

Transcatheter Arterial Chemoembolization of
Rabbit VX2 Liver Tumor;
Cisplatin-Iodized Oil Suspension VS Emulsion

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Introduction.

- Transcatheter arterial chemoembolization (TACE) is now recognized as world standard palliative therapy for advanced HCC.
- Cisplatin is one of the key drugs for HCC, but the most effective protocol of TACE with cisplatin has not been established.
- Iodized oil (Lipiodol Ultrafluid) is used as both an embolic agent and a carrier of anticancer drugs in TACE.
- This drug delivery system makes it possible to maintain a high platinum concentration in the tumor.
- Mixtures of cisplatin and iodized oil are classified into suspension and emulsion.
- There are no studies comparing the efficiency of suspension and emulsion.

Purpose.

To evaluate and compare the antitumor effect and toxicity of cisplatin suspension and emulsion as a therapeutic agent for the treatment of rabbit VX2 hepatic tumors with TACE.

Materials and Methods.

Animal model

- 12 adult Japanese white rabbits weighing 2.77–3.22 kg (mean, 2.92 kg).
- VX2 tumors were transplanted into the the left medial hepatic lobe.
- The animals were used for experiments 3 weeks after tumor implantation.

Experimental groups

I. Suspension group (n=6)

cisplatin powder (1mg/kg) + iodized oil (0.1ml/kg)

II. Emulsion group (n=6)

cisplatin powder (1mg/kg)

+ iodized oil (0.1ml/kg) and saline solution (0.1ml/kg)

Evaluation and Comparison

- platinum pharmacokinetics
- toxicity
- antitumor effects,
based on tumor growth and pathological investigation

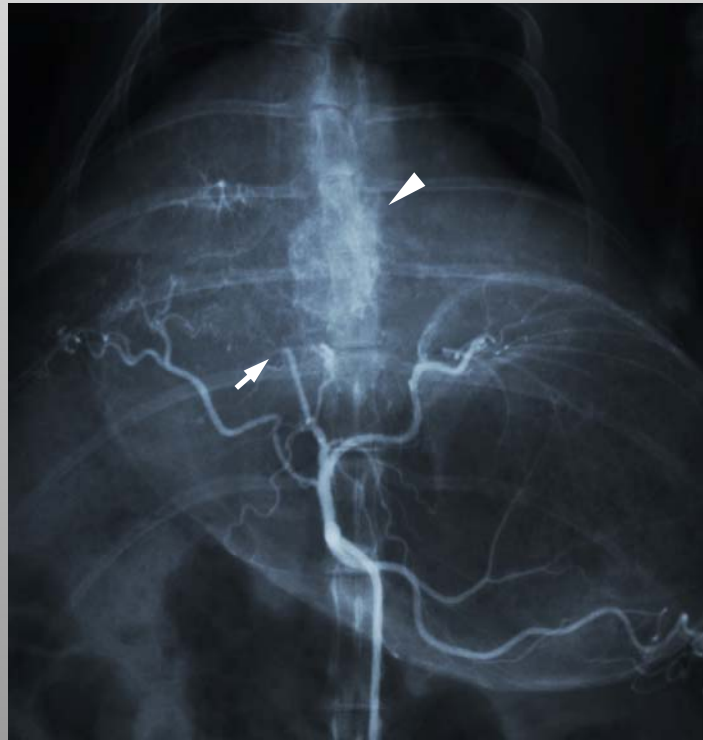
TACE procedure.

- Under general anesthesia (thiopental sodium c.i.v., 40mg/kg/h)
- A 4-Fr sheath was inserted from the common femoral artery with surgical incision.
- The middle hepatic artery, identified as the main feeding artery in all rabbits, was catheterized with a 2.3-Fr microcatheter, and the therapeutic agent was injected.

a.



b.



- a. Therapeutic agent was administered via a 2.3-Fr microcatheter inserted to middle hepatic artery (arrow).
- b. Celiac angiogram after TACE shows embolic effect of middle hepatic artery (arrow) and accumulation of iodized oil in the tumor (arrowhead).

Data analysis.

Pharmacokinetics.

Blood samples were collected at 0, 0.5, 1, 3, 6, and 24 h after administration of chemotherapeutic agent, and plasma platinum concentration were measured.

Toxicity.

Blood samples were collected before and at 1, 3, 5, and 7 days after TACE. Plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and creatinine levels were measured.

Ultrasonographic size measurement and growth ratio.

- Before and 7 days after TACE, tumor size measurement with Sonazoid enhanced ultrasonography was performed.
- The space occupied by the tumor sections and the growth ratio was calculated with the following formulas :

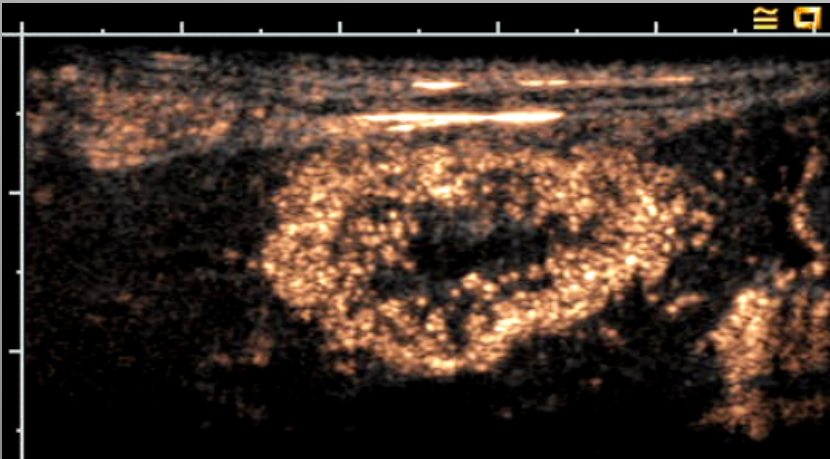
$$\text{Space (S)} = 3.14 * XY / 2$$

(X is the shorter and Y the longer diameter on the orthogonal axis.)

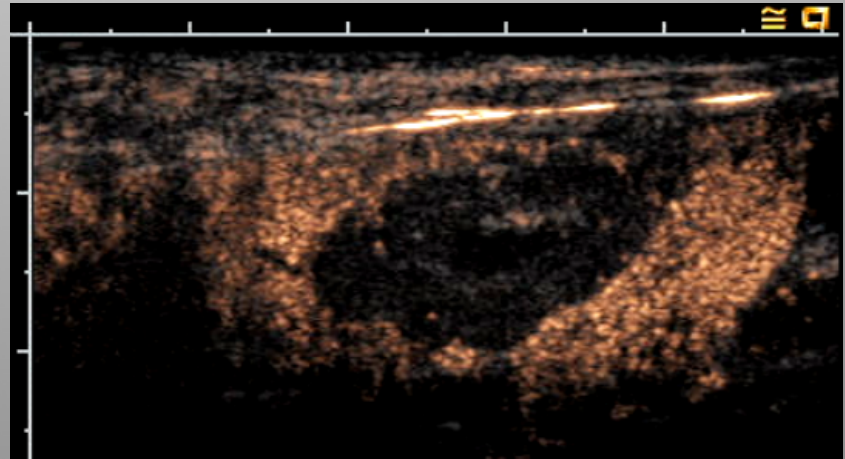
$$\text{The growth ratio} = (S7/S0 - 1) * 100. \text{ (S0: before TACE, S7: 7 days after TACE)}$$

US system : Siemens ACUSON SEQUOIA 512 (20 frames/sec, 10-13MHz, Cadence Contrast Pulse Sequence mode)

a.



b.

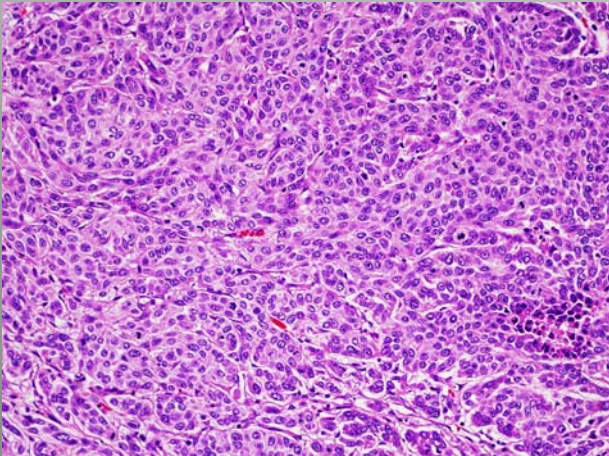


a. Immediately after administration of Sonazoid, strong tumoral contrast effect is observed especially in the marginal area according to vascular distribution. b. 10 minutes after administration (Kupffer phase), only the tumor lacks contrast effect and the edge is clearly visualized.

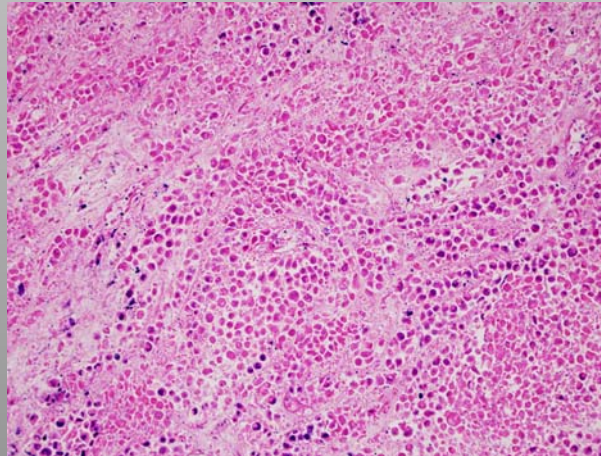
Pathological Investigation.

- 7 days after TACE, the rabbits were sacrificed with an overdosed anesthesia.
- Part of the extracted liver including tumors was sliced into sagittal sections and utilized as specimens.
- Cellular colonies with adequately stained nuclei, cytoplasm were classified as viable. Colonies without adequate nuclear staining were classified as necrotic.
- The viable proportion of the entire tumor section was estimated.

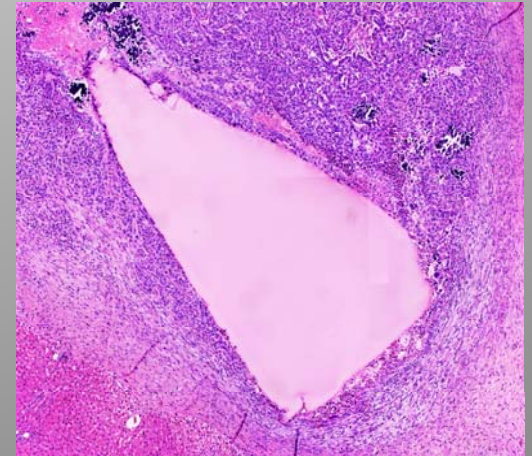
a.



b.



c.



In the viable portion (a), cellular colonies with adequately stained nuclei and cytoplasm are observed, but without in the necrotic portion (b). In the destructive vascular structure, a deposit of iodized oil remains (c).

(a-c: hematoxylin-eosin stain; original magnification, x20)

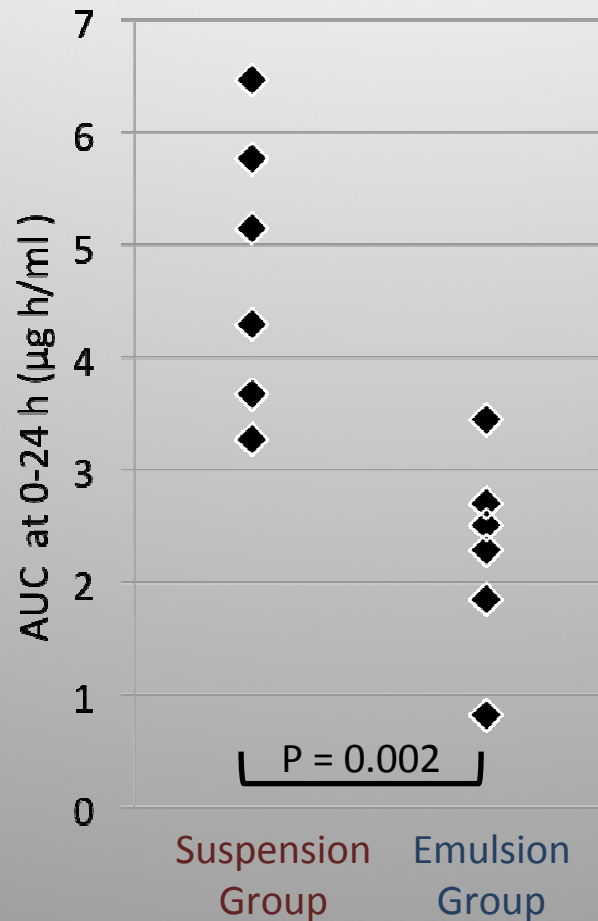
Result 1. Pharmacokinetics.

Table 1. Plasma Platinum Concentration ($\mu\text{g/ml}$)

time (h)	Suspension	Emulsion	P
0	2.09 \pm 0.30	1.85 \pm 0.57	0.336
0.5	0.70 \pm 0.21	0.33 \pm 0.11	0.004
1	0.29 \pm 0.10	0.14 \pm 0.07	0.02
3	0.22 \pm 0.06	0.09 \pm 0.04	0.01
6	0.18 \pm 0.06	0.08 \pm 0.03	0.01
24	0.12 \pm 0.05	0.05 \pm 0.03	0.004

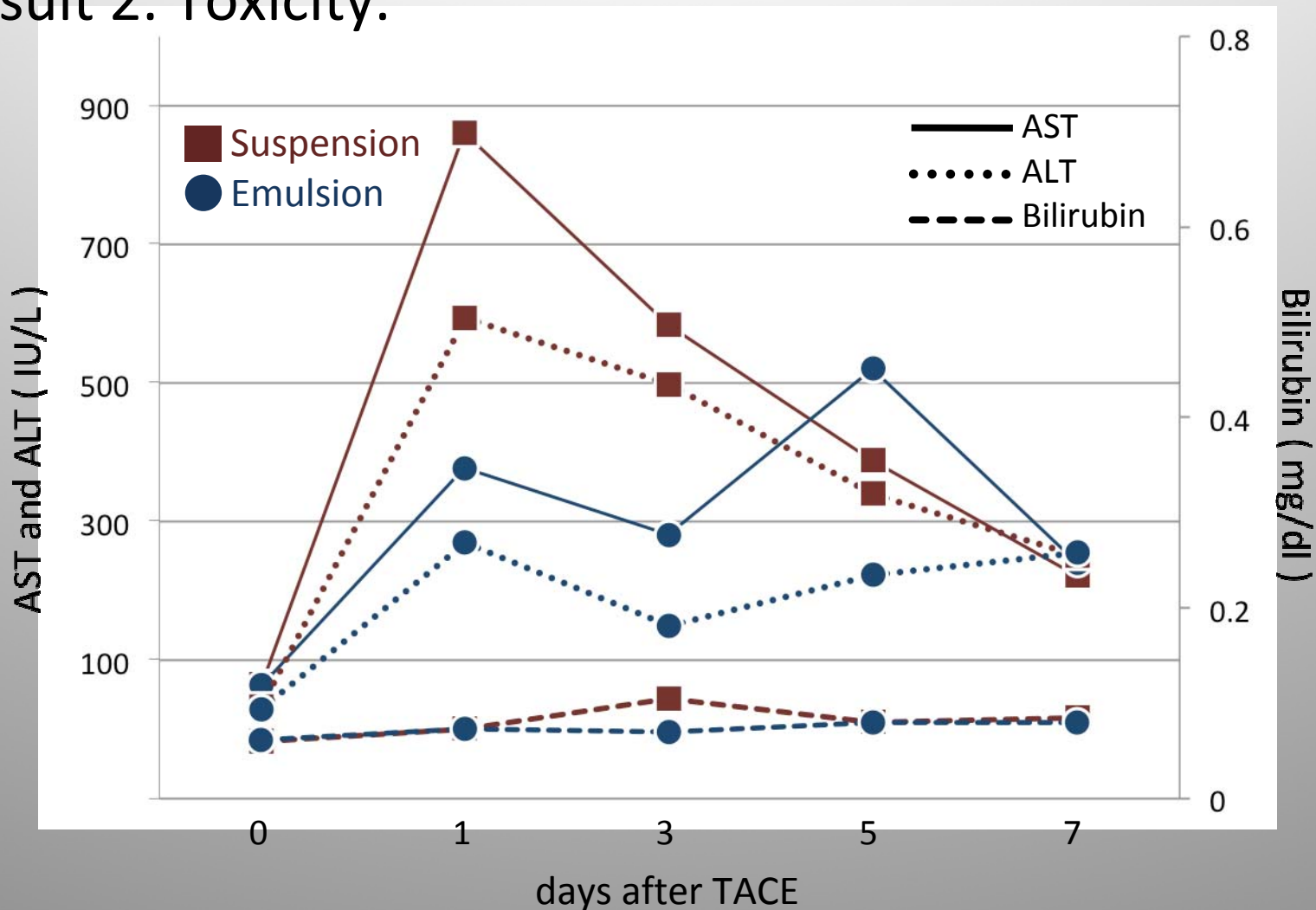
At 0.5, 1, 3, 6 and 24 hours, plasma platinum concentration values from suspension group were significantly higher than emulsion group ($P < 0.05$, Unpaired T test).

Result 1-2. AUC for Plasma Platinum Concentration.



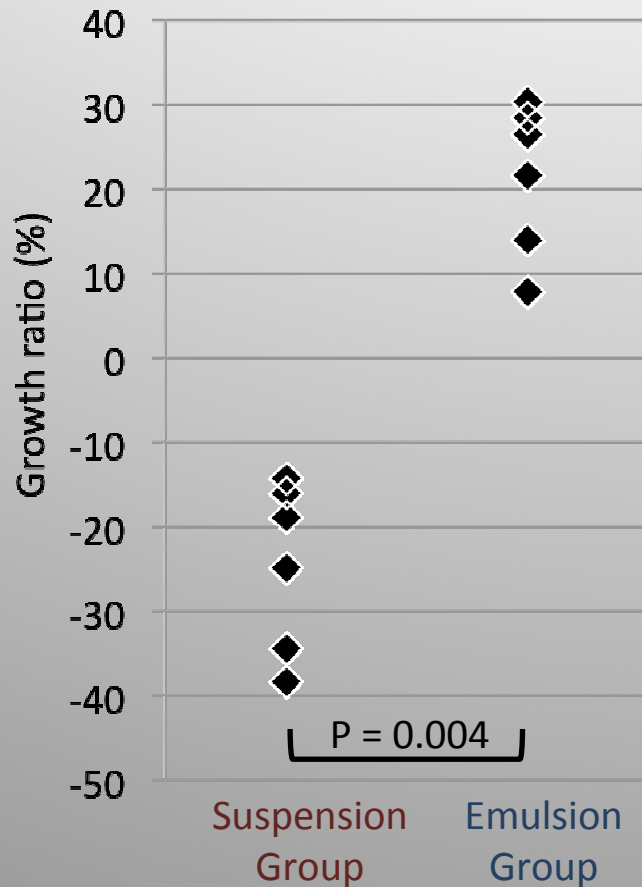
AUC at 0-24 hours were $4.77 \pm 1.24 \mu\text{g/ml h}$ for the suspension group,
 $2.26 \pm 0.88 \mu\text{g/ml h}$ for the emulsion group.
The value of AUC was significantly higher in the suspension group.
($P = 0.002$, Unpaired T test).

Result 2. Toxicity.



AST and ALT levels increased for a few days after TACE, but tended to return to baseline levels over the experimental period. The increase in liver enzymes was slightly greater in the suspension group than in the emulsion group ($P > 0.05$).

Result 3. Ultrasonographic size measurement and Growth ratio.



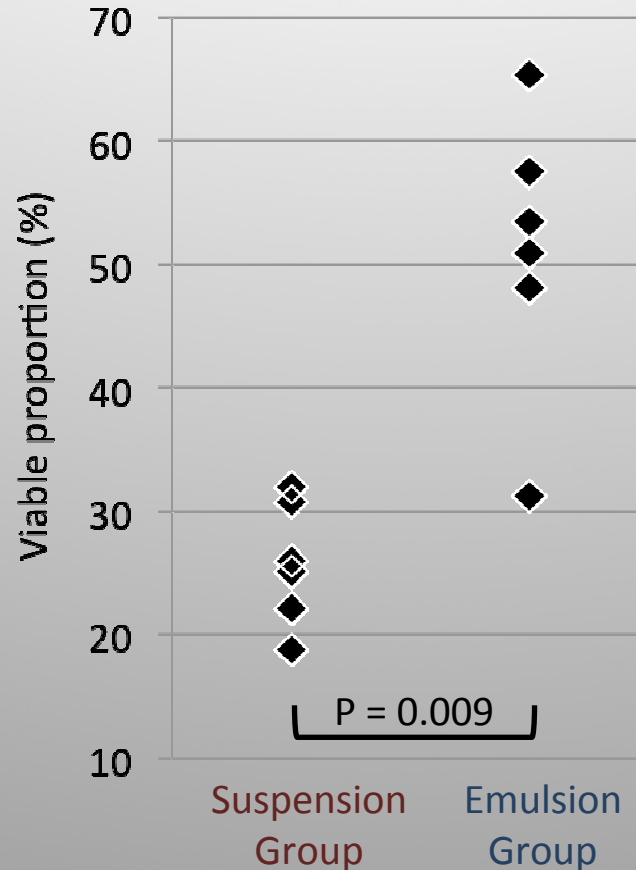
S0: $2.05 \pm 0.23 \text{ cm}^2$ in the suspension group
 $1.67 \pm 0.23 \text{ cm}^2$ in the emulsion group (NS).

Tumor volumes in the suspension group showed shrinkage (-38.4 to -14.4 %), and increased in the emulsion group (7.8 to 30.3 %).

Growth ratio in the two groups were significantly different

(P = 0.004, Mann-Whitney U test).

Result 4. Pathological investigation, Viable Proportion.



Viable proportions ranged from 18.8 to 32.0 % in the suspension group, 31.3 to 65.4 % in the emulsion group. Proportion in the suspension groups was significantly smaller than the emulsion group (P = 0.009, Mann-Whitney U test).

Discussion.

The intrahepatic distribution of iodized oil after hepatic artery injection

AP anastomosis.

1. peribiliary plexus
2. terminal AP anastomosis
3. vasa vasora on the PV wall
4. direct AP connections

Hepatic Artery

propagation of iodized oil
24h after arterial injection

Portal Venule

Portal Vein

Sinusoid

Tumor

Kan Z, *et al.* Radiology 1993; 187: 621-626.

Kan Z, *et al.* Radiology 1993; 186: 861-866.

lipid staining in peritumoral sinusoids, portal venules, and tumor neovasculature is observed 24 h after iodized oil administration via the hepatic artery.

Miller DL, *et al.* Radiology 1987;162:849-852.

Discussion.

- Plasma platinum concentration at 0.5 - 24 h after TACE
Suspension > Emulsion

Emulsion:

aqueous phase containing cisplatin powder diluted in blood and rapidly passed from hepatic tissue into blood after administration.

Suspension:

cisplatin powder directly mixed with the oil phase,
similarly to iodized oil alone.
→ distribution in the portal venules and sinusoid over 24 h.
→ longer cisplatin release time at the tumor border and longer-term chemotherapeutic activity could be achieved.

The longer activity of the chemotherapeutic agent resulted in a superior antitumor effect, as evaluated by growth ratio and pathological investigation.

Conclusion.

Cisplatin-iodized oil suspensions made the slow release of cisplatin possible at the tumor border.

Suspension is preferable to emulsion for both drug delivery and antitumor effect in the TACE treatment of VX2 liver tumors.

In the next stage of this investigation, we are preparing a randomized controlled trial comparing TACE with platinum-iodized oil suspension to TACE with platinum-iodized oil emulsion in the near future.

Reference.

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