Endometrial cancer with a *POLE* mutation progresses frequently through the type I pathway despite its high-grade endometrioid morphology: A cohort study at a single institution in Japan
（日本人における*POLE*変異子宮内膜癌の臨床病理学的解析：単施設におけるコホート研究）

Background and Purpose:
Endometrial cancer (EC) with a *POLE* mutation is frequently correlated with high-grade endometrioid histology, which represents immunohistochemical and genetic heterogeneity in the dualistic classification of EC, type I and type II. The present study aimed to assess the clinicopathology and pathogenesis of *POLE*-mutated EC due to the scarcity of related information for Asian women.

Methods:
Exonuclease domain variants spanning exons 9 to 14 in the *POLE* gene were examined in tissues of Japanese women with EC by Sanger sequencing. The tumor mutation burden (TMB) in the tissues was assessed when a *POLE* variant of unknown significance was identified. In the *POLE*-mutated EC tissues, the immunostaining expression of CD8, estrogen receptor (ER), progesterone receptor (PR), and p53 was evaluated, and the *POLE* variants in cancer and atypical endometrial hyperplasia (AEH) lesions were assessed by laser-capture microdissection.

Results:
POLE variants were identified in five patients (3.9%) with high-grade endometrioid carcinoma among 127 eligible patients with EC: S459F was found in two and P441P, which was of unknown significance, was found in three tissues with a high TMB. The five cancer tissues showed marked CD8-positive cell infiltration and coexisted with normal endometrium and/or AEH. In the four patients with AEH, both AEH and cancer cells showed ER and PR positivity and harbored the same *POLE* mutation. In two patients with cancer lesions that showed a subclonal overexpression pattern of p53, the same subclonal pattern was observed in AEH.

Conclusions:
EC with a *POLE* mutation progresses through the type I pathway, even though it frequently shows high-grade endometrioid morphology. The common *POLE* mutation sites in EC might vary among races.