

# Gambaran status metilasi gen promotor methylguanine deoksiribonucleic acid methyltransferase pada astrositoma dan faktor-faktor yang mempengaruhinya = Methylation status of the methylguanine deoksiribonucleic acid methyltransferase gene promoter among patients with astrocytomas

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## Abstrak

Latar belakang: Metilasi dari gen promotor O6-methylguanine-DNA methyltransferase (MGMT) adalah salah satu faktor yang berperan pada karsinogenesis dan berkembang menjadi marker dalam menilai progresivitas dan respons terapi astrositoma.

Tujuan: Untuk mendapatkan gambaran frekuensi status metilasi gen promotor MGMT pada pasien astrositoma menggunakan methylation specific polymerase chain reaction (MS-PCR) dan methylation specific high resolution melting (MS-HRM).

Metode: Dilakukan pengumpulan data klinis, imaging dan blok parafin jaringan astrositoma di RSCM dalam kurun waktu 2008-2012. Status metilasi gen promotor MGMT dianalisis menggunakan MS-PCR dan MS-HRM serta dihubungkan dengan berbagai faktor prognostik klinis. Penelitian ini adalah penelitian potong-lintang.

Hasil: Didapatkan 13 sampel yang terdiri dari 7 astrositoma derajat rendah dan 6 astrositoma derajat tinggi. Metilasi gen promotor MGMT didapatkan pada 1/13 sampel astrositoma dengan MS-PCR dan 4/13 sampel dengan MS-HRM yang seluruhnya adalah astrositoma derajat rendah. Terdapat perbedaan yang bermakna antara status metilasi gen promotor MGMT dengan derajat keganasan astrositoma yaitu astrositoma derajat rendah 4/7 sampel, tanpa ditemukan pada astrositoma derajat tinggi ( $p=0.049$ ) sedangkan faktor lain seperti usia, jenis kelamin, karnofsky performance scale (KPS), lokasi astrositoma dan derajat WHO tidak terdapat perbedaan yang bermakna ( $p=1,000$ ;  $p=0,657$ ;  $p=0,354$ ;  $p=0,538$ ).

Simpulan: Penelitian saat ini menunjukkan frekuensi status metilasi gen promotor MGMT pada astrositoma sedikit berbeda dengan berbagai penelitian lain sebelumnya yaitu hipermetilasi hanya terjadi pada astrositoma derajat rendah. Penelitian ini merupakan penelitian pertama di Indonesia yang melaporkan gambaran status metilasi gen promotor MGMT pada pasien astrositoma.

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Background: Astrocytoma is the most common primary central nervous system tumor with difficult management as it requires a combination of surgery, chemotherapy and radiotherapy. This multimodal approach increases patients survival rate significantly, however chemotherapy resistance is now commonly seen. One of the potential causes of chemotherapy resistance is the epigenetic factors from O6 methylguanine-DNA methyltransferase (MGMT) gene. MGMT gene has role in DNA repair and also have a protective effect against exogenous and endogenous alkylating agent. The methylation of MGMT gene promoter leads to the decrease of MGMT protein, attenuating its function. Therefore, the methylation status of MGMT gene promoter can act as an indicator for astrocytomas progressivity and treatment aggressiveness.

Objective: To determine the frequency of MGMT gene promoter methylation among patients with

astrocytomas using methylation specific polymerase chain reaction (MS-PCR) and methylation sensitive high resolution melting (MS-HRM).

Methods: Clinical data, imaging and paraffin blocks from astrocytoma patients were collected in RSCM from 2008-2012. The methylation status of MGMT gene promoter was confirmed using MS-PCR and MS-HRM. This is cross-sectional study.

Results: The total of 13 samples collected including 7 low-grade and 6 high-grade astrocytomas. The MGMT gene promoter was methylated in 1/13 cases using MS-PCR and 4/13 cases using MS-HRM. All methylated cases were low-grade astrocytoma. There was significant association between methylation status of MGMT gene promoter with degree of malignancy which is 4/7 samples hypermethylated in low-grade with no hypermethylation in high-grade astrocytomas ( $p=0.049$ ). While other factors like age, sex, KPS and astrocytomas location have no significant association ( $p= 1,000$ ;  $p= 0,657$ ;  $p= 0,354$ ;  $p= 0,538$ ).

Conclusions: The present study showed difference of methylation of MGMT gene promoter in astrocytomas with others studies which is hypermethylated MGMT only found in low grade astrocytomas. Our study was the first to report the frequency of MGMT promoter methylation among Indonesian astrocytoma patients.