Objectives Co-registration of SPECT and CT images may substantially improve tumor diagnosis by combining the functional information from scintigraphic images with the anatomical localization obtainable from CT images. Additionally, when CT-based attenuation maps are used in attenuation and scatter corrections, quantitative analysis of the data can help radiotherapy planning by providing accurate dosimetry for tumors and critical organs. Since CT and SPECT are usually performed on different days and using separate imaging systems, they clearly require co-registration. However, even if the scans are done on a combined SPECT/CT camera substantial image misalignments have been reported due to patient movement, therefore these images may also need to be co-registered. Co-registration however poses a major challenge, especially in high target-to-background images where tumors are well visible but almost none of the other body elements, providing no landmarks for registration. This situation would be much improved if anatomical markers, such as bone structures that are clearly visible in CT, could be used in co-registration. Methods In order to facilitate co-registration our method proposes an injection of bone radiotracer simultaneously with a tumor agent. This approach not only helps co-registration but may additionally diagnose potential metastases. Our automatic co-registration method uses mutual information as the registration criterion. To improve the robustness and accuracy of the algorithm, a multi-resolution approach is used in which registration is performed in a coarse-to-fine manner. During registration, the metric value is optimized over the parameter space defined by the translation parameters using a gradient-descent minimization scheme. The algorithm was tested on clinical data corresponding to pelvic and thoracic CT and SPECT-bone studies. Results Validation was done by visual inspection of 2D and 3D images and by observing the convergence in the similarity metric and the transformation parameters. Additionally, the effect of initial misalignment of the paired volumes and the reproducibility of the registration were evaluated. In all studies, registration with multi-resolution converged close to a final alignment. Initial misalignments of up to 50mm in the X and Y-axes, and 10mm in the Z-axis resulted in 61 of 66 successful registrations for the pelvic and 54 of 66 for the thoracic studies. The translation errors were 0.712mm±0.313mm and 1.312mm±0.623mm, respectively. The average computation time (on a 3.0GHz PC) was < 4 minutes for the entire registration procedure. Conclusion An automatic SPECT-CT co-registration method based on bone tomoscinography has been developed and validated.