Int J Clin Exp Pathol 2015;8(9):11560-11564
www.ijcep.com /ISSN:1936-2625/IJCEP0012290

Original Article

Prognosis value of MGMT promoter methylation for patients with lung cancer: a meta-analysis

Chao Chen, Haiqing Hua, Chenglong Han, Yuan Cheng, Yin Cheng, Zhen Wang, Jutao Bao

Department of Respiratory Medicine, Jiangyin Hospital of Traditional Chinese Medicine, Nanjing Traditional Chinese Medcine University, Jiangyin 214400, China

Received July 2, 2015; Accepted August 20, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: The role of MGMT promoter methylation in lung cancer (LC) remains controversial. To clarify the association of MGMT promoter methylation with survival in LC, we performed a meta-analysis of the literature with meta-analysis. Trials were selected for further analysis if they provided an independent assessment of MGMT promoter methylation in LC and reported the survival data in the context of MGMT promoter methylation status. Subgroup analyses were conducted according to the study characteristic. A total of 9 trials, which comprised 859 patients, were included in the meta-analysis. The combined hazard ratio (HR) of 1.27 [95% CI 0.88-1.82; test for heterogeneity P = 0.027] suggests that MGMT promoter methylation has none impact on patient survival. In Stage I-III or younger populations, a significant association was found for MGMT promoter methylation in the prognosis of LC. In addition, the heterogeneity disappeared when the analysis was restricted to Stage I-III LC. Our analysis indicates that MGMT promoter methylation in stage I-III or younger patients was significantly correlated with wore survival. Further study is needed to determine these specific subgroups of LC patients.

Keywords: MGMT, prognosis, lung cancer, methylation, meta-analysis

Introduction

Lung cancer (LC) containing two histological types, small-cell lung cancer (SCLC) and non-small lung cancer (NSCLC), is the leading cause of global cancer deaths in recent decades [1]. A combination of chemotherapy and radiotherapy have been investigated in patients post operation. A great deal of patients exhibited a five-year survival rate of approximately 17%, despite improvements in therapies over the past decades [2]. Most recently, a number of potential prognostic biomarkers for lung cancer have been identified, including EGFR, k-Ras, p53, ERCC1 and BRCA1 [3]. Combined with advances in therapies, these prognostic biomarkers can aid in treatment planning and potentially improve the survival of lung cancer patients.

O^6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein, and MGMT deficiency is thought to arise from MGMT gene silencing or a lack of synthesis [4]. It can protect cells from the effects of alkylating agents by removing adducts from the O^6 position of guanine [5]. Therfore, high levels of MGMT activity in cancer cells blunt the therapeutic effects of alkylating agents and thus can be an important determinant of treatment failure [6, 7]. Epigenetic silencing of MGMT via methylation of specific CpG islands of its promoter leads to loss of MGMT activity in tumor tissues of various cancers, including lung tumors [8-10]. and improved sensitivity to alkylating agents [6, 7]. Clinical evidence has also indicated a correlation between MGMT promoter methylation and prognosis in several cancer types, such as melanoma [11], glioblastoma [12], colorectal adenocarcinoma [13], breast cancer [14], and gastric cancer [15]. Nevertheless, inconsistent data have emerged regarding the ability of MGMT promoter methylation to predict survival in LC. Multiple studies failed to achieve statistical significance on this association in a multivariate analysis [16-22]; however, two studies have shown that LC patients with MGMT promoter methylation have worse overall survival (OS) [23, 24].

Table 1. Characteristic of the studies for meta-analysis for MGMT methylation on LCs

First author	Country	Ethnicity	Number of patients	Median age	Histology	Stage
Botana-Rial, 2012	Spain	Caucasian	30	63	ADC	IV
Brabender, 2003	U.S.A	Caucasian	90	63	47.7% SCC, 35.6% ADC, 16.7% LCC	49% I, 21% II, 30% IIIa
Buckingham, 2010	U.S.A	Caucasian	132	64	37.1% SCC, 47.7% ADC, 15.2% others	61% I, 39% II
Drilon, 2014	U.S.A	Caucasian	107	68	18.7% SCC, 77.6% ADC, 3.7% LCC	61.7% I, 25.2%II, 13.1% IIIa
Hashimoto, 2012	Japan	Asian	55	58	20.0% SCC, 72.7% ADC, 7.3% LCC	IV
Hoffmann, 2009	Germany	Caucasian	76	48	37% SCC, 47% ADC, 16% LCC	17% I, 54% II, 29% IIIa
Pietanza, 2012	U.S.A	Caucasian	27	67	SCLC	NR
Pulling, 2003	U.S.A	Caucasian	237	65	ADC	55.5% I, 21.6% II, 13.2% III, 9.7% IV
Safar, 2005	U.S.A	Caucasian	105	67	NSCLC	38% I, 8% II, 32% III, 22% IV

SCC Squamous cell carcinoma, ADC Adenocarcinoma, LCC Large cell carcinoma.

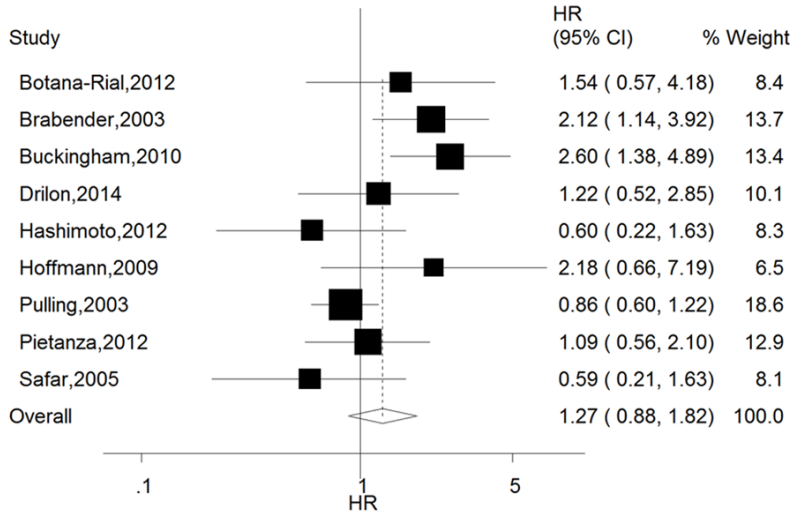

Figure 1. Forest plot of the HR. The size of the squares reflects each study's relative weight and the diamond (◇) represents the aggregate HR and 95% CI.

To clarify the relationship between MGMT promoter methylation and its prognosis value for patients with LC, a detailed meta-analysis of the relevant published studies was performed. This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [25].

Methods

Publication search

The PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) electronic databases were used to search for the studies. The terms used to search these databases were "MGMT", and "lung cancer". The most recent research included was from before November 30, 2014, but we did not apply a limit on how far in the past the research had been published. The published studies that were eligible for inclusion in this meta-analysis met the following criteria: (1) measured MGMT promoter methylation in LC; (2) provided information on patient survival. Studies that did not meet the inclusion criteria were excluded from this analysis.

Data extraction

The key characteristics of each study, such as the authors, year of publication, country in which the research was conducted, ethnic group of the study population, number of patients,median age of patients, histology and stage, were noted.

Statistical analysis

Survival outcome data were synthesized using the time-to-event HR (a benefit of survival would be represented by an HR < 1). When HR values were not provided in a paper, crude HR with 95% confidence interval (CI) were calculated [26, 27]. To account for the inherent heterogeneity between the included studies, we assumed the presence of statistical heterogeneity and used a random effects model before pooling the data. Heterogeneity between the studies was tested using Q-statistics. Heterogeneity was considered statistically significant at $P < 0.10$. In meta-analyses with at

Table 2. Subgroup analysis according to the study characteristics

	HR	I^2 (%)	*P* value
	Random effects (95% CI)		Q test
Total	1.27 (0.88-1.82)	53.9	0.027
Patient number > 100	1.16 (0.63-2.16)	71.2	0.015
Caucasian	1.35 (0.93-1.97)	54.7	0.031
Median age < 65	1.75 (1.09-2.81)	36.8	0.176
NSCLC	1.29 (0.85-1.97)	59.4	0.016
Stage I-III	2.05 (1.41-2.98)	0	0.574

least four trials, Begg's test [28] and Egger's test [29] were performed to determine whether there was a publication bias (P < 0.05 indicated a statistically significant publication bias). All calculations were performed using STATA 10.0.

Results

Study characteristics

Nine of the studies identified met the inclusion criteria. They were published between 2003 and 2014, and 859 patients were included in the pooled analysis [16-24]. **Table 1** lists the identified studies and their main characteristics. Within these studies, the sample sizes ranged from 27 to 237 patients. Methylation-specific PCR was used to determine the MGMT promoter methylation status in all of the included studies.

Meta-analysis results

The main results of this meta-analysis are summarized in **Figure 1**. The overall HR was 1.27 [95% CI 0.88-1.82; test for heterogeneity *P* = 0.027]. Subgroup analyses were conducted to evaluate whether modifying the inclusion criteria of this meta-analysis affected the outcome or eliminated heterogeneity. Modifications to the inclusion criteria involved limiting the meta-analysis to studies that included more than 100 patients, Caucasian, Stage I-III, NSCLC and median age < 65 years patients. These results are shown in **Table 2**.

Publication bias

The Egger's test (*P* = 0.583) and Bgger's test (*P* = 0.835) results indicate that the publication bias had insignificant funnel plot asymmetry, which was determined by comparing the HR in all patients.

Discussion

To address the prognosis value of MGMT promoter methylation in LC patients, we performed a meta-analysis of previously published studies to derive an overall, pooled assessment of the relationship between MGMT promoter methylation status and patient survival. Based on our results, MGMT promoter methylation status is not a prognostic factor for poor survival in LC patients. Subgroup analyses were conducted to evaluate whether modifying the inclusion criteria of this meta-analysis affected the outcome or eliminated heterogeneity. In Stage I-III or younger populations, a significant association was found for MGMT promoter methylation in the prognosis of LC. Disease stage is one of the most well-established prognostic factors in NSCLC [30]. Age is also a valuable prognostic factor in LC [31].

MGMT is a key enzyme involved in DNA repair, providing protection from mutagenic agents and conferring resistance to alkylating chemotherapeutic drugs. MGMT protein expression is lost frequently in tight association with hypermethylation of the promoter region [21, 32]. It is found that MGMT protein expression in brain metastases was significantly correlated with better survival [33]. Recently, NF-κB was found to regulate MGMT expression independent of methylation status of the promoter [34]. These findings suggest that regulation of MGMT expression is a more complex phenomenon and that promoter hypermethylation is not the only overruling factor.

This meta-analysis also has some limitations, and the results should be interpreted with caution. First, due to the lack of relevant information in the original studies, we could not perform subgroup analyses according to the patients' comorbidity, sex, performance status, and nutrition; thus, it is unclear whether MGMT promoter methylation status is an independent prognostic factor. Second, heterogeneity is a potential problem when interpreting the results of our meta-analysis. The presence of heterogeneity can result from differencesfactors. Third, our result was merely based on the subgroup analyses that the HR was significant in the subgroup of studies with median age < 65

years. It is known that if the subgroup analyses were based on the study level, the results do not necessarily apply to the patient level (ie, studies with median age < 65 do not equal to patients with age < 65). For patient and intervention characteristics, differences in subgroups that are observed within studies are more reliable than analyses of subsets of studies (Cochrane handbook Chapter 9.6.).

In conclusion, our analysis indicates that MGMT promoter methylation in stage I-III or younger patients was significantly correlated with wore survival. Further study is needed to determine these specific subgroups of LC patients.

Disclosure of conflict of interest

None.

Address correspondence to: Haiqing Hua, Department of Medical Oncology of PLA Cancer Center, 81st Hospital of PLA, Nanjing 210002, China. Tel: +86-25-80864499; Fax: +86-25-80864499; E-mail: 149764146@qq.com

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