Abstract:
We recently demonstrated tumor-selective iodide uptake and therapeutic efficacy of radioiodine in neuroblastoma tumors after systemic nonviral polyplex-mediated sodium iodide symporter (NIS) gene delivery. In the present study, we used novel polyplexes based on linear polyethylenimine (LPEI), polyethylene glycol (PEG), and the synthetic peptide GE11 as an epidermal growth factor receptor (EGFR)-specific ligand to target a NIS-expressing plasmid to hepatocellular carcinoma (HCC) (HuH7). Incubation of HuH7 cells with LPEI-PEG-GE11/NIS polyplexes resulted in a 22-fold increase in iodide uptake, which was confirmed in other cancer cell lines correlating well with EGFR expression levels. Using (123)I-scintigraphy and ex vivo \(\gamma\)-counting, HuH7 xenografts accumulated 6.5-9% injected dose per gram (ID/g) (123)I, resulting in a tumor-absorbed dose of 47 mGray/Megabecquerel (mGy/MBq) (131)Iodide ((131)I) after intravenous (i.v.) application of LPEI-PEG-GE11/NIS. No iodide uptake was observed in other tissues. After pretreatment with the EGFR-specific antibody cetuximab, tumoral iodide uptake was markedly reduced confirming the specificity of EGFR-targeted polyplexes. After three or four cycles of polyplex/(131)I
application, a significant delay in tumor growth was observed associated with prolonged survival. These results demonstrate that systemic NIS gene transfer using polyplexes coupled with an EGFR-targeting ligand is capable of inducing tumor-specific iodide uptake, which represents a promising innovative strategy for systemic NIS gene therapy in metastatic cancers.