Integration Of Imaging Data And Genomic Information For Enhancing Personalized Treatment In Glioblastoma Multiforme

Askia Khryss Roxas

Abstract

Glioblastoma Multiforme (GBM) is a highly aggressive and deadly brain tumor with a poor prognosis, featuring a 5-year survival rate of only 7.2%. Current treatment methods, including surgery, chemotherapy, and radiation, offer limited long-term success, particularly due to the tumor's heterogeneity and the presence of glioma-initiating cells that resist treatment. This review explores the potential of integrating imaging techniques, such as MRI and PET, with genomic information to enhance personalized treatment strategies for GBM. MRI, including advanced methods like PWI and MRS, provides detailed anatomical and metabolic insights, while PET imaging assesses tumor activity and hypoxia. Genomic profiling, through technologies like Next-Generation Sequencing (NGS) and gene expression profiling, identifies key genetic alterations in GBM. Combining these imaging and genomic data sets through approaches like radiomics and radiogenomics could improve diagnosis, treatment planning, and prognostication, ultimately leading to more effective and tailored therapies. However, further research and clinical trials are essential to validate and optimize these integrative strategies for clinical application.

Introduction

Glioblastoma Multiforme (GBM) is an aggressive and deadly malignant brain tumor with a dismal prognosis, having only a 7.2% survival rate after 5 years (Wu et al., 2021). Despite current treatments, such as surgical resection, chemotherapy, and radiation, long-term outcomes for GBM patients are limited. Moreover, GBM is the most commonly diagnosed malignant primary brain tumor in older individuals, particularly in the 75-84 age group, and is more common in men and Caucasians (Wu et al., 2021; Grech et al., 2020).

Considering the severity of the situation, there is an urgent need to explore novel approaches to enhance personalized treatment planning and improve outcomes for GBM patients. This review focuses on the potential of integrating imaging data and genomic information to enhance diagnosis, prognosis, and treatment prediction, focusing on personalized treatment strategies in GBM.

Background

The pathogenesis of GBM is complex because it comes from various changes in a patient’s genes (Vastrad et al., 2020). Considering GBM can arise from over 5 independently mutated genes, this makes the tumor unique and hard to treat; in other terms, this diversity is called the tumor’s heterogeneity (Hanif et al., 2017). Recently, scientists have been trying to understand GBM better, and they have discovered potentially important genes that might be a clue in GBM’s progression. These include MYC, ARRB1, RPL7A, SNAP25, SOD2, SVOP, ABCC3, and ABCA2 which were identified as hub genes during genetic analysis in an attempt to understand how proteins interact with each other (Vastrad et al., 2020).

Inside GBM tumors, there are special cells called glioma-initiating cells (GICs), which makes it more complicated. They have stem cell-like properties, enabling them to survive targeted treatments such as radiation therapy and chemotherapy. These also make GBM highly invasive in nature because GICs spread beyond the main tumor, even beyond what doctors can

see using modern imaging techniques. These cells are so invasive that despite the current aggressive treatments of GBM including surgery, chemotherapy, and radiation, these tumors come back (Hatoum et al., 2019; Wu et al., 2021).

To address these issues, scientists are exploring novel approaches that target the specific problems in each person's tumor. Since every person's tumor is a bit different, doctors want to understand the exact genetic changes in each patient's tumor. Through this, they can identify novel approaches like developing personalized treatments that work better for each patient, ultimately improving outcomes and extending survival rates for GBM.

Imaging Techniques in GBM Management

In efforts to understand GBM better, scientists use special pictures known as “imaging techniques.” Among them, Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are the most commonly used for diagnosing, treatment planning, and monitoring. These imaging methods provide insights into the tumor’s characteristics, guiding experts on treatments (Overcast et al., 2021).

MRI provides detailed anatomical pictures of the brain, acting like a special map showing the location of the different parts of the tumor such as areas of necrosis, active tumor growth, and infiltrative margins; making it important for doctors as it helps in identifying areas to operate and areas to give special treatments like radiation (Shukla, 2017). Under MRI, are other techniques such as Functional MRI (fMRI) and Diffusion Tensor Imaging (DTI). Moreover, fMRI measures oxygen changes in blood flow to help doctors find brain cortices in relation to the tumor. Knowing this helps them plan surgery better to avoid hurting these critical areas (RadiologyInfo.org, n.d.). On the other hand, DTI looks at the pathways in the brain around the tumor, which are called white matter pathways. This is crucial for preserving brain function and optimizing surgical approaches (Overcast et al., 2021).

While conventional MRI is used as a go-to imaging technique because of how helpful it is, it does come with its limitations. Oftentimes, smaller parts that do not look brighter may be missed, leading to inaccurate assessments by physicians. Additionally, there are challenges in identifying changes that are results of treatment or the tumor itself, making it more difficult to detect the exact size of the tumor (Overcast et al., 2021). Nonetheless, this common imaging may be useful, but it does not show everything.

To overcome these limitations, researchers are actively engaged in developing better MRI to help them understand GBM tumors even more. These include Perfusion-weighted Imaging (PWI), MR Spectroscopy (MRS), and Chemical Exchange Saturation Transfer (CEST) and these provide valuable information about the tumor’s vascularity, metabolism, and molecular profiles. Tumors need a supply of blood in order to grow, so doctors use PWI to measure the blood flow inside the tumor by using a special contrast agent injected into the bloodstream to show where the tumor has lots of blood flow, helping in assessing what approach they will utilize in treating it. Due to the methods of how PWI functions, physicians may use this to measure blood flow within a tumor, in contrast to the already used fMRI which can only detect blood flow in surrounding areas (RadiologyInfo.org, n.d.; Overcast et al., 2021). MRS enables them to look at special molecules inside the tumor called metabolites, which give clues about how the tumor uses energy. This is important to provide information about tumor recurrence. Lastly, CEST enables doctors to see the tumor's proteins and learn more about its surroundings, enhancing understanding of the tumor’s heterogeneity and aiding in targeted therapy planning (Overcast et al., 2021).

Another imaging method is PET. This plays a crucial role in assessing the way GBM tumor behaves inside the brain, showing how active it is. In PET imaging, doctors use special substances called "PET tracers" or "radiotracers." These tracers help doctors by showing how fast the tumor is growing and identifying areas within the tumor that have low oxygen levels (hypoxia). Hypoxia, defined as a lack of oxygen in the tissues of the brain, is harmful for GBM patients because it makes the tumor challenging to treat with drugs, it helps GBM grow and spread, and it hinders the immune system (Park & Lee, 2022). Marking the tracers early is important because it helps in 'metastasis' or identifying the spread of cancer, determining the most effective treatment option, in order to implement them promptly. In GBM patients, various PET tracers have been studied, including [11C]methionine, [18F]fluoro-ethyl-L-tyrosine, [18F]Fluorodopa, [18F]fluoro-thymidine, and [18F]clofarabine, which are used to study proliferation markers in tissues. Additionally, tracers like [18F]FMISO, [18F]FET-NIM, [18F]EF5, [18F]HX4, and [64Cu]ATSM are used to sense areas of hypoxia in the tumor. Using these PET tracers helps doctors gain valuable insights into the different aspects of the tumor, such as its growth rate and inflammation, ultimately helping to predict the effectiveness of given treatments for each patient (Drake et al., 2020).

Through MRI and PET, doctors have learned important information regarding GBM traits within patient populations. Additionally, methods for analyzing individual tumor's genetic information are becoming more common. By combining these two data sets together, it may lead to more targeted and effective treatment strategies, ultimately improving patient outcomes in GBM.

Genomic Profiling in GBM Diagnosis

Since GBM tumors are hetero-genetic and arise from various types of genetic mutations, experts are turning to approaches of studying the tumor’s genetic code, known as genomic profiling. By studying the tumor’s DNA, experts can determine the genetic changes implicated in the tumor’s growth and behavior (Lombardi & Assem, 2017). Next-generation sequencing (NGS) and gene expression profiling are advanced techniques in genomic profiling.

NGS is a technology used to study the genetic information on cells, providing detailed information on DNA sequences (Thermo Fisher, n.d.). For instance, a study by Kolostova et al. (2021) uses this technology to analyze Circulating tumor cells (CTCs) which are tumor cells that float in the blood of GBM patients. They did this to understand the nature of the tumor and where it was spreading. NGS, in this regard, acted like a special blood test. The study revealed that CTCs possess important information about the tumor. Upon looking at the genes in the tumor cells, they have found crucial ones that are key players in the tumor’s behavior. These identified genes were EGFR, PTEN, TP53, and IDH1.

In another way, gene expression profiling is a technique examining how genes are expressed in cells, revealing which genes are "turned on" (actively expressed) or "turned off" (silenced) (Thermo Fisher, n.d.). For example, a study by Yeon-Joo Lee et al. (2020) used this technique to investigate how a new treatment called tumor-treating fields (TTFields) affects GBM while considering a particular gene called TP53. The results revealed essential information about how the genes in the tumor reacted to the TTFields treatment. Key genes were discovered, including EGFR, PTEN, TP53, and IDH1, impacting the tumor’s behavior.

The synthesis of findings from the genomic profiling studies highlights the importance of using these approaches to identify key genes that will offer crucial insights about the specific

spots in the body that can be targeted by drugs and treatment plans that are tailored to each patient's needs.

Elaboration on Imaging-Gene Integration

Combining imaging data and genomic information holds great potential for enhancing diagnosis, prognosis, and treatment prediction in GBM.

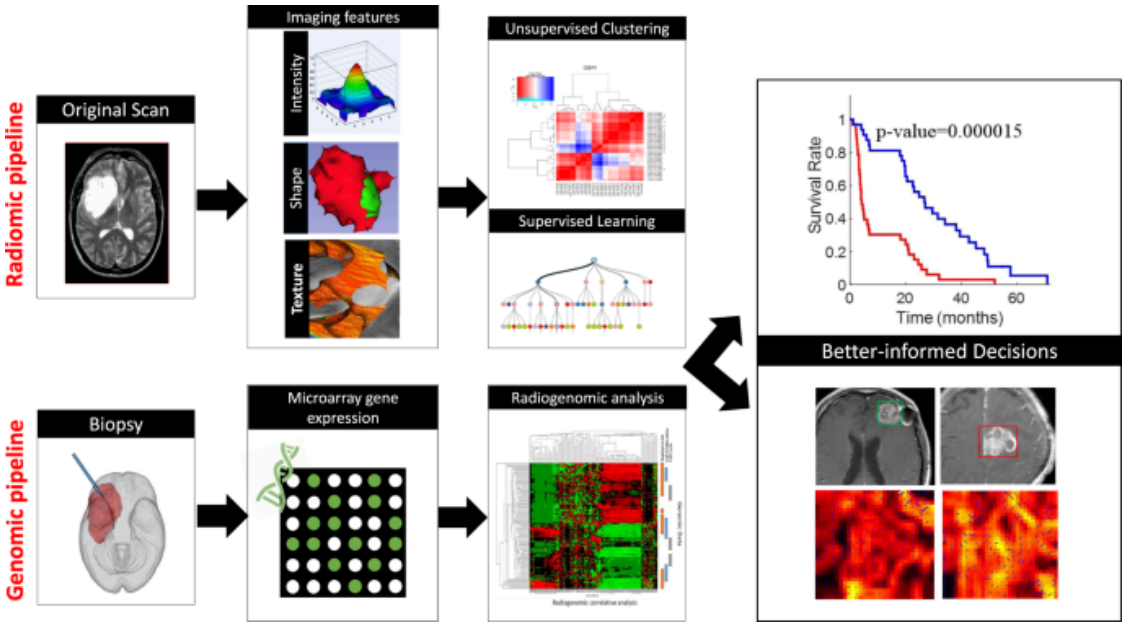

Figure 1: Radiomics and Radiogenomics Process
(Adapted from Singh et al., 2021, Radiomics and Radiogenomics Workflow)

Radiomics and radiogenomics are approaches used in imaging-gene integration to better understand GBM and enhance personalized treatment planning. Radiomics is a method that uses advanced imaging techniques to extract quantitative information from medical images (Chaddad et al., 2019).

Furthermore, a study by Singh et al. (2021), breaks down the process behind radiomics: first is looking for pictures and preparing it for analysis. Based on these pictures, then specific areas of interest are selected and studied. Following this, key essential indicators of the current health condition of the tissue are selected. After, machine learning classifiers and statistical methods like Cox-proportional Hazards models build models of the tumor and its given traits. The extraction of information from images happens in this phase. Radiogenomics is then applied once the most important information is extracted from the radiomic analysis. In cases of cancer, radiogenomics obtains genetic material from tumor samples and utilizes advanced techniques like sequencing and immunohistochemical analysis to detect mutations in genes and abnormalities in gene expression (Shui et al., 2021). This imaging-gene integration has the potential to help experts do more than just diagnosis and planning treatment. By understanding genetic clues hidden in the images, experts can predict treatment success and overcome the tumor's recurrence.

Conclusion

Integrating imaging and genomic data can enhance GBM management. Since GBM is unique in every patient, tailored approaches based on the tumor's characteristics will lead to better outcomes. Imaging techniques provide crucial insights about the tumor, including its shape, growth, and behavior. By understanding genomic profiling of GBM tumors, experts can employ targeted therapy planning, which can help in overcoming the tumor's resistance to treatment. Correlating imaging features with specific genetic alterations (radiogenomics) and extracting descriptions from medical images (radiomics), experts can understand the tumor's biology, guiding them on treatment planning. In conclusion, integrating these complementary data can enhance personalized treatment planning. However, to ensure its efficacy, further research and clinical trials are needed.

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