Prediktor Diagnosis Karsinoma Tiroid Papiler dengan Mutasi BRAFV600E dan RAS Menggunakan Profil Klinis, Histopatologis dan Ekspresi Phosphorylated Extracellular Signal-regulated Kinase 1/2 = Prediktor Diagnosis Karsinoma Tiroid Papiler dengan Mutasi BRAFV600E dan RAS Menggunakan Profil Klinis, Histopatologis dan Ekspresi Phosphorylated Extracellular Signal-regulated Kinase 1/2

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Abstrak

Karsinoma tiroid papiler (KTP) merupakan karsinoma tiroid yang paling sering ditemukan. Pada KTP terdapat driver mutation utama yakni BRAFV600E dan RAS. KTP dengan mutasi BRAFV600E umumnya menunjukkan perangai lebih agresif daripada RAS, keduanya harus dibedakan karena menentukan arah penatalaksanaan selanjutnya. Di Indonesia,pemeriksaan BRAFV600E dan RAS belum dilakukan rutin karena keterbatasan sumber daya. Tujuan penelitian ini adalah menganalisis aspek klinis, histopatologis dan ekspresi pERK1/2 sebagai prediktor diagnosis KTP dengan BRAFV600Eatau RAS. Penelitian ini menggunakan desain potong lintang yang dilakukan di RSUPN dr. Cipto Mangunkusumo pada bulan Maret 2022–Maret 2023. Subjek adalah pasien KTP yang menjalani tiroidektomi total sebanyak 222 pasien. Status mutasi diperiksa dengan PCR dan sekuensing DNA, menunjukkan 64 mutasi BRAFV600E, 42 mutasi RAS dan 116 non-BRAFV600E non-RAS. Ekspresi pERK1/2 diperiksa dengan imunohistokimia dan dihitung dalam satuan persentase. Terdapat hubungan antara karakteristik histopatologis (skor inti, kapsul, varian histopatologis, invasi jaringan lunak peritiroid dan metastasis kelenjar getah bening) dengan mutasi BRAFV600E. Terdapat hubungan antara varian histopatologis dengan mutasi RAS. Ekspresi pERK1/2 lebih tinggi secara bermakna pada BRAFV600E dan RAS, dibandingkan non-BRAFV600E non-RAS. Model prediksi BRAFV600E adalah skor inti 3 + tidak berkapsul + varian agresif + ekspresi pERK1/2 > 10%. Variabel skor inti 3, tidak berkapsul dan varian agresif masing-masing memberikan skor 1, sedangkan ekspresi pERK1/2 > 10% memberikan skor 2. Total skor 5 menunjukkan probabilitas 82% mutasi BRAFV600E. Model prediksi RAS adalah varian folikular + ekspresi pERK1/2 > 10%, masing-masing memberikan skor 1. Total skor 2 menunjukkan probabilitas 70% mutasi RAS. Selanjutnya dilakukan validasi internal dengan mengelompokkan total skor berdasarkan pertimbangan probabilitas dan spesifisitas. Kombinasi 1 (skor BRAFV600E 0–2dan skor RAS 0–1) menunjukkan proporsi non-BRAFV600E non-RAS lebih banyak ditemukan. Kombinasi 2 (skor BRAFV600E 0–2 dan skor RAS 2) atau RAS-like menunjukkan proporsi mutasi RAS secara bermakna lebih banyak ditemukan. Kombinasi 3 (skor BRAFV600E 3–5 dan skor RAS 0–1) atau BRAFV600E-like menunjukkan proporsi mutasi BRAFV600E secara bermakna lebih banyak ditemukan. Kombinasi 4 (skor BRAFV600E 3–5 dan skor RAS 2menunjukkan proporsi mutasi RAS secara bermakna lebih banyak ditemukan dibandingkan kelompok lainnya. Tata laksana standar atau eskalasi diusulkan berdasarkan stratifikasi risiko American Thyroid Association.

.....Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma. PTC has two main driver mutations, namely BRAFV600E and RAS. PTC with BRAFV600E mutation is more aggressive than RAS and the two must be distinguished as they determine therapeutic strategy. In Indonesia, BRAFV600E and RAS examinations have not been carried out routinely due to limited resources. The aim of this study

was to analyze the clinical profile, histopathological characteristics and pERK1/2 expression as a diagnostic predictor of PTC with BRAFV600E and RAS mutation. This study used a cross-sectional design conducted at RSUPN dr. Cipto Mangunkusumo (RSCM) from March 2022–March 2023. Subjects were 222 patients diagnosed with PTC who underwent total thyroidectomy. Mutation status was examined with PCR and DNA sequencing, consisting of 64 BRAFV600E mutations, 42 RAS mutations and 116 non-BRAFV600E non-RAS. pERK1/2 was examined using immunohistochemistry and calculated in percentage units. There was an association between histopathological characteristics (nuclear score, capsule, histopathological variants, peri-thyroidal soft tissue invasion and lymph node metastases) with BRAFV600E mutation. There was an association between histopathological variants and RAS mutation. The expression of pERK1/2 was significantly higher in BRAFV600E andRAS than non-BRAFV600E non-RAS. The BRAFV600E prediction model is a nuclear score of 3 + non-encapsulated + aggressive variant + pERK1/2 expression > 10%. Nuclear score of 3, non-encapsulated and aggressive variant variables each gave a score of 1, while expression of pERK1/2 > 10% gave a score of 2. The total score of 5 indicated 82% probability for BRAFV600E mutation. The predictive model for RAS is follicular variant + pERK1/2 expression > 10%. Each variable gave a score of 1. A total score of 2 indicated 70% probability for RAS mutation. Furthermore, internal validation was carried out by dividing the total score based on probability and specificity considerations. Combination 1 (BRAFV600E score 0–2 and RAS score 0–1) showed that non-BRAFV600E non-RAS were more commonly found. Combination 2 (BRAFV600E score 0–2 and RAS score 2) or RAS-like showed a significantly higher proportion of RASmutations. Combination 3 (BRAFV600E score 3–5 and RAS score 0–1) or BRAFV600E-like showed a significantly higher proportion of BRAFV600E mutations. Combination 4 (BRAFV600E score 3–5 and RAS score 2) showed a significantly higher proportion of RAS mutations than other groups. Standard management or escalation recommendation are proposed based on American Thyroid Association risk stratification.