

Produced under an educational grant from CeloNova BioSciences, Inc.

40- μm Tightly Calibrated Embozene™ Color-Advanced Microspheres

New technical and clinical possibilities in transarterial embolization of liver tumors:
Bland and microsphere-enhanced chemoembolization.

Transarterial chemoembolization (TACE) and transarterial embolization (TAE or “bland” embolization) have shown to be effective in improving survival in both primary and secondary liver tumors. The physician choice of TAE versus TACE, including the use of drug-charged microspheres, remains controversial as to any significant differences in survival rates. Regardless of the treatment modality chosen, there seems to be a general agreement on the following scientific and technical concepts:

- Liver tumors, primary and metastatic, are mainly or exclusively fed by arteries, making transarterial therapeutic delivery of chemotherapy and/or embolization devices possible. Portal flow rarely feeds these tumors directly.
- The mechanism of action of TAE is through tissue ischemia and necrosis.
- Classic chemoembolization acts primarily through a chemotherapeutic mechanism.
- The possibility to combine TACE with an embolization device, by closing the vessels with it at the end of the procedure, conceptually attempts to combine the effects of both techniques (chemotherapy and necrosis) and is at times referred to as *particle-enhanced TACE*.
- When the treatment goal is *lesion* devascularization, super-selective embolization may lead to complete tumor devascularization. A more distal embolization leads to better outcomes.
- When the treatment goal is *liver or lobe* devascularization, proximal embolization is desired to reach the blood circulation of the entire liver or lobe.
- Technically, the materials being injected need to permit preservation of the vasculature (this is a concern with chemoembolization) and to keep the main access vessels to the tumor patent so that any subsequent necessary procedures are possible if needed. This was not possible with



Figure 1. 100- μm Embozene™ Microspheres (orange) and 40- μm super-selective Embozene™ Microspheres (black).

older embolic agents that clumped and aggregated and occluded the main feeders of the tumor.

- Pulmonary shunts must be carefully detected and excluded when microspheres of $<100\ \mu\text{m}$ are being used.
- The least damage possible should be done to healthy liver tissue surrounding the tumor, especially if the liver being treated is already damaged and cirrhotic.
- Inflammation is not desired.

The introduction in 2006 of Embozene™ Microspheres (CeloNova BioSciences, Inc., Newnan, GA) brought added value to liver treatment and made proper treatment delivery possible, whether it is super-selective embolization, anti-inflammatory bland embolization, or particle-enhanced chemoembolization (Figure 1).

Embozene™ Color-Advanced Microspheres are the spherical embolic platform for today and for the future. Implanted in thousands of European patients for more than two years now, Embozene™ Microspheres have been engineered so that each parameter that is relevant to an embolization sphere is optimized. These parameters are: biocompatibility,

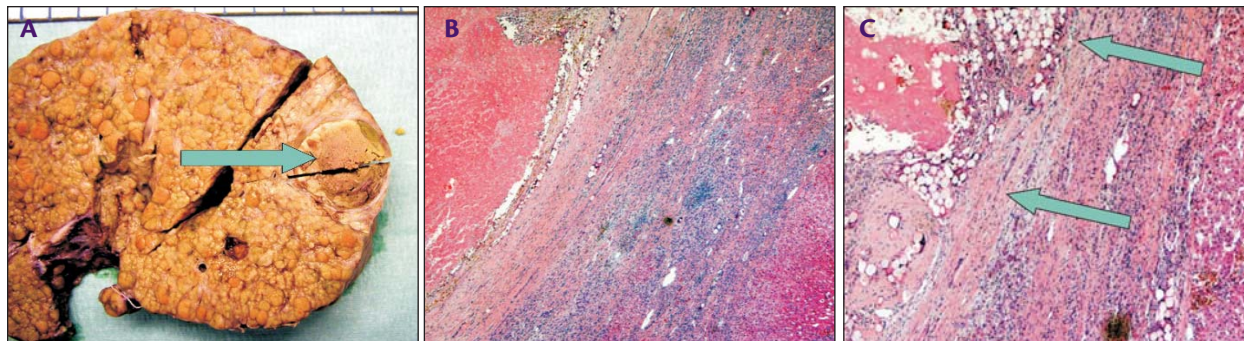


Figure 2. Complete necrosis of liver tumor found after liver transplant (A). No inflammatory reaction around Embosphere™ Microspheres (B). No collateral damage to the surrounding liver (C).

calibration, suspension, and microsphere integrity.

This article provides an examination of how each of these features is relevant to embolization of liver tumors with 40- μm Embosphere™ Microspheres, in both bland as well as particle-enhanced TACE technique, regardless of the treatment choice.

BIOCOMPATIBILITY

Embosphere™ Microspheres are composed of a hydrogel core and coated with Polyzene®-F, which is anti-inflammatory, bacterial-resistant, and does not allow platelet adhesion or activation. In liver tumors, it has been shown that posttreatment inflammation may lead to post-TAE/TACE residual tumor growth factors (eg, VEGF, EGFR, IL-8, TGF- α). Therefore, there is a need to avoid inflammatory reactions, and, among all embolization devices available, this is only possible with Embosphere™ Color-Advanced Microspheres because they are coated with Polyzene®-F.

CALIBRATION

Giving the highest degree of confidence, granulometry studies ensure that 40- μm Embosphere™ Microspheres are calibrated to $\pm 10 \mu\text{m}$. This is the appropriate size for the target vessels of liver tumors, and such a precise range is only available with Embosphere™ Microspheres. The fact that there are no microspheres lying outside this size range gives full confidence to the user and allows for deep intratumoral, intravascular penetration, while leaving the main feeders patent. Better tumor control outcomes are achieved when the embolization reaches as distally as possible into the tumor bed. If pulmonary shunts are detected, upsizing to 100 μm ($\pm 25 \mu\text{m}$) tightly calibrated Embosphere™ Microspheres is advised, and precise calibration gives confidence that these shunts will be avoided. Studies have also shown that the precise calibration of Embosphere™ Microspheres ensures that no collateral damage is done to the healthy surrounding tissue, while ensuring complete tumor necrosis.

SUSPENSION

The vascular pattern inside the liver lesions, depending on the size of the vessels, density, and presence of arteriovenous shunts, may influence the blood flow resistance and, therefore, the flow speed to the tumor. The ability to control the rate of injection and the endpoint is essential in such small vessels. The exceptionally durable suspension of Embosphere™ Microspheres frees the operator from the need to vigorously shake the spheres before injection, unlike with other spherical and nonspherical particles. This gives the operator complete control over the rate of injection.

MICROSPHERE INTEGRITY

Embosphere™ Microspheres do not fragment or deform in the solution during injection or after settling in the target vessel. This allows a high correlation between the diameter of the sphere used and the size of the target vessel being embolized.

CONCLUSION

Clinical experience with TAE in liver cancer and liver metastases, and with particle-enhanced TACE using tightly calibrated 40- μm Embosphere™ Color-Advanced Microspheres, shows that precise, selective, and superselective, transarterial chemoembolization and bland embolization are feasible. The Embosphere™ Microspheres penetrate into the liver tumor bed and cause deep and complete necrosis even in hypovascular lesions (eg, metastases) without causing inflammation and without collateral damage to the surrounding healthy tissue, while leaving the access vessel patent (Figure 2).

The vehicle has been proven to work. Possible future applications could be related to the ability of Polyzene®-F to elute drugs, hormones, biologicals, or other agents. Embosphere™ Color-Advanced Microspheres are the platform for today and for the future. ■