

Clinical and Molecular Characterization of Incidentally Discovered Lower-Grade Gliomas with Enrichment of Aerobic Respiration

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Purpose: Incidentally discovered diffusely infiltrating lower-grade gliomas (incidental LGGs, iLGGs) are defined as gliomas occasionally found in patients without tumor-related symptoms. At present, very few in-depth research studies on incidental LGGs were reported. We aimed to find out the inherent difference between iLGGs and LGGs with tumor-related symptoms.

Patients and Methods: We enrolled 2486 all-grade gliomas and screened 1594 lower-grade gliomas for further analysis. Medical records were retrospectively reviewed for iLGGs. Clinical and mRNA sequencing data were collected for in-depth analysis.

Results: We found that with increasing grade, the proportion of incidental glioma patients decreased obviously. In 1594 patients who underwent craniotomy for LGG, 80 (5%) patients were discovered incidentally. Grade II patients (88%) and patients bearing 1p/19q co-deletion in their tumors (23%) were more likely to be diagnosed as iLGGs. Regular radiological screening (48%) and trauma (24%) were the main complaint for brain imaging for iLGGs. Kaplan–Meier survival analysis indicated that iLGGs patients lived a significantly longer survival and Cox regression analysis revealed that iLGGs were an independent indicator of better prognosis. Subsequent gene set enrichment analysis and differential expression analysis based on the gene expression profile revealed that mitochondrial aerobic respiration process was enriched in iLGGs. Moreover, we found that iLGGs tended to generate energy by unique mitochondrial aerobic respiration.

Conclusion: These results provided a primitive exploration of iLGGs, which may potentially assist clinical neurosurgeons with personalized management of iLGGs.

Keywords: glioma, lower-grade gliomas, incidental, survival, aerobic respiration

Introduction

Glioma is the most prevalent and fatal primary cancer originated from the central nervous system (CNS).^{1,2} Patients with lower-grade gliomas (LGGs, WHO Grade II/III) have a median overall survival of 7 years while patients with glioblastomas (GBM, WHO Grade IV) only have a median overall survival of 15 months, despite treatment with surgery, radiation and/or chemotherapy.^{3,4} Although patients with LGG survive much longer than those with GBM, nearly all LGGs would eventually progress to secondary GBM.⁵ The Statistics of Surveillance, Epidemiology and End Results (SEER) program showed that overall survival of LGG patients has had no significant improvement since 1973.⁶

Most patients who suffered from glioma came to their doctors with initial symptoms such as headache, vomiting, seizure and so on. However, a small amount

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of glioma patients came to their doctors with few clinical manifestations. Incidental lower-grade gliomas (iLGGs) are LGGs without tumor-related symptoms. Incidental detection may result from regular screening or complaint of trauma, dizziness, atypical headaches,^{7,8} etc. With the development and popularization of imaging technology, the discovery rate and diagnosis rate of iLGGs increased greatly.⁹ However, management of iLGGs is still one of the most controversial areas in clinical neuro-oncology because of the poor understanding and less relevant literature.¹⁰

Heretofore, only a few studies described incidental gliomas of WHO Grade II^{7,8,11} and the number of cases in these studies was limited. To further explore the characteristics of iLGGs, we retrospectively reviewed 1594 LGG patients treated in two hospitals and analyzed the clinical and molecular features of iLGGs. Our study is conducive to comprehensive understanding of iLGGs and provides enlightenment for the clinical personal management of iLGGs. This is the first integrative study characterizing incidental gliomas of WHO Grade II and III molecularly and clinically.

Patients and Methods

Clinical Characteristics of Patients

We retrospectively reviewed patients with all-grade gliomas who underwent surgery in Beijing Tiantan Hospital and Beijing Sanbo Brain Hospital between January 2006 and May 2018. Written informed consent was provided for all patients and our research was approved by the Beijing Tiantan Hospital Capital Medical University Institutional Review Board (IRB KY2013-017-01).¹² Clinical information (including age at diagnosis, gender, presenting symptoms, extent of resection, etc.) was obtained from electronic medical records including resident admit notes, discharge notes, operative report, etc. Meanwhile, the glioma grade and molecular pathological diagnosis (including IDH, and 1p/19q co-deletion status) were established by two neuropathologists according to 2016 WHO CNS tumor guidelines.¹³ It was common to employ a pyrosequencing technique to detect IDH mutation in CGGA.¹⁴ “Incidental” gliomas are detected in brain imaging that was checked for complaint not owing to the tumor, such as screening, trauma, dizziness, headache without related occupied effect or intracranial hypertension, or research purposes. Lower-grade gliomas, ranging

from WHO Grade II to III, were included for further research.

Survival and Follow-Up

Postoperative follow-up was achieved via subsequent visit or telephone. The period starting from resection to death or the last follow-up was overall survival (OS) by definition. Progression-free survival (PFS) started from resection to progression in imaging.

Gene Set Enrichment Analysis (GSEA) and Gene Ontology (GO)

We collected mRNA sequencing data of 190 samples of lower-grade glioma from the Chinese Glioma Genome Atlas (CGGA) database, generated with the Illumina HiSeq platform.¹⁵ GSEA software (<http://software.broadinstitute.org/gsea/index.jsp>)¹⁶ was run for gene set enrichment analysis. We filtered differently expressed genes (fold change >2, FDR <0.05) between 17 iLGG and 173 niLGG patients in the CGGA dataset. Then, up-regulated genes in iLGGs were chosen to perform gene ontology (GO) analysis in DAVID. (<https://david.ncifcrf.gov/>)

Statistical Analysis

R language (version 3.5.1, <http://www.r-project.org>) was the main software environment for our statistical operation and graphics.¹⁷ Difference in clinicopathological characteristics between iLGG and non-incidental lower-grade glioma (niLGG) patients was assessed with Student's *t*-test or chi-squared test. The Kaplan–Meier estimate was performed in survival analysis with two-sided log rank test. We further evaluate the prognostic role of clinicopathological factors with univariate and multivariate Cox regression analysis. The rest of the figures were drawn with some R packages, such as *survminer*, *ggplot2* and *Hmisc*. It was considered to be statistically significant when a *p* value was less than 0.05.

Results

Incidentally Discovered Gliomas Were More Common in Lower Grade Tumors

Two thousand four hundred and eighty-six glioma patients were enrolled into our research totally, who were treated in Beijing Tiantan Hospital and Beijing Sanbo Brain Hospital between January 2006 and May 2018. In our cohort, 928 (37.3%) patients were diagnosed with WHO Grade II glioma, 666 (26.8%) patients with Grade III and 892

Table 1 Distribution of Incidental Gliomas in All Grades of Glioma

Characteristics	No. of Patients (%)		
	WHO Grade II	WHO Grade III	WHO Grade IV
Incidental	70 (7.54%)	10 (1.50%)	14 (1.57%)
Not incidental	858 (92.46%)	656 (98.50%)	878 (98.43%)
Total	928 (100%)	666 (100%)	892 (100%)

(35.9%) patients with Grade IV (Table 1). Among them, we found 70 (7.54%) incidental gliomas (iGs) in Grade II glioma, 10 (1.50%) iGs in Grade III glioma and 14 (1.57%) iGs in Grade IV glioma. With the increase of grade, the proportion of incidental glioma patients decreased obviously (Figure S1). Early tumor symptoms of higher-grade tumor patients are more susceptible to be noticed, leading to incidental gliomas being less common in these tumors.

Characteristics of Patients with Incidental Lower-Grade Gliomas

To further study incidental gliomas, we focused on 1594 lower-grade patients (WHO Grade II/III). The main characteristics of these patients are shown in Figure 1

and summarized in Table 2. Eighty patients (5.0%) meeting the criteria were included for iLGGs. In these iLGGs, the median age was 41 (from 14 to 63) years. Forty-three (54%) patients were male. Between iLGGs and niLGGs, there was no significant difference in the tumor location ($p>0.05$) and extent of tumor resection ($p>0.05$). Among iLGGs, 28 patients were IDH mutant, and there was no significant difference from niLGGs ($p>0.05$). Compared with niLGGs, there were more Grade II patients (88%, $p<0.001$) and 1p/19q co-deletion (23%, $p<0.05$) in iLGGs, and only a small percentage of patients (21%, $p<0.001$) received post-operative chemotherapy.

Radiological screening (48%, $n=38$) was the top complaint of iLGGs, followed by trauma (24%, $n=19$),

**Figure 1** The main clinical and pathological characteristics of 1594 lower-grade patients (80 iLGGs and 1514 niLGGs).

Notes: * $p<0.05$, *** $p<0.001$.

Table 2 Baseline Patient Characteristics

Characteristics		iLGG	niLGG	p-value	Total
No. of Patients (%)		80 (5%)	1514 (95%)		1594
Age	Median (range)	41 (14–63)	40 (4–78)	>0.05	
Gender	Male	43 (54%)	879 (58%)	>0.05	
	Female	37 (46%)	635 (42%)		
Extent of resection	Gross total	47 (59%)	795 (53%)	>0.05	
	Subtotal	33 (41%)	589 (39%)		
	NA	0	130 (9%)		
Lobes	Frontal	57 (71%)	459 (30%)	>0.05	
	Temporal	29 (36%)	266 (18%)		
	Parietal	7 (9%)	74 (5%)		
	Occipital	2 (3%)	41 (3%)		
	Deep central	32 (40%)	190 (13%)		
	NA	0	842 (56%)		
WHO Grade	Grade II	70 (88%)	858 (57%)	<0.001*	
	Grade III	10 (13%)	656 (43%)		
Pathological type	A	27 (34%)	688 (45%)	>0.05	
	O	27 (34%)	361 (24%)		
	OA	26 (33%)	465 (31%)		
IDH mutation	Yes	28 (35%)	724 (48%)	>0.05	
	No	6 (8%)	278 (18%)		
	NA	46 (58%)	512 (34%)		
1p/19q status	Co-deletion	18 (23%)	184 (12%)	<0.05*	
	Intact	13 (16%)	408 (27%)		
	NA	49 (61%)	922 (61%)		
Radiotherapy	Yes	36 (45%)	1035 (68%)	>0.05	
	No	14 (18%)	261 (17%)		
	NA	30 (38%)	218 (14%)		
Chemotherapy	Yes	17 (21%)	670 (44%)	<0.05*	
	No	30 (38%)	568 (38%)		
	NA	33 (41%)	276 (18%)		
Censor	Alive	51 (64%)	816 (54%)	<0.001*	
	Death	3 (4%)	483 (32%)		
	NA	26 (33%)	215 (14%)		
Follow-up time (years)	Median (range)	2.9 (0.8–13.2)	4.0 (0.2–13.3)	>0.05	
mRNA seq		17	173		190

Note: *Significant.

dizziness (19%, n=15), headaches (6%, n=5) and others (4%, n=3) (Table 3). Dizziness and headaches were chronic and did not increase gradually. Moreover, nausea or vomiting because of tumor affect did not accompany, and there was no mass effect like edema in imaging.

Incidental Lower-Grade Glioma Patients Had a Better Prognosis

To explore the survival difference between two groups of patients, we performed Kaplan–Meier survival analysis. In the two groups, survival data were available for 54 and

Table 3 The Discovery Mode of 80 iLGGs

Mode of Discovery	Value
Screening	38 (48%)
Trauma	19 (24%)
Dizziness	15 (19%)
Headaches	5 (6%)
Other	3 (4%)
Total	80 (100%)

1299 patients, respectively. As shown in [Figure 2A](#) and [D](#), iLGG patients lived a significantly longer survival (OS and PFS) than niLGG patients ($p < 0.05$). While in WHO grade II ([Figure 2B](#) and [E](#)) and grade III ([Figure 2C](#) and [F](#)), Kaplan–Meier curves showed a similar pattern. Considering the effect of molecular characteristics and surgery on the prognosis of patients, we divided LGG into groups according to IDH (mutant and intact, [Figure S2A](#)), 1p/19q (co-deletion and intact, [Figure S2B](#)) and extent of resection (total and subtotal, [Figure S2C](#)),

and found that the survival trend of the iLGGs was better in all groups.

To further assess the prognostic value of grouping, we conducted multivariate Cox regression analysis, adjusting previous widely accepted prognostic and predictive factors (gender, age, resection, grade). As shown in univariate analysis, age, grade and group were associated with survival ([Table 4](#), $p < 0.01$). After adjusting with age and grade, group was still associated with survival significantly ($p < 0.01$). These results indicated that iLGGs served as an independent prognostic factor.

Altered Functional Characteristics in iLGGs

In order to further investigate the altered functional characteristics in iLGGs, we performed gene set enrichment analysis (GSEA) between iLGGs and niLGGs. We have collected mRNA sequencing data of 190 lower-grade glioma samples from the CGGA database, comprising 17

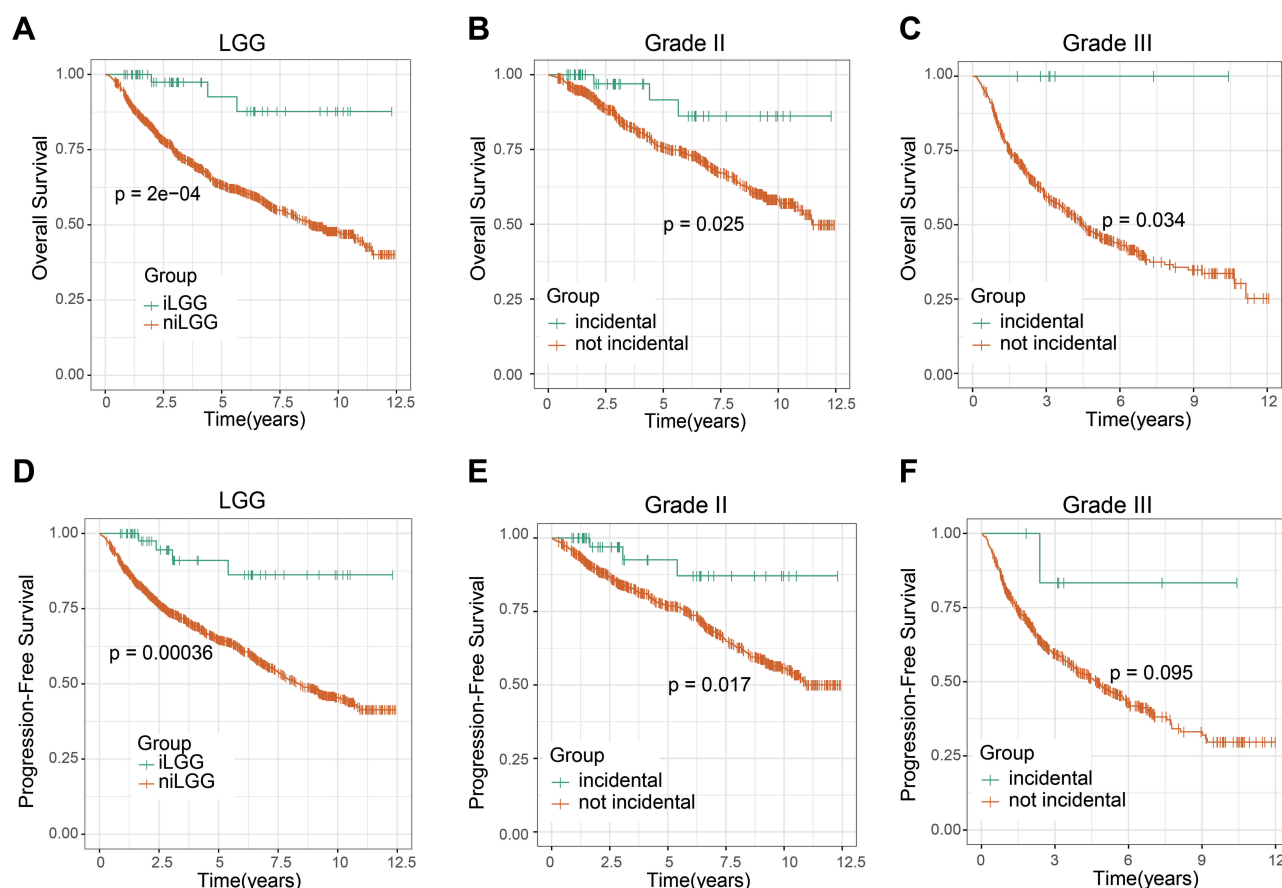


Figure 2 Kaplan–Meier analysis of OS and PFS based on different groups. Patients with iLGG had significantly improved OS ($p < 0.0001$, log rank test) ([A](#)) and longer PFS ($p = 0.00036$, log rank test) ([D](#)). Similarly, both in Grade II ([B](#) and [E](#)) and Grade III ([C](#) and [F](#)), survival (OS and PFS) was improved in the incidental group.

Table 4 Univariate- and Multivariate Cox Regression Analyses for OS

	Univariate Cox			Multivariate Cox		
	HR	95% CI for HR	p-value	HR	95% CI for HR	p-value
Age (>45 vs ≤45)	1.7267	1.4330–2.0810	<0.001	1.5159	1.2560–1.8297	<0.001
Gender (male vs female)	0.9319	0.7784–1.1160	0.4420			
Extent of resection (total vs subtotal)	0.8414	0.6974–1.0150	0.0714			
Grade (III vs II)	2.7290	2.2710–3.2780	<0.001	2.5249	2.0976–3.0392	<0.001
Group (iLGG vs niLGG)	0.1544	0.0496–0.4803	<0.01	0.1986	0.0637–0.6186	<0.01

Note: Factors with prognostic significance in univariate Cox regression analysis were included in further multivariate Cox analysis.

Abbreviation: HR, hazard ratio.

iLGGs and 173 niLGGs. Surprisingly, GSEA results showed that GO terms related to mitochondrial aerobic respiration were enriched in iLGGs, including “mitochondrial respiratory chain complex assembly” (NES=1.637, $p=0.019$), “inner mitochondrial membrane protein complex” (NES=1.652, $p=0.020$), “respiratory chain” (NES=1.580, $p=0.021$) and “electron transport chain” (NES=1.702, $p=0.077$, Figure 3). In Figure S3, the heatmap shows the enrichment of GO terms related to mitochondrial aerobic respiration in iLGGs compared to niLGGs.

Meanwhile, we compared the expression difference and calculated the fold change with FPKM value between iLGGs and niLGGs. Significantly altered genes (fold change >2 or <0.5, and FDR of Student t -test <0.05, Tables S1 and S2) were displayed in a volcano plot (Figure 4A). We chose the up-regulated genes (489 genes, fold change >2) for GO analysis in DAVID and detected enrichment in the biological process of mitochondrial respiratory chain complex I assembly (FDR=0.025, Benjamini=0.018), and mitochondrial electron transport, NADH to ubiquinone (FDR=0.039, Benjamini=0.014) (Figure 4B), which was consistent with aerobic respiration.

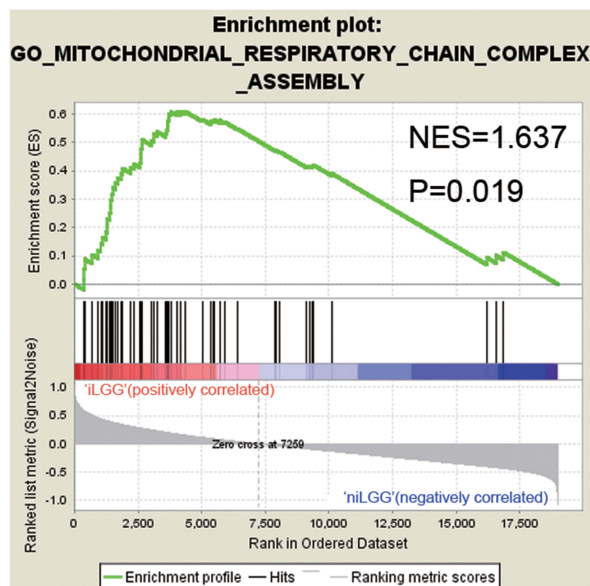
Discussion

The incidental findings of brain imaging were defined as potential clinically relevant abnormalities that were not previously discovered, and these abnormalities were discovered incidentally, regardless of the purpose of the examination.

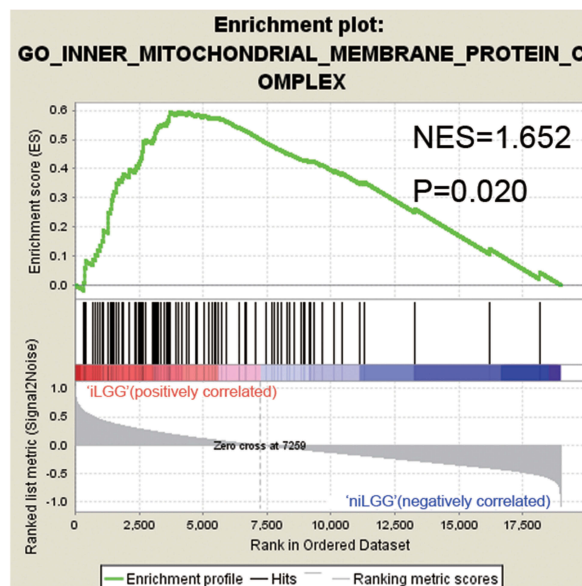
iLGGs were usually diagnosed by investigating non-specific or unrelated symptoms, such as screening (48%), trauma (24%), dizziness (19%), headaches (6%) and others (4%). We found iLGGs accounting for 7.54% in our Grade II gliomas, a ratio similar to that reported in the literature (5%–6.8%).^{7,18} As more and more brain imaging techniques are used by clinicians and researchers, these incidental findings are occurring more frequently.^{19,20} Currently, there are no guidelines for the treatment of this group of patients and the proper management of iLGGs is controversial. Some advocate a traditional wait-and-see approach: surgical intervention until clinical symptoms or radiological evidence of growth manifest. However, numerous untreated iLGG patients have neuropsychological impairments, such as tiredness, attentional impairment, altered executive functions and working memory impairment.¹¹ While some literature has reported that early resection of tumor may be beneficial to survival of incidental patients.^{7,21} For neurosurgeons and radiologists, it is a dilemma crossing medicine and ethics to determine the interventions after routine brain imaging. On the one hand, it may cause harm rather than symptom relief after receiving surgery; but on the other, patients who were treated with conservative observation may be exposed to the risk of tumor progression.

In this study, we retrospectively reviewed 1594 lower-grade gliomas and infiltrated 80 incidental LGG patients for further study. We found that WHO Grade II and 1p/19q co-deletion were more common in iLGGs. Few iLGG patients received chemotherapy due to most iLGGs being resected totally. Survival analysis indicated that iLGG patients lived a significantly longer survival (OS and PFS) than niLGG

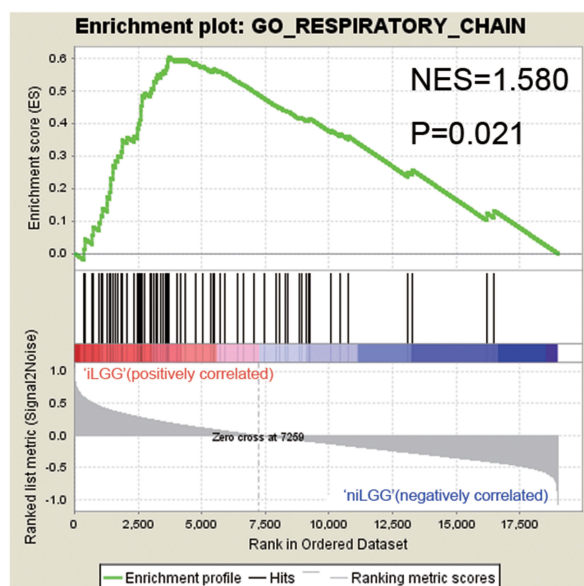
A



B



C



D

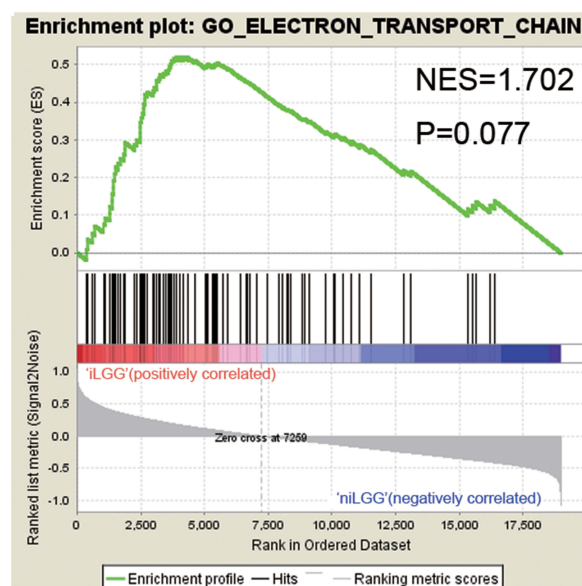


Figure 3 Altered functional characteristics in iLGGs (A–D). GO terms related to mitochondrial aerobic respiration were enriched in iLGGs.

patients and that iLGG was an independent indicator of better prognosis. Hence, our study verified survival benefit of the surgical management in incidental LGGs and as a management option for these people.

Aerobic glycolysis, also known as the “Warburg effect”, was defined as the process of converting glucose into lactic acid in an aerobic environment. Increasing activity of aerobic glycolysis characteristically exists in tumor.²² Aerobic glycolysis has the advantage of generating energy with high

speed and providing biomass for synthesis of amino acids and fatty acids, meeting the need of rapid cell proliferation.^{23,24} Increased production of acids due to upregulation of glycolysis leads to microenvironmental acidosis, which promotes invasion by damaging nearby normal populations, degrading the extracellular matrix and promoting angiogenesis.²⁵ Glioma also converts its energy metabolism into high levels of glycolysis to produce cellular ATP.^{26–28} However, functional analysis and differential expression

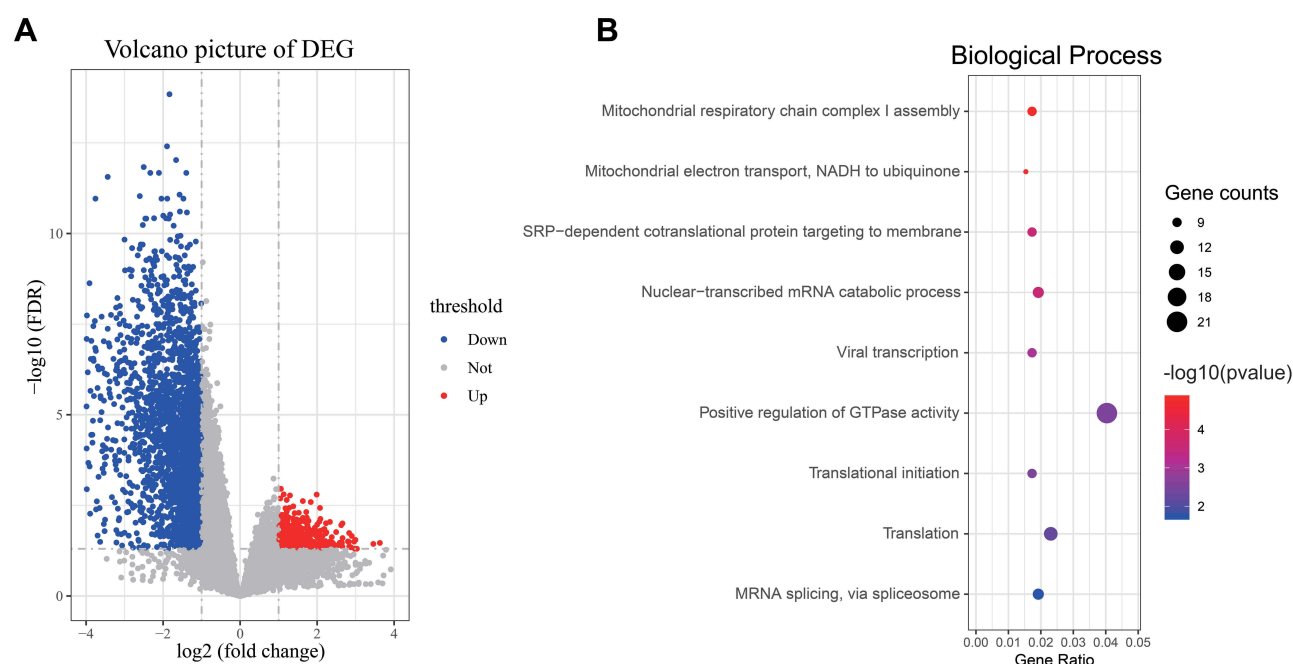


Figure 4 Differential expression analysis between iLGGs and nLGGs. Volcano plot showed differentially expressed genes (A). Bubble plot showed an upregulated biology process in iLGGs (B).

analysis in our study revealed the enrichment of mitochondrial aerobic respiration in iLGG patients, contrary to symptomatic gliomas. This unique metabolic pattern in iLGGs was not conducive to the proliferation of tumor cells, resulting in slow growth of tumors, few symptoms and a better prognosis in patients.

In the tricarboxylic acid cycle, isocitrate dehydrogenase 1/2 (IDH1/2) catalyze isocitrate to α -KG. Mutations in Arg132 of IDH1 or Arg172 appear in over 80% of Grade II/III gliomas and secondary GBMs.^{29,30} The data of IDH mutant status were available for 34 iLGGs, including 28 (82%) IDH mutant iLGGs in our study. The coexistence of IDH mutation and aerobic respiration in iLGGs seem to be contradictory. But simultaneous mutations of IDH1 and IDH2 are rare in glioma cells and the common genotype is IDH1 mutation and IDH2 wild-type.³¹ Wild-type IDH2 could catalyze the oxidative decarboxylation of isocitrate in IDH1 mutant iLGGs as well. On the other hand, the main effect of IDH mutation is causing genome-wide methylation and globally increases the methylation of histones H3 and H4.³² And 85%–90% of GBMs do not harbor IDH mutations but favor higher rates of glycolysis for ATP generation.^{27,33,34} In conclusion, glioma glycolysis or aerobic respiration is not determined by IDH mutation status. Despite numerous IDH mutations in iLGGs, mitochondrial aerobic respiration is not affected.

Conclusions

In summary, we found iLGG patients had a significantly better survival and iLGG was a potential prognostic marker. Unlike other gliomas, iLGGs mainly adopted the metabolic mode of aerobic respiration. Our study extends the understanding of iLGGs and contributes to better clinical management of patients with this type of tumor.

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Disclosure

The authors report no conflicts of interest in this work.

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