

## ABSTRACT

**Background.** *O6-methylguanine-DNA methyltransferase (MGMT) is tumor suppressor gene that repair mutagenic DNA lesion. Promotor methylation can be used as predictive biomarker to targeted therapy such as IDH1 mutation and can predict outcome of alkilation chemotherapy in glioma. The gold standard examination for the methylation is methylation-specific quantitative real-time polymerase Chain Reaction (qMSP). However, this technique is not widely available in Indonesia for daily practice. Thus, simpler and easier method such as immunohistochemistry (IHC) is needed as alternative examination.*

**Objective.** *To predict diagnostic accuracy of immunohistochemistry in detecting MGMT methylation status in glioma.*

**Methods.** *Cross-sectional study from glioma's patients with Formalin-Fixed Paraffin Embedded (FFPE) of private and public hospitals in Yogyakarta and Klaten, October 2017 to October 2019. Diagnosis based on clinical, radiological, and histopathological findings. MGMT methylation was determined based on IHC and qMSP analysis. The diagnostic test and the optimal cut-off value were analyzed statistically.*

**Results.** *Based on 64 samples examined, there were 67.2% (43 samples) showing concordancy of MGMT methylation between IHC and qMSP. Glioma grade IV showed the greatest distribution of methylation among all degrees of glioma. IHC detected MGMT methylation with a sensitivity: 77.8%, specificity: 63.1%, positive predictive value: 45.2%, negative predictive value: 87.9% and accuracy: 67.2%. The area under curve (AUC) value is 0.704 and the optimal cut of point is 7.5% and 10%.*

**Conclusion.** *Imunohistochemistry can be used as an alternative method of screening MGMT methylation status for therapeutic candidates and predictive better outcome of TMZ therapy in Indonesia, with an accuracy of 67.2%. Further studies are needed to analyze MGMT methylation status using IHC with considering tumor heterogeneity and examination protocol.*

**Keywords:** *Glioma, methylated MGMT, IHC, qMSP, diagnostic study*

## ABSTRAK

**Latar Belakang.** *O6-methylguanine-DNA methyltransferase* (MGMT) merupakan gen supresor tumor yang memperbaiki lesi DNA mutagenik dan mencegah ketidaksesuaian dalam replikasi dan transkripsi DNA. Metilasi MGMT dapat digunakan sebagai biomarker prediktif untuk terapi yang ditargetkan seperti mutasi IDH1 dan dapat memprediksi hasil kemoterapi alkilasi pada glioma. *Methylation-specific quantitative real-time polymerase Chain Reaction (qMSP)* adalah pemeriksaan standar yang direkomendasikan saat ini. Namun teknik ini belum banyak tersedia di Indonesia. Oleh karena itu, diperlukan metode pemeriksaan yang lebih sederhana dan mudah seperti imunohistokimia (IHK) sebagai alternatif pemeriksaan.

**Tujuan.** Menilai akurasi diagnostik imunohistokimia dalam mendeteksi status metilasi MGMT pada glioma.

**Metode.** Penelitian potong lintang pasien glioma menggunakan *Formalin-Fixed Paraffin Embedded* (FFPE) dari rumah sakit swasta dan umum di Yogyakarta dan Klaten rentang Oktober 2017 hingga Oktober 2019. Diagnosis berdasar temuan klinis, radiologis, dan histopatologi. Metilasi MGMT ditentukan berdasarkan analisis IHK dan PCR. Uji diagnostik dan nilai titik potong optimal dianalisis secara statistik.

**Hasil.** Berdasarkan 64 sampel yang diperiksa, terdapat 67,2% (43 sampel) menunjukkan kesesuaian metilasi MGMT antara IHK dan qMSP. Glioma derajat IV menunjukkan distribusi metilasi terbanyak diantara semua derajat glioma. IHK mendeteksi metilasi MGMT dengan sensitivitas: 77,8%, spesifisitas: 63,1%, nilai prediksi positif: 45,2%, nilai prediksi negatif: 87,9% dan akurasi: 67,2%. Nilai *Area under curve* (AUC) 0,704 dan titik potong optimal ada pada 7,5% dan 10%.

**Kesimpulan.** Metode IHK dapat digunakan sebagai suatu metode alternatif skrining metilasi MGMT untuk kandidat terapi dan prediktif keberhasilan terapi TMZ di Indonesia dengan akurasi 67,2%. Diperlukan penelitian lebih lanjut analisis metilasi MGMT menggunakan IHK dengan mempertimbangkan heterogenitas tumor dan protokol pemeriksaan.

**Kata kunci:** Glioma, MGMT termetilasi, IHK, qMSP, studi diagnostik