

Neuro-Oncology

HISTOLOGICAL NECROSIS AND IDH STATUS IN GLIOBLASTOMA: Contribution of a Prospective Study and VEGFR2 Redocking

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ABSTRACT

Background. Necrosis is a major histological feature of grade 4 astrocytic tumors and, according to published experimental and tissue-based evidence, occurs within a hypoxic perinecrotic microenvironment associated with activation of the HIF-1 α -VEGF-A-VEGFR2 axis. The presence of necrosis alone, however, is not a measurement of hypoxia or VEGFR2 activity.

Objective. The primary objective was to characterize the frequency of histological necrosis in a prospective cohort of 100 tumors initially diagnosed as glioblastoma and to study its association with IDH status when documented. The secondary objectives were to place this phenotype within the published biological rationale of the hypoxia-VEGF/VEGFR2 axis and to validate, by redocking the co-crystallized ligand 42Q, the ability of an AutoDock Vina protocol to reproduce an experimental pose in the VEGFR2 kinase domain.

Methods. The source cohort comprised 100 patients managed prospectively at Frantz-Fanon University Hospital between June 2022 and June 2025 for a tumor initially diagnosed as glioblastoma on pathological examination. All had undergone preoperative CT and MRI. Histological necrosis was recorded as present or absent in pathology reports. IDH status was known in 85 patients (71 wild-type, 14 mutant) and unspecified in 15; these 15 cases were retained in the cohort description but excluded from the inferential IDH-necrosis analysis. The principal comparison used a two-sided Fisher's exact test. Ligand 42Q was redocked into VEGFR2 (PDB 3VHE) using AutoDock Vina v1.2.7 and then evaluated by direct RMSD over the 32 heavy atoms of the ligand.

Results. Histological necrosis was reported in 86/100 patients (86.0%; Wilson 95% CI: 77.9–91.5). Among the 85 patients with known IDH status, necrosis was present in 65/71 tumors recorded as IDH-wildtype (91.5%) and 9/14 IDH-mutant tumors (64.3%), corresponding to an absolute difference of 27.3 percentage points (Newcombe 95% CI: 6.0–53.2). The empirical odds ratio was 6.02, the exact conditional 95% CI was 1.16–28.90, and the two-sided Fisher's exact test yielded $p = 0.0154$. Among the 15 patients with unspecified IDH status, 12 had necrosis and three did not; no distinct biological interpretation was assigned to this group. Redocking generated 20 modes; the highest-scoring mode had a Vina score of -12.832 kcal/mol and a direct RMSD of 0.860 Å relative to the crystallographic pose.

Conclusion. Histological necrosis was frequent in this cohort and was reported more often in tumors whose IDH status was recorded as wild-type. The hypoxia-HIF-1 α -VEGF-A-VEGFR2 axis constitutes a mechanistic framework established by the literature, but it was not measured directly in the tumors studied. Redocking 42Q provides a geometric validation restricted to the VEGFR2-3VHE system and establishes a structural basis for subsequent pharmacological investigations, without demonstrating therapeutic efficacy or clinical benefit.

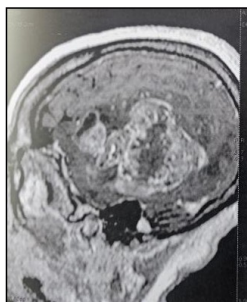
Keywords: glioblastoma; grade 4 astrocytoma; necrosis; IDH; hypoxia; VEGF; VEGFR2; molecular docking.

1. Introduction

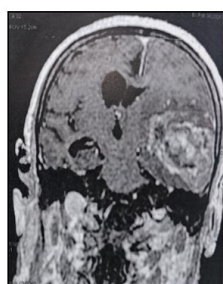
Glioblastoma is the most aggressive adult-type diffuse glioma and remains associated with frequent recurrence despite maximal safe resection followed, in eligible patients, by radiotherapy with concomitant and then adjuvant temozolomide [1–3]. The 2021 WHO classification now reserves the term “glioblastoma” for IDH-wildtype diffuse astrocytic gliomas meeting grade 4 criteria. Grade 4 IDH-mutant tumors belong to the entity astrocytoma, IDH-mutant, grade 4 [1]. This nosological evolution is particularly important when analyzing cohorts assembled from historical diagnoses or practices in which molecular characterization was not uniform.

From a neuroradiological perspective, preoperative MRI permits assessment of tumor heterogeneity, extent, and relationships with adjacent structures. In the illustrative case presented in Figure 1, the left temporal lesion appears heterogeneous, while the coronal section and MR spectroscopy complement its morphological and metabolic characterization.

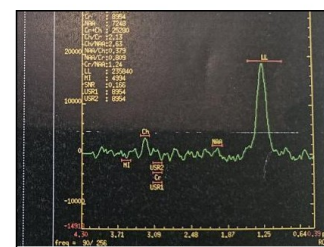
A



B



Coronal section



MR spectroscopy

Figure 1. Preoperative imaging of a left temporal glioblastoma. A, sagittal section showing a heterogeneous tumor mass. B, coronal section and associated MR spectroscopy, illustrating the morphological and metabolic heterogeneity of the lesion.

Neurosurgical management is based on maximal safe resection, adapted to tumor location, neurovascular relationships, and functional constraints. Figure 2 illustrates the microsurgical setting under an operating microscope during tumor resection.



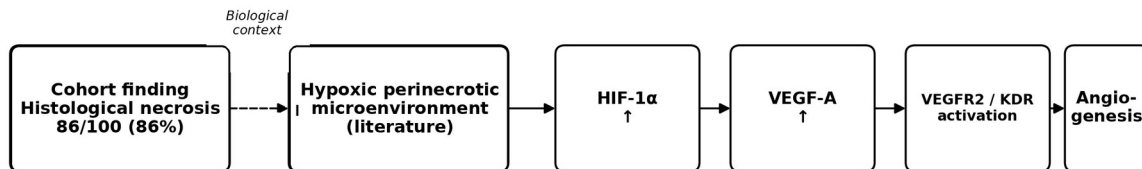
Figure 2. Intraoperative view during microsurgical resection under an operating microscope. The procedure aims to achieve maximal cytoreduction while preserving functional and neurovascular structures.

Necrosis and microvascular proliferation are major morphological features of grade 4 astrocytic tumors. Perinecrotic pseudopalisades have been described as biologically active regions containing hypoxic and migratory tumor cells [4]. Hypoxia stabilizes HIF factors and promotes VEGF expression, contributing to pathological angiogenesis [5]. VEGF-A exerts a substantial proportion of its angiogenic effects through VEGFR2/KDR, a receptor tyrosine kinase whose catalytic domain is accessible to small molecules. This mechanistic chain is well established in the literature, but must not be confused with patient-by-patient demonstration of hypoxia, VEGF-A, or VEGFR2 in a cohort in which these markers were not measured.

The human VEGFR2 kinase domain has been crystallized in complex with the pyrrolopyrimidine ligand 42Q in PDB structure 3VHE, resolved at 1.55 Å [6,7]. Redocking a co-crystallized ligand is a conventional methodological control designed to determine whether a docking protocol can reproduce a known experimental pose [8,9]. However, pose recovery validates neither the ability to discriminate active from inactive compounds nor pharmacological or clinical efficacy.

The primary objective of this study was to characterize histological necrosis and its association with documented IDH status in a prospective cohort of 100 tumors initially diagnosed as glioblastoma. The secondary objectives were to place this phenotype within the published mechanistic framework of the hypoxia–HIF-1 α –VEGF-A–VEGFR2 axis and to validate the geometric reproducibility of the VEGFR2–42Q complex by molecular redocking. These two analytical levels were interpreted separately to avoid attributing unavailable molecular measurements to the patients. The conceptual framework linking the observed necrotic phenotype to the hypoxia–VEGF/VEGFR2 pathway is summarized in Figure 3.

From the observed necrotic phenotype to the hypoxia-VEGF/VEGFR2 rationale



*HIF-1α, VEGF-A and VEGFR2 were not measured in the cohort tumors.
The link between necrosis and VEGF/VEGFR2 is based on published mechanistic evidence, not on patient-by-patient molecular correlation.*

Figure 3. Relationship between the observation in the cohort and the published biological rationale. Histological necrosis is a finding from the series; perinecrotic hypoxia, HIF-1α, VEGF-A, and VEGFR2 represent the literature-based mechanistic framework. These markers were not measured in the cohort tumors.

2. Patients and methods

2.1. Study design and population

This prospective single-center study included 100 patients managed in the Neurosurgery Department of Frantz-Fanon University Hospital, Blida, between June 2022 and June 2025. All included patients had an initial pathological diagnosis of glioblastoma in the department's clinical database. The initial diagnostic designations were retained in the descriptive analysis and interpreted in light of the 2021 WHO nomenclature [1]. Reporting of the observational component follows the applicable STROBE principles [26].

Under the current interpretation, the 14 tumors recorded as IDH-mutant are not equated with IDH-wildtype glioblastomas. In the absence of an integrated review of every specimen with all required markers, they are described as tumors initially diagnosed as glioblastoma with recorded IDH-mutant status.

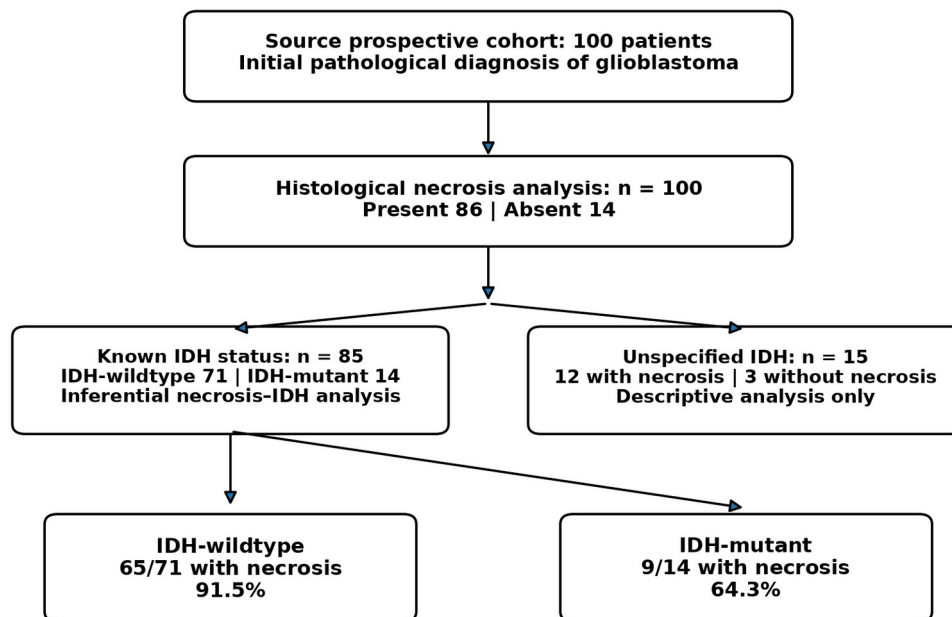
2.2. Inclusion and exclusion criteria and analytical flow

Patients were retained for analysis if they were included in the source prospective cohort between June 2022 and June 2025; had an initial pathological diagnosis of glioblastoma after resection or biopsy; had preoperative brain imaging with CT and MRI; and had a pathology report from which the presence or absence of necrosis could be extracted. IDH status was not an inclusion criterion and could be absent or unspecified.

This component excluded patients without pathological evidence of the tumor, tumor diagnoses incompatible with the source cohort, absence of preoperative imaging, or inability to extract histological necrosis status. All 100 patients in the cohort were evaluable for the necrosis variable. IDH status was known in 85 patients and unspecified in 15; these 15 patients were retained in the

general description but excluded from the inferential comparison between IDH-wildtype and IDH-mutant tumors. The analytical flow of the cohort is shown in Figure 4.

Analytical flow of the cohort



Main comparison: two-sided Fisher's exact test; empirical OR 6.02; $p = 0.0154$.

Figure 4. Analytical flow of the cohort. The 15 unspecified IDH results are treated as missing molecular information rather than as a third biological group.

2.3. Neuroradiological and surgical data

All patients had undergone brain CT and MRI; spectroscopy was available when feasible in clinical practice. Imaging was used for localization, assessment of extent, and treatment planning. The source database does not contain standardized quantification of radiological necrotic volume across the 100 patients; no frequency of “radiological necrosis” was therefore assigned to the cohort in this analysis. The illustrative images are descriptive and do not constitute a measurement of tissue hypoxia.

Surgical management consisted of total or partial microsurgical resection where possible, or stereotactic biopsy. The extent of resection used in this manuscript corresponds to categories recorded in the clinical database, rather than centralized postoperative volumetry.

2.4. Pathological and molecular variables

Histological necrosis was extracted from pathology reports as a binary variable, present or absent. It was documented for all 100 patients. Necrotic area, the extent of pseudopalisades, and microvascular proliferation were not centrally quantified in this analysis.

IDH status corresponds to the result recorded in the pathology report. It was recorded as IDH-wildtype in 71 patients, IDH-mutant in 14, and unspecified/NOS in 15. The available documents do not allow uniform patient-by-patient reconstruction of the exact technique used to determine IDH; no additional methodological assumption was introduced. The 15 unspecified results are treated as missing data for the inferential analysis.

2.5. Statistical analysis

Qualitative variables are described as counts and percentages. The proportion of histological necrosis in the complete cohort was accompanied by a 95% confidence interval calculated using the Wilson method. The principal analysis of the necrosis–IDH association was restricted to the 85 patients with known IDH status. Necrosis proportions in tumors recorded as IDH-wildtype and IDH-mutant were compared using a two-sided Fisher’s exact test. The empirical odds ratio was calculated as the ratio of cross-products; the 95% confidence interval was obtained using the exact conditional method. The absolute difference in proportions was accompanied by a Newcombe confidence interval. The 15 unspecified IDH cases were described separately, without a three-group biological test. No multivariable adjustment, imputation, or survival analysis by necrosis status was performed in this exploratory component.

2.6. Structural target and verification of ligand chemistry

PDB structure 3VHE corresponds to the human VEGFR2 kinase domain, chain A, in complex with ligand 42Q and resolved by X-ray diffraction at 1.55 Å [6]. The entry contains a construct of 359 residues, of which 303 are modeled in the crystallographic structure, together with 467 water molecules and one 42Q ligand. The 56 unmodeled residues were not reconstructed in the redocking protocol; residues explicitly analyzed in the binding pocket, notably Glu885, Cys919, and Asp1046, are present in the experimental structure [6,10].

The chemical identity of 42Q was checked using the Protein Data Bank Chemical Component Dictionary rather than inferred from PDB coordinates alone. The compound is a nonpolymeric ligand with formula C₂₁H₁₅F₄N₅O₂, zero formal charge, and no chiral center; its connectivity, bond orders, and InChIKey TWOLOZGQZKJZKJ-UHFFFAOYSA-N are defined in the RCSB resource [10]. This verification addresses the need to preserve chemical information during small-molecule preparation, since PDB coordinate files are not designed to exhaustively encode bond orders and ionization states [17].

For redocking, the co-crystallized ligand was separated from the receptor, and crystallographic water molecules were not included in the receptor PDBQT file. Hydrogens and partial charges compatible with AutoDockTools/MGLTools 1.5.6 were assigned during preparation. The neutral form of 42Q defined in the chemical dictionary was retained; no exhaustive ensemble of tautomers or alternative protonation microstates was generated. Cys919 was treated as a standard noncovalent residue; no covalent ligand–cysteine bond model was specified. Alternative histidine microstates were not systematically sampled. These choices describe the reproduced protocol and are considered when interpreting its scope. The crystallographic reference structure is presented in Figure 5.

Crystal structure of the VEGFR2 kinase domain - PDB 3VHE
Co-crystallized ligand 42Q in the binding pocket

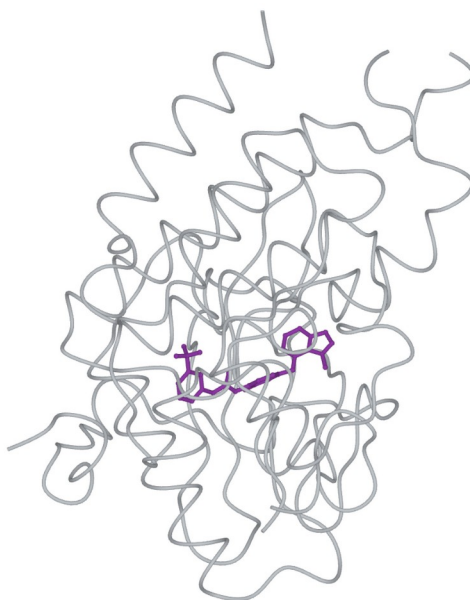


Figure 5. Crystallographic structure of the human VEGFR2 kinase domain (PDB 3VHE), with co-crystallized ligand 42Q in the binding pocket. 42Q is used as the reference ligand for redocking.

2.7. Redocking parameters and geometric validation

Receptor and ligand preparation was performed with AutoDockTools in the MGLTools 1.5.6 environment. The receptor was kept rigid and five ligand torsions were active. Redocking was performed using AutoDock Vina v1.2.7 and the Vina scoring function [8,9]. The search box was centered on the position of the co-crystallized ligand. One calculation with a fixed random seed was analyzed; the generated modes do not constitute independent experimental replicates. The redocking workflow and its geometric assessment are summarized in Figure 6.

Table 1. Parameters for redocking 42Q into VEGFR2.

Parameter	Value
Receptor structure	VEGFR2, PDB 3VHE, chain A
Reference ligand	42Q / compound 20d
Software	AutoDock Vina v1.2.7
Box center (x; y; z)	-24.303; -0.681; -8.955 Å
Dimensions	22 × 20 × 22 Å
Exhaustiveness	32
Maximum number of modes	20
Energy range	5 kcal/mol
Random seed	20260911
Flexibility	Rigid receptor; 5 active ligand torsions

The top-ranked pose was compared with the crystallographic pose by matching the names of the 32 heavy atoms of 42Q. RMSD was calculated in the fixed receptor reference frame, without independent ligand fitting by rotation or translation and without permutation of chemically equivalent atoms. An RMSD below 2 Å was used as a conventional benchmark for pose recovery, without equating it with general validation of the protocol's predictive ability.

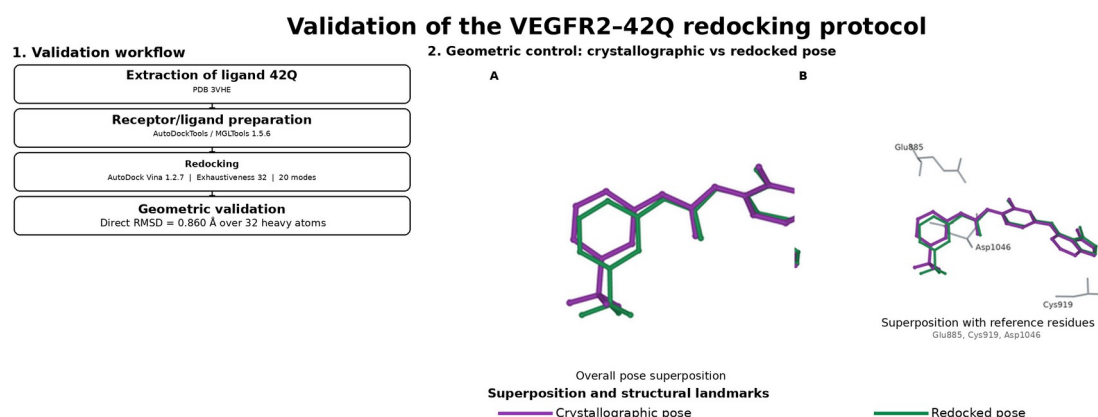


Figure 6. VEGFR2–42Q redocking validation workflow and geometric comparison of the crystallographic and redocked poses.

3. Results

3.1. Cohort characteristics

The cohort included 100 patients, comprising 70 men and 30 women. Mean age was 55 years, with a range of 26–70 years. Macroscopically total resection was reported in 70 cases, partial resection in 25, and biopsy in five. All patients had preoperative CT and MRI. Representative

preoperative and operative illustrations are presented in Figures 1 and 2. General population characteristics are summarized in Table 2.

Table 2. General characteristics of the clinical cohort.

Variable	Count / value
Mean age	55 years (26–70)
Men	70/100
Women	30/100
Macroscopically total resection	70/100
Partial resection	25/100
Biopsy	5/100
Histological necrosis present	86/100
Recorded IDH-wildtype	71/100
Recorded IDH-mutant	14/100
Unspecified IDH	15/100

3.2. Histological necrosis and IDH status

Histological necrosis was explicitly reported in 86 patients and absent in 14, corresponding to a frequency of 86.0% (Wilson 95% CI: 77.9–91.5). Among the 85 patients with known IDH status, 74 had necrosis and 11 did not. Necrosis was present in 65/71 tumors recorded as IDH-wildtype (91.5%) and 9/14 IDH-mutant tumors (64.3%). The overall frequency of necrosis is illustrated in Figure 7, and its distribution by IDH status is detailed in Table 3.

Table 3. Distribution of histological necrosis by recorded IDH status.

Known IDH status	Necrosis present	Necrosis absent	Total	Necrosis (%)
IDH-wildtype	65	6	71	91.5
IDH-mutant	9	5	14	64.3
Total	74	11	85	87.1

The absolute difference in proportions was 27.3 percentage points (Newcombe 95% CI: 6.0–53.2). The empirical odds ratio was 6.02, with an exact conditional 95% CI of 1.16–28.90. The two-sided Fisher’s exact test yielded $p = 0.0154$. Among the 15 unspecified IDH cases, 12 had histological necrosis and three did not; these cases were not included in the principal test. The graphical comparison of necrosis proportions by known IDH status is presented in Figure 8.

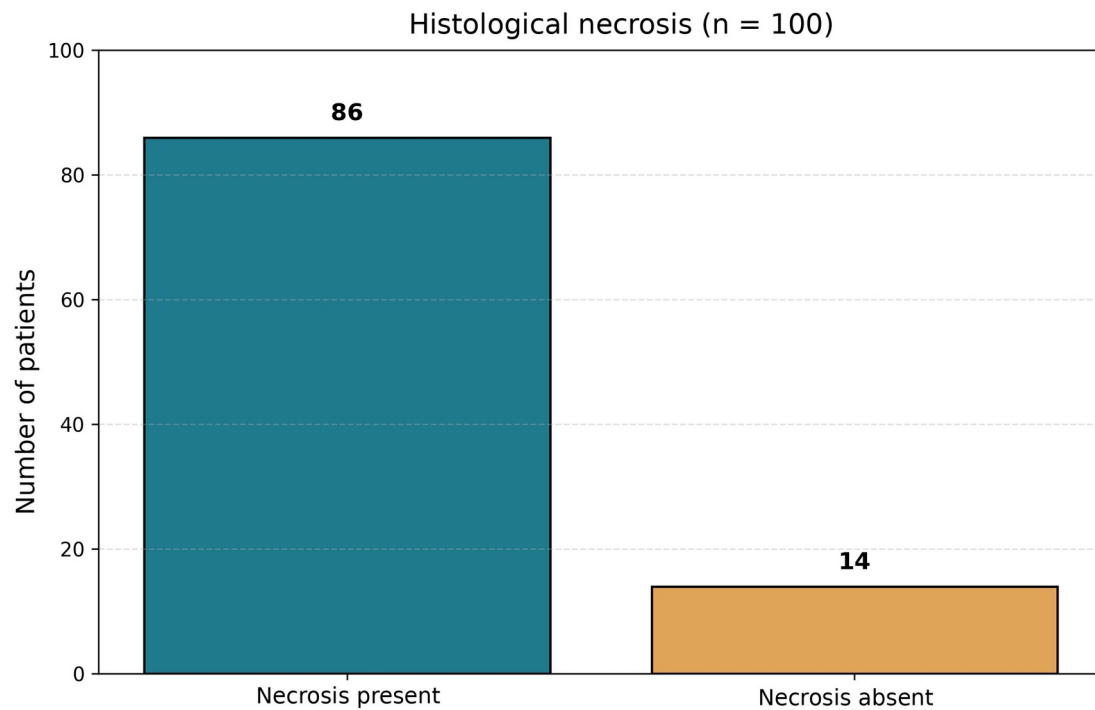


Figure 7. Frequency of histological necrosis in the complete cohort (n = 100).

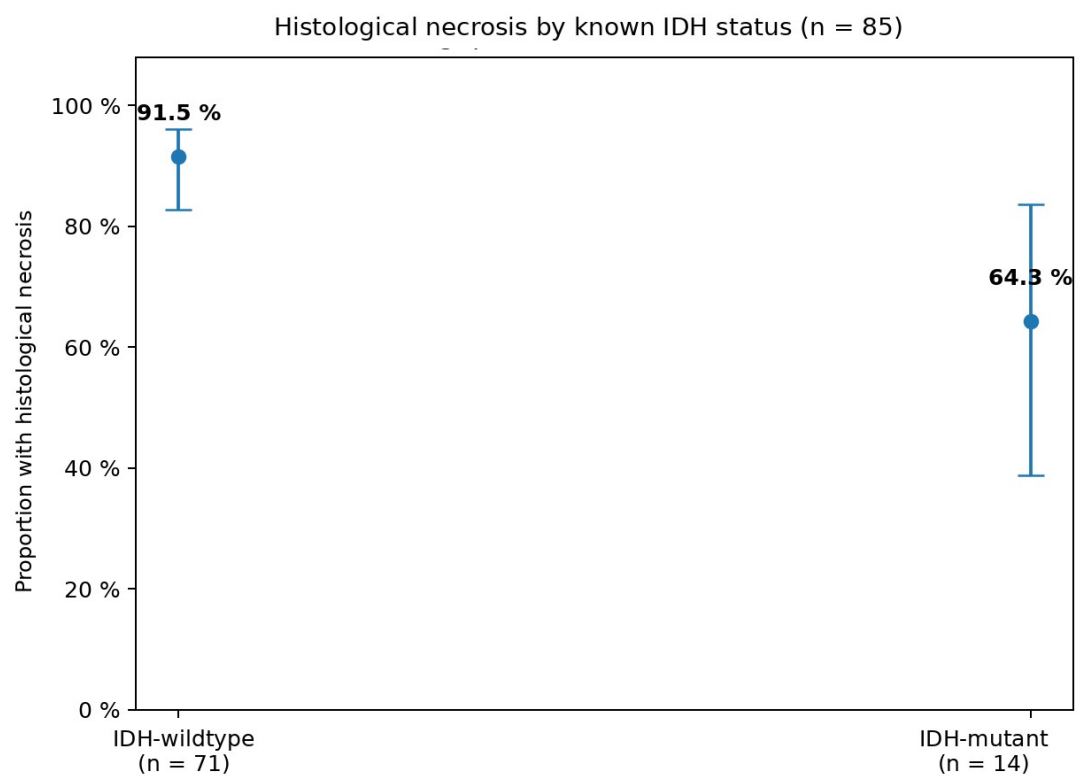


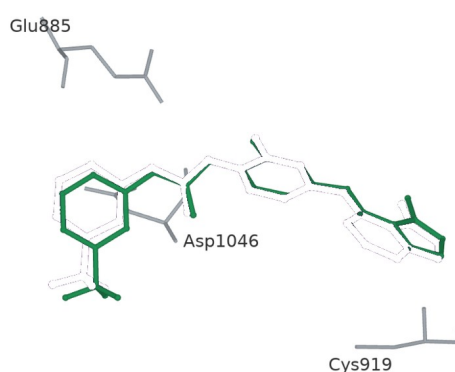
Figure 8. Proportion of histological necrosis by known IDH status (n = 85), with Wilson 95% confidence intervals.

3.3. Redocking of the reference ligand 42Q

The Vina calculation generated 20 modes. The top-ranked pose had a Vina score of -12.832 kcal/mol. Direct comparison of its 32 heavy atoms with the crystallographic pose yielded an RMSD of 0.859944 Å, rounded to 0.860 Å. This value indicates satisfactory geometric recovery of the pose in the complex studied. The highest-scoring redocked pose is presented in Figure 9.

In the redocked pose, several heteroatoms of 42Q lay close to Glu885, Cys919, and Asp1046. Selected interatomic distances ranged from 2.80 to 3.15 Å. These describe geometric proximities consistent with a polar binding environment; they are neither individual binding energies nor evidence of dynamic persistence of the contacts. Three-dimensional superposition with the crystallographic pose and the quantitative summary are presented in Figures 10 and 11; selected interatomic distances are detailed in Table 4.

Redocked reference ligand 42Q in the VEGFR2 pocket



Reference residues: Glu885, Cys919, Asp1046 | Vina score: -12.832 kcal/mol

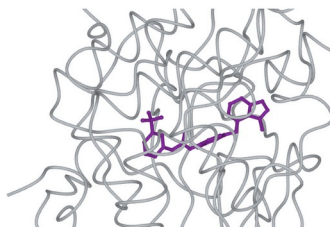
Figure 9. Redocked pose of 42Q in the VEGFR2 pocket. Residues Glu885, Cys919, and Asp1046 are shown as structural landmarks. Vina score for mode 1: -12.832 kcal/mol.

3D superposition of 42Q in the VEGFR2 pocket

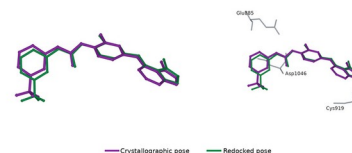
A. Overall receptor context



B. Binding-pocket close-up



C. Pose superposition



Visible receptor residues:
Glu885, Cys919, Asp1046

Crystallographic pose Redocked pose

The protein context is shown in A-B; poses are compared in the same receptor reference frame in C.
Direct RMSD over 32 heavy atoms: 0.860 Å

Figure 10. Structural superposition of 42Q with the receptor context visible. A, global view of VEGFR2; B, close-up of the binding pocket; C, comparison of the crystallographic and redocked poses in the same protein reference frame. Direct RMSD over 32 heavy atoms: 0.860 Å.

Quantitative summary of VEGFR2-42Q redocking

Vina score -12.832 kcal/mol	Direct RMSD 0.860 Å	Heavy atoms 32
Modes 20	Exhaustiveness 32	Box 22 × 20 × 22 Å

Selected polar proximities

N2	Cys919 (N)	2.91 Å
N27	Glu885 (OE2)	3.02 Å
N29	Glu885 (OE2)	2.80 Å
O31	Asp1046 (N)	3.15 Å

Additional parameters

Seed:	20260911
Energy range:	5 kcal/mol
Receptor:	Rigid
Ligand :	5 active torsions

Distances represent geometric proximities, not individual binding energies.

Figure 11. Quantitative summary of VEGFR2-42Q redocking. The indicated distances are interatomic proximities, not binding energies.

Table 4. Selected interatomic proximities in the redocked pose of 42Q.

Ligand atom	VEGFR2 residue	Protein atom	Distance (Å)
N2	Cys919	N	2.91
N27	Glu885	OE2	3.02
N29	Glu885	OE2	2.80
O31	Asp1046	N	3.15

4. Discussion

4.1. Frequency of necrosis and relationship with IDH status

Histological necrosis was reported in 86% of tumors in this cohort. This high frequency is consistent with the initial selection of tumors diagnosed as glioblastoma in clinical practice: necrosis itself contributes to the morphological recognition of grade 4 astrocytic tumors. It should therefore not be interpreted as a frequency applicable to all diffuse gliomas, or as an independent biomarker of aggressiveness in an unselected population.

The principal analysis restricted to the 85 known IDH results showed a higher proportion of necrosis in tumors recorded as IDH-wildtype than in IDH-mutant tumors. The absolute difference was 27.3 percentage points, but the confidence interval for the odds ratio remained wide because of the small IDH-mutant group. The observed association is exploratory and does not establish a causal effect of IDH status on necrosis. The 15 patients with unspecified IDH status were retained in the cohort description but excluded from inference, avoiding the conversion of missing information into a biological category.

The nosological distinction is essential. Under WHO 2021, a grade 4 IDH-mutant diffuse astrocytoma is no longer classified as glioblastoma. The findings in this cohort therefore describe categories as they were recorded in the source database, rather than a uniform retrospective molecular reclassification [1].

4.2. From necrosis to the hypoxic microenvironment: level of evidence

Histological necrosis observed in the cohort and tumor hypoxia are distinct variables. The work of Brat and colleagues established the hypoxic and migratory nature of glioblastoma pseudopalisades [4], while hypoxia-induced VEGF expression has been demonstrated experimentally and in tumor tissues [5]. These data provide a coherent mechanistic framework linking the perinecrotic compartment to an angiogenic response. They do not show that HIF-1 α , VEGF-A, or VEGFR2 was activated in every patient in this cohort.

The source database contains no standardized quantitative measurement of radiological necrosis across all 100 patients. All patients had CT and MRI, but the images cannot retrospectively be turned into a quantitative variable without segmentation and standardized reading protocols. Presumed radiological necrosis, histological necrosis, and tissue hypoxia must therefore remain three distinct levels.

4.3. Robustness and scope of VEGFR2–42Q redocking

The direct RMSD of 0.860 Å shows that the protocol reproduced the experimental position of 42Q in complex 3VHE with high geometric agreement. Comparison was performed in the fixed receptor reference frame, assessing the relative positioning of the ligand in the pocket rather than simple conformational similarity after independent superposition. The Vina score of –12.832 kcal/mol describes the value of the scoring function under the calculation conditions; it is not an experimental binding free energy and must not be converted into a clinical affinity constant.

Chemical preparation parameters that may influence docking reproducibility were explicitly documented. Entry 3VHE contains 303 modeled protein residues from a construct of 359 residues and 467 water molecules [6]. Unmodeled residues were not reconstructed. The chemistry of 42Q was checked against the Chemical Component Dictionary, including connectivity, bond orders, zero formal charge, and lack of chirality [10]. Preparation retained a single reference protonation/tautomeric form; it did not sample every possible microstate. This transparency reduces the risk of confusing pose recovery with general pharmacological validation.

Nevertheless, redocking relies on a single complex, a rigid receptor, one seed, and a ligand known to bind the site. It tests neither discrimination between active and inactive compounds, robustness to alternative preparations, receptor flexibility, nor the effect of structural water molecules. The result must therefore be regarded as pose validation restricted to the 3VHE–42Q system.

4.4. Biological relevance of VEGFR2 and antiangiogenic evidence

The biological relevance of VEGFR2 in glioblastoma rests on the importance of pathological angiogenesis and the vascular response to hypoxia. Preclinical models have shown that VEGFR2 blockade can produce a transient phase of vascular normalization accompanied by improved oxygenation and radiation response [11]. Human observations with cediranib have also associated improved perfusion with better oxygenation in some settings [12].

These observations do not justify equating VEGF/VEGFR2 inhibition with assured clinical benefit. In first-line trials, adding bevacizumab to chemoradiotherapy did not improve overall survival, although some progression-free survival and symptom-control measures may have changed [13,14]. In recurrent glioblastoma, cediranib and various antiangiogenic combinations have not demonstrated a uniform overall survival benefit [21,23]. The redocking presented here tests neither bevacizumab nor the efficacy of 42Q and must be interpreted as a structural step preceding any potential pharmacological assessment.

4.5. Neurosurgical implications, recurrence, and the multimodal pathway

Recurrence remains a major component of the course of glioblastoma. Maximal safe resection reduces tumor burden but does not eliminate infiltrating cells beyond radiological boundaries. A strategy targeting the vascular microenvironment could theoretically be studied as an adjunct to postoperative treatments, but no result in this manuscript demonstrates prevention of recurrence or a reduction in the need for reoperation.

At first recurrence, the indication for further surgery depends particularly on functional status, location, potentially resectable extent, and the ability to continue oncological treatments. Data from the RANO resect group associated low residual tumor volume after reoperation with more

favorable survival in selected patients, subject to the limitations inherent in retrospective analyses [22]. The RANO 2.0 criteria also emphasize the need to distinguish tumor progression, pseudoprogression, and treatment effects, particularly during the first weeks after radiotherapy and during antiangiogenic therapy [16].

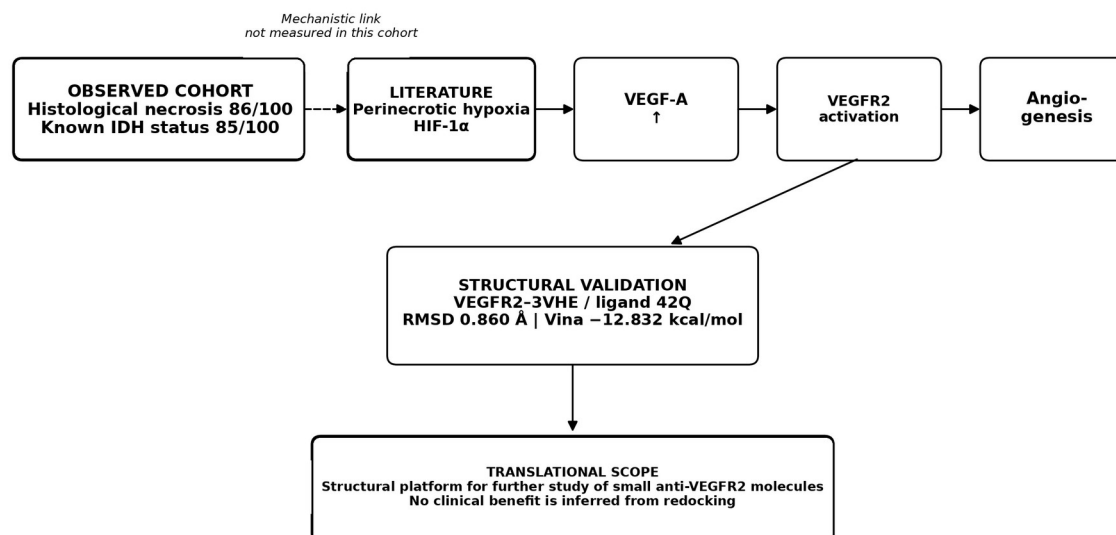
Trials in the recurrent setting illustrate the possible dissociation between radiological control, progression-free survival, and overall survival. Lomustine–bevacizumab improved progression-free survival without an overall survival benefit in EORTC 26101 [23]. In NRG Oncology/RTOG1205, adding reirradiation to bevacizumab improved six-month progression-free survival without a significant difference in overall survival [24]. These data place structural exploration of VEGFR2 within a multimodal pathway still dominated by clinical patient selection, follow-up imaging, surgery, radiotherapy, and systemic treatments.

4.6. Limitations

This study has several limitations. The clinical component is single-center and concerns a cohort historically assembled from initial glioblastoma diagnoses, with 15 unspecified IDH results and no uniform integrated molecular review. Histological necrosis is binary and was not subject to morphometric quantification or centralized rereview. The database does not permit systematic quantification of radiological necrosis or spatial matching of imaging with specimens. HIF-1 α , VEGF-A, and VEGFR2 were not measured in the tumors; no individual relationship between necrosis, hypoxia, VEGFR2 activation, and clinical response can therefore be established.

The structural component is independent of patient samples and relies on a public structure. Only one co-crystallized ligand and one calculation were analyzed; the receptor is rigid, and no exhaustive sampling of tautomers, protonation states, structural waters, or alternative conformations was performed. Redocking validates recovery of a known pose in a specific setting, rather than the performance of a molecular screen or the efficacy of an anti-VEGFR2 strategy in glioblastoma. Figure 12 summarizes the relationship between cohort findings, the biological rationale, and the structural component.

Integrative figure: observed findings, published mechanism and structural validation



The levels of evidence are distinct: histological observation ≠ hypoxia measurement ≠ VEGFR2 activation ≠ therapeutic efficacy.

Figure 12. Integration of the levels of evidence. Histological necrosis is observed in the cohort; the hypoxia–HIF-1α–VEGF-A–VEGFR2 link comes from the literature; redocking validates a reference binding geometry in VEGFR2. These levels are not interchangeable and do not demonstrate clinical benefit.

5. Conclusion

In this prospective cohort of 100 tumors initially diagnosed as glioblastoma, histological necrosis was reported in 86% of cases. Among the 85 patients with documented IDH status, necrosis was more frequent in tumors recorded as IDH-wildtype than in IDH-mutant tumors. The 15 unspecified IDH results were retained in the cohort description but excluded from the inferential analysis, consistent with their nature as missing molecular data.

The relationship between necrosis, hypoxia, and activation of the VEGF/VEGFR2 axis rests on published mechanistic evidence and was not measured directly in this cohort. Redocking 42Q into VEGFR2–3VHE reproduced the crystallographic pose with a direct RMSD of 0.860 Å. With ligand chemistry, receptor preparation, and structural limitations explicitly described, this result constitutes methodological pose validation rather than evidence of therapeutic efficacy. The scientific value of this work lies in explicitly connecting three distinct levels: an observed histological phenotype, a documented biological mechanism, and in silico structural validation.

DECLARATIONS

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Availability of data and materials

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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