Studies examining acute perfusion changes (<1 month) in irradiated fields are limited. Hyperspectral imaging (HSI) is a novel method of scanning spectroscopy that provides direct measurement of cutaneous tissue perfusion that is non-invasive. In this clinical study, we examine the ability of HSI to assess cutaneous changes in skin perfusion during the acute period following irradiation in patients. Patients undergoing external beam breast conserving radiotherapy (n=15) or post-mastectomy radiation (n=3) were enrolled. Total treatment doses ranged between 42 Gy and 50 Gy. Baseline images were obtained before irradiation for bilateral breasts in each patient and then subsequently at each dose fraction. Skin reaction assessment was also performed on the patients. In the irradiated breast, total perfusion was found to increase prior to skin reaction formation and continued to steadily increase over the first 30 days in all patients. Skin reactions included erythema and dry desquamation starting at day 11. These findings suggest that HSI can identify early changes of tissue oxygenation and perfusion in acute radiation injury and may be able to predict the severity of such injuries. Future work will look at mitigating acute injury with topical applications and studying the perfusion changes in chronically irradiated skin.