Supplementary Figure Legend

**Supplementary Figure S1.** Schematic representation of tumor specific adaptation for energy metabolism and building block supply in context with the system $\text{x}_{\text{C}^-}$ and CD44 in glutathione biosynthesis and the cysteine-cystine redox cycle. Tumors are characterized by adaptation of several catabolic and anabolic pathways as well as by transport systems needed to meet their demands for energy, growth and detoxification. In particular, the glycolytic and glutaminolytic pathways along with a truncated tricarboxylic acid cycle (TCA) cycle are pronounced. High rates of metabolic fluxes together with an impaired mitochondrial respiratory chain result in an increase in oxidative intermediates, an altered redox potential and excessive reactive oxygen species (ROS) levels which are compensated for at least in part by an increased glutathione biosynthesis, cysteine and the cysteine-cystine redox cycle. The truncated TCA cycle in tumors leads to an efflux of mitochondrial citrate into the cytosol providing building blocks. Here, glutamate serves as the major anaplerotic substrate to refuel the TCA cycle. Glutamate is primarily obtained from glutamine degradation via glutaminase and accumulates intracellularly at high concentrations. In addition, glutamate is one component of the tripeptide glutathione and is consumed for its biosynthesis or is used as an exchange substrate for the uptake of cystine via the system $\text{x}_{\text{C}^-}$ driving the cysteine-cystine redox cycle. Extracelluarily, glutamate and cystine bind with similar affinities to system $\text{x}_{\text{C}^-}$. [$^{18}\text{F}$]FSPG is taken up via the system $\text{x}_{\text{C}^-}$ in a similar manner and retained intracellularly. A CD44 splice variant interacts with the xCT subunit of system $\text{x}_{\text{C}^-}$, and promotes its proper localization and function.
**Supplementary Figure S2.** Mean and standard deviation of the SUVmean of $[^{18}\text{F}]$FSPG distribution in selected normal organs and cancer as function of time.

**Supplementary Figure S3.** A scattergram showing a modest correlation between SUVmax of $[^{18}\text{F}]$FSPG and that of $[^{18}\text{F}]$FDG of reference lesions in patients with NSCLC ($\rho = 0.69$, $P < 0.001$) or breast cancer ($\rho = 0.61$, $P < 0.005$).

**Supplementary Figure S4.** A 40 year-old female patient with invasive ductal carcinoma in the right breast (Case 13). Maximum-intensity projection of $[^{18}\text{F}]$FDG (A) and $[^{18}\text{F}]$FSPG (B) PET/CT show the primary tumor in the right breast (dotted arrows) as well as multiple metastatic lymph nodes in the right axillary area (arrow). Note that all lesions are better visualized on $[^{18}\text{F}]$FDG than on $[^{18}\text{F}]$FSPG PET. The lesions in the internal mammary lymph node chain are evident only on $[^{18}\text{F}]$FDG, which are not seen in $[^{18}\text{F}]$FSPG PET/CT.

**Supplementary Figure S5.** The correlation analysis between the staining intensity of $\text{x_C}^-\text{transporter$ and CD44 expression ($\rho = 0.77$, $P < 0.01$). The data points are labeled with the respective patient number (Table 1).

**Supplementary Movie S1.** Maximum-intensity projections of $[^{18}\text{F}]$FDG (S1A) and $[^{18}\text{F}]$FSPG PET (S1B) at 60 min after injection in a lung cancer patient (Patient 2).

**Supplementary Movie S2.** Maximum-intensity projections of $[^{18}\text{F}]$FDG (S2A) and $[^{18}\text{F}]$FSPG PET (S2B) at 60 min after injection in a breast cancer patient (Patient 13).