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The uptake of soluble and nanoparticulate imaging isotope in model liver tumours after intra-venous and intra-arterial administration

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Delivery of chemotherapeutic drugs to tumours by reformulation as nanoparticles has often been proposed as a means of facilitating increased selective uptake, exploiting the increased permeability of the tumour vasculature. However realisation of this improvement in drug delivery in cancer patients has met with limited success. We have compared tumour uptake of soluble Tc99m-pertechnetate and a colloid of nanoparticles with a Tc99m core, using both intra-venous and intra-arterial routes of administration in a rabbit liver VX2 tumour model. The radiolabelled nanoparticles were tested both in untreated and cationised form. The results from this tumour model in an internal organ show a marked advantage in intra-arterial administration over the intra-venous route, even for the soluble isotope. Tumour accumulation of nanoparticles from arterial administration was augmented by cationisation of the nanoparticle surface with histone proteins, which consistently facilitated selective accumulation within microvessels at the periphery of tumours.

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1. Introduction

The growth of a tumour in a host organ is accompanied by angiogenesis that not only markedly changes the architecture of the vascular network [1–3], but also considerably increases access to the extravascular space due to the increased permeability of the new vessels [4]. This provides opportunity for improvement in delivery of chemotherapeutic agents by reformulation into nanoparticulate composites that can extravasate into tumours [5].

Nanoparticles tend to be rapidly removed from the circulation by the phagocytic cells resident in the liver and spleen (reticuloendothelial system; RES), but it has been suggested they can also escape through the highly fenestrated walls of tumour capillaries and distribute within the tumour matrix [6]. Extravasation of macromolecules into tumours has been known for many years, visualised earlier for example by increased dye uptake [7], and this has become known as the enhanced permeability and retention (EPR) effect [8]. Thus it is the object of much current research to exploit tumour EPR by administration of nanoparticulate formulations of cytotoxic agents [9,10]. It should be noted however that while most preclinical studies have been done in animal models of subcutaneously implanted tumours, data on extravasation, penetration and accumulation of nanoparticles in tumours of internal organs, like many of those cancers occurring in human patients, is especially lacking. In this context, it is also important to explore different routes of administration, especially intra-arterial instillation.

In this report we have investigated tumour uptake of imaging radioisotope in the form of a soluble compound (Tc99m-pertechnetate) and compared this with uptake of a nanoparticulate isotope

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preparation. Further, we have performed these imaging investigations in a rabbit tumour model of liver cancer, where we could study biodistribution inside this internal organ after intravenous and intra-arterial administration of both types of agents.

2. Materials and methods

2.1. Nanoparticle synthesis

Carbon-caged Tc-99m, (FibrinLite; FL) was synthesised as described in detail in US patent 8,778,300 [11]. The nanoparticle technology employed was based on Technegas™, a radioactive aerosol preparation developed for diagnostic ventilation imaging of the lungs [12]. Vapour-phase particle sizing using an electrostatic particle classifier (TSI Inc, MN USA) showed the aerosol comprises log-normal distributed particles with the bell curve centred on 150–350 nm, and negligible particles below 100 nm or above 400 nm. Electron microscope characterisation shows metallic platelets surrounded by multiple lamellae of carbon [13]. Using the patented FL process, sodium Tc99m-pertechnetate solution was loaded into a graphite crucible and after removing sodium chloride by sublimation at 1650°C, the isotope was plasma ablated at 2750°C into an argon gas stream. Aerosol nanoparticles were collected into water (6.0 mL) from the gas stream using a Browitt sonicating precipitator [14], thus producing a stable colloidal dispersion of FL. The radioactive FL colloid was filtered through a 450 nm hydrophilic membrane (mixed cellulose ester (MCE); Millipore) before use. A typical preparation of FL contained approximately 5 μg/mL of graphitic carbon with a specific activity of 20 MBq/μg. FL nanoparticles are highly stable, and integrity of the isotope encapsulation is preserved under standard autoclave conditions of 20 min at 120°C.

2.1.1. Coating of FL with polycations

We have previously shown using a membrane filtration model and microwell binding assays that polycations such as polylysine bind to the surface of FL with high affinity [15]. We have proposed [15] that this is mediated by multi-site pi-cation interactions [16,17] between the positively charged amino groups of the amino acid side-chains and the pi-electrons of the planar carbon rings of the graphite surface. The histone family of proteins are also polycations due to a high content of arginine and lysine residues [18] and binding of these proteins to FL can only be reversed with strong ionic detergents such as sodium dodecyl sulphate [19]. Binding of these polycations to FL is also stable under in vivo conditions, as shown by our previous imaging studies of polycation coated FL in the capillary network of rabbit lungs [15,19].

In the present study, FL was treated with a selection of polycations, including protamine sulphate (PS; 20 μg/mL), poly-D-lysine (PDL; 6 μg/mL) and calf thymus histone proteins (CTH; 10 μg/mL), all from Sigma Aldrich, Castle Hill, Sydney. FL was buffered with 0.5 mM Tris acetate buffer (pH 7.2) before addition of polycations, which were then allowed to bind for 1 h at 20°C before use of the coated FL preparations in animal imaging experiments.

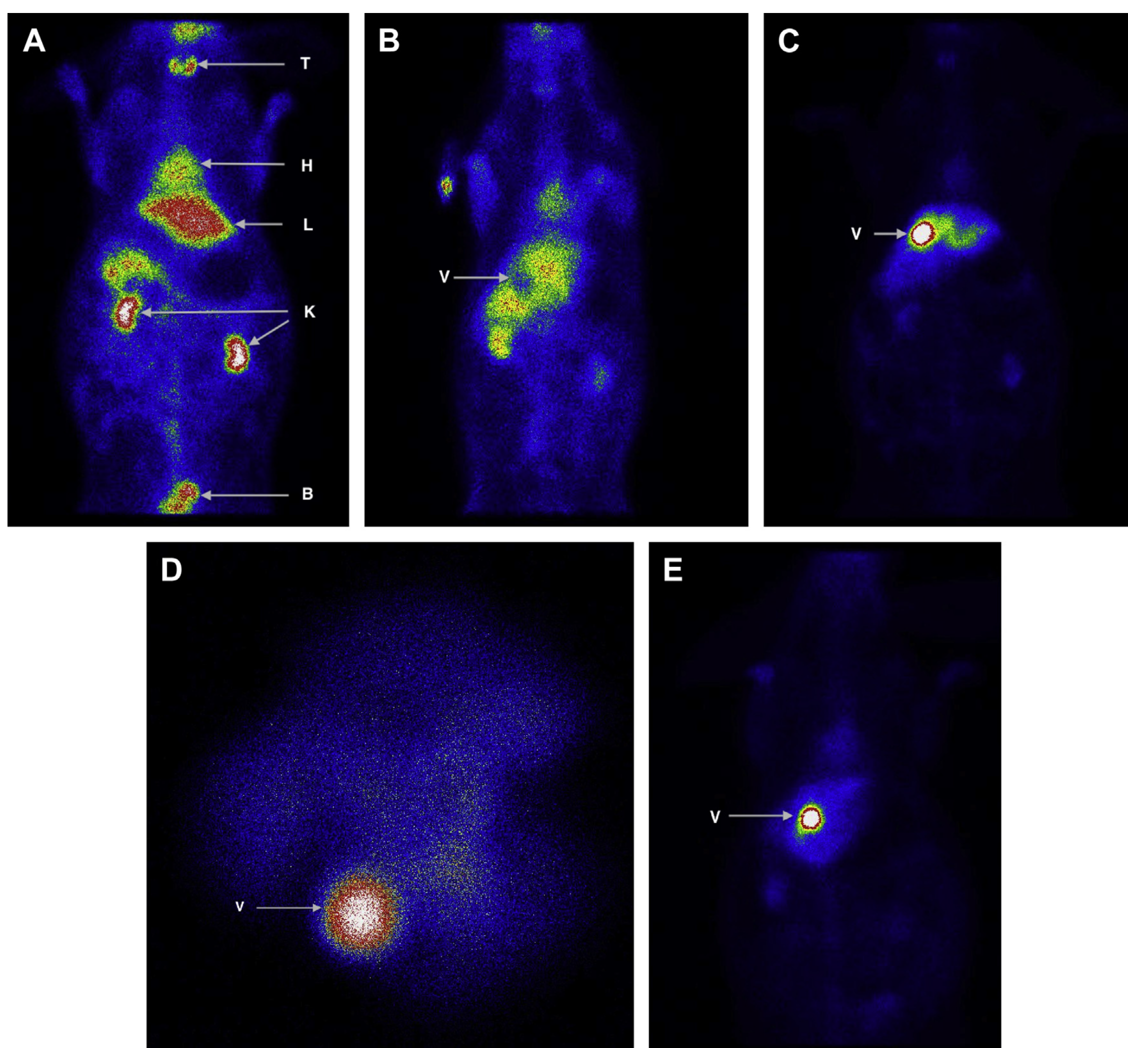

Fig. 1. Tc99m-pertechnetate biodistribution in normal rabbits and in rabbits with VX2 tumour implants. The gamma camera images show radioisotope activity in the liver of a normal rabbit (Fig. 1A) and livers of rabbits hosting a VX2 implant (Fig. 1B–E), 1 h after administration of Tc99m-pertechnetate (130 MBq) by intra-venous injection (3 mL; Fig. 1A and B) or intra-arterial instillation (5 mL; Fig. 1C–E). Organs in Fig. 1A are labelled as thyroid (T), heart (H), liver (L) kidneys (K) and bladder (B). Note the negative image of the VX2 tumour (indicated by V) in the liver in Fig. 1B, and compare with the positive imaging of the tumour (V) in the intact rabbit in Fig. 1C, and in the excised liver from Fig. 1C shown in Fig. 1D. Positive imaging of the tumour in a rabbit by intra-arterial Tc99m-pertechnetate was not abolished (V in Fig. 1E) by prior intra-venous injection of sodium perchlorate (3 mg/kg), an inhibitor of the active transport of iodide and pertechnetate [22]. Images were acquired with a GE Hawkeye Infinia gamma camera.

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