EFFICACY OF ^{177}LU- AND ^{90}Y-LABELED NANOPARTICLES IN TARGETED TUMOR THERAPY IN A MOUSE CT26 AND 4T1 XENOGRAFT MODEL

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Nanoparticle delivery to solid tumors after an intravenous injection has shown to be very limited in its ability to achieve therapeutic dosage in the tumor due to nonspecific nanoparticle uptake by RES. To overcome these problems, local intratumoral injection of nanoparticles is being investigated as more relevant route of administration. In the present study, superparamagnetic iron oxide nanoparticles (SPIONs) were synthetized, coated with citric (CA) or dimercaptosuccinic acid (DMSA) and radiolabeled with ^{90}Y or ^{177}Lu, aiming to develop radioactive nanoparticles for localized tumor therapy. Biodistribution and antitumor efficacy of radiolabeled SPIONs after local intratumoral administration in CT26 or 4T1 xenografts-bearing BALB/c mice were studied. Tracking the radioactivity distribution of injected ^{90}Y-CA-SPIONs and ^{177}Lu-DMSA-SPIONs revealed that due to the size of the nanoparticles, their diffusive escape from the tumor into healthy organs and tissues is slowed down; the particles remain at the injection site up to 14 days after the injection, and thereby increasing the tumor's exposure to radiation. Lower therapeutic efficacy of ^{177}Lu-DMSA-SPIONs in CT26 or 4T1 tumor can be explained by slight diffusion of particles from injection sites into distant tumor regions and moderate-energy β-particles emitted by ^{177}Lu (0.5MeV). These studies suggest that ^{90}Y-CA-SPIONs is superior to ^{177}Lu-DMSA-SPIONs at inhibiting both tumors growth, due to the high-energy β-particles emitted by ^{90}Y (2.27MeV) and a longer path length.^{90}Y is therapeutically superior to ^{177}Lu in investigated xenograft models. We believe that an intratumorally injected radiolabeled SPIONs can be considered as a potential therapeutic agent for localized cancer therapy.

EFIKASNOST ^{177}LU- I ^{90}Y-OBELEŽENIH NANOČESTICA U CILJANOJ TERAPIJI TUMORA NA MODELU MIŠJIH CT26 I 4T1 KSENOGRAFTA

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Prethodna istraživanja su pokazala da se intravenskim načinom aplikacije nanočestica ne postiže zadovoljavajuća terapijska doza u solidnim tumorima, zbog nespecifičnog preuzimanja nanočestica od strane retikuloendotelnog sistema. Da bi se prevazišli ovi problemi, smatra se da je intratumorski način aplikacije pogodniji način primene nanočestica u terapiji solidnih tumora. Sa ciljem da se razvije radiofarmaceutik za lokalizovanu terapiju tumora, u ovim ispitivanjima, superparamagnetne nanočestice oksida gvožđa (SPION) su sintetisane, površinski obložene limunskom (CA) i dimerkaptoćilibarnom (DMSA) kiselinom i radioobeležene sa ^{90}Y i ^{177}Lu. Posebna pažnja je posvećena ispitivanjima distribucije i antitumorske efikasnosti radioaktivno obeleženih SPIONa nakon lokalne intratumorske primene u ksenografte indukovane supkutanim injekcijama CT26 i 4T1 ćelija BALB/c miševima. Praćenje distribucije intratumorski injektovanih ^{90}Y-CA-SPION-a i ^{177}Lu-DMSA-SPION-a je pokazalo da je zbog veličine nanočestica njihova migracija iz tumorskog tkiva u zdrave organe i tkiva usporena, pa čestice ostaju na mestu ubrizgavanja do 14 dana, čime se značajno povećava izloženost tumora zračenju. Niža terapijska efikasnost ^{177}Lu-DMSA-SPION-a u CT26 ili 4T1 tumorima se može objasniti slabom migracijom čestica sa mesta aplikacije do udaljenih tumorskih ćelija kao i kratkim dometom u tkivu β^- čestica koje emituje ^{177}Lu zbog energije zračenja od 0,5MeV. Ova ispitivanja su pokazala da je ^{90}Y-CA-SPION značajno efikasniji od ^{177}Lu-DMSA-SPION u inhibiciji rasta obe vrste tumora, zbog visokoenergetskih β^- čestica koje emituje ^{90}Y (2,27MeV) i većeg dometa u tkivu. ^{90}Y je terapeutski superiorniji od ^{177}Lu u istraživanim modelima ksenografta. Mišljenja smo da se intratumorski primenjeni radioaktivno obeleženi SPION-i mogu smatrati potencijalnim terapijskim agensom za lokalizovanu terapiju solidnih, inoperabilnih i teško dostupnih tumora.