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ORIGINAL ARTICLE

Association between Immunohistochemical markers and MRI features in patients with glioblastoma multiforme underwent surgery

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ABSTRACT

Background: *Glioblastoma multiforme (GBM) is a common and fatal primary brain tumor. Magnetic resonance imaging (MRI) is an important tool used for diagnosing GBM. Tumor biology lights on nature and behavior of tumor which is a prime prognosticator of disease and treatment outcome and easily understood by immunohistochemical markers. If the association between Immunohistochemistry and MRI features could be established.* ***Objectives:*** *To investigate and find out association between immunohistochemical markers namely p53, Ki-67, MGMT and MRI features including Contrast tumor enhancement/T2 ratio, percentage of tumor necrosis/tumor volume, peritumoral edema.* ***Materials & Methods:*** *MRI features were taken as Contrast tumor enhancement/T2 ratio, percentage of tumor necrosis, peritumoral edema.Then associations were evaluated between p53, Ki-67, MGMT and Contrast tumor enhancement/T2 ratio, percentage of tumor necrosis/tumor volume, peritumoral edema in chi- square (χ^2) test.* ***Results:*** *The results showed the mean age (±SD) of the population was 46.4+13.6. The age range started from minimum 13 years to maximum 70 years. Male: Female ratio was 1.75:1. Most common symptoms were headache, seizures and hemiparesis. The association between MRI features and immunomarkers in some extents were significant. The association between CTE/T2 ratio and p53 (p value 0.035), between percentage of tumor necrosis and Ki-67 (p value 0.018) and between tumor edema and MGMT (p value 0.010) were statistically significant.* ***Conclusion:*** *Imaging features of brain Glioblastoma such as CTE/T2, tumor necrosis percentage, degree of edema has a close association with tumor molecular pathology indicators such as the P53, Ki-67 and MGMT.*

Keywords: *Glioblastoma multiforme, Magnetic resonance imaging, Immunohistochemistry, Ki-67, MGMT*

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INTRODUCTION

Glioblastoma multiforme (GBM) is the common and most aggressive form of primary malignant brain tumor. Presently known as glioblastoma, it is Isocitrate dehydrogenase 1 (IDH1)-wild type grade IV astrocytic tumor according to WHO classification [1]. It comprises of 12-15% of all intracranial tumors and 50-60% of all astrocytic tumors [2]. GBM is a fatal intracranial malignancy with an incidence rate of 0.59 to 3.69 per 100 000 people. This incidence increases with age, reaching a maximum between 75 and 84 years. Due to the proliferative and diffusely infiltrative nature of the tumor, current standard of care treatment involving surgery, radiation, and chemotherapy ultimately fails [3]. Magnetic resonance imaging is an important perhaps widely used tool for the diagnosis of glioblastoma. Certain MRI features can deliver clues to find out tumoral behavior and act as phenotypic surrogates of tumor biology [4]. Certain biological markers like p53, Ki-67, MGMT which are now a day can be measured by means of immunohistochemistry, reflect the biological behavior of glioblastoma tumors [5].

Better understanding of pathogenesis and molecular genetics of GBM is very much important in clinical practice. Pathogenesis of GBMs includes several molecular and signaling pathways. Activation of these pathways results from genetic abnormalities in the form of amplification of pro-oncogenes and inactivation of tumor suppressor genes. Glioblastoma is divided into two categories according to clinico-pathological features. Histologically, primary and secondary GBMs are practically indistinguishable, but they differ in their genetic and epigenetic profiles [6]. GBMs histologically and genetically show significant inter-tumoral and intra-tumoral heterogeneity and also exhibit different mutations in genetic pathways. These non-unified epigenetic states reflect genomic instability that can affect different therapy choices and clinical outcomes [7,8].

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Ki- 67 known as proliferative index (PI) is expressed in all phases of cell cycle and its expression level indicates grade of astrocytomas [9]. In addition, the Ki-67 is correlated with postoperative survival in gliomas and with the time to recurrence in primary glioblastomas [10]. High Ki-67 is linked to patients with the classical subtype of glioblastoma. The clinical implications in that the classical subtype also was finds to respond the best to aggressive treatment, which includes surgery, radiation, and chemotherapy [11]. Magnetic resonance imaging (MRI) is the most commonly used means of non-invasive diagnostic imaging and it has a crucial role in the evaluation of patients with GBM for diagnosis, surgical and medical treatment planning, and follow-up. The imaging features of GBMs have been well defined; most commonly show heterogeneous pattern of enhancement, edema around the lesion and necrosis [12].

MRI features the phenotypic expression of GBM that could reflect biological characteristics of tumor. Imaging features of enhancement may reflect vascularity, hypoxia and gene expression associated with proliferation [13]. Some imaging features in GBM patients like location, tumor volume, pattern of enhancement, edema and necrosis pattern exhibits differences in biological expressions [4]. Moreover, same histological GBM patients show different imaging pattern in MRI. Several MRI features like contrast tumor enhancement, T2 hypointensity, tumor crossing midline, multiple lesions and peritumoral edema are associated with expression of different molecules on immunohistochemistry like TP53, Ki-67, and MGMT [5]. Some studies have explored the relationship between MRI features and gene expression. Somatic mutations occur in glioblastoma gene are associated with phenotypic differences in MRI derived volumetric measurements [14]. Necrosis exhibited in MRI reflects growth pattern of tumor and high expression of proliferative index Ki-67 [9]. Pattern of enhancement and necrosis in MRI of GBM is linked to expression of P53 [15].

This study focuses on the association between immunohistochemical markers and some MRI features of glioblastoma. We have tried to find out the association among certain biological markers namely TP53, Ki-67, MGMT and MRI features in patients with Glioblastoma multiforme.

METHODS & MATERIALS

This study was a cross-sectional type of experimental study. Study was carried out in the Department of Neurosurgery at National Institute of Neurosciences and Hospital, Dhaka, Bangladesh from January 2020 to December 2021, sample size was 55. Patients of all age and sex with clinically and radiologically suspected intracranial glioblastoma were admitted and underwent surgery and confirmed by histopathology.

Inclusion criteria

Patients of all age and sex with clinically and radiologically suspected intracranial glioblastoma. Patients had MRI of brain. Patients who underwent surgery for glioblastoma. Histologically proved glioblastoma with WHO grade.

Exclusion criteria

Recurrent cases of Glioblastoma. Patient who received previous chemotherapy and radiation treatment. MRI features were suggestive of glioblastoma but histopathological report was not consistent with GBM.

Data collection instrument:

A Preformed data collection sheet was prepared considering key variables like demographic data, short clinical presentation, radiographic data; pathological data including immunohistochemistry of each sample.

Data collection methods

Data collection was conducted at department of neurosurgery, NINS&H. Study subjects were selected according to inclusion and exclusion criteria. On admission written informed consent was taken from each study patient. A detailed history regarding the patient's illness and thorough general and neurological examinations were carried out. Clinical portion of data collection sheet was filled according to history and examination.

Data quality control

Data collection sheet was designed by researcher himself and approved by the Institutional Review Board (IRB). Clinical data were collected by the investigator and checked by guide in regular interval. Lab technician was blind to clinical data. Immunohistochemistry reporting was done by histopatholigist who was blind to both clinical and radiological data. All MRI data were reported by expert radiologist who was blind to both clinical and pathological data. All data were checked by guide. Analysis was done with the help of expert statistician.

Statistical Analysis

For statistical analysis Statistical Package for Social Science (SPSS) software version 25 was used. The chi-square (x^2) test was performed to find out the association between categorical variables. p value <0.05 was considered statistically significant.

Ethical considerations

Ethical clearance for the study was taken from the Department of Neurosurgery and Ethical Review committee, National Institute of Neuroscience & Hospital, Dhaka, Bangladesh. Written informed consent was taken from the patients and/or their legal guardians. Every steps of the study followed the recommendations according to Helsinki Declaration in 2000.

RESULTS

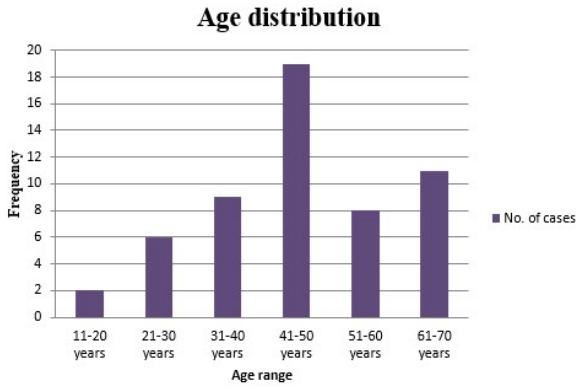

Figure 1: Bar diagram showing age distribution of the study population

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The mean age (±SD) of the study respondents was 46.4±13.6 with ranges from 13 years to 70 years. Age of the population was distributed into 7 categories according to the decades of age. The highest frequency (19, 34.5%) of cases was noted at the range 5th decade (41-50years). The next highest (11, 20%) is in 7th decade (61-70 years). No case was noted in 1st decade (0-10 years) and the lowest is in 2nd decade (11-20 years) *Figure 1*.

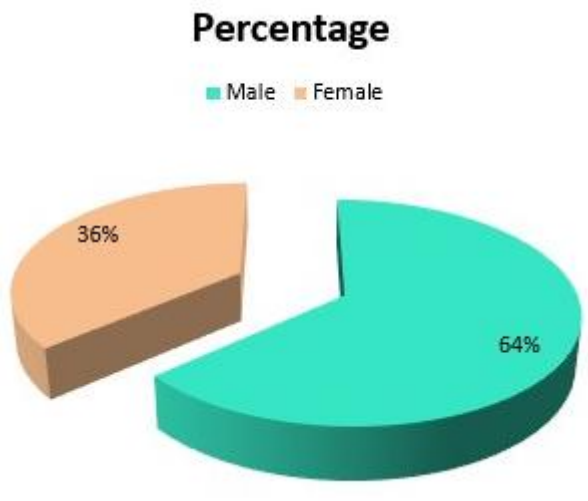

Figure 2: Sex distribution of the study population (*n*=55)

The majority of study population 35 (64%) cases were male whereas 20 (36%) cases were female. male female ratio was 1.75:1 (*Figure 2*).

Among the clinical features the commonest presenting feature was headache 42 (76.4%) cases, 2nd common was seizures 25 (45.5%) cases, next common was hemiparesis 22 (40%) cases, 21 (38.2%) cases had nausea/vomiting where the least common was aphasia 5 (9.1%) cases (*Table I*).

Table I: Distribution of study respondents by clinical features (*n*=55)

Clinical Features	Frequency	Percent
Headache	42	76.4
Nausea/Vomiting	21	38.2
Seizures	25	45.5
Hemiparesis	22	40.0
Aphasia	5	9.1
Visual impairment	12	21.8
Urinary incontinence	9	16.4
Mental changes	13	23.6
Memory impairment	7	12.7

In 29 (52.7%) cases Contrast tumor enhancement/T2 hypointensity ratio obtained from MRI was less than 1 whereas 26 (47.3%) cases showed the ratio equal or greater than 1 (*Table II*).

Table II: Distribution of population by Contrast tumor enhancement/T2 ratio (*n*=55)

Contrast tumor enhancement/ T2 ratio	Frequency	Percent
Ratio<1	29	52.7
Ratio≥1	26	47.3

In 21 (38.2%) cases the percentage of necrosis obtained from MRI was less than 25% of total tumor volume whereas 34 (61.8%) cases showed the necrosis more than 25% (*Table III*).

Table III: Distribution of population by Percentage of tumor necrosis (*n*=55)

Percentage of tumor necrosis	Frequency	Percent
Less than 25%	21	38.2
Equal or more than 25%	34	61.8

Degree of tumor edema obtained from MRI was none to mild in 30 (54.5%) cases whereas 25 (45.5%) cases showed the edema moderate to severe (*Table IV*).

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Table IV: Distribution of population by Degree of edema (*n*=55)

Degree of edema	Frequency	Percent
None to mild	30	54.5
Moderate to severe	25	45.5

Distribution of study population by the expression of TP53 showed that low labeling index (LI) of p53 that was defined as less than 24% of cells expressed p53 was observed in 32 (58.2%) cases and high labeling index (LI) was observed in 23 (41.8%) cases (*Table V*).

Table V: Distribution of population by Expression of TP53 (*n*=55)

TP53	Frequency	Percent
Low LI<24%	32	58.2
High LI≥24%	23	41.8

Distribution of study population by Ki-67 showed that low labeling index of Ki-67 that was defined as less than 28% cells expressed Ki-67 was observed in 23 (41.8%) cases and high labeling index was observed in 32 (58.2%) cases (*Table VI*).

Distribution of population by Expression of Ki-67

Distribution of study population by MGMT showed that low labeling index of MGMT that was defined as less than 42% of cells expressed MGMT was observed in 27 (49.1%) cases and high labeling index was observed in 28 (50.9%) cases (*Table VII*).

Table VII: Distribution of population by Expression of MGMT (*n*=55)

Ki-67	Frequency	Percent
Low LI<28%	23	41.8
High LI≥28%	32	58.2

In case of contrast tumor enhancement/T2 hypointensity (CTE/T2) ratio less than 1 on MRI p53 labeling index was low in 13 (45%) cases and high in 16 (55%) cases. In case of CTE/T2 ratio equal or more than 1 on MRI p53 labeling index was low in 19 (73%) cases and high in 9 (35%) cases. The association between CTE/T2 ratio and p53 expression was measured in chi-square (χ^2) test and it was statistically significant (p = 0.034) (*Table VIII*).

Table VIII: Association between CTE/T2 ratio and expression of p53 (*n*=55)

Contrast tumor enhancement/T2 hypointensity (CTE/T2)	TP53		p value
	Low LI<24%	High LI≥24%	
Ratio<1(n = 29)	13 (45%)	16 (55%)	0.034
Ratio≥1(n = 26)	19 (73%)	7 (27%)	

In case of contrast tumor enhancement/T2 hypointensity (CTE/T2) ratio less than 1 on MRI Ki-67 labeling index was low in 11 (38%) cases and high in 18 (62%) cases. In case of CTE/T2 ratio equal or more than 1 on MRI Ki-67 labeling index was low in 12 (46%) cases and high in 14 (54%) cases. The association between CTE/T2 ratio and Ki-67 expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.537) (*Table IX*).

Table IX: Association between CTE/T2 ratio and expression of Ki-67 (N=55)

MGMT	Frequency	Percent
Low LI<42%	27	49.1
High LI≥42%	28	50.9

Contrast tumor enhancement/T2 hypointensity (CTE/T2)	Ki-67		p value
	Low LI<28%	High LI≥28%	
Ratio<1(n = 29)	11 (38%)	18 (62%)	0.537
Ratio≥1(n = 26)	12 (46%)	14 (54%)	

In case of contrast tumor enhancement/T2 hypointensity (CTE/T2) ratio less than 1 on MRI MGMT labeling index was low in 17 (59%) cases and high in 12 (41%) cases. In case of CTE/T2 ratio equal or more than 1 on MRI MGMT labeling index was low in 10 (38%) cases and high in 16 (62%) cases. The association between CTE/T2 ratio and MGMT expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.135) (*Table X*).

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Table X: Association between CTE/T2 ratio and expression of MGMT (*n*=55)

Contrast tumor enhancement/T2 hypointensity (CTE/T2)	MGMT		p value
	Low LI<42%	High LI≥42%	
Ratio<1(n = 29)	17 (59%)	12 (41%)	0.135
Ratio≥1(n = 26)	10 (38%)	16 (62%)	

In case of tumor percentage of tumor necrosis less than 25% on MRI p53 labeling index was low in 13 (45%) cases and high in 16 (55%) cases. In case of percentage of tumor necrosis equal or more than 25% on MRI p53 labeling index was low in 19 (73%) cases and high in 9 (35%) cases. The association between percentage of tumor necrosis and p53 expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.902) (*Table XI*).

Table XI: Association between Tumor necrosis and expression of p53 (*n*=55)

Percentage of Tumor Necrosis hypointensity (CTE/T2)	TP53		p value
	Low LI<24%	High LI≥24%	
Less than 25% (n = 21)	12 (57%)	9 (43%)	0.902
Equal or more than 25% (n = 34)	20 (59%)	14 (41%)	

In case of tumor percentage of tumor necrosis less than 25% on MRI Ki-67 labeling index was low in 13 (62%) cases and high in 8 (38%) cases. In case of percentage of tumor necrosis equal or more than 25% on MRI Ki-67 labeling index was low in 10 (29%) cases and high in 24 (71%) cases. The association between percentage of tumor necrosis and Ki-67 expression was measured in chi-square (χ^2) test and it was statistically significant (p = 0.018) (*Table XII*).

Table XII: Association between Tumor necrosis and expression of Ki-67 (*n*=55)

Percentage of Tumor Necrosis	Ki-67		p value
	Low LI<28%	High LI≥28%	
Less than 25% (n = 21)	13 (62%)	8 (38%)	0.018
Equal or more than 25% (n = 34)	10 (29%)	24 (71%)	

In case of tumor percentage of tumor necrosis less than 25% on MRI MGMT labeling index was low in 9 (43%) cases and high in 12 (57%) cases. In case of percentage of tumor necrosis equal or more than 25% on MRI MGMT labeling index was low in 18 (53%) cases and high in 16 (47%) cases. The association between percentage of tumor necrosis and MGMT expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.467) (*Table XIII*).

Table XIII: Association between Tumor necrosis and expression of MGMT (*n*=55)

Percentage of Tumor Necrosis	MGMT		p value
	Low LI<42%	High LI≥42%	
Less than 25% (n = 21)	9 (43%)	12 (57%)	0.467
Equal or more than 25% (n = 34)	18 (53%)	16 (47%)	

In case of tumor degree of none to mild tumor edema on MRI p53 labeling index was low in 21 (70%) cases and high in 9 (30%) cases. In case of percentage of degree of moderate to severe tumor edema on MRI p53 labeling index was low in 11 (44%) cases and high in 14 (56%) cases. The association between degree of tumor edema and p53 expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.052) (*Table XIV*).

Table XIV: Association between Degree of edema and expression of p53 (*n*=55)

Degree of tumor edema	TP53		p value
	Low LI<24%	High LI≥24%	
None to mild (n = 30)	21 (70%)	9 (30%)	0.052
Moderate to severe (n = 25)	11 (44%)	14 (56%)	

In case of tumor degree of none to mild tumor edema on MRI Ki-67 labeling index was low in 14 (47%) cases and high in 16 (53%) cases. In case of percentage of degree of moderate to severe tumor edema on MRI Ki-67 labeling index was low in 9 (36%) cases and high in 16 (64%) cases. The association between degree of tumor edema and Ki-67 expression was measured in chi-square (χ^2) test and it was statistically insignificant (p = 0.425) (*Table XV*).

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Table XV: Association between Degree of edema and expression of Ki-67 (*n*=55)

Degree of tumor edema	Ki-67		p value
	Low LI<28%	High LI≥28%	
None to mild (n = 30)	14 (47%)	16 (53%)	
Moderate to severe (n = 25)	9 (36%)	16 (64%)	0.425

In case of tumor degree of none to mild tumor edema on MRI MGMT labeling index was low in 10 (33%) cases and high in 20 (67%) cases. In case of percentage of degree of moderate to severe tumor edema on MRI MGMT labeling index was low in 17 (68%) cases and high in 8 (32%) cases. The association between degree of tumor edema and MGMT expression was measured in chi-square (χ^2) test and it was statistically significant (p = 0.010) (*Table XVI*).

Table XVI: Association between Degree of edema and expression of MGMT (*n*=55)

Degree of tumor edema	MGMT		p value
	Low LI<42%	High LI≥42%	
None to mild (n = 30)	10 (33%)	20 (67%)	
Moderate to severe (n = 25)	17 (68%)	8 (32%)	0.010

DISCUSSION

Magnetic resonance imaging has been used for decades for the diagnosis of Glioblastoma multiforme. It suggests different features in favor of GBM like intra axial ring enhancement, central necrosis, peritumoral edema, mass effect etc. These features direct clinicians in the decision making for the treatment of GBM. Several studies have also suggested these features can predict clinical outcomes and prognosis [16,17,18].

In our study we have studied total number of 55 GBM patients by their MRI features and expressions of Immunomarkers. We have found the mean age (±SD) of the study populations is 46.4±13.6. Majority of cases is found in 5th decade and 2nd peak in 7th decade. According to the previous studies the peak incidence of the GBM is in the 7th and 8th decade [2,19]. This discordance may be due to smaller number of cases, less life expectancy of population in our country, inability to express actual age and lack of birth registrations and lack of national cancer survey. Moreover, there are limited numbers of population-based surveys regarding GBM in South Asian ethnicity.

Our study reveals GBM is 1.75 times higher in males than females. Tamimi and Juweid, have shown that there is male preponderance of GBM by 1.6 times higher rate [19]. So, our study shows similarity to other international studies regarding sex distribution. However, nationwide further study in large scale is needed to solidify the data.

The biological markers like p53 and MGMT expression is higher in secondary GBM [20]. We have found over 50% patients have higher expression of p53 mutation but study patients were not categorized as primary and secondary due to lack of DNA profiling for determination of point of mutation. MGMT methylation status is also higher in about 60% of cases which goes also in favor of secondary GBM. Our study reveals both p53 and MGMT higher expression in about half of the cases that may indicate that most of them are secondary.

The association between MRI features and immunomarkers in some extents are significant. The association between CTE/T2 ratio and p53 is statistically significant (p = 0.035). The high expression of p53 is related with low CTE/T2 ratio which is a negative relationship. Li et al, finds there is inverse relationship between p53 and CTE/T2 that is similar to our study [5]. Gutman et al, shows contrast enhancing and necrosis volumes are significantly smaller for mutated p53 tumors that are compatible to our study [14]. In their study Mut et al, finds high expression of p53 is associated with more circumscribed ring enhancement and low contrast uptake that is also some extent related to our study [15]. We find no significance of high/low p53 with other imaging features like tumor edema (p = 0.052) and necrosis percentage (p = 0.902). Some studies show there is association with necrotic volume.

We have also found significance in the association between the percentage of tumor necrosis and Ki-67 (p = 0.018). The result shows high expression label of Ki-67 (>28% cells) is associated with higher necrotic volume (>25%) and low expression is associated with lower necrosis (<25%). Henker et al, finds similar results that GBMs with necrotic volume fraction with mean (±SD) 0.25±0.3 have been associated with higher Ki-67 expression [9]. We find no significance of Ki-67 with CTE/T2 (p = 0.573) and tumor edema (p = 0.425). Moreover, Ki-67 has high predictive value of tumor recurrence. Sehroder, Feisel and Ernestus, finds recurrent GBMs have nearly similar kind of median expression (14.5%) showed by primary tumors (13%) [10]. Hammoud et al, finds significant relationship between tumor necrosis and outcome survival [21]. They have showed patients with no or less amount of necrosis (<25%) has longer survival time. Thus, GBMs with higher amount of Ki-67 expression are associated with higher amount of necrosis on MRI and higher rate of recurrence and poor outcome survival.

MRI features can be used to predict tumor behavior in patients with Glioblastoma. It can be used clinically to set treatment strategy for each individual patient. Newer MRI modalities like ADC, DWI, Susceptibility Weighted Image (SWI), DTI, functional MRI can be used for more detailed and precised treatment regimen. Perfusion weighted images (PWI) can predict pseudo progression of disease after treatment [22]. These imaging features may also carry some biological information. Zinn et al, finds 133 types of radiomics in MRI can predict genetic subsets and survival in GBM. Further studies in large scale may bring out the treasure [23].

CONCLUSION

Imaging features of brain glioblastoma such as CTE/T2, tumor necrosis percentage, degree of edema have a close association with tumor molecular pathology indicators such as the P53, Ki-67 and MGMT. So, MRI data could be applied to infer the molecular pathology of tumor target and to guide clinical diagnosis and treatment.

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CONFLICT OF INTEREST
None declared

ETHICAL CONSIDERATION
The study was approved by ethical review committee.

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