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Review Article

Research advances in the recurrence patterns of glioblastoma

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Abstract
Introduction
Section snippets
References (134)

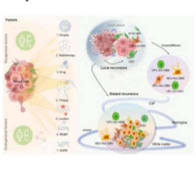
Highlights

- Local recurrence remains the predominant pattern of GBM recurrence, but nonlocal recurrence is increasing.
- EGFR abnormalities, MGMT methylation, tumor site, resection, radiotherapy and chemotherapy affect GBM recurrence patterns.
- Beyond local control, preventing distant recurrence in GBM should be considered to improve survival and clinical benefits.
- OPC-like, NPC-like, and neuron-like GBM cells and glioma stem cells invade WM, targeting them may slow distant recurrence.

Abstract

Glioblastoma (GBM) is the most aggressive type of primary brain tumor, and recurrence remains virtually inevitable despite standard treatment. The prevention of recurrence represents a critical unmet need. However, the evolutionary characteristics of GBM recurrence patterns and their determinants are incompletely understood, limiting improvements in multimodal treatment. We systematically reviewed studies on GBM recurrence patterns from 1980 onward. Recurrence patterns were harmonized using two classification systems—anatomical distance and radiation isodose overlap—and dichotomized into local versus nonlocal recurrence for a pooled analysis. Although local recurrence predominates, nonlocal recurrence has steadily increased and correlates with therapeutic advances (e.g., extended resection, precision chemoradiotherapy, and tumor treatment fields). MGMT promoter methylation, EGFR aberrations, and the involvement of the cortex or cerebellum promote nonlocal recurrence. Oligodendroglial progenitor cell-like, neuron-like, neural progenitor cell-like, and mesenchymal-like GBM cells undergo distal invasion along white matter tracts through multiple mechanisms. Distant recurrence, a representative nonlocal subtype, only prolongs progression-free survival without prolonging overall survival. Current therapies remain insufficient to prevent distant dissemination, and the underlying mechanisms require further elucidation. Therefore, building a multiparametric recurrence risk stratification system and developing targeted adjuvant strategies are essential for improving the long-term survival of patients with GBM.

Graphical abstract



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Keywords

GBM; recurrence patterns; influencing factors; clinical significance

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Introduction

Glioblastoma (GBM) is characterized by highly invasive and infiltrative growth [1], profound heterogeneity [2], and a high recurrence rate. It represents the most malignant primary central nervous system tumor in adults and carries a dismal prognosis [3], [4]. Maximal safe tumor resection followed by radiotherapy combined with temozolomide (TMZ) chemotherapy is the established standard treatment for GBM [5]. However, despite receiving standard treatment, approximately 90% of patients experience recurrence within a short period [3], [6], [7], which constitutes the leading cause of death among GBM patients [8]. Therefore, reducing or preventing recurrence remains a critical unmet clinical need in the management of GBM.

Notably, GBM exhibits multiple recurrence patterns [8], and patient outcomes differ substantially across these patterns [9], [10], [11]. Chan DT et al. reported that the median overall survival (OS) was only 12.8 months for patients with local recurrence, 21.7 months for those with nonlocal recurrence, and approximately 18.5 months for patients with recurrence via cerebrospinal fluid (CSF) dissemination. Compared with nonlocal recurrence, local recurrence is associated with a worse prognosis [12]. In contrast, other studies have reported that distant recurrence has an even poorer prognosis than local recurrence does [13], [14]. These discrepancies indicate that the relationship between GBM recurrence patterns and prognosis remains controversial. The underlying reason may be the lack of standardized criteria for defining recurrence patterns. Moreover, several factors, including the GBM molecular subtype, extent of resection, treatment strategy, extent of ventricular opening, and involvement of specific cerebral structures, have been implicated in modulating recurrence patterns and the prognosis [14], [15], [16], [17], [18], [19]. However, due to the use of different classification systems for recurrence patterns, distinct anatomical sites of primary tumors, and different treatment regimens, the features differentiating different types of GBM recurrence remain poorly characterized, which substantially impedes the clinical advancement of individualized multimodal therapy for GBM.

Therefore, this review aims to systematically examine the current research advances in GBM recurrence patterns, with a focus on summarizing the various recurrence classification criteria, spatial distribution patterns, prognostic value, and associated influencing factors, thus providing evidence-based guidance for the postoperative stratification of the recurrence risk, optimization of precision individualized treatment strategies, and selection of salvage therapeutic regimens for patients with GBM and ultimately offering a theoretical reference to further improve the overall prognosis of patients with GBM.

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Search strategy

We searched PubMed (https://pubmed.ncbi.nlm.nih.gov/) for clinical data published from 1980 to the present using the search terms "Glioblastoma recurrence patterns", "Glioblastoma progression patterns", and "Glioblastoma failure patterns". According to the inclusion and exclusion criteria described below, a total of 89 studies on GBM recurrence patterns were ultimately included (Fig. 1). …

Evolution of the systems for classifying GBM recurrence patterns

Since 1980, various approaches for classifying GBM recurrence patterns have been reported. These criteria have progressively evolved from early qualitative descriptions to a quantitative classification system that integrates the anatomical location, radiation dose–volume parameters, disease progression, and molecular subtyping. Here, based on the 89 included studies of GBM recurrence patterns (Table 1), we chronologically delineate four decade-based developmental phases to systematically …

Factors influencing non-local recurrence of GBM

The aforementioned findings confirm that in the context of modern multimodal therapy, the proportion of patients experiencing nonlocal recurrence of GBM has continued to increase, potentially posing a significant challenge to the long-term survival of GBM patients. Therefore, elucidating the factors that influence nonlocal recurrence patterns is highly clinically important for optimizing the patient risk stratification and formulating individualized preventive and therapeutic strategies. In …

Prognostic differences between local and distant recurrence

Notably, distant recurrence is the core subtype of nonlocal progression of GBM (Fig. 2). We compared survival outcomes between patients with local and distant recurrence using median progression-free survival (mPFS) and median overall survival (mOS) as primary endpoints to further determine the clinical value of recurrence patterns. From the 89 included studies, we selected those reporting paired mPFS or mOS data for local versus distant recurrence following standard therapy. This approach …

Prospects

Here, we systematically reviewed studies spanning more than three decades on the initial recurrence patterns observed in GBM patients. By adopting a dual classification framework based on the anatomical distance and radiation isodose lines, together with a dichotomized local versus nonlocal grouping, we confirm that local recurrence remains the dominant pattern. However, as comprehensive treatment strategies, including surgical resection, precision chemoradiotherapy, targeted agents, and …

Consent for publication

Not applicable. This review article analyses previously published data and contains no individual person's data; therefore, ethical approval and informed consent were not needed. …

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Authors contribution

Tao Zhang and Nian Chen retrieved and screened the literature. Both of them drafted the manuscript and prepared the figures. Jun Wang and Shi-cang Yu conceived and revised the review and acquired funding. …

Declaration of generative AI in scientific writing

Generative AI was not used to produce this review. …

Declaration of competing interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest. …

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The funders did not play a role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. …

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1 These authors contributed equally to this study.

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