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RESEARCH ARTICLE

A Novel Association of *EGFR* Gene Alteration with Decreased Glioblastoma Patient Survival Rate

June Hyun

Harrow School, 5 High St, Harrow, Middlesex, HA1 3HP, United Kingdom; junehyun2024@gmail.com
Mentor: Professor Woo Rin Lee

ABSTRACT: Glioblastoma multiforme (GBM) is the most aggressive and prevalent adult central nervous system (CNS) tumor. Epidermal growth factor receptor (EGFR) alterations are prognostic and diagnostic markers of GBM. Our study aims to investigate the association of *EGFR* alteration with changes in GBM patients' overall survivability. cBioPortal genomic data analysis was used to retrieve genomic data and clinical attributes from 1,122 GBM patients. We performed a comparative study on *EGFR*-altered and non-altered patient groups, mutation and amplification frequency analysis, *EGFR* mutation analysis, and clinical attribute analysis. The mutation and amplification frequency analysis showed that only the *EGFR* gene had higher amplification and mutation counts in the deceased group, indicating a notable association between *EGFR* alteration and decreased survivability. Mutation analysis identified the mechanism by which *EGFR* mutation altered signal transduction and cell proliferation, leading to uncontrolled cell division. A clinical attribute analysis on the relationship between *TERT* expression, *EGFR* alteration, and chromosome 7 gain/chromosome 10 loss (Chr 7 gain/Chr 10 loss) suggested the viability of targeting *EGFR* signaling for GBM therapy. Genomic data analysis revealed a strong association between *EGFR* gene alteration and decreased GBM patient survival rate. Thus, potential *EGFR* molecular alteration is a field of therapeutic value.

KEYWORDS: Biomedical Engineering, Cancer Biology; Genetics; *EGFR*; Patient Survival; Glioblastoma.

Introduction

Glioblastoma multiforme (GBM) is a grade IV astrocytoma that accounts for 47.7% of all central nervous system (CNS) tumor diagnoses; over 12,000 Americans receive a GBM diagnosis annually.[1] 90% of GBMs occur *de novo* in the brain, while the remaining 10% develop from low-grade astrocytomata. Malignant cells transfer to adjacent brain cells, contributing to the tumor's rapid growth. Web-like vein synthesis and the sheer size of the mass often cause peritumoral edema, intracranial hypertension, and tumor-induced epilepsy. Thus, the median survival time is 15 months, and the 5-year survival is less than 5%.[2] Although surgical removal of over 85% of the tumor does prolong survival, radio-chemo-therapy-resistant GBM relapse is common. *IDH1* mutation, MGMT methylation status, *TERT* promoter mutation, and *EGFR* mutation are all prognostic and diagnostic markers of GBM.[3] Therefore, our research aims to describe the relationship between *EGFR* mutation and overall patient survivability to address the therapeutic value of the molecular alteration.

The accumulation of genetic and epigenetic alterations causes cancer development.[4] DNA mutations, rearrangements, deletion, and amplification are well-known abnormalities in cancer cells. Recent advancements in sequencing technology allow the study of the human genome in nucleotide resolution. Identifying the genetic differences that may cause cancer is possible by sequencing DNA or RNA. By sequencing DNA or RNA, identifying the genetic differences that may cause cancer is possible. This approach also quantifies the activity of genes encoded in human DNA to understand the proteins involved in cancer cell characteristics, such as uncontrolled cell growth.[5]

When cancer-causing genetic alterations are identified, we can better understand the molecular basis of cancer development. Therefore, clinical data that describes each cancer patient and their genomic data are essential.[6] Recently, cBioPortal, the open-source cancer genomic database with patient clinical data, was shared with researchers worldwide. As cBioPortal provides a significant portion of worldwide cancer genomic data, it opens new opportunities for discovering gene alterations that cause cancer development.[7]

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein receptor tyrosine kinase (RTK) responsible for cell proliferation, differentiation, and survival.[8] Seven ligands, EGF, TGFα, AREG, EREG, BTC, HBEGF, and EPGN, bind to the extracellular domain. The ligand interaction with the receptor homodimerizes or heterodimerizes EGFR with a protein of the ErbB (RTK) family.[9] The dimerization enables the intracellular c-terminus of the EGFR to autophosphorylate, triggering many different canonical and non-canonical intracellular cascades. Point mutation, amplification, and up-regulation of the *EGFR* gene are hallmarks of tumorigenesis and are often used in diagnosing non-small cell lung cancer (NSCLC) and anal cancer.[10] *EGFR*-positive adenocarcinoma of the lung has a median overall survival of 36.9 months, while *EGFR*-negative adenocarcinoma has a median overall survival of 55.4 months. Loss of regulation of *EGFR* is present in 50% of GBM patients. Therefore, investigating the relationship between *EGFR* gene up-regulation and patient survival is vital to identify a new *EGFR*-targeting treatment pathway in GBM.[11]

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Since gene copy number alteration and mutation may cause the loss of regulation of *EGFR*, we investigated the gene using the genomic data of 1,122 GBM patients in this study. The low survivability of GBM and common relapses necessitate investigations to discover novel genetic associations with GBM. However, research has yet to thoroughly investigate the relationship between patients' survival rate and *EGFR* gene mutation in GBM patients. Therefore, we hypothesized that genetic alteration of *EGFR* may affect the GBM patient survival rate.

Methods

cBioPortal genomic data analysis:

We used the cBioPortal database was used to retrieve genomic data and clinical attributes from 1,122 GBM patients and performed two comparative survival analyses.[12] The first analysis divided the patients into two groups - *EGFR*-amplified and *EGFR*-non-amplified patients. The second analysis divided the patients into *EGFR*-mutated and *EGFR*-non-mutated groups. Then, we analyzed the overall patients' survival with statistical analysis by calculating the Log-rank p-value.

Analyzing EGFR amplification and mutation frequency:

We performed gene amplification and mutation enrichment analysis using cBioPortal. After collecting the genomic and survival data of 1,122 GBM patients, we divided the patients into living and deceased groups. First, enrichment analysis ranked the most amplified and mutated genes in 1,122 GBM patients. Then, we performed statistical analysis to calculate the p-value using Wilcoxon Test.

EGFR mutation analysis:

The cBioPortal mutation analysis function plotted the illustration of *EGFR* mutation numbers and positions. The x-axis represented the position of the amino acid sequence of *EGFR* and the position of the mutations within the protein domain; the y-axis represented the number of mutations found in GBM patients.

GBM patient's clinical attribute analysis:

cBioPortal is a web-based tool that allows users to analyze and visualize the clinical attributes of cancer patients. Using cBioPortal, we analyzed the clinical attributes of 1,122 GBM patients within two groups: patients with or without *EGFR* alterations. In addition,cBioPortal generates a visual representation of the data, such as a bar chart or scatter plot.

Results

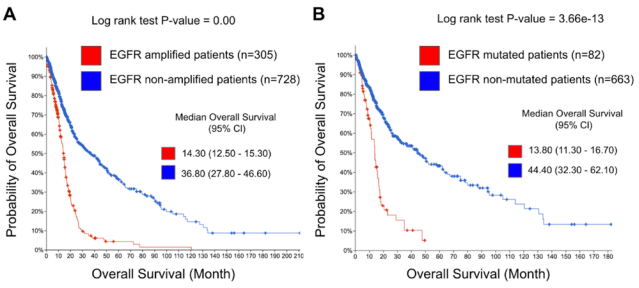

Figure 1: ***EGFR-amplified and mutated GBM patients show significantly lower survival rates than EGFR-non-amplified and non-mutated GBM patients.*** (A) A graph indicating the probability of overall survival (y-axis) and overall survived month (x-axis) of two groups: *EGFR* amplified patients and *EGFR* non-amplified patients. (B) A graph indicating the probability of overall survival (y-axis) and overall survived month (x-axis) of two groups: *EGFR* mutated patients and *EGFR* non-mutated patients. The p-value (log-rank test) and median overall survival (95% CI) are indicated in the graph.

We analyzed *EGFR* amplification and *EGFR* mutation against the patient's overall survival months to investigate the genetic association between the *EGFR* gene and GBM survivability. We used the cBioPortal database to retrieve genomic data from 1,122 GBM patients and performed two comparative survival analyses. The first analysis divided the patient group into *EGFR*-amplified and *EGFR*-non-amplified patients; the second analysis divided the patient group into *EGFR*-mutated and *EGFR*-non-mutated patients. The overall survival analysis result indicates that *EGFR*-amplified patients have a significantly decreased survival rate than *EGFR*-non-amplified patients (Figure 1A). The median overall survival in months is 14.30 for *EGFR*-amplified patients; the median overall survival in months is 36.80 for *EGFR*-non-amplified patients (Figure 1A). The difference in the median overall survival, 22.50 months, indicates *EGFR* amplification's role in poor prognosis in GBM patients (Figure 1A). The second patient's comprehensive survival analysis shows that *EGFR* mutation decreases the survival rate compared to *EGFR* non-mutated patients (Figure 1B). *EGFR*-mutated patients' median overall survival in months is 13.80, while *EGFR*-non-mutated patients' median overall survival in months is 44.40 (Figure 1B). The even more significant difference between the median overall survival, 30.60 months, suggests that *EGFR* mutation influences GBM patient prognosis negatively (Figure 1B). *EGFR* amplification and *EGFR* mutation are significant factors that affect GBM patient survival rates. However, since *EGFR* mutation has a more considerable difference between median overall survival in months than *EGFR* amplification, the *EGFR* gene mutation might be a more significant factor in overall survival.

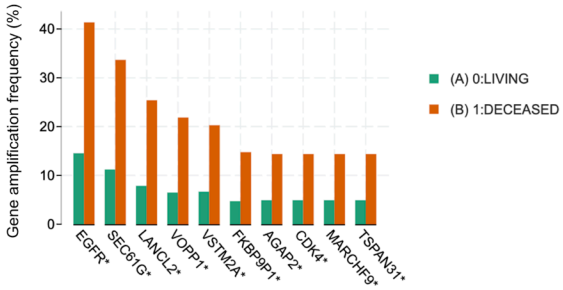

Figure 2: ***EGFR gene amplification event frequency is the highest of the ten genes, with the largest disparity in amplification frequency between living and deceased patient groups in GBM. Living (n=477) and deceased (n=268) patients were analyzed. P < 0.05 (*)***

Since gene amplification occurs in many genes in GBM patients, we analyzed the frequency of gene amplification in the whole genome of living and deceased GBM patients. We found ten genes with the most significant difference (represented by an asterisk) in amplification frequency between living and deceased patient groups (Figure 2). The top ten amplified genes were: *EGFR, SEC61G, LANCL2, VOPP1, VSTM2A, FKBP9P1, AGAP2, CDK4, MARCHF9,*

and *TSPAN31* (Figure 2). All ten genes showed significantly higher amplification frequency in the deceased group (Figure 2). The *EGFR* gene showed the highest amplification frequency in the deceased group and the largest difference between amplification frequency in living and deceased groups (Figure 2). Since the deceased group had a higher amplification frequency than the living group in all ten genes, the entire genome of the deceased group may have low stability. Furthermore, the high amplification frequency of *EGFR* in the deceased group suggests that the amplification of *EGFR* may contribute to a lower survival rate of GBM patients.

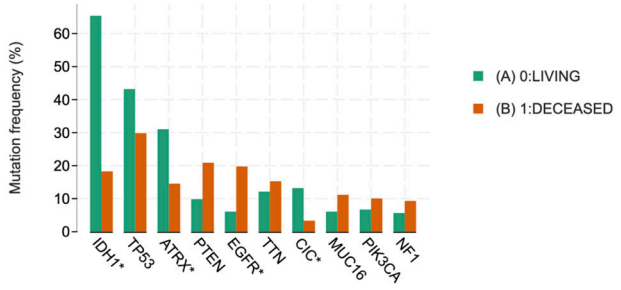

Figure 3: ***EGFR mutation frequency is significantly higher in the deceased than in the living patient group. Living (n=477) and deceased (n=268) patients were analyzed. P < 0.05 (*)***

Mutation occurs throughout the genome of a GBM patient; thus, we analyzed the mutation frequency of the whole genome of living and deceased patients. We found the top ten genes with the most difference in mutation frequency between living and deceased groups. Only four genes, *IDH1*, *ATRX*, *EGFR*, and *CIC*, showed a significant difference in mutation frequency (Figure 3). Of the four genes, *IDH1*, *ATRX*, and *CIC* showed a higher mutation frequency in the living group, while *EGFR* displayed a higher mutation frequency in the deceased group (Figure 3). The significantly higher mutation frequency in the living group for the *IDH1*, *ATRX*, and *CIC* genes suggests that a high mutation frequency in the living group may not be associated with a lower patient survival rate. Since *EGFR* is the only gene with a significant mutation frequency in the deceased group, a high mutation frequency of *EGFR* may lower the survival rate of GBM (Figure 3).

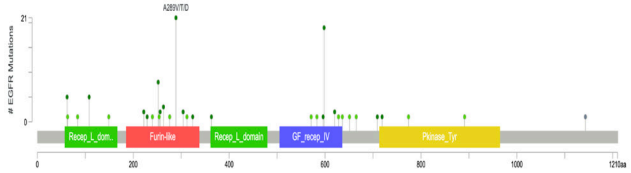

Figure 4: Representation of mutation position in amino acid of *EGFR* in GBM patients. The x-axis represents the amino acids 0-1210 aa of the *EGFR* amino acid sequence; the y-axis represents the number of mutations found in each *EGFR* amino acid position.

The EGFR gene is significantly mutated in deceased patients. Thus, we analyzed the position of *EGFR* mutation in the *EGFR* amino acid sequence to find important mutation positions associated with lower survival in GBM patients. We found five separate domains in the *EGFR* amino acid sequence: Receptor L domain (57-167 aa), Furin-like cysteine-rich region (185-338 aa), Receptor L domain (361-480 aa), Growth factor receptor domain IV (505-636 aa), and Protein tyrosine kinase (713-965 aa) (Figure 4). The number of EGFR mutations was highest in the Furin-like cysteine-rich region (Figure 4). The growth factor receptor domain IV had the second highest number of *EGFR* mutations out of the domains (Figure 4). Previous studies confirm that *EGFR* mutations at alanine 289 (*EGFR* A289D/T/V) of the Furin-like cysteine-rich region are associated with a significant reduction in the overall survival of GBM patients.[13] Therefore, the high number and frequency of *EGFR* mutations in the Furin-like cysteine-rich region and the growth factor receptor domain IV suggest that mutations in the two domains may be significantly associated with lower survival rates in GBM patients.

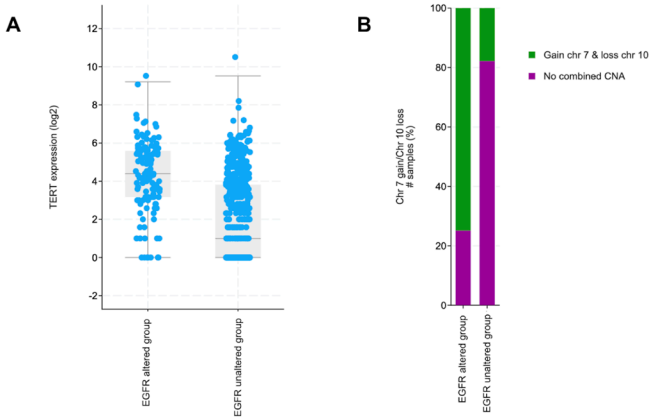

Figure 5: ***The EGFR-altered patient group significantly increased TERT expression level and Chr 7 gain/Chr 10 loss***. (A) The graph shows the *TERT* expression level (log 2) of *EGFR*-altered and *EGFR*-unaltered patient groups (Wilcoxon Test, $p < 10^{-10}$). (B) The graph shows the percentage of samples with Chr 7 gain/Chr 10 loss of *EGFR*-altered and *EGFR*-unaltered patient groups (Wilcoxon Test, $p < 10^{-10}$).

TERT expression increase led to poor overall survival in GBM patients in previous studies. Therefore, we analyzed *TERT* expression in *EGFR*-altered and unaltered patient groups to investigate whether *EGFR* alteration affected *TERT* expression. In addition, we also analyzed the percentage of Chr 7 gain/Chr 10 loss in *EGFR*-altered and unaltered patient groups to study the genomic instability of GBM patients with *EGFR* alteration. We found that the *EGFR*-altered group (median = 4.39) showed significantly increased *TERT* expression levels than the *EGFR*-unaltered group (median = 1) (Figure 5A). Furthermore, the *EGFR*-altered group showed significantly higher Chr 7 gain/Chr 10 loss (78.87%) than the *EGFR*-unaltered group (17.82%) (Figure 5B). In conclusion, the high level of *TERT* expression in the *EGFR*-altered group suggests a significant association between *EGFR* alteration and increased *TERT* expression that may cause a poor survival rate in GBM patients. Also, increased Chr 7 gain/Chr 10 loss in the *EGFR*-altered group further suggests an association between *EGFR* alteration and increased genomic instability, influencing overall survivability.

Discussion

This paper is the first study to investigate the association of *EGFR* gene amplification and mutation with overall survivability in GBM patients. Figure 1 shows the comparison of survival months of *EGFR*-amplified, non-amplified, mutated,

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and non-mutated patients. The graph shows an apparent reduction in survival for *EGFR*-amplified and mutated patients, highlighting a significant association between amplification, mutation, and the deceased patient group. Furthermore, *EGFR*-mutated and non-mutated groups have a larger difference in median overall survivability than *EGFR*-amplified and non-amplified groups, suggesting that *EGFR* mutation, rather than amplification, may more significantly affect patient survivability in GBM. The strong association between *EGFR* gene status and patient survival suggests that the gene status may be used as a new biomarker factor to consider when predicting GBM patient prognosis, improving the prediction accuracy, and providing patients and relatives with a confident disclosure.

Previous studies show similar *EGFR* gene relationships with patient survivability in NSCLC. The likelihood of *EGFR* amplification increases in advanced clinical stages of lung cancer. Furthermore, *EGFR* amplification increases with *EGFR* tyrosine kinase inhibitor (TKI) resistance. As TKI is a common drug used to treat NSCLC, TKI resistance is associated with poor outcomes in NSCLC patients.[14] Therefore, *EGFR* amplification is significantly associated with low survivability of patients, which agrees with our study's result from Figure 1.

Past studies investigating *EGFR* in GBM corroborate the result. *EGFR* amplification observed in this paper may lead to *EGFR* overexpression in approximately 50-60% of GBM tumors.[15] Furthermore, *EGFR* mutations lie primarily in the extracellular domain. Most mutations in Figure 4 lie between amino acids 0-600 aa in the extracellular domain showing consistency with the previous study.[16]

We analyzed the gene amplification and mutation frequency in the whole genome of living and deceased GBM patients to further investigate the association of *EGFR* amplification and mutation with decreased patient survivability. Many genes, including *EGFR*, displayed significantly higher amplification frequency in deceased patient groups than in living patient groups, suggesting that genetic instability of the whole genome contributes to the lower survivability of patients with *EGFR* amplification observed in previous analyses. On the other hand, mutation frequency analysis identified four genes (*IDH1, ATRX, EGFR*, and *CIC*) with significant differences between living and deceased group mutation frequency. *IDH1, ATRX,* and *CIC* displayed higher mutation frequency in living groups, suggesting that mutations in these genes do not lower the survivability of GBM patients. However, *EGFR* had a higher mutation frequency in the deceased group. Therefore, the analysis found that *EGFR* is the only gene in the GBM patient's whole genome with a higher amplification and mutation frequency which may lower survivability, highlighting the importance of further research on the role of *EGFR* in GBM. This study analyzed the position of mutations in the *EGFR* amino acid sequence to identify mutations that significantly affect survivability. We categorized five distinct domains in the sequence, of which three (furin-like cysteine-rich region, growth factor receptor domain IV, and receptor L domain) contained many *EGFR* mutations. Furin-like domain facilitates receptor aggregation for signal transduction by RTKs. A mutation in the furin-like domain may enhance the internal signaling, promoting uncontrolled cell growth. Furthermore, previous studies indicate that mutation in the furin-like domain correlates with less effective targeted therapy and potential drug resistance, decreasing survivability in GBM patients.

Growth factor receptor domain IV facilitates the dimerization of *EGFR* when EGF is received, which regulates phosphorylation and subsequent signal transduction for cell growth. Ligand stimulation in mutated growth factor receptor domain IV results in the formation of a tyrosine-phosphorylated, disulfide-bonded dimer without EGF. Therefore, the mutation causes *EGFR* to trigger cell growth without EGF binding, leading to unregulated cell growth in GBM.

The analysis of mutation positions in the *EGFR* amino acid sequence identified that most mutations in the receptor L domain occurred in the L1 subdomain, located near the N-terminus and responsible for the binding of ligands. The L1 subdomain causes a conformational change in EGFR when a ligand binds to the receptor, influencing the intracellular domain to trigger downstream signaling pathways that promote cell growth and division. Therefore, a mutation in L1 can disrupt ligand binding to EGFR or enhance the signaling pathways, promoting cancer growth. Furthermore, previous studies suggest a link between L1 subdomain mutation and cancer drug resistance. The analysis highlights the multitude of *EGFR* mutations that affect signal transduction triggering cell growth and division, suggesting that *EGFR* may be an area of interest for therapeutic research for GBM drugs.

We investigated *EGFR* alteration association with TERT expression and Chr 7 gain/Chr 10 loss to compare the clinical attributes of GBM patients with and without *EGFR* alteration. The previous study indicated that *EGFR* signaling induces TERT expression by transcription factors such as c-Myc, Sp1, and Ets-2. [20] Since TERT is often increased in cancer cells that activate the infinite cell division, targeting *EGFR* signaling is considered an effective therapeutic strategy for lung cancer. 21 Chr 7 gain/Chr 10 loss is also often associated with EGFR gene mutation in lung cancer.[22] Previous studies indicate that these mutations may activate *EGFR* signal pathways, contributing to cancer development and growth. Our study shows a similar relationship between *EGFR, TERT*, and Chr 7 gain/Chr 10 loss exists in GBM, demonstrating the importance of further investigation into the targeting of *EGFR* alteration for novel therapeutic pathways.[22]

■ Conclusion

In this study, we found that *EGFR* amplification and mutation significantly reduce GBM patient survival rate and that mutation might significantly influence overall survivability. *EGFR* amplification had the highest frequency in the deceased group out of the top ten genes, with the largest disparity in frequency between living and deceased groups, suggesting that *EGFR* amplification may affect survivability. Out of four significant mutations, only the *EGFR* mutation had a significant mutation frequency in the deceased group; thus, a higher *EGFR* mutation frequency may lower the survival rate. When we further analyzed the *EGFR* mutation position, the high mutation frequency was detected in the furin-like cysteine-

rich region. Growth factor receptor domain IV suggests a significant association between lower survivability and the two domains. We also analyzed the clinical attributes associated with *EGFR*-altered patient groups. We found that high levels of TERT expression and Chr 7 gain/Chr 10 loss in *EGFR*-altered groups show that alteration in *EGFR* may lower survivability in GBM patients and increase genomic instability.

This study analyzed patient genomic data associated with decreased survival rates from one published database. Therefore, we must conduct *in vitro* experiments to further analyze the effect of *EGFR* amplification and mutation on cancer cell function, such as the speed of cancer cell division, migration, and invasion. Also, we should perform an *in vivo* mouse experiment or xenograft to verify the results, indicating that *EGFR* amplification and mutation decrease the patient's survival rate. In addition, many other genes, such as SEC61G and LANCL2, have high amplification frequencies in the deceased group. Thus, we must analyze other amplified genes in the deceased group indicated in Figure 2 to discover any interactions between genes that lead to decreased survival rates in GBM patients.

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Author

June Hyun is a junior at Harrow School in the United Kingdom. As the Scientific Society President, he is involved in various school volunteering and research activities. His interest in neurology, neurodegenerative diseases, and robotic neurorehabilitation drive his aspiration to become a physician-researcher.

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