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Titel des Beitrags: An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis.

Abstract: BACKGROUND: Phaeochromocytomas and paragangliomas are neuro-endocrine tumours that occur sporadically and in several hereditary tumour syndromes, including the phaeochromocytoma-paraganglioma syndrome. This syndrome is caused by germline mutations in succinate dehydrogenase B (SDHB), C (SDHC), or D (SDHD) genes. Clinically, the phaeochromocytoma-paraganglioma syndrome is often unrecognised, although 10-30% of apparently sporadic phaeochromocytomas and paragangliomas harbour germline SDH-gene mutations. Despite these figures, the screening of phaeochromocytomas and paragangliomas for mutations in the SDH genes to detect phaeochromocytoma-paraganglioma syndrome is rarely done because of time and financial constraints. We investigated whether SDHB immunohistochemistry could
effectively discriminate between SDH-related and non-SDH-related phaeochromocytomas and paragangliomas in large retrospective and prospective tumour series. METHODS: Immunohistochemistry for SDHB was done on 220 tumours. Two retrospective series of 175 phaeochromocytomas and paragangliomas with known germline mutation status for phaeochromocytoma-susceptibility or paraganglioma-susceptibility genes were investigated. Additionally, a prospective series of 45 phaeochromocytomas and paragangliomas was investigated for SDHB immunostaining followed by SDHB, SDHC, and SDHD mutation testing. FINDINGS: SDHB protein expression was absent in all 102 phaeochromocytomas and paragangliomas with an SDHB, SDHC, or SDHD mutation, but was present in all 65 paraganglionic tumours related to multiple endocrine neoplasia type 2, von Hippel-Lindau disease, and neurofibromatosis type 1. 47 (89%) of the 53 phaeochromocytomas and paragangliomas with no syndromic germline mutation showed SDHB expression. The sensitivity and specificity of the SDHB immunohistochemistry to detect the presence of an SDH mutation in the prospective series were 100% (95% CI 87-100) and 84% (60-97), respectively. INTERPRETATION: Phaeochromocytoma-paraganglioma syndrome can be diagnosed reliably by an immunohistochemical procedure. SDHB, SDHC, and SDHD germline mutation testing is indicated only in patients with SDHB-negative tumours. SDHB immunohistochemistry on phaeochromocytomas and paragangliomas could improve the diagnosis of phaeochromocytoma-paraganglioma syndrome. FUNDING: The Netherlands Organisation for Scientific Research, Dutch Cancer Society, Vanderes Foundation, Association pour la Recherche contre le Cancer, Institut National de la Santé et de la Recherche Médicale, and a PHRC grant COMETE 3 for the COMETE network.