We present a series of 10 primary esophageal melanomas of Caucasian patients characterized clinicopathologically and on the molecular level. Mutation analysis for c-Kit (exons 9, 11, 13 and 17), PDGFR (exons 12, 14 and 18), NRAS and KRAS were determined using PCR and direct sequencing. Analysis of the V600E mutation of BRAF was performed using mutation-specific PCR. Expression of c-Kit and PDGFR-A was additionally determined using immunohistochemistry. One tumor harbored a missense mutation in the c-Kit (p.F504L) and in the KRAS gene (p.G12S). A different c-Kit mutation (c.1507_1508 ins TTGCC) was detected in another case. A third case had a V600E BRAF mutation. Using immunohistochemistry, c-Kit expression could be detected in all cases. The two cases with c-Kit mutations showed high c-Kit expression. None of the tumors showed a PDGFR mutation or expression or a NRAS mutation. We conclude that molecular analysis can identify targets for a specific therapy such as tyrosin kinase inhibitors as additional treatment option in these highly malignant tumors.