There is a pressing clinical need to provide image guidance during surgery. Currently, assessment of tissue that needs to be resected or avoided is performed subjectively leading to a large number of failures, patient morbidity and increased healthcare cost. Because near-infrared (NIR) light propagates deeply within living tissues and interacts with molecular constituents, it offers unparalleled capabilities for objectively identifying healthy and diseased tissue intraoperatively. These capabilities are well illustrated through the ongoing clinical translation of fluorescence imaging during oncologic surgery. In this presentation, we will review our efforts to provide real-time image-guidance during surgery using visible and NIR light. We will present our latest results in fluorescence and endogenous imaging towards real-time monitoring and image-guided surgical intervention.