Radiopaque Microspheres for Improved Transarterial Chemical Embolization of Tumors.

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Introduction. TACE aims at blocking the feeding artery of a solid tumor and subsequent local release of drugs, to shrink the size of the tumor. The interventional radiologist injects the microspheres via a catheter into the feeding artery of a tumor (figure 1). This treatment is often applied for the minimal-invasive treatment of hepatocellular carcinomas, or of uterine fibroids in women.[1,2] The ultimate aim is to shrink the tumor without damage to the surrounding tissue, i.e. to conserve as much liver function as possible or to conserve the uterus respectively.

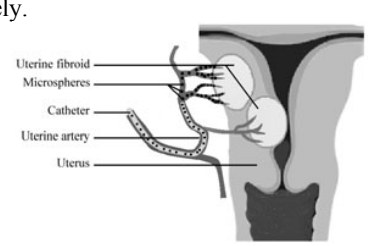

Figure 1. Scheme of the embolization of a uterine fibroid, a solid tumor of the uterus wall.

The commercially available embolization microspheres are composed of poly(vinylalcohol) (Contour SE, Bead Block, DC beads) or tris-acryl-gelatin (Embosphere). These are solid, hydrophilic spheres that are available in a wide range of sizes, and can be loaded with the anti-tumor drug doxorubicin (DC Bead).[3] The tumor is thus attacked in two ways: 1) by blocking arterial blood flow and 2) local release of doxorubicin. Microspheres used for uterine fibroid embolization are loaded with ibuprofen to combat post-operative pain.
Commercial embolization microspheres have some disadvantages namely they are radiolucent, i.e. X-ray invisible, and they have limited drug-loading capacity, and often suffer of premature release of drug (before and during the procedure). Here we present preliminary data on a range of new microspheres that combine radiopacity, i.e. X-ray visibility, with increased drug loading capacity and temperature induced drug release.

Methods. Microspheres were prepared by suspension polymerization as described earlier.[4] Radiopacity of the microspheres was caused by the incorporation of the iodine containing monomer 2-[4-iodobenzoyloxy]-ethyl methacrylate (4IEMA).[4] In order to obtain porosity, the monomer mixture was supplemented with pMMA dissolved in toluene, before polymerization of the microspheres. The pMMA could be dissolved from the solid microspheres, resulting in microporosity.[5] Microspheres were loaded with rhodamine or doxorubicin by soaking, which resulted in complete filling of the spheres. Release from individual spheres was determined in phosphate-buffered-saline (pH7.4) or fetal-bovine-serum (FBS).

Results. The synthesis of radiopaque, hydrophilic microspheres was successful. The spheres displayed fine porosity as can be seen from figure 2. Radiopacity of the microspheres was confirmed by X-ray fluorimetry.

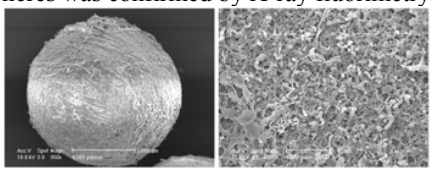

Figure 2. SEM images of a porous microsphere (left) and a close-up of the surface(right). The microporosity of the sphere is clearly visible.

The microspheres could be easily filled with rhodamine or doxorubicin. The release-profile was dependent on the medium in which the experiment was performed. Release in serum was faster than when determined in buffer. The release profiles of the drugs demonstrate an initial burst release followed by a slow release for up to at least 48 hours.

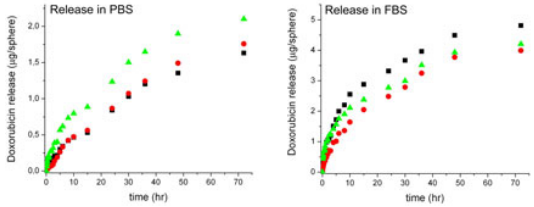

Figure 3. doxorubicine release from individual microspheres in PBS (left) or FBS(right).

Since doxorubicin has limited (thermo)stability, release for more than 2 days is probably not effective. The porosity of these microspheres increased the drug-loading capacity 2- to 3-fold, as compared to the published data for the doxorubicin containing DC beads.[6] The application of a coating around the micrpsheres allowed for temperature-sensitive drug release. At ambient temperature no release was observed, but at 37ºC the coating dissolved and drug was released.

Conclusions. The here presented radiopaque, porous microspheres can be used to improve some of the shortcomings of the currently used embolic particles in TACE. The traceability of the spheres during and after the embolisation, combined with increased drug-loading capacity, can make this procedure safer and more efficient. The next step will be to assess the performance of these microspheres in vivo in an animal tumor model.

References.

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