Multispectral autofluorescence endoscopy is a non-invasive optical imaging modality that can provide contrast between malignant and benign oral tissue. We hypothesized that discrimination of cancerous and precancerous from benign oral lesions can be achieved through machine-learning (ML) models developed with multispectral autofluorescence intensity features. In vivo multispectral autofluorescence endoscopic images of benign, precancerous, and cancerous oral lesions were acquired from 67 patients and used to optimize ML models for discrimination between cancerous/precancerous and benign lesions. This study demonstrates the potentials of a ML-assisted system based on multispectral autofluorescence endoscopy for automated discrimination of cancerous and precancerous from benign oral lesions.