Appendix 1

Drug loading process of three microspheres launched in China

Preparation steps of DC Bead dug-loaded microspheres

Step 1

Load 50 mg chemotherapy: Use a 5 mL syringe to pump 2 mL of sterile water for injection, then dilute and transfer 5 bottles of chemotherapeutic drug (doxorubicin, epirubicin or pirarubicin) one by one, to reach a concentration of 25 mg/mL after dilution.

Load 75 mg chemotherapy: Use a 5 mL syringe to pump 3 mL of sterile water for injection, and then dilute and transfer 8 bottles of chemotherapeutic drug (doxorubicin, epirubicin or pirarubicin) one by one, to reach a concentration of 25 mg/mL after dilution.

Step 2

Use a 30 mL or 20 mL syringe to pump out the drug-loaded microspheres, and then stand still for 1 minute in a vertical position. Replace to filtering needle, and push the supernatant off (the storage solution of microspheres contains ions, which would affect the drug-loading efficiency).

Step 3

Using a tee joint to mix 2 mL (50 mg) or 3 mL (75 mg) chemotherapy drug into a 30 mL syringe containing microspheres and mix them gently.

Step 4

Shake the syringe gently every 10–15 min.

Step 5

- After loading drug for 45–60 minutes, use a filtering needle to push the supernatant from the syringe;
- Use a 20 mL syringe to draw 15–20 mL non-ionic contrast medium, mix it with the bead diluent via a tee joint, and then shake the mixture gently for several times;
- If the microspheres float up, add sterilized water for injection 1 mL per time;
- If the microspheres sink down, add the contrast medium 1 mL per time;
- Make the microspheres suspended evenly.

For contrast mediums of different brands with different densities (such as 320 or 350 mgI/mL), the use volume of microspheres, sterilized water for injection and non-ionic contrast mediums needs to be adjusted for the first time of use. Generally, after the initial adjustment, the use volume for each preparation could be determined.

Preparation steps of CalliSpheres

Material preparation: 1 20 mL syringe, 2 10 mL syringes, 1 1 mL luer lock syringe, 1 tee joint, 1 bottle of CalliSpheres drug-loadable microspheres, appropriate amount of water for injection or 5% glucose solution, chemotherapeutic drug (specific dosage and type of which are depending on clinical needs) and contrast agent.

Step 1

Open the microsphere bottle cap, insert a syringe needle, balance the pressure in the bottle, and gently shake the penicillin bottle to make the microspheres distributed evenly.

Tilt the penicillin bottle and withdraw the microspheres and saline with a 20 mL syringe.

Place the microsphere-containing syringe upright for 1–2 min until the microspheres have settled completely, and push out the supernatant as far as possible

Step 2

The type and dosage of chemotherapeutic drugs depend on clinical needs.

The higher the concentration of chemotherapeutic drug, the faster the loading speed, therefore, it is recommended that the preparation of the chemotherapeutic drug with a concentration of not less than 20 mg/mL could only use water for injection or 5% glucose solution.

Step 3

Use a tee joint to connect the microsphere-loaded syringe (20 mL) and the syringe containing chemotherapeutic drug (10 mL).

Ensure steady tee link and pay attention to the flow direction.

Push the syringe containing chemotherapeutic drug (10 mL) while pulling the microsphere-loaded syringe (20 mL).

Mix microspheres and chemotherapeutic drug into one syringe (20 mL).

Cap the syringe containing microspheres and chemotherapeutic drug, stand it still, and shake it every 5 minutes. After loading for 15 minutes in total, it could be seen that a large amount of chemotherapeutic drug would load into microspheres.

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Step 4

After the microspheres have been loaded with the chemotherapeutic drugs, add high-contrast contrast medium (such as iodophorol 350) immediately, with no need to wait until the TACE operation.

Measure the liquid amount of the chemotherapeutic drug containing microspheres, add the non-ionic contrast medium at a ratio of 1:1–1:2 and mix them evenly, and then stand the mixture still for 5 minutes before using.

Step 5

Use a tee joint to connect a 1 mL luer lock syringe with a syringe containing microspheres + chemotherapeutic drug + contrast medium (20 mL). Make sure to connect firmly, and shake the microspheres in the large syringe (20 mL) before injecting microspheres into the 1 mL syringe.

Use a small syringe to connect the catheter, shake the microspheres in the 1 mL syringe, and inject through adopting pulse injection method injecting at an injection speed of 1 mL/min.

Hepashere preparation method

Adopt the preparation method of loading one bottle of hepasphere with 50 mg epirubicin (thp) (four times method)

Step 1: medicine preparation: 30 mL syringe, 18 g (No. 12) needle ×2, 0.9% normal saline; thp ×5 bottles;

Step 2: start to prepare about 20–30 minutes before surgery;

Step 3: draw 20 mL normal saline with a 30 mL syringe, add it into thp (5 bottles, 4 mL per bottle), and dissolve them fully;

Step 4: draw the dissolved thp solution of 20 mL in total and inject 10 mL of it into a hepasphere bottle;

Step 5: sway the microsphere bottle gently, but do not shake it vigorously, then wait for 10 minutes (during which the microsphere bottle could be inverted for many times), to make the microsphere fully mix with thp solution;

Step 6: replace to 18 g needle, and use the syringe containing the remaining 10 mL thp solution to draw the solution (10 mL) in the microsphere bottle, thus to obtain a 20 mL suspension;

Step 7: remove the needle, cover syringe cap, and cover with a sterile sheet if possible;

Step 8: wait 30–60 minutes so that the hepasphere could fully absorb drug, and gently shake the syringe every 10 minutes during this period of time;

Step 9: transfer to the operating table via a tee joint;

Step 10: stand it still for about 10 minutes, to enable the microspheres to settle, drain the upper layer of liquid as much as possible, and then draw 20 mL of non-ionic contrast medium, and mix thoroughly for use;

Step 11: The preparation has been completed.

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Table S1 U.S. Preventive Services Task Force grading method, which could be used to evaluate the quality of evidence for treatment or screening

Level of evidence	Description
Evidence level I	Evidence obtained from at least one well-designed randomized controlled clinical trial
Evidence level II-1	Evidence obtained from well-designed non-randomized controlled trials
Evidence level II-2	Evidence obtained from well-designed cohort or case-control studies (preferably multi-center studies)
Evidence level II-3	Evidence obtained from multiple time series studies with or without intervention. Significantly different results concluded in non-controlled trials are sometimes considered as evidence of this level
Evidence level III	Authoritative opinions from clinical experience, descriptive researches or expert committee reports.

Table S2 Recommendation evaluation by the U.S. Preventive Services Task Force

Recommendation grading	Description
Grade A recommendation	There are good scientific evidences suggesting that the benefits of such medical practice substantially outweigh its potential risks
	Clinicians should discuss the medical practice with applicable patients
Grade B recommendation	There are at least acceptable evidences suggesting that the benefits of such medical practice outweigh its potential risks.
	Clinicians should discuss such medical practice with applicable patients
Grade C recommendation	There are at least acceptable scientific evidences suggesting that such medical practice could provide benefits, but its benefits are very close to the risks
	Clinicians could not make general recommendations, and are not required to provide such medical practice unless there are certain individual considerations
Grade D recommendation	There are at least acceptable scientific evidences suggesting that the potential risks of such medical practice outweigh its potential benefits
	Clinicians should not routinely perform such medical practice on asymptomatic patients
Grade I recommendation	Such medical practice lacks scientific evidence, or its evidences are of low quality or conflict with each other, such as the inability to measure and evaluate risks
	Clinicians should help patients understand the uncertainty of such medical practice

Table S3 Cheng's classification of portal vein tumor thrombus

Typing	Description
I_0	Tumor thrombus under the microscope
I	Tumor thrombus invades the portal vein branch of liver lobe or hepatic segments
II	Tumor thrombus invades the left and right branches of portal vein
III	Tumor thrombus invades to main portal vein
IV	Tumor thrombus invades to the superior mesenteric vein

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Table S4 Child-Pugh grading

Clinical biochemical indicators	Score 1	Score 2	Score 3
Hepatic encephalopathy (grade)	None	1–2	3–4
Ascites	None	Mild	Moderate and severe
Bilirubin (μmol/L)	<34	34–51	>51
Albumin (g/L)	>35	28–35	<28
Increased prothrombin time (second)	<4	4–6	>6

Table S5 BCLC staging classification

BCLC staging	Behavioral status	Tumor status	Liver function status
0 (the earliest stage)	0	Single tumor ≤2 cm	Normal bilirubin, without portal hypertension
A (early stage)			
A1	0	Single tumor ≤5 cm	Normal bilirubin, without portal hypertension
A2	0	Single tumor ≤5 cm	Normal bilirubin, with portal hypertension
A3	0	Single tumor ≤5 cm	Abnormal bilirubin, with portal hypertension
A4	0	3 tumors ≤3 cm	Child-Pugh A-B
B (middle stage)	0	Multiple or single tumor >5 cm	Child-Pugh A-B
C (advanced stage)	1–2 points	Vascular invasion or metastasis	Child-Pugh A-B
D (end stage)	3–4 points	Any tumor	Child-Pugh C

BCLC, Barcelona Clinic Liver Cancer.

Table S6 Catheter and microsphere matching

Calibration range	Matching catheter
DC Bead M1 70–150 μm	1.8–2.0 Fr
DC Bead 100–300 μm	2.2–2.4 Fr
DC Bead 300–500 μm	2.4–2.7 Fr
DC Bead 500–700 μm	≥2.7 Fr

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