Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Indicazioni radioterapiche e terapie integrate: stato dell'arte

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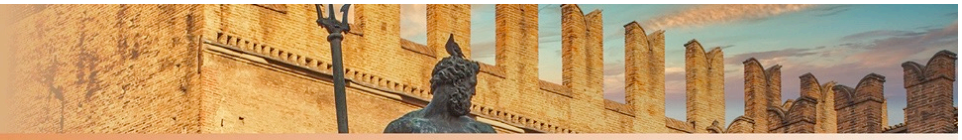
UNIVERSITÀ LUM



DICHIARAZIONE

Relatore: ALBA FIORENTINO

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

Indicazioni radioterapiche e terapie integrate: stato dell'arte

1. *Elderly: WHO ARE THEY?*
2. *Elderly: Brain Tumors*
3. *Elderly and GB: Radiotherapy*
4. *Elderly and GB: Integrated Therapy*
5. *Conclusion*

O. Cohen-Inbar/Journal of Clinical Neuroscience

https://doi.org/10.1016/j.jocn.2019.05.064

1. *Indicazioni radioterapiche e terapie integrate: stato dell'arte*

Elderly: WHO ARE THEY?

The United Nations defines "aged people" as those >60 years, whereas the World Health Organization (WHO) sets the bar at ≥65 years.

REALLY?

Carolina 93 anni

O. Cohen-Inbar/Journal of Clinical Neuroscience
https://doi.org/10.1016/j.jocn.2019.05.064

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly: WHO THEY ARE?

series, the concept of frailty as a clinical tool helps clinicians to gauge a patient's overall health status and risk of adverse events

O. Cohen-Inbar/Journal of Clinical Neuroscience
https://doi.org/10.1016/j.jocn.2019.05.064

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly: WHO THEY ARE?

Phenotype Frailty Model

(Cardiovascular Health Study *[n=5,210]* Fried et al 2001)

Weight loss:	> 4.5kg or > 5% per year
Fatigue:	US Centre for Epidemiological Studies Depression Scale
Sedentary Life:	< 383 Kcal/week men < 270Kcal/week women
Slow gait speed:	Standardised cut-off times to walk 4.57m stratified by sex & height
Weakness:	Dynamometer measurement stratified by sex & BMI

O. Cohen-Inbar/Journal of Clinical Neuroscience

https://doi.org/10.1016/j.jocn.2019.05.064

Rockwood e Coll. (2005) hanno individuato, attraverso il Canadian Study on Health and Aging (CSHA), 70 item comprendenti segni, sintomi e test anormali che, a loro giudizio, possono caratterizzare la fragilità.

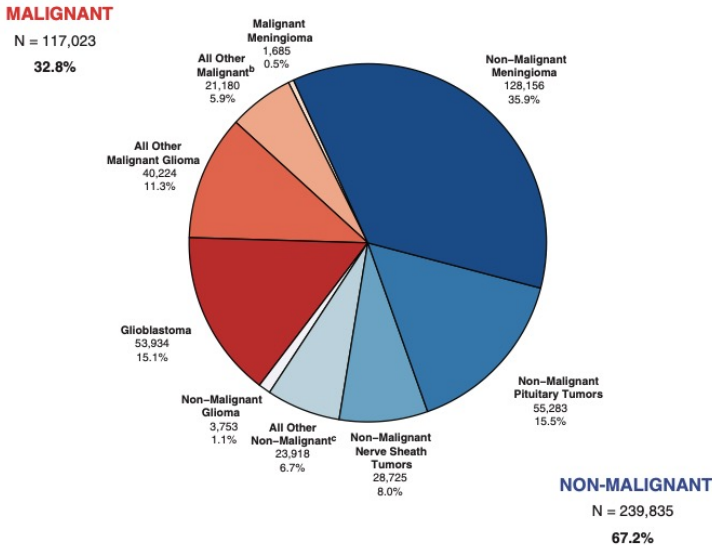
Lista delle variabili utilizzate dal CSHA per costruire l' "Indice Fragilità"

Cambiamenti nelle attività quotidiane	Tristezza, abbattimento, depressione	Crisi epilettiche parziali complesse
Problemi alla testa e al collo	Storia di stati depressivi	Crisi epilettiche generalizzate
Scarso tono muscolare del collo	Stanchezza cronica	Sincope o svenimenti
Bradicinesia facciale	Depressione (diagnosi di)	Mal di testa
Problemi a vestirsi	Disturbi del sonno	Problemi cerebrovascolari
Problemi a farsi il bagno	Agitazione	Storia d'ictus
Problemi nell'igiene personale	Disturbi della memoria	Storia di diabete mellito
Incontinenza urinaria	Indebolimento della memoria a breve termine	Ipertensione arteriosa
Problemi ad andare in bagno	Indebolimento della memoria a lungo termine	Perdita polsi periferici
Difficoltà nel transito intestinale	Disturbi delle funzioni mentali generali	Problemi cardiaci
Problemi rettali	Disturbi cognitivi iniziali	Infarto del miocardio
Problemi gastrointestinali	Confusione o delirium	Aritmia
Problemi a cucinare	Tratti paranoici	Insufficienza cardiaca congestizia
Problemi di suzione	Storia rilevante di disturbi cognitivi	Problemi ai polmoni
Problemi a uscire da solo	Familiarità rilevante di disturbi cognitivi	Problemi respiratori
Motilità compromessa	Alterazione della sensibilità vibratoria	Anamnesi di malattia della tiroide
Problemi muscoloscheletrici	Tremore a riposo	Problemi della tiroide
Bradicinesia degli arti	Tremore posturale	Problemi della pelle
Scarso tono muscolare degli arti	Tremore intenzionale	Tumori maligni
Scarso coordinamento degli arti	Familiarità di malattie degenerative	Problemi al seno
Scarso coordinamento del busto		Problemi addominali
Scarso mantenimento della postura		Presenza di riflesso del muso
Andatura irregolare		Presenza di riflesso palmomentoniero
Cadute		Altro
Problemi dell'umore		

2. *Indicazioni radioterapiche e terapie integrate: stato dell'arte*

Elderly: Brain Tumors

Glioblastoma-Multiforme (GBM) is the most common primary brain tumour in adults [12], with an annual incidence of 6000 elderly patients in the U.S. [13], rising in recent decades mostly in patients aged >70 years [14]. The number of elderly GBM patients is expected to double in the coming 2 decades [15,16].

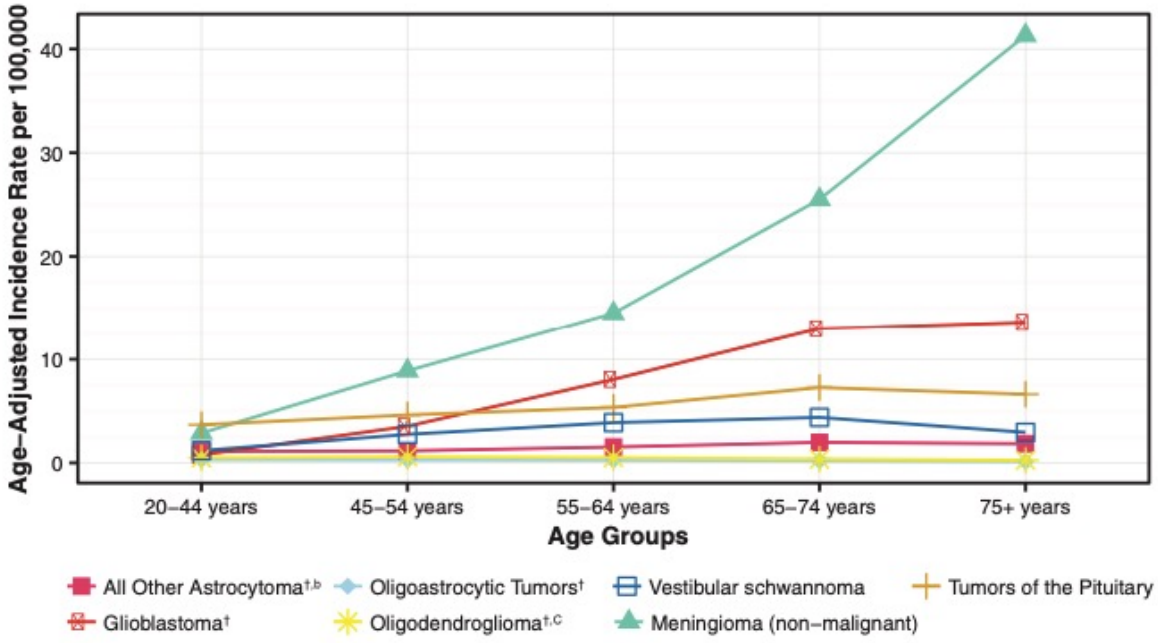


O. Cohen-Inbar/Journal of Clinical Neuroscience
https://doi.org/10.1016/j.jocn.2019.05.064

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly: Brain Tumors

Neuro-Oncology 17:iv1–iv62, 2015.
doi:10.1093/neuonc/nov189



Indicazioni radioterapiche e terapie integrate: stato dell'arte

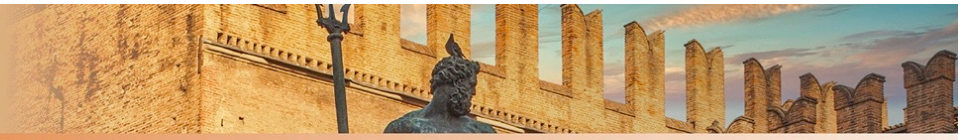
Elderly and GB: Issue

Highlights

- Management of elderly GBM is unclear, excluded from most large controlled trials.
- Age and poor performance status are negative prognosticators in patients with GBM.

O. Cohen-Inbar/Journal of Clinical Neuroscience

https://doi.org/10.1016/j.jocn.2019.05.064



Indicazioni radioterapiche e terapie integrate: stato dell'arte

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Elderly and GB: Issue

EXPERT REVIEWS

Elderly patients with glioblastoma: the treatment challenge

Alba Fiorentino*[1], Pasquale De Bonis[2], Silvia Chiesa[3], Mario Balducci[3] and Vincenzo Fusco[1]

Expert Rev. Neurother. 13(10), 1099–1105 (2013)

Neuroepidemiology 2009;33:23–24
DOI: 10.1159/000210018

Elderly Patients with Glioblastoma Multiforme – An Underestimated Subpopulation?

Markus Hutterer

Restricted access | Research article | First published online September-October 2010

Treatment of Glioblastoma in Elderly Patients: An Overview of Current Treatments and Future Perspective

Gaetano Lanzetta and Dr Giuseppe Minniti ✉ View all authors and affiliations

Volume 96, Issue 5 | https://doi.org/10.1177/030089161009600502

3. *Indicazioni radioterapiche e terapie integrate: stato dell'arte*

Elderly and GB: Radiotherapy

Lancet Oncol. 2009 May;10(5):459-66.

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Overall							
Radiotherapy	278/286	1·0	12·1 (11·2–13·0)	10·9 (7·6–14·8)	4·4 (2·4–7·2)	3·0 (1·4–5·7)	1·9 (0·6–4·4)
Combined	254/287	0·6 (0·5–0·7)	14·6 (13·2–16·8)	27·2 (22·2–32·5)	16·0 (12·0–20·6)	12·1 (8·5–16·4)	9·8 (6·4–14·0)
Age <50 years							
Radiotherapy	83/88	1·0	13·6 (11·6–15·6)	14·8 (8·3–23·0)	6·5 (2·5–13·1)	4·9 (1·5–11·3)	4·9 (1·5–11·3)
Combined	79/95	0·6 (0·4–0·8)	17·4 (15·3–21·5)	34·7 (25·3–44·3)	25·4 (17·0–34·7)	20·1 (12·4–29·1)	17·0 (9·8–25·9)
Age >60 years							
Radiotherapy	86/87	1·0	11·8 (10·4–12·7)	5·7 (2·1–12·0)	2·3 (0·4–7·2)	2·3 (0·4–7·3)	0
Combined	74/83	0·7 (0·5–0·97)	10·9 (8·9–14·9)	21·8 (13·5–31·2)	12·3 (6·1–20·8)	8·8 (3·6–16·9)	6·6 (2·1–14·7)

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

Researchers have surmised hypofractionated RT may limit tumor repopulation (61), increase cell kill (62), and improve local control in certain radioresistant tumors (63) while decreasing overall treatment time.

Chin Clin Oncol. 2022 Oct;11(5):38. doi: 10.21037/cco-22-76.

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

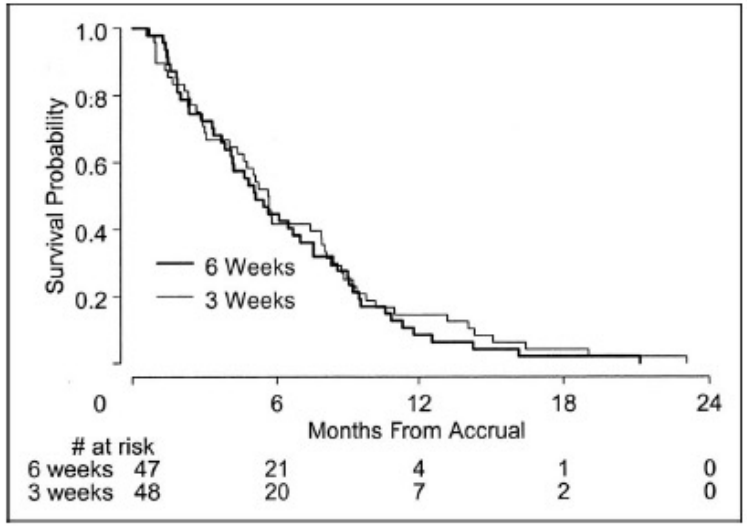
Study	Design	Results
NCIC (Roa JCO 2004)	phase III trial, 100 pts age >=60 years, KPS>=50 randomized to 60 Gy/30 fx vs 40 Gy/15 fx	No difference in MS (5.1 vs 5.6 mo). Fewer patients in short course arm required increased steroids (23 vs 49%)
Nordic (Malmstrom Lancet Onc 2012)	291 pts age >60, randomized to TMZ alone, RT with 34 Gy/10 fx, RT with 60 Gy/30 fx	MS better with TMZ than standard RT; for pts age >70, survival better with TMZ or hypofractionated RT
IAEA (Roa JCO 2015)	Phase III non-inferiority, 98 patients >=65 years, KPS 50-70, or both, randomized to 25 Gy/5 fx vs 40 Gy/15 fx	No difference in OS (7.9 vs 6.4 mo), PFS (4.2 mo for both), or QOL
NCIC CTG CE.6 (Perry, NEJM 2017)	Phase III, 562 pts, 65 years or older, randomized to short course RT (40 Gy/15 fx) +/- TMZ (adjuvant + concurrent)	TMZ improved MS (9.3 vs 7.6 mo) and PFS (5.3 vs 3.9 mo); for MGMT unmethylated, MS 10 vs 7.9 mo (p = 0.055)

Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

GBM, age 60 years or older, were randomly assigned to receive standard RT (60 Gy in 30 fractions over 6 weeks) versus a biologically similar shorter course (40 Gy in 15 fractions over 3 weeks). The experimental schedule was selected because it was well tolerated by patients with brain metastases.[11]

ROA et AL, J Clin Oncol 22:1583-1588

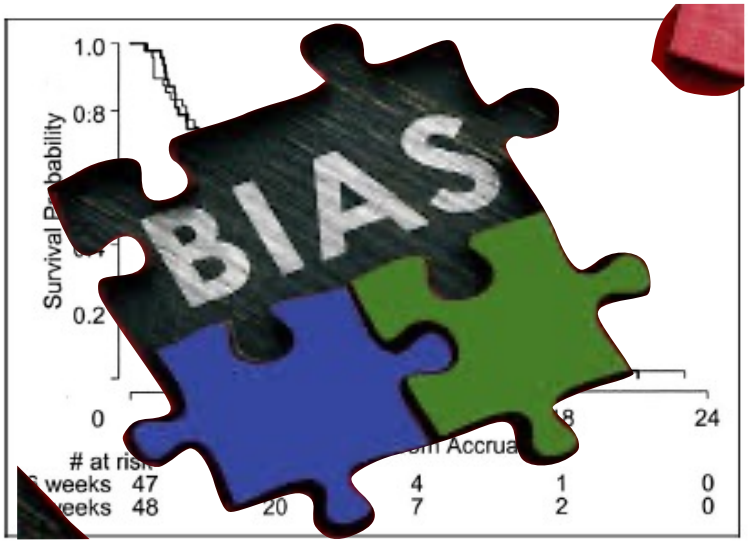


Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

The target sample size was calculated following the method of Makuch and Simon.[12] We expected 50% of the patients receiving standard RT would be alive at 6 months, and we considered the clinical efficacy of the shorter course to be equivalent if the proportion surviving at 6 months was at least 35%. For an 80% probability that the one-sided 90% CI for a difference at 6 months did not exceed 15% when in reality the treatments were equivalent, 101 patients would be required in each treatment arm. Allow-

ROA et AL, J Clin Oncol 22:1583-1588



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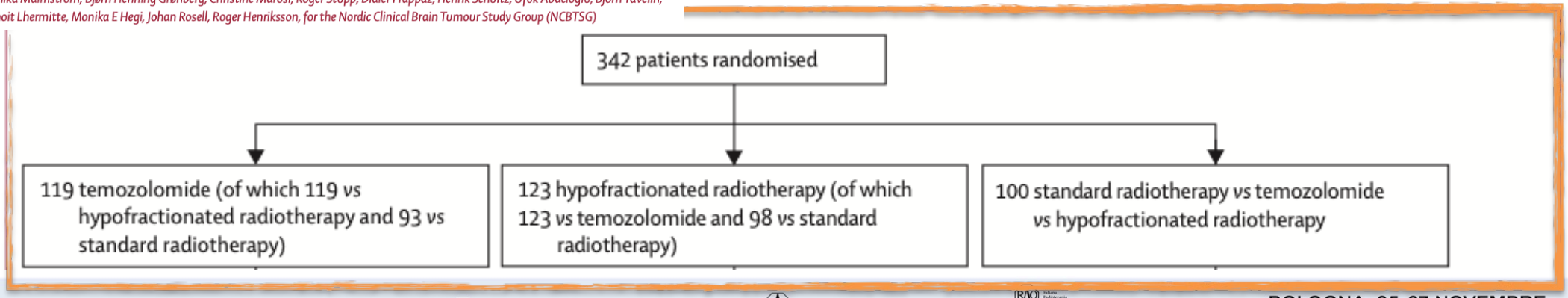
Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

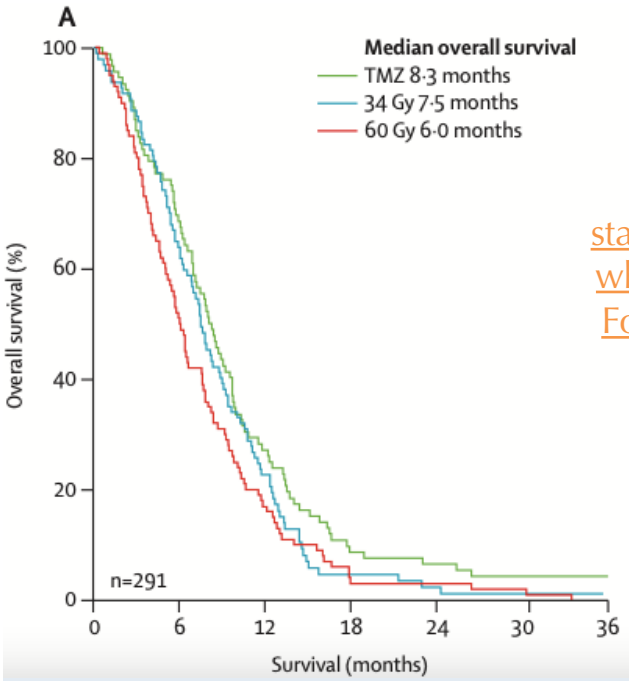
Temozolomide (200 mg/m2 on days 1–5 of every 28 days for up to six cycles), hypofractionated radiotherapy (34·0 Gy administered in 2 weeks), or standard radiotherapy (60·0 Gy administered over 6 weeks)



Lancet Oncol 2012; 13: 916–26

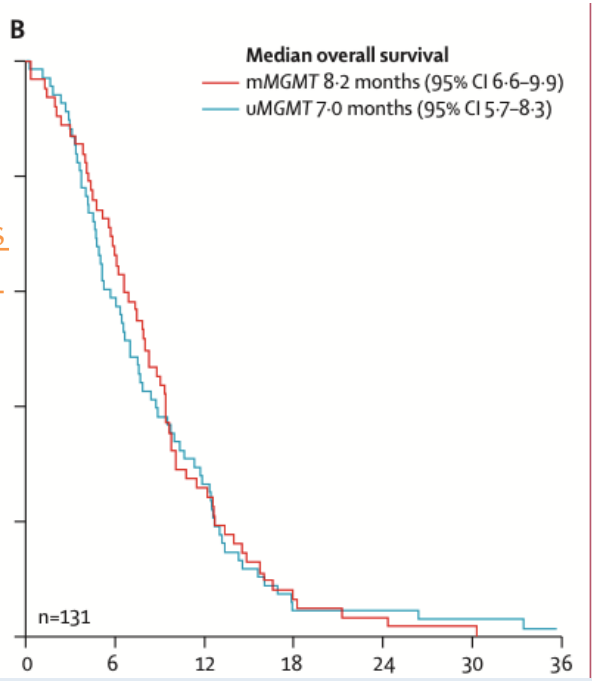
Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy



Median OS was significantly longer with TMZ compared to standard RT (8.3 vs. 6.0 months), but OS was similar for patients who received TMZ or hypofractionated RT (8.4 vs. 7.4 months). For patients older than 70 years, TMZ and hypofractionated RT resulted in improved survival compared to standard RT

In RT arms, OS was similar irrespective of m-MGMT



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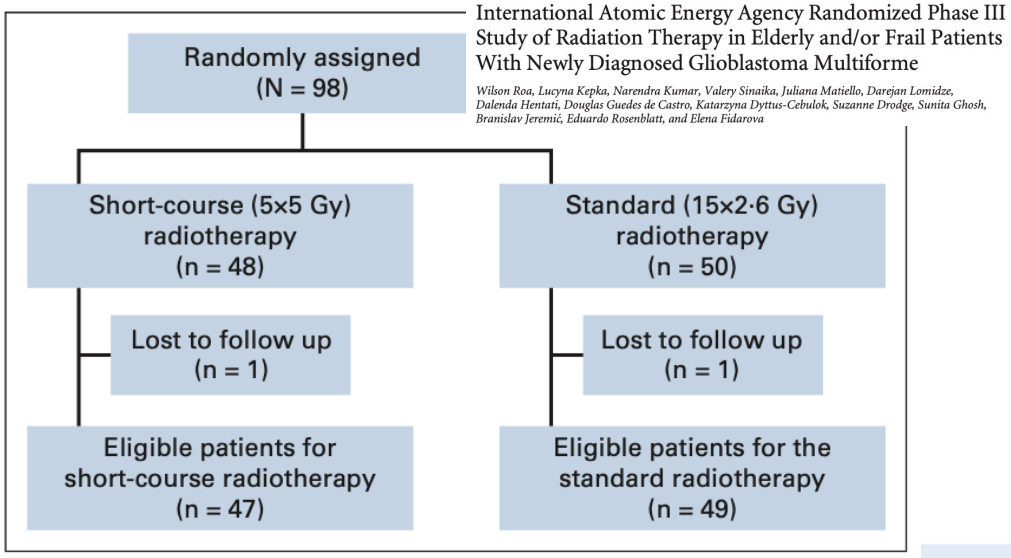
Elderly and GB: Hypofractionation Radiotherapy

Study Design and Random Assignment

This is a phase III, randomized, international, multicenter, prospective, noninferiority trial (ClinicalTrials.gov identifier: NCT1450449). Patients were randomly assigned to one of two groups in a 1:1 ratio and stratified by age (< and ≥ 65 years), Karnofsky performance status (KPS), and extent of surgery (near total/complete/gross total or incomplete/partial resection). Patients were randomly assigned to either short-course RT (25 Gy in five fractions delivered in 1 week) or commonly used RT (40 Gy in 15 fractions delivered in 3 weeks). Random assignment was performed using Excel with the RAND option function (Microsoft, Redmond, WA). All eligible patients admitted to the trial were observed until death.



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J Clin Oncol 33. © 2015

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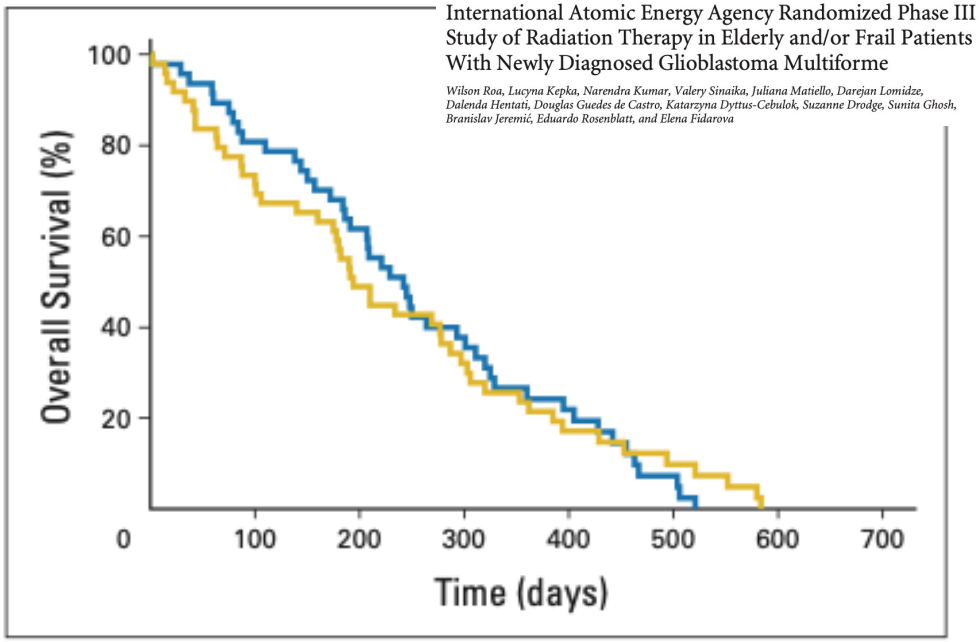
International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Juliana Matiello, Darejan Lomidze, Dalenda Hentati, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Suzanne Drodge, Sunita Ghosh, Branislav Jeremić, Eduardo Rosenblatt, and Elena Fidarova



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ORIGINAL ARTICLE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

Elderly and GB: Hypofractionation Radiotherapy

TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive either radiotherapy alone or radiotherapy plus temozolomide. Radiation was planned with the use of three-dimensional planning systems for a total dose of 40.05 Gy, administered in 15 daily fractions over a period of 3 weeks. Concurrent temozolomide was administered with radiotherapy at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days from day 1 until the final day of radiotherapy. Adjuvant temozolomide was administered

KEY ELIGIBILITY CRITERIA

This randomized, phase 3 trial enrolled patients 65 years of age or older who had newly diagnosed glioblastoma (World Health Organization grade IV astrocytoma), which was histologically confirmed after surgery or biopsy performed less than 28 days before randomization. Patients were deemed by their physicians not to be suitable to receive conventional radiotherapy (60 Gy in 30 fractions over a period of 6 weeks) in combination with temozolomide. Eligible patients had an Eastern

N Engl J Med 2017;376:1027-37.

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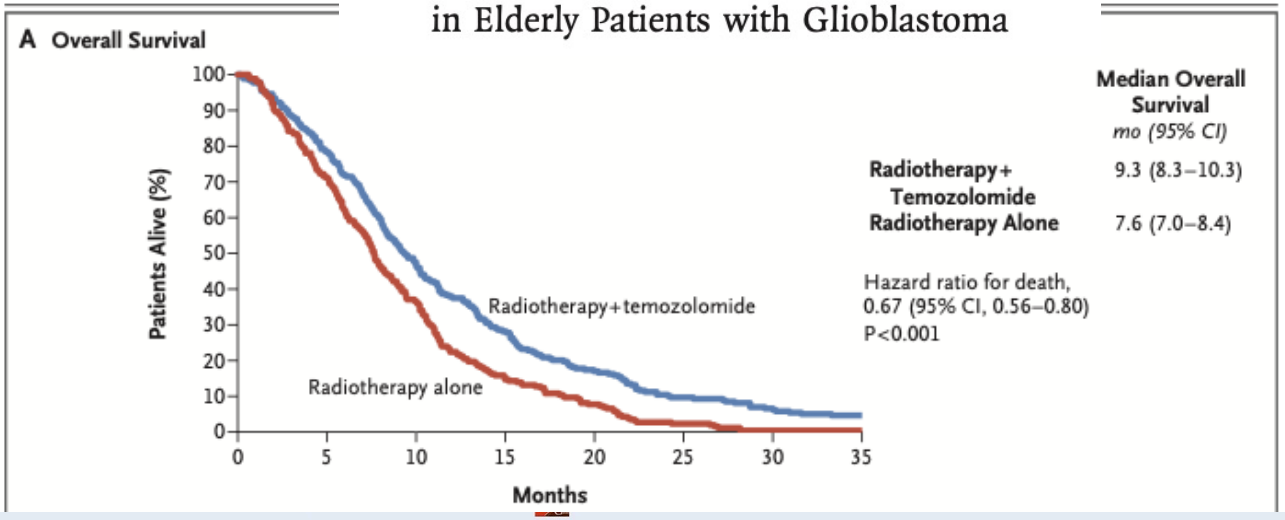
N Engl J Med 2017;376:1027-37.

Associazione Italiana Radioterapia e Oncolog

ORIGINAL ARTICLE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma



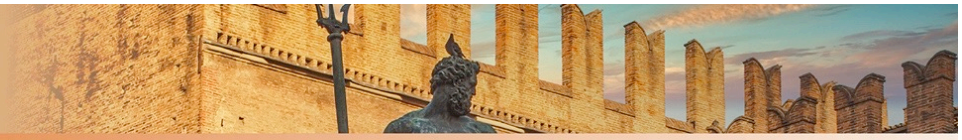
Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy

Today, a standard RT prescription for elderly patients with GBM is 40 Gy in 15 fractions. However, the BED for 40 Gy in 15 fractions is lower than the BED for 60 Gy in 30 fractions. Previous studies have shown dose escalation from 45 to 60 Gy has significant survival improvement at each interval, suggesting that elderly patients receiving 40 Gy in 15 fractions may be underdosed (15). An analysis

52,5Gy in 15 fr = 60 in 30 fr

N Engl J Med 2017;376:1027-37.



Indicazioni radioterapiche e terapie integrate: stato dell'arte

Elderly and GB: Hypofractionation Radiotherapy Dose-escalated

Clinical Study | *Journal of Neuro-Oncology* **156**, 399–406 (2022)

Dose-escalated accelerated hypofractionation for elderly or frail patients with a newly diagnosed glioblastoma

Original Article

Accelerated hypofractionated radiation for elderly or frail patients with a newly diagnosed glioblastoma: A pooled analysis of patient-level data from 4 prospective trials

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Cancer 2022;128:2367-2374.

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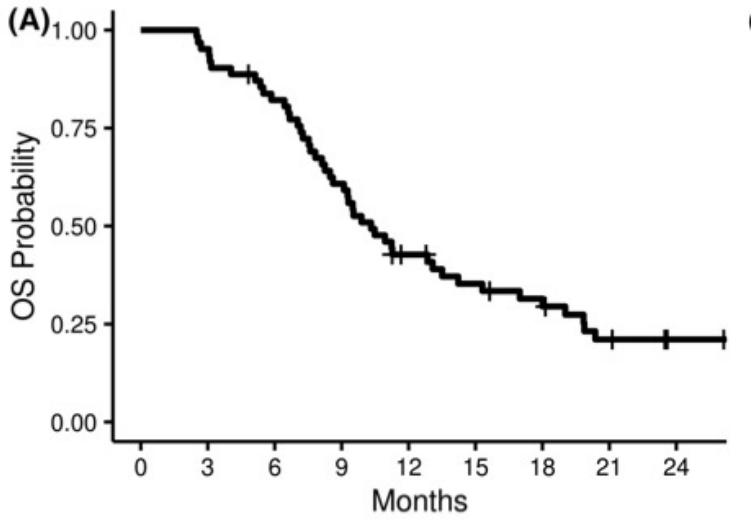
TABLE 1. Studies Pooled for Analysis

Study	No.	Median Age, y	Median KPS	Median OS, mo	Radiation Dose and Fractionation
Ammirati, 2014[12]	5	72	70	8.4	5250 cGy/15 fractions
Navarria, 2019[13]	30	75	60	8.0	5250 cGy/15 fractions
Perlow, 2022[15,a]	20	69	70	10.6	4005 cGy/15 fractions with SIB to 5250 cGy
Scoccianti, 2018[14]	7	69	80	11.6	5250 cGy/15 fractions with SIB to 6750 cGy



Cancer 2022;128:2367-2374.

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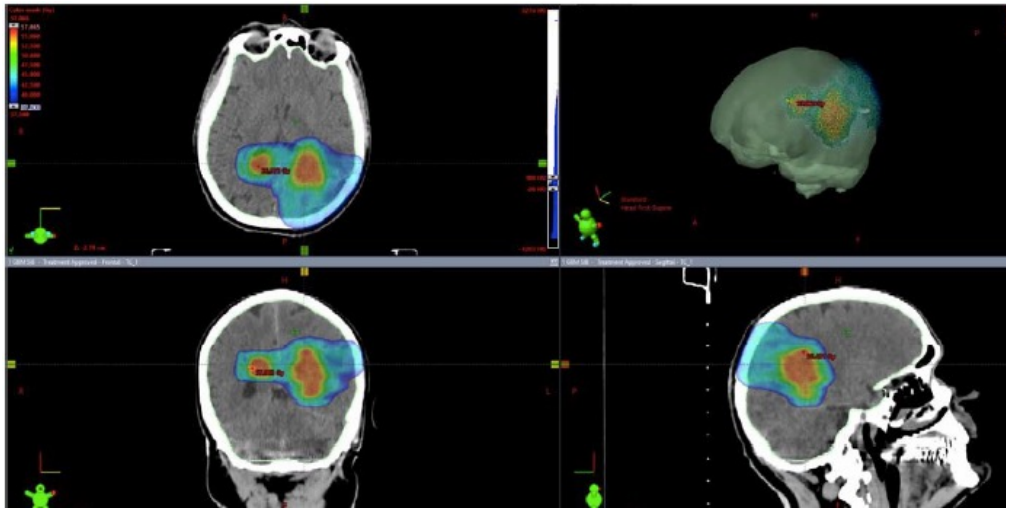
Journal of *Personalized Medicine*

Article

Poor-Prognosis Patients Affected by Glioblastoma: Retrospective Study of Hypofractionated Radiotherapy with Simultaneous Integrated Boost and Concurrent/Adjuvant Temozolomide

Fabiana Gregucci [1], Alessia Surgo [1], Ilaria Bonaparte [1], Letizia Laera [2], Maria Paola Ciliberti [1], Roberta Carbonara [1], Maria Annunziata Gentile [3], David Giraldi [4], Roberto Calbi [3], Morena Caliandro [1], Nicola Sasso [2], Salvatore D'Oria [4], Carlo Somma [4], Gaetano Martinelli [3], Giammarco Surico [2], Giuseppe Lombardi [5] and Alba Fiorentino [1,*]



J. Pers. Med. 2021, 11, 1145.

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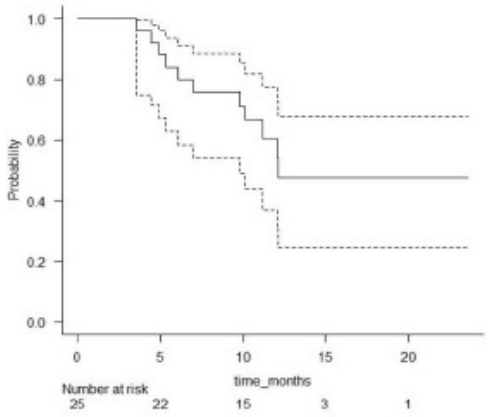
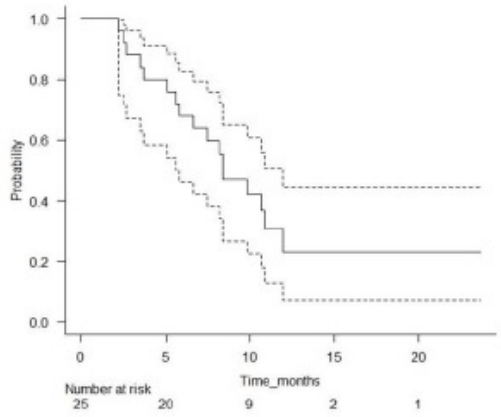


OS



PFS

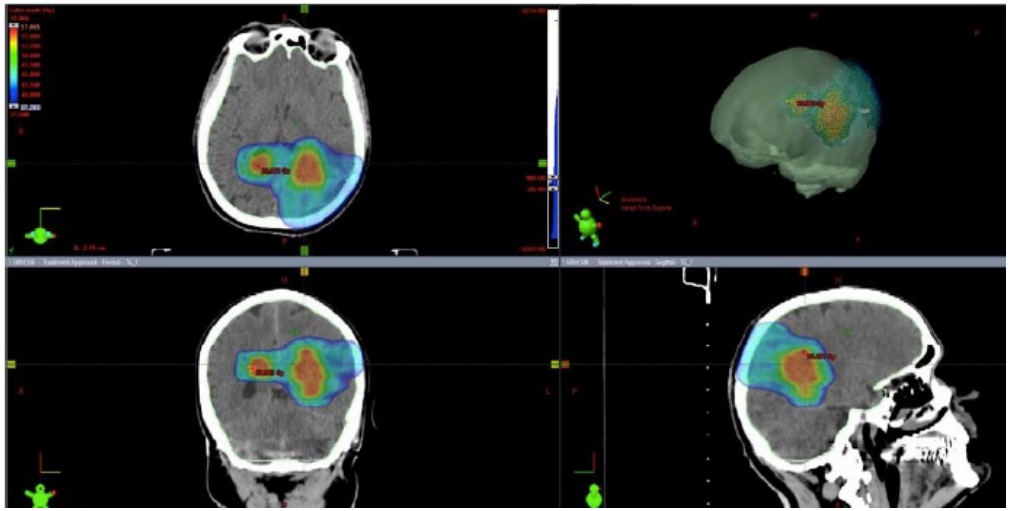
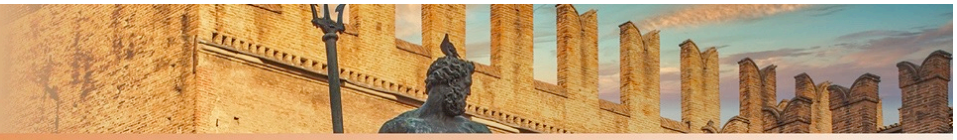


Table 4. Literature review of studies regarding elderly/frail patients with high-grade gliomas and treated with hypofractionated RT.

Author/Publication Year	Study Years	Study Type	Patient Selection	Comparison	No. of Patients	RT Schedule	Median PFS	Median OS	Toxicities
Phillips et al. 2003 [9]	1990–1996	Randomized Phase III	Age > 45 y ECOG 0–3	Hypo-RT Standard RT	32 36	35 Gy/10 fx (WB) 60 Gy/30 fx	NS	8.7 months 10.3 months	None
Roa et al. 2004 [11]	1996–2001	Randomized Phase III	Age ≥ 60 y KPS ≥ 50	Hypo-RT Standard RT	48 47	40 Gy/15 fx 60 Gy/30 fx	NS	5.6 months 5.1 months	NS
Malmström et al. 2012 [12]	2000–2009	Randomized Phase III	Age ≥ 60 y ECOG 0–2	TMZ Hypo-RT Standard RT	93 98 100	NA 34 Gy/10 fx 60 Gy/30 fx	NS	8.3 months 7.5 months 6 months	No G > 3 acute toxicity
Roa et al. 2015 [18]	2010–2013	Randomized Phase III	Age ≥ 65 y KPS 50–70	Hypo-RT Hypo-RT	48 50	25 Gy/5 fx 40 Gy/15 fx	4.2 months 4.2 months	7.9 months 6.4 months	No G > 3 acute toxicity
Guedes de Castro et al. 2017 [19]	NS	Randomized Phase III	Age ≥ 65 y KPS 50–70	Hypo-RT Hypo-RT	26 35	25 Gy/5 fx 40 Gy/15 fx	4.3 months 3.2 months	6.8 months 6.2 months	No G > 3 acute toxicity
Perry et al. 2017 [16]	2007–2013	Randomized Phase III	Age ≥ 65 y ECOG 0–2	Hypo-RT + TMZ Hypo-RT	281 281	40 Gy/15 fx	5.3 months 3.9 months	9.3 months 7.6 months	No G > 3 acute toxicity
Pedretti et al. 2019 [24]	2010–2015	Randomized Phase II	RPA Class 5 or 6	Hypo-RT alone TMZ alone	14 17	30 Gy/6 fx over 2 weeks	3.8 months	6.3 months	No G > 3 acute toxicity
Bauman et al. 1994 [27]	1990–1992	Prospective	Age ≥ 65 y KPS ≤ 50	Hypo-RT	29	30 Gy/10 fx (WB)	NS	6 months	NS
Thomas et al. 1994 [29]	1991–1993	Prospective	KPS ≤ 50 or Age 55–70 y KPS 50–70 or Age ≥ 70 y	Hypo-RT	38	30 Gy/6 fx over 2 weeks	NS	6 months	None
Hulshof et al. 2000 [19]	1988–1998	Prospective	Age ≥ 65 y MRC ≥ 2	Hypo-RT Hypo-RT Standard RT	48 41 66	28 Gy/4 fx 40 Gy/8 fx 66 Gy/33 fx	NS	6.6 months 5.6 months 7 months	Mild; No difference between groups
Minniti et al. 2009 [21]	2002–2006	Prospective	Age ≥ 70 y KPS ≥ 60	Hypo-RT + adj TMZ	43	30 Gy/6 fx over 2 weeks	6.3 months	9.3 months	8 patients presented neurological deterioration (Grade 2/3 confusion and/or somnolence). 12 patients had Grade 3/4 hematological toxic effects

Table 4. *Cont.*

Author/Publication Year	Study Years	Study Type	Patient Selection	Comparison	No. of Patients	RT Schedule	Median PFS	Median OS	Toxicities
Omuro et al. 2014 [26]	NS	Prospective	Age ≥ 18 years (median 55 y) KPS ≥ 70 (median 90) Partial resection or biopsy (75%)	Hypo-RT + TMZ + BEV	40	30 Gy/6 fx over 2 weeks	10 months	19 months	None
Navarria et al. 2019 [17]	2013–2016	Prospective	Age ≥ 70 y KPS ≤ 60	Hypo-RT	30	52.5 Gy/15 fx	5 months	8 months	No severe acute or late neurologic toxicity was recorded
McAleese et al. 2003 [8]	1991–1999	Retrospective	KPS ≤ 50 or Age 50–70 y KPS 50–90 or Age ≥ 70 y	Hypo-RT	92	30 Gy/6 fx over 2 weeks	NS	5 months	NS
Chang et al. 2003 [10]	1988–2001	Retrospective	RPA Class ≥ 4	Hypo-RT	59	50 Gy/20 fx	3.9 months	7 months	3 patients showed radio-necrosis
Minniti et al. 2015 [23]	2004–2013	Retrospective	Age ≥ 65 y KPS ≥ 60	Hypo-RT + TMZ Standard RT + TMZ	116 127	40 Gy/15 fx 59.4–60 Gy/30–33 fx	6.7 months 5.6 months	12.5 months 12 months	28 patients receiving standard RT and 11 subjected to short-course RT had acute worsening of neurologic status. 20 patients receiving standard RT and 3 patients receiving short-course RT had late neurologic deterioration (G2–3 cognitive disability) G3–4 thrombocytopenia and lymphocytopenia were seen in 24 patients and 51 patients. G3 neutropenia developed in 14 patients, and 10 patients displayed G3 anemia
Jablonska et al. 2019 [15]	2010–2017	Retrospective	RPA Class ≥ 4	Hypo-RT with SIB + TMZ	17	50–45–40 Gy/15 fx	7 months	7 months	No acute G3–5 toxicities were observed. Radio-necrosis occurred in 1 patient
Present study	2019–2021	Retrospective	Poor prognosis RPA Class ≥ 4	Hypo-RT with SIB + TMZ	25	52.5–40 Gy/15 fx	8.4 months	13 months	No acute or late neurological side effects of grade ≥ 2 were reported. No cases of radio-necrosis. Grade 3–4 hematologic toxicity occurred in 3 cases.



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4.

Elderly and GB: Integrated Therapy

EXPERT REVIEWS

Elderly patients with glioblastoma: the treatment challenge

Alba Fiorentino*[1], Pasquale De Bonis[2], Silvia Chiesa[2], Mario Balducci[3] and Vincenzo Fusco[1]

Expert Rev. Neurother. 13(10), 1099–1105 (2013)

The NOA-08 trial randomized patients over 65 affected by high-grade glioma (GBM and anaplastic astrocytoma) to either TMZ (100 mg/m^2, administered on days 1–7, 1 week on, 1 week off) or RT alone (60 Gy administered in 30 fractions). This trial failed to demonstrate the superiority of TMZ; in fact, the median OS was 8.6 versus 9.6 months in the TMZ and RT group, respectively, without statistical significance [13]. All categories of acute side effects were less frequent in RT arm compared with TMZ.

The Nordic Brain Tumor Study Group (NCBTSG trials) [29] randomized GBM patients over 60 to standard RT alone (60 Gy), hypofractionated RT alone (HRT: 34 Gy) and TMZ alone (200 mg/mï¿½ doses on days 1–5 of every 28 days for up to six cycles). Median survival was 6 versus 8.3 and 7.4 months for standard RT, TMZ and HRT, respectively. This trial con-

Moreover, as highlighted by some authors [2,30], the two randomized trials reported contradictory results [13,29]: TMZ and RT did not differ in terms of survival in both trials but, in the RT arms the median survival was 9.7 versus 6 months in the NOA-08 and NCBTSG trials, respectively, which are, surely, inferior to the age-matched results reported by Stupp *et al.* [1,31]. Finally, these trials supported the use of TMZ alone in patients with methylated *O*6-methylguanine methyltransferase (MGMT) status and, in the un-methylated group, the use of RT (standard or hypofractionated) even if these data were not conclusive. In fact, in the methylated group, the NCBTSG trial, reported a median survival of 9.7 and 8.2 months for TMZ and RT arms, respectively, without statistical significance (p = 0.07); while the NOA-08 trial reported that the methylation status was associated with differences in event-free survival, and a trend was shown for OS between treatments modalities (TMZ vs RT). Moreover, the authors reported a lower compliance in the chemotherapy group compared with RT, due to the more side effect of TMZ, and a higher risk of progression disease during TMZ

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Elderly and GB: Radiotherapy, TMZ

Cochrane Library
Cochrane Database of Systematic Reviews

Treatment of newly diagnosed glioblastoma in the elderly: a network meta-analysis (Review)

Hanna C, Lawrie TA, Rogozińska E, Kernohan A, Jefferies S, Bulbeck H, Ali UM, Robinson T, Grant R

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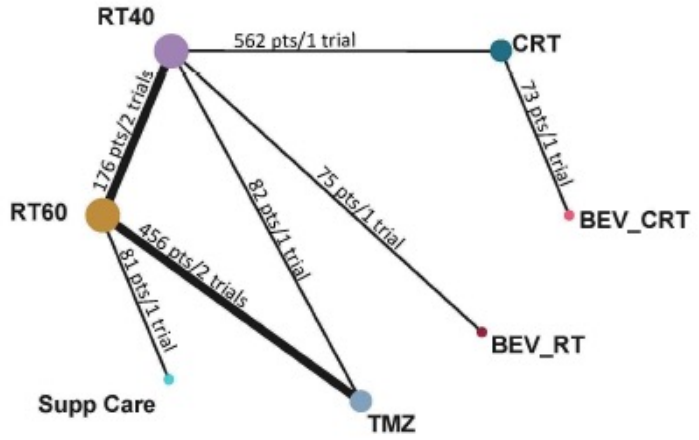

Main network of treatment interventions for glioblastoma in the elderly

Outcome: Overall Survival (time-to-event data)

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Elderly and GB: Radiotherapy, TMZ

Comparison: supportive care only

Outcome: overall survival

All intervention options (7 RCTs; 1540 participants in total)*	**Relative effect (network estimate) ** (95% CI)**	**Illustrative absolute effects for death at 6 months (95% CIs)**	**Certainty of the evidence (GRADE)**	**Ranking¥**
Supportive care only*** (1 RCT, 81 participants)	**Reference comparator**	76 per 100***	Reference comparator	7.0 (worst)
RT60 (5 RCTs; 713 participants)	**HR 0.47** (0.29 to 0.76)	49 per 100 (34 to 66)	⊕⊕⊕○ **Moderate[1]**	5.0
BEV_RT (1 RCT; 75 participants)	**HR 0.48** (0.23 to 1.00)	50 per 100 (28 to 76)	Not graded[2]	4.7
RT40 (4 RCTs; 930 participants)	**HR 0.44** (0.25 to 0.77)	47 per 100 (30 to 67)	⊕⊕○○ **Low[3]**	4.3
TMZ (3 RCTs, 538 participants)	**HR 0.42** (0.25 to 0.71)	45 per 100 (30 to 64)	⊕⊕○○ **Low[3]**	3.8
CRT (2 RCTs; 635 participants)	**HR 0.30** (0.17 to 0.53)	35 per 100 (22 to 53)	Not graded[2]	1.8
BEV_CRT (1 RCT; 73 participants)	**HR 0.25** (0.11 to 0.54)	30 per 100 (15 to 54)	Not graded[2]	1.4

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Elderly and GB: Radiotherapy, TMZ

Comparison: hypofractionated radiotherapy (RT 40)

Outcome: overall survival

All intervention options (7 RCTs; 1540 participants in total)*	Relative effect (network estimate) ** (95% CI)	Illustrative absolute effects for death at 12 months (95% CIs)	Certainty of the evidence (GRADE)
RT 40 (4 RCTs; 930 participants)	**Reference comparator**	78 per 100***	**Reference comparator**
BEV_RT (1 RCT; 75 participants)	**HR 1.08** (0.66 to 1.78)	81 per 100 (63 to 93)	⊕⊕○○ **Low[1]**
TMZ (3 RCTs, 538 participants)	**HR 0.95** (0.71 to 1.26)	76 per 100 (66 to 85)	⊕⊕○○ **Low[1]**
CRT (2 RCTs; 635 participants)	**HR 0.67** (0.56 to 0.80)	64 per 100 (57 to 70)	⊕⊕⊕⊕ **High**
BEV_CRT	**HR 0.56** (0.31 to 0.99)	57 per 100	⊕⊕⊕○ **Moderate[2]**

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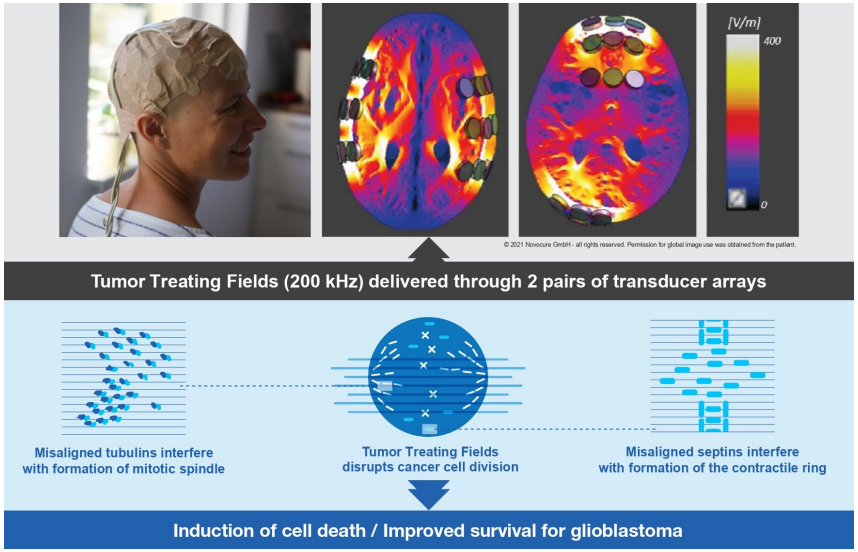
Elderly and GB: Radiotherapy, TMZ, TTF

Tumor-treating fields (TTFields)

TTFields is a non-invasive treatment approach involving alternating electrical fields (34). Researchers propose TTFields are able to inhibit cancer cell proliferation by interfering with microtubule polymerization (35). Stupp *et al.* demonstrated the addition of tumor-treating fields to RT and TMZ resulted in a statistically significant improvement in PFS and OS (36). In their final analysis, the authors reported median OS was 20.9 months in the radiation, TMZ, and tumor-treating field group and 16.0 months in the radiation and TMZ-alone group. In the subgroup analysis, patients ≥65 years maintained the survival benefit with the addition of tumor-treating fields (17.4 *vs.* 13.7 months).



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5

Conclusion

Definition of elderly (a ***better understanding of frailty and comprehensive geriatric assessments***).
In elderly patients in good functional status, adjuvant ***TMZ and RT*** therapy are ***well tolerated*** and appropriate for these patients and other approaches.

Further insights into the unique molecular drivers of elderly GBM, or ***dose escalated hypo RT plus chemo,***

Frail patients may be considered for less aggressive approaches such as ***hypofractionated RT*** or single-agent TMZ.

Clinical judgment coupled with an open, honest and respectful ***discussion with patients and families***, are pivotal
Increasing the role of integration of ***hospital and hospice/domiciliary Assistance***

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Ente Ecclesiastico Ospedale Generale Regionale MIULLI art Advanced Radiation Therapy against ~~Cancer~~

Thanks for your attention

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