

# Transarterial embolization for hepatocellular adenomas: a literature review

Bao-Hong Yuan<sup>1</sup>, Ru-Hong Li<sup>1</sup>, Bhavesh-K. Ahir<sup>2</sup>, Wei-Ping Yuan<sup>3</sup>, Jian-Hong Gu<sup>4,5</sup>, Tian Yang<sup>6</sup> and Liang Ma<sup>3</sup>

<sup>1</sup> Department of General Surgery, Yan'An Hospital Affiliated to Kunming Medical University, Kunming, China

<sup>2</sup> Department of Medicine, Section of Hematology and Oncology, University of Illinois at Chicago, Chicago, IL, USA

<sup>3</sup> Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China

<sup>4</sup> College of Veterinary Medicine, Yangzhou University, Yangzhou, China

<sup>5</sup> Jiangsu Co-innovation Center for Prevention and Control of Important Animal Infectious Diseases and Zoonoses, Yangzhou, China

<sup>6</sup> Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China

\* These authors have contributed equally to this work

**Correspondence to:** Tian Yang, **email:** yangt9371@gmail.com

Liang Ma, **email:** maliang0123@126.com

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## ABSTRACT

Since the utilization of transarterial embolization (TAE) for hepatocellular carcinoma, TAE is used to treat bleeding hepatocellular adenomas (HCAs) and occasionally, in symptomatic HCAs with large tumors. However, the role of TAE in an elective setting is uncertain. The present review aims to evaluate the benefits and harms of TAE in bleeding and non-bleeding HCAs, especially in an elective setting. A systematic review of studies published from January 2000 to December 2016 in the EMBASE, PubMed and Scopus databases was performed. Avoidance of resection and tumor reduction after TAE were the primary outcomes measure in both bleeding and non-bleeding HCAs. Twenty-one case series involving 1481 patients with HCAs were included in the analysis. Most of them were underwent hepatic resection. Only 148 (10%) patients (involving 189 lesions) received TAE, including 93 (62.8%) patients with bleeding HCAs and 55 (37.2%) patients with non-bleeding HCAs. Based on data of 107 tumors, the rates of Complete Response and Partial Response were 10.3% and 73.8%, respectively. Hepatic resection was avoided in 72 of 148 (48.6%) TAE treated patients. Intended elective TAE was performed in 45/148 (30.4%) patients; 95.6% of them did not require further hepatic resection. No mortality or adverse side effects were reported during the hospitalization period. Therefore, Either in an elective setting or in the setting of bleeding, TAE can be considered safe in the management of HCAs. In the elective setting, TAE can be regarded as a reasonable alternative management to hepatic resection. High-quality prospective study with long-term follow-up is warranted.

## INTRODUCTION

Hepatocellular adenomas (HCAs) is a very rare disease with malignant potential in Asian, but is highly prevalent in Europe [1]. The annual incidence of HCA is estimated to be 1/10<sup>6</sup> among all population and 3 to 4 per

100,000 women with long-term use of oral contraceptives [2, 3]. Symptomatic bleeding may be occurred in more than 14% patients with HCAs, and this risk will be higher with increasing tumor diameter [4]. The risk of malignant transformation, that is hepatocellular carcinoma (HCC), is about 4 to 6% in women and up to 47% in

men in a long-term follow-up [4-7]. HCA is a benign tumor composed of hepatocytes. However, its exact pathophysiological mechanism remains unknown. The use of oral contraceptives is regarded as the main risk factor for HCAs among women. New risk factors for HCAs have emerged in recent years, including obesity, metabolic syndrome, and anabolic steroids exposure.

HCAs are usually discovered either incidentally on liver function test abnormalities or abdominal imaging performed for unrelated reasons. Therefore, most patients with HCAs have large tumors (> 5cm) at their first diagnosis. Due to the high risk of hemorrhage and potential malignant transformation, hepatic resection is considered as a treatment for HCAs. However, emergent hepatic resection for ruptured HCAs is associated with a mortality rate of 5 to 10% [8]. Elective transarterial embolization (TAE) prior to surgery is another choice of treatment because delayed hepatic resection may be associated with less blood loss and lower postoperative complications [8]. As HCA is hypervascular arterial lesion, TAE is also recommended for HCAs complicated by hemorrhage [8]. In addition, TAE may lead to size reduction in large and/or multiple HCAs or those unfavorably localized for hepatic resection, and then theoretically reduce the risk of malignant transformation [9].

Though some case series studies and case reports from single-center experiences in the clinical management of HCAs were reported, these studies included only a limited number of patients. On the other hand, the role of TAE used in an elective setting where no acute intervention is needed is unknown. The aim of the present systematic review is to describe presentation, surgery avoided, tumor size reduction and incidence of malignant transformation in patients undergoing TAE for HCAs.

## RESULTS

### Results of literature search

A total of 231 studies were identified using our search criteria for screening (Figure 1). Following assessment by exclusion criteria adopted, 26 were rejected and 180 studies remained for abstract review. Following abstract review, 137 studies were excluded and 43 studies remained for full-text eligibility assessment. Twenty-one studies meeting the inclusion criteria were identified after thorough assessment of the full manuscripts [10-30]. Of these, two studies by Dokmak [18, 19] and other two

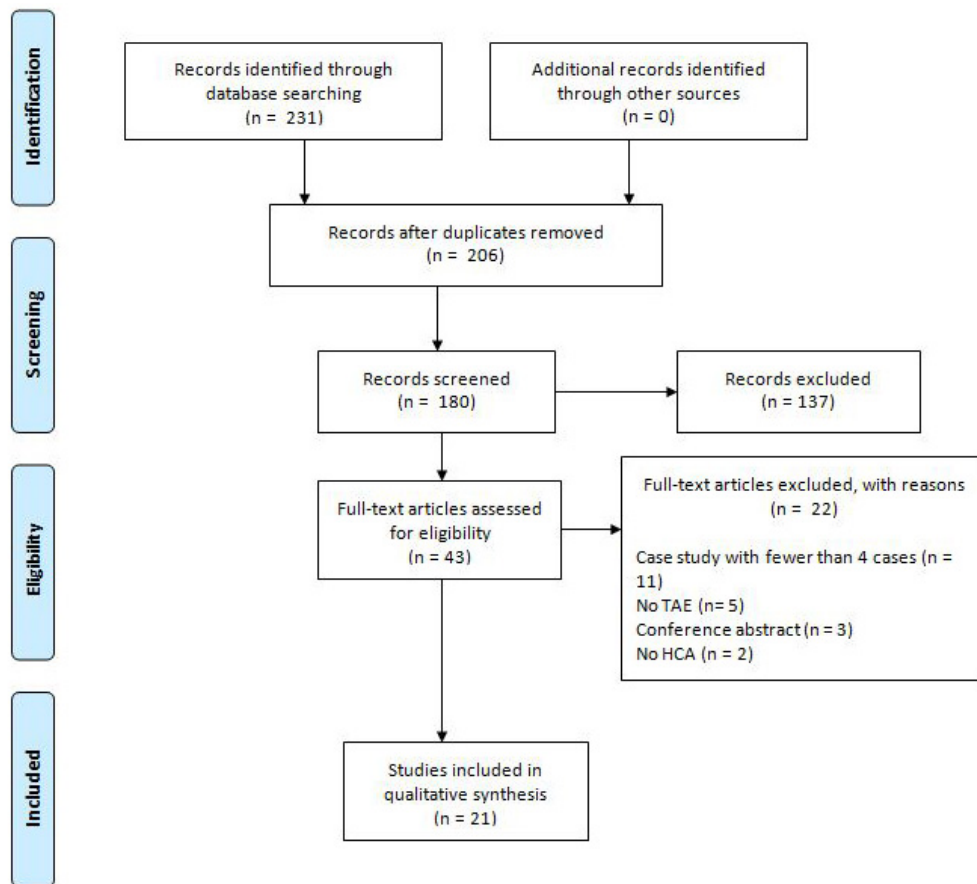


Figure 1: PRISMA flow diagram.

**Attached Table: Quality appraisal checklist for case series studies based on the Institute of Health Economics criteria [39]**

Author (year)	Study objective	Study design			Study population			Intervention and co-intervention		Outcome measure				Statistical analysis	Results and conclusions					Competing interests and sources support	Total score§
	1	2	3*	4	5	6	7	8	9	10	11†	12	13	14	15‡	16	17	18	19	20	
Abu Hilal 2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Partial	Yes	Yes	No	14
Battula 2012	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Partial	Yes	Yes	Yes	15
Bieze 2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	17
Bunchohmavakul 2011	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	16
Cho 2008	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Partial	Yes	Yes	Yes	15
de'Angelis 2014	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	16
Deneve 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	18
Deodhar 2011	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	No	Yes	Yes	Yes	14
Dokmak 2009	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Dokmak 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Yes	Yes	Unclear	Yes	Yes	Partial	Yes	Yes	Yes	15
Erdogan 2006	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	15
Erdogan 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Yes	Yes	Unclear	No	Yes	No	Yes	Yes	No	13
Karkar 2013	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Kim 2007	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	16
Laurent 2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	16
Marini 2002	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Partial	Yes	Unclear	No	Yes	No	Yes	Yes	No	12
Ramia 2014	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	16
Srirattanapong 2014	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	15
Stoot 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Partial	Yes	Yes	No	15
Toso 2005	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	No	13
van der Windt 2006	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	16

\* Item 3: most of the studies were based on single center.

† Item 11: we do not know if the outcome assessors were blinded to the intervention that patients receive.

‡ Item 15: follow-up of at least 36 months was considered appropriate to judge the change of tumor diameter and new lesions developed.

§ All the total score were more than 14 (86%). These studies were deemed sufficient.

**Table 1: Characteristics of the included studies**

Studies	Country	Included period	No. of total	Characteristics of patients with transarterial embolization							
				No. of elective patients	M/F	Mean yr*	Age	Patients embolized (bleeding/non-bleeding)	Tumors embolized (bleeding/non-bleeding)	Adenomatosis	Median follow-up (months)
Abu Hilal 2011 [10]	UK	2005-2009	13	0	0/3	27		3/0	5/0	2	-
Battula 2012 [11]	UK	1995-2011	27	0	-	-		2/0	2/0	0	57
Bieze 2014 [12]	Netherlands	2008-2012	45	0	1/44*	39		7/2	7/3	0	14
Bunchohmavakul 2011 [13]	USA	2005-2010	60	7	4/56*	36		4/13	4/13	0	31
Cho 2008 [14]	USA	1988-2007	41	0	3/38*	38		1/0	1/0	0	23
de'Angelis 2014 [15]	France	1989-2012	62	0	3/59*	36		6/0	6/0	0	12
Deneve 2009 [16]	USA	1997-2006	124	5	8/116*	39		6/5	6/5	0	36
Deodhar 2011 [17]	USA	2006-2007	8	7	1/7	36		1/7	2/15	0	24
Dokmak 2009 [19]	France	1990-2004	122	0	14/108*	37		12/0	12/0	0	70
Dokmak 2015 [18]	France	2004-2013	116	0	19/97	42		2/0	2/0	0	38
Erdogan 2006 [20]	Netherlands	1990-2005	22	0	0/22	36		1/1	1/1	0	25
Erdogan 2007 [21]	Netherlands	-	6	0	1/5	40		6/0	6/0	0	24
Karkar 2013 [22]	USA	1992-2011	52	19	7/45*	39		5/20	5/33	7	56
Kim 2007 [23]	Korea	1989-2006	7	6	5/2	25		1/6	3/6	0	88
Laurent 2016 [24]	Europe†	1986-2013	573	0	62/511*	37		15/0	15/0	0	91
Marini 2002 [25]	France	1995-2000	20	0	0/3	35		3/0	3/0	0	6
Ramia 2014 [26]	Spain	1995-2011	81	0	20/61*	40		1/0	1/0	0	43
Srirattanapong 2014 [27]	USA	2002-2012	18	1	1/1	24		1/1	1/1	0	41
Stoot 2007 [28]	Netherlands	2001-2006	11	0	1/10	34		11/0	17/8	0	19
Toso 2005 [29]	Netherlands	1980-2003	25	0	2/23*	38		2/0	2/0	0	72
van der Windt 2006 [30]	Netherlands	2000-2005	48	0	0/48*	36		3/0	3/0	0	24
<b>Total (median, %)</b>	-	-	<b>1481</b>	<b>45</b>	<b>152/1259 (M, 11%; F, 89%)</b>	<b>36</b>		<b>148 (93/55)</b>	<b>189 (104/85)</b>	<b>9</b>	<b>40</b>

-, not available; F, female; M, male.

\*Data of total cohort instead of embolized patients only if the specific information was not described in the original paper.

† All patients from 27 European high-volume HPB units were underwent hepatic resection.

by Erdogan [20, 21] were from the same department, respectively. All of them were included because the inclusion period was different [18-21]. Thus, the final list of included studies was formed by 21 studies (Table 1). In one study, TAE was performed with chemotherapy (TACE) [23]. Seven of these followed a prospective design [10, 12, 18, 21, 25, 28, 30] and the overall quality of the studies was deemed sufficient (Attached Table).

### Characteristics of included patients

These 21 studies included 1481 patients with HCAs, predominantly female (89.2%). The median age was 36 years old. Of the 21 included studies [10-30], most of them (account for 99.5% population) were based on Western population [10-22, 24-30]. Of the total populations, most of them were underwent hepatic resection. Only 148 (10%) patients (involving 189 lesions) received TAE, including 93 (62.8%) patients with bleeding HCAs and 55 (37.2%) patients with non-bleeding HCAs. Intended elective TAE was performed in 45/148 (30.4%) patients, with a total of 73/189 (38.6%) HCAs. Adenomatosis was observed in 9/148 (6.1%) of the patients.

### Tumor reduction and symptoms improvement

Eight of the twenty-one studies involving 78 (52.7%) HCAs patients receiving TAE reported the change of the tumor size [13, 17-18, 21-23, 27-28]. In the study by Bunchorntavakul and coworkers [13], only 14/17 patients with good follow-up obtained partial imaging response. Of the 14 patients, 11 (79%) showed tumor size reduction, according to the revised RECIST [31]. Therefore, only 14 of the 17 patients were included into tumor reduction calculation. In other two studies [17, 22], tumor reduction calculation was based on number of tumors but not number of patients. Therefore, data of 107 tumors was suitable for application of the revised RECIST criteria (Table 2). The rates of Complete Response, Partial Response, Progressive Disease, and Stable Disease were 10.3% (11/107), 73.8% (79/107), 3.7% (4/107), and 12.1% (13/107), respectively. Tumor overall response rate (Complete Response + Partial Response) was 84.1%.

Only one study involving seven patients received TACE reported symptoms improvement [23]. Presenting symptoms included abdominal pain ( $n = 4$ ) and lower-extremity edema ( $n = 1$ ). Two patients had no symptoms at presentation. Preexisting symptoms were relieved within 1 month after TACE (Table 2).

### Malignant transformation and surgery avoided

Within a median follow-up time of 40 months, no malignant transformation was observed after TAE (Table

3). Hepatic resection was avoided in 72 of 148 (48.6%) TAE treated patients. Of these, 23 (31.9%) patients were with bleeding before TAE while 49 (68.1%) with non-bleeding.

Of the 45 patients with intended elective TAE, 43 (95.6%) patients did not require subsequent (and not further) hepatic resection. However, hepatic resection was avoided in only 24.7% (23/93) patients with bleeding after acute TAE.

### Complications of TAE

Most studies did not find complications related to TAE. No procedural complication or mortality was reported. However, some patients experienced self limited post-TAE syndrome, including pain, fever, nausea/vomiting, and fatigue, but very few patients did this lead to a prolonged ( $> 24$  h) hospital stay. Two patients with moderately post-TAE syndrome, leading to extended hospital stay or returning to emergency department [13]. Other two patients developed diabetic ketoacidosis<sup>13</sup> or sepsis due to cyst after TAE [10].

## DISCUSSION

Determining treatment options for HCAs is important. Many studies have developed criteria revolving around tumor size/number, oral contraceptives use, gender and more recently molecular classification, to help determine which patients require positive treatment [4, 19, 32-33]. Though hepatic resection is the primary mode of treatment to treat and/or prevent HCAs complications such as haemorrhage or malignant is suspected, some case reports and case series have reported the feasibility of TAE for the treatment of HCAs because of the utilization of TAE for HCC [10-30]. However, the role of TAE to treat and prevent (re)bleeding, especially used in an elective setting, is unknown.

The present systematic review included 21 studies involving 1481 patients with HCAs. Of them, 148 patients (with 189 lesions) were treated with TAE for bleeding or non-bleeding HCAs. Tumor overall response rate was reach up to 84%. Hepatic resection was avoided in near half of the TAE treated patients. In an elective setting, 95.6% patients did not require further surgical management. Even in the setting of bleeding, hepatic resection was also avoided in 25% patients. Moreover, TAE was safe for HCAs.

The main risk of HCAs in the long-term is bleeding and malignant transformation. The risk of bleeding increases with increasing tumor diameter [4, 12]. Others suggest that bleeding in tumors  $< 5$  cm is scarcely possible [16]. Therefore, HCAs  $\geq 5$  cm are recommended to be treated with hepatic resection [7, 16, 19]. However, many HCA patients are with multiple tumors. Resection and

**Table 2: Outcomes of the included studies**

Study	Reason of TAE	Resection avoided (bleeding/non-bleeding)	Reason (not) to perform resection	Malignant transformation	Tumor and reduction symptom improvement	Complications
Abu Hilal 2011 [10]	Bleeding (n = 3)	0/0	Need to rule out malignancy (n = 2); preoperative diagnosis of large HA (n = 1)	-	-	Sepsis due to cyst after TAE (n = 1)
Battula 2012 [11]	Bleeding (n = 2)	2/0	No resection needed: tumor regression (n = 2)	0	-	No complications
Bieze 2014 [12]	Bleeding (n = 7); TAE to avoid intraoperative bleeding (n = 2)	1/0	No resection needed: tumor regression (n = 1); Resection according to protocol (n = 8)	0	-	No complications
Bunchorntavakul 2011 [13]	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: tumor regression (n = 9); resection according to protocol (n = 8)	0	Good response and reduction of the tumor lesions in 79%; CR (n = 0), PR (n = 11), PD (n = 1); SD (n = 2) <sup>‡</sup>	Two with moderately severe postembolisation syndrome, leading to extended hospital stay or returning to emergency department. One developed diabetic ketoacidosis.
Cho 2008 [14]	Bleeding (n = 1)	0/0	Resection according to protocol (n = 1)	0	-	No complications
de'Angelis 2014 [15]	Bleeding (n = 6)	0/0	Resection according to protocol (n = 6)	0	-	No complications
Deneve 2009 [16]	Bleeding (n = 6); reason not described (n = 5)	0/5	No resection needed: reason not clear (n = 5); resection according to protocol (n = 6)	0	-	No complications
Deodhar 2011 [17]	Bleeding (n = 1); abdominal pain (n = 1); presumed increased risk of bleeding (n = 6)	1/5	No resection needed: tumor regression (n = 6); resected for continued peripheral enhancement (n = 2)	0	CR (n = 2), PR (n = 10), PD (n = 2); SD (n = 3) <sup>†</sup>	No procedural complications. Most patients had elements of self limited postembolization syndrome, including pain, fever, nausea/vomiting, and fatigue, but in no patient did this lead to a prolonged (>24 h) hospital stay.
Dokmak 2009 [19]	Bleeding (n = 12)	0/0	Resection according to protocol (n = 12)	0	-	No complications
Dokmak 2015 [18]	Bleeding (n = 2)	0/2	No resection needed: tumor regression (n = 2)	0	CR (n = 1), PR (n = 1), PD (n = 0); SD (n = 0)	No complications
Erdogan 2006 [20]	Bleeding (n = 2)	1/0	No resection needed: tumor regression (n = 1); resection according to protocol (n = 1)	0	-	No complications
Erdogan 2007 [21]	Bleeding (n = 4); to reduce the tumor mass >5 cm (n = 2)	0/4	No resection needed: tumor regression (n = 4); laparotomy for removal of the large, intra-abdominal hematoma (n = 2)	0	CR (n = 1), PR (n = 4), PD (n = 0); SD (n = 1)	No complications

Karkar 2013 [22]	Suspicion of malignancy ( <i>n</i> = 14); haemorrhage ( <i>n</i> = 5); large tumor ( <i>n</i> = 1); local recurrence after resection ( <i>n</i> = 1) <sup>†</sup>	5/19	No resection needed: tumor regression ( <i>n</i> = 24)	0	CR ( <i>n</i> = 5), PR ( <i>n</i> = 22), PD ( <i>n</i> = 0), SD ( <i>n</i> = 7) <sup>†</sup>	No complications
Kim 2007 [23]	Impending rupture ( <i>n</i> = 6); bleeding ( <i>n</i> = 1)	1/6	No resection needed: regression tumor ( <i>n</i> = 7)	0	Preexisting symptoms were relieved within 1 month after TACE. CR ( <i>n</i> = 2), PR ( <i>n</i> = 4), PD ( <i>n</i> = 1); SD ( <i>n</i> = 0)	Immediately after TACE, most patients experienced nausea, fever, or abdominal pain; however, all symptoms disappeared within 5 days.
Laurent 2016 [24]	Bleeding ( <i>n</i> = 15)	0/0	Resection according to protocol ( <i>n</i> = 15)	0	-	-
Marini 2002 [25]	Bleeding ( <i>n</i> = 3)	0/0	Resection according to protocol ( <i>n</i> = 3)	0	-	No complications
Ramia 2014 [26]	Bleeding ( <i>n</i> = 1)	0/0	Resection according to protocol ( <i>n</i> = 1)	0	-	No complications
Srirattanapong 2014 [27]	High risk for resection ( <i>n</i> = 1); remaining adenoma after surgery ( <i>n</i> = 1)	1/1	No resection needed: tumor regression ( <i>n</i> = 2)	0	CR ( <i>n</i> = 0), PR ( <i>n</i> = 2), PD ( <i>n</i> = 0); SD ( <i>n</i> = 0)	No complications
Stoot 2007 [28]	Bleeding ( <i>n</i> = 11)	9/0	No resection needed: tumor regression ( <i>n</i> = 9); elective resection according to protocol ( <i>n</i> = 2)	0	The median decrease in tumor size was 5.0 cm after TAE. CR ( <i>n</i> = 0), PR ( <i>n</i> = 25), PD ( <i>n</i> = 0); SD ( <i>n</i> = 0)	No complications
Toso 2005 [29]	Bleeding ( <i>n</i> = 2)	0/0	Resection according to protocol ( <i>n</i> = 2)	0	-	No complications
van der Windt 2006 [30]	Bleeding ( <i>n</i> = 3)	0/0	Emergency resection ( <i>n</i> = 1); due to pregnant ( <i>n</i> = 1), or for persistent tumor ( <i>n</i> = 1)	0	-	No complications
<b>Total (%)</b>	<b>Bleeding (<i>n</i> = 93), other reasons (<i>n</i> = 55)</b>	<b>Surgery avoided, <i>n</i> = 72 (23/49)</b>	<b>Performed resection, <i>n</i> = 76</b>	<b>0</b>	<b>CR (<i>n</i> = 11), PR (<i>n</i> = 79), PD (<i>n</i> = 4); SD (<i>n</i> = 13)</b>	<b>-</b>

–, not available; TAE, transarterial embolization; TACE, transarterial chemoembolization.

\* Only 14/17 patients with good follow-up.

† Number of tumors but not number of patients.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

radiofrequency ablation (RFA) may be not practical for such patients because each is limited by tumor size and number, location, and volume of liver. Moreover, resection carries an increased risk of postoperative morbidity and a long recovery time, which limited resection as the optimal therapy. TAE may be an optional treatment. Karkar and coworkers [22] retrospectively compared the outcomes of resection, TAE, and observation for 52 patients with 100 adenomas. They found solitary HCA are frequently resected, multifocal HCAs are often TAE, and small HCAs can safely be observed. Due to the heterogeneity among included studies and missing data in more than half of the

included studies, we did not extract data of tumor size and number. So the present systematic review can't find out the association between indication of TAE and tumor size/number.

Both TAE and RFA are percutaneous minimally invasive techniques that spare liver parenchyma and avoid laparotomy. They are preferred over hepatic resection in selected HCC [34]. In selected HCAs, these two techniques are also safe and effective. Cost-effective analysis found RFA is the most favorable treatment strategy for patients with small HCAs. However, in cases unsuitable for RFA, watchful waiting combined

with TAE had the highest effectiveness and lowest costs [35]. Because HCAs most frequently occurs in young females, RFA and TAE with favorable cosmetic results are attractive. More importantly, TAE can be applied to most patients. In the present review, elective TAE can lead to 95% HCAs patients avoided further resection. One quarter HCAs patients with haemorrhage also avoided further resection after TAE. In addition, higher tumor response rate will significantly relief symptoms. Therefore, the efficacy of TAE for select HCAs is definite.

In general, TAE is safe since significant complications were rare. The most common complication among patients included in this systematic review was self limited post-TAE syndrome, including pain, fever, nausea/vomiting, and fatigue. Diabetic ketoacidosis or sepsis due to cyst after TAE was developed in one (0.7%) patient, respectively. No mortality was found in this review. However, in-hospital mortality associated with TAE was 1.0% in big national survey [36]. Whether this discrepancy is caused by an actual physiological difference between HCAs and HCC is unclear. Another reason may be the usage of chemotherapeutic agents. One included study used TACE for HCAs [23]. Because HCAs are benign tumors, addition of chemotherapeutic agents to TAE may have no beneficial effects, but may results in chemotherapy-related side effects.

More than half of the included patients were evaluated tumor reduction with revised RECIST criteria [31]. This method allows us objective and quantitative assessment of the data [37]. However, using the revised RECIST criteria only base on tumor size also has limitations. On one hand, persistent contrast enhancement during imaging may be concomitant with tumor size reduction. On the other hand, the range of Partial Response and Progressive Disease are too wide, leading to inevitable loss of detail.

The short median follow-up of 40 months precluded any statement regarding the ability of TAE to mitigate the risk of malignant transformation. As a benign tumor, HCA grows slowly. Lack of high level evidence studies in literature is another limitation. Retrospectively designed studies have potential bias that the positive effects of TAE are overestimated, as cases with unsuccessful TAE are less likely to be reported. However, hepatic resection is always the first-line therapy for HCAs, may lead to an underestimation of actual beneficial effect of TAE. The second underestimation the efficacy of TAE is hepatic resection performed after TAE for size reduction. Some patients with Partial Response or Stable Disease after TAE may not need further surgical management, but they still received hepatic resection. And last, HCAs patients received TAE alone, TAE before resection, or TAE after resection were included into analysis, therefore, potentially has lead to overestimation or underestimation of the number of avoided resections after TAE.

In conclusion, either in an elective setting or in the setting of bleeding, TAE can be considered safe in the

management of HCAs. The ability of elective TAE to reduce tumor size and symptoms of tumors, especially avoid surgical management, make it as a reasonable alternative management to hepatic resection. However, since the limitations of the present review and the risk of malignant transformation after TAE is still uncertain, large prospective studies with long-term follow-up would be helpful in confirming the role of TAE in the management of HCAs.

## **MATERIALS AND METHODS**

### **Literature search strategy**

A systematic search of EMBASE, Scopus and PubMed databases was performed for articles published between 1 January 2000 and 20 December 2016 relevant to TAE for HCAs. The systematic review was carried out in accordance with the PRISMA statement for reporting systematic reviews of studies that evaluate healthcare interventions [38]. The medical subject headings (MeSH) “hepatocellular adenoma” and “embolization” were used and the following keywords were added to refine the literature research: “hepatic adenoma” and “transarterial embolization”. Results from the two electronic databases were compared to obtain a list of unique articles for screening. Relevant references of all included studies were also searched manually to identify additional studies. Gray literature was not included in the present analysis.

### **Literature screening**

Two authors (B.-H.Y and Y.-H.L) independently conducted an initial screen to identify articles clearly relevant by title, abstract and keywords of publication. Then, study selection was accomplished through three levels of screening. At level 1, studies were excluded because they were reviews, letters, editorials, or comments, or were in languages other than English. Then, these two independent reviewers (B.-H.Y and Y.-H.L) assessed the studies for relevance, inclusion or not. At level 2, abstracts of retained studies were reviewed for relevance. Abstracts entered the subsequent screening level if they reported clinical outcome of series of patients with HCAs treated with TAE. For level 3 screening, the full text was obtained for relevant studies and for any references for which a decision could not be made on the basis of the abstract. And methodological quality was assessed in level 3.

### **Selection criteria**

Criteria for final study inclusion of the present systematic review were: (a) studies published after

2000 when radiological interventional techniques were commonly utilized; (b) study population included patients with HCAs treated by elective or emergent TAE (TAE alone, prior to surgery, or after surgery); (c) comparative studies, cohort studies, case series or case reports with at least four patients that reported on the outcomes of TAE in patients with HCAs. In cases in which a study was followed by a more complete study or studies that included the original data set, the complete report was chosen. Such linked studies were identified on the grounds of authorship, institutions, and included period. In order to reduce selection bias, case reports with less than three patients were excluded. Studies reporting rather than outcomes of TAE (for example, cost-effectiveness) were also excluded.

## Data collection and definitions

Data were extracted by two authors (B.-H.Y and Y.-H.L) using standardized forms. The following data were collected: family name of the first author and publication year, country and included period of included populations, study design, demographics of patients with TAE, and outcomes of TAE. Data collected with respect to the primary objective were: reported reduction in tumor size, indication for TAE (elective or emergency setting), number and reason of avoided resections, reason (not) to perform hepatic resection, malignant transformation, and complications of TAE. Any discrepancies in inclusion were resolved by discussion between the reviewers and a third investigator (Y.-P.Y). The quality of each selected study was assessed by means of the quality appraisal tool for case series studies using a modified Delphi technique [39].

TAE can be used as electivity and emergency. Emergent TAE was always used to treat active bleeding or avoid intraoperative bleeding. Elective TAE was defined as an alternative treatment to resection and used for non-bleeding HCAs or not for prevention of intraoperative blood loss. Avoided hepatic resection was defined as no further resection was necessary after TAE due to reduction of tumor size or involution of tumor, and/or relief of complaints within the follow-up period. However, those with tumor stable in size or unresectable tumor before and after TAE were not regarded as avoided hepatic resection.

Tumor response rate of target lesions defined according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) represented another primary outcome measures [31].

Complete Response: Disappearance of all target lesions.

Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions.

Stable Disease: Neither sufficient shrinkage to qualify for Partial Response nor sufficient increase to qualify for Progressive Disease, taking as reference the smallest sum diameters while on study.

## Statistical analysis

Meta-analysis was not performed because of substantial heterogeneity among studies. Data were tabulated and presented as numbers (with percentages) and mean or median values. When studies reported continuous variables as median and range, the mean and variance were estimated taking into account the size of the sample as proposed by Wan and coworkers [40].

## Authors' contributions

Guarantors of integrity of entire study, L.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, B.H.Y., R.H.L.; statistical analysis, B.H.Y., B.K.A.; and manuscript editing, L.M., T.Y., W.P.Y.

## CONFLICTS OF INTEREST

There is no conflict of interest.

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