Supporting Information

Gram-scale synthesis of neodymium chelate as a spectral CT and second near-infrared window imaging agent for visualizing gastrointestinal tract in vivo

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Experiment Section

Chemicals and Materials

All chemicals are of analytical reagent grade. Nd_2O_3, La_2O_3, Gd_2O_3, Er_2O_3, Lu_2O_3, Indocyanine green (ICG), Diethylenetriaminepentaacetic acid (DTPA), NaOH, $NdCl_3 \cdot 6H_2O$, Xylenol orange (XO), and Iohexol were brought from Aladdin Reagent (Shanghai, China). Pure water was provided by Hangzhou Wahaha Group Co. Ltd. (Hangzhou, China). Cell counting kit-8 (CCK8) was bought from DOJINDO Laboratories (Shanghai, China). Dulbecco's Modified Eagle's Medium (DMEM) was provided by Gibco (Thermo Scientific, China).

Characterization

The content of the Nd element in Nd-DTPA was measured by inductively coupled plasma-optical emission spectroscopy (ICP-OES, Thermo Ele-mental, USA). The absorption spectra of $NdCl_3$, DTPA, and Nd-DTPA were recorded by a UV-vis-NIR spectrophotometer (UV-3600 plus, Japan). The molecular mass of Nd-DTPA without NaOH adjustment was characterized using the high-resolution mass spectrum (HR-MS). Fourier transform infrared (FTIR) spectra of Nd-DTPA and DTPA were obtained by a Nicolet iS10 spectrometer (Thermo Scientific, USA). The NIR II fluorescence spectra of Nd-DTPA and $NdCl_3$ were recorded on a Photoluminescence Spectrometer (Edinburgh FLS980, UK). The fluorescence quantum yield of Nd-DTPA in water was measured by using the IR-26 dye (QY=0.5%) in 1,2-dichloroethane (DCE) as a reference. Different thicknesses (2 mm, 3 mm, 4 mm, 5 mm) of chicken was used to evaluate the tissue penetration depth of Nd-DTPA (0.5 M). The biodistribution and metabolism of Nd in the vital organs (heart, liver, spleen, lung, kidney, stomach, intestine, and colon) after oral administration of Nd-DTPA by inductively coupled plasma mass spectrometry.

NIR II fluorescence imaging system

A home-made animal NIR II imaging system fitted out thermoelectric cooled InGaAs camera (Model: NIRvana™ Camera System, operating temperature: -80 °C, Princeton Instruments) and fiber-coupled MDL-H 808 lasers were used for NIR II imaging. The fluorescence signal was detected by the camera (exposure time: 200 ms) installed with an 808 nm laser (excitation power density of 1 W/cm^2) as a light source and filtered by a 1250 nm long-pass filter. The images were acquired by LightField® on the computer and analyzed by ImageJ.

Supporting Figures

Fig. S1 Gram-scale synthesis of Nd-DTPA via a green and mild method through the reaction of Nd_2O_3 and DTPA.

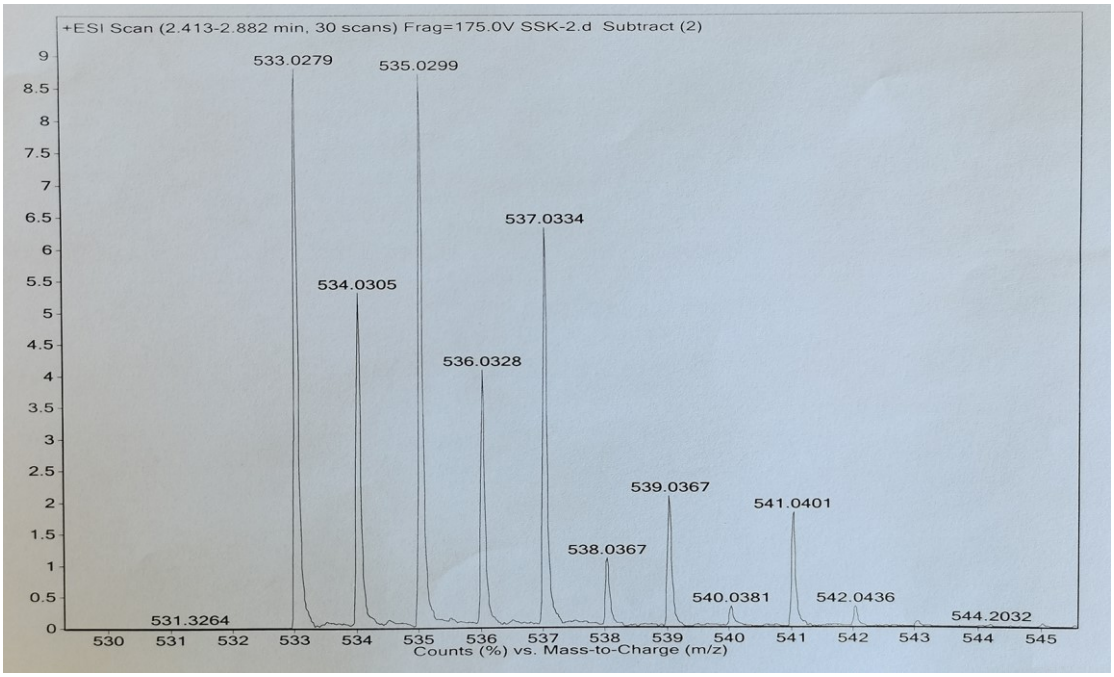

Fig. S2 HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{21}N_3O_{10}Nd$: 533.0299; found 533.0279.

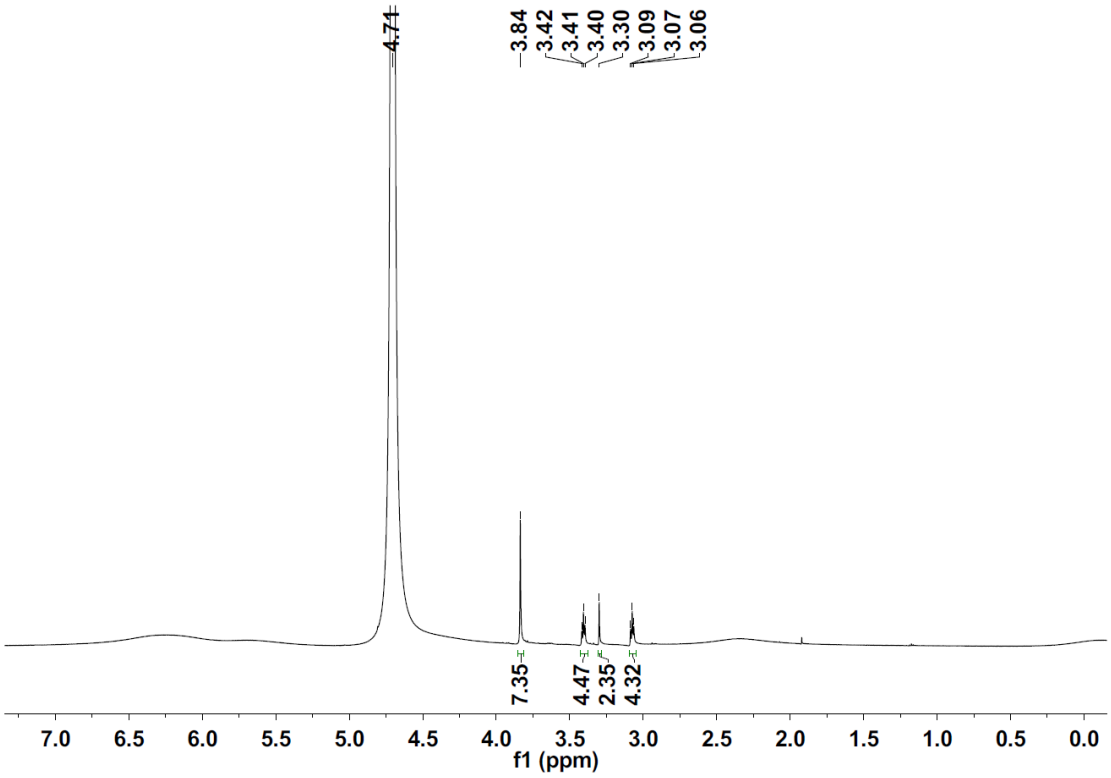

Fig. S3 ^{1}H NMR spectrum of Nd-DTPA. ^{1}H NMR (600 MHz, D_2O) δ 3.84 (s, 1H), 3.41 (t, J = 6.7 Hz, 1H), 3.30 (s, 1H), 3.07 (t, J = 6.7 Hz, 1H).

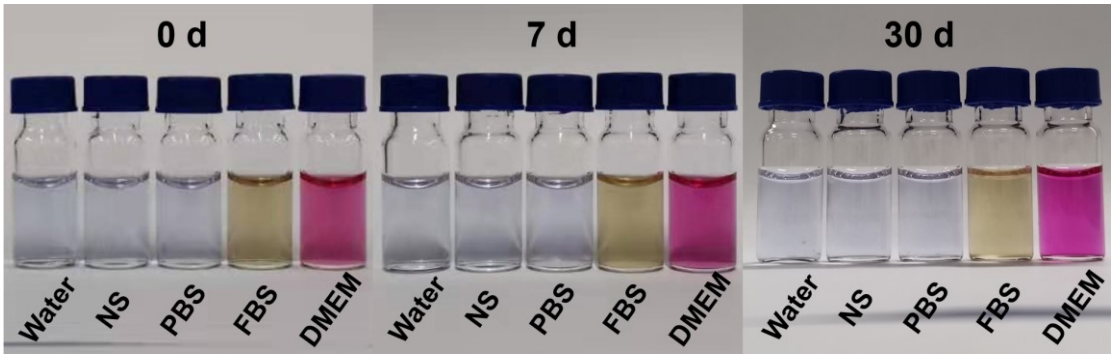

Fig. S4 Solution stability (0, 7, and 30 d) studies of Nd-DTPA. Dissolving Nd-DTPA (0.5 M) in water, saline solution (NS), PBS, FBS and DMEM for 30 d at room temperature.

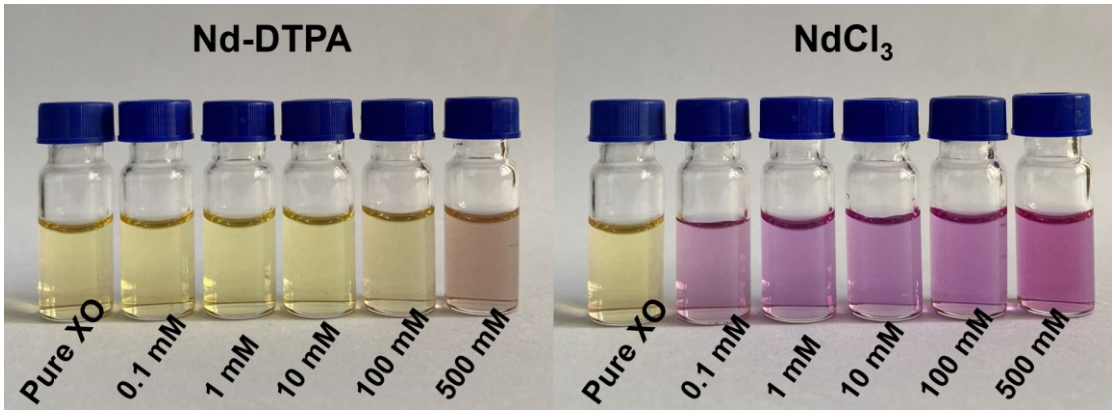

Fig. S5 Detecting the leakage of Nd^{3+} in Nd-DTPA (left) and $NdCl_3$ (right) in HAc-NaAc buffer solution (pH=5) by using the XO indicator. The concentration of Nd-DTPA and $NdCl_3$ from left to right is 0.1, 1, 10, 100, and 500 mM (the first bottle contains pure 0.2% XO solution).

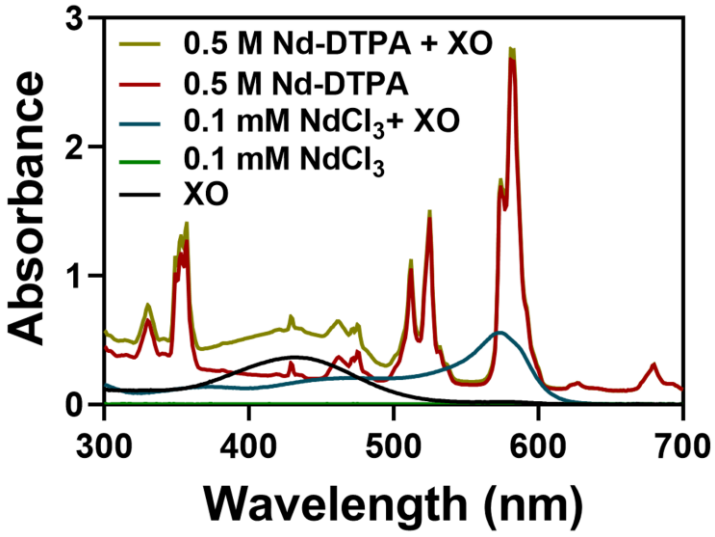

Fig. S6 The UV-vis-NIR absorption spectra of pure XO, $NdCl_3$, and Nd-DTPA solution.

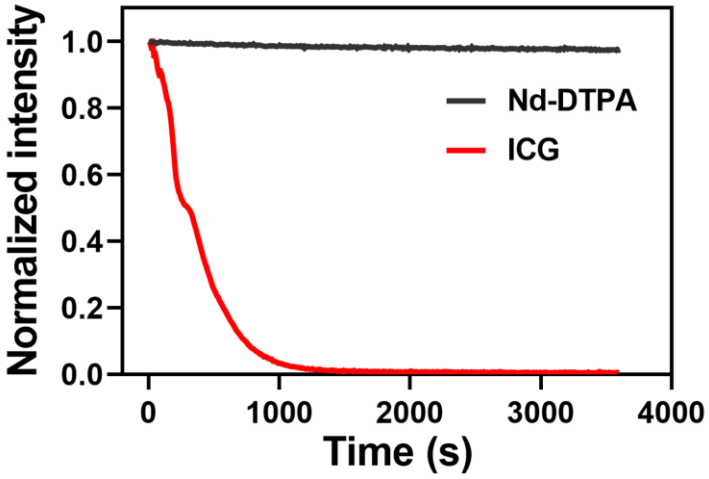

Fig. S7 The photostability curve of Nd-DTPA and ICG solution measured by a fiber optical spectrometer under excitation of 808 nm laser (laser power density of 1 W/cm^2) for 60 min.

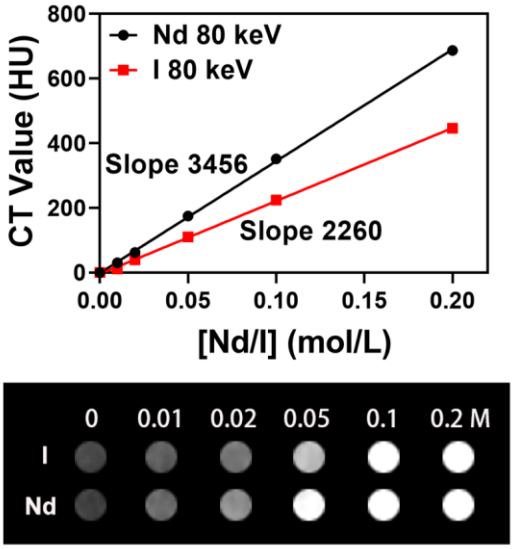

Fig. S8 Spectral CT HU curves and images of Nd-DTPA and iohexol with different concentrations (0.01, 0.02, 0.05, 0.1, and 0.2 M Nd or I) at 80 keV.

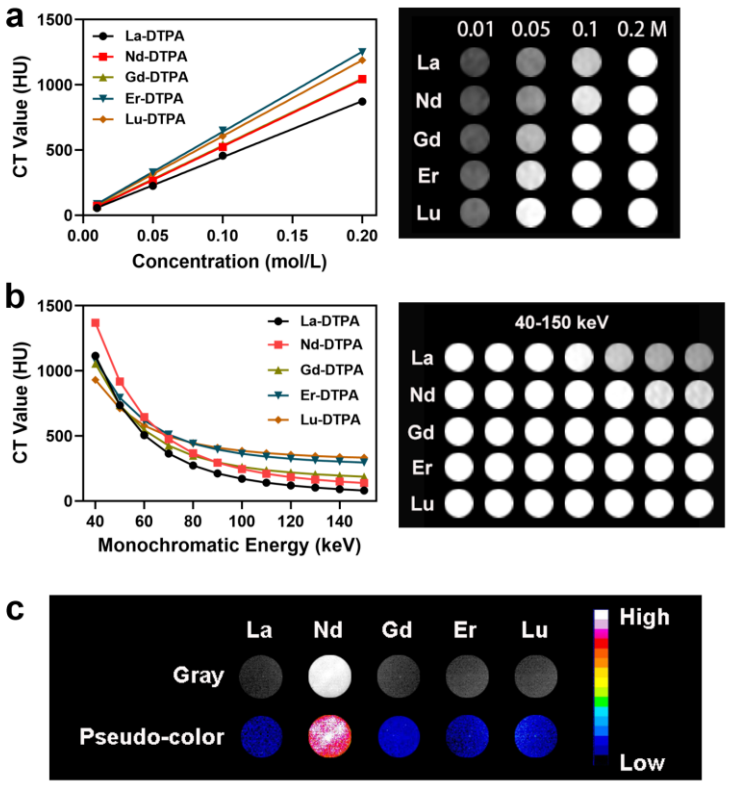

Fig. S9 (a) HU curves and CT images of La-DTPA, Nd-DTPA, Gd-DTPA, Er-DTPA and Lu-DTPA with different concentrations (0.01, 0.05, 0.1, and 0.2 M) at 120 kV. (b) Spectral CT HU curves and images of La-DTPA, Nd-DTPA, Gd-DTPA, Er-DTPA and Lu-DTPA (0.1 M) at different mono-chromatic energies. (c) The NIR II fluorescence images of La-DTPA, Nd-DTPA, Gd-DTPA, Er-DTPA and Lu-DTPA (0.1 M).

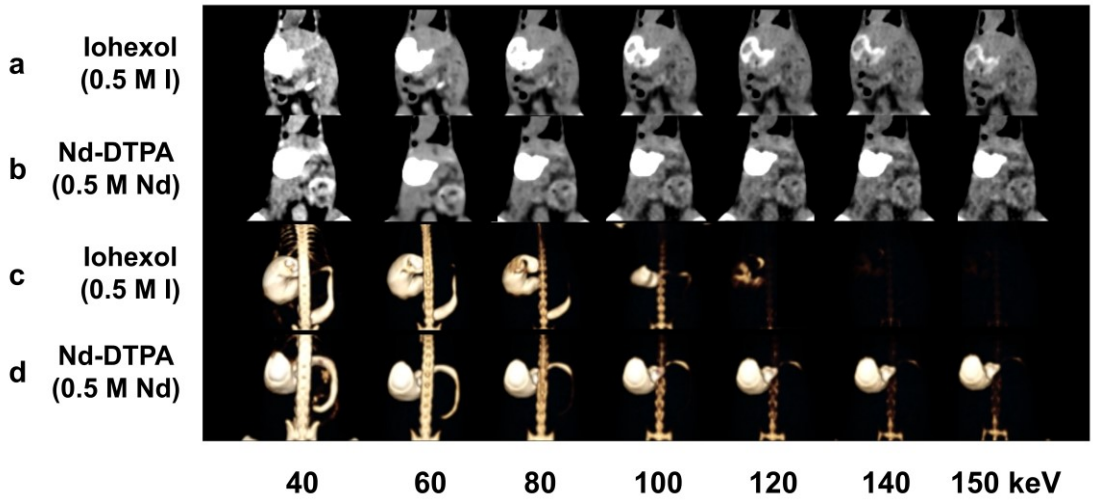

Fig. S10 Spectral CT imaging of stomach at 5 min after oral administration of Nd-DTPA or iohexol (0.5 M Nd/I) (tube voltage 90/150 Sn). (a) Coronal CT imaging using iohexol at different monochromatic energies. (b) Coronal CT imaging using Nd-DTPA at different monochromatic energies. (c) 3D reconstruction images using iohexol at different monochromatic energies. (d) 3D reconstruction images using Nd-DTPA at different monochromatic energies.

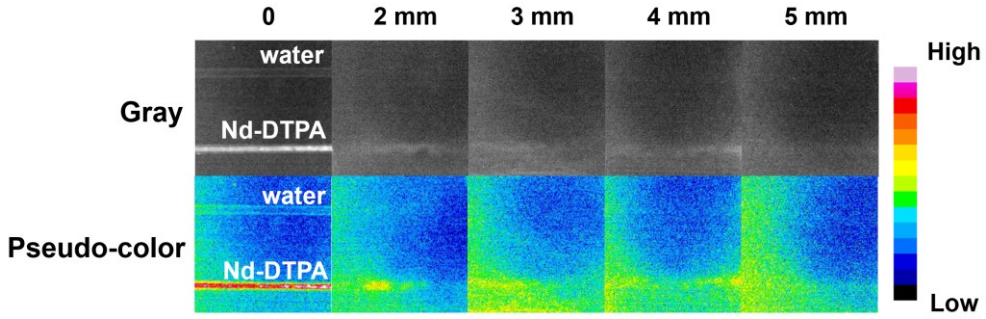

Fig. S11 In vitro NIR-II fluorescence images (grayscale and pseudo-color) of Nd-DTPA (0.3 M) and water covered with different thicknesses (0 mm, 2 mm, 3 mm, 4 mm, 5 mm) of chicken for measuring the tissue penetration depth.

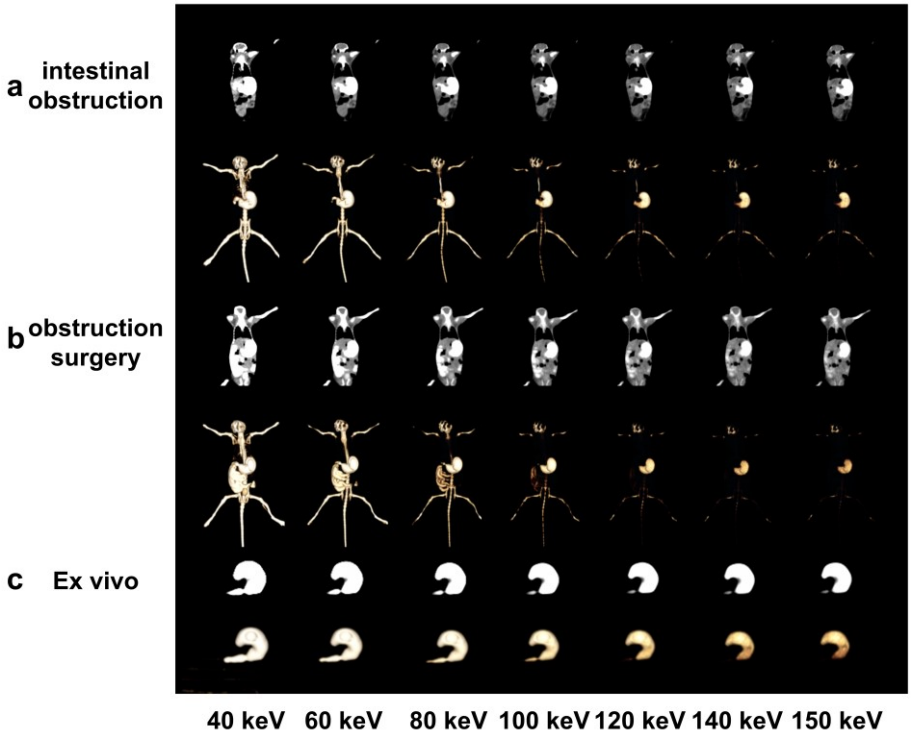

Fig. S12 Spectral CT imaging of intestinal obstruction after oral administration of Nd-DTPA (400 μL, 0.5 M) (tube voltage 90/150 Sn). (a) Coronal CT and 3D reconstruction imaging of intestinal obstruction at 30 min after gavage at different monochromatic energies. (b) Coronal CT and 3D reconstruction imaging of intestinal obstruction at 90 min after surgery at different monochromatic energies. (c) Coronal CT and 3D reconstruction imaging of ex vivo of the GI tract in mice with intestinal obstruction (30 min after gavage) in different monochromatic energies.

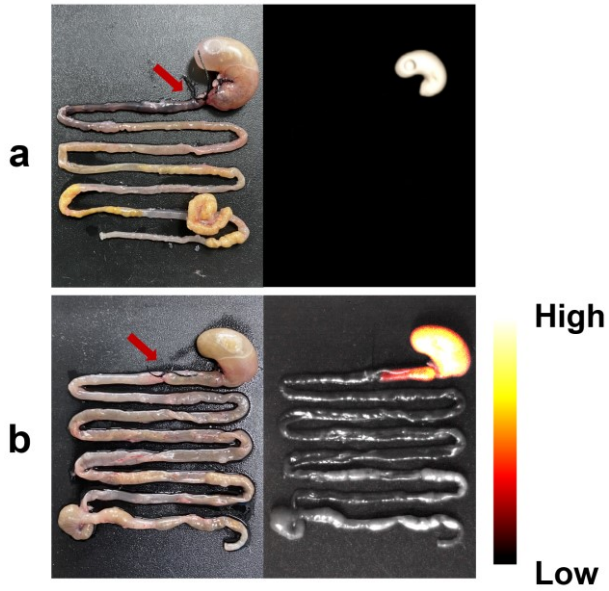

Fig. S13 (a) Ex vivo CT image of the GI tract in mice with intestinal obstruction at 30 min after the administration of Nd-DTPA. Left: digital photograph, Right: CT reconstructed image. (b) Ex vivo NIR II fluorescence image of the GI tract in mice with intestinal obstruction at 30 min after the administration of Nd-DTPA. Left: digital photograph, Right: NIR II fluorescence image. The ligation position was indicated by the red arrow.

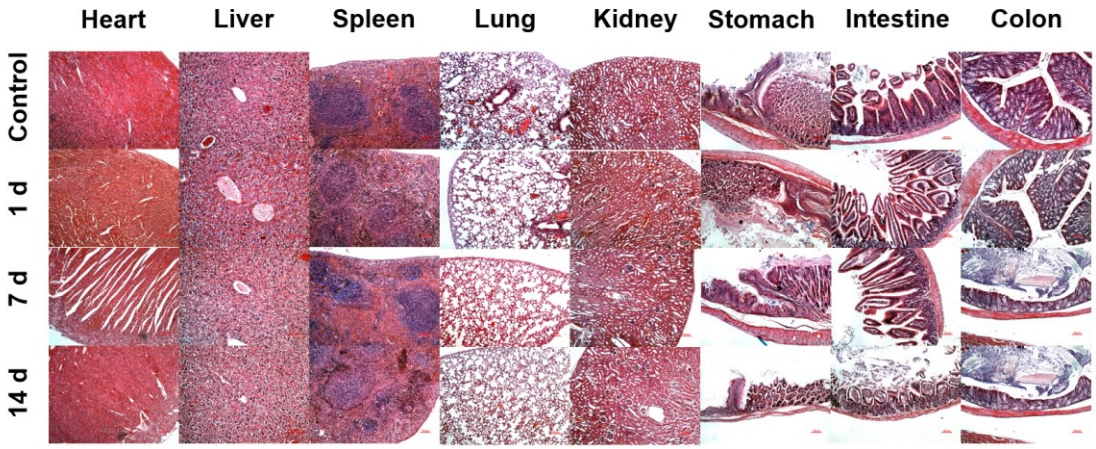

Fig. S14 H&E stained images of heart, liver, spleen, lung, kidney, stomach, intestine, and colon after oral administration of Nd-DTPA (400 μL, 0.5 M) at 1, 7, and 14 day or not.

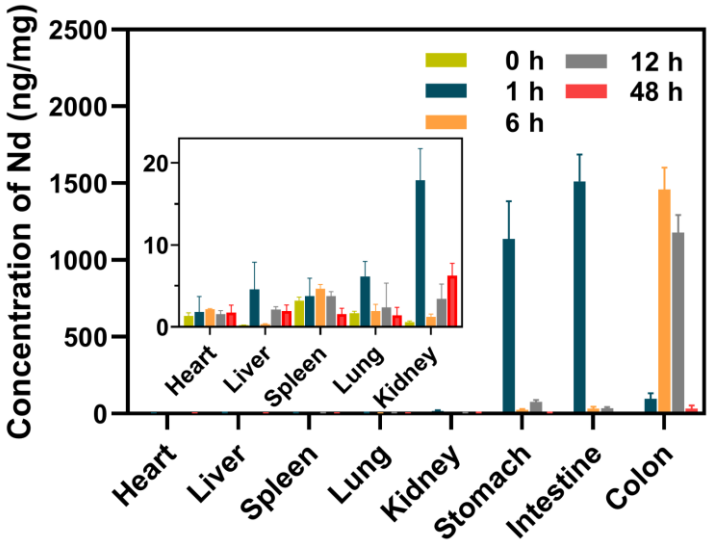

Fig. S15 Quantitative biodistribution of Nd in the vital organs (heart, liver, spleen, lung, kidney, stomach, intestine, and colon) collected after oral administration of Nd-DTPA (400 μL, 0.5 M, n=3) at different time points (0 h, 1 h, 6 h, 12 h, and 48 h).