Extended Data

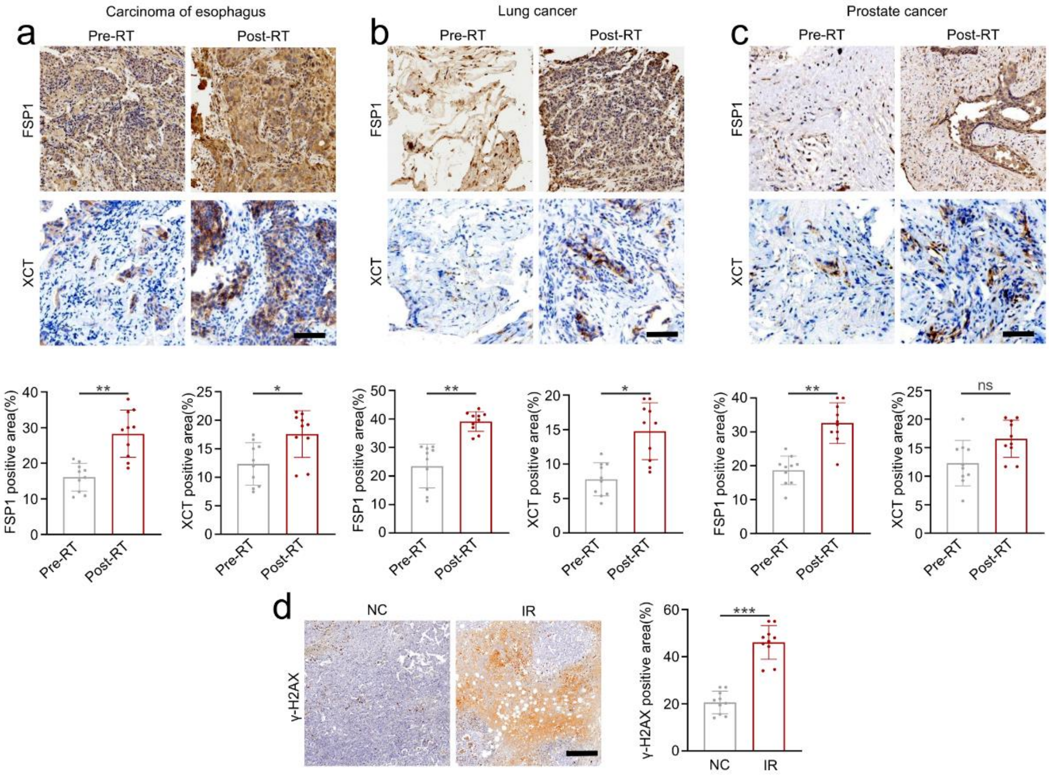

Figure 1 | Expression of ferroptosis-related genes across malignancies post-radiotherapy

a-c Representative IHC staining images (scale bar: 100 μm) of FSP1 and xCT in pan-cancer patients before and after radiotherapy. **d** IHC staining showing γ-H2AX expression in tumor tissues of a mouse PCa subcutaneous xenograft model pre- and post-irradiation (representative images; scale bar: 100 μm).

Data: Mean ± SD; ns = not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

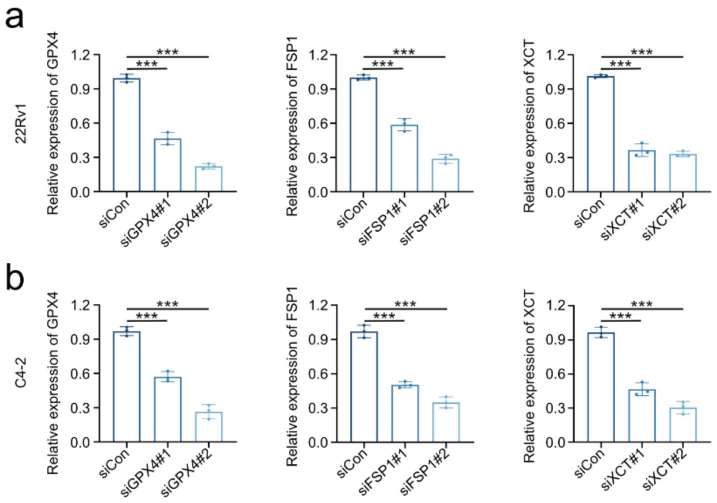

Figure 2 | Screening optimal FINs for radiosensitization

a-b Validation of the knockdown efficiency of two siRNA pairs targeting multiple ferroptosis-related genes using qPCR.

Data: Mean ± SD; ***$p < 0.001$.

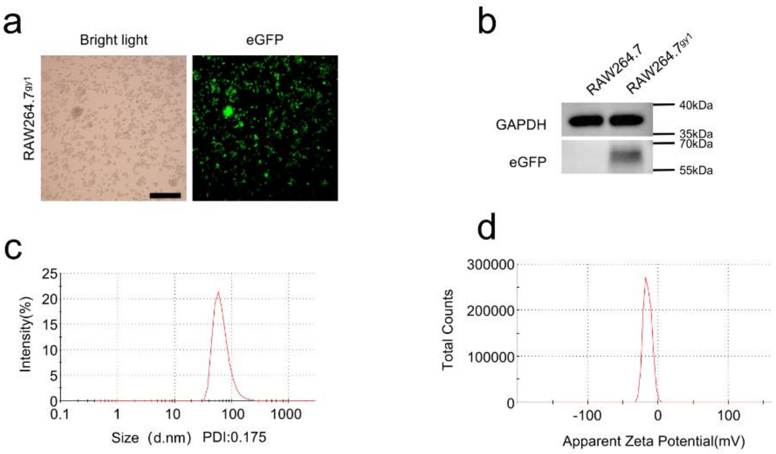

Fig. 3 | Fabrication and functional characterization of Au-MOF/RSL3@M-gy1

a. Fluorescence microscopy of RAW264.7 macrophages expressing PSMA-targeting gy1 antibody (green: eGFP signal; scale bar: 100 μm). **b**. Western blot validation of eGFP-tagged gy1 expression in engineered RAW264.7 cells. **c**. Hydrodynamic size distribution of Au-MOF nanoparticles by DLS. **d**. Zeta potential analysis of Au-MOF.

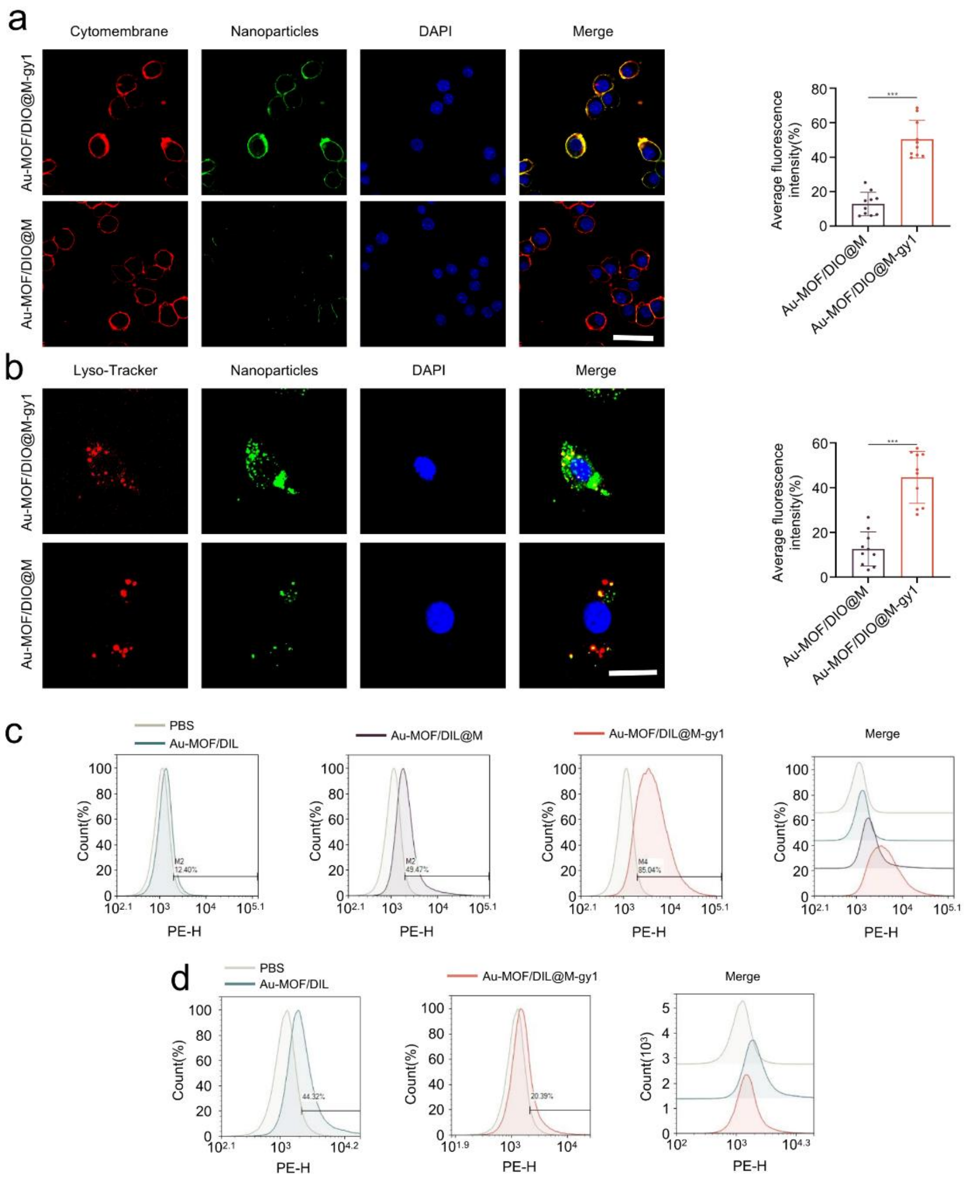

Fig. 4 | The targeting capability of Au-MOF/RSL3@M-gy1

a-c) Evaluation of targeting specificity in C4-2 cells: a. Immunofluorescence co-localization analysis of Au-MOF@M-gy1 binding to target cells (Nanoparticles: green; scale bars: 40 μm). **b**. Intracellular internalization efficiency of Au-MOF@M-gy1 visualized by confocal microscopy (Nanoparticles: green; scale bars: 20 μm). **c** Quantitative flow cytometry analysis of cellular uptake. **d** Phagocytic efficiency of target cells (macrophages) towards Au-MOF@M-gy1 analyzed by flow cytometry.

Data: Mean ± SD; ***$p < 0.001$.

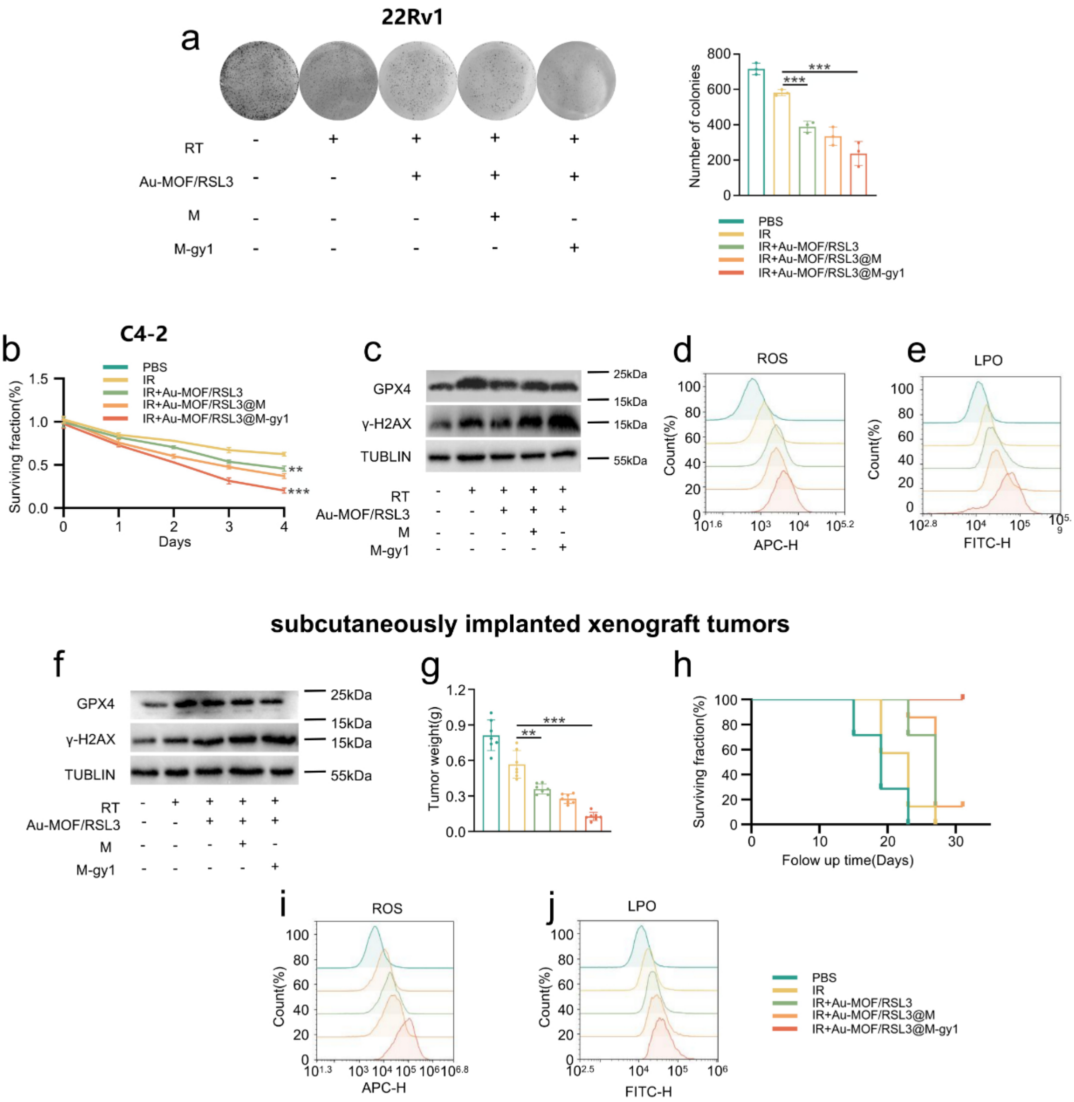

Fig. 5 | Evaluation of the radiosensitization effect of Au-MOF/RSL3@M-gy1.

a. Clonogenic assay demonstrating radiosensitization efficacy in 22Rv1 prostate cancer cells.

b-e). Validation in C4-2 cells: b. CCK-8 viability assay under X-ray irradiation (2 Gy). **c**. Western blot analysis of GPX4 and γ-H2AX. **d-e**. Flow cytometry quantification of ROS and LPO.

f-j). In vivo assessment in xenografted mice: f. Western blot of tumor lysates for GPX4、γ-H2AX expression. **g**. Tumor weight comparison across treatment groups. **h**. Survival curves of mice in different treatment groups. i-j. Flow cytometry analysis of tumor tissue ROS、LPO levels.

Data: Mean ± SD; $^{**}p < 0.01$, $^{***}p < 0.001$.

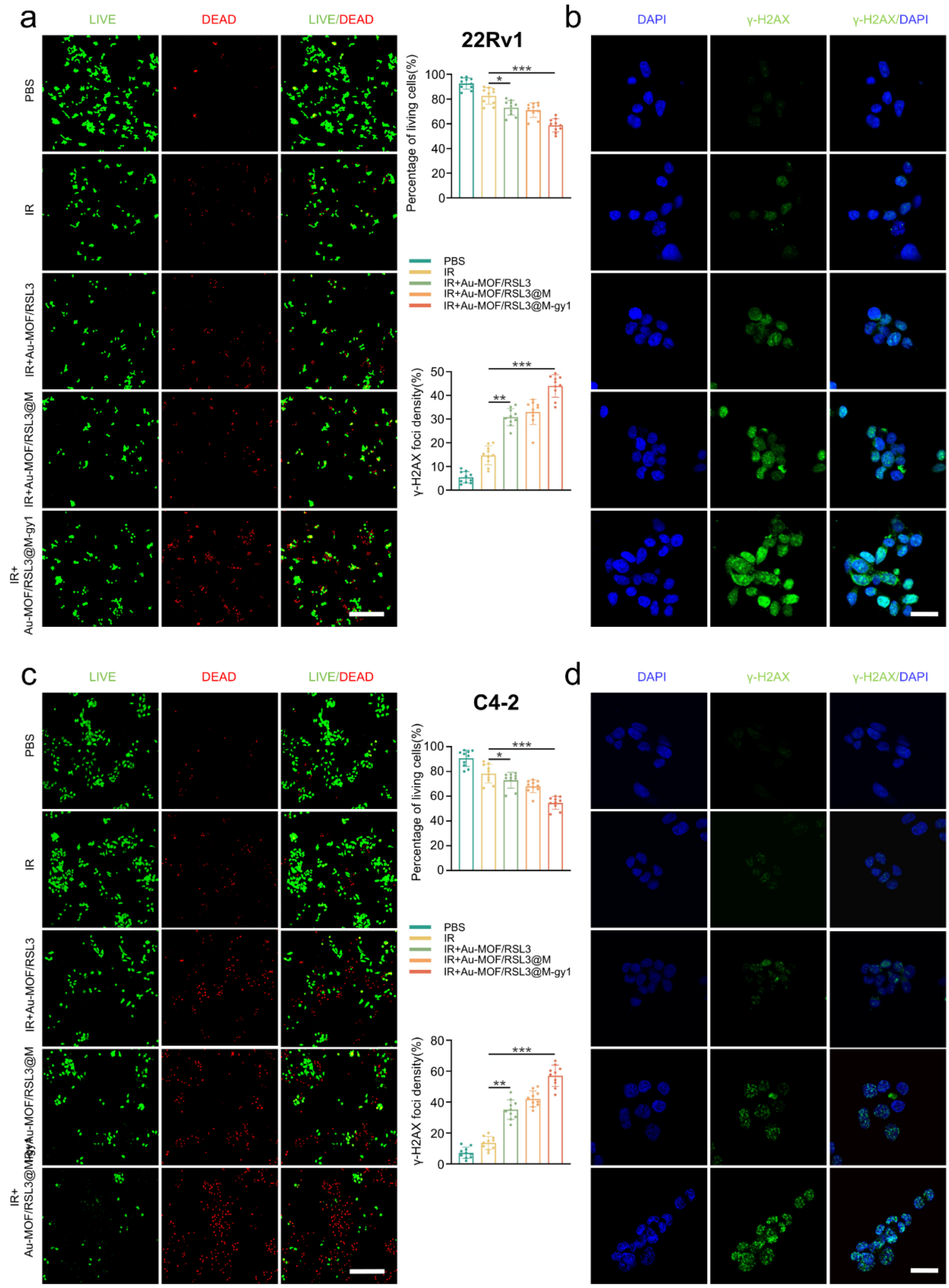

Fig. 6 | Evaluation of the radiosensitization effect of Au-MOF/RSL3@M-gy1.

a-b) Evaluation in 22Rv1 cells: **a.** Live/dead cell staining assay assessing radiosensitization effects (representative images; scale bar: 100 μm). **b.** Immunofluorescence co-localization assay quantifying γ-H2AX foci formation (representative images; scale bar: 40 μm).

c-d) Validation in C4-2 cells: **c.** Live/dead cell staining assay under radiation treatment (representative images; scale bar: 100 μm). **d.** Immunofluorescence analysis of γ-H2AX expression (representative images; scale bar: 40 μm).
Data: Mean ± SD; $^{**}p < 0.01$, $^{***}p < 0.001$.

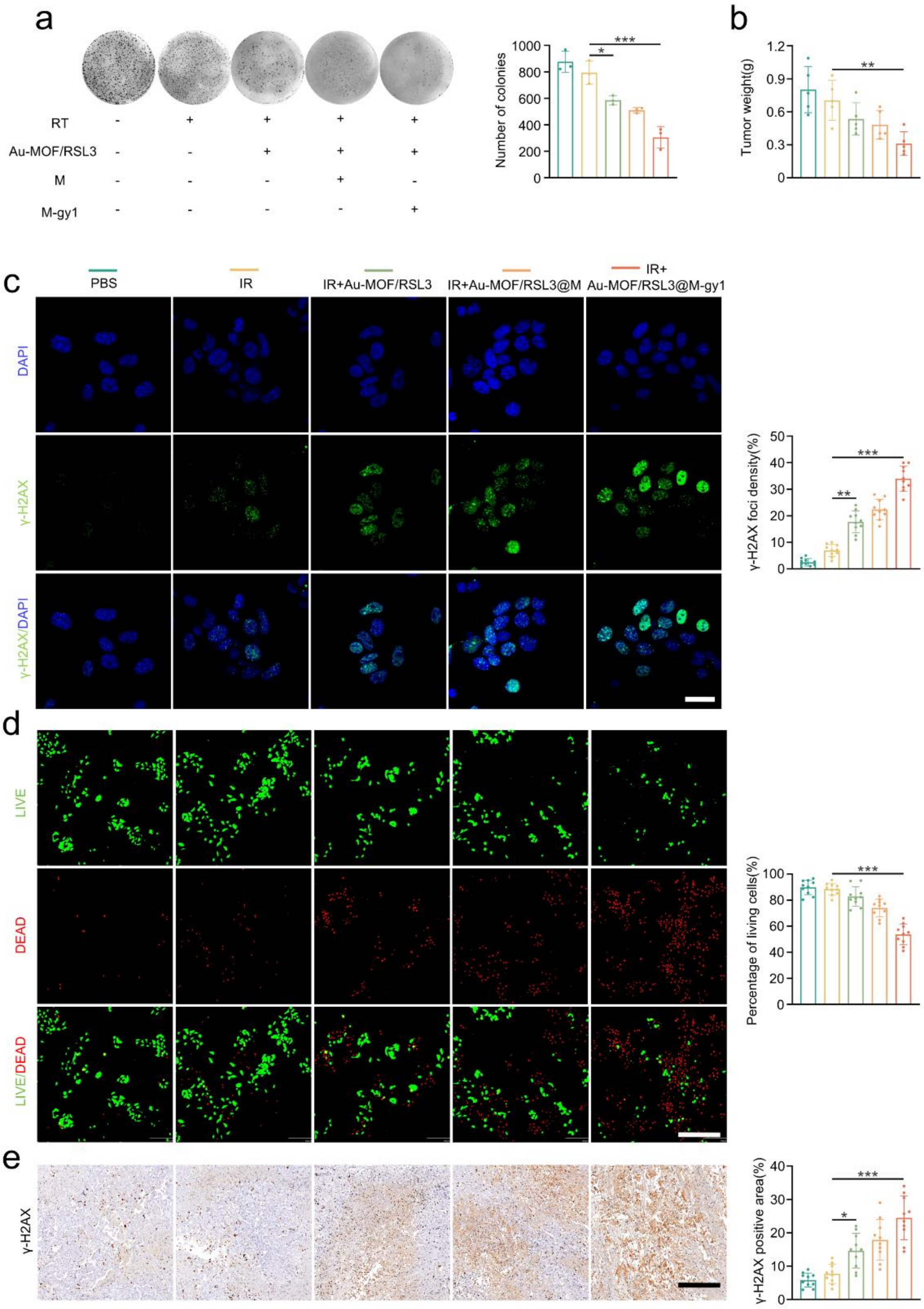

Fig. 7 | Radiosensitization efficacy validation of Au-MOF/RSL3@M-gy1 in radioresistant prostate cancer models

a. Clonogenic assay quantifying radiosensitization effects in radiation-resistant 22Rv1-RR

cells. **b**. Subcutaneous tumor mass quantification in radioresistant murine xenografts (n = 5). **c**. Immunofluorescence co-localization analysis of γ-H2AX foci across treatment groups (representative images; scale bar: 40 μm). d. Live/dead cell staining demonstrating the radiosensitization of Au-MOF/RSL3@M-gy1 in 22Rv1-RR cells (representative images; scale bar: 100 μm). e. Immunohistochemical staining of γ-H2AX expression in radioresistant tumor tissues (representative images; scale bar: 100 μm).
Data: Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001.

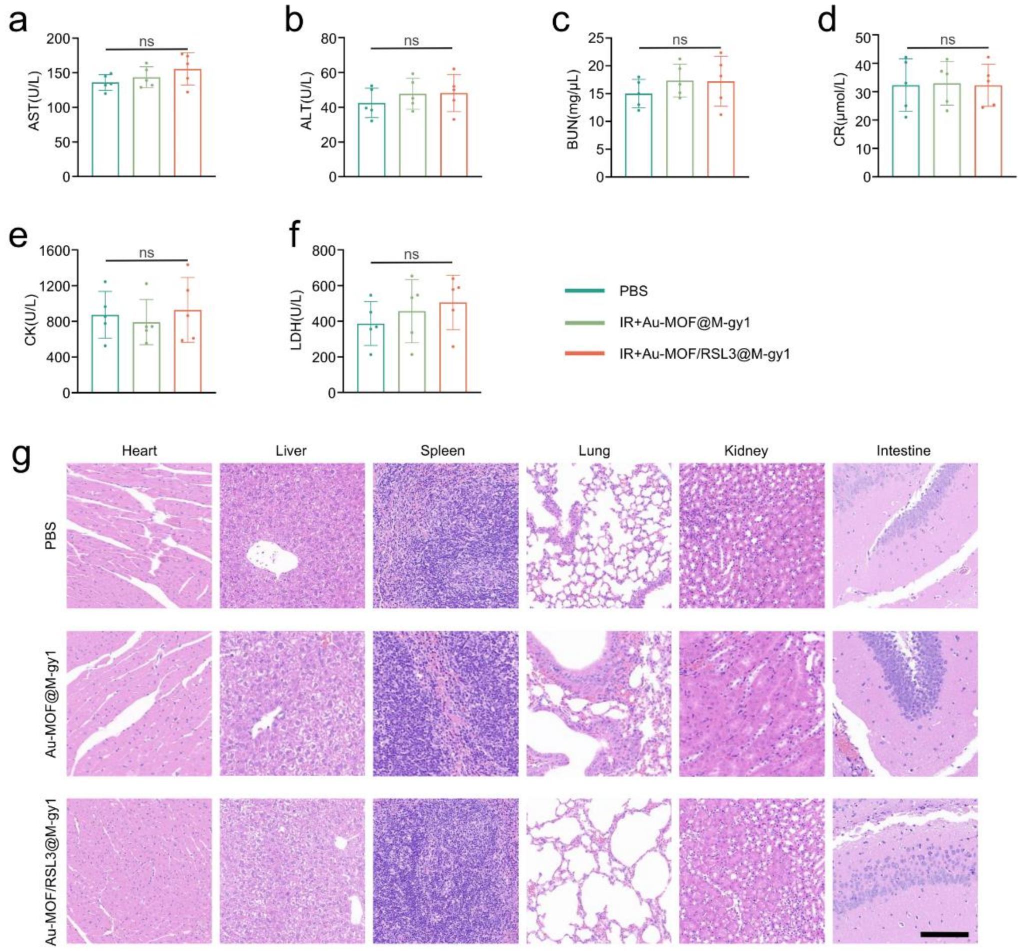

Fig. 8 | Biosafety evaluation of Au-MOF/RSL3@M-gy1

a-f). Serum biochemical profiling: **a.** Aspartate aminotransferase (AST) levels. **b.** Alanine aminotransferase (ALT) levels. **c.** Blood urea nitrogen (BUN) levels. **d.** Creatinine (CR) levels. **e.** Creatine kinase (CK) levels. **f.** Lactate dehydrogenase (LDH) levels. **g.** H&E staining of major organ paraffin sections (representative images; scale bar: 100 μm).
Data: Mean ± SD; ns = not significant.