ADJUVANT \textsuperscript{131}I-LIPIODOL FOR HCC • Dumortier et al. 877

The prevention of tumor recurrence after curative treatment of hepatocellular carcinoma (HCC) is unresolved. Postoperative intraarterial injection of \textsuperscript{131}I-labeled lipiodol has been proposed as adjuvant treatment. The aim of this prospective randomized trial was to evaluate if a single dose of postoperative adjuvant intraarterial \textsuperscript{131}I-lipiodol (vs. unlabeled lipiodol) could reduce the rate of intrahepatic recurrence at 2 y. \textbf{Methods:} Patients who underwent curative treatment for HCC and recovered within 6 wk were randomly assigned to receive a single 2,200-MBq \textsuperscript{131}I-lipiodol dose or a single unlabeled lipiodol dose on a 1:1 basis. Recurrence-free and overall survival rates were analyzed. \textbf{Results:} Between June 2005 and February 2009, we included 58 patients (median age of 63 y [range, 23–85 y]): 29 received intraarterial \textsuperscript{131}I-lipiodol and 29 received lipiodol adjuvant treatment. At 2 y after treatment, the rate of patients with intrahepatic recurrence was 28% in the \textsuperscript{131}I-lipiodol group and 56% in the lipiodol group ($P = 0.0449$). The Kaplan–Meier analysis confirmed this result, with a 2-y recurrence-free survival in the \textsuperscript{131}I-lipiodol and lipiodol groups of 73% and 45%, respectively ($P = 0.0259$). The 5-y recurrence-free survival rates in the \textsuperscript{131}I-lipiodol and lipiodol groups were 40% and 0%, respectively ($P = 0.0184$). The overall and specific survivals were not significantly different between groups ($P = 0.9378$ and $P = 0.1339$, respectively). \textsuperscript{131}I-lipiodol had no severe toxic effects. \textbf{Conclusion:} After curative treatment of patients with HCC, one 2,200-MBq dose of intraarterial \textsuperscript{131}I-lipiodol significantly decreased the rate of intrahepatic recurrence but failed to improve overall or specific survival.

\textbf{Key Words:} hepatocellular carcinoma; \textsuperscript{131}I-labeled lipiodol; adjuvant therapy; recurrence; survival


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\textbf{Hepatocellular carcinoma (HCC) is the most frequent malignant tumor of the liver, and the incidence of HCC is increasing in many countries (1). Its prognosis is usually poor when untreated, with survival times of 11.5 mo (stage I), 3 mo (stage II), and 0.9 mo (stage III) according to the Okuda classification (2). Hepatic resection or liver transplantation are the first choice of curative treatment but are rarely possible because of associated underlying liver disease, tumor multiplicity, or local extension. Percutaneous ablation (using injection of acetic acid or ethanol or using radiofrequency) has been proposed as an alternative curative treatment for small HCC (3). Recurrence after curative treatment is almost universal; intrahepatic recurrence is frequently the only site of recurrence and has happened in more than 80% of patients by 5 y (4). In addition, most postoperative deaths are due to recurrent disease (5). Intrahepatic recurrence can represent either intrahepatic metastasis (clonally identical) of the first neoplasm or de novo tumor formation in a cirrhotic liver. Therefore, the objectives of adjuvant therapy are to prevent recurrence from the primary tumor or to reduce the incidence of a second HCC and, ultimately, reduce death related to recurrent HCC. Different therapies have been proposed as adjuvant treatment for HCC, with a preference for locoregional therapy since HCC has a tendency to stay within the liver until at a disseminated stage of the disease with distant metastases. So far, systemic treatments such as chemotherapy and immunotherapy or locoregional treatments such as transarterial chemotherapy, transarterial radioembolization, and transarterial chemoembolization have been tried. Among more than 650 clinical studies relevant to adjuvant (or chemopreventive) therapy for HCC, only 28 (\(<5\%\)) were randomized controlled studies and most came from Asia (6). Only interferon (in patients with chronic hepatitis C) and oral acyclic retinoid can possibly be considered effective therapy (6). Data on \textsuperscript{131}I-labeled lipiodol and tumor vaccination were considered promising but needing further confirmation. Transarterial injection of \textsuperscript{131}I-lipiodol has been proposed as a palliative treatment for unresectable HCC and also as adjuvant treatment (7). Until now, adjuvant \textsuperscript{131}I-lipiodol has been evaluated in only a single randomized controlled study from Hong Kong (8,9).}
The purpose of the present randomized study was to evaluate if a single 2,200-MBq dose of $^{131}$I-lipiodol versus unlabeled lipiodol would reduce the rate of recurrence of HCC after curative treatment. Side effects and patient tolerance were assessed in both groups.

MATERIALS AND METHODS

Study Design

This was a multicenter, randomized controlled study conducted in French academic hospitals of the Rhône-Alpes area. Patients were required to have undergone hepatic resection or percutaneous ablation of HCC within 8–20 wk before adjuvant therapy and to have no documented evidence of disease recurrence on abdominal sonography and CT scanning or MR imaging 4 wk before inclusion. Patients had to be older than 18 y, with a Child–Pugh score of no more than 7, World Health Organization Performance Status below 3, no ascites, total bilirubinemia below 18 y, and serum creatinine of no more than 120 µmol/L.

The concomitant use of other therapy was not allowed. All patients were required to give written informed consent. The trial was approved by the ethics committee CCPPRB (Comité consultatif de protection des personnes dans la recherche biomédicale) Lyon B on December 21, 2004, and by the French Health Authority (Agence française de sécurité sanitaire des produits de santé [AFSSaPS]) on February 9, 2005.

Good Clinical Practice guidelines. The study was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines.

Randomization

The randomization list was prepared using SAS software (SAS Institute Inc.) by the research unit (Unité de recherche clinique, Hospices Civils de Lyon). Afterward, the investigator contacted the search unit by fax to obtain the randomization group. Patients were randomly assigned within 6 wk after curative treatment of HCC to receive either an adjuvant intraarterial hepatic injection of $^{131}$I-lipiodol (treatment arm) or unlabeled lipiodol (control arm) on a 1:1 basis. Randomization was centralized and stratified according to the first treatment of HCC (surgery or ablation). Because of the constraints related to radioactive therapy, the study was not masked.

Therapy

The volume of $^{131}$I-lipiodol (Lipiocis; CIS Bio International) to be injected was 10 mL, and the activity was uniformly 2,200 MBq for each treatment dose. To protect the thyroid from uptake of free $^{131}$I-lipiodol during cellular degradation of $^{131}$I-lipiodol, patients were given 2 drops (0.05 mL) of Lugol iodine solution 3 times daily for 1 wk before and 4 wk after treatment. On the day of treatment, the patients underwent selective cannulation of the hepatic artery by the Seldinger technique, which was performed by the interventional radiologist who administered $^{131}$I-lipiodol. The catheter for angiography was removed after the treatment. The patients remained in an isolation room for radiation protection purposes and were discharged home once the activity of $^{131}$I-lipiodol was below 370 MBq (about 7 d, depending on the effective half-life of $^{131}$I-lipiodol).

In the control group, a similar injection of 10 mL of lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet) was performed.

We recorded any side effects such as pain or fever. Liver function tests were performed every day during the hospital stay.

Follow-up

Medical history and physical examination, as well as complete blood count and liver function tests, were assessed after months 1, 3, and 6 after adjuvant therapy and then every 6 mo until 5 y. The survey for recurrent tumors included a serum $\alpha$-fetoprotein check every 6 mo and thoracic and abdominal CT scanning every 6 mo or whenever clinically indicated.

The study had to be stopped early in April 2011 because the study product constraints related to radioactive therapy, the study was not masked.

The primary endpoint was the recurrence rate at 2 y, with recurrence defined as an intrahepatic recurrence (local recurrence or second HCC) occurring more than 6 mo after the initial treatment.

Local recurrence was defined as recurrence in the same liver segment as the initial tumor. A second HCC was defined as recurrence in a different liver segment or at a distance of 2 cm from the initial tumor. Intrahepatic recurrence was diagnosed by histology or by MR imaging, CT scanning (doubled surface, hypervascularized hepatic tumor), or a significant elevation of serum $\alpha$-fetoprotein levels (>80 ng/mL).

Secondary endpoints were recurrence-free survival, overall and specific survival, occurrence of extrahepatic metastasis, liver function evolution, and treatment toxicity in both groups.
Analysis of Populations

The study population comprised all randomized patients available at injection time; that is, any patients who had been wrongly included, had withdrawn before injection, or had a recurrence within 6 mo were not considered.

The efficacy population comprised all randomized patients having effectively received the injection and with follow-up available at 2 y (patients who had been lost to follow-up, had received a transplant, or had died before 2 y were excluded). Patients with recurrence within the first 6 mo after initial treatment were also excluded.

The injected population comprised all randomized patients having effectively received the injection; patients with recurrence within the first 6 mo after initial treatment were also excluded.

The safety population consisted of all patients injected.

Sample Size

Assuming that the recurrence rate at 2 y was 40%, we expected that 131I-lipiodol would reduce this rate to 15%. To achieve 80% power with an α level of 5%, a total of 47 patients per group had to be assessed. To take into account loss of follow-up, 60 patients were included (120 patients overall).

Statistical Analysis

For quantitative variables, parameters at inclusion were presented as mean followed by SD in parentheses and median followed by minimum and maximum in parentheses and were compared using the Student t test (or the Mann–Whitney test in case of nonnormality). For qualitative variables, parameters at inclusion were presented as number followed by percentage in parentheses and were compared using the χ2 test (or the Fisher exact test when conditions for χ2 were not fulfilled).

The rate of recurrence at 2 y was computed on the efficacy population and compared using a χ2 test. This analysis was completed with a recurrence-free survival analysis on the injected population. Time to recurrence was computed from the injection date to the recurrence date or to the latest follow-up for patients without recurrence (end of study, transplantation date, or death date). Groups were compared using the log-rank test.

Overall survival was analyzed for the injected population. Time was computed from the injection date to the death date or to the latest follow-up for surviving patients. Specific survival was computed by considering as censored all patients with a cause of death not related to the disease. Groups were compared using the log-rank test.

The impact of tumor size and cirrhosis on 2-y recurrence-free survival and on specific survival was tested using a Cox model. In cases of significance, a model was created involving the variable, the treatment group, and their interaction.

Adverse events were recorded and were encoded using the MedDRA System Organ Class. All analyses were performed using SAS software, version 9.2.

### TABLE 1
Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>131I-lipiodol (n = 29)</th>
<th>Lipiodol (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (27.6%)</td>
<td>3 (10.3%)</td>
<td>0.0940*</td>
</tr>
<tr>
<td>Male</td>
<td>21 (72.4%)</td>
<td>26 (88.7%)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>64.23 (9.39)</td>
<td>62.93 (12.39)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>Number of HCC nodules (n) 1</td>
<td>25 (86.2%)</td>
<td>23 (82.1%)</td>
<td>0.7748*</td>
</tr>
<tr>
<td>2</td>
<td>3 (10.3%)</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (3.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (3.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest nodule diameter (mm)</td>
<td>50.07 (35.43)</td>
<td>52.42 (37.37)</td>
<td>0.8578*</td>
</tr>
<tr>
<td>Liver cirrhosis (n)</td>
<td>17 (60.7%)</td>
<td>15 (51.7%)</td>
<td>0.4941*</td>
</tr>
<tr>
<td>Etiology of liver disease (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>14</td>
<td>7</td>
<td>0.2076*</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1</td>
<td>3</td>
<td>0.3002*</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>6</td>
<td>5</td>
<td>1.0000*</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>0</td>
<td>4</td>
<td>0.0286*</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>4</td>
<td>1.0000*</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
<td>9</td>
<td>0.0988*</td>
</tr>
<tr>
<td>HCC initial treatment (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>23</td>
<td>22</td>
<td>0.7529*</td>
</tr>
<tr>
<td>Percutaneous radiofrequency ablation</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh score at inclusion</td>
<td>5.30 (0.67)</td>
<td>5.32 (0.72)</td>
<td>1.0000*</td>
</tr>
<tr>
<td>Prothrombin rate (%)</td>
<td>82 (16.78)</td>
<td>84.82 (10.69)</td>
<td>0.8729*</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>12.37 (6.3)</td>
<td>14.17 (10.74)</td>
<td>0.6857*</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>39.26 (7.66)</td>
<td>39.85 (5.81)</td>
<td>0.2508*</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.44 (1.54)</td>
<td>13.26 (1.28)</td>
<td>0.6311*</td>
</tr>
<tr>
<td>Platelets (G/L)</td>
<td>195.17 (132.57)</td>
<td>184.55 (69.01)</td>
<td>0.6859*</td>
</tr>
<tr>
<td>White blood cells (G/L)</td>
<td>6.17 (2.75)</td>
<td>5.99 (2.06)</td>
<td>0.9628*</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>72.76 (14.67)</td>
<td>68.13 (15.01)</td>
<td>0.2405*</td>
</tr>
</tbody>
</table>

*χ2 test or Student t test.  
†Fisher exact test or Mann–Whitney test.  
Qualitative data are expressed as numbers followed by percentages in parentheses; continuous data are expressed as mean followed by SD in parentheses.
RESULTS

Baseline Characteristics

Between June 2005 and February 2009, 58 patients (median age, 63 y [range, 23–85 y]) were included and were available for analysis (Fig. 1). The characteristics of the patients are shown in Table 1. The sex ratio, age, stage and size of tumor, Child–Pugh score, and biologic variables were similar in both groups.

Lipiodol and 131I-Labeled Lipiodol Injection

There were no complications related to angiography. After injection of 131I-lipiodol, mild extrahepatic radionucleotide diffusion was observed (on scintigraphy) in the thyroid or lung in 8 of 29 patients, without clinical consequence.

HCC Recurrence

The efficacy population comprised 50 patients followed for at least 2 y. Complementary recording allowed a median of 4.4 y of follow-up to be reached. At 2 y after treatment, there were 7 cases of intrahepatic recurrence (28%) in the 131I-lipiodol group and 14 (56%) in the lipiodol group ($P = 0.0449$). These recurrences were local in 4 cases (1 and 3, respectively) and were a second tumor in 17 (6 and 11, respectively).

The Kaplan–Meier analysis on the 56 patients of the injected population confirmed this result, with a 2-y recurrence-free survival in the 131I-lipiodol and lipiodol groups of 73% and 45%, respectively ($P = 0.0259$) (Fig. 2). Initial treatment of HCC recurrence consisted of surgery ($n = 2$), percutaneous ablation ($n = 2$), transarterial chemoembolization ($n = 10$), chemotherapy ($n = 1$), or best supportive care ($n = 6$).

Tumor size and presence of cirrhosis had no impact on 2-y recurrence-free survival.

When the data were not restricted to the first 2 y, the number of patients with intrahepatic recurrence was 12 (48%) in the 131I-lipiodol group and 19 (76%) in the lipiodol group ($P = 0.0414$). In addition, 2 patients (all in the lipiodol group) presented extrahepatic metastases during follow-up (bone and lung metastases in both cases).

Patients with cirrhosis had a higher risk of recurrence ($P = 0.0236$). The Cox model with interaction showed that the effect of treatment was significantly different between patients with and without cirrhosis ($P = 0.0203$), with radioactive treatment being more efficient in patients without cirrhosis.

Similarly, the 5-y recurrence-free survival rates in the 131I-lipiodol and lipiodol groups were 40% and 0%, respectively ($P = 0.0184$).

Overall Survival

The number of deaths was 10 (34.5%) in the 131I-lipiodol group and 9 (31.0%) in the lipiodol group. According to Kaplan–Meier analysis (Fig. 3), the overall survival was not significantly different ($P = 0.9378$).
The 2-y overall survival rates in the 1³¹I-lipiodol and lipiodol groups were 83% and 88%, respectively. Concerning related deaths, 3 and 7 deaths were observed in the 1³¹I-lipiodol and lipiodol groups, respectively. The specific survival was not significantly different (P = 0.1339).

The specific survival rate at 2 y was 92% in both groups (Fig. 4).

**Tolerance and Adverse Events**

Data on tolerance and adverse events are presented in Table 2. The safety population consisted of 58 patients. There was no significant difference between groups regarding clinical or biologic (including liver function) late (6-, 12-, and 24-mo) side effects after injection, except a higher level of alanine aminotransferase in the lipiodol group, (P = 0.0075). There was also no significant difference between groups regarding clinical or biologic (including liver function) early (1-mo) side effects after injection, except a higher level of alanine aminotransferase in the lipiodol group (P = 0.0075). There was no significant difference between groups regarding immediate clinical side effects (including liver function) late (6-, 12-, and 24-mo) side effects after injection (data not shown).

A total of 266 adverse events occurred in 55 patients; among these, 124 were severe. There was no significant difference between groups: 96.8% of the patients in the 1³¹I-lipiodol group versus 92.6% in the lipiodol group (P = 0.59) for adverse events and 96.8% in the 1³¹I-lipiodol group versus 92.6% in the lipiodol group for severe adverse events (P = 1.00).

**DISCUSSION**

In this prospective French randomized trial, one 2,200-MBq dose of adjuvant 1³¹I-lipiodol after curative treatment of HCC in European patients with chronic liver disease (and cirrhosis in most cases) of various origins, mainly alcoholic, reduced by half the rate of recurrence but failed to improve overall and specific survival. The primary endpoint was recurrence rate at 2 y. However, receipt of a transplant, loss to follow-up, and death before this timeline make the per-protocol analysis unsatisfactory. Intention-to-treat analysis was not presented since imputation would have been necessary for more than 20% of patients. Therefore, the only valid method for analyzing data with these characteristics is survival analysis. This is why we decided to complete the simple proportion comparison with a Kaplan–Meier analysis.

HCC commonly arises from chronic viral or alcoholic liver diseases as is in accordance with our study population, most of whom had alcoholic liver disease—the main etiology of cirrhosis in France. We report here the largest randomized controlled study and the first in a European setting. Twenty years ago, Lau et al. recruited (from April 1992 to August 1997) 43 patients in Hong Kong who were randomly allocated to receive intraarterial 1³¹I-lipiodol (n = 21) or no adjuvant treatment (n = 22) (8,9). The 5-y actuarial recurrence-free survival was significantly better in the treatment group (61.9% vs. 31.8%, P = 0.0397). In addition, the 5-y overall survival was significantly better in the treatment group (66.7% vs. 36.4%, P = 0.0433). The median intrahepatic recurrence interval after curative resection was 19 mo (range, 2–120 mo) and 7 mo (range, 2–25 mo) in the treatment and control groups, respectively (P = 0.013). Interestingly, the differences in recurrence-free and overall survival became statistically insignificant 8 y after randomization. The authors hypothesized that this finding could have been related to one of two factors: the small sample size due to the early stopping of randomization after interim analysis, or the inability of a single injection of 1³¹I-lipiodol to prevent new tumor formation in a cir-
rhetic liver over the very long term, as expected. Since $^{131}$I-lipiodol emits both $\beta$ rays and $\gamma$ rays, patients treated with $^{131}$I-lipiodol need to stay in the hospital for approximately 7–14 d to allow radiation to decrease to a safe level before discharge. On the one hand, it can be postulated that this agent could be used as an adjuvant treatment after curative treatment of HCC to deliver a sufficient dose of radiation to the liver remnant and eradicate microscopic disease. On the other hand, such treatment is probably not able to prevent delayed recurrence presenting as new tumor (10). A second injection of $^{131}$I-lipiodol, for example, 2 y after the first one (and thereafter iterative), could be of interest and would need evaluation. The main limiting factor for $^{131}$I-lipiodol use is the patient isolation required for radioprotection, because serious adverse effects are quite rare. Potassium iodide premedication is usually used to decrease thyroid iodide uptake and the risk of hypothyroidism. As observed in our study, undesirable effects reported fairly frequently consist of moderate and temporary fever (29%), moderate and temporary disturbances of the biologic liver test (20%), and hepatic pain during injection (12.5%) (7). Moderate and reversible leukopenia is observed more rarely (7%) (7). Intersitial pneumonia is probably the most severe complication of $^{131}$I-lipiodol and has been reported at an estimated prevalence of 15.5 cases per 1,000 treated patients (7).

In comparison to ours, there were less recurrence and better survival in the Asian study, probably related to very different patient characteristics in the two randomized studies: hepatitis B–positive young (52-y-old) patients without cirrhosis in the study of Lau et al. versus older (63-y-old) patients with alcoholic cirrhosis in ours. This HCC epidemiology is the opposite of that in Asia and Europe. Therefore, the clinical impact of adjuvant therapy after curative treatment of HCC is probably different in these two different settings.

Before the present randomized study, two French nonrandomized studies also suggested clinical efficacy for adjuvant $^{131}$I-lipiodol. The single-arm prospective trial reported by Partensky et al. (on 28 patients treated from January 1991 to June 1997 in Lyon) showed 3- and 5-y overall survival rates of 86% and 65%, respectively (11). The French case-control study reported by Boucher et al. (on 38 patients treated from January 1999 to September 2001) reported that the number of recurrences in the first 2 y was significantly lower in the $^{131}$I-lipiodol group (7/38 [18.4%] vs. 15/38 [39.5%]), and this finding is in accordance with our results. In addition, recurrence-free survival was better in the $^{131}$I-lipiodol group than in the control group (2-, 3-, and 5-y rates of 77%, 63%, and 42% vs. 47%, 34%, and 27%, respectively, $P < 0.03$). Overall survival did not differ between the groups even though there was a trend toward better survival in the $^{131}$I-lipiodol group (2-, 3-, and 5-y rates of 76%, 68%, and 51% vs. 68%, 53%, and 39%, respectively, $P = 0.09$) (12,13). Similarly, in the study of Chua et al. from Australia, 41 patients who received adjuvant $^{131}$I-lipiodol after hepatic resection were compared with a matched group of 41 patients who underwent resection only (14). The median disease-free and overall survivals were 24 mo versus 10 mo ($P = 0.032$) and 104 mo versus 19 mo ($P = 0.001$) in the experimental and control groups, respectively. Interestingly, rates of intrahepatic-only recurrences (73% vs. 37%, $P = 0.02$) and surgical and nonsurgical treatments for recurrences (84% vs. 56%, $P = 0.04$) were higher in the experimental group than in the control group.

To date, $^{131}$I-lipiodol is the only radionuclide agent that has been evaluated as an adjuvant treatment for HCC, but this agent is no longer available in France from CIS Bio International. Nevertheless, this status could change in the future if efficacy is supported by clinical studies, and $^{131}$I-lipiodol can also be purchased elsewhere, as is done in Hong Kong by Lau et al. (8,9) (labeling of lipiodol is done in their radioisotope laboratory by an atom-to-atom exchange reaction). Nevertheless, there are also other radionuclide agents that are currently being investigated. $^{188}$Re-HDD (4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol)/lipiodol has favorable characteristics for radionuclide therapy, and first trials disclosed promising tolerance and response rates (15). More interesting is the potential role of transarterial radioembolization using $^{90}$Y microspheres. In a metaanalysis of 14 published studies, Venti et al. showed almost 80% response of any type after palliative treatment of 325 patients with HCC (16). Although $^{90}$Y microspheres are currently the preferred method for treating HCC, rather than $^{131}$I-lipiodol, the strong embolic ability of $^{90}$Y microspheres makes severe liver dysfunction a contraindication for their use (17). This consideration would not be relevant in the context of adjuvant therapy, especially in patients without cirrhosis. Ultimately, techniques using $^{90}$Y-labeled products tend to cost up to 10 times more than therapy with $^{131}$I-lipiodol.

**CONCLUSION**

Our study strongly confirmed the findings of the first randomized study from Hong Kong including hepatitis B virus–positive patients. Adjuvant $^{131}$I-lipiodol after curative treatment of HCC was able to significantly improve recurrence-free survival in patients with chronic liver disease of various origins, mainly alcohol, in a European setting. Randomized controlled trials will soon be necessary to evaluate the role of new radionuclide agents in this indication. Associations between locoregional and systemic adjuvant treatments could probably increase efficacy and need to be evaluated.

**DISCLOSURE**

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