

Molecular biomarkers in hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma

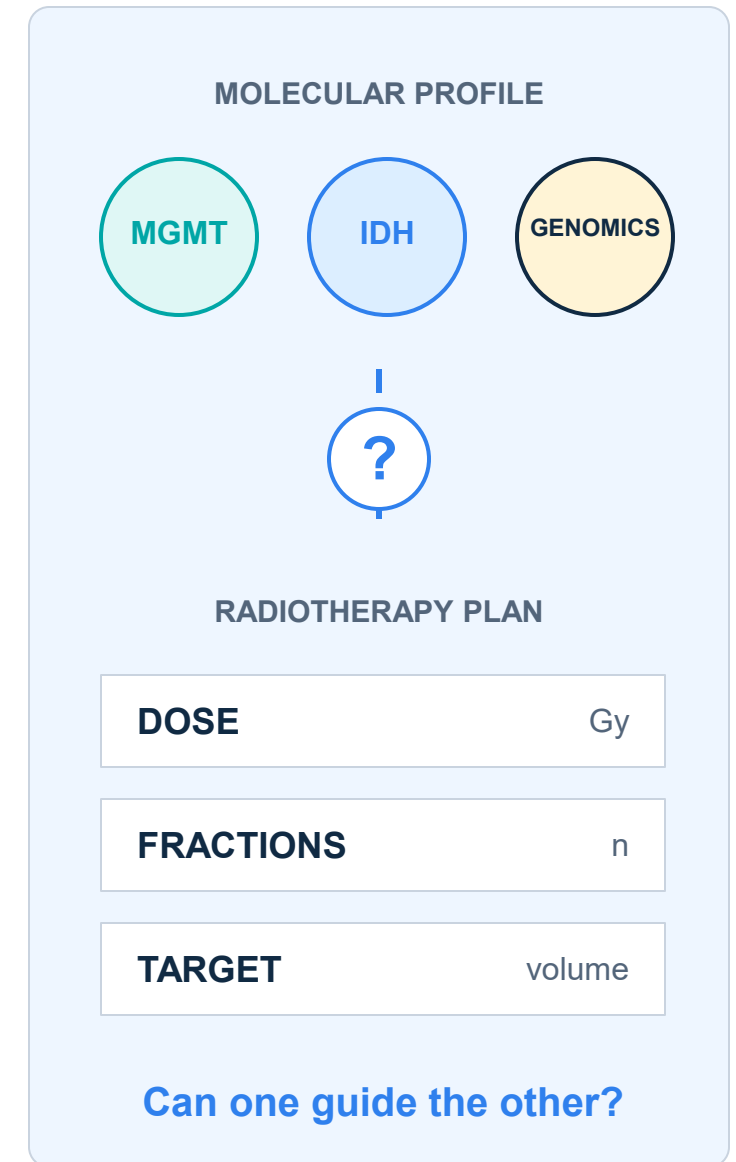
A scoping review

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Five- or six-fraction stereotactic RT is different

ESTABLISHED FOR SUITABLE ADULTS

60 Gy / 30 fractions

~6 weeks · 2 Gy per fraction



RANDOMISED EVIDENCE IN OLDER ADULTS

40.05 Gy / 15 fractions

~3 weeks · 2.67 Gy per fraction



COMPLETED COHORTS IN THIS REVIEW

5-6 stereotactic fractions

~1-2 weeks · larger dose per fraction



Fewer fractions do not mean interchangeable evidence: target definition, margins, setup and verification become especially important.



MGMT and IDH answer different clinical questions

TEMOZOLOMIDE CONTEXT

MGMT

DNA-repair gene

Promoter
methylated



Reduced MGMT
expression

Temozolomide-induced DNA damage is less readily repaired

Associated with benefit from temozolomide-containing treatment

DIAGNOSTIC CONTEXT

IDH

Tumour-defining alteration

Glioblastoma
IDH-wildtype

≠

Grade 4
astrocytoma
IDH-mutant

Older diagnostic labels may mix biologically different tumours

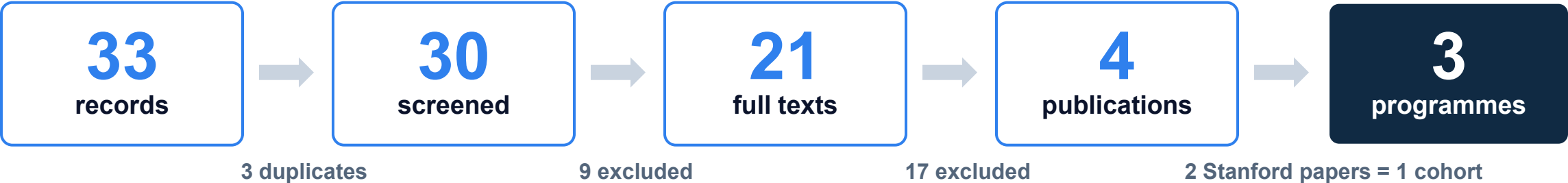
OUR REVIEW QUESTION

Was the biomarker only reported, or did it choose dose, fractions or target?

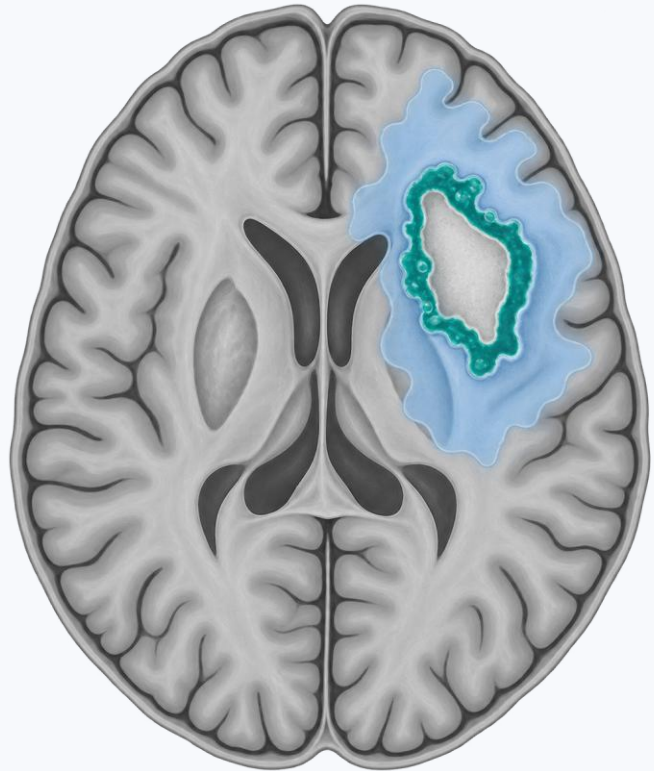
Methodology



Database-specific strategies for PubMed and the Cochrane Library · searched 1 March 2026



Omuro used two target volumes and two dose levels



INNER TEAL
Contrast enhancement

OUTER BLUE
FLAIR abnormality

Omuro et al., 2014 · PHASE II · n=40

Dose painting

Two dose levels delivered across the same six attendances

36 Gy / 6

contrast-enhancing region

24 Gy / 6

wider FLAIR region

- Selected tumour volume $\leq 60 \text{ cm}^3$
- Monday / Wednesday / Friday over 2 weeks
- Temozolomide + bevacizumab

Two volumes · two doses · temozolomide + bevacizumab

Stanford and HSK-010 used different strategies

STANFORD · COMPLETED DOSE-FINDING COHORT · n=30

One five-fraction schedule per patient

25 Gy

5 Gy / fraction

30 Gy

6 Gy / fraction

35 Gy

7 Gy / fraction

40 Gy

8 Gy / fraction

Dose increased between cohorts · not a randomised comparison



Delivery

CyberKnife stereotactic RT



Target

Cavity + residual enhancement + 5-mm margin

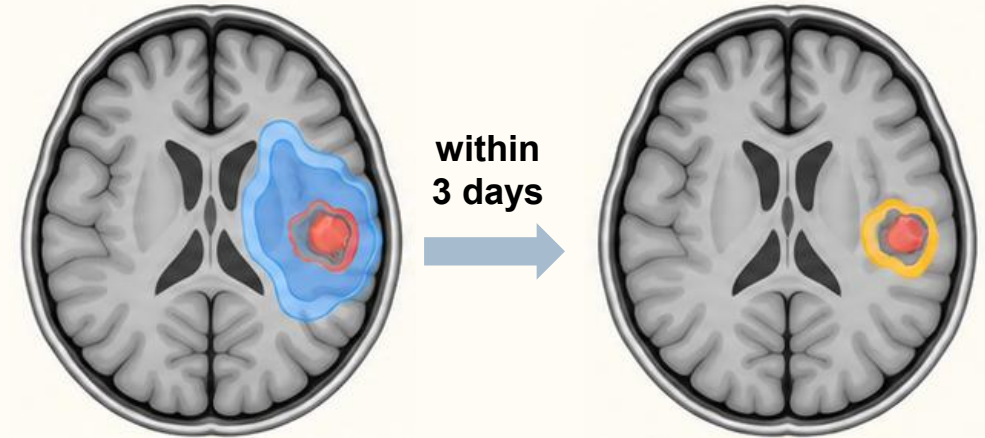


Systemic therapy

Concurrent temozolomide · adjuvant temozolomide in 27/30 patients

HSCK-010 · PROTOCOL ONLY · NO OUTCOME DATA

Wider field IMRT, followed by a focal HSRT boost



STEP 1 · WIDER TARGET

20 Gy / 10

2 Gy per fraction · IMRT
Treats peritumoural oedema volume

STEP 2 · FOCAL BOOST

30 Gy / 5

6 Gy per fraction · HSRT
Treats resection cavity + enhancing tumour



Temozolomide planned during and after treatment

Stanford contributed outcome data; HSK-010 contributed protocol design only

Outcome signals from two non-comparable cohorts

Omuro

SINGLE-ARM · N=40

Selected tumour volume $\leq 60 \text{ cm}^3$ · temozolomide + bevacizumab

MEDIAN OS

19.0

months

MEDIAN PFS

10.0

months

1-year OS 93% (95% CI 84-100)

SAFETY

Serious toxicity during combined treatment

Haematological and thromboembolic events

RT + TMZ + bevacizumab → attribution to fractionation not possible

Stanford

SINGLE-ARM · N=30

Four dose-escalation cohorts · temozolomide

MEDIAN OS

14.8

months

MEDIAN PFS

8.2

months

SAFETY

Late adverse radiation effects: 8/30, all grade 1-2; none grade 3-5

Two acute protocol-defined dose-limiting events at 40 Gy

Small single-arm cohorts + different treatments + no common control = no valid comparison

Association with survival ≠ biomarker-guided radiotherapy

Biomarkers were reported, but they did not select RT

NO

No biomarker selected dose, fractions or target volume

MGMT

Stanford

19.9 vs 11.3 mo

hypermethylated n=13 vs
non-hyper/unknown n=17

p=0.031 · association detected

Longer OS with hypermethylation
Association ≠ differential RT benefit

Omuro

18 vs 22 mo

methyated n=9 vs unmethyated n=28
(unknown n=3)

p=0.56 · no detectable difference

Non-significance ≠ equivalence

IDH

Omuro

25 tested · 0 mutant

No IDH subgroup
comparison was possible

Stanford: not reported

HSCK-010: IDH1/2-mutant
disease excluded

TARGETED PROFILING

**Targeted 81-gene
NanoString**

Exploratory expression and
copy-number analysis

No treatment allocation

No sequencing-guided
radiotherapy strategy

0 treatment-by-biomarker interaction tests

No study tested whether radiotherapy effect differed by biomarker status.

What evidence could change practice?



THERAPEUTIC RADIOGRAPHERS MAKE THE COMPARISON REPRODUCIBLE

Consistent planning · immobilisation · IGRT · intrafraction monitoring · QA · protocol deviations · patient-centred follow-up

Abbreviated stereotactic RT is feasible; biomarker guidance is unproven

70

treated participants
in two completed cohorts

0

biomarkers used to select RT
dose · fractions · target

1

Evidence

Feasible, but small and non-comparative.

2

Meaning

Biomarkers characterised cohorts;
none selected RT.

3

Next trial

Compare schedules within molecular
strata and test the interaction.

MEASURE the biomarker → STANDARDISE the pathway → TEST the interaction

THANK YOU · REVIEW TEAM

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Key references

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CLINICAL AND METHODOLOGICAL CONTEXT

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