours to examine disease response rates based on the revised RECIST criteria (Table 2). Response rates were as follows: complete response, 10.6% (12/113); partial response, 71.7% (81/113); progressive disease, 3.5% (4/113); and stable disease, 14.2% (16/113). The rate of overall (complete + partial) response was 82.3%.

Only one study involving seven patients who received TACE reported on whether or not symptoms improved after the procedure.[27] Four patients presented with

Table 1 | Characteristics of the included studies

Study	Country	Enroll. period	Study design	Total no. of patients	Patients embolised (bleeding/ no bleeding)	Treatments of remaining patients	Characteristics of patients with transarterial embolisation			
							Mean Age, year*	Tumours embolised (bleeding/ no bleeding)	Adenomatosis	Median follow-up (months)
Abu Hilal 2011	UK	2005–2009	P	13	3/0	Resection (*n* = 13)†	27	5/0	2	–
Battula 2012	UK	1995–2011	R	27	2/0	Resection (*n* = 3); conservative (*n* = 22)	–	2/0	0	57
Bieze 2014	Netherlands	2008–2012	P	45	7/2	Resection (*n* = 29); conservative (*n* = 7)	39	7/3	0	14
Bunchorntavakul 2011	USA	2005–2010	R	60	4/13	Resection (*n* = 17); conservative (*n* = 26)	36	4/13	0	31
Cho 2008	USA	1988–2007	R	41	1/0	Resection (*n* = 41)†	38	1/0	0	23
de'Angelis 2014	France	1989–2012	R	62	6/0	Resection (*n* = 62)†	36	6/0	0	12
Deneve 2009	USA	1997–2006	R	124	6/5	Resection (*n* = 119)†	39	6/5	0	36
Deodhar 2011	USA	2006–2007	R	8	1/7	–	36	2/15	0	24
Dokmak 2009	France	1990–2004	R	122	12/0	Resection (*n* = 118); large biopsy (*n* = 3); liver transplantation (*n* = 1)†	37	12/0	0	70
Dokmak 2015	France	2004–2013	P	116	2/0	Resection (*n* = 106); conservative (*n* = 8)	42	2/0	0	38
Erdogan 2006	Netherlands	1990–2005	R	22	1/1	Resection (*n* = 4); conservative (*n* = 16)	36	1/1	0	25
Erdogan 2007	Netherlands	–	P	6	6/0	–	40	6/0	0	24
Karkar 2013	USA	1992–2011	R	52	5/12	Resection (*n* = 36)†; conservative (*n* = 9)	39	5/33	7	56
Kim 2007	South Korea	1989–2006	R	7	1/6	–	25	3/6	0	88
Laurent 2016	Europe‡	1986–2013	R	573	15/0	Resection (*n* = 573)†	37	15/0	0	91
Marini 2002	France	1995–2000	P	7	3/0	Resection (*n* = 4)	35	3/0	0	6
Ramia 2014	Spain	1995–2011	R	81	1/0	Resection (*n* = 81)†	40	1/0	0	43
Srirattanapong 2014	USA	2002–2012	R	18	1/1	Resection (*n* = 9)†; conservative (*n* = 8)	24	1/1	0	41
Stoot 2007	Netherlands	2001–2006	P	11	11/0	–	34	17/8	0	19
Toso 2005	Netherlands	1980–2003	R	25	2/0	Resection (*n* = 25)†	38	2/0	0	72
van der Windt 2006	Netherlands	2000–2005	P	48	3/0	Resection (*n* = 12)†; conservative (*n* = 36)	36	3/0	0	24
Total (median, %)	–	–	–	1468	140 (93/47)	Resection (*n* = 1252), conservative (*n* = 132), liver transplantation (*n* = 1), biopsy (*n* = 3)	36	189 (104/85)	9§	40

–, not available; P, prospective; R, retrospective.

*Data are reported for the total cohort instead of only embolised patients if the necessary data were not reported in the original study.

†Including patients with pre- or postoperative embolisation.

‡All patients from 27 high-volume hepatobiliary hospital units in Europe underwent hepatic resection.

§Adenomatosis was defined as at least 10 lesions.

abdominal pain and one presented with lower-extremity oedema, while the remaining two did not have any symptoms at presentation. These symptoms ceased within 1 month after TACE (Table 2).

Most studies recorded no complications related to TAE. None of the studies reported procedural complications or mortality. Nevertheless, some patients experienced self-limited post-TAE syndrome, including pain,

Table 2 | Outcomes of TAE in the included studies

Study	No. patients/ tumours embolised	Reason for TAE	Resection avoided (bleeding/ nonbleeding)	Reasons for conducting or not conducting post-TAE resection	Tumour reduction and symptom improvement	Complications
Abu Hilal 2011	3/5	Bleeding (n = 3)	0/0	Resection according to protocol (n = 3)	–	Sepsis due to cyst after TAE (n = 1)
Battula 2012	2/2	Bleeding (n = 2)	2/0	No resection needed: tumour regression (n = 2)	–	No complications
Bieze 2014	9/10	Bleeding (n = 7), TAE to avoid intraoperative bleeding (n = 2)	1/0	No resection needed: tumour regression (n = 1); resection according to protocol (n = 8)	–	No complications
Bunchorntavakul 2011	17/17	TAE prior to resection (n = 6), TAE after resection (n = 2), pregnancy (n = 1), study purpose (n = 6), not clear (n = 2)	2/7	No resection needed: tumour regression (n = 9); resection according to protocol (n = 8)	Good response and reduction of tumour lesions in 79%; CR (n = 0), PR (n = 11), PD (n = 1); SD (n = 2)*	Two with moderately severe post-embolisation syndrome, leading to extended hospital stay or a return to the emergency department. One developed diabetic ketoacidosis.
Cho 2008	1/1	Bleeding (n = 1)	0/0	Resection according to protocol (n = 1)	–	No complications
de'Angelis 2014	6/6	Bleeding (n = 6)	0/0	Resection according to protocol (n = 6)	–	No complications
Deneve 2009	11/11	Bleeding (n = 6), reason not described (n = 5)	0/5	No resection needed: reason not clear (n = 5); resection according to protocol (n = 6)	–	No complications
Deodhar 2011	8/17	Bleeding (n = 1), abdominal pain (n = 1), presumed increased risk of bleeding (n = 6)	1/5	No resection needed: regression tumour (n = 6); resected for continued peripheral enhancement (n = 2)	CR (n = 2), PR (n = 10), PD (n = 2); SD (n = 3)	No procedural complications. Most patients had elements of self-limited postembolisation syndrome, including pain, fever, nausea/vomiting and fatigue, but in no patient did this lead to a prolonged (>24 h) hospital stay.
Dokmak 2009	12/12	Bleeding (n = 12)	0/0	Resection according to protocol (n = 12)	–	No complications
Dokmak 2015	2/2	Bleeding (n = 2)	2/0	No resection needed: regression tumour (n = 2)	CR (n = 1), PR (n = 1), PD (n = 0); SD (n = 0)	No complications
Erdogan 2006	2/2	Bleeding (n = 2)	1/0	No resection needed: tumour regression (n = 1); resection according to protocol (n = 1)	–	No complications
Erdogan 2007	6/6	Bleeding (n = 4), to reduce the tumour mass >5 cm (n = 2)	4/0	No resection needed: tumour regression (n = 4); laparotomy for intra-abdominal hematoma (n = 2)	CR (n = 1), PR (n = 4), PD (n = 0); SD (n = 1)	No complications
Karkar 2013	17/38	Suspicion of malignancy (n = 14), haemorrhage (n = 5), large tumour (n = 1), local recurrence after resection (n = 1)†	5/11	No resection needed: tumour regression (n = 16)	CR (n = 6), PR (n = 22), PD (n = 0), SD (n = 10)	No complications
Kim 2007	7/9	Impending rupture (n = 6), bleeding (n = 1)	1/6	No resection needed: tumour regression (n = 7)	Preexisting symptoms were relieved within 1 month after TACE. CR (n = 2), PR (n = 6), PD (n = 1); SD (n = 0)	Immediately after TACE, most patients experienced nausea, fever or abdominal pain; however, all symptoms disappeared within 5 days.
Laurent 2016	15/15	Bleeding (n = 15)	0/0	Resection according to protocol (n = 15)	–	–

Table 2 | (Continued)

Study	No. patients/ tumours embolised	Reason for TAE	Resection avoided (bleeding/ nonbleeding)	Reasons for conducting or not conducting post-TAE resection	Tumour reduction and symptom improvement	Complications
Marini 2002	3/3	Bleeding (n = 3)	0/0	Resection according to protocol (n = 3)	–	No complications
Ramia 2014	1/1	Bleeding (n = 1)	0/0	Resection according to protocol (n = 1)	–	No complications
Srirattanapong 2014	2/2	High risk for resection (n = 1), remaining adenoma after surgery (n = 1)	1/1	No resection needed: tumour regression (n = 2)	CR (n = 0), PR (n = 2), PD (n = 0); SD (n = 0)	No complications
Stoot 2007	11/25	Bleeding (n = 11)	9/0	No resection needed: tumour regression (n = 9); resection according to protocol (n = 2)	The median decrease in tumour size was 5.0 cm after TAE. CR (n = 0), PR (n = 25), PD (n = 0); SD (n = 0)	No complications
Toso 2005	2/2	Bleeding (n = 2)	0/0	Resection according to protocol (n = 2)	–	No complications
van der Windt 2006	3/3	Bleeding (n = 3)	0/0	Emergency resection (n = 1); due to pregnancy (n = 1) or to persistent tumour (n = 1)	–	No complications
Total (%)	140/189	Bleeding (n = 93), other reasons (n = 55)	Surgery avoided, n = 64 (29/35)	Performed resection, n = 75	CR (n = 12), PR (n = 81), PD (n = 4); SD (n = 16)	–

–, not available; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TAE, transarterial embolisation; TACE, transarterial chemoembolisation.

*Only 14/17 patients with follow-up data.

†Based on number of tumours, not number of patients.

fever, nausea/vomiting and fatigue. In rare cases, this led to a hospital stay >24 h. Two patients experienced moderate post-TAE syndrome, requiring a hospital stay >24 h or a return to the emergency room.[17] One patient developed diabetic ketoacidosis after TAE,[17] while another patient experienced sepsis due to a cyst.[14]

DISCUSSION

Though hepatic resection is the primary mode of treatment for treating or preventing HCA-related complications such as haemorrhage or malignant transformation, some case reports and case series have described TAE as an alternative procedure, analogous to its use in treating HCC.[14–34] The safety and efficacy of TAE to treat and prevent HCA-related (re)bleeding, especially when performed as an elective procedure, remains unclear. The present systematic review of 21 studies involving 1468 HCA patients suggests that TAE is safe for patients with bleeding or nonbleeding HCA, and that it can help patients avoid the need for hepatic resection. In fact, nearly half of all patients who underwent TAE were able to avoid resection, including 92% of those who underwent elective TAE and 31% of those with bleeding HCA. Overall tumour response rate was as high as 82% after TAE.

The primary long-term problems associated with HCA are bleeding and malignant transformation, and the risk of bleeding increases with tumour diameter.[1, 16] Since bleeding risk is thought to be quite low for tumours <5 cm,[20] hepatic resection is recommended for HCA involving tumours ≥5 cm.[7, 20, 23] However, such patients may not be suitable for resection because they have multiple tumours, their tumour is difficult to reach or residual liver volume would be insufficient. Moreover, resection is associated with higher risk of postoperative morbidity and longer recovery than other therapies. Our review of available evidence strongly suggests that TAE is a safe and effective alternative to resection for many of these patients.

It would be helpful to understand whether TAE is better suited to patients with certain sizes or numbers of tumours. Our review could not address this question because most studies did not report adequate data. Karkar and coworkers[26] retrospectively compared the

outcomes of resection, TAE or observation for 52 patients with 100 HCA lesions. They found that patients with solitary HCA usually underwent resection, those with multifocal HCA usually underwent TAE and those with small HCA were usually observed. Future study should examine possible dependence of TAE safety and efficacy on tumour size and number.

In recent years, HCA subtypes based on distinct molecular alterations or mediating pathways have been identified.[1, 35, 36] These types are: (i) H-HCA, involving an inactivating mutation in the gene encoding hepatocyte nuclear factor-1α; (ii) β-HCA, involving an activating mutation in the gene encoding β-catenin; (iii) I-HCA, corresponding to inflammatory HCA, and (iv) U-HCA, corresponding to unclassified HCA.[36] This classification is important and may impact the choice of treatment even more than lesion size. For example, activating mutations of β-catenin (4.5% in this study) may be associated with malignant transformation, while mutations in hepatocyte nuclear factor 1α may be associated with steatotic lesions. Unfortunately, our systematic review could not compare post-TAE outcomes for different HCA subtypes because of inadequate data reporting in the included studies.

Like TAE, radiofrequency ablation (RFA) is a minimally invasive percutaneous technique that spares liver parenchyma and avoids the need for laparotomy. Both techniques appear to be safe and effective for HCA.[37] In fact, cost-benefit analysis found RFA to be the best treatment for patients with small HCA, while the best treatment for patients unsuited to RFA was a combination of TAE and watchful waiting.[38] Both RFA and TAE are attractive therapy options for women, who make up most HCA patients, because they alter the outward appearance less than surgery does.

The available evidence suggests that TAE is quite safe, with significant complications rarely occurring. The most common complication among patients in this systematic review was self-limited post-TAE syndrome, which includes pain, fever, nausea/vomiting and fatigue. Among the included studies, one patient each developed diabetic ketoacidosis or sepsis due to a cyst after TAE. No mortality was reported in any of the studies in this review; a national survey of in-hospital mortality in Japan found TAE to be associated with a 1.0% mortality rate.[39] In contrast, TAE applied to HCC patients has been associated with complication rates around 4.5%,[39] which can rise to 19% when TAE is combined with chemotherapy to treat intermediate and advanced HCC.[40, 41] This difference in complication rates for HCA and HCC patients may reflect intrinsic differences between the two diseases. It may also reflect the use of chemotherapy. Only one study in our review used TACE to treat HCA.[27] The available evidence suggests caution when using TACE in HCA: since HCAs are benign tumours, chemotherapeutic agents may not improve TAE outcomes, while at the same time triggering adverse effects.

TAE was associated with tumour reduction in nearly half of patients in our review, based on revised RECIST criteria,[11] which allow relatively objective assessment.[42] These results suggest good ability to reduce tumour size. On the other hand, the proportions of patients showing partial response or progressive disease varied widely across studies, suggesting the need to systematically optimise TAE treatment, such as patient criteria for elective TAE. The median follow-up time of 40 months in the studies in this review is too short to assess whether TAE can reduce the risk of malignant transformation. HCA is a slow-growing benign tumour, so longer follow-up studies are needed. Another important issue is how to select the embolising agent for TAE. Unfortunately we could not compare outcomes for different agents in this review because of inadequate reporting in the included studies.

The results of this systematic review should be considered with caution in light of several limitations. One is the retrospective nature of many of the studies, which increases the risk that positive effects of TAE are overestimated through positive publication bias: cases in which TAE is unsuccessful are less likely to be reported. The ability of TAE to eliminate the need for hepatic resection may be underestimated in this review because some patients showing partial response or stable disease after TAE may have undergone resection even though they did not need it. In fact, the avoidance of hepatic resection reported in this review may be unreliable because HCA patients were pooled regardless of whether they received TAE without resection or before or after resection.

In conclusion, the available evidence suggests that TAE can be considered safe for treating HCA, either as an elective procedure or when performed as an acute intervention because of bleeding. Elective TAE can be a reasonable alternative to hepatic resection for HCA, since it can reduce tumour size and alleviate disease symptoms, reducing the likelihood that surgery will be necessary. The available evidence on these points should be strengthened through large prospective studies with long-term follow-up, which will also

help clarify whether TAE alters the risk of malignant transformation.

AUTHORSHIP

Guarantor of the article: JH Zhong.

Author contributions: JH Zhong was involved in study concept and design, acquisition of data, analysis and interpretation of data and drafting of manuscript. C Zhao was involved in study concept and design, analysis and interpretation of data and drafting of manuscript. SL Pei and YL Ma was involved in analysis and interpretation of data. A Cucchetti, TJ Tong and LQ Li were involved in acquisition of data and in critical revision of manuscript.

The authors declare that they have participated in the preparation of the manuscript and have seen and approved the final version.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. IHE quality appraisal checklist for case series studies.

Table S2. Quality appraisal of the included studies, based on criteria of the Institute of Health Economics.

ACKNOWLEDGEMENTS

Declaration of personal interests: The authors have no conflict of interest.

Declaration of funding interests: This study was supported in part by the Guangxi University of Science and Technology Research Projects (KY2015LX056), the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (Z2016512, Z2015621, GZZC15-34, Z2014241), the Innovation Project of Guangxi Graduate Education (YCBZ2015030), Guangxi Science and Technology Development Projects (14124003-4), the National Science and Technology Major Special Project (2012ZX10002010001009).

REFERENCES

1. Nault JC, Couchy G, Balabaud C, *et al.* Molecular classification of hepatocellular adenoma associates with risk factors, bleeding, and malignant transformation. *Gastroenterology* 2017; **152**: 880–94.e6.
2. Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. *J Hepatol* 2008; **48**: 163–70.
3. Rooks JB, Ory HW, Ishak KG, *et al.* Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. *JAMA* 1979; **242**: 644–8.
4. Bioulac-Sage P, Balabaud C, Zucman-Rossi J. Focal nodular hyperplasia, hepatocellular adenomas: past, present, future. *Gastroenterol Clin Biol* 2010; **34**: 355–8.
5. Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V. Changing trends in malignant transformation of hepatocellular adenoma. *Gut* 2011; **60**: 85–9.
6. An SL, Wang LM, Rong WQ, *et al.* Hepatocellular adenoma with malignant transformation in male patients with non-cirrhotic livers. *Chin J Cancer* 2015; **34**: 217–24.
7. Stoot JH, Coelen RJ, De Jong MC, Dejong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB (Oxford)* 2010; **12**: 509–22.
8. Agrawal S, Agarwal S, Arnason T, Saini S, Belghiti J. Management of Hepatocellular Adenoma: recent Advances. *Clin Gastroenterol Hepatol* 2015; **13**: 1221–30.
9. Bioulac-Sage P, Laumonier H, Couchy G, *et al.* Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 2009; **50**: 481–9.
10. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700.
11. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
12. Flejou JF, Barge J, Menu Y, *et al.* Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 1985; **89**: 1132–8.
13. Moga C, Guo B, Schopflocher D, Harstall C. *Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique*. Edmonton AB: Institute of Health Economics, 2012.
14. Abu Hilal M, Di Fabio F, Wiltshire RD, Hamdan M, Layfield DM, Pearce NW. Laparoscopic liver resection for hepatocellular adenoma. *World J Gastrointest Surg* 2011; **3**: 101–5.
15. Battula N, Tsapralis D, Takhar A, *et al.* Aetio-pathogenesis and the management of spontaneous liver bleeding in the West: a 16-year single-centre experience. *HPB (Oxford)* 2012; **14**: 382–9.
16. Bieze M, Phoa SS, Verheij J, van Lienden KP, van Gulik TM. Risk factors for bleeding in hepatocellular adenoma. *Br J Surg* 2014; **101**: 847–55.
17. Bunchorntavakul C, Bahirwani R, Drazek D, *et al.* Clinical features and natural history of hepatocellular adenomas: the impact of obesity. *Aliment Pharmacol Ther* 2011; **34**: 664–74.
18. Cho SW, Marsh JW, Steel J, *et al.* Surgical management of hepatocellular adenoma: take it or leave it? *Ann Surg Oncol* 2008; **15**: 2795–803.
19. de'Angelis N, Memeo R, Calderaro J, *et al.* Open and laparoscopic resection of hepatocellular adenoma: trends over 23 years at a specialist hepatobiliary unit. *HPB (Oxford)* 2014; **16**: 783–8.
20. Deneve JL, Pawlik TM, Cunningham S, *et al.* Liver cell adenoma: a multicenter analysis of risk factors for rupture and malignancy. *Ann Surg Oncol* 2009; **16**: 640–8.
21. Deodhar A, Brody LA, Covey AM, Brown KT, Getrajdman GI. Bland embolization in the treatment of hepatic adenomas: preliminary experience. *J Vasc Interv Radiol* 2011; **22**: 795–9; quiz 800.
22. Dokmak S, Belghiti J. Will weight loss become a future treatment of hepatocellular adenoma in obese patients? *Liver Int* 2015; **35**: 2228–32.

23. Dokmak S, Paradis V, Vilgrain V, *et al.* A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 2009; **137**: 1698–705.
24. Erdogan D, Busch OR, van Delden OM, Ten Kate FJ, Gouma DJ, van Gulik TM. Management of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single centre experience. *Liver Int* 2006; **26**: 433–8.
25. Erdogan D, van Delden OM, Busch OR, Gouma DJ, van Gulik TM. Selective transcatheter arterial embolization for treatment of bleeding complications or reduction of tumor mass of hepatocellular adenomas. *Cardiovasc Intervent Radiol* 2007; **30**: 1252–8.
26. Karkar AM, Tang LH, Kashikar ND, *et al.* Management of hepatocellular adenoma: comparison of resection, embolization and observation. *HPB (Oxford)* 2013; **15**: 235–43.
27. Kim YI, Chung JW, Park JH. Feasibility of transcatheter arterial chemoembolization for hepatic adenoma. *J Vasc Interv Radiol* 2007; **18**: 862–7.
28. Laurent A, Dokmak S, Nault JC, *et al.* European experience of 573 liver resections for hepatocellular adenoma: a cross-sectional study by the AFC-HCA-2013 study group. *HPB (Oxford)* 2016; **18**: 748–55.
29. Marini P, Vilgrain V, Belghiti J. Management of spontaneous rupture of liver tumours. *Dig Surg* 2002; **19**: 109–13.
30. Ramia JM, Bernardo C, Valdivieso A. et al.. *Cir Esp* 2014; **92**: 120–5.
31. Srirattanapong S, Angthong W, Kim BS, *et al.* Liver adenomatosis: serial investigation on MRI. *Abdom Imaging* 2014; **39**: 269–82.
32. Stoot JH, van der Linden E, Terpstra OT, Schaapherder AF. Life-saving therapy for haemorrhaging liver adenomas using selective arterial embolization. *Br J Surg* 2007; **94**: 1249–53.
33. Toso C, Majno P, Andres A, *et al.* Management of hepatocellular adenoma: solitary-uncomplicated, multiple and ruptured tumors. *World J Gastroenterol* 2005; **11**: 5691–5.
34. van der Windt DJ, Kok NF, Hussain SM, *et al.* Case-orientated approach to the management of hepatocellular adenoma. *Br J Surg* 2006; **93**: 1495–502.
35. Bioulac-Sage P, Balabaud C, Zucman-Rossi J. Subtype classification of hepatocellular adenoma. *Dig Surg* 2010; **27**: 39–45.
36. Bioulac-Sage P, Rebouissou S, Thomas C, *et al.* Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. *Hepatology* 2007; **46**: 740–8.
37. van Vledder MG, van Aalten SM, Terkivatan T, de Man RA, Leertouwer T, Ijzermans JN. Safety and efficacy of radiofrequency ablation for hepatocellular adenoma. *J Vasc Interv Radiol* 2011; **22**: 787–93.
38. van der Sluis FJ, Bosch JL, Terkivatan T, de Man RA, Ijzermans JN, Hunink MG. Hepatocellular adenoma: cost-effectiveness of different treatment strategies. *Radiology* 2009; **252**: 737–46.
39. Sato M, Tateishi R, Yasunaga H, *et al.* Mortality and morbidity of hepatectomy, radiofrequency ablation, and embolization for hepatocellular carcinoma: a national survey of 54,145 patients. *J Gastroenterol* 2012; **47**: 1125–33.
40. Zhong JH, Xiang BD, Gong WF, *et al.* Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS ONE* 2013; **8**: e68193.
41. Zhong JH, Ke Y, Gong WF, *et al.* Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg* 2014; **260**: 329–40.
42. Edeline J, Boucher E, Rolland Y, *et al.* Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. *Cancer* 2012; **118**: 147–56.