Essais qui changent les pratiques

Neurologie

Métastases osseuses

28 Novembre 2024

Novotel Bordeaux Lac

Dr Eivind Blais

Groupe de Radiothérapie et d'oncologie des Pyrénées - Pau

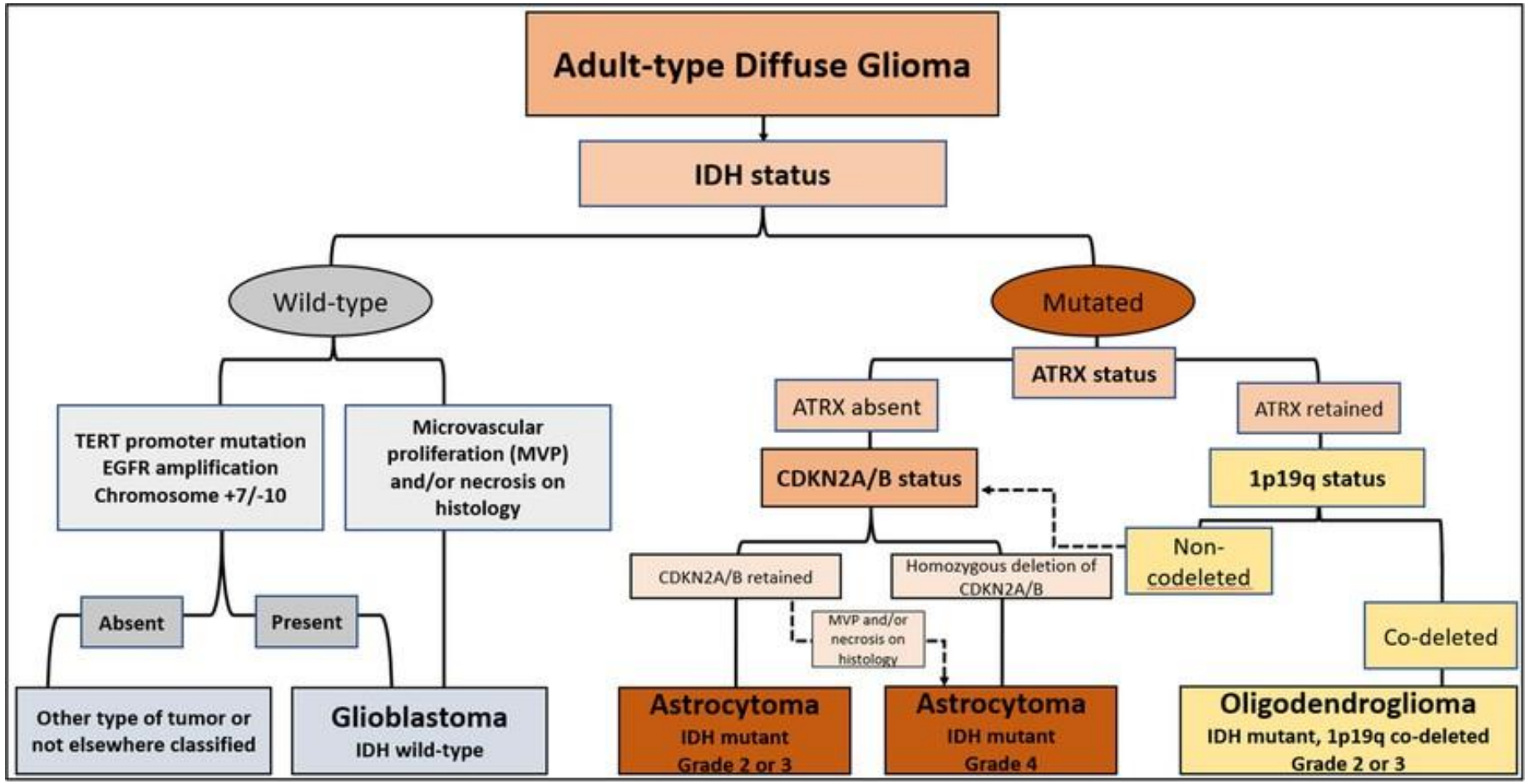
1e rencontre de radiothérapie en Nouvelle-Aquitaine

Liens d’intérêts

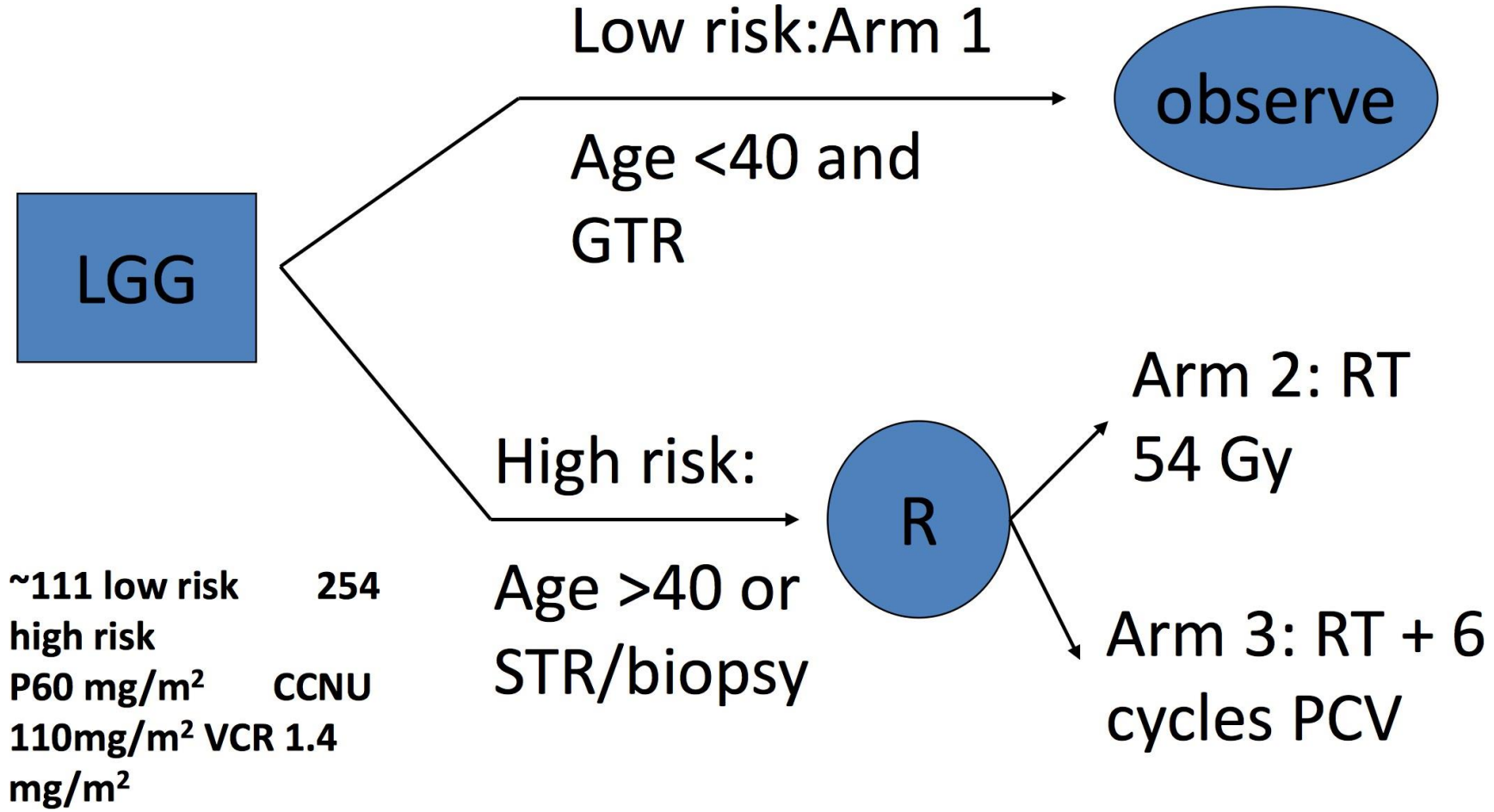
- Aucun conflit d’intérêt déclaré

Tumeurs primitives encéphaliques

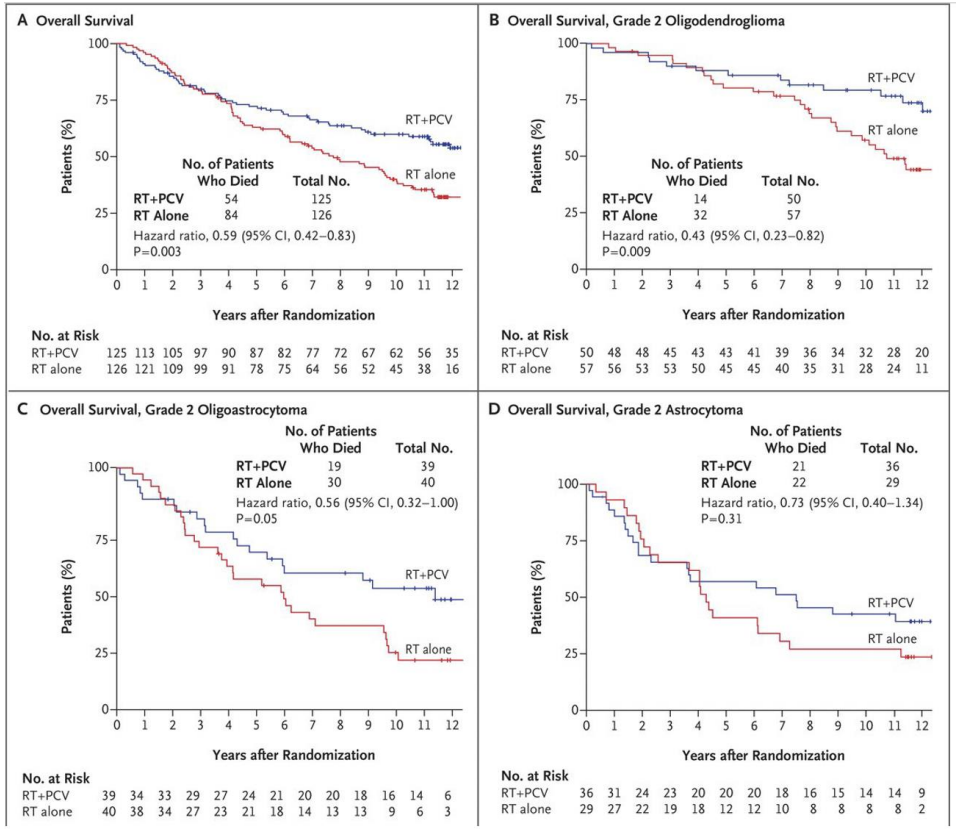
Gliomes : classification OMS 2021

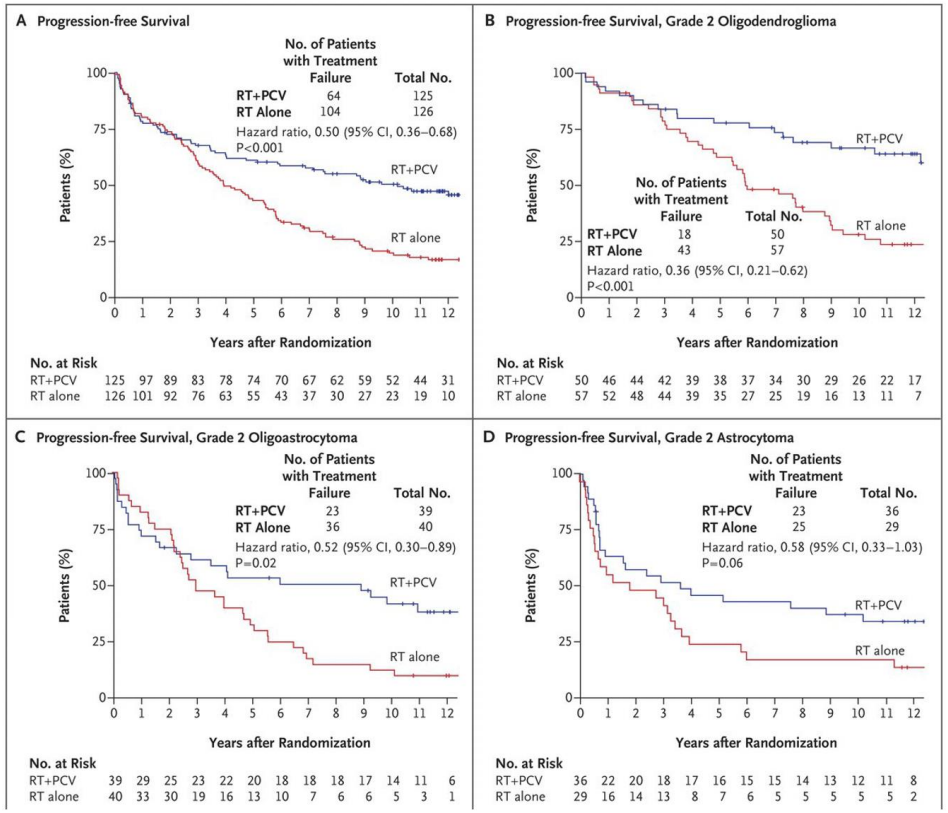


RTOG 9802


Low risk:Arm 1
observe
Age <40 and
GTR
LGG
High risk:
R
Arm 2: RT
54 Gy
Age >40 or
STR/biopsy
Arm 3: RT + 6
cycles PCV
~111 low risk 254
high risk
P60 mg/m²
CCNU
110mg/m² VCR 1.4
mg/m²

RTOG 9802

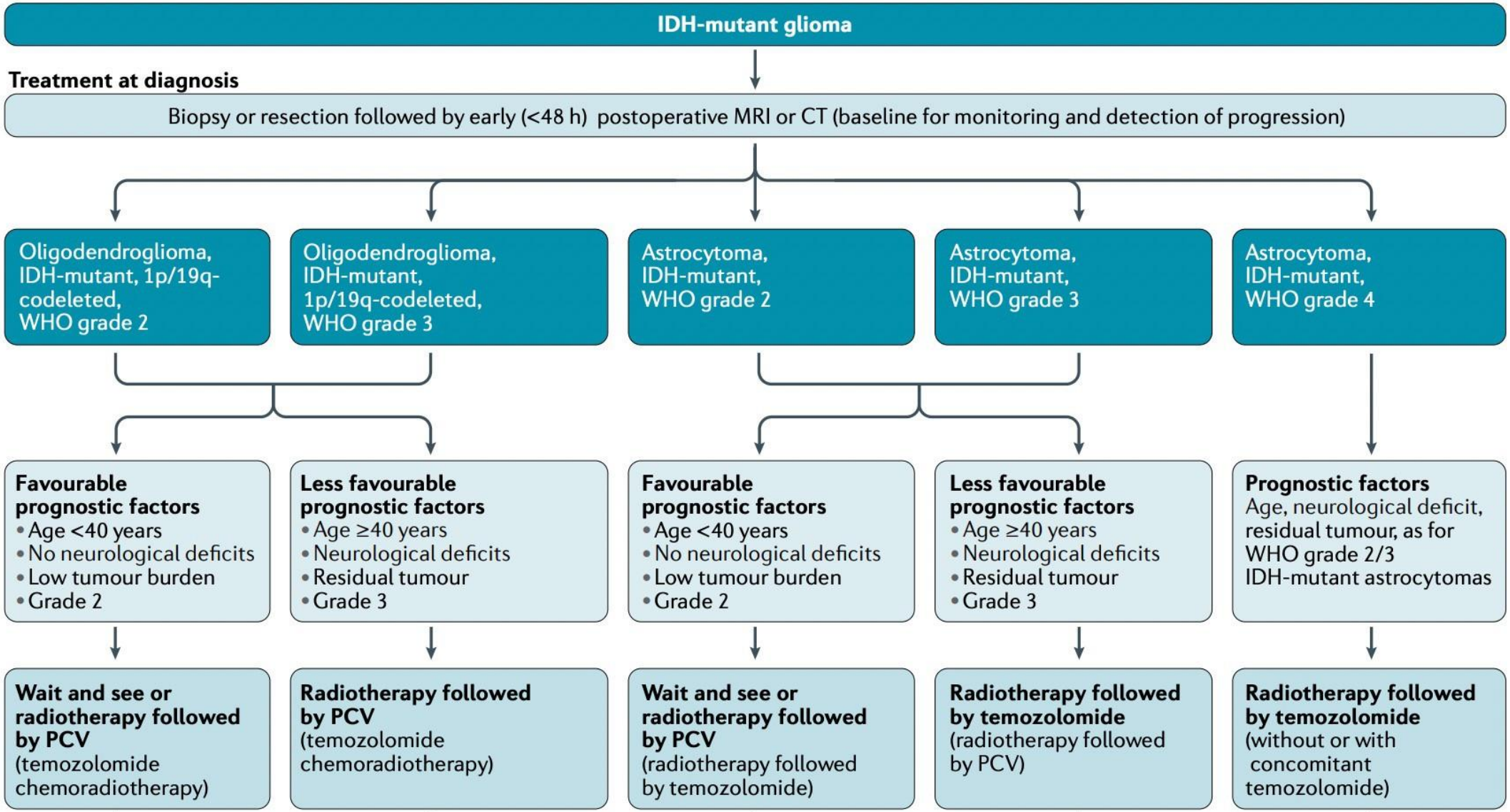




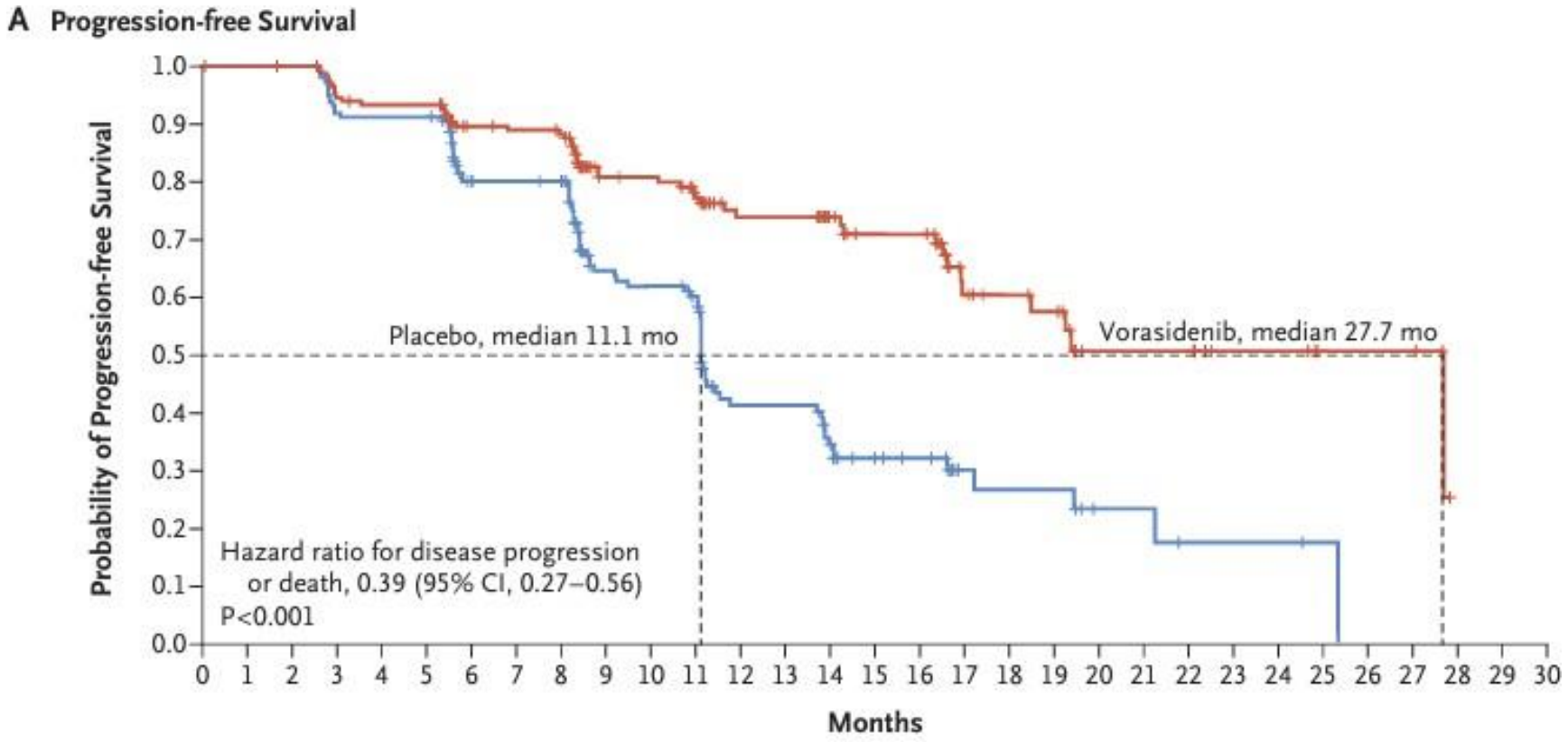
Buckner et al, NEJM, 2016

Buckner et al.

NEJM 2016


IDH-mutant glioma
Treatment at diagnosis
Biopsy or resection followed by early (<48 h) postoperative MRI or CT (baseline for monitoring and detection of progression)
Oligodendroglioma, IDH-mutant, 1p/19q-codeleted, WHO grade 2
Oligodendroglioma, IDH-mutant, 1p/19q-codeleted, WHO grade 3
Astrocytoma, IDH-mutant, WHO grade 2
Astrocytoma, IDH-mutant, WHO grade 3
Astrocytoma, IDH-mutant, WHO grade 4
Favourable prognostic factors
• Age <40 years
• No neurological deficits
• Low tumour burden
• Grade 2
Less favourable prognostic factors
• Age ≥40 years
• Neurological deficits
• Residual tumour
• Grade 3
Favourable prognostic factors
• Age <40 years
• No neurological deficits
• Low tumour burden
• Grade 2
Less favourable prognostic factors
• Age ≥40 years
• Neurological deficits
• Residual tumour
• Grade 3
Prognostic factors
Age, neurological deficit, residual tumour, as for WHO grade 2/3 IDH-mutant astrocytomas
Wait and see or radiotherapy followed by PCV
(temozolomide chemoradiotherapy)
Radiotherapy followed by PCV
(temozolomide chemoradiotherapy)
Wait and see or radiotherapy followed by PCV
(radiotherapy followed by temozolomide)
Radiotherapy followed by temozolomide
(radiotherapy followed by PCV)
Radiotherapy followed by temozolomide
(without or with concomitant temozolomide)

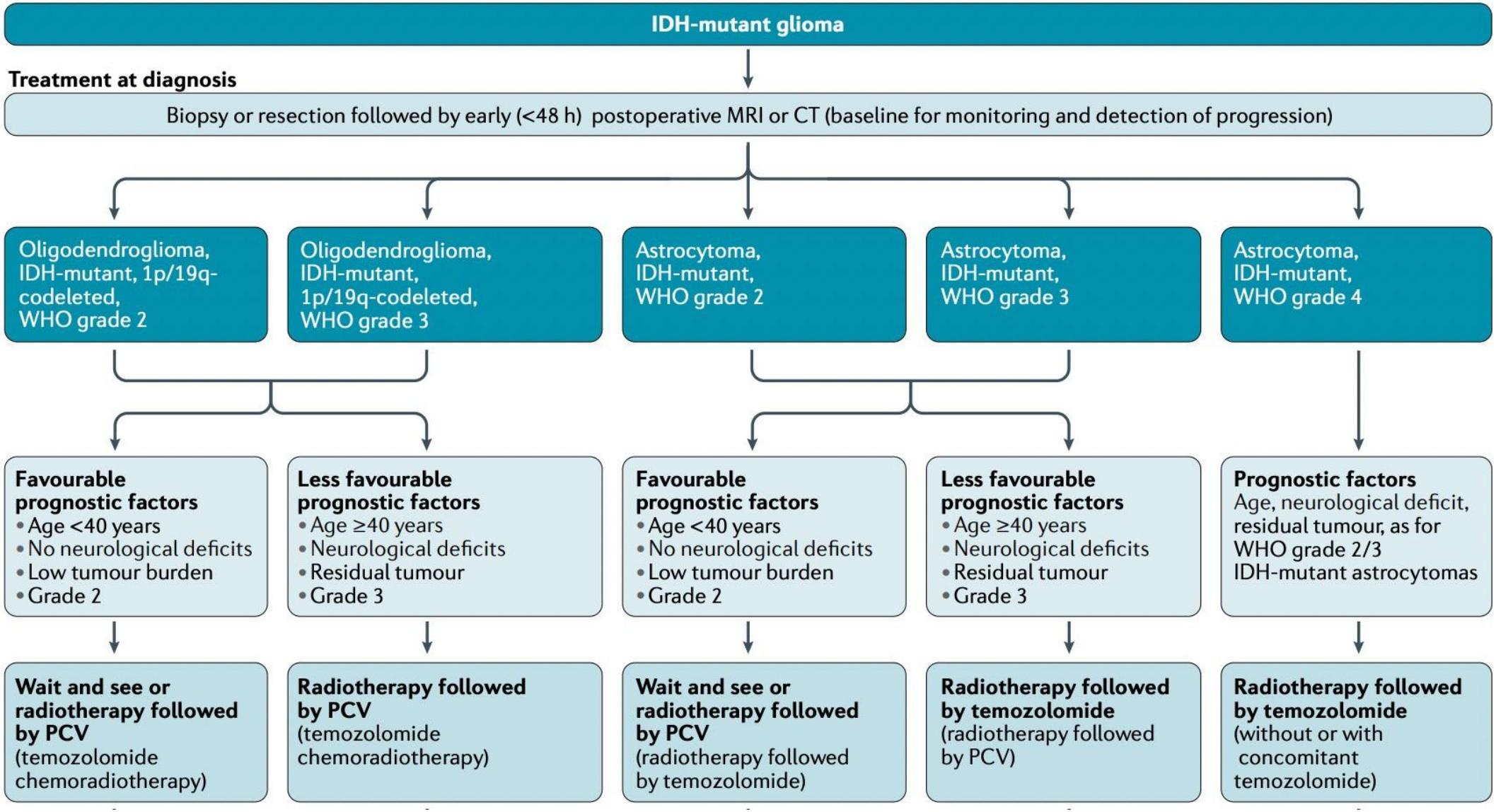
INDIGO



No. at Risk

Vorasidenib	168	166	166	157	154	154	133	131	129	93	91	81	63	63	52	45	45	25	22	20	11	11	11	7	7	4	4	4	0
Placebo	163	162	161	146	145	145	117	116	114	73	70	65	38	38	29	21	19	9	8	8	4	4	2	2	2	1	0		

Mellinghoff et al. NEJM 2023



Place de l'anti-IDH dans stratégie thérapeutique?

Survival Outcomes Associated With First-Line Procarbazine, CCNU, and Vincristine or Temozolomide in Combination With Radiotherapy in IDH-Mutant 1p/19q-Codeleted Grade 3 Oligodendroglioma

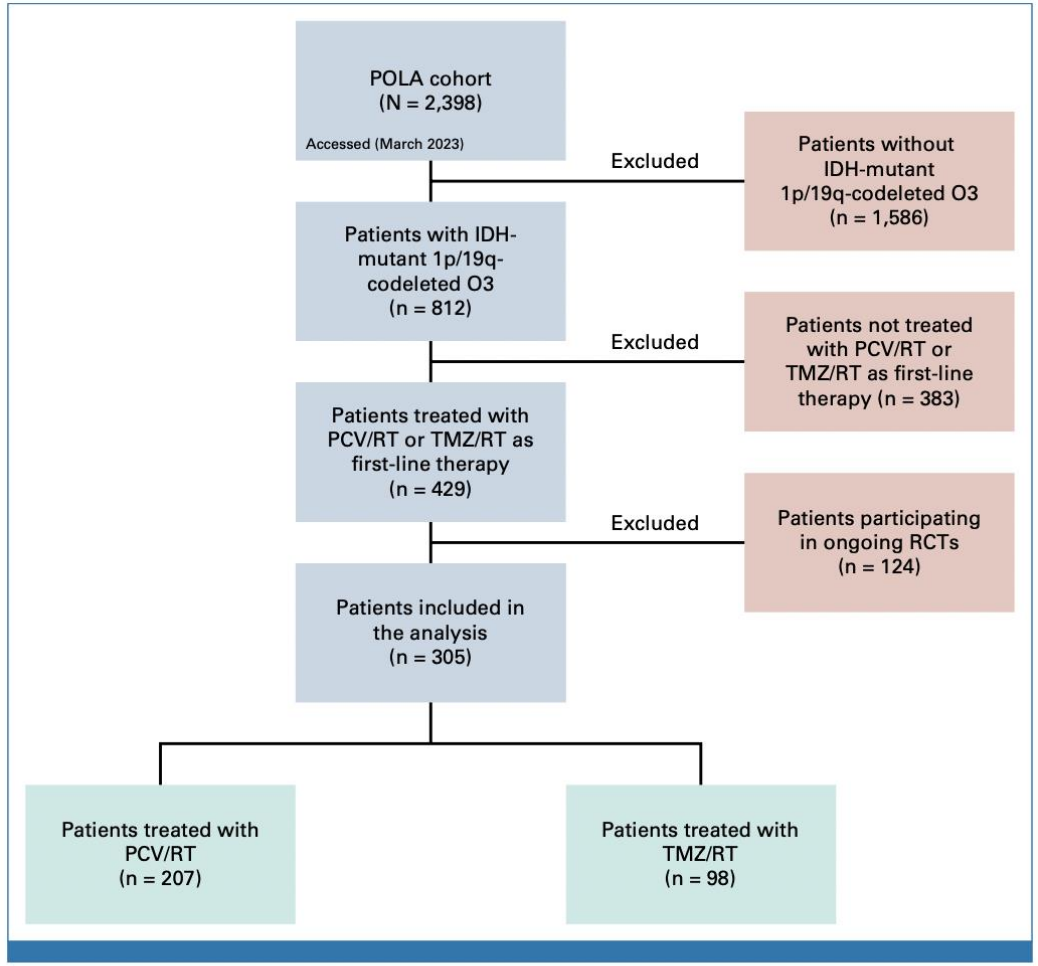
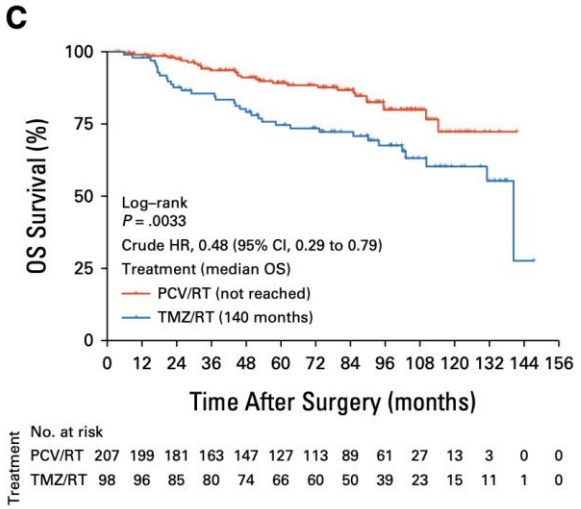
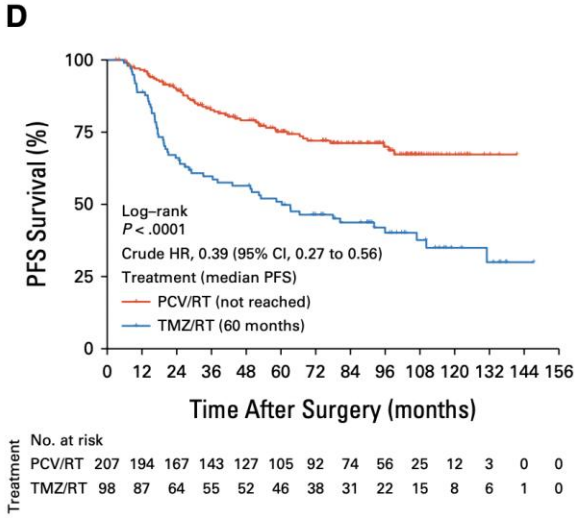


FIG 1. Consort diagram of the study. PCV, procarbazine, CCNU, and vincristine; RT, radiation therapy; TMZ, temozolomide.

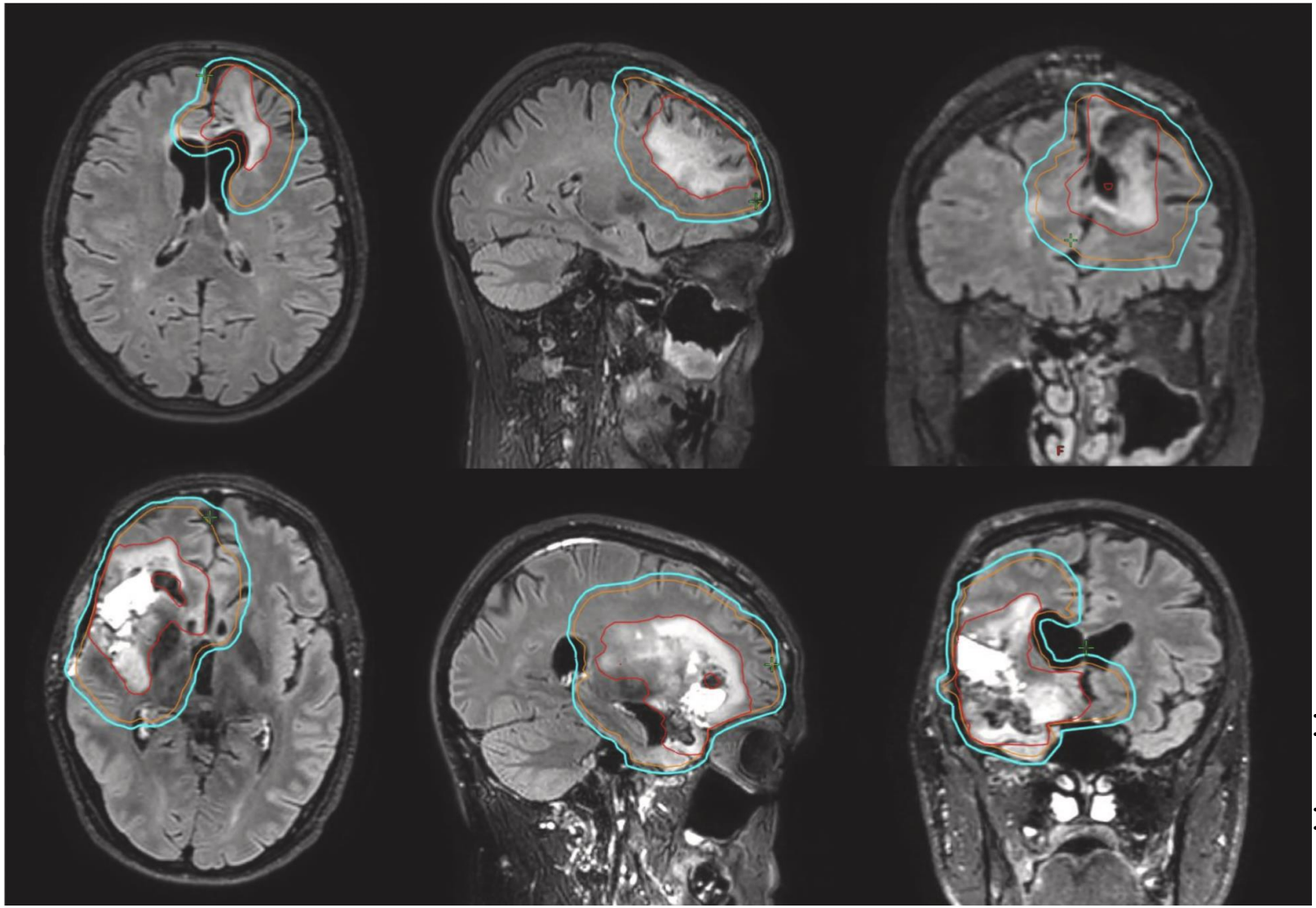




O. Kacimi et al.
JCO 2024

Tumeurs gliales : marges au CTV

ESTRO-EANO guideline on target delineation and radiotherapy for IDH-mutant WHO CNS grade 2 and 3 diffuse glioma



BG. Baumert et al.
Rad. Onc. 2024

Limited margins?

- Retrospective University of Alabama
- 95 pts
- 46 Gy to FLAIR+5mm+3mm
- 14 Gy boost to gad+5mm+3mm

Table 1 ABTC guidelines for target definition

Target volume	Definition
GTV1	T1 enhancing and non-enhancing tumor volume (T2 or FLAIR)
GTV2	T1 enhancing tumor volume
CTV1;2	GTV plus a margin of 5 mm
PTV1;2	CTV plus a margin of 3–5 mm

Note: GTV volume is based on postoperative day 0–1 MRI. GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, planning target volume; ABTC, Adult Brain Tumors Consortium.

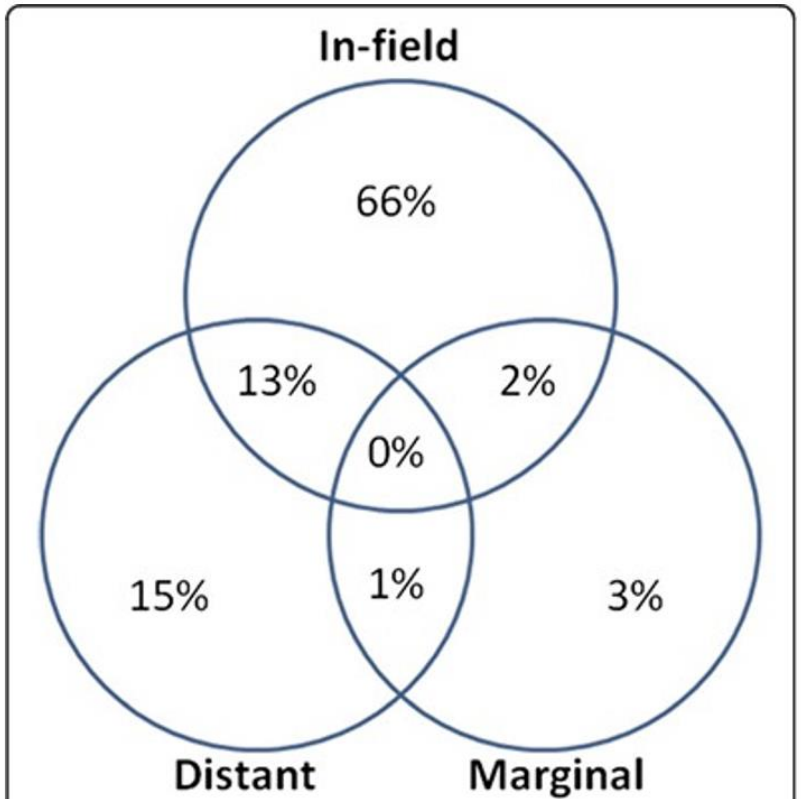
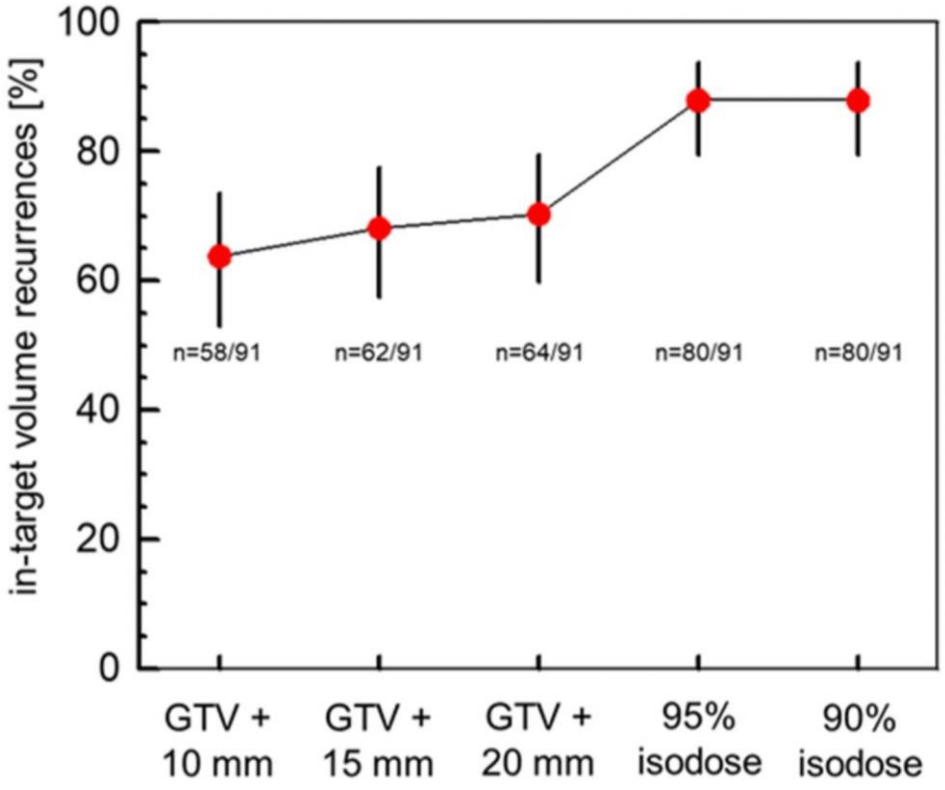
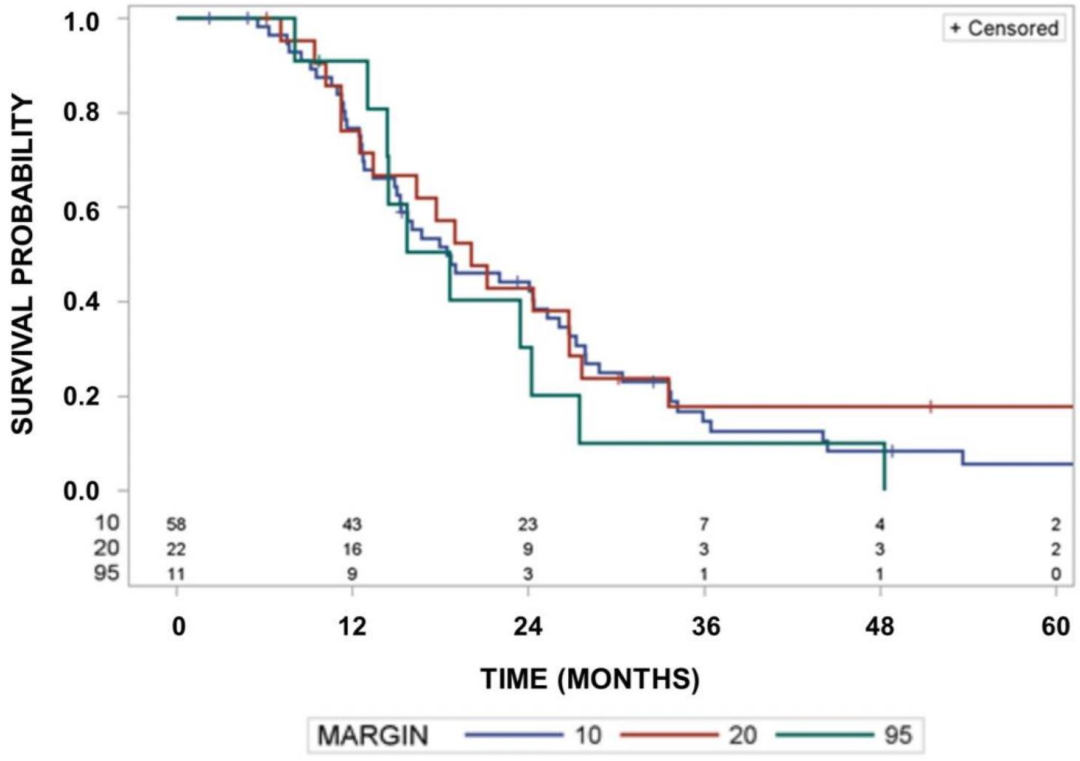


Figure 1 Patterns of Failure.

Gebhardt, Radiation Oncology, 2014

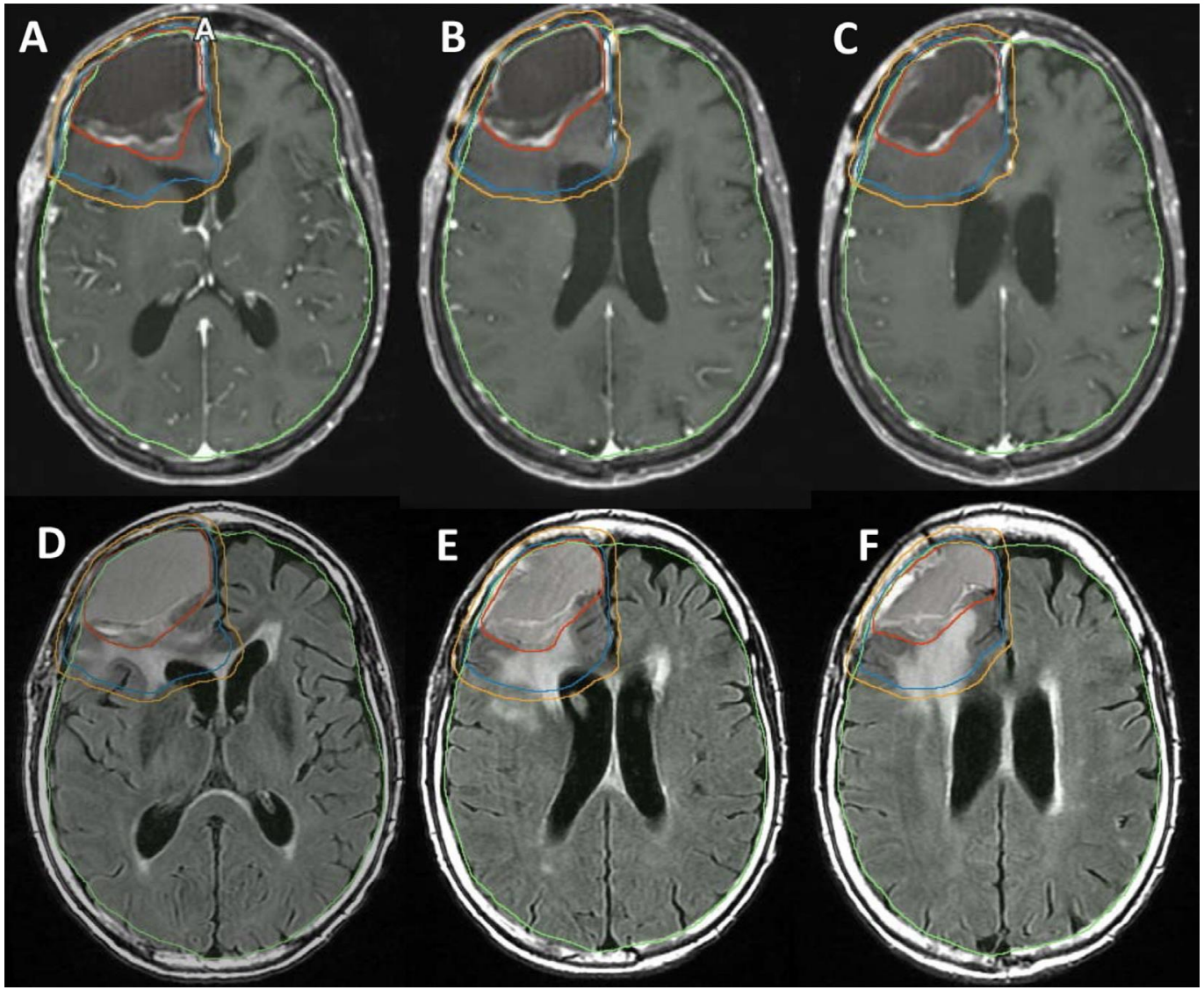
Location of Recurrences after Trimodality Treatment for Glioblastoma with Respect to the Delivered Radiation Dose Distribution and Its Influence on Prognosis





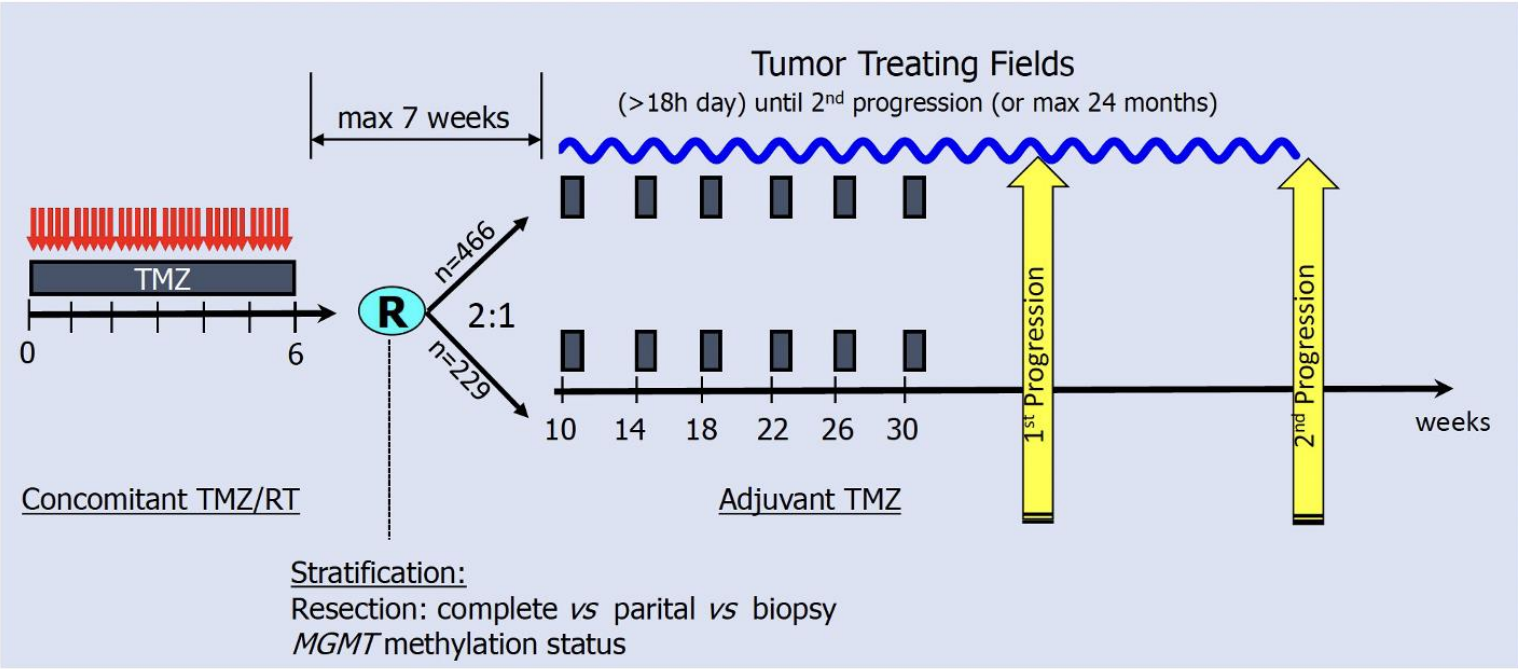
N. Guberina et al. Cancers 2023

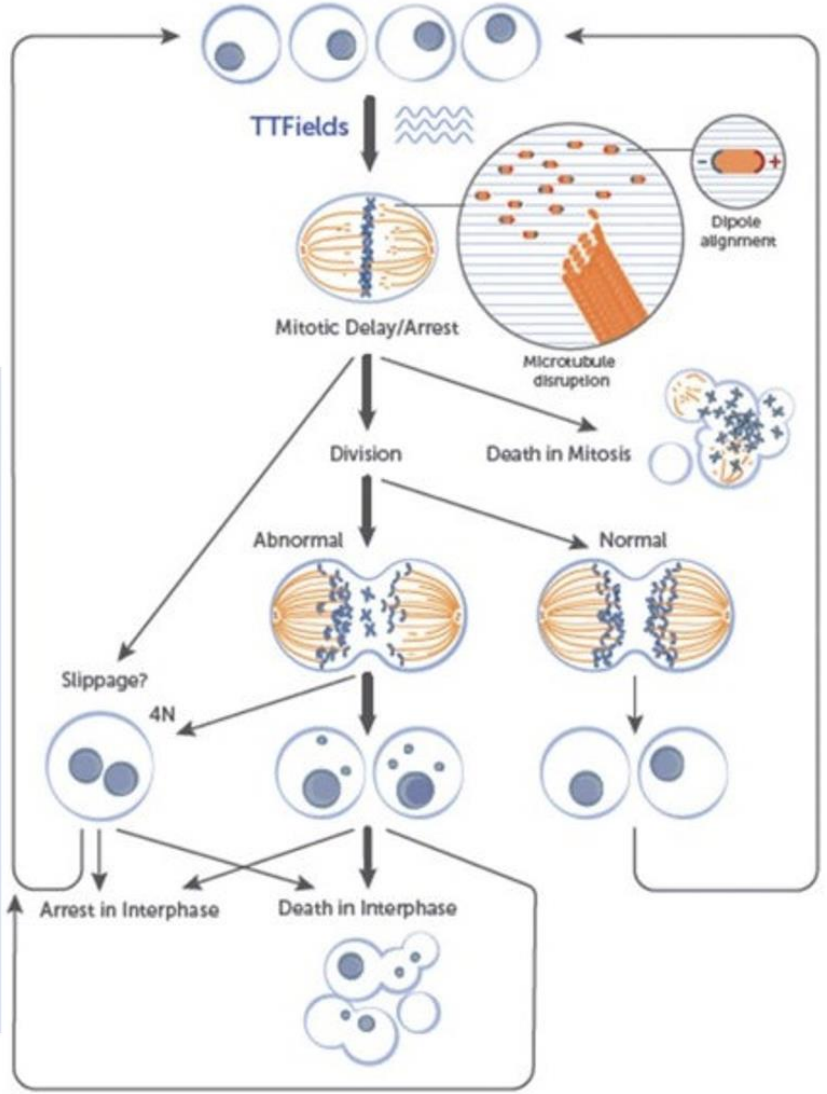
ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma



M. Niyazi et al.
Rad. Onc. 2023

TTF Mechanism

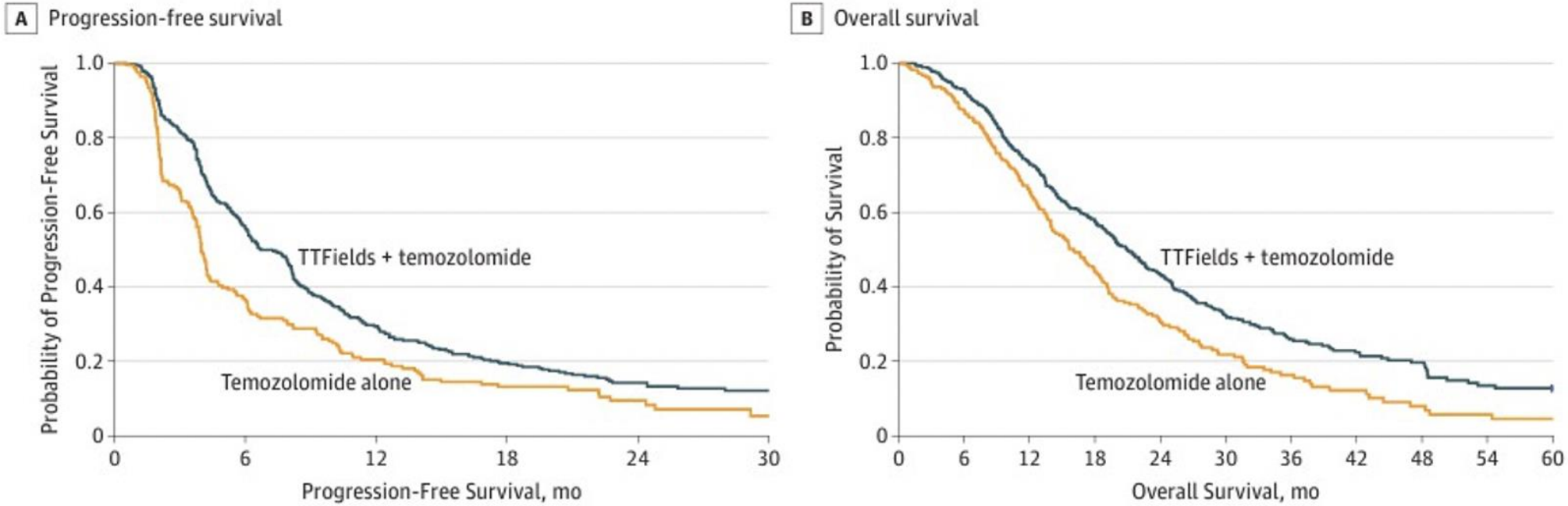




Giladi, Sci rep, 2015

Tumor Treating Fields

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



No. at risk

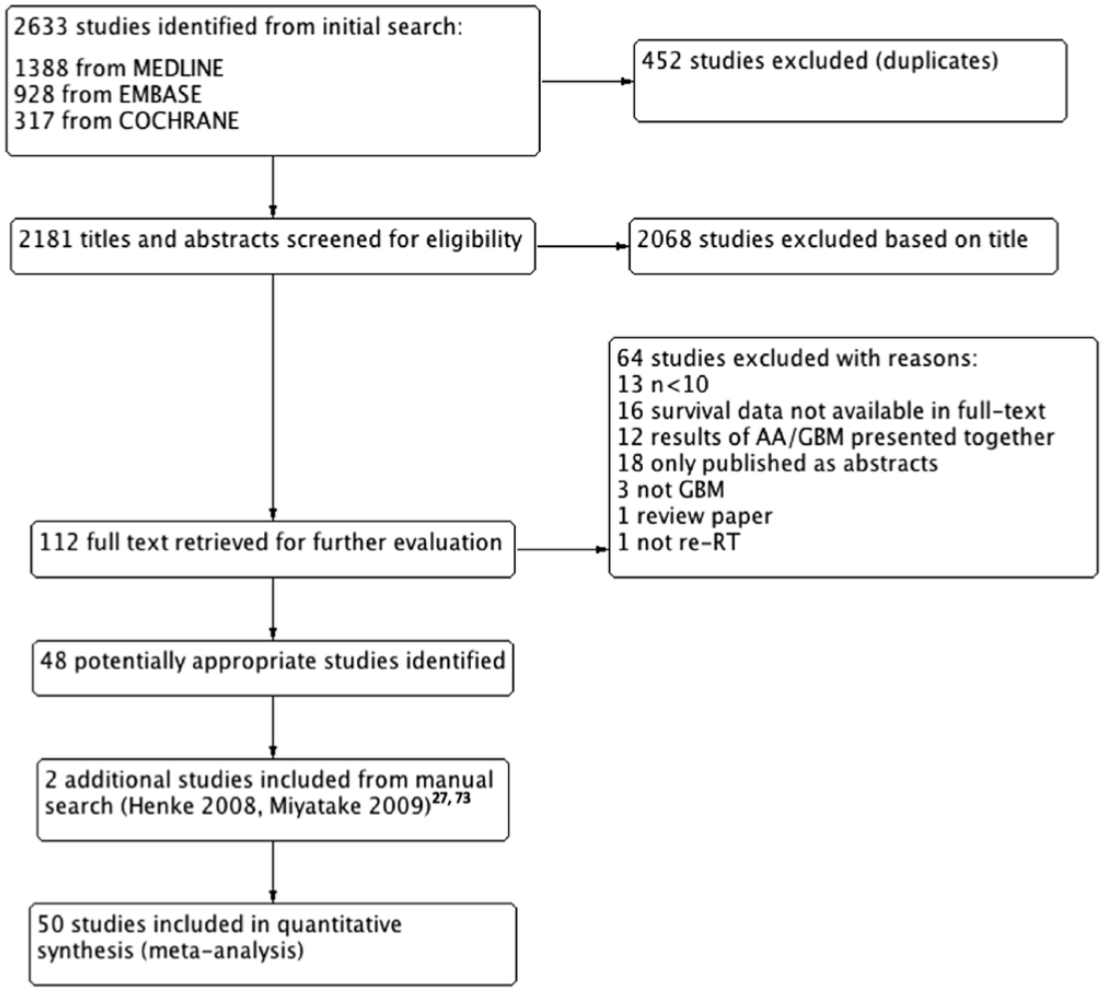
TTFields	466	229	100	62	30	18	466	424	333	256	174	107	65	45	30	19	16
Temozolomide	229	66	35	18	9	2	229	191	144	95	60	33	22	13	7	5	2

A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow up was 44 months (range, 25-91 months) in both groups.

Stupp et al, JAMA, 2017

Re-irradiation for recurrent glioblastoma (GBM): a systematic review and meta-analysis

Farasat Kazmi[1] · Yu Yang Soon[1] · Yiat Horng Leong[1] · Wee Yao Koh[1] · Balamurugan Vellayappan[1,2]



Abbreviations: GBM= Glioblastoma, AA= Anaplastic astrocytoma, RT= radiotherapy

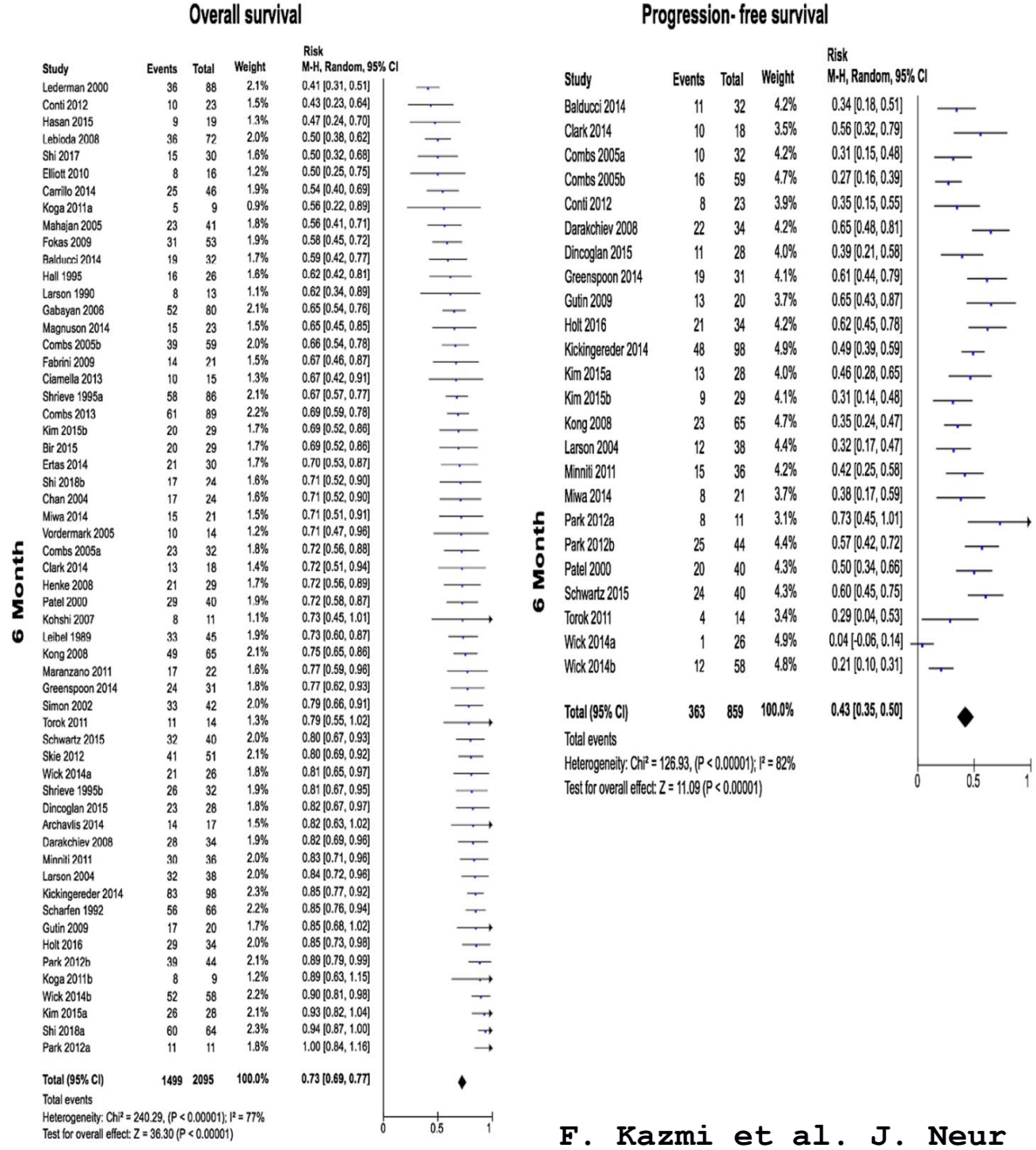


Fig. 2 Pooled event rate for 6-month overall and progression-free survival

F. Kazmi et al. J. Neur Onc 2019

Table 3 Subgroup analysis

Subgroup	6M OS	12M OS	6M PFS	12M PFS	G 3+
External beam radiotherapy	70% (64–75%)	34% (29–39%)	40% (32–49%)	16% (21–21%)	8% (3–12%)
Brachytherapy	75% (70–81%)	44% (38–49%)	51% (40–61%)	18% (12–24%)	6% (1–10%)
Interaction P (IP)	0.17	**0.01**	0.13	0.71	0.52
Prospective design	76% (67–85%)	40% (30–50%)	43% (37–49%)	28% (15–26%)	16% (8–25%)
Retrospective design	70% (65–75%)	35% (31–39%)	42% (26–58%)	15% (11–19%)	4% (2–7%)
IP	0.28	0.76	0.90	0.08	**0.008**
With concurrent systemic therapy	77% (77–86%)	31% (29–49%)	48% (37–60%)	20% (11–29%)	9% (4–15%)
Without concurrent systemic therapy	71% (67–75%)	36% (32–40%)	39% (29–49%)	15% (12–18%)	5% (1–9%)
IP	0.20	0.54	0.22	0.33	0.22
*Median dose < 36 Gy	73% (65–80%)	38% (30–45%)	44% (36–51%)	19% (15–23%)	9% (2–15%)
*Median dose ≥ 36 Gy	70% (64–77%)	31% (24–38%)	36% (21–51%)	13% (6–20%)	8% (3–12%)
IP	0.63	0.19	0.38	0.14	0.22
*Fractions ≤ 5	71% (65–77%)	37% (31–42%)	47% (40–55%)	18% (13–24%)	7% (2–12%)
*Fractions > 5	71% (64–79%)	30% (20–39%)	26% (14–39%)	13% (7–20%)	9% (0–18%)
IP	0.95	0.19	**0.005**	0.21	0.69

OS overall survival, *PFS* progression-free survival, *G 3+* grade 3 toxicity or higher

*Analysis was only performed in the external beam radiotherapy studies where dose was reported, median dose 36 Gy represented as equivalent dose in 2 Gy (EQD2)

F. Kazmi et al. J. Neur Onc 2019

Expert consensus on re-irradiation for recurrent glioma

Table 1 Factors considered in offering re-irradiation as a treatment option

	Responder number/(%)			
Factor	Extremely relevant	Very relevant	Somewhat relevant	Not at all relevant
Tumor volume	5 (38)	7 (54)	1 (8)	0 (0)
Time since previous radiation therapy	6 (46)	6 (46)	1 (8)	0 (0)
Dose previously administered to organs at risk in the field	6 (46)	4 (31)	3 (23)	0 (0)
Patient performance status	5 (38)	4 (31)	4 (31)	0 (0)
Patient age	0 (0)	8 (62)	4 (31)	1 (8)
Original histology	1 (8)	4 (31)	6 (46)	2 (15)
Number of lines of previous treatment	0 (0)	5 (38)	6 (46)	2 (15)
Previous use of Bevacizumab or Bevacizumab failure	1 (8)	4 (31)	6 (46)	2 (15)
Available tissue documentation of tumor progression	1 (8)	3 (23)	7 (54)	2 (15)
Perfusion characteristics on diffusion weighted imaging (DWI)	0 (0)	6 (46)	7 (54)	0 (0)
PET avidity of the lesion	0 (0)	4 (31)	3 (23)	6 (46)

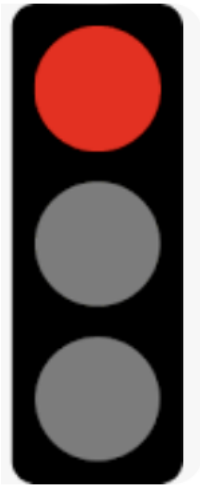
V. Krause Rad Onc 2017

1 Offer re-RT to patients with smaller recurrences, especially if:

- located in a favorable location.
- ability to spare or minimize dose to OAR.
- long interval since previous RT defined as greater than or equal to 6 months.
- well defined area of recurrence ie. no previous use of BEV/BEV failure.
- consider SRS or hypofractionated dose/fractionation in cases that meet size and location criteria above.

3 Consider re-RT on a case by case basis in scenarios where:

- OAR have received maximal dose previously and cannot be spared if further RT given.
- Surgical resection possible.
- If re-RT is proposed in cases where OAR toxicity is a concern, most responders would favor conventional fractionation over hypofractionation.



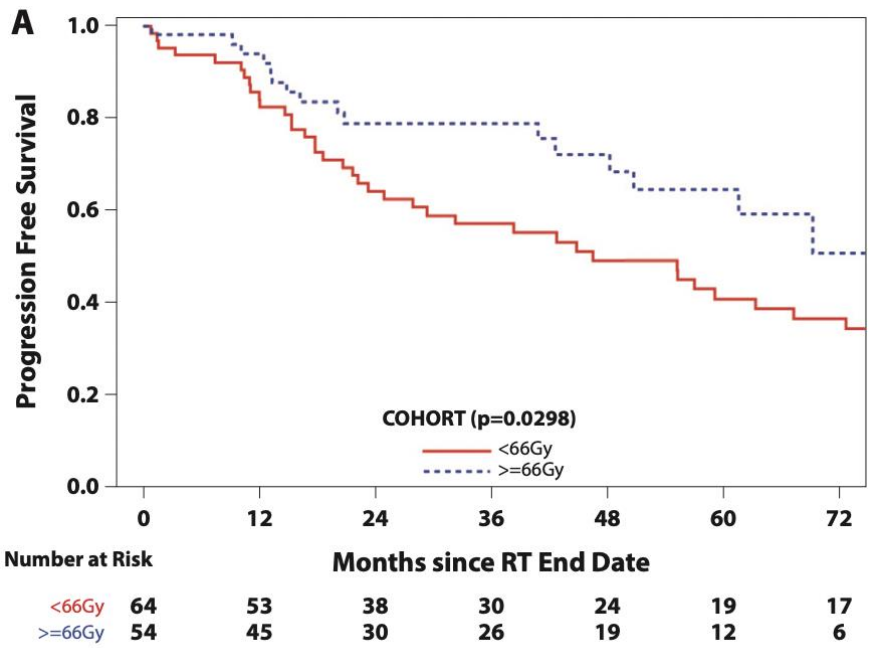
2 Consider clinical trial, systemic treatment or best supportive care in cases with:

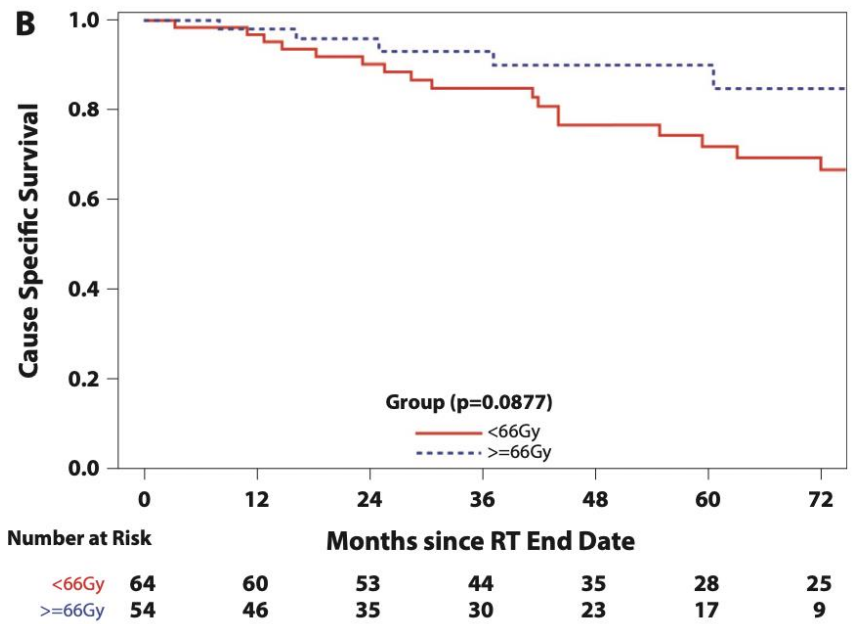
- Large volume recurrence.
- Short interval since previous RT defined as less than 6 months.
- unclear clinical and radiographic progression in the absence of tissue confirmation.

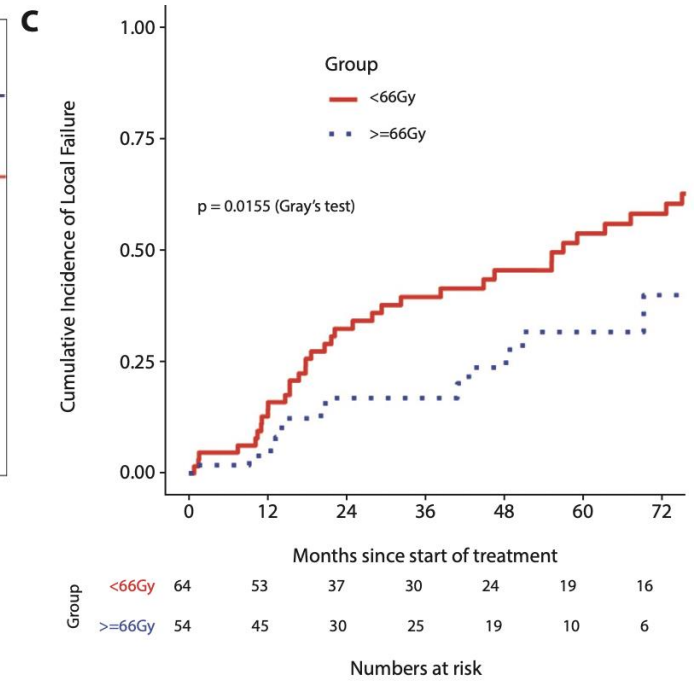
V. Krause Rad Onc 2017

Méningiomes

Dose-Escalated Radiation Therapy Is Associated With Improved Outcomes for High-Grade Meningioma







K. Liang Zeng et al.
IJROBP 2023

Tumeurs secondaires encéphaliques

CNS penetrant drugs

- Osimertinib
- Retrospective series show good tumor control

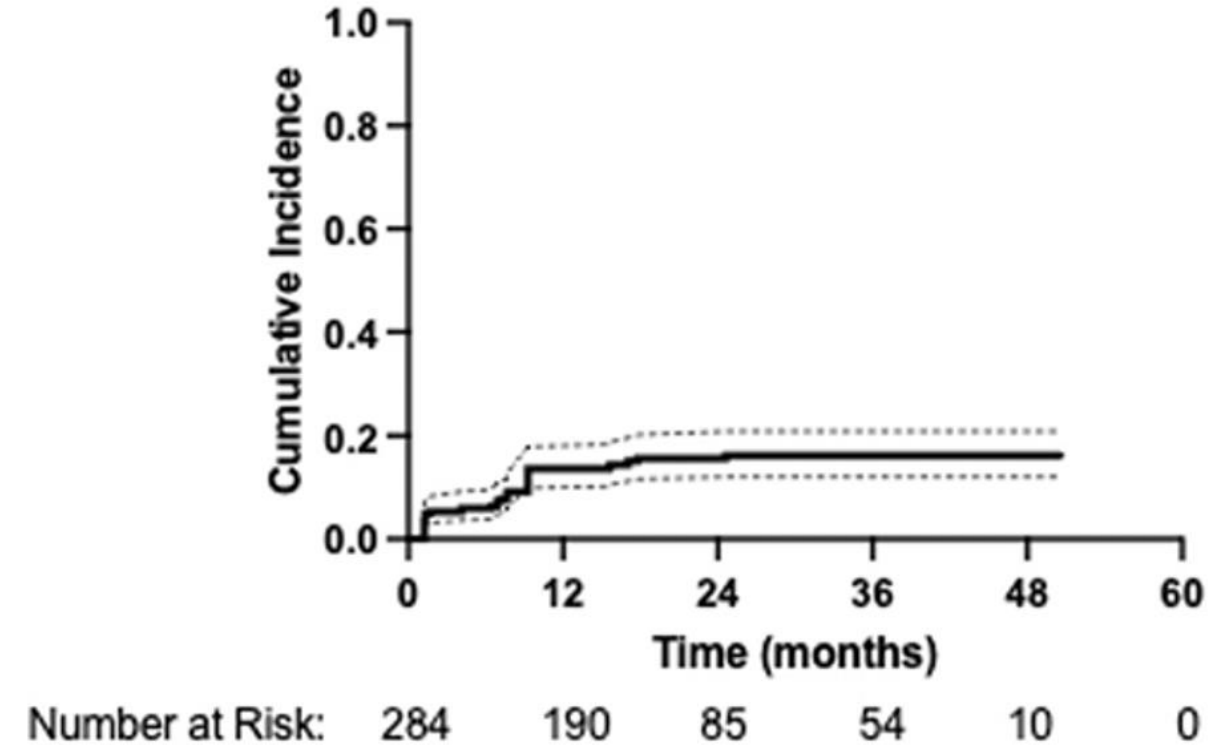


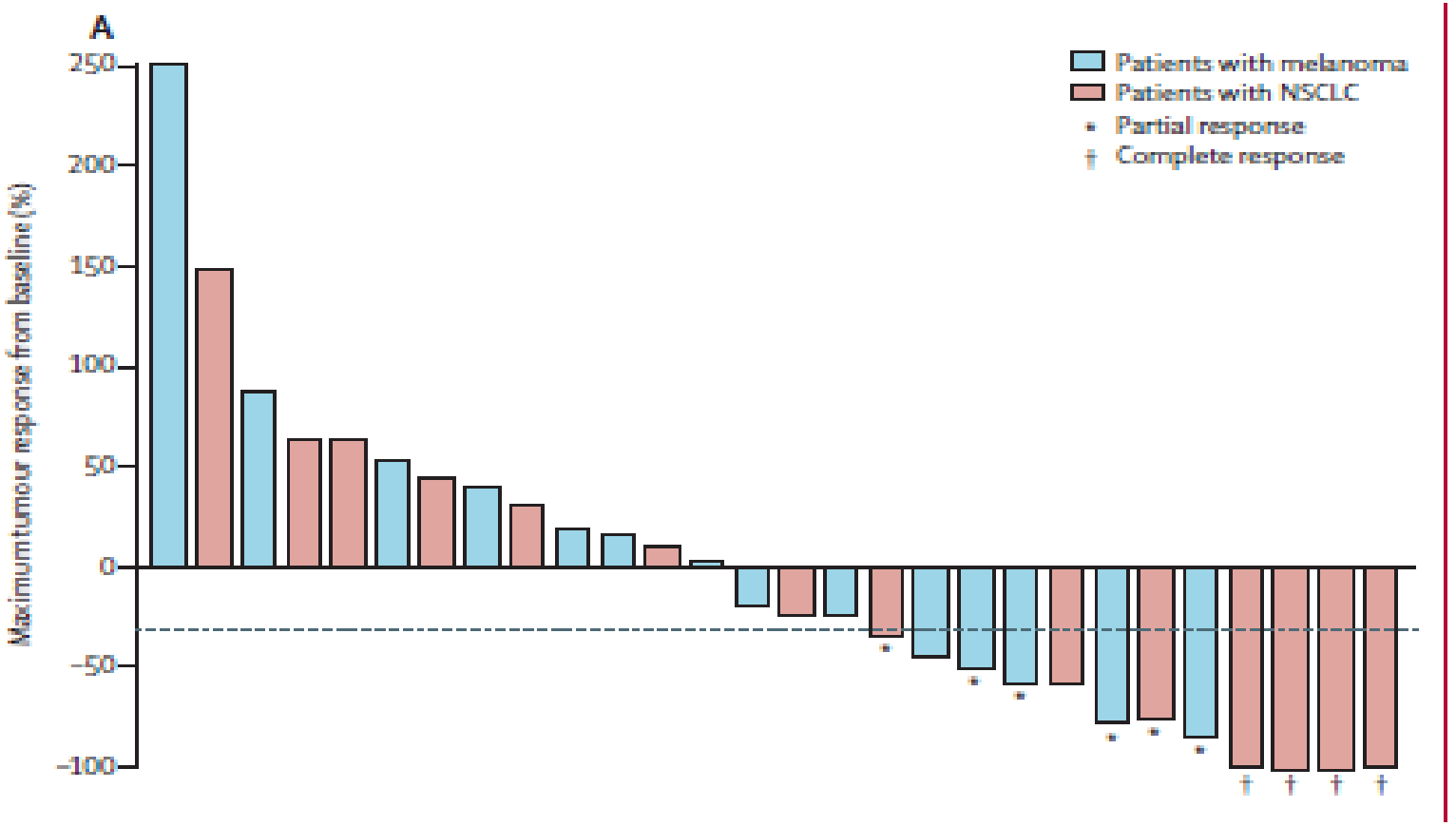
Fig. 1 Cumulative incidence curve of LRiB on a per-lesion basis

Hui, JNO, 2022

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Balabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger

- Immunotherapy less consistent



Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Traitement systémique

Recommendation 2.3. Osimertinib or icotinib may be offered to patients with asymptomatic brain metastases from *EGFR*-mutant non–small-cell lung cancer (NSCLC). If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

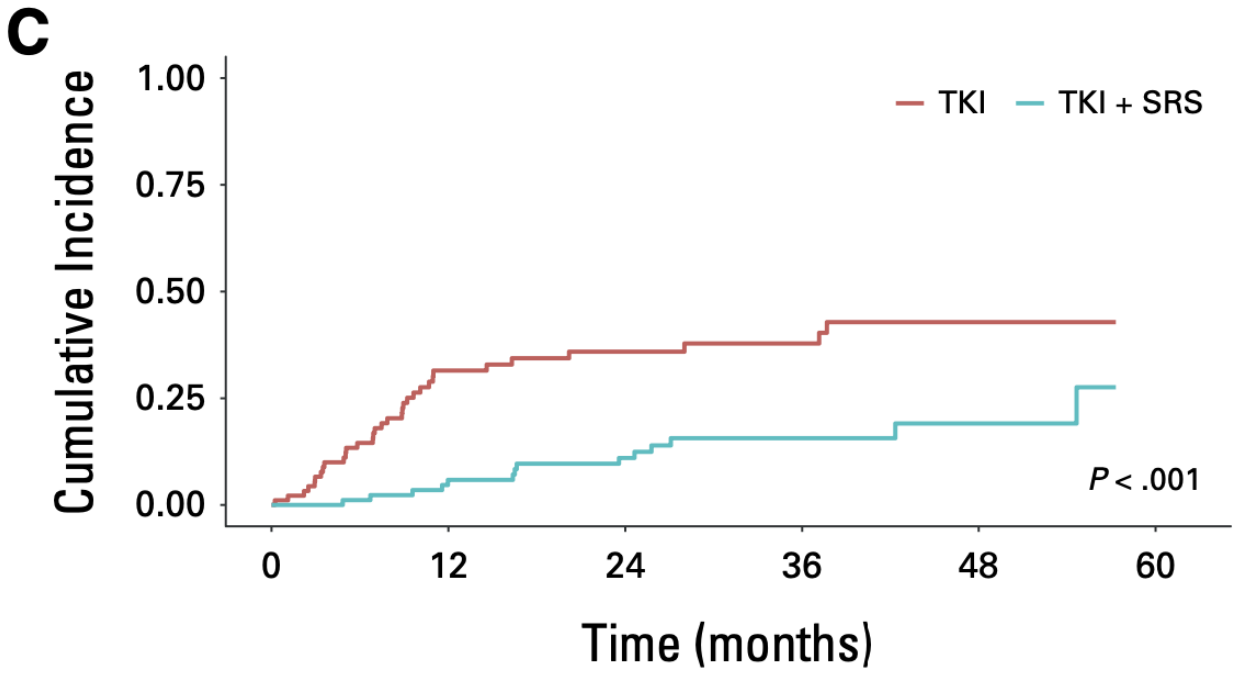
Qualifying Statement: The expert panel recognizes that as of this publication, icotinib is not approved by the US Food and Drug Administration or the European Medicines Agency.

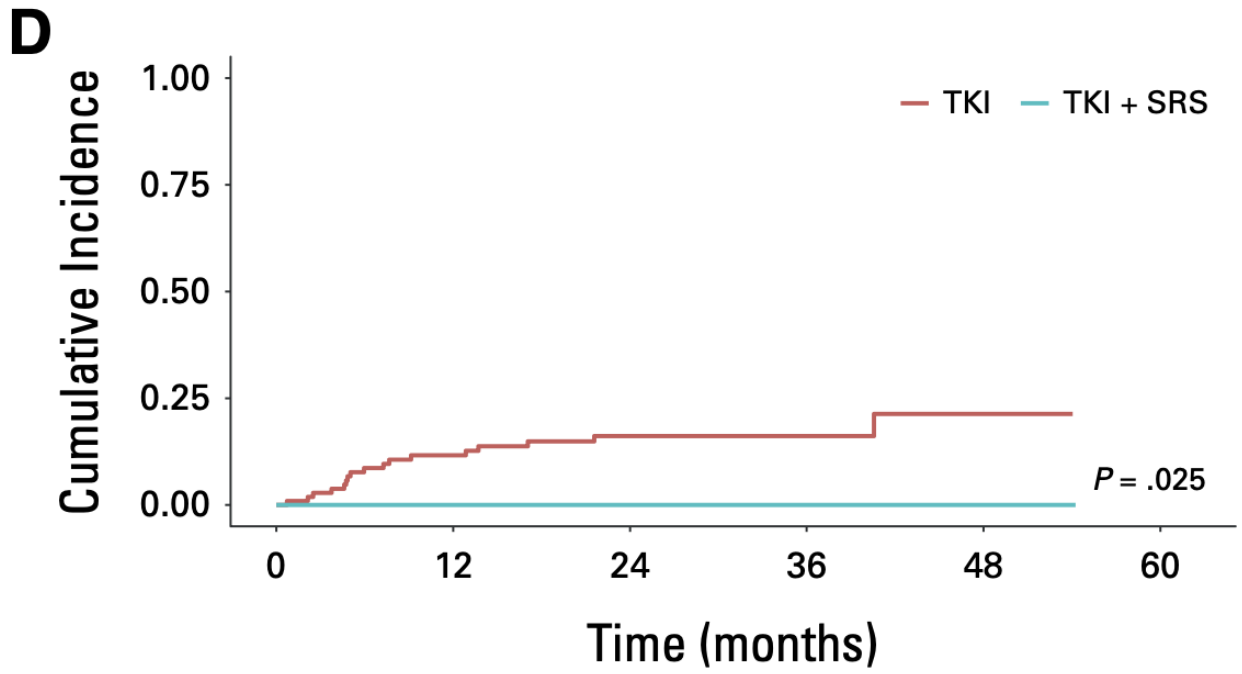
Recommendation 2.4. Alectinib, brigatinib, or ceritinib may be offered to patients with asymptomatic brain metastases from *ALK*-rearranged NSCLC. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.5. Pembrolizumab may be offered to patients with asymptomatic brain metastases from immunotherapy-naïve, programmed death-ligand 1–NSCLC who are also receiving pemetrexed and a platinum agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). *NOTE: See Recommendation 2.2 regarding local therapy.*

Vaugelbaum et al. JCO 2021

Tyrosine Kinase Inhibitors With and Without Up-Front Stereotactic Radiosurgery for Brain Metastases From *EGFR* and *ALK* Oncogene–Driven Non–Small Cell Lung Cancer (TURBO-NSCLC)





L.R.G. Pike et al.
IGO 2024

Données non validées par les autorités de santé à ce jour

Radiothérapie stéréotaxique encéphalique et chirurgie : Irradiation pré op ou post op?

Stéréotaxie POST opératoire

Inconvénients

Volumes importants — Expansion CTV (1-2mm) + voie d'abord + sinus veineux + méninges

Risque accru de complications — Radionécrose 15-25%

Risque important de dissémination lepto-méningée — Taux de 15-28%

Taux d'adhésion suboptimal — ~ 20%

Séquence thérapeutique « longue » — ~ 1 mois

Stéréotaxie PRE vs POST opératoire

Comparing Preoperative With Postoperative Stereotactic Radiosurgery for Resectable Brain Metastases: A Multi-institutional Analysis

Patel et al, Neurosurgery, 2016

2005 and 2013
2 institutions

66 patients Pre-SRS

114 patients Post-SRS

Bien balancé entre groupes à part plus de PS0 et seins dans le bras pre SRS

Pas de différence d'OS
Pas de différence de contrôle local

Plus de RN symptomatiques en post-SRS

16.4% vs 4.9% à 2 ans ($p<0.05$)

Plus de récidives lepto-méningées en post-SRS

16.6% vs 3.2% à 2 ans ($p<0.05$)

Stéréotaxie PRE vs POST opératoire

Comparing pre-operative versus post-operative single and multi-fraction stereotactic radiotherapy for patients with resectable brain metastases

Haley K. Perlow [a], Cindy Ho [b], Jennifer K. Matsui [c], Rahul N. Prasad [a], Brett G. Klamer [a], Joshua Wang [d], Mark Damante [d], Rituraj Upadhyay [a], Evan Thomas [a], Dukagjin M. Blakaj [a], Sasha Beyer [a], Russell Lonser [a], Douglas Hardesty [a], Raju R. Raval [a], Roshan Prabhu [e,f], James B. Elder [a], Joshua D. Palmer [a]

2016 and 2020
2 institutions
279 patients

- Pre-op SRS (n=27)
- Pre-op FSRT (n=53)
- Post-op FSRT (n=189)

FSRT (3 à 5 fractions)

Endpoint composite:
LF + LMD + Grade≥2 RN

	Pre-op SRS	Pre-op FSRT	Post-op FSRT
Local failure	3.7%	0%	4.2%
LMD	7.4%	5.7%	9%
Grade≥2 RN	3.7%	1.9%	5.3%
Composite	15%	7.5%	17%

PRE opératoire		POST opératoire
★	Niveau de preuve	★
★	Contrôle local	★
★	Dissémination lepto-méningée	★
★	Radionécrose	★
★	Histologie	★
★	Toute situation	★

Stéréotaxie pré-opératoire est un traitement prometteur

Attendre les résultats d'essais prospectifs pour être un standard

Fractionnement? Délai avec la chirurgie?

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Exérèse neurochirurgicale

Recommendation 1.1. Surgery may be offered for patients with brain metastases, considering the following factors:

- Patients with suspected brain metastases without a primary cancer diagnosis may benefit from surgery to attain a diagnosis and undergo tumor removal.
- Patients with large tumors with mass effect likely benefit from surgery.
- Patients with multiple brain metastases and/or uncontrolled systemic disease are less likely to benefit from surgery unless the remaining disease is controllable via other measures (Type: informal consensus; Evidence quality: mixed, see the Clinical Interpretation section; Strength of recommendation: moderate).

Vaugelbaum et al. JCO 2021

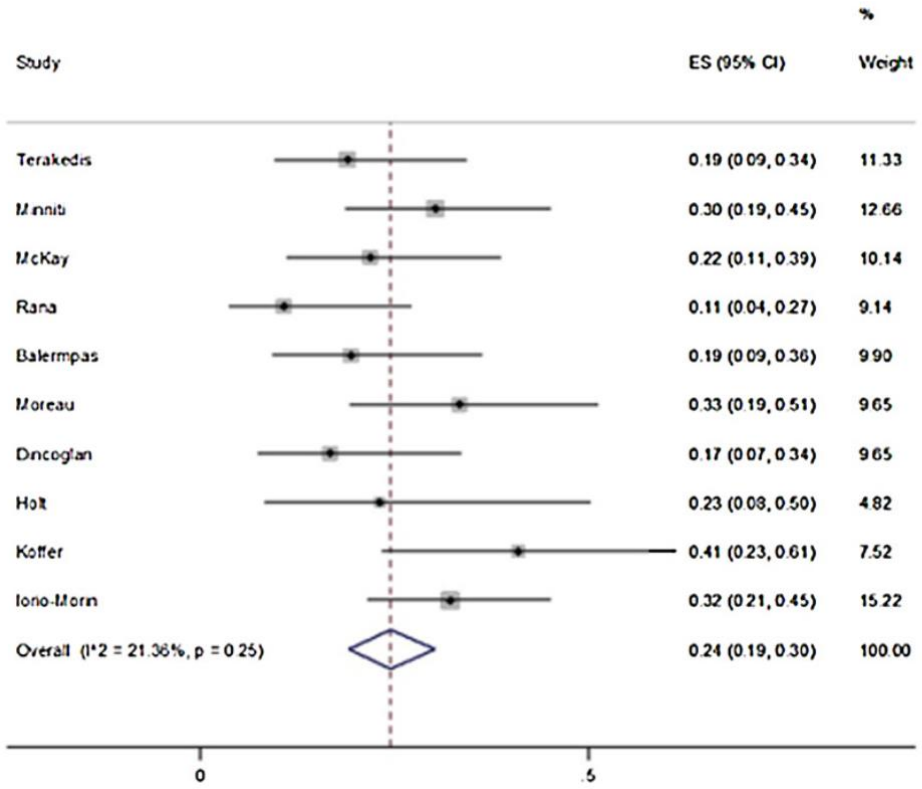
Réirradiation stéréotaxique des métastases encéphaliques

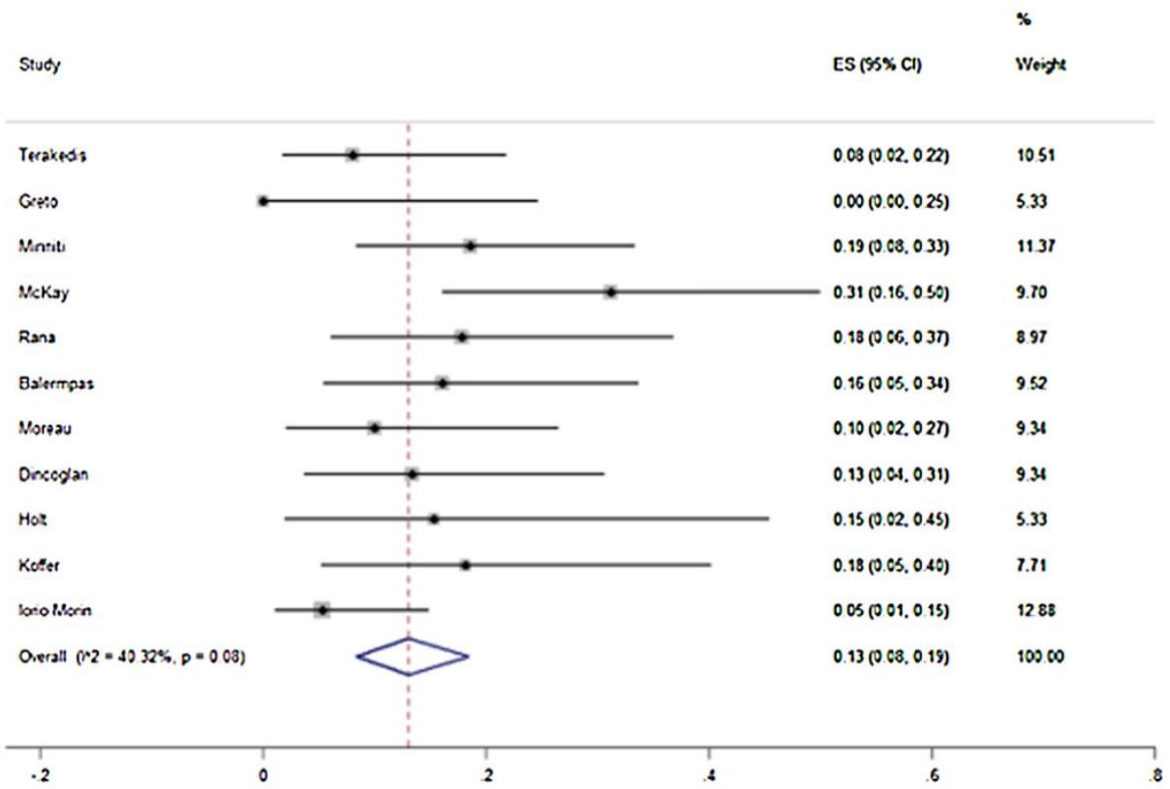
Stereotactic reirradiation for local failure of brain metastases following previous radiosurgery: Systematic review and meta-analysis

Mauro Loi[a,*], Saverio Caini[b], Silvia Scoccianti[a], Pierluigi Bonomo[a], Kim De Vries[c], Giulio Francolini[a], Gabriele Simontacchi[a], Daniela Greto[a], Isacco Desideri[a], Icro Meattini[a], Joost Nuyttens[c], Lorenzo Livi[a]

Summary of studies characteristics and clinical features. KPS: Karnofsy performance status. RCC: renal cell carcinoma. rCBV: Relative Cerebral Blood Volume. Cho/Cr: Choline Creatine ratio. *All sarcoma cases ^(reported per metastasis).

Study	Type	Number of patients	Number of metastases	Median Age (range)	KPS > 80 %	Primary Tumor					Prior Surgery	Biopsy Available	Diagnostic Modality	Diagnostic Criteria	Median Follow-up in months (range)
						Lung	Breast	RCC	Melanoma	Other					
Terakedis	Retrospective	37	43	51(27 – 84)	n/a	9^	8	2	20	4*	13	n/a	MRI	RECIST	7 (1 – 45)
Greto	Retrospective	11	11	47(33 – 77)	7	4	3	n/a	n/a	4	n/a	n/a	MRI	RECIST	4 (1 – 7)
Minniti	Retrospective	43	43	61 (n/a)	n/a	17^	9	n/a	11	6	n/a	n/a	perfusion MRI + F DOPA PET	rCBV > 2	19 (2 – 27)
McKay	Retrospective	32	46	59 (36 – 88)	12	16	9	2	2	3	23	11	perfusion MRI	RECIST	24 (12 – 124)
Rana	Retrospective	28	32	60 (n/a)	23	3	5	5	11	4	9	n/a	MRI	RECIST	n/a
Balermpas	Retrospective	31	32	65 (43 – 81)	20	10	10	1	5	5	9	0	MRI	iRANO	12 (1 – 66)
Moreau	Retrospective	30	36	59 (39 – 83)	26	15	5	0	4	6	3	3	perfusion MRI	RANO-BM	14 (1 – 107)
Dincoglan	Retrospective	30	30	57 (n/a)	16	11	9	3	4	3	n/a	n/a	MRI spectroscopy	rcBV > 2 + Cho/Cr	22 (10 – 45)
Holt	Retrospective	13	15	53 (30 – 70)	13	1^	2	1	9	2	15	15	n/a	n/a	9 (2.2 – 54.9)
Koffer	Retrospective	22	24	59 (43 – 80)	n/a	9	2	2	0	9	5	5	MRI spectroscopy	rcBV > 2 + Cho/Cr	8.8 (n/a)
Iorio-Morin	Retrospective	56	75	56 (27 – 81)	n/a	33	11	1	4	7	12	n/a	MRI	RANO-BM	11 (n/a)





6 m. local failure 7% (CI95% 4-12%)

12 m. local failure 24% (CI95% 19-30%)

RN 13% (CI95% 8-19%)

M. Loi et al. Crit. Rev. Onc. Hem. 2020

A prospective phase II trial on reirradiation of brain metastases with radiosurgery

Ernesto Maranzano [a,*], Sara Terenzi [a,1], Paola Anselmo [a,1], Michelina Casale [a,1], Fabio Arcidiacono [a], Fabio Loreti [b], Alessandro Di Marzo [a], Lorena Draghini [a], Marco Italiani [a], Fabio Trippa [a]

[a] *Radiotherapy Oncology Centre, "S. Maria" Hospital, Terni, Italy*
[b] *Nuclear Medicine Service, "S. Maria" Hospital, Terni, Italy*

Distribution of the 59 eligible patients according to KPS, NFS, primary tumor histology and status of extracranial disease.

Variables	Number of patients	%
Sex		
M	21	36
F	38	64
KPS		
100	32	54
90	21	36
80	4	7
70	2	3
NFS		
0	45	76
1	14	24
Primary tumor histology		
Breast	20	34
Non-small cell lung cancer	18	31
Small cell lung cancer	9	16
Melanoma	3	5
Colorectal	2	3
Ovarian	2	3
Kidney	2	3
Others	3	5
Status of extracranial disease		
controlled primary tumor	46	77
local or indolent progressive disease	13	23

Legends: KPS, Karnofsky performance status; NFS, neurologic functional status.

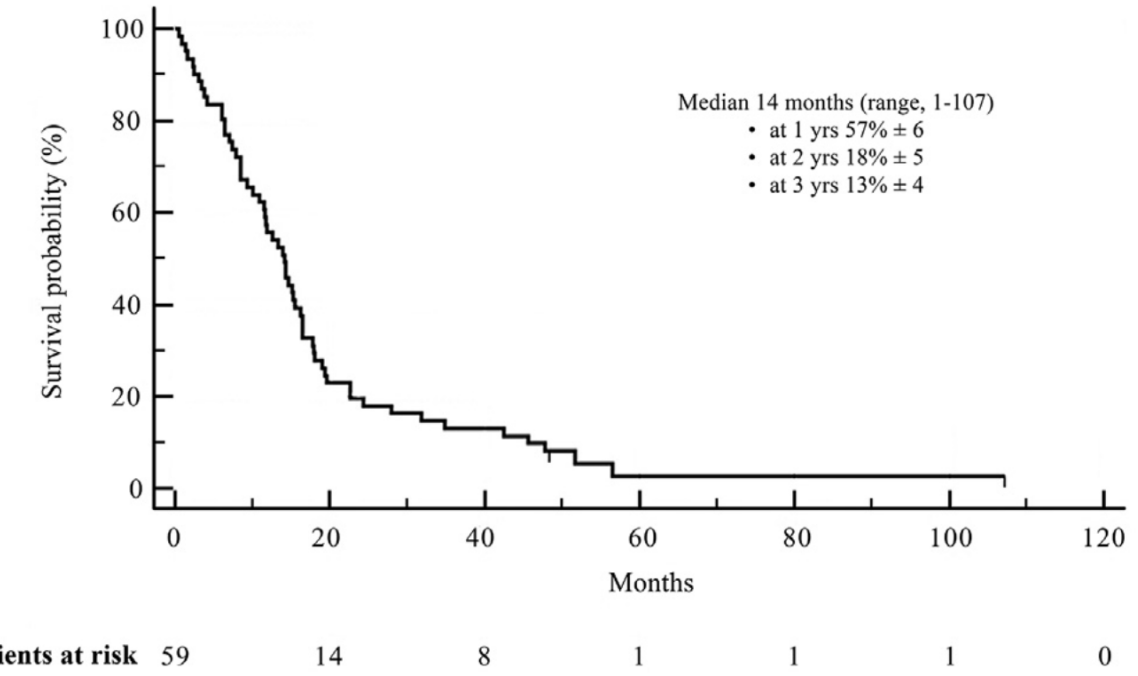


Fig. 1. Overall survival probability from reirradiation with radiosurgery (median survival 14 months).

E. Maranzo et al. ctRO 2019

Métastases osseuses

Dose-intensified stereotactic body radiotherapy for painful vertebral metastases: A randomized phase 3 trial

6-month assessment			
Pain score reduction ≥2 on VAS	25 of 32 (78.1)	13 of 30 (43.3)	.005
Change in pain score: Mean ± SD	−3.4 ± 4.0	−2.1 ± 2.7	.29
Change in OMED intake: Mean ± SD, mg	1.1 ± 47.0	9.5 ± 42.7	.69
Complete pain response	8 (25.0)	9 (30.0)	.66
Progressive pain	4 (12.5)	12 (40.0)	.01

M. Guckenberger et al.
Cancer 2024

Prophylactic Radiation Therapy Versus Standard of Care for Patients With High-Risk Asymptomatic Bone Metastases: A Multicenter, Randomized Phase II Clinical Trial

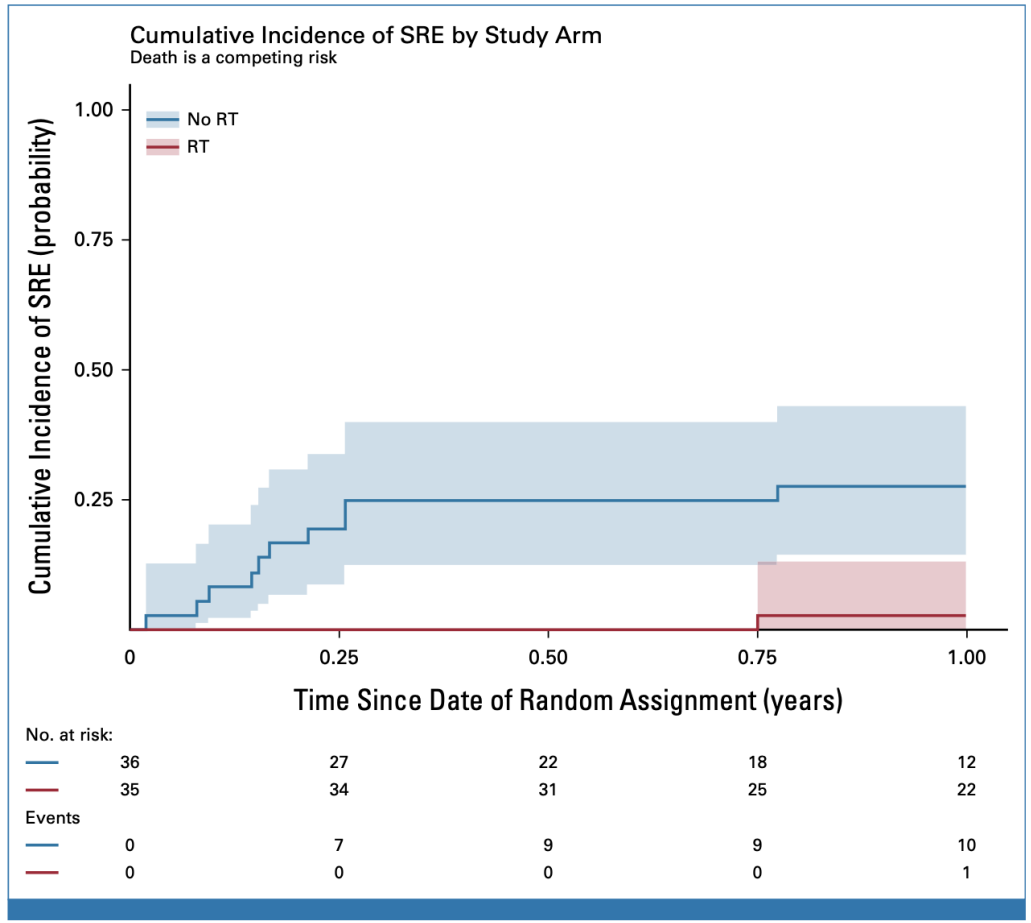


FIG 2. Time-to-SRE on the basis of randomization arm among patients evaluable for the primary end point (n = 111 bone metastases among 71 total patients). RT, radiation therapy; SRE, skeletal-related event.

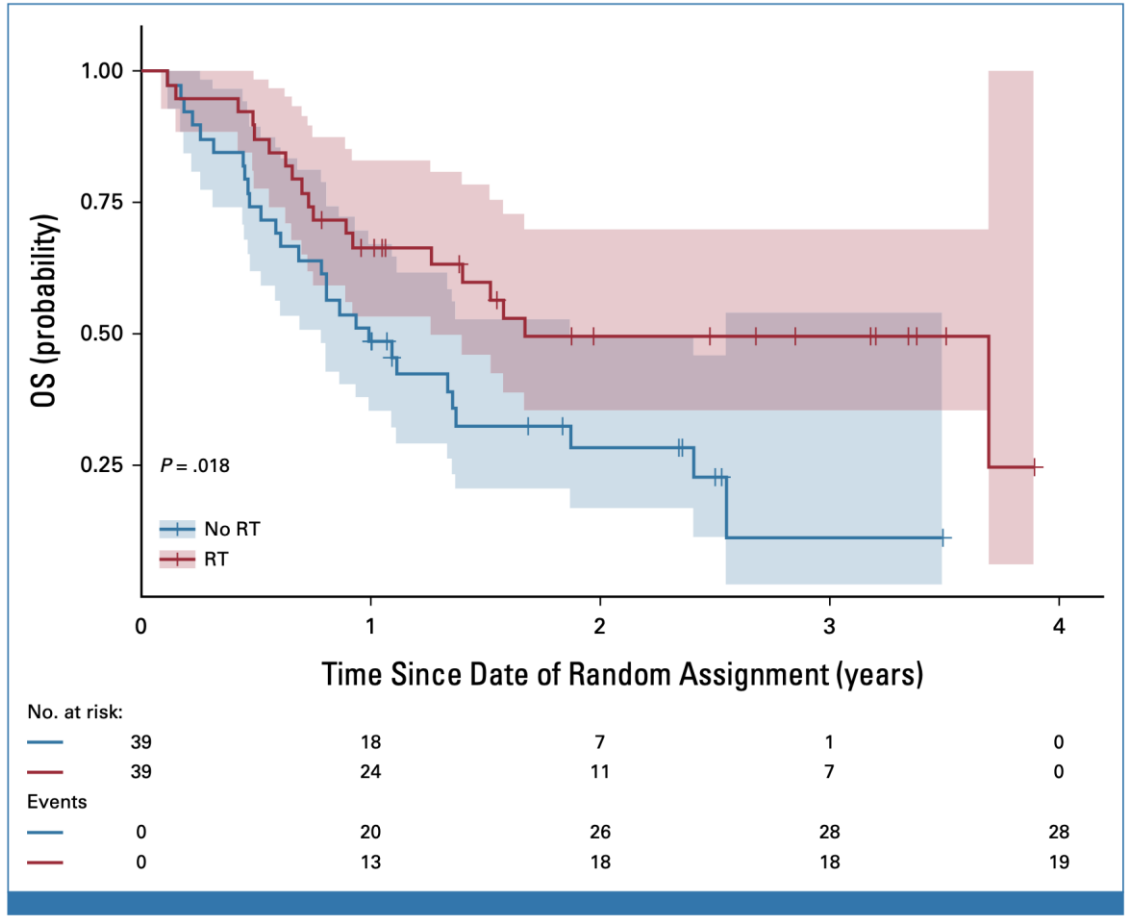


FIG 3. OS in the intention-to-treat population (n = 78 patients) by randomization arm. OS, overall survival; RT, radiation therapy.

E. F. Gillespie et al.
ICO 2024

Données non validées par les autorités de santé à ce jour

Conclusions : Neuro-oncologie

Tumeurs primitives

- Gliome bas grade : vorasidenib
- ➔ Séquences thérapeutique
- Oligodendro G3 : RT+PCV
- GBM : marges CTV et TTFields
- Réirradiation stéréo des GBM
- doses méningiomes haut grade

Tumeurs secondaires

SRS pré op

➔séquence thérapeutique?

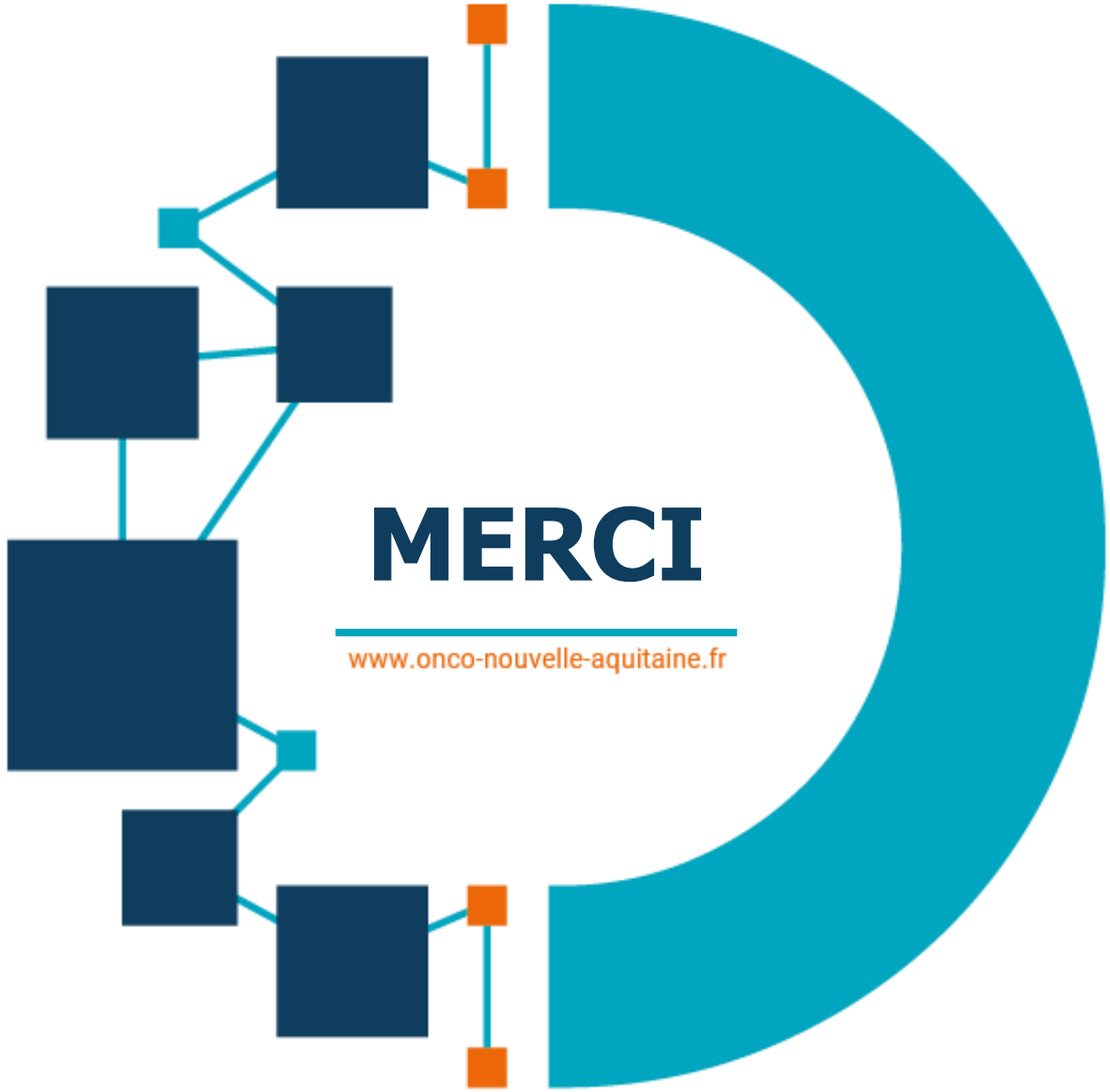
Discuter SRS si addiction oncogénique (>1cm)

Réirradiation

Conclusions : métastases osseuses

Effet antalgique de la SBRT

Irradiation prophylactique osseuse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