Multispectral autofluorescence lifetime imaging (maFLIM) endoscopy can be used to clinically image a plurality of metabolic and biochemical autofluorescence biomarkers of oral precancer and cancer. We tested the hypothesis that maFLIM-derived autofluorescence biomarkers can be used as features in machine-learning models to automatically discriminate precancerous and cancerous from healthy oral tissue. Clinical widefield maFLIM endoscopy images of cancerous and precancerous oral lesions from 57 patients were acquired and used to develop and validate a computer-aided detection (CAD) system. This study demonstrates the potentials of a maFLIM endoscopy-based CAD system for automated in situ clinical detection of oral precancer and cancer.