Impact of MGMT methylation on overall survival in solid tumors: A systematic review and meta-analysis

ABDULLA ALZIBDEH[1], ALA'A KHANFAR[1], MAYSA AL-HUSSAINI[2], RAMIZ ABUHIJLIH[1], ISSA MOHAMAD[1], HIKMAT ABDEL-RAZEQ[3] and FAWZI ABUHIJLA[1]

[1]Department of Radiation Oncology, King Hussein Cancer Center, Amman 11941, Jordan; [2]Department of Pathology, King Hussein Cancer Center, Amman 11941, Jordan; [3]Department of Medical Oncology, King Hussein Cancer Center, Amman 11941, Jordan

Received August 14, 2025; Accepted November 21, 2025

DOI: 10.3892/etm.2025.13048

Abstract. O6-methylguanine-DNA methyltransferase (MGMT) serves a crucial role in DNA repair by removing alkyl lesions from the O6 position of guanine, maintaining genomic stability. Loss of MGMT expression, often due to promoter methylation, is linked to enhanced sensitivity to chemotherapy. While MGMT methylation has been observed in various cancers, its impact on overall survival (OS) in solid tumors remains uncertain. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, studies were selected from PubMed that examined the impact of MGMT methylation on OS in adult patients with solid tumors. Data were extracted where methylation status was defined, and OS was reported through hazard ratios (HRs) and confidence intervals (CIs) from either univariate or multivariable analyses. R version 4.4.2 and the 'meta' package were employed for the meta-analysis, using both fixed-effects (Mantel-Haenszel method) and random-effects (DerSimonian-Laird method with Hartung-Knapp adjustment) models based on the I^2 statistic for heterogeneity. Subgroup analyses were performed by cancer type, and publication bias was assessed through funnel plot inspection and Egger's regression. A total of 21 studies involving 2,946 patients met the inclusion criteria. The fixed-effects model showed a significant association between MGMT promoter methylation and poorer OS (HR=1.27; 95% CI, 1.13-1.42; P<0.0001); however, notable heterogeneity (I^2=64.7%) led to a non-significant result under the random-effects model (HR=1.26; 95% CI, 0.97-1.65; P=0.084). Subgroup analyses revealed that MGMT methylation was strongly associated with decreased survival in biliary tract (HR=2.31), cervical (HR=2.50) and duodenal cancers (HR=4.25), whereas melanoma exhibited improved survival (HR=0.32). Other cancer types, including colorectal, esophageal, head and neck, leiomyosarcoma, non-small cell lung cancer and pancreatic neuroendocrine tumors, demonstrated no notable relationship between MGMT methylation and OS. Sensitivity analyses confirmed the stability of these findings despite the inherent heterogeneity. In conclusion, MGMT promoter methylation may be a prognostic biomarker in select solid tumors; however, its impact on OS varies by cancer type. Further studies with standardized methylation assessment methods are warranted to clarify its prognostic and predictive utility, especially on OS.

Correspondence to: Dr Fawzi Abuhijla, Department of Radiation Oncology, King Hussein Cancer Center, Queen Rania Street, Al-Jubeiha, Amman 11941, Jordan
E-mail: fhijle@khcc.jo

Key words: MGMT methylation, overall survival, solid tumors, meta-analysis, prognostic biomarker, precision medicine, personalized medicine

Introduction

O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein responsible for combating adducts from O6-guanine (1,2). Alkylation at the O6 position of guanine renders the DNA vulnerable to point mutation and the formation of DNA crosslinks; all of which can predispose an individual to cancer (3). MGMT protein is expressed in lower amounts in some cancers, predominantly due to the hypermethylation of the MGMT promoter CpG (4,5). Abnormal methylation of gene promoters leads to a loss of gene function, which can confer a selective advantage to neoplastic cells, similar to the effects seen with genetic mutations (6). MGMT serves a pivotal role in repairing DNA damage caused by environmental carcinogens and alkylating chemotherapy drugs such as temozolomide (3); therefore, loss of MGMT function due to promoter methylation compromises DNA repair mechanisms, rendering tumor cells more vulnerable to alkylating agents and increasing DNA damage and apoptosis (7-9).

MGMT methylation has been extensively studied in glioblastoma, where numerous clinical studies have demonstrated that methylation of the MGMT promoter is an independent predictor of improved survival. For instance, a meta-analysis of 11 studies exclusively involving patients with glioblastoma revealed that patients with a methylated MGMT promoter experienced improved outcomes, with improvements in overall survival (OS) (10). MGMT promoter methylation also serves as a predictive marker for chemotherapy response in patients with glioblastoma (11,12).

Similar to high-grade gliomas (13), emerging data suggests MGMT methylation is also a prognostic factor for response to treatment in advanced neuroendocrine tumors (NETs). Studies have documented an association between MGMT status and clinical outcomes with alkylating agents (temozolomide, dacarbazine and streptozotocin-based therapies) in NET (14-16). A hypermethylated MGMT phenotype has been identified in multiple premalignant and malignant solid tumors, including colorectal (17), urothelial (18), pheochromocytomas and paragangliomas (19) and oral (20) tumors. However, the prognostic role of MGMT methylation on OS in solid tumors remains to be determined.

In the present systematic review and meta-analysis, the prognostic importance of MGMT methylation on OS in solid tumors was investigated. By pooling data from diverse studies, the analysis sought to evaluate the prognostic significance of MGMT methylation across different tumor types and identify cancers where MGMT methylation may serve as a predictive biomarker.

Materials and methods

The present meta-analysis and systematic review were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21).

Eligibility criteria. Studies were included in the meta-analysis if they met the following inclusion criteria: i) Population: Only studies involving human subjects were included, with research based solely on cell lines without accompanying clinical data, as well as studies focused on pediatric populations, being excluded. Additionally, studies concerning gliomas, lymphomas, leukemias or benign/premalignant conditions were not considered. However, investigations of brain metastases originating from solid tumors were included; ii) Methodology: MGMT methylation status had to be assessed using a method that was stated in detail, and the research needed to focus on malignant solid tumors; iii) Outcome: OS had to be reported as a study outcome and presented numerically, through hazard ratios (HRs) and 95% confidence intervals (95% CIs). HR estimates derived from either univariate or multivariate analyses comparing MGMT-methylated vs. non-methylated patients were accepted. When HR or 95% CI values were not provided in a paper, the paper was excluded; and iv) Language: Finally, only English-language articles published in peer-reviewed international journals were included, whereas review papers, meta-analyses and conference abstracts were excluded.

Search strategy. A systematic search of the literature was conducted in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) up to October 26, 2024. The search strategy in PubMed was structured as follows: ['MGMT' (title/abstract) OR 'O6-methylguanine-DNA methyltransferase' (title/abstract)] AND ['methylation' (title/abstract) OR 'promoter methylation' (title/abstract) OR 'epigenetic' (title/abstract)] AND ['prognosis' (title/abstract) OR 'survival' (title/abstract) OR 'outcome' (title/abstract)] OR 'mortality' (title/abstract) OR 'prognostic' (title/abstract) OR 'predictive' (title/abstract)] AND ['solid tumor' (title/abstract) OR 'solid cancer' (title/abstract) OR 'carcinoma' (title/abstract) OR 'sarcoma' (title/abstract) OR 'neoplasms' (Medical Subject Headings terms) NOT ['review' (publication type) OR 'meta-analysis' (publication type) OR 'systematic review' (publication type)] NOT ['glioma' (title/abstract) OR 'glioblastoma' (title/abstract) OR 'astrocytoma' (title/abstract) OR 'brain tumor' (title/abstract) OR 'brain cancer' (title/abstract)].

Study selection and data extraction. The titles and abstracts were independently screened two by reviewers, followed by a full-text assessment of studies that potentially satisfied the eligibility criteria. Any disagreements were resolved by consulting a third reviewer. Data extraction was performed using a standard form, capturing the title, first author, publication year, country, study design, cancer type, total sample size, number of cases with MGMT methylation, age, metastatic status, follow-up period, sample type, detection method, analysis type [multivariate (MV); yes or no], OS HR and upper and lower CIs.

Meta-analysis. Statistical analyses were performed in R (version 4.4.2; RStudio, Inc.), using the 'meta' (22) and 'metafor' packages (23). HR and corresponding 95% CI were utilized to assess the association between MGMT methylation status and OS. The overall effect estimate was derived using a fixed-effects model (Mantel-Haenszel method) and a random-effects model (DerSimonian-Laird method). Heterogeneity was assessed via Cochran's Q test and the I^2 statistic. Heterogeneity was considered significant when the χ^2 test $P<0.05$ and the I^2 statistic >50% (24); in the presence of significant heterogeneity, a random-effects model was adopted. Subgroup analyses stratified by cancer type were performed to explore heterogeneity sources. Publication bias was evaluated through funnel plot inspection and Egger's linear regression test. A sensitivity analysis, excluding individual studies iteratively, was conducted to assess the robustness of the results. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Included studies. A total of 21 studies met the inclusion criteria, comprising 2,946 patients (Fig. 1; Table I). The most frequently represented cancer types were colorectal cancer (n=6) and head and neck cancer (n=6), followed by non-small cell lung cancer (NSCLC) (n=2). The remaining cancer types were each represented by a single study: Pancreatic NET, biliary tract cancer, cervical cancer, duodenal cancer, esophageal cancer, leiomyosarcoma and melanoma.

In the included studies, a range of methylation detection techniques were used, including methylation-specific polymerase chain reaction (MSP), real-time quantitative MSP and pyrosequencing. A summary of the study characteristics is provided in Table I (25-45).

Pooled analysis. A total of two meta-analytic models were computed, fixed-effects and random-effects. Using the fixed-effects model (Mantel-Haenszel method), MGMT promoter methylation was significantly associated with worse OS, with a pooled HR of 1.27 (95% CI, 1.13-1.42; $P<0.0001$).

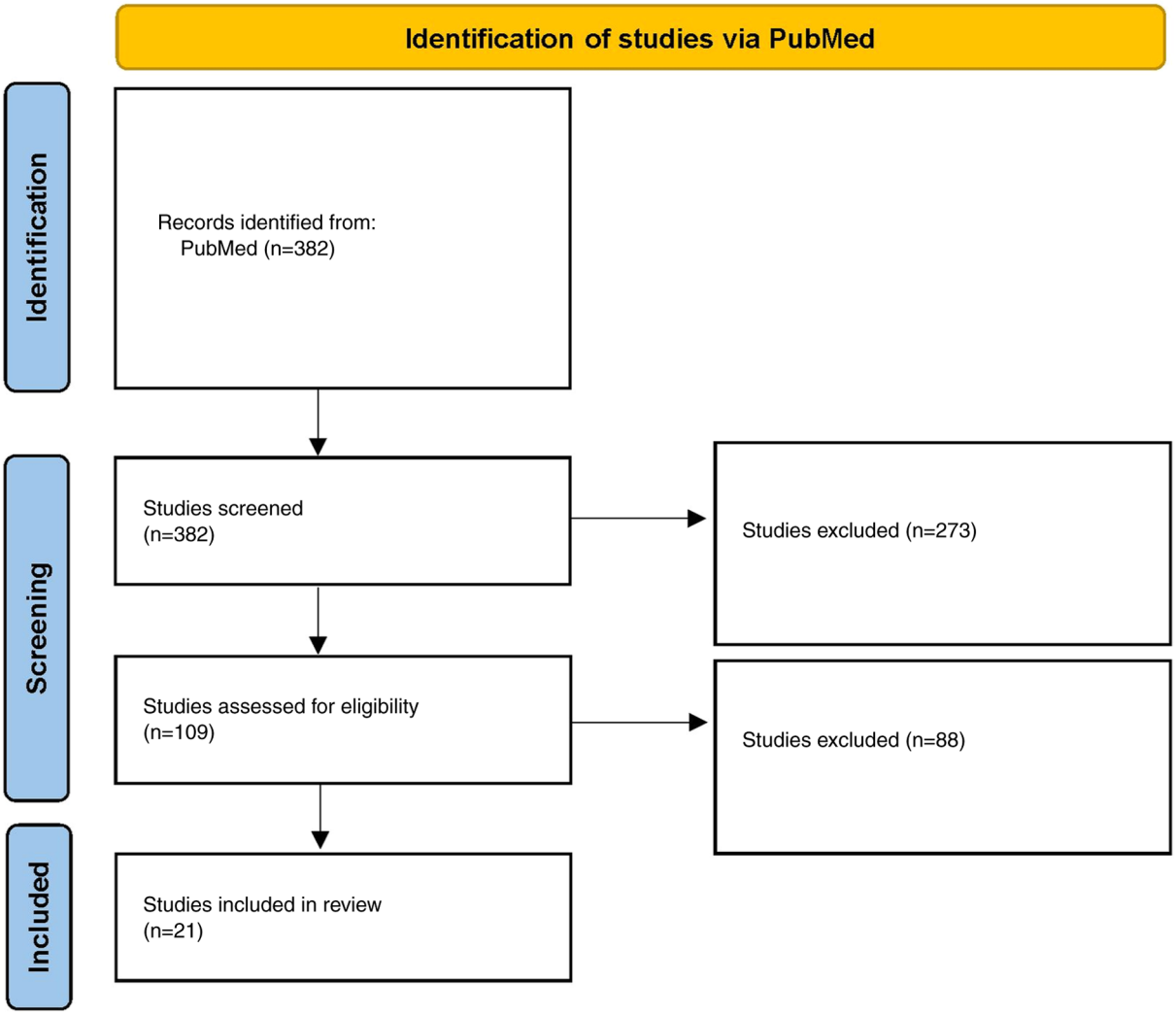

Figure 1. Study selection flow diagram. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrates the study selection process.

However, due to significant heterogeneity across studies [Q=56.68; degrees of freedom (df)=20; P<0.0001; I^2=64.7%], a random-effects model using the DerSimonian-Laird estimator with Hartung-Knapp adjustment was employed. Under this model, the association between MGMT methylation and OS was not statistically significant, with a pooled HR of 1.26 (95% CI, 0.97-1.65; P=0.084).

Subgroup analysis. Subgroup analyses stratified by cancer type demonstrated a significant difference in the effect of MGMT methylation on OS across tumor types (Q=28.60; df=9; P=0.0008). The corresponding pooled subgroup HRs and CIs are shown in Figs. 2 and 3. In biliary tract cancer, MGMT methylation was associated with a significantly worse OS (HR=2.31; 95% CI, 1.44-3.71). A similar detrimental effect was observed in cervical cancer (HR=2.50; 95% CI, 1.20-5.20) and duodenal cancer, which showed the highest HR among all subgroups (HR=4.25; 95% CI, 2.00-9.04). By contrast, melanoma demonstrated a significant association with improved survival (HR=0.32; 95% CI, 0.12-0.87). For colorectal cancer, the pooled estimate was HR=1.08 (95% CI, 0.77-1.51), indicating a non-significant relationship; similarly, head and neck cancer showed a non-significant association (HR=1.15; 95% CI, 0.82-1.61). Other cancer types, including esophageal cancer (HR=1.00; 95% CI, 0.55-1.80), leiomyosarcoma (HR=1.70; 95% CI, 0.67-4.29), NSCLC (HR=1.14, 95% CI, 0.37-3.55) and pancreatic NET (HR=2.06; 95% CI, 0.44-9.61), were also not significantly associated with OS.

Publication bias. The Egger's regression test was not significant (t=-0.13; P=0.895), suggesting no substantial evidence of publication bias among the included studies (Fig. 4).

Sensitivity analysis. A leave-one-out sensitivity analysis was performed for the overall pooled meta-analysis using a random-effects model with Hartung-Knapp adjustment. The analysis demonstrated that no single study exerted a disproportionate influence on the overall pooled estimate. Across all iterations, the HR remained relatively stable (ranging from 1.20 to 1.33), and heterogeneity (I^2) was within a moderate range (59-67%). Notably, the removal of certain studies [such as that by Guadagni *et al*, 2017 (41) or that by Nilsson *et al*, 2013 (28)] led to a significant association (P<0.05), but the overall findings remained generally consistent (Fig. 5).

Table I. Characteristics of included studies.

Author, year	Country	Study design	Cancer type	Age (median or mean)	Patients, n	Patients with MGMT methylation status	Metastatic patients included	Metastatic patients, %	Sampling method	Methylation detection method	Multi-variable analysis	OS, HR (95% CI)	PFS, HR (95% CI)	(Refs.)
Gupta *et al*, 2023	India	Retrospective	Cervical	48.44	220	48	Yes	7.30	Serum	Nested MSP	Yes	2.50 (1.20-5.19)	Not reported	(25)
Cannella *et al*, 2023	Italy	Retrospective	Leiomyo-sarcoma	58	32	32	Yes	100	Tissue	MSP	No	1.70 (0.66-4.20)	2.2 (1-4.8)	(26)
Jamai *et al*, 2023	Tunisia	Retrospective	Colorectal	63	111	111	Yes	50	Tissue	MSP	Yes	1.75 (1.30-2.35)	Not reported	(37)
Shima *et al*, 2011	USA	Retrospective	Colorectal	66.2	855	855	Yes	NA	Tissue	MethyLight (Q-MSP)	Yes	1.08 (0.88-1.32)	Not reported	(39)
Fu *et al*, 2016	China	Retrospective	Duodenal	64.2	64	64	No	0	Tissue	MethyLight (MSP)	Yes	4.25 (2.00-9.05)	2.80 (1.43-5.48)	(33)
Niger *et al*, 2022 (29)	Italy	Retrospective	Biliary tract cancer	66	164	164	Yes	NA	Tissue	Pyrose-quencing for methylation	Yes	2.31 (1.44-3.71)	1.24 (0.78-1.98)	(40)
Guadagni *et al*, 2017	Italy	Retrospective	Melanoma	64.1	27	27	No	0	Tissue	MS-MLPA	Yes	0.32 (0.12-0.89)	Not reported	(41)
Viúdez *et al*, 2016 (31)	USA	Retrospective	Pancreatic neuroendo-crine cancer	57	92	92	No	0	Tissue	MSP	Yes	2.06 (0.44-9.57)	1.09 (0.52-2.29)	(42)
Supic *et al*, 2011	Serbia	Retrospective	Head and neck	58	47	47	No	0	Tissue	MSP	No	1.23 (0.41-3.87)	Not reported	(43)
Taioli *et al*, 2009	USA	Retrospective	Head and neck	62.2	88	88	Yes	39.80	Tissue	MSP; Q-MS using pyro-sequencing	Yes	2.17 (1.11-4.23)	3.49 (1.62-7.52)	(44)
Chen *et al*, 2009 (42)	Taiwan	Retrospective	Colorectal	65.5	117	117	Yes	21.40	Tissue	MSP	Yes	1.33 (0.61-2.92)	Not reported	(34)
Morano *et al*, 2018	Italy	Prospective	Colorectal	62	25	25	Yes	100	Tissue	MSP	No	0.75 (0.24-2.11)	0.46 (0.13-0.95)	(45)
Safar *et al*, 2005	USA	Retrospective	NSCLC	67	105	105	Yes	22	Tissue	MSP	Yes	0.59 (0.21-1.63)	Not reported	(27)
Nilsson *et al*, 2013 (36)	Sweden	Retrospective	Colorectal	NA	111	111	No	0	Tissue	Pyrosequen-cing for methylation	Yes	0.36 (0.15-0.87)	Not reported	(28)

Table I. Continued.

Author, year	Country	Study design	Cancer type	Age (median or mean)	Patients, n	Patients with MGMT methylation status	Metastatic patients included	Metastatic patients, %	Sampling method	Methylation detection method	Multi-variable analysis	OS, HR (95% CI)	PFS, HR (95% CI)	(Refs.)
Lu *et al*, 2011	China	Retrospective	Esophageal	61.8	125	120	Yes	1	Tissue	MSP	No	1.00 (0.55-1.79)	Not reported	(35)
Brabender *et al*, 2003 (37)	Multi-national	Retrospective	NSCLC	63.3	90	90	No	0	Tissue	Q-MSP (TaqMan)	Yes	1.89 (1.06-3.37)	2.60 (1.60-3.60)	(29)
Dikshit *et al*, 2007	Multi-national	Retrospective	Head and neck	60.4	235	212	No	0	Tissue	MSP	Yes	1.02 (0.66-1.58)	Not reported	(30)
Šupić *et al*, 2009	Serbia	Retrospective	Head and neck	58	77	77	No	0	Tissue	MSP	Yes	0.67 (0.34-1.33)	Not reported	(31)
Li *et al*, 2014 (45)	China	Retrospective	Colorectal	58.8	282	282	Yes	NA	Tissue	MS-HRM	Yes	1.05 (0.69-1.61)	Not reported	(38)
Zuo *et al*, 2004	USA	Retrospective	Head and neck	63.5	94	94	Yes	38	Tissue	MS-HRM	No	1.66 (1.11-5.18)	2.38 (1.14-7.26)	(32)
Sun *et al*, 2012	USA	Prospective	Head and neck	58	197	185	Yes	66	Saliva	Q-MSP	Yes	0.91 (0.47-1.75)	0.96 (0.53-1.73)	(36)

OS, overall survival; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; NSCLC, non-small cell lung cancer; MSP, methylation specific PCR; Q-MSP, quantitative MSP; MS-HRM, methylation-sensitive high-resolution melting; MS-PCR, multiplex nested methylation-specific PCR; MS-MLPA, methylation-specific multiplex ligation-dependent probe amplification.

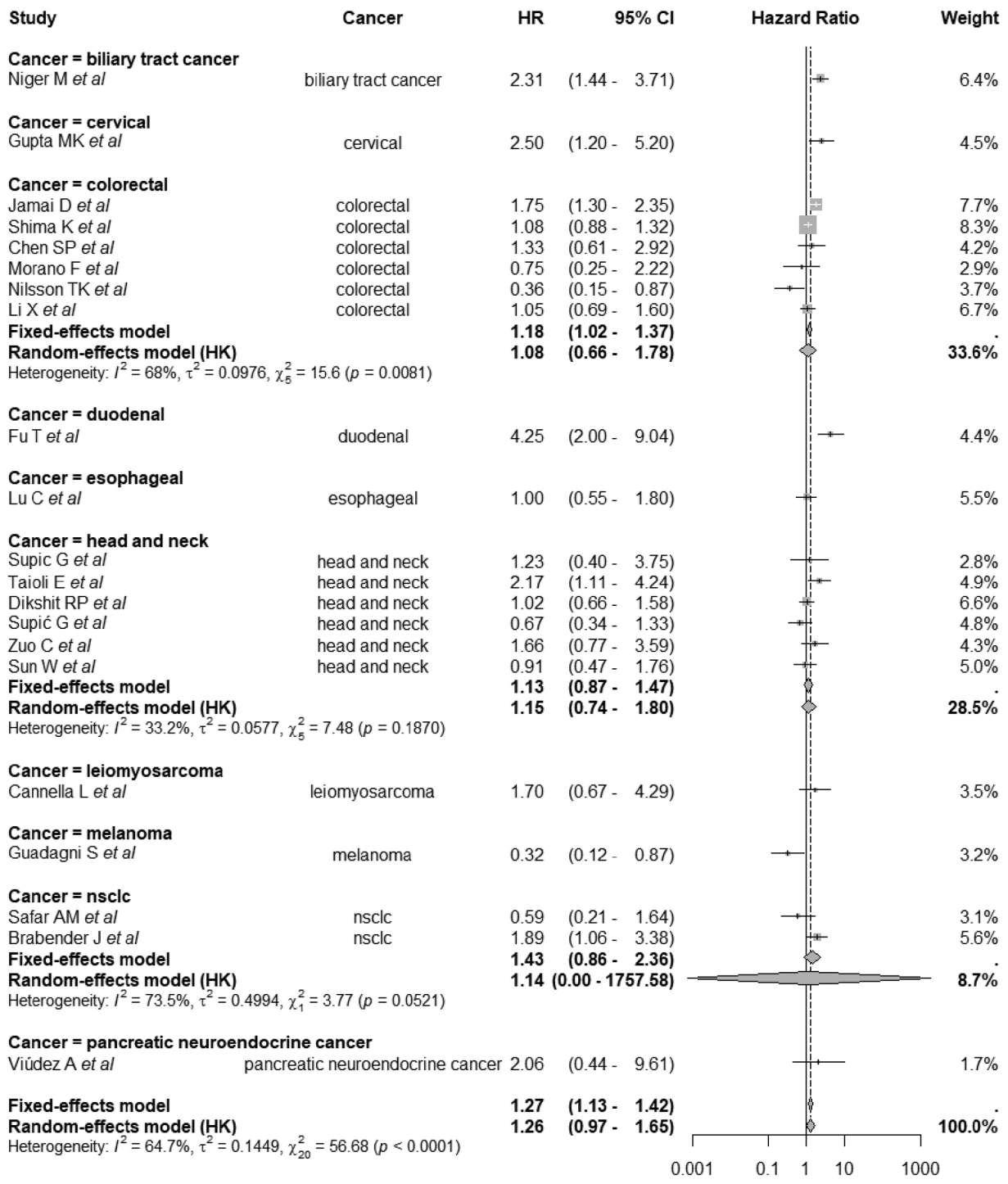

Figure 2. Forest plot of MGMT promoter methylation and OS. The forest plot displays individual HRs with corresponding 95% CIs for the association between MGMT promoter methylation and OS across the included studies. Both fixed-effects and random-effects model estimates are presented, along with heterogeneity statistics. OS, overall survival; CI, confidence intervals; HR, hazard ratio; MGMT, O6-methylguanine-DNA methyltransferase.

Discussion

Against the backdrop of the need for prognostic biomarkers for cancer, to the best of our knowledge, the present meta-analysis investigated for the first time the prognostic relevance of MGMT promoter methylation on OS across a mix of non-glioma solid cancers in adult patients. A total of 21 studies involving 2,946 patients were included, encompassing diverse solid cancer types. The findings provide a nuanced understanding of the potential role of MGMT methylation as a prognostic biomarker.

MGMT promoter methylation is a relatively common epigenetic finding in numerous solid tumors, which are found in ~33% of colorectal cancers (46), frequently arising early in the adenoma-carcinoma sequence (47). Similarly, the frequency of MGMT promoter methylation appears on the order of 20-30% in patients with duodenal cancer, independent of microsatellite instability or KRAS status (33). In head

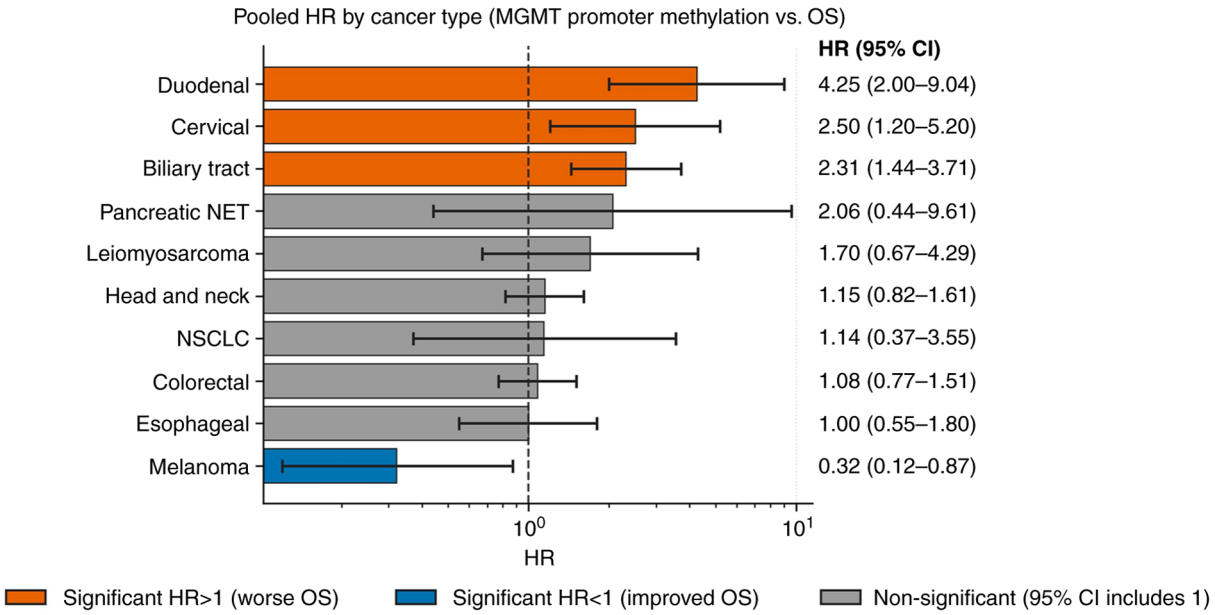

Figure 3. Histogram-style summary of the pooled HRs for OS associated with MGMT promoter methylation across different solid tumor types. Bars represent pooled HR for each cancer type with horizontal lines indicating 95% CIs. The vertical dashed line (HR=1) represents the null reference line (no effect). Orange bars indicate a significant association with worse OS (HR>1), blue bars indicate a significant association with improved OS (HR<1) and gray bars represent non-significant associations where the 95% CI includes 1. The plot uses a logarithmic x-axis to facilitate comparison across cancer types with differing effect magnitudes. HR, hazard ratio; CI, confidence interval; OS, overall survival; NSCLC, non-small cell lung cancer; NET, neuroendocrine tumor; MGMT, O6-methylguanine-DNA methyltransferase.

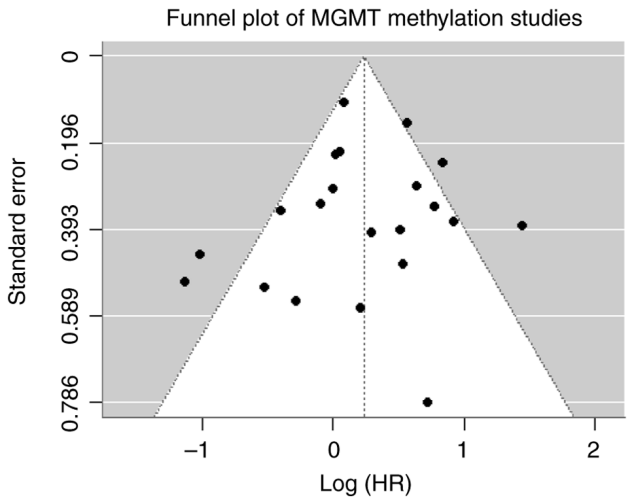

Figure 4. Funnel plot assessing publication bias. This funnel plot examines the potential for publication bias among the included studies. It shows the distribution of study effect sizes relative to their standard errors. The symmetrical distribution observed, alongside the non-significant Egger's test (P=0.895), suggests no substantial publication bias. HR, hazard ratio; MGMT, O6-methylguanine-DNA methyltransferase.

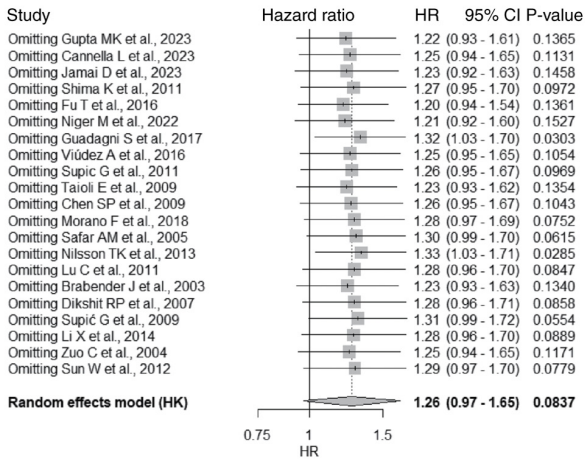

Figure 5. Sensitivity analysis. The sensitivity analysis was performed using the leave-one-out approach, and the figure demonstrates the robustness of the pooled HR by sequentially excluding each study. The analysis confirms that the overall effect estimate remains stable (HR range: 1.20-1.33) and that no single study disproportionately influences the results, despite moderate heterogeneity. The pooled estimate is based on a random-effects model with HK adjustment. HR, hazard ratio; CI, confidence interval; HK, Hartung-Knapp.

and neck cancers, MGMT promoter methylation occurs in ~47% of cases (48), and is consistently observed in a notable portion of oral, pharyngeal and laryngeal tumors. Such alteration often co-occurs with tobacco and alcohol exposure and human papillomavirus (HPV) infection, suggesting a field defect in carcinogenesis (48). Similarly, MGMT promoter methylation is often part of the HPV-driven CpG island hypermethylation phenotype in cervical carcinogenesis (49). It occurs in a minority of cervical carcinomas but rises with disease progression, with 20-30% of invasive cervical cancers harboring MGMT methylation, increasing from <5% in low-grade lesions to >25% in invasive cancer (49).

In NSCLC, frequency of this alteration ranges between 20-35% of tumors, with MGMT methylation being slightly more common in advanced-stage NSCLC compared with early-stage disease (50). Smoking appears to affect MGMT promoter methylation status in tumors; for example, in patients with esophageal cancer with a history of heavy tobacco or

betel use, MGMT promoter methylation has been detected in up to 70% of cases using serum DNA assays (51). Notably, tissue-based studies report lower frequencies; MGMT methylation is noted in 30-40% of esophageal tumors (51,52).

Moreover, one-third of pancreatic neuroendocrine tumors exhibit MGMT hypermethylation and loss of MGMT expression (53), with MGMT protein loss occurring more frequently in higher-grade tumors (54). MGMT promoter methylation is observed in ~38% of biliary tract cancers, with intrahepatic cholangiocarcinomas showing 38% methylation, extrahepatic cholangiocarcinomas showing 26% and gallbladder cancers showing up to 62% (55). In leiomyosarcoma, MGMT methylation is less studied, but it was reported in a study that it was present in 5 of 9 uterine leiomyosarcoma cases (56). By contrast, among soft-tissue sarcomas overall, MGMT methylation is less common, occurring in ~13% of cases (57), and in melanoma, MGMT promoter methylation occurs in 15-30% of cases (58).

In the present study the pooled analysis under the fixed-effects model revealed a significant association between MGMT promoter methylation and worse OS. However, the presence of substantial heterogeneity (I^2=64.7%) warranted the use of a random-effects model with Hartung-Knapp adjustment, which yielded a non-significant association.

In the subgroup analysis performed in the present study, MGMT promoter methylation had variable impact on OS across cancer types, occasionally reaching significance. The divergent prognostic effects of MGMT methylation noted on subgroup analysis may be explained by the role of the MGMT gene in DNA repair. Encoded by the gene, MGMT protein is a key DNA repair enzyme that counteracts adduct formation at the O6 position of guanine (1,2). When alkylated, DNA becomes prone to point mutations and the formation of crosslinks (3). The resultant compromise in DNA repair capacity has two major consequences; this includes increased chemo-sensitivity and genomic instability and progression. Tumor cells lacking MGMT cannot easily repair the lethal O6 guanine lesions induced by alkylating chemotherapeutic agents (including temozolomide and dacarbazine). As a result, MGMT-methylated cancers are more sensitive to these drugs, manifesting as improved treatment response and survival. This mechanism underlies the use of MGMT status to predict benefit from temozolomide in patients with glioblastoma. In a prospective study, MGMT-promoter methylation was associated with improved progression-free survival and OS (although 95% CI were not mentioned) with temozolomide-based treatment in patients with advanced NETs (53); this was also reported in melanomas (58). Notably, in the present analysis, the only cancer showing a significant increase in OS with MGMT methylation was melanoma, with a HR of 0.32.

On the other hand, MGMT loss permits accumulation of O6-methylguanine lesions from spontaneous alkylation via environmental carcinogens or cellular processes (51). These unrepaired lesions lead to a characteristic G:C to A:T mutation pattern due to misrepair (51); consequently, MGMT-methylated cells can acquire additional driver mutations (46), therefore contributing to cancer development and progression. This may be associated with the aforementioned relationship between the exposure to smoking and betel nut and MGMT promoter methylation status. Moreover, the mutator phenotype from MGMT loss might produce more aggressive subclones, associating with advanced stage or recurrence; for example, MGMT-methylated head and neck squamous cell carcinoma have been associated with more frequent lymph node metastases and tumor recurrences (48). In cervical cancer, methylation-induced MGMT downregulation is associated with poor survival (49), likely as it occurs as part of a broader CpG island hypermethylation phenotype leading to concurrent epigenetic inactivation of multiple tumor suppressor genes (such as CDKN2A, DAPK, RARB and HIC1) (59,60). Therefore, in the absence of effective alkylator therapy, MGMT methylation often portends a worse prognosis due to increased genomic instability and tumor aggressiveness. According to the present analysis, cancers demonstrating a significant decrease in survival were duodenal, biliary tract and cervical cancers.

Finally, the remaining cancer types, colorectal, esophageal, head and neck, leiomyosarcoma, NSCLC and pancreatic NET, demonstrated no significant relationship with OS in the present analysis. Lack of association in the present results does not exclude the presence of a clinically relevant relationship, as a subset of patients may still derive an advantage or disadvantage from harboring MGMT promoter methylation, but further studies are needed to confirm this.

The present study has several limitations. First, the evidence is drawn mostly from observational studies, a number of which studied MGMT promoter methylation status as part of a larger methylation panel, making results of such studies prone to bias and confounding. Additionally, such studies are also predisposed to residual confounding; MGMT promoter methylation might coincide with other genetic or epigenetic alterations that drive prognosis, making it challenging to isolate the effect of MGMT promoter methylation *per se*. Second, a number of tumor types were represented by a single study with modest sample sizes; this limited evidence base within each subgroup reduces statistical power and confidence in the subgroup-specific estimates. Also, the inclusion of different cancer subtypes in a single analysis makes it hard to draw insights on such a heterogeneous group of patients. Third, there was considerable heterogeneity in the methodologies for determining MGMT methylation status; for example, there was no centralized standard for what threshold defines the 'methylated' status; this can result in misclassification and variability in results across studies. Fourth, the high between-study heterogeneity in the pooled analysis limits the strength of conclusions from the summary estimate; thus, the lack of a significant overall effect in the random-effects model may be due to true differences in effect rather than absence of any biological effect. Publication bias is another concern, as studies finding a significant prognostic effect of a biomarker are more likely to be published. While the present study attempted to assess this (via funnel plot symmetry and Egger's test), the interpretability was limited by the small number of studies in numerous subgroups. Overall, these limitations suggest that the findings should be interpreted with caution.

There is a need for well-designed prospective studies that uniformly evaluate MGMT promoter methylation and follow patients for survival outcomes, especially OS, as progression-free survival or other potentially surrogate survival outcomes may not be truly significant for the clinical journey for the patient. Studies should also work on harmonizing the MGMT promoter methylation evaluation procedures, which includes agreeing on an optimal laboratory method and defining clinically relevant cut-off values.

In summary, MGMT promoter methylation may be associated with worse OS in select cancer types, but the evidence remains inconsistent when accounting for heterogeneity. The findings highlight the importance of tumor-specific context in biomarker research and reinforce the need for further high-quality studies to validate the prognostic utility of MGMT methylation. Moreover, laboratory studies are needed to understand the mechanisms behind MGMT promoter methylation impact on tumor behavior, which could inform targeted therapeutic strategies.

Acknowledgements

This abstract was presented at the American Society of Clinical Oncology annual meeting, June 2025, which was held in Chicago, Illinois, and was published as Abstract no. 3146.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AA and FA designed the overall concept and outline of the manuscript. AA, AK, MAH, RA, IM, HAR and FA contributed to data collection and review of literature; in addition these authors contributed to the writing and editing of the manuscript. AA performed the statistical analysis. All authors have read and approved the final version of the manuscript. AA and FA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Montesano R, Becker R, Hall J, Likhachev A, Lu SH, Umbenhauer D and Wild CP: Repair of DNA alkylation adducts in mammalian cells. Biochimie 67: 919-928, 1985.
2. Pegg AE, Dolan ME and Moschel RC: Structure, function, and inhibition of O6-alkylguanine-DNA alkyltransferase. Prog Nucleic Acid Res Mol Biol 51: 167-223, 1995.
3. Jacinto FV and Esteller M: MGMT hypermethylation: A prognostic foe, a predictive friend. DNA Repair (Amst) 6: 1155-1160, 2007.
4. Esteller M, Hamilton SR, Burger PC, Baylin SB and Herman JG: Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. Cancer Res 59: 793-797, 1999.
5. Qian XC and Brent TP: Methylation hot spots in the 5'flanking region denote silencing of the O6-methylguanine-DNA methyltransferase gene. Cancer Res 57: 3672-3677, 1997.
6. Jones PA and Baylin SB: The fundamental role of epigenetic events in cancer. Nat Rev Genet 3: 415-428, 2002.
7. Bernd K, Fritz G, Mitra S and Coquerelle T: Transfection and expression of human O6-methylguanine-DNA methyltransferase (MGMT) cDNA in Chinese hamster cells: The role of MGMT in protection against the genotoxic effects of alkylating agents. Carcinogenesis 12: 1857-1867, 1991.
8. Glassner BJ, Weeda G, Allan JM, Broekhof JLM, Carls NHE, Donker I, Engelward BP, Hampson RJ, Hersmus R, Hickman MJ, *et al*: DNA repair methyltransferase (Mgmt) knockout mice are sensitive to the lethal effects of chemotherapeutic alkylating agents. Mutagenesis 14: 339-347, 1999.
9. Hansen RJ, Nagasubramanian R, Delaney SM, Samson LD and Dolan ME: Role of O6-methylguanine-DNA methyltransferase in protecting from alkylating agent-induced toxicity and mutations in mice. Carcinogenesis 28: 1111-1116, 2007.
10. Wang S, Song C, Zha Y and Li L: The prognostic value of MGMT promoter status by pyrosequencing assay for glioblastoma patients' survival: A meta-analysis. World J Surg Oncol 14: 261, 2016.
11. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, *et al*: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352: 997-1003, 2005.
12. Hegi ME, Liu L, Herman JG, Stupp R, Wick W, Weller M, Mehta MP and Gilbert MR: Correlation of O6-Methylguanine Methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. J Clin Oncol 26: 4189-4199, 2008.
13. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB and Herman JG: Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med 343: 1350-1354, 2000.
14. Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, Meyerhardt JA, Clark JW, Stuart K, Fuchs CS and Redston MS: O6-methylguanine DNA methyltransferase deficiency and response to Temozolomide-based therapy in patients with neuroendocrine tumors. Clin Cancer Res 15: 338-345, 2000.
15. Walter T, Van Brakel B, Vercherat C, Hervieu V, Forestier J, Chayvialle JA, Molin Y, Lombard-Bohas C, Joly MO and Scoazec JY: O6-Methylguanine-DNA methyltransferase status in neuroendocrine tumours: Prognostic relevance and association with response to alkylating agents. Br J Cancer 112: 523-531, 2015.
16. Kunz PL, Graham NT, Catalano PJ, Nimeiri HS, Fisher GA, Longacre TA, Suarez CJ, Martin BA, Yao JC, Kulke MH, *et al*: Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). J Clin Oncol 41: 1359-1369, 2023.
17. Svrcek M, Buhard O, Colas C, Coulet F, Dumont S, Massaoudi I, Lamri A, Hamelin R, Cosnes J, Oliveira C, *et al*: Methylation tolerance due to an O6-methylguanine DNA methyltransferase (MGMT) field defect in the colonic mucosa: An initiating step in the development of mismatch repair-deficient colorectal cancers. Gut 59: 1516-1526, 2010.
18. Millis SZ, Bryant D, Basu G, Bender R, Vranic S, Gatalica Z and Vogelzang NJ: Molecular profiling of infiltrating urothelial carcinoma of bladder and nonbladder origin. Clin Genitourin Cancer 13: e37-e49, 2015.
19. Hadoux J, Favier J, Scoazec JY, Leboulleux S, Ghuzlan AAl, Caramella C, Déandreis D, Borget I, Loriot C, Chougnet C, *et al*: SDHB mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma. Int J Cancer 135: 2711-2720, 2014.
20. Mithani SK, Mydlarz WK, Grumbine FL, Smith IM and Califano JA: Molecular genetics of premalignant oral lesions. Oral Dis 13: 126-133, 2007.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med 18: e1003583, 2021.
22. Balduzzi S, Rücker G and Schwarzer G: How to perform a Meta-analysis with R: A practical tutorial. Evid Based Ment Health 22: 153-160, 2019.
23. Viechtbauer W: Conducting Meta-analyses in R with the metafor package. J Stat Softw 36: 1-48, 2010.

24. Higgins JPT, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 327: 557-560, 2003.
25. Gupta MK, Kushwah AS, Singh R, Srivastava K and Banerjee M: Genetic and epigenetic alterations in MGMT gene and correlation with concomitant chemoradiotherapy (CRT) in cervical cancer. J Cancer Res Clin Oncol 149: 15159-15170, 2023.
26. Cannella L, Della Monica R, Marretta AL, Iervolino D, Vincenzi B, De Chiara AR, Clemente O, Buonaiuto M, Barretta ML, Di Mauro A, *et al*: The impact of O6-Methylguanine-DNA methyltransferase (MGMT) promoter methylation on the outcomes of patients with leiomyosarcoma treated with dacarbazine. Cells 12: 1635, 2023.
27. Safar AM, Spencer H III, Su X, Coffey M, Cooney CA, Ratnasinghe LD, Hutchins LF and Fan CY: Methylation profiling of archived non-small cell lung cancer: A promising prognostic system. Clin Cancer Res 11: 4400-4405, 2005.
28. Nilsson TK, Löf-Öhlin ZM and Sun XF: DNA methylation of the p14ARF, RASSF1A and APC1A genes as an independent prognostic factor in colorectal cancer patients. Int J Oncol 42: 127-133, 2013.
29. Brabender J, Usadel H, Metzger R, Schneider PM, Park J, Salonga D, Tsao-Wei DD, Groshen S, Lord RV, Takebe N, *et al*: Quantitative O(6)-methylguanine DNA methyltransferase methylation analysis in curatively resected non-small cell lung cancer: Associations with clinical outcome. Clin Cancer Res 9: 223-227, 2003.
30. Dikshit RP, Gillio-Tos A, Brennan P, De Marco L, Fiano V, Martinez-Peñuela JM, Boffetta P and Merletti F: Hypermethylation, risk factors, clinical characteristics, and survival in 235 patients with laryngeal and hypopharyngeal cancers. Cancer 110: 1745-1751, 2007.
31. Šupić G, Kozomara R, Branković-Magić M, Jović N and Magić Z: Gene hypermethylation in tumor tissue of advanced oral squamous cell carcinoma patients. Oral Oncol 45: 1051-1057, 2009.
32. Zuo C, Ai L, Ratliff P, Suen JY, Hanna E, Brent TP and Fan CY: O6-Methylguanine-DNA methyltransferase gene: Epigenetic silencing and prognostic value in head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 13: 967-975, 2009.
33. Fu T, Sharmab A, Xie F, Liu Y, Li K, Wan W, Baylin SB, Wolfgang CL and Ahuja N: Methylation of MGMT is associated with poor prognosis in patients with stage III duodenal adenocarcinoma. PLoS One 11: e0162929, 2016.
34. Chen SP, Chiu SC, Wu CC, Lin SZ, Kang JC, Chen YL, Lin PC, Pang CY and Harn HJ: The association of methylation in the promoter of APC and MGMT and the prognosis of Taiwanese CRC patients. Genet Test Mol Biomarkers 13: 67-71, 2009.
35. Lu C, Xie H, Wang F, Shen H and Wang J: Diet folate, DNA methylation and genetic polymorphisms of MTHFR C677T in association with the prognosis of esophageal squamous cell carcinoma. BMC Cancer 11: 91, 2025.
36. Sun W, Zaboli D, Wang H, Liu Y, Arnaoutakis D, Khan T, Khan Z, Koch WM and Califano JA: Detection of TIMP3 promoter hypermethylation in salivary rinse as an independent predictor of local recurrence-free survival in head and neck cancer. Clin Cancer Res 18: 1082-1091, 2012.
37. Jamai D, Gargouri R, Selmi B and Khabir A: ERCC1 and MGMT methylation as a predictive marker of relapse and FOLFOX response in colorectal cancer patients from south tunisia. Genes (Basel) 14: 1467, 2023.
38. Li X, Hu F, Wang Y, Yao X, Zhang Z, Wang F, Sun G, Cui BB, Dong X and Zhao Y: CpG island methylator phenotype and prognosis of colorectal cancer in Northeast China. Biomed Res Int 2014: 236361, 2014.
39. Shima K, Morikawa T, Baba Y, Nosho K, Suzuki M, Yamauchi M, Hayashi M, Giovannucci E, Fuchs CS and Ogino S: MGMT promoter methylation, loss of expression and prognosis in 855 colorectal cancers. Cancer Causes Control 22: 301-309, 2011.
40. Niger M, Nichetti F, Casadei-Gardini A, Morano F, Pircher C, Tamborini E, Perrone F, Canale M, Lipka DB, Vingiani A, *et al*: MGMT inactivation as a new biomarker in patients with advanced biliary tract cancers. Mol Oncol 16: 2733-2746, 2022.
41. Guadagni S, Fiorentini G, Clementi M, Palumbo G, Masedu F, Deraco M, De Manzoni G, Chiominto A, Valenti M and Pellegrini C: MGMT methylation correlates with melphalan pelvic perfusion survival in stage III melanoma patients: A pilot study. Melanoma Res 27: 439-447, 2017.
42. Viúdez A, Carvalho FLF, Maleki Z, Zahurak M, Laheru D, Stark A, Azad NS, Wolfgang CL, Baylin S, Herman JG, *et al*: A new immunohistochemistry prognostic score (IPS) for recurrence and survival in resected pancreatic neuroendocrine tumors (PanNET). Oncotarget 7: 24950-24961, 2016.
43. Supic G, Kozomara R, Jovic N, Zeljic K and Magic Z: Prognostic significance of tumor-related genes hypermethylation detected in cancer-free surgical margins of oral squamous cell carcinomas. Oral Oncol 47: 702-708, 2011.
44. Taioli E, Ragin C, Wang X hong, Chen J, Langevin SM, Brown AR, Gollin SM, Garte S and Sobol RW: Recurrence in oral and pharyngeal cancer is associated with quantitative MGMT promoter methylation. BMC Cancer 9: 354, 2009.
45. Morano F, Corallo S, Niger M, Barault L, Milione M, Berenato R, Moretto R, Randon G, Antista M, Belfiore A, *et al*: Temozolomide and irinotecan (TEMIRI regimen) as salvage treatment of irinotecan-sensitive advanced colorectal cancer patients bearing MGMT methylation. Ann Oncol 29: 1800-1806, 2018.
46. Ogino S, Kawasaki T, Kirkner GJ, Suemoto Y, Meyerhardt JA and Fuchs CS: Molecular correlates with MGMT promoter methylation and silencing support CpG island methylator phenotype-Low (CIMP-Low) in colorectal cancer. Gut 56: 1564-1571, 2017.
47. Li Y, Lyu Z, Zhao L, Cheng H, Zhu D, Gao Y, Shang X and Shi H: Prognostic value of MGMT methylation in colorectal cancer: A meta-analysis and literature review. Tumour Biol 36: 1595-1601, 2015.
48. Cai F, Xiao X, Niu X, Shi H and Zhong Y: Aberrant Methylation of MGMT Promoter in HNSCC: A Meta-Analysis. PLoS One 11: e0163534, 2016.
49. Choi B, Na Y, Whang MY, Ho JY, Han MR, Park SW, Song H, Hur SY and Choi YJ: MGMT Methylation is associated with human papillomavirus infection in cervical dysplasia: A longitudinal study. J Clin Med 12: 6188, 2023.
50. Chen L, Wang Y, Liu F, Xu L, Peng F, Zhao N, Fu B, Zhu Z, Shi Y, Liu J, *et al*: A systematic review and meta-analysis: Association between MGMT hypermethylation and the clinicopathological characteristics of non-small-cell lung carcinoma. Sci Reports 8: 1439, 2018.
51. Das M, Sharma SK, Sekhon GS, Saikia BJ, Mahanta J and Phukan RK: Promoter methylation of MGMT gene in serum of patients with esophageal squamous cell carcinoma in North East India. Asian Pac J Cancer Prev 15: 9955-9960, 2014.
52. Zhang L, Lu W, Miao X, Xing D, Tan W and Lin D: Inactivation of DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation and its relation to p53 mutations in esophageal squamous cell carcinoma. Carcinogenesis 24: 1039-1044, 2003.
53. Brighi N, Lamberti G, Andrini E, Mosconi C, Manuzzi L, Donati G, Lisotti A and Campana D: Prospective evaluation of MGMT-Promoter methylation status and correlations with outcomes to Temozolomide-based chemotherapy in Well-differentiated neuroendocrine tumors. Curr Oncol 30: 1381-1394, 2023.
54. Yagi K, Ono H, Kudo A, Kinowaki Y, Asano D, Watanabe S, Ishikawa Y, Ueda H, Akahoshi K, Tanaka S and Tanabe M: MGMT is frequently inactivated in pancreatic NET-G2 and is associated with the therapeutic activity of STZ-based regimens. Sci Reports 13: 7535, 2023.
55. Niger M, Morano F, Manglaviti S, Nichetti F, Tamborini E, Perrone F, Marcuzzo M, Peverelli G, Brambilla M, Pagani F, *et al*: 732P-Is MGMT methylation a new therapeutic target for biliary tract cancer? Ann Oncol 30: v281, 2019.
56. Bujko M, Kowalewska M, Danska-Bidzinska A, Bakula-Zalewska E, Siedecki JA and Bidzinski M: The promoter methylation and expression of the O6-methylguanine-DNA methyltransferase gene in uterine sarcoma and carcinosarcoma. Oncol Lett 4: 551-555, 2012.
57. Jakob J, Hille M, Sauer C, Ströbel P, Wenz F and Hohenberger P: O6-methylguanine-DNA methyltransferase (MGMT) Promoter methylation is a rare event in soft tissue sarcoma. Radiat Oncol 7: 180, 2012.
58. Schraml P, Von Teichman A, Mihic-Probst D, Simcock M, Ochsenbein A, Dummer R, Michielin O, Seifert B, Schläppi M, Moch H and von Moos R: Predictive value of the MGMT promoter methylation status in metastatic melanoma patients receiving First-line temozolomide plus bevacizumab in the trial SAKK 50/07. Oncol Rep 28: 654-668, 2012.
59. Kazanets A, Shorstova T, Hilmi K, Marques M and Witcher M: Epigenetic silencing of tumor suppressor genes: Paradigms, puzzles, and potential. Biochim Biophys Acta 1865: 275-288, 2025.
60. Esteller M: CpG island hypermethylation and tumor suppressor genes: A booming present, a brighter future. Oncogene 21: 5427-5440, 2002.