Ancillary studies (Non-core)

Parafibromin is the protein encoded by the *CDC73* gene (previously known as HRPT2).[1] Germline mutations and deletions in the *CDC73* gene occur in the autosomal dominant HPT-JT syndrome with somatic second hits occurring in carcinomas and adenomas arising in this setting. Patients presenting with apparently sporadic parathyroid carcinoma may have occult HPT-JT syndrome.[2-7] Somatic only double hit mutation/inactivation also occur frequently in parathyroid carcinomas not associated with HPT-JT.[7] Immunohistochemistry for parafibromin is not widely available and may be technically difficult to perform and interpret.[2] Immunohistochemical evaluation of parafibromin shows nuclear staining in normal parathyroid cells and most benign parathyroid tumours. Loss of nuclear expression of parafibromin occurs in most but not all tumours associated with biallelic *CDC73* mutation/ deletion.[7-10] Loss of parafibromin expression is not completely sensitive for *CDC73* mutation but may be used to triage genetic testing for HPT-JT syndrome in patients with atypical parathyroid neoplasms and parathyroid carcinoma. Parafibromin loss may be associated with a higher likelihood of recurrence in parathyroid carcinoma.[2,7-9,11-13] It has been suggested that tumours which demonstrate loss of parafibromin expression may show subtle morphological clues including sheet like growth, eosinophilic cytoplasm, perinuclear cytoplasmic clearing and nuclear enlargement.[7]

Ki-67 proliferative index has also been reported as elevated in parathyroid neoplasms though with some overlap with hyperplasia and adenomas.[1,10,14-16] If performed, evaluation of Ki-67 immunohistochemical staining of the parathyroid neoplasm should be recorded as a percent of tumour cells staining in hot spots (the areas with greatest Ki-67 expression). The method used to calculate the Ki-67 percent should be specified (e.g., manual count and the number of cells evaluated, or automated computer assisted calculation including the number of cells counted).

Other markers might include Cyclin D and/or galectin-3 overexpression or retinoblastoma (Rb) loss of expression which has also been studied with an association in carcinomas compared to adenomas.[16-18] Protein Gene Product 9.5 (PGP9.5) is also overexpressed in the majority of parathyroid carcinomas and has shown similar performance in parathyroid carcinomas as parafibromin immunohistochemical evaluation.[12]

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