PARATHYROID CARCINOMA

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Parathyroid carcinoma is a rare malignancy occurring in approximately 1% of cases of PHPT , with an estimated prevalence of 0.005% of all cancers. While the aetiology remains unclear, recent advances in molecular biology suggest that there may be an underlying genetic basis. Currently , a history of previous neck irradiation remains the only known environmental risk factor. However, given that it can arise in patients with end-stage renal disease as well as in those with MEN type 1, malignant transformation in hyperplastic glands may also occur. A significant proportion of patients (>10%) with a para thyroid carcinoma will have HPT-JT . The underlying mutation is in the HRPT2 / CDC73 gene at chromosome 1q21–q31, a tumour suppressor gene that encodes the protein parafibromin. Parafibromin is involved in the regulation of cellular transcrip tion and histone modification. HRPT2 mutations, leading to inactivation of parafibromin, are therefore an important con tributor to the pathogenesis of parathyroid carcinoma. Simi larly , up to 18% of patients with a parathyroid carcinoma will have an inactivating mutation of the PRUNE2 gene, located on chromosome 9q21.2. This is a tumour suppressor gene that encodes the RAS homologue family member A, leading to sup pression of oncogenic cellular transformation. Parathyroid carcinoma remains di ffi cult to diagnose preoperatively as it biochemically resembles PHPT . There are, however, a number of suggestive features. First, the diagnosis is typically made a decade earlier, with an equal gender preponderance when compared with PHPT . Second, a greater proportion of these patients will be symptomatic at presentation. A palpable neck mass is found in 36–52% of patients with parathyroid carcinomas but rarely (<5%) in cases of PHPT . Finally , the biochemical abnormalities tend to be 3.97 /uni00A0 mmol/L and a PTH level 5–10 times the normal range. The leading cause of morbidity and mortality from para - thyroid carcinoma is hypercalcaemia due to inappropriate PTH secretion. Tr eatment is focused on controlling hypercal - caemia and removal of the carcinoma where possible . Surgery remains the mainstay of treatment for primary presentations and locally recurrent disease. Complete resection of the tumour, av oiding spillage, is vital in preventing seeding and thus recurrent disease. En bloc resection of the tumour, asso - ciated thyroid lobectomy and central neck dissection remain controversial. Complete R0 resection was thought to provide the only means of a cure. However, a number of r ecent studies have failed to demonstrate an improvement in local r ecurrence rates with such comprehensive resection. Adjuvant chemotherapy has not been shown to confer a disease-free or overall survival benefit. Use of external beam radiotherapy should be con - sidered on an individual basis. Traditionally , it has not been deemed e ff ective, but more recent single-institution case series challenge this assumption. It may be considered where it is di ffi cult to achieve a complete surgical resection or in patients with m ultifocal recurrent soft-tissue deposits. Histological confirmation of a parathyroid carcinoma remains di ffi cult. The World Health Organization criteria (2017) for the diagnosis of a parathyroid carcinoma emphasise the need for definite invasion of the sur rounding soft tissue and/or metastatic disease. The classical description that included trabecular architecture, mitotic figures, thick fibrous bands and capsular and vascular invasion is largely non-specific. New molecular markers may aid the diagnosis and stratify patients for more intensive follow-up (Figure

56.11). Immunohistochemical evidence of downregulation of parafibromin has a sensitivity of 67% and a specificity of 100% for detecting parathyroid carcinoma and the protein gene product 9.5 (PGP 9.5). Parafibromin immunohistochemistry may be used with immunohistochemistry for PGP 9.5. This is - a protein encoded by ubiquitin carboxyl-terminal esterase LI. It is upregulated in parathyroid carcinoma and has a sensitivity of 78% and a specificity of 100%. All parafibromin-negative and PGP 9.5-positive tumours should be considered for genetic - screening. - - -

Atypical parathyroid tumour Para /f_i bromin Para /f_i bromin NEGATIVE POSITIVE PGP 9.5 PGP 9.5 NEGATIVE POSITIVE High risk of Low risk of Carcinoma malignancy malignancy Figure 56.11 Proposed decision tree for atypical parathyroid tumours using para /f_i bromin and PGP 9.5 immunohistochemistry.

ease. Metastatic spread can occur to the lungs, liver and bones. Recurrence rates range from 33% to 80% and it typically occurs in the first 3 years. Overall survival is reported to be 85–90% at 5 years and 49–77% a t 10 years. Summary box 56.4 Parathyroid carcinoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

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