Original Research

Identification of a three-long non-coding RNA signature for predicting survival of temozolomide-treated isocitrate dehydrogenase mutant low-grade gliomas

Ruichun Li[1], Wei Chen[1], Ping Mao[1], Jia Wang[1], Jiangpeng Jing[1], Qinli Sun[2], Maode Wang[1] and Xiao Yu[1]

[1]Department of Neurosurgery, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; [2]Department of Diagnostic Radiology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
Corresponding author: Xiao Yu. Email: doctoryuxiao@163.com

Impact statement

Currently, no biomarkers known could predict the survival time of IDH mutant LGGs effectively. We discovered and validated a risk scoring model based on three lncRNAs. With this model, three-, four-, and five-year survival time of LGGs could be predicted more accurately, and LGGs could be stratified before TMZ therapy, which is helpful for the precision therapy afterward.

Abstract

Temozolomide (TMZ) is the major chemotherapy agent in glioma, and isocitrate dehydrogenase (IDH) is a well-known prognostic marker in glioma. O6-methylguanine-DNA methyltransferase promoter methylation (MGMTmethyl) is a predictive biomarker in overall gliomas rather than in IDH mutant gliomas. To discover effective biomarkers that could predict TMZ efficacy in IDH mutant low-grade gliomas (LGGs), we retrieved data of IDH mutant LGGs from TMZ arm of the EORTC22033-26033 trial as the training-set ($n = 83$), analyzed correlations between long non-coding RNAs (lncRNAs) and progression-free survival (PFS) using Lasso-Cox regression, and created a risk score (RS) to stratify patients. We identified a three-lncRNA signature in TMZ-treated IDH mutant LGGs. All of the three lncRNAs, as well as the RS derived, were significantly correlated with PFS. Patients were classified into high-risk and low-risk groups according to RS. PFS of the high-risk group was significantly worse than that of the low-risk group ($P < 0.001$). AUCs of the three-, four-, and five-year survival probability predicted by RS were 0.73, 0.79, and 0.76, respectively. The predictive role of the three-lncRNA signature was further validated in an independent testing-set, the TCGA-LGGs, which resulted in a significantly worse PFS ($P < 0.001$) in the high-risk group. Three-, four-, and five-year survival probabilities predicted by RS were 0.65, 0.69, and 0.84, respectively. Functions of these three lncRNAs involve cell proliferation and differentiation, predicted by their targeting cancer genes. Conclusively, we created a scoring model based on the expression of three lncRNAs, which can effectively predict the survival of IDH mutant LGGs treated with TMZ.

Keywords: Low-grade glioma, isocitrate dehydrogenase, temozolomide, long non-coding RNA, risk score, signature

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Introduction

Gliomas account for approximately 80% of the primary central nervous system neoplasms among adults.[1] Acting as an alkylating agent, temozolomide (TMZ) is currently the most effective chemotherapeutic agent for treating gliomas. Being used to primary therapy, TMZ monotherapy exhibited similar efficacy to radiotherapy in high-risk low-grade glioma (LGG).[2] When TMZ was combined with radiotherapy, the survival time of patients was improved as revealed by RTOG 0424 trial.[3] Though some LGG patients could benefit from TMZ regimen, there are still a lot of patients who progress soon after TMZ therapy. So precisely predicting TMZ efficacy is of pivotal importance. Nowadays, stratifying by isocitrate dehydrogenase (IDH) mutation status, 1p/19q co-deletion (codel) status, and TERT promoter mutation status (TERTp) has been commonly used in survival prediction of LGG.[4,5] Clinical trials like the CATNON[6] have been launched to study the efficacy of TMZ based on these molecules.

To date, the only well-known predictive marker of TMZ is O6-methylguanine-DNA methyltransferase (MGMT),

patients with MGMT promoter methylation (MGMTmethyl) survive longer than those without.[7] As both IDH mutation and MGMTmethyl indicate good outcomes, the relationship between the two molecular markers has been still under debate. Bell *et al.* analyzed molecular status in RTOG 0424 trial and proposed that MGMTmethyl was an independent prognostic biomarker of high-risk LGGs treated with TMZ and radiotherapy.[8] To the contrary, Wick *et al.* analyzed the correlation between molecular status and patient progression-free survival (PFS) in NOA-04 trial, suggested MGMTmethyl was a predictive biomarker of the alkylating agent in IDH wildtype patients, but not IDH mutant ones.[9] Notably, nearly all patients with IDH mutation and 1p/19q codel were also MGMT promoter methylated, and more than 90% of patients with IDH mutation and 1p/19q non-codel were MGMT promoter methylated,[10] which made it incompetent for MGMTmethyl to predict the outcome of IDH mutant patients. Therefore, to discover what kind of IDH mutant patients could benefit from TMZ therapy was of much greater practical importance than to answer whether IDH or MGMT was the independent predictive marker of TMZ.

Bady *et al.* analyzed methylation data of the EORTC 22033 trial and proposed a model which was composed of seven-CpG to be predictive of longer PFS in TMZ-treated patients.[11] Meanwhile, Gao *et al.* analyzed expression data of the same trial and identified six intrinsic glioma subtypes which were associated with specific molecular subtype and were predictive markers.[12] Recently, the role of long non-coding RNAs (lncRNAs) has gained a growing interest in gliomas pathogenesis and treatment. As transcriptional regulators, lncRNAs can alter gene expression through several mechanisms at both transcriptional and translation levels, including transcriptional interference, chromatin remodeling, binding to splicing factors, and suppression of protein synthesis.[13,14] In light of the functional relevance of lncRNAs, several lines of evidence have shown associations between specific lncRNA expression patterns and histological subtypes, malignant progression, and patient outcome in gliomas, suggesting potential clinical values of LGG-associated lncRNAs as therapeutic targets and biomarkers.[15,16] By clustering lncRNA expression, Li *et al*. classified gliomas into three subtypes (namely LncR1, LncR2, and LncR3).[17] However, these three subtypes were largely overlapped with the existing molecular subtypes defined by IDH and 1p/19q.

To discover what kind of IDH mutant patients could benefit from TMZ therapy from the perspective of lncRNA, we analyzed lncRNA expression of IDH mutant LGG patients in TMZ arm of the EORTC22033-26033 trial and identified a lncRNA signature that could predict patient survival probability. The identified signature was further validated in an independent dataset.

Materials and methods

Data acquisition

Clinical data and microarray expression data of the EORTC22033-26033 trial were downloaded from GEO (GSE107850), then data of IDH mutant patients were selected as training-set ($n = 83$). TCGA-LGG data including somatic mutation, RNA expression normalized by FPKM, and treatment history were acquired by the R package TCGAbiolinks from GDC Data Portal (https://portal.gdc.cancer.gov/). Clinical data of TCGA-LGG were retrieved from the cBioportal website (https://www.cbioportal.org/). Then IDH mutant patients who were treated with TMZ within 180 days after surgical resection were used as testing-set ($n = 140$).[18] TERTp mutation status and MGMTmethyl status in the testing-set were gathered from published studies.[19] MGMTmethyl status was determined by MGMT-STP27 Model.[20,21] IDs of patients enrolled in the training-set and testing-set were presented in Supplementary Table S1.

Data cleaning and annotation

Histological types in training-set and testing-set were reclassified according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System,[22] which updated the histological classification of glioma by adding molecular biomarkers. In brief, samples with IDH mutation and 1p/19q codel were reclassified to oligodendroglioma, samples carried IDH mutation and 1p/19q non-codel were reclassified to astrocytoma. Samples previously denoted as oligoastrocytoma and carried IDH wild-type were re-marked as oligoastrocytoma, NOS. Patients with unknown TERTp status in the testing-set were relabeled according to TERT expression status, as TERT expression measured by RNA sequencing was a highly sensitive (91%) and specific (95%) surrogate for the presence of TERTp mutation.[19] Annotations of lncRNA were downloaded from GENCODE (https://www.gencodegenes.org/). A filter was applied, lncRNAs whose expression was absent in more than 50% of all samples were removed.

Construction of a predictive model based on risk score derived from a multi-lncRNA signature

Correlation between lncRNA expression and PFS was analyzed by univariate Cox regression. LncRNAs that significantly correlated with PFS were further filtered by least absolute shrinkage and selection operator (LASSO) Cox regression,[23] which was implemented by R package glmne. Then, multivariate Cox regression analysis was conducted to screen the independent prognostic factors from robust markers produced in the previous step. Risk score (RS) was calculated by summing the expression values of the selected lncRNAs weighted by their corresponding coefficients generated from multivariate Cox regression analysis. Receiver operating characteristic (ROC) analysis which was used to estimate the accuracy of the RS model in predicting survival probability was implemented by the survivalROC package of R. Using Kaplan–Meier (KM) method, survivalROC package computed time-dependent ROC curve from censored survival data. Samples were next divided into low-RS and high-RS groups according to the optimal RS threshold calculated by R package survival. KM survival analysis was performed to show the relationship

between RS and the survival time, and the log-rank test was utilized to analyze the differences between groups. Multivariate Cox regression with a stepwise method based on the Akaike Information criterion (AIC) calculation was utilized to estimate the independency of RS.

External validation of the multi-lncRNA signature model

Using the lncRNAs and the corresponding coefficients generated from the training-set, we tested the performance of the three-lncRNA signature in the independent TCGA-LGG dataset (testing-set). KM survival and log-rank test were applied to display the survival difference between high-RS and low-RS groups, and ROC analysis was utilized to estimate the accuracy of the model for survival prediction. Multivariate Cox regression was utilized to estimate the independency of RS.

Functional annotation of lncRNA

The interacting mRNA targets of each lncRNA were detected by an online tool, LncRRIsearch,[24] which applied RIblast to human transcriptome to predict RNA–RNA interactions.[25] In brief, RIblast was based on the seed-and-extension approach, it discovered seed regions using suffix arrays and subsequently extended seed regions based on an RNA secondary structure energy model. Cancer genes that were defined by COSMIC were then selected from targeting mRNAs, and the correlation of expression between each cancer gene and its corresponding lncRNA was calculated. The function of lncRNAs in cancer was represented by their significantly correlated targeting cancer genes.

Results

Identification of a three-lncRNA signature in IDH mutant LGG

Expression data of IDH mutant LGG patients who were treated by TMZ monotherapy in the EORTC22033-26033 trial were retrieved from GEO (GSE107850) as training-set. Eight hundred twenty-nine lncRNAs were annotated and expression of 100 lncRNAs showed significant (FDR adjusted P value <0.05) correlation with PFS. LASSO algorithm was further conducted to reduce features and nine robust markers with non-zero coefficient were identified. Furthermore, followed by choosing the smallest AIC via the stepwise method, the optimal predictive signatures ("AL606760.2", "FAM13A-AS1", "AC079228.1") were determined and nominated as "three-lncRNA signature" (Table 1). Based on the expression of the three lncRNAs and their corresponding coefficients determined by multivariate Cox regression, a RS for IDH mutant LGG was calculated

$$RS = 1.052407 \times AL606760.2 - 0.642708 \times FAM13A.AS1 - 1.028242 \times AC079228.1$$

Each patient was endowed with an RS and was classified into a high-risk group or low-risk group based on the optimal threshold of RS which was defined as the threshold that generated the smallest P value in the KM survival analysis. The distribution of RS stratified by risk group, of PFS time stratified by survival state, and of expression of the three lncRNAs normalized by z-score was illustrated in Figure 1(a). Along with the increase of RS, the death events were accumulated and the expressions of risk markers (coefficient >0, "AL606760.2") were increased, while that of the protective markers (coefficient <0, "FAM13A-AS1", "AC079228.1") were decreased. KM survival analysis revealed that patients in the high-risk group presented a remarkably shorter PFS than those in the low-risk group (HR 3.27, 95% CI: 1.73–6.18, P <0.001). Median PFS time in the high-risk group and low-risk group was 35.77 and 55.83 months, respectively (Figure 1(b)). The PFS of the high-risk and low-risk groups treated with TMZ monotherapy was further compared with that of patients treated with RT monotherapy in the EORTC22033-26033 trial. The high-risk patients treated with TMZ showed significantly worse PFS than the patients treated with radiotherapy (log-rank P <0.01), while the latter displayed similar PFS to that of the low-risk patients treated with TMZ (log-rank P: 0.39, Figure 1(b)). Meanwhile, as IDH mutation status is a well-known prognostic biomarker, we compare the survival time of IDH mutant patients stratified by RS to that of IDH wild-type (IDHwt) patients (Supplementary Figure S1A). As expected, the survival time of IDHmut patients with high risk was shorter than that of IDHwt patients, though not significantly ($P = 0.06$), which probably because only seven IDHwt patients were enrolled in this dataset.

Table 1. Univariate- and multivariate-Cox regression analysis between the nine robust markers and PFS.

	Univariate Cox			Multivariate Cox		
Biomarkers	**Coeff**	**HR**	***p***	**Coeff**	**HR**	***p***
ENSG00000236723	1.131	3.097	0.030	1.052	2.865	0.041
ENSG00000236882	−0.611	0.543	0.012			
ENSG00000183470	2.189	8.930	0.003			
ENSG00000248019	−0.565	0.569	0.032	−0.642	0.526	0.030
ENSG00000196273	1.437	4.209	0.010			
ENSG00000271853	−0.852	0.427	0.027			
ENSG00000171987	−1.627	0.197	0.038			
ENSG00000280184	−1.176	0.309	0.004			
ENSG00000278943	−1.407	0.245	0.005	−1.028	0.358	0.045

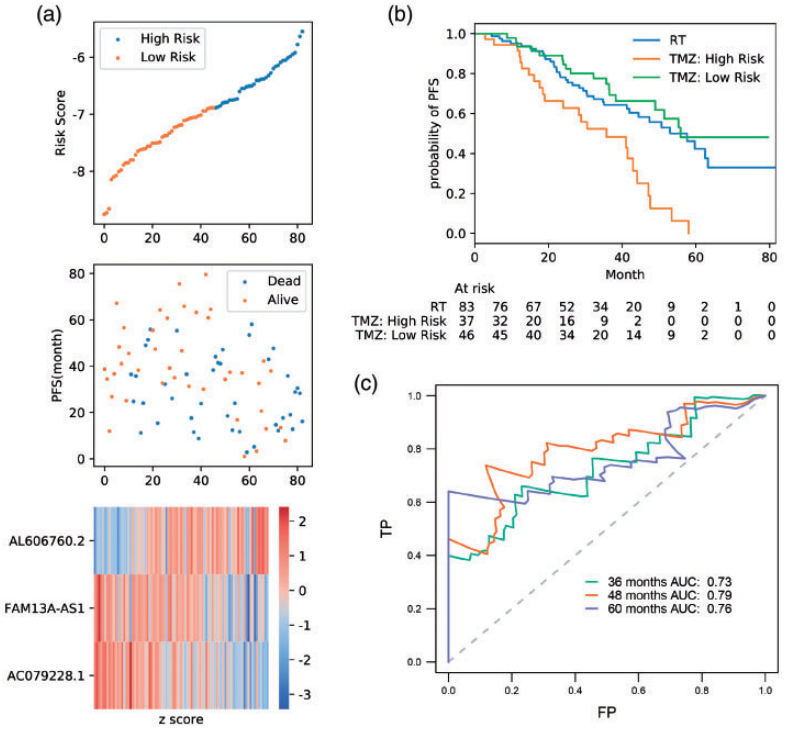

Figure 1. The predictive value of the three-lncRNA signature in the training-set. (a) The association of RS with PFS, survival status, and the expression of three lncRNAs. (b) KM survival analysis of the high-risk and low-risk group defined by RS in training-set. KM survival analysis of the patients treated with radiotherapy in the EORTC22033-26033 trial was also displayed. (c) The predictive performance of the three-lncRNA signature for three-, four-, and five-year survival probabilities.

Table 2. Characteristics of patients in the training-set.

Characteristics	Overall	High-risk group	Low-risk group	*p* value
Gender				
Male	49	24	25	Reference
Female	34	13	21	0.38
Age at diagnosis	43 (27–67)	41 (28–63)	45 (27–67)	
Histological type				
AO	41	15	26	Reference
AA	21	9	12	0.78
AOA,NOS	21	13	8	0.06
Performance status				
PS 0	55	25	30	Reference
PS 1	28	12	16	1
Surgery type				
Partial remove	55	24	31	Reference
Total remove	19	9	10	0.79

To measure the ability of the RS model in predicting survival probability, survival time-dependent ROC analysis was conducted. As shown in Figure 1(c), the accuracy of predicting was indicated by the area-under-curve (AUC) at a series of time points. AUCs corresponding to three-, four-, and five-year survival probability were 0.73, 0.79, and 0.76, respectively. As age is a commonly used marker to evaluate prognosis, we also estimated the survival probability predictive by age, which resulted in AUCs of 0.4, 0.38, and 0.23 separately corresponding to three-, four-, and five-year survival probability (Supplementary Figure S2A). Therefore, the RS model was better than age in predicting survival probability in IDH mutant LGGs pronouncedly.

Correlation between clinical characteristics and RS was evaluated afterward. Clinical characteristics including gender, age at diagnosis, histological type, performance status, and surgical type were well balanced between the high-risk and low-risk groups (Table 2). Univariate Cox regression including the above variables revealed that variables correlated with PFS significantly were age ($P = 0.033$) and RS ($P < 0.001$). Multivariate Cox analysis confirmed the only variate that independently significantly correlated

with PFS was RS (Figure 2. HR 0.32, 95% CI: 0.15–0.67; $P = 0.003$).

Validation of the three-lncRNA signature using the TCGA-LGG dataset

FPKM normalized RNA expression data of TCGA-LGG patients who were treated by TMZ within 180 days after surgical resection was gathered as an independent testing-set. Using the three lncRNAs and their corresponding coefficients determined by training-set, RS of each patient was calculated and used to classified patients into the low-risk and high-risk groups. As expected, patients in the high-risk group exhibited significantly shorter PFS than those in the low-risk group (HR 3.41, 95% CI: 1.46–8.00, $P < 0.001$). Median PFS time in the high-risk group was 41.09 months, while that was not reached in the low-risk group (Figure 3(a)). The accuracies of RS in predicting three and four-year survival probability, which were represented by AUCs, were 0.65 and 0.69, respectively (Figure 3(b)). Notably, the AUC of this model for predicting the five-year survival probability was as high as 0.84. The survival predicting ability of age was also estimated, which resulted in AUCs of 0.51, 0.56, and 0.48 separately corresponding to three-, four-, and five-year survival probability (Supplementary Figure S2B). Therefore, RS was better than age for predicting survival probability in TMZ-treated IDH mutant patients in the TCGA-LGGs dataset.

Clinical characteristics including gender, age at diagnosis, histological grade, radiation therapy status, and MGMTmethyl status were well balanced between the high-risk and low-risk groups (Table 3); none of these variables was correlated with PFS significantly. However, patients in the low-risk group showed a significantly higher frequency of 1p/19q codel and TERTp mutant. As these two biomarkers were well-known prognostic biomarkers in glioma, we evaluated the predictive effect of them in our dataset. PFS was similar between 1p/19q-noncodel and 1p/19q-codel groups, so was it between TERTp mutant and wildtype groups (Figure 3(c) and (d)), which was consistent with some previous studies.[26] Though the frequency of MGMTmethyl status was not significantly different between the two risk groups (Table 3), there was a trend towards a higher frequency of MGMTmethyl in the low-risk group. So we further compared PFS between MGMTmethyl and MGMTunmethyl groups, no significant difference was detected either (Supplementary Figure S3).

To determine the independence of 1p/19q codel status, TERTp mutation status, MGMTmethyl status, and RS, we conducted multivariate Cox regression of these variables against PFS. It was RS that was independently significantly correlated with PFS (Figure 4; HR 0.22, 95% CI: 0.074–0.66, $P = 0.007$). Taking other clinical characteristics into consideration, RS was still the only variable that was significantly correlated with PFS (Supplementary Figure S4; HR 0.20, 95% CI: 0.065–0.59, $P = 0.004$).

Functional annotation of these three lncRNAs

As the functions of the three lncRNAs were largely unknown, we explored the targeting mRNAs of each of

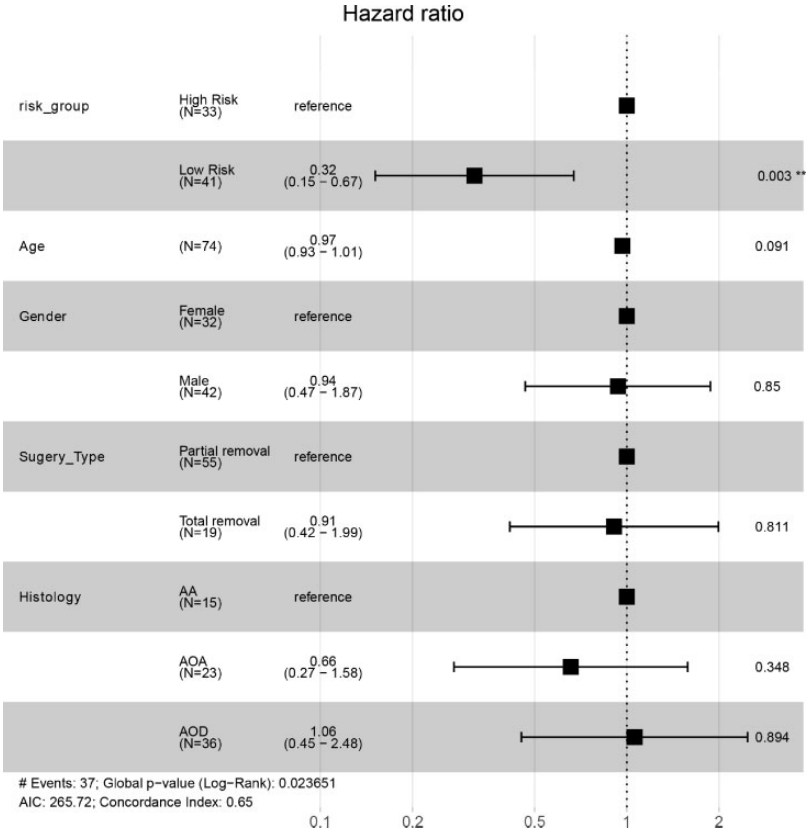

Figure 2. Multivariate Cox regression of features against PFS. Age was used as a continuous variable, while the rest were categorical variables.

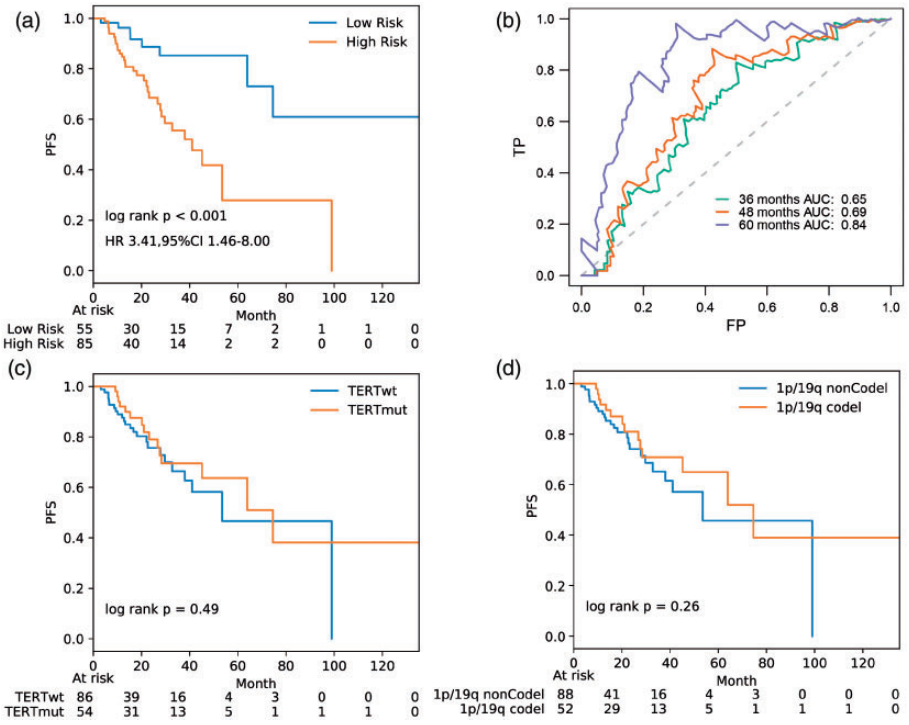

Figure 3. The predictive value of the three-lncRNA signature in the testing-set. (a) KM survival analysis of the high-risk and low-risk groups defined by RS in testing-set. (b) The predictive performance of the three-lncRNA signature for three-, four-, and five-year survival probabilities. (c) KM survival analysis of TERTp mutation status against PFS. (d) KM survival analysis of 1p/19q codel status against PFS.

Table 3. Characteristics of patients in the testing-set.

Characteristics	Overall	High-risk group	Low-risk group	P-value
Gender				
Male	77	51	26	reference
Female	63	34	29	0.17
Age at diagnosis	40 (22–74)	39 (22–74)	41 (22–71)	
1p/19q status				
Codel	52	21	31	reference
Non-Codel	88	64	24	<0.001
Histological grade				
Grade III	100	62	38	reference
Grade II	39	22	17	0.57
Radiation status				
Yes	116	68	48	reference
No	31	16	15	0.3
MGMTmethy status				
Methylated	134	79	55	reference
Un-methylated	6	6	0	0.08
TERTp status				
Mutant	53	21	32	reference
Wild-type	86	63	23	<0.001

the three lncRNAs. The top 100 targeting mRNAs with energy greater than −16 kcal/mol were selected for further analysis. Since our focus here was on cancer, we extracted known cancer genes defined by the COSMIC database from the predicted target genes. Then, the correlation of expression between the extracted cancer genes and their corresponding lncRNAs was calculated (Table 4).

The expression of AL606760.2 was significantly positively correlated with SMAD2 which mediated the signal of the transforming growth factor (TGF)-beta,[27] suggesting the function of AL606760.2 in regulating cellular processes, including cell proliferation, apoptosis, and differentiation. The expression of FAM13A-AS1 was significantly correlated with UBR5 which was an E3 ubiquitin-protein ligase and played a role in the regulation of cell proliferation or differentiation.[28,29] The only two cancer genes that were in the targeting mRNAs list of AC079228.1 were PRPF40B and ZFHX3. PRPF40B involves in pre-mRNA splicing,[30,31] while ZFHX3 encodes a transcription factor with multiple homeodomains and zinc finger motifs, and regulates

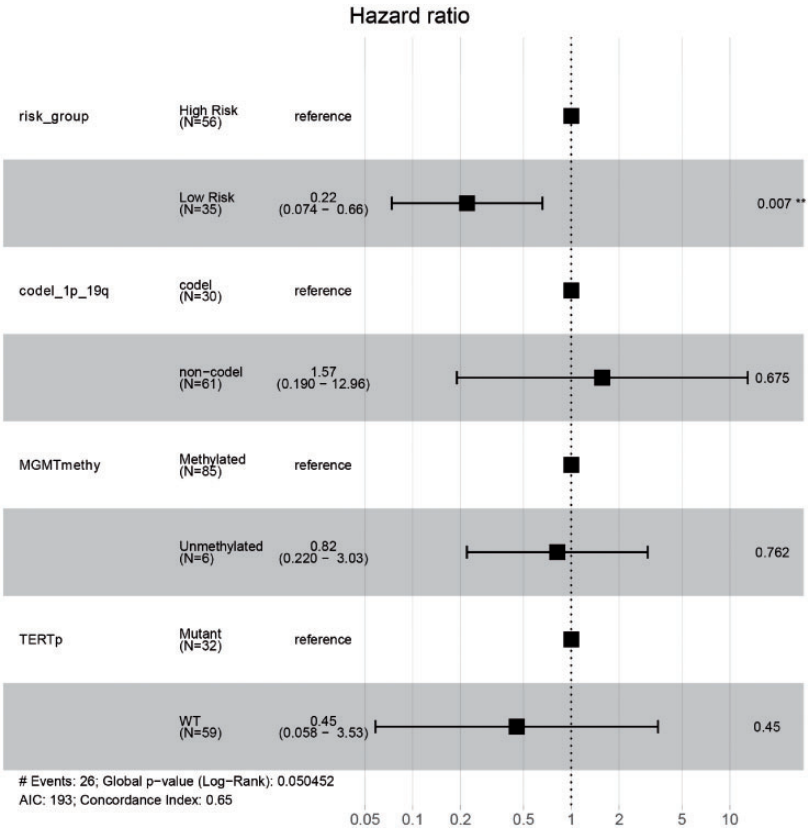

Figure 4. Multivariate Cox regression of RS, 1p/19q codel status, TERTp mutation status, and MGMTmethyl status against PFS.

Table 4. Correlation of expression between cancer genes and the corresponding lncRNAs.

lncRNA	Target gene	Sum of energy	Min of energy	Corr. *R*	Corr. *P*
AL606760.2	ALDH2	−330.25	−57.35	0.124	1.000
AL606760.2	SDHC	−242.37	−45.51	0.135	1.000
AL606760.2	SMAD2	−204.93	−51.23	0.302	0.006
AL606760.2	USP8	−552.82	−43.09	0.260	0.951
FAM13A-AS1	CDKN2A	−127.02	−21.99	−0.072	1.000
FAM13A-AS1	EBF1	−126.73	−19.92	0.083	1.000
FAM13A-AS1	PRPF40B	−129.7	−21.29	−0.030	1.000
FAM13A-AS1	UBR5	−70.74	−19.65	0.424	0.004
AC079228.1	PRPF40B	−397.43	−22.52	−0.042	1.000
AC079228.1	ZFHX3	−269.33	−21.91	−0.278	0.641

myogenic and neuronal differentiation.[32,33] However, expression of AC079228.1 was correlated with none of the two cancer genes.

Discussion

It was well-known that 1p/19q codel status is a prognostic biomarker in IDH mutant glioma.[4,5] A few studies suggested 1p/19q codel status was also a predictive marker of procarbazine/lomustine/vincristine chemotherapy.[34–36] However, whether the 1p/19q codel status is also a predictive marker of TMZ sensitivity is unresolved yet. Speirs *et al.* retrospectively reviewed 111 anaplastic glioma patients who were treated with concurrent TMZ and radiotherapy and found patients with 1p/19q-codel had similar PFS compared to 1p/19q non-codel patients.[26] On the contrary, a few earlier studies reported 1p/19q codel status was significantly correlated with response to TMZ and survival time including PFS and OS.[37,38] As lacking studies comparing the survival time between TMZ therapy and other therapies in both 1p/19q codel and 1p/19q non-codel patients, the role of 1p/19q codel in TMZ therapy is still ambiguous. In our testing-set, we found patients carried with or without 1p/19q codel have similar PFS when treated by TMZ, which did not support the predictive role of 1p/19q in TMZ treatment.

Recently, a study involved more than 1000 gliomas, found TERTp mutation was present in all cases of grade II and III IDH mutant oligodendrogliomas, and in only 10% of IDH mutant astrocytomas,[39] which suggested the high overlap between TERTp mutation and 1p/19q codel in IDH mutant LGGs. It was well-known that triple-positive (LGGs

that were positive for IDH, 1p/19q, and TERT) had the best overall survival,[4] whereas, LGGs with TERT mutation only (IDH-wildtype and 1p/19q non-codel) that represented 10% of all LGGs had the worse prognosis, with a median survival that resembled that of GBM. These findings suggested the presence of only TERTp mutation in LGGs identified a disease status with a particularly aggressive clinical behavior. However, the potential role of TERTp mutation as a predictive biomarker in gliomas has not been clarified. Our results suggested that TERTp mutation could not predict sensitivity to TMZ in IDH mutant LGGs. MGMT promoter methylation was commonly used as a predictor of TMZ in glioma. However, as we know, more than 90% of IDH mutant LGG patients also carried MGMTmethyl. In our testing-set, only 6 out of 140 TMZ-treated IDH mutant LGG patients were MGMTunmethyl, and no significant difference of PFS between MGMTmethyl and MGMTunmethyl groups was detected.

Compared to the above biomarkers, our three-lncRNA signature could stably identify high-risk IDH mutant patients from low-risk ones when treated with TMZ. Specific treatment like increasing dose density regimen or intensive supervising may be given to those high-risk patients reasonably. Of note, for predicting long-term survival, the three-lncRNA signature exhibited far better performance than age in both training-set and testing-set. The functions of the three lncRNAs were further explored by predicting their targeting genes. As the expression of AL606760.2 was significantly positively correlated with SMAD2, AL606760 probably enhances the function of SMAD2 in promoting glioma cell proliferation.[27] Meanwhile, FAM13A-AS1 probably reinforces the function of UBR5 as the expression of them was highly positively correlated. UBR5 has been shown to directly interact with numerous proteins implicated in a wide variety of cellular processes, including the cell cycle, transcriptional and translational machinery, and DNA damage repair.[40] Though two cancer genes among the targeting genes of AC079228.1 were identified, no significant correlation of expression between the two cancer genes and AC079228.1 was detected, therefore, further work is needed to explore the function of AC079228.1 in glioma.

In summary, we explored the TMZ arm of the EORTC22033-26033 trial and identified a three-lncRNA signature as an independent predictive biomarker. These three lncRNAs were involved in cell proliferation, apoptosis, and differentiation. The three-lncRNA signature can be used to classify IDH mutant patients into low-risk and high-risk groups and predict the survival benefit of them from TMZ therapy. And AUC of five-year survival probability predicted by the three-lncRNA signature can be as high as 80%. Practically, patients with high risk could be discovered ahead and given combined therapy to improve their survival probability.

Authors' contributions: All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; RL and XY conducted the experiments, WC and PM verified the statistical analysis, JJ, QS, and MW wrote the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

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ORCID iD

Xiao Yu https://orcid.org/0000-0001-6463-5628

SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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