Adjuvant Intrahepatic Injection Iodine-131-Lipiodol Improves Prognosis of Patients with Hepatocellular Carcinoma After Resection: a Meta-Analysis

Ye Hong¹ · Lu-Peng Wu¹ · Feng Ye¹ · Yan-Ming Zhou¹

Received: 18 December 2014 / Accepted: 9 March 2015 / Published online: 23 May 2015
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Abstract High incidence of intrahepatic recurrence is a major surgical limitation following hepatectomy of hepatocellular carcinoma (HCC). This study was intended to investigate the effects of adjuvant intrahepatic injection of iodine-131-lipiodol on disease recurrence and survival in patients with HCC who underwent resection. A computerized literature search was performed to identify relevant articles. Data synthesis was performed using Review Manager 5.0 software, and results are presented as odds ratio (OR) with 95 % confidence intervals. Two randomized controlled trials and three *case-control* studies with a total of 334 participants were analyzed. Iodine-131-lipiodol treatment achieved significantly lower rates of intrahepatic recurrence (OR=0.48, 95 % confidence interval (95 % CI)=0.30–0.74; $P=0.001$) and early recurrence (<2 year) (OR=0.45, 95 % CI=0.23–0.89; $P=0.02$). Likewise, iodine-131-lipiodol treatment improved both the 5-year disease-free survival and overall survival significantly (OR=1.85, 95 % CI=1.13–3.03; $P=0.01$; OR=2.00, 95 % CI=0.99–4.04; $P=0.05$, respectively). Adjuvant intrahepatic injection of iodine-131-lipiodol resulted in a preventive effect on recurrence and improved survival after resection of HCC. Further larger, multi-centred, randomized prospective trial is warranted.

Keywords Hepatocellular carcinoma · Iodine-131-lipiodol · Recurrence · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide [1]. Although hepatectomy of HCC provides a 5-year survival of 23.8–54.8 % in highly selected patients [2–5], 78 to 96 % of cases experience tumour recurrence in the liver remnant, as a result of either intrahepatic metastasis from the primary tumour or de novo carcinogenesis [6]. Hence, it is imperative to develop effective strategies to prevent the recurrence of HCC after resection.

Lipiodol is an iodinated derivative of poppy seed oil, containing ethyl esters of linoleic, oleic, palmitic, and stearic acids, with an iodine content of 38–40 % w/v. Lipiodol was shown to be selectively taken up and retained by HCC. This provides the rationale for delivery-targeted therapies using Lipiodol via the hepatic artery to HCC. Targeted radiotherapy has been used by substituting the iodine in Lipiodol with 131-iodine (¹³¹I) [7]. ¹³¹I-Lipiodol emits gamma radiation with energy of 364 keV with a mean penetration of 0.4 mm. ¹³¹I-Lipiodol therapy have been proven to be a safe and effective palliative treatment of unresectable HCC [8–10]. However, studies on the role of adjuvant ¹³¹I-lipiodol in preventing the recurrence of HCC have been relatively limited and have yielded conflicting results [11–14]. We accordingly conducted a meta-analysis to examine the effectiveness on the recurrence of HCC after resection of adjuvant intrahepatic injection of ¹³¹I-lipiodol.

Methods

Study Selection

The electronic databases of Medline, EMBASE, OVID, and Cochrane Library were systematically searched from the time

✉ Yan-Ming Zhou
zhouymxy@sina.cn

¹ Department of Hepatobiliary & Pancreatovascular Surgery, First affiliated Hospital of Xiamen University, 55 Zhenhai Road, Xiamen 361003, China

of inception to May 2014. The following medical subject heading (MeSH) terms were used: “hepatectomy,” “hepatocellular carcinoma,” “Lipiodol,” and “Iodine-131.” Only studies on humans and in the English language were considered for inclusion. A manual search of reference lists of all identified articles was performed to identify additional studies.

Inclusion and Exclusion Criteria

Primary studies that evaluated the efficacy of adjuvant intrahepatic injection of ^{131}I -lipiodol on HCC recurrence were considered for inclusion. Duplication of the previous publication, reviews without original data, case reports, and without control population studies were excluded. Studies that include evaluation of recurrent HCC or unresectable diseases were also excluded.

Outcomes of Interests

The primary outcomes evaluated in this meta-analysis were recurrence, disease-free, and overall survival rate.

Data Extraction

We extracted the following information from each study: first author, year of publication, country of study location, study population characteristics, study design, inclusion and exclusion criteria, the number of subjects in each arm, and outcomes of interests. Disagreement was resolved through consensus and discussion.

Qualitative Analysis

The randomized controlled trials (RCTs) were scored using the Jadad composite scale [15], and non-RCTs were scored using the methodological index for nonrandomized studies [16].

Statistical Analysis and Synthesis

Summary odds ratio (OR) estimates with their corresponding 95 % confidence interval (95 % CI) were calculated for dichotomous variables. Between-study heterogeneity was evaluated by Cochran Q and I^2 statistics. Data that were not significantly heterogeneous ($P>0.1$) were calculated using a fixed-effects model, and heterogeneous data ($P<0.1$) were calculated using a random-effects model. All statistical tests for this meta-analysis were performed with Review Manager version 5.0 (The Cochrane Collaboration, Software Update, Oxford). A value of $P<0.05$ was considered statistically significant. Publication bias was assessed visually using a funnel plot.

Results

Eligible Studies

Seven studies that matched the selection criteria were retrieved from the electronic databases [11–14, 17–19]. Of these studies, two studies were excluded due to overlap of author [11, 12]. Finally, five articles, including two RCTs [14, 17] and three case–control studies [13, 18, 19], were included in the meta-analysis. The characteristics of the five studies are shown in Table 1. A total of 334 patients were included: 161 patients in the ^{131}I -lipiodol group and 173 patients in the control group. The number of patients in each study varied from 30 to 103 patients.

Overall Meta-Analysis

The results from overall meta-analysis are summarized in Table 2.

All five studies reported on intrahepatic recurrence, which ranged from 25.4 to 63.4 % in ^{131}I -lipiodol group and 46.1 to

Table 1 Baseline characteristics of studies included in the meta-analysis

Author	Year	Country	Study type	Group	No. of patients	M/F	Mean age (years)	Tumour size	Viral hepatitis	Study quality
Tabone et al. [13]	2007	Italy	Case–control	^{131}I -Lipiodol	10	10/0	67.0 (51–76)	—	10	17
				Control	20	18/2	68.1 (59–82)	—	20	
Boucher et al. [18]	2008	France	Case–control	^{131}I -Lipiodol	38	37/1	64±7.9	4.97±2.8	—	19
				Control	38	36/2	65.6±7.0	5.89±3.1	—	
Lau et al. [17]	2008	Hong Kong	RCT	^{131}I -Lipiodol	21	17/4	51 (23–71) ^a	4.4 (1.4–11) ^a	19	3
				Control	22	18/4	54 (24–75) ^a	3.8 (1.5–10) ^a	19	
Chua et al. [19]	2009	Australia	Case–control	^{131}I -Lipiodol	41	30/11	61±12	8.2±5.2	19	19
				Control	41	33/8	62±13	8.7±5.2	23	
Chung et al. [14]	2013	Singapore	RCT	^{131}I -Lipiodol	51	41/10	65 (22–82) ^a	4.2 (0.4–30.0) ^a	29	4
				Control	52	45/7	63 (42–84) ^a	3.8 (1.4–18.0) ^a	32	

RCT randomized controlled trial, M male, F female

^a Median with range

Table 2 Results of overall meta-analysis

Outcomes	No. of studies	No. of patients		Results		OR (95 % CI)	P value	HG P value
		¹³¹ I-Lipiodol	Control	¹³¹ I-Lipiodol (%)	Control (%)			
Intrahepatic recurrence	5	161	173	39.1	57.2	0.48 (0.30, 0.74)	0.001	0.98
Early recurrence	2	79	79	32.9	50.6	0.45 (0.23, 0.89)	0.02	0.50
3-year disease-free survival	5	161	173	53.4	35.3	2.08 (1.33, 3.23)	0.001	0.13
5-year disease-free survival	4	151	153	39.7	26.8	1.85 (1.13, 3.03)	0.01	0.64
3-year overall survival	5	161	173	72.6	53.2	2.64 (1.14, 6.10)	0.02	0.02
5-year overall survival	4	151	153	54.3	39.2	2.00 (0.99, 4.04)	0.05	0.09

OR odds ratio, CI confidence interval, HG heterogeneity

71 % in control group. Pooled analyses showed that ¹³¹I-lipiodol treatment significantly decreased intrahepatic recurrence (OR=0.48, 95 % CI=0.30–0.74; $P=0.001$). Only two studies reported on early recurrence (<2 year), which was found to be significantly lower in the ¹³¹I-lipiodol group (OR=0.45, 95 % CI=0.23–0.89; $P=0.02$).

The 3-year disease-free survival was 42–74.5 % for ¹³¹I-lipiodol and 24–48.1 % for control in five studies. The 5-year disease-free survival was 21–61.9 % for ¹³¹I-lipiodol and 18–32.5 % for control in four studies. Pooled analyses showed that preoperative ¹³¹I-lipiodol was associated with significant improvement in 3- and 5-year disease-free survival rate (OR=2.08, 95 % CI=1.33–3.23; $P=0.001$; OR=1.85, 95 % CI=1.13–3.03; $P=0.01$, respectively) (Fig. 1a, b).

The 3-year overall survival was 68.4–84.8 % for ¹³¹I-lipiodol and 30–70 % for control in five studies. The 5-year overall survival was 50.9–66.7 % for ¹³¹I-lipiodol and 23–54.3 % for control in four studies. Pooled analyses showed that preoperative ¹³¹I-lipiodol was associated with significant improvement in 3- and 5-year overall survival (OR=2.64, 95 % CI=1.14–6.10; $P=0.02$; OR=2.00, 95 % CI=0.99–4.04; $P=0.05$, respectively) (Fig. 2a, b).

Significant heterogeneity was found to be present in 5-year overall survival outcome measures ($I^2=54$ %, $P=0.09$). No heterogeneity was detected for any other outcome assessed (Table 2).

Publication Bias

The funnel plot (Fig. 3) for intrahepatic recurrence in the included studies demonstrated symmetry, indicating no evidence of publication bias.

Discussion

A number of modalities for preventing HCC recurrence after resection have been proposed and analyzed. Both preoperative and adjuvant transcatheter arterial chemoembolization (TACE) were found to be unable to reduce the risk of postoperative recurrence significantly or confer a survival advantage [20, 21]. Vitamin K (VK) is a fat-soluble vitamin that regulates clotting factor production by acting as a coenzyme for a VK-dependent carboxylase that catalyzes carboxylation of

Fig. 1 Forest plot for the 3-year disease-free survival (a) and 5-year disease-free survival (b). Squares indicate point estimates of treatment effect. The pooled OR is represented by the diamond

Fig. 2 Forest plot for the 3-year overall survival (a) and 5-year overall survival (b). *Squares* indicate point estimates of treatment effect. The pooled OR is represented by the *diamond*

glutamic acid residues into gamma-carboxyglutamic acid. The findings in vitro have indicated that VK2 has an antiproliferative effects against hepatoma cell lines, but its efficacy in suppressing HCC recurrence was not confirmed in human studies [22]. Interferon has a variety of biologic properties, including antiviral, immunomodulatory, antiproliferative, antiangiogenic, and tumouricidal effects. It is reported that interferon is effective in preventing the development of HCC recurrence after its curative treatment in HCV-related cirrhosis [23]. However, interferon treatment also has side-effects, including flu-like symptoms, fatigue, neutropenia, thrombocytopenia, depression, bone marrow suppression, and unmasking or exacerbation of autoimmune illnesses, which lead either to treatment disruption or dose modification. Polyprenoic acid, an acyclic retinoid, reportedly is effective in prevention of second primary hepatomas, but long-term safety and efficacy data are lacking [24].

The results from present analysis revealed that adjuvant intrahepatic injection of ^{131}I -lipiodol may reduce the risk of HCC recurrence after surgical resection and improve overall and recurrence-free survival. More importantly, we found this treatment to be safe. Only two serious adverse effects were reported, one patient was found to be hypothyroid on routine testing and subsequently prescribed thyroxine replacement. The other was due to hepatic artery intimal dissection during hepatic angiography for treatment. This injury was self-limiting [14]. No patients showed interstitial pneumonitis consequent to lung shunting or hepatic decompensation, and no patients were withdrawn during the follow-up period.

^{131}I -Lipiodol was found to be selectively and highly cytotoxic against the human HCC and colorectal metastatic cancers but not against the benign endothelial cells. Besides, cancer cells, unlike non-malignant cells, are unable to expel Lipiodol [7]. This may further enhance the cytotoxic effect

Fig. 3 Funnel plot analysis of publication bias. The outcome was the intrahepatic recurrence

of ^{131}I -lipiodol in cancer cells. Adjuvant ^{131}I -lipiodol can eradicate the invisible minute tumour foci that are not identified by preoperative imaging modalities, and this significantly improves the surgical outcome [17].

According to point of recurrence time from the date of hepatectomy, intrahepatic recurrence was classified into early (<2 year) and late (>2 year) recurrences [25]. In the current study, the incidence of early recurrences was significantly lower in patients given adjuvant treatment, apparently because of microscopic tumour foci that have been proved to be a significant predictive factors of early recurrence. Tabone et al. [13] found that the preventive effect of ^{131}I -lipiodol treatment on HCC recurrence was completely lost after 36 months when disease-free survival was similar to the control patients. Lau et al. [17] reported that adjuvant ^{131}I -lipiodol therapy could not significantly decrease the intrahepatic recurrence rate (42.9 vs. 54.5 %, $P=0.28$) in the long-term follow-up (at 8 years after randomization). Because late recurrence was mainly attributable to hepatitis activity-related multi-centric carcinogenesis, it is therefore reasonable to conclude that ^{131}I -lipiodol has no effect on late recurrence.

Our meta-analysis is limited by the small number of participants. Despite intrahepatic injection of ^{131}I -lipiodol is technically feasible, it requires a cumbersome logistic organization and the collaboration of different motivated specialists, such as surgeon, hepatologist, interventional radiologist, and nuclear medicine doctors. As a result, there are very only a few centres equipped to perform this treatment [13]. In addition, there is great heterogeneity among the trials in terms of the time interval of treatment from surgery and dosage of ^{131}I -lipiodol employed. Tabone et al. [13] administered 1100 MBq within the 6th month since liver resection. Boucher et al. [18] administered 2400 MBq between the 8th and 12th postoperative weeks. Lau et al. [17] administered 1850 MBq within 6 weeks from surgery; Chua et al. [19] administered a median dosage of 2000 MBq (range 500–2000 MBq) within a median interval of 59 days (range 8–166 days) after surgery. Chung et al. [14] administered 2035–2331 MBq within 4–6 weeks from surgery.

In conclusion, despite the abovementioned limitations, we conclude that adjuvant intrahepatic injection of ^{131}I -lipiodol resulted in a preventive effect on recurrence and improved survival after resection of HCC. Further larger, multi-centred, randomized prospective trial is warranted.

Conflict of Interest None.

References

1. Forner A, Hessheimer AJ, Isabel Real M, Bruix J (2006) Treatment of hepatocellular carcinoma. *Crit Rev Oncol Hematol* 60:89–98
2. Katz SC, Shia J, Liao KH, Gonen M, Ruo L, Jarnagin WR et al (2009) Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg* 249: 617–623
3. Zhou Y, Sui C, Li B, Kan T, Yang J, Wu M (2011) Safety and efficacy of trisectionectomy for hepatocellular carcinoma. *ANZ J Surg* 81:895–899
4. Fan ST, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK et al (2011) Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. *Ann Surg* 253:745–758
5. Shrager B, Jibara G, Schwartz M, Roayaie S (2012) Resection of hepatocellular carcinoma without cirrhosis. *Ann Surg* 255:1135–1143
6. Tung-Ping Poon R, Fan ST, Wong J (2000) Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg* 232:10–24
7. Al-Mufti RA, Pedley RB, Marshall D, Begent RH, Hilsen A, Winslet MC et al (1999) In vitro assessment of Lipiodol-targeted radiotherapy for liver and colorectal cancer cell lines. *Br J Cancer* 79:1665–1671
8. Raoul JL, Guyader D, Bretagne JF, Duvauferrier R, Bourguet P, Bekhechi D et al (1994) Randomized controlled trial for hepatocellular carcinoma with portal vein thrombosis: intra-arterial iodine-131-iodized oil versus medical support. *J Nucl Med* 35:1782–1787
9. Yoo HS, Lee JT, Kim KW, Kim BS, Choi HJ, Lee KS et al (1991) Nodular hepatocellular carcinoma. Treatment with subsegmental intra-arterial injection of iodine 131-labeled iodized oil. *Cancer* 68:1878–1884
10. Yumoto Y, Jinno K, Inatsuki S, Moriwaki S, Hanafusa T, Yumoto E et al (1992) Treatment of hepatocellular carcinoma by transcatheter hepatic arterial injection of radioactive iodized oil solution. *Cancer Chemother Pharmacol* 31:S128–S136
11. Lau WY, Leung TW, Ho SK, Chan M, Machin D, Lau J et al (1999) Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 353:797–801
12. Boucher E, Corbinais S, Rolland Y, Bourguet P, Guyader D, Boudjema K et al (2003) Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology* 38:1237–1241
13. Tabone M, Vigano' L, Ferrero A, Pellerito R, Carbonatto P, Capussotti L (2007) Prevention of intrahepatic recurrence by adjuvant (131)iodine-labeled lipiodol after resection for hepatocellular carcinoma in HCV-related cirrhosis. *Eur J Surg Oncol* 33:61–66
14. Chung AY, Ooi LL, Machin D, Tan SB, Goh BK, Wong JS et al (2013) Adjuvant hepatic intra-arterial iodine-131-lipiodol following curative resection of hepatocellular carcinoma: a prospective randomized trial. *World J Surg* 37:1356–1361
15. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al (1996) Assessment the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 17:1–12
16. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 73: 712–716
17. Lau WY, Lai EC, Leung TW, Yu SC (2008) Adjuvant intra-arterial iodine-131-labeled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial-update on 5-year and 10-year survival. *Ann Surg* 247:43–48
18. Boucher E, Bouguen G, Garin E, Guillygomarch A, Boudjema K, Raoul JL (2008) Adjuvant intraarterial injection of 131I-labeled lipiodol after resection of hepatocellular carcinoma: progress report of a case-control study with a 5-year minimal follow-up. *J Nucl Med* 49:362–366

19. Chua TC, Saxena A, Chu F, Butler SP, Quinn RJ, Glenn D et al (2011) Hepatic resection with or without adjuvant iodine-131-lipiodol for hepatocellular carcinoma: a comparative analysis. *Int J Clin Oncol* 16:125–132
20. Lau WY, Lai EC, Lau SH (2009) The current role of neoadjuvant/adjuvant/chemoprevention therapy in partial hepatectomy for hepatocellular carcinoma: a systematic review. *Hepatobiliary Pancreat Dis Int* 8:124–133
21. Zhou Y, Zhang X, Wu L, Ye F, Su X, Shi L et al (2013) Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patients with resectable hepatocellular carcinoma. *BMC Gastroenterol* 13:51
22. Riaz IB, Riaz H, Riaz T, Rahman S, Amir M, Badshah MB et al (2012) Role of vitamin K2 in preventing the recurrence of hepatocellular carcinoma after curative treatment: a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 12:170
23. Singal AK, Freeman DH Jr, Anand BS (2010) Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther* 32:851–858
24. Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT et al (1996) Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 334:1561–1567
25. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S et al (2003) Risk factors contributing to early and slow phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 38:200–207