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Histopathological validation of β-amyloid - targeting PET tracers: Lessons from the Phase III clinical diagnostic trials

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Abstract Abnormal brain amyloid-beta deposition is thought to be a key early etiologic event in the pathophysiology of Alzheimer's disease (AD). Recent therapeutic approaches focus on removal of amyloid-beta in probable and prodromal AD by interrupting pathological brain mechanisms of production and impaired brain clearance of the protein. Concurrent with this therapeutic focus has been the development of amyloid-specific ^{18}F PET radiotracers, serving as both diagnostic biomarkers and an objective means to track of putative changes in patient cohorts undergoing amyloid-targeted therapy. Recently, ^{18}F florbetapir PET has been approved for clinical use by the FDA as an adjunct to assist in the accurate diagnosis of Alzheimer's patients. Two other F18 labeled PET tracers, florbetaben and flutemetamol, have completed Phase III studies similar in design to florbetapir in which large cohorts of patients recruited near death underwent PET amyloid brain imaging and upon expiration donated their brains for postmortem histopathological assessment and comparison with the *in vivo* PET determination of brain amyloid. These recently concluded, groundbreaking studies provide important lessons in understanding properties and validation of PET radiotracers interrogating brain amyloid. This lecture summarizes this evolving work with focus on issues of PET radiotracer validation where a histopathological standard is utilized.