HIGHLIGHTS in RADIOTERAPIA | Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021

Quale strategia terapeutica nel trattamento delle metastasi encefaliche?

Silvia Scoccianti

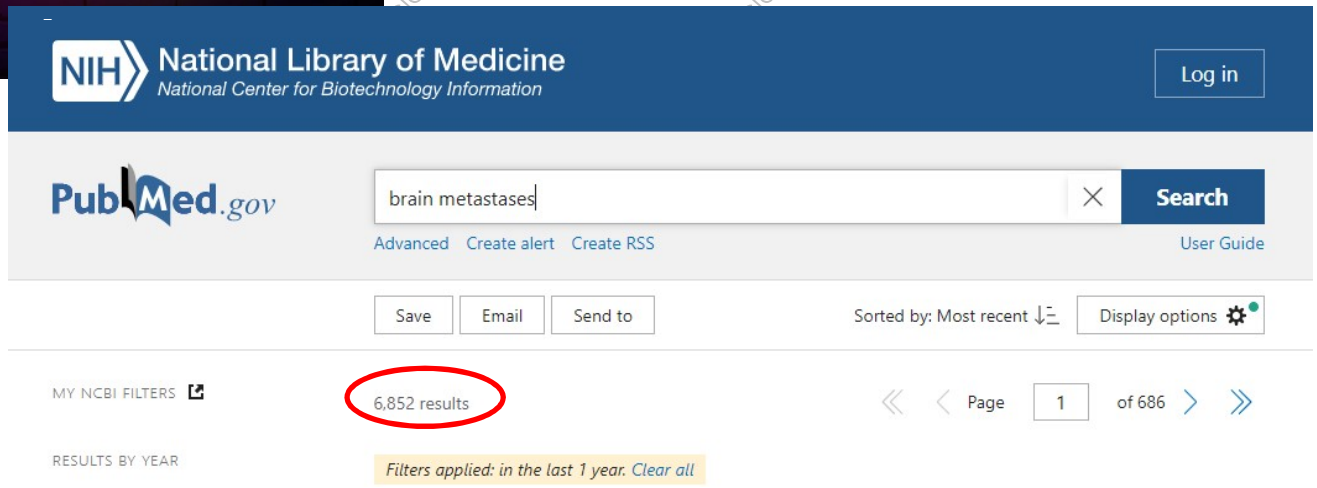
Radioterapia Oncologica,
Ospedale Santa Maria Annunziata,
Firenze

VIRTUAL 27 GENNAIO 2022

Associazione Italiana
Radioterapia e Oncologia clinica

HIGHLIGHTS in RADIOTERAPIA

Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021



New Guidelines

ANNALS OF ONCOLOGY
driving innovation in oncology

SPECIAL ARTICLE

Volume 32 ■ Issue 11 ■ 2021

EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

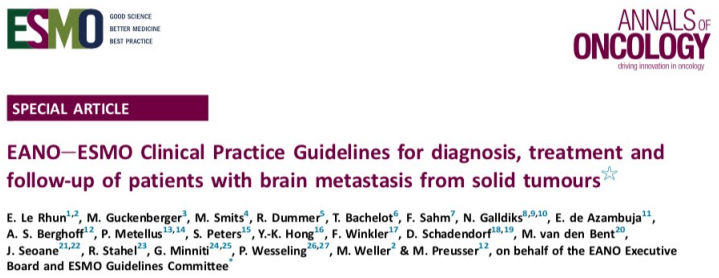
Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Journal of Clinical Oncology®

Diagnosis of BM

Should a screening for detecting asymptomatic BM be recommended?



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

Staging

- All lung tumors except for NSCLC stage I
- Stage IV melanoma
- Stage IV HER-2 + or Triple negative breast cancer

Screening at diagnosis is justified

- **Brain MRI** with at least 1.5 T field strenght
- T1w, T2w and/or FLAIR, DWI sequences
- Cranial CT should be limited to patients with contraindications for MRI

Diagnosis of BM

Local therapy and/or Systemic therapy

When Local treatment is recommended?

ASCO ASTRO SNO

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Journal of Clinical Oncology®

Against Local therapy withdrawal!

Symptomatic BM

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Local therapy should not be delayed regardless of the systemic therapy used for extracranial disease

Asymptomatic BM

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Local therapy should not be delayed unless deferral until intracranial progression is specifically recommended and only based on a multidisciplinary discussion

Diagnosis of BM

Local therapy

ASCO ASTRO SNO

and/or

Systemic therapy

Surgery

When surgery is indicated?

ASCO ASTRO SNO ESMO

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Journal of Clinical Oncology®

Surgery

Suspected BM without a primary cancer diagnosis

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

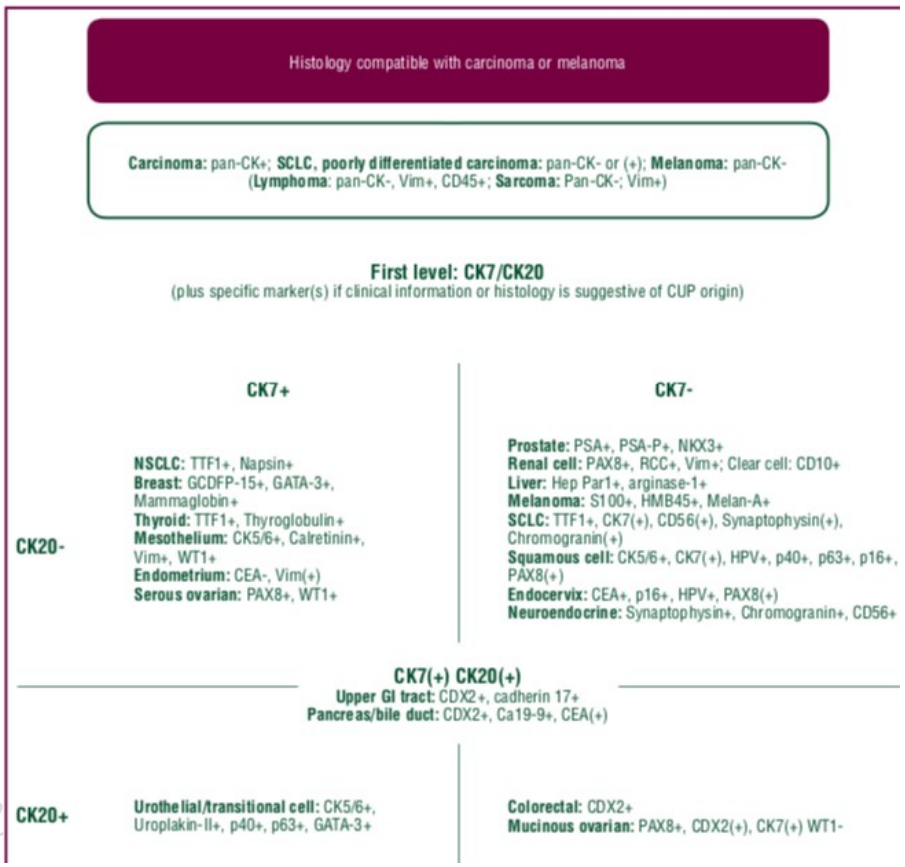
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

EANO—ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee

Unknown primary: immunoistochemical markers



Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Journal of Clinical Oncology®

Surgery

Suspected BM without a primary cancer diagnosis

Surgery

Large tumors with mass effect

Surgery

Recommendation 1.2. Where surgery is considered, no recommendation regarding the method of resection (piecemeal *v* en bloc) can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

EANO—ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

Surgery

- Cystic or necrotic BM
- More than one primary tumors
- Primary tumour that rarely generates BM

Silvia Scoccianti, Firenze; Highlights in radioterapia; 27 Gennaio 2022

- All indications for surgical interventions in BM, except emergency situations, should be assessed for risk and benefit in a **multidisciplinary tumour board**
- Specifically, **the role of surgery versus SRT needs to be weighted**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

EANO—ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

Surgery

- Surgery may be considered for patients requiring steroids, who are candidates for immune checkpoint inhibition

- Cases in which changes in molecular profile compared with the primary tumour may impact clinical decision making

- All indications for surgical interventions in BM, except emergency situations, should be assessed for risk and benefit in a **multidisciplinary tumour board**
- Specifically, **the role of surgery versus SRT needs to be weighted**

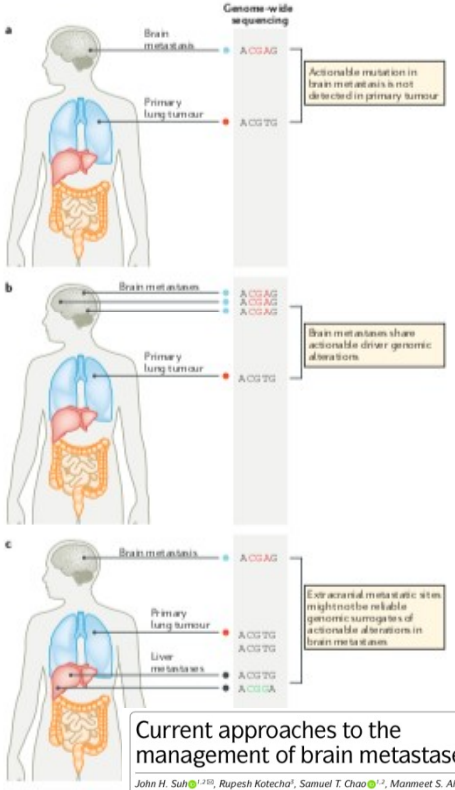
Neuro-Oncology Advances
3(1), 1–9, 2021 | https://doi.org/10.1093/noajnl/vdab166 | Advance Access date 10 November 2021

Systematic review and meta-analysis of PD-L1 expression discordance between primary tumor and lung cancer brain metastasis

Raees Tonse, Muni Rubens, Haley Appel, Martin C. Tom, Matthew D. Hall, Yazmin Odia, Michael W. McDermott, Manmeet S. Ahluwalia, Minesh P. Mehta, and Rupesh Kotecha

Table 1. Predictive markers

Entity	Molecular markers/targets
Breast	HER2, ER/PR, BRCA1/2 ('BRCAness'), PIK3CA, PD-L1
Non-small-cell lung	EGFR, ROS1, NTRK, ALK, RET, MET, KRAS, BRAF, PD-1/PD-L1
Squamous cell	FGFR1
Melanoma	BRAF, KIT, NF1, NRAS, PD-L1
Colorectal	KRAS, BRAF, NRAS, PD-L1, MSI
Upper gastrointestinal	HER2, MET
Urothelial/transitional Cell	PD-L1
Endometrium	MSI
Ovarian (serous)	ER/PR, MSI
Ovarian (mucinous)	MSI



Current approaches to the management of brain metastases

John H. Suh, Rupesh Kotecha, Samuel T. Chao, Manmeet S. Ahluwalia, Arjun Sahgal and Eric L. Chang

Discordance between BM and primary tumor in terms of molecular profile

PD-L1 discordance occurs in ~20% of Lung cancer BM, with the greatest discordance in the 1–50% expression category.

Screening for BM at diagnosis of advanced cancer

Diagnosis of BM

Local therapy

and/or

Systemic therapy

Surgery

SRT

When Stereotactic radiotherapy is indicated?

RS o SRT

Stereotactic RT

One to four BM, excluding SCLC

ASCO ASTRO SNO

Evidence-based	
Evidence Quality	Strength of Recommendation
Intermediate	Moderate

RS alone is recommended

ESMO EANO

More than four BM and KPS ≥70

ASCO ASTRO SNO

Informal consensus	
Evidence Quality	Strength of Recommendation
Low	Weak

RS alone is the preferred option for better prognosis or where available systemic therapy active in the CNS

5-10 BM with a cumulative tumor volume <15 mL

ESMO EANO

RS alone may be considered

Stereotactic Radiosurgery Versus Whole-brain Radiation Therapy For Patients With 4-15 Brain Metastases: A Phase III Randomized Controlled Trial

Jing Li, MD, PhD
University of Texas MD Anderson Cancer Center

ASTRO ANNUAL MEETING

Key Eligibility Criteria:

- Adult patient with 4-15 untreated brain mets confirmed by neuroradiology (up to 20 lesions allowed at the time of treatment)
- All lesions amenable to SRS treatment
- KPS >/=70
- No LMD (radiographic or cytological)
- No prior WBRT
- Prior SRS to 1-3 brain mets with > 6 weeks intervals allowed
- Excluded prior surgical resection of brain mets
- Excluded histology: melanoma, small cell carcinoma, lymphoma/leukemia, or germ cell histology
- Systemic therapy allowed at the discretion of treating oncologist

R (1:1)

N=50 → **SRS arm**
- 15-24 Gy per RTOG 9005

N=50 → **WBRT Arm**
- 30 Gy in 10 fractions
- Memantine strongly encouraged after 2013

Stratification factors:

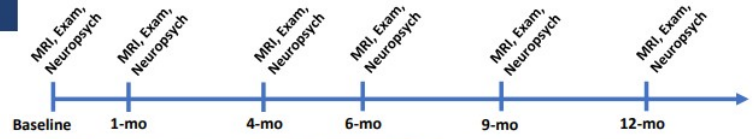
- **Histology** (breast vs. other)
- **Age** (18-59 vs. 60 and over)
- **Number of lesions** (4-7 vs. 8-15)
- **KPS** (70-80 vs. 90-100)
- **Extra-cranial disease status** (progressive disease prior to enrollment vs. no progression)
- **Baseline HVLT** (</= 17 vs. >/=28
- **Radiotherapy** (Prior SRS vs. no prior SRS)

Neurocognitive function tests:

- **Memory:** HVLT_R_TR, HVLT_R_DR, HVLT_R Recognition
- **Executive function:** COWA, and Trail Making test Part B (TMTB)
- **Attention Span:** WAIS-III Digit Span
- **Psychomotor Speed:** WAIS-III Digit Symbol, Trail Making test Part A (TMTA)
- **Motor dexterity:** Grooved Pegboard

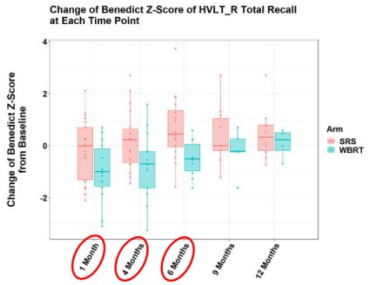
Primary Endpoints

- Memory function at 4 mo (HVLT_R_TR)
- Local control at 4 mo



Memory Function at 4 Months
-- Primary Endpoint

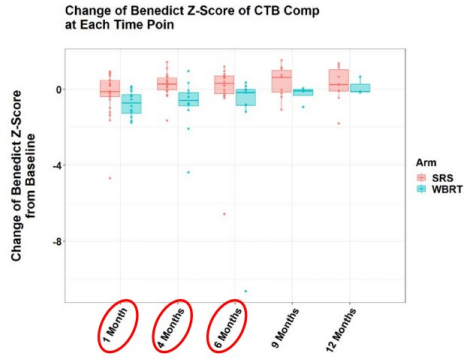
- HVLT_R_TR: change of Z-score from baseline
- **At 4 months**
  - **SRS:** Increased by 0.21 (SD 1.15) (n=18)
  - **WBRT:** Decreased by 0.74 (SD 1.31) (n=13)
  - ***p*=0.041**
- **At 1 month and 6 months**
  - Clinically meaningful and statistically significant benefit with SRS was also observed at **1 month (*p*= 0.033)** and **6 months (*p*=0.012)**



Global Cognitive Function Measure
(Clinical Trial Battery Composite Score)

- Composite score
  - Mean Z-score from HVLT_R_TR, HVLT_R_DR, and HVLT_R Rec, COWA, TMTA, and TMTB
  - Change from baseline
- **Better cognitive composite scores in SRS arm**
  - **Statistically significant at months 1, 4 and 6**

Follow up Time Point	SRS	WBRT	p
1-mo (median [IQR])	-0.12 [-0.38, 0.47]	-0.71 [-1.26, -0.28]	0.024
4-mo (median [IQR])	0.28 [-0.03, 0.60]	-0.57 [-0.88, -0.17]	0.004
6-mo (median [IQR])	0.31 [-0.23, 0.70]	-0.16 [-0.84, -0.01]	0.027
9-mo (median [IQR])	0.64 [-0.16, 1.00]	-0.08 [-0.32, -0.01]	0.153
12-mo (median [IQR])	0.25 [-0.09, 1.03]	-0.12 [-0.14, 0.27]	0.823

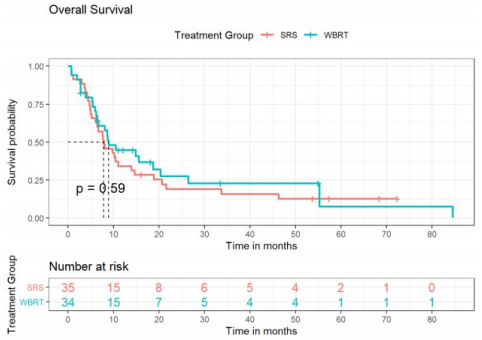


Overall Survival

- **Overall survival by intention-to-treat**
  - 69 out of 72 pts evaluable for OS
    - 35 for SRS and 34 for WBRT
  - Estimate median OS

	N	Events (death)	Median (month)	95% CI (month)
SRS	35*	30	7.8	6.1 – 14.6
WBRT	34**	26	8.9	6.4 – 26.4

*Include 6 patients who had more than 20 lesions at time of SRS planning and received WBRT off protocol
** Include 4 patients received SRS and 2 patients received HA-WBRT off protocol



Estimating Overall Survival Curves with the Kaplan-Meier Method by intention-to-treat: *P*= 0.59

Other Results

- Local Control at 4 mo
  - 95% (SRS) vs 87% (WBRT), p-value 0.79
- Distant brain control
  - 60% (SRS) vs 80% (WBRT), p-value 0.37
- Toxicities
  - ≥ Grade 3 toxicities 8% (SRS) vs 15% (WBRT)
  - Radiation necrosis: 17% at patient level and 4% at lesion level

2020 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING

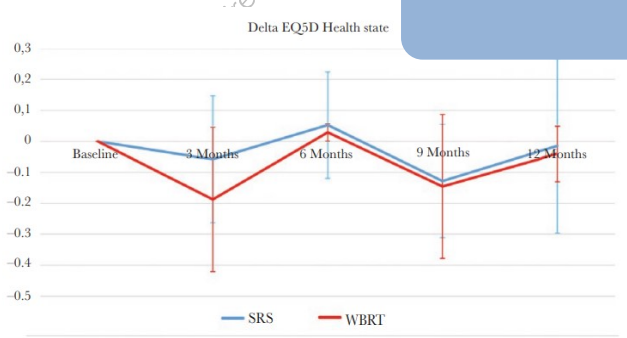
Stereotactic RT for 4-10 BM

Neuro-Oncology Advances
3(1), 1–9, 2021 | doi:10.1093/noajnl/vdab021 | Advance Access date 01 February 2021

1

A Dutch phase III randomized multicenter trial: whole brain radiotherapy versus stereotactic radiotherapy for 4–10 brain metastases

Dianne Hartgerink, Anna Bruynzeel, Danielle Eekers, Ans Swinnen, Coen Hurkmans, Ruud Wiggenraad, Annemarie Swaak-Kragten, Edith Dieleman, Peter-Paul van der Toorn, Bing Oei, Lieneke van Veelen, Joost Verhoeff, Frank Lagerwaard, Dirk de Ruysscher, Philippe Lambin, and Jaap Zindler



Methods. Patients with 4–10 BM were randomized between the standard arm WBRT (total dose 20 Gy in 5 fractions) or SRS (single fraction or 3 fractions). The primary endpoint was the difference in quality of life (QOL) at 3 months post-treatment.

Conclusion. In patients with 4–10 BM, SRS alone resulted in 1-year survival for 57% of patients while maintaining quality of life. Due to the premature closure of the trial, no statistically significant differences could be determined.

Key Points

- SRS is a promising treatment option for patients with multiple brain metastases.
- In patients with brain metastases, SRS resulted in >50% OS while maintaining QOL.
- The main reason for poor inclusion was patient and referrer preference for SRS.

Clinical Oncology 33 (2021) 314–321

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Group and Individual Change in Cognitive Functioning in Patients With 1 to 10 Brain Metastases Following Gamma Knife Radiosurgery

W.C.M. Schimmel *†‡1, E. Verhaak *†‡1, M. Bakker §, P.E.J. Hanssens *†, M.M. Sitskoorn ††, K. Gehring *††

* Gamma Knife Center, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
† Department of Neurosurgery, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
‡ Department of Cognitive Neuropsychology, Tilburg University, Tilburg, the Netherlands
§ Department of Methodology and Statistics, Tilburg University, Tilburg, the Netherlands

Cognitive functioning in patients with 1 to 10 brain metastases was preserved, or improved, up to 9 months after GKRS. Neither number nor volume of brain metastases influenced cognitive performance

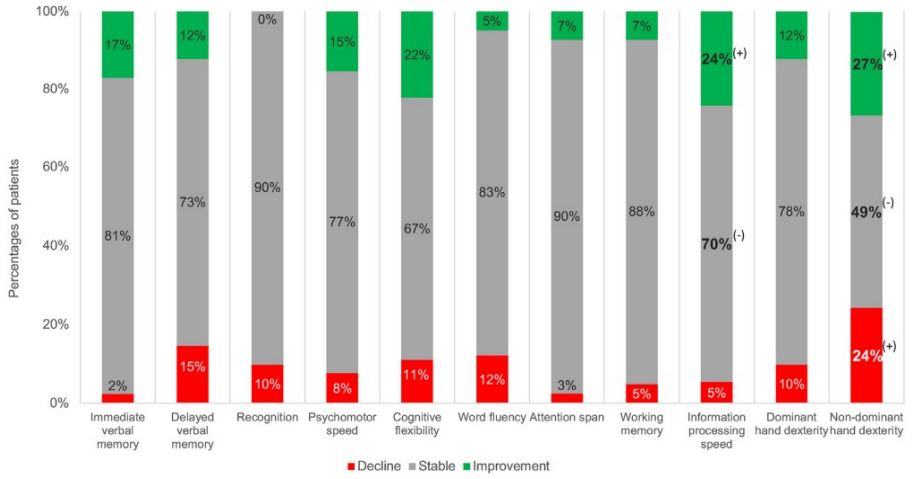


Fig 1. Individual cognitive changes at the test level over 9 months after radiosurgery (T0–T9; $n = 36–41$). Note: bold text indicates a st significant difference in the proportions of patients and controls with declined, stable or improved performance (+/− indicates that centage is significantly higher/lower in patients compared with controls).

Radiosurgery dose prescription

International Journal of Radiation Oncology biology • physics
www.redjournal.org

HyTEC Organ-Specific Paper: Brain and Eye

Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Kristin J. Redmond, MD,* Chengcheng Gui, BS,* Stanley Benedict, PhD,† Michael T. Milano, MD,‡ Jimm Grimm, PhD,§ J. Austin Vargo, MD,‖ Scott G. Soltys, MD,¶ Ellen Yorke, PhD,# Andrew Jackson, PhD,# Issam El Naqa, PhD,** Lawrence B. Marks, MD,†† Jinyu Xue, PhD,‡‡ Dwight E. Heron, MD, MBA,§§ and Lawrence R. Kleinberg, MD*

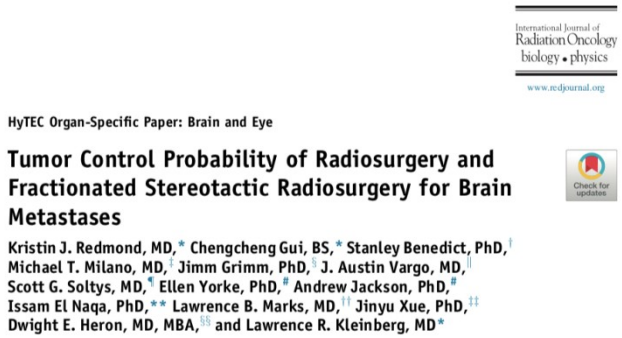
Where we are now

EBM
EVIDENCE-BASED MEDICINE

RS: Prescription dose in phase III trials

Author	n	Number of lesions and maximum diameter	WBRT Dose	RS Dose
Andrews 2004	333	**1-3 lesions** Maximum diameter **4 cm** for the largest lesion and additional lesions not exceeding 3 cm in diameter	WBRT 37.5 Gy in 15 fractions (2.5 Gy)	<2 cm: 24 Gy; 2-3 cm: 18 Gy; 3-4 cm: 15 Gy
Aoyama 2006	**132**	**1-4 lesions** Maximum diameter **3 cm**	WBRT 30 Gy in 10 or 12 fractions (2.5 or 3 Gy)	≤2cm: 22-25 Gy; 2-3 cm: 18-20 Gy *(RS dose reduction for concomitant WBRT:* *≤2cm: 15.4-17.5 Gy;* *>2cm: 12.6-14 Gy)*
Kocher 2011	359	**1-3 lesions** Maximum diameter **3.5 cm** for single lesion and 2.5 cm for multiple lesions	WBRT 30 Gy in 10 fractions (3 Gy)	<3.5 cm: 20 Gy
Brown 2015	215	**1-3 lesions** Maximum diameter **3 cm**	WBRT 30 Gy in 12 fractions (2.5 Gy)	≤2cm: 24 Gy; >2cm: 20 Gy *(RS dose reduction for concomitant WBRT:* *≤2cm: 22 Gy;* *>2cm: 18 Gy)*

≤2cm	22-25 Gy
2-3 cm	18-20 Gy
3-3,5 cm	15-20 Gy
3,5-4 cm	15 Gy


International Journal of Radiation Oncology biology • physics
www.redjournal.org

HyTEC Organ-Specific Paper: Brain and Eye

Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Kristin J. Redmond, MD,* Chengcheng Gui, BS,* Stanley Benedict, PhD,† Michael T. Milano, MD,‡ Jimm Grimm, PhD,§ J. Austin Vargo, MD,‖ Scott G. Soltys, MD,¶ Ellen Yorke, PhD,# Andrew Jackson, PhD,# Issam El Naqa, PhD,** Lawrence B. Marks, MD,†† Jinyu Xue, PhD,‡‡ Dwight E. Heron, MD, MBA,§§ and Lawrence R. Kleinberg, MD*

The AAPM team reviewed the published literature to evaluate dosimetric and clinical predictors of tumor control.

Of 2951 potentially eligible manuscripts, only 56 included sufficient dose-volume data for analyses

1) **Dosing guidelines** are typically **reported in aggregate, and not on individual patient scenario** (location, number of lesions, histology, etc);
2) Clear definitions for **local control** are not reported across the literature
3) Difficulties in extracting consistent data of **size and dose-based lesion (vs patient) outcomes**;
4) **Tumor coverage** often is not reported
5) **Local versus marginal failures** are not differentiated;
6) **Planning target volume expansions** differs across studies, institutions, and treatment platforms
7) **Prior treatment with WBRT** was delivered in approximately 44% of cases and may influence tumor control

International Journal of Radiation Oncology biology • physics
www.redjournal.org

HyTEC Organ-Specific Paper: Brain and Eye

Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Kristin J. Redmond, MD,* Chengcheng Gui, BS,* Stanley Benedict, PhD,† Michael T. Milano, MD,‡ Jimm Grimm, PhD,§ J. Austin Vargo, MD,‖ Scott G. Soltys, MD,¶ Ellen Yorke, PhD,# Andrew Jackson, PhD,# Issam El Naqa, PhD,** Lawrence B. Marks, MD,†† Jinyu Xue, PhD,†† Dwight E. Heron, MD, MBA,‡‡ and Lawrence R. Kleinberg, MD*

Tumor maximum dimension	Dose/fractionation	1-Year local control pooled estimate
≤2 cm	18–24 Gy /1 fraction	85%–95%
2–3 cm	18 Gy/1 fraction	75%
3–4 cm	15 Gy/1 fraction	69%

≤2cm	22-25 Gy
2-3 cm	18-20 Gy
3-3,5 cm	15-20 Gy
3,5-4 cm	15 Gy

Tolerance of the brain

International Journal of Radiation Oncology biology • physics
www.redjournal.org

HyTEC: Organ-Specific Paper

Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain

Michael T. Milano, MD, PhD,* Jimm Grimm, PhD,† Andrzej Niemierko, PhD,‡ Scott G. Soltys, MD,§ Vitali Moiseenko, PhD,‖ Kristin J. Redmond, MD,¶ Ellen Yorke, PhD,# Arjun Sahgal, MD,** Jinyu Xue, PhD,†† Anand Mahadevan, MD,† Alexander Muacevic, MD,‡‡ Lawrence B. Marks, MD,§§ and Lawrence R. Kleinberg, MD¶

HIGHLIGHTS in RADIOTERAPIA

Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021

Prior local treatments
- Surgery
(- WBRT)

Systemic therapy

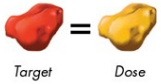
Target location
Brainstem
Thalamus
Basal ganglia
Occipital lobes
Temporal lobes

Age
Comorbidity

Radionecrosis
Edema
Neurotoxicity

Target type
Malignant tumors
- Benign tumors
-AVM

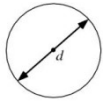
Conformality

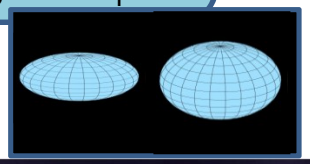


Dose to OARs

Prescription dose

Target maximal diameter
Target volume
Target shape





Different primary tumors

HIGHLIGHTS in RADIOTERAPIA

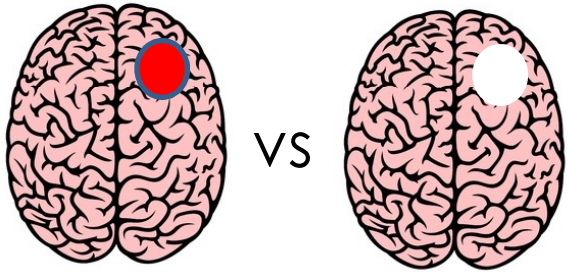
Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021

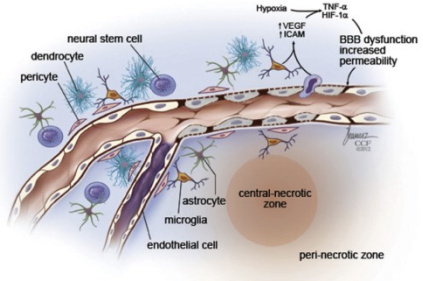
Points you should consider

Grade of radionecrosis

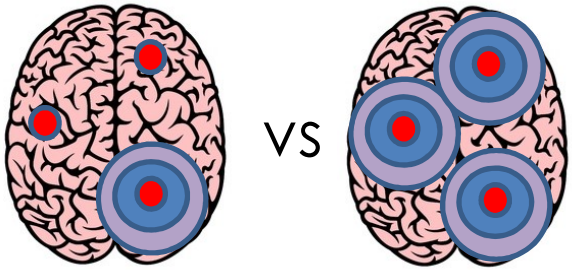
CTCAE version 4 (from 2009)	
Grade 0	None
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate symptoms; corticosteroids indicated
Grade 3	Severe symptoms; medical intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated

Inclusion or exclusion of TARGET from Vx: tissueV12 vs brainV12





V12: individual lesion-based calculation vs a cumulative brain dose composite



QUANTEC, Lawrence et al, IJROBP 2010	Toxicity increases rapidly once V12 is >5-10 cc	«The substantial variation between the reported treatment parameters and outcomes from different centers has prevented us from making precise toxicity risk predictions»
UK consortium: Stereotactic ablative body radiation therapy (SABR), 2019	V12 *whole brain - GTV* should be 10 cc	Endpoint: **Any grade** radiation necrosis

HyTEC Organ-Specific Paper: Brain and Eye

Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain

Michael T. Milano, MD, PhD,* Jimm Grimm, PhD,† Andrzej Niemierko, PhD,‡ Scott G. Soltys, MD,§ Vitali Moiseenko, PhD,‖ Kristin J. Redmond, MD,¶ Ellen Yorke, PhD,# Arjun Sahgal, MD,** Jinyu Xue, PhD,†† Anand Mahadevan, MD,† Alexander Muacevic, MD,‡‡ Lawrence B. Marks, MD,§§ and Lawrence R. Kleinberg, MD¶

Published reports on AVM and brain mets 1995-2018

V12 of brain *including target volume*	Risk of **symptomatic necrosis ≥G2**
5 cc	10 %
10 cc	15 %
>15 cc	20 %

V14 of brain *including target volume*	Risk of **G3 necrosis**
5 cc	0,4%
10 cc	0,8%
20 cc	3,4%

Combination of RS+IOT

Combination of RS+IOT

Stereotactic radiosurgery with immune checkpoint inhibitors for **brain metastases**: a meta-analysis study.

Badrigilan S, Meola A, Chang SD, Rezaeian S, Nemati H, Almasi T, Rostampour N.

Br J Neurosurg. 2022 Jan 4:1-11. doi: 10.1080/02688697.2021.2022098. Online ahead of print.

PMID: 34979828

BACKGROUND: Immune checkpoint inhibitors (ICIs) are an emerging tool in the treatment of **brain metastases** (BMs), Stereotactic radiosurgery (SRS), traditionally used for BMs, elicits an immune **brain** response and can act synergistically with ICIs. ...The overal ...

Selected trials of SRS and immune checkpoint inhibitors in patients with brain metastasis

Trial Registration No.	Study Location	Tumor Type	Study Design	Immunotherapy Agent	*n*	Primary Endpoint	Study Start Date	Estimated Completion Date
NCT03483012	Dana-Farber Cancer Institute	Breast	Phase II	Atezolizumab	45	PFS	Sep 2021	Sep 2025
NCT03449238	Weill Medical College of Cornell University	Breast	Phase II	Pembrolizumab	41	RR, OS	Nov 2018	Dec 2026
NCT03807765	H. Lee Moffitt Cancer Center and Research Institute	Breast	Phase I	Nivolumab	14	DLT	Jan 2019	Jan 2022
NCT02886585	Massachusetts General Hospital	Any solid tumor	Phase II	Pembrolizumab	102	RR, OS	Oct 2016	Sep 2022
NCT02097732	University of Michigan Rogel Cancer Center	Melanoma	Phase II	Ipilimumab	40	LC	April 2014	July 2020
NCT03340129	Melanoma Institute Australia	Melanoma	Phase II	Nivolumab & Ipilimumab	218	NSCD	Aug 2019	Aug 2025
NCT03297463	Masonic Cancer Center, University of Minnesota	Melanoma	Phase I/II	Ipilimumab	40	MTD, ORR	Jan 2018	Feb 2020
NCT02716948	Sidney Kimmel Comprehensive Cancer Center	Melanoma	Phase I	Nivolumab	90	AE	Jun 2016	Mar 2023
NCT02858869	Emory University	Melanoma, NSCLC	Phase I	Pembrolizumab	30	DLT	Oct 2016	Oct 2021
NCT02696993	M.D. Anderson Cancer Center	NSCLC	Phase I/II	Nivolumab & Ipilimumab	88	DLT, PFS	Dec 2016	Dec 2020
NCT02978404	Centre hospitalier de l'Université de Montréal (CHUM)	NSCLC, RCC	Phase II	Nivolumab	26	PFS	Jun 2017	Jun 2022

n = number; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; OS = overall survival; PFS = progression-free survival; DLT = dose limiting toxicity; AE = adverse events; LC = local control; MTD = maximum tolerated dose; RR = response rate; ORR = objective response rate; NSCD = neurological specific cause of death.

Tonse et al., 2021

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Journal of Clinical Oncology®

Local therapy withdrawal

Symptomatic BM

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Local therapy should not be delayed regardless of the systemic therapy used for extracranial disease

Asymptomatic BM

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Local therapy should not be delayed unless deferral until intracranial progression is specifically recommended and only based on a multidisciplinary discussion

HIGHLIGHTS in RADIOTERAPIA

Update degli Studi Practice Changing 2021
Quali novità da Congressi Internazionali 2021

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD[1]; Paul D. Brown, MD[2]; Hans Messersmith, MPH[3]; Priscilla K. Brastianos, MD[4]; Stuart Burri, MD[5]; Dan Cahill, MD, PhD[4]; Ian F. Dunn, MD[6]; Laurie E. Gaspar, MD, MBA[7,8]; Na Tosha N. Gatson, MD, PhD[9,10]; Vinai Gondi, MD[11]; Justin T. Jordan, MD[4]; Andrew B. Lassman, MD[12]; Julia Maues, MA[13]; Nimish Mohile, MD[14]; Navid Redjal, MD[15]; Glen Stevens, DO, PhD[16]; Erik Sulman, MD, PhD[17]; Martin van den Bent, MD[18]; H. James Wallace, MD[19]; Jeffrey S. Weinberg, MD[20]; Gelareh Zadeh, MD, PhD[21]; and David Schiff, MD[22]

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Journal of Clinical Oncology®

Asymptomatic BM

Evidence-based

Evidence Quality	Strength of Recommendation
High	Strong

Local therapy should not be delayed unless deferral until intracranial progression is specifically recommended and only based on a multidisciplinary discussion

NSCLC

Informal consensus

Evidence Quality	Strength of Recommendation
Low	Weak

- EGFR-mutant → Osimertinib, Icotinib
- ALK-rearranged → Alectinib, Brigatinib, Ceritinib
- PDL1-expressing → Pembrolizumab in pts who are also receiving PEM+platinum

Melanoma

Informal consensus

Evidence Quality	Strength of Recommendation
Low	Weak

- any BRAF-status → Ipi + Nivo
- BRAF-V600E mutated → Dabra + Trametinib

Breast cancer

Informal consensus

Evidence Quality	Strength of Recommendation
Low	Weak

- HER-2 + → Tucatinib + Trastuzumab + Capecitabine (in pts previously treated with trastuzumab, pertuzumab and/or trastuzumab emtasine-based therapy)

Comparative Efficacy of Systemic Agents for **Brain Metastases** From Non-Small-Cell Lung Cancer With an EGFR Mutation/ALK Rearrangement: A Systematic Review and Network Meta-Analysis.

Taslimi S, Brar K,
MS, Khasraw M,
Front Oncol. 202
PMID: 34950579
BACKGROUND: **B**
carry significant r
therapies. ...METI

Association of **Brain Metastases** With Immune Checkpoint Inhibitors Effi Advanced Lung Cancer: A Systematic Review and Meta-Analysis.

Wang Y, Zhang Q, Chen C, Hu Y, Miao L, Zhou Y.

Front Oncol. 2021 Dec 8;11:721760. doi: 10.3389/fonc.2021.721760. eCollection 2021.

PMID: 34956860 **Free PMC article.**

RESULTS: Nine eligible **randomized** controlled trials involving 6241 patients (682 [11%] with **metastases** and 5559 [89%] without **brain metastases**) were included in the analysis. ...H patients without **brain metastases** bene ...

Efficacy of PD-1/L1 inhibitors in **brain metastases** of non-small-cell lung cancer: pooled analysis from seven **randomized** controlled trials.

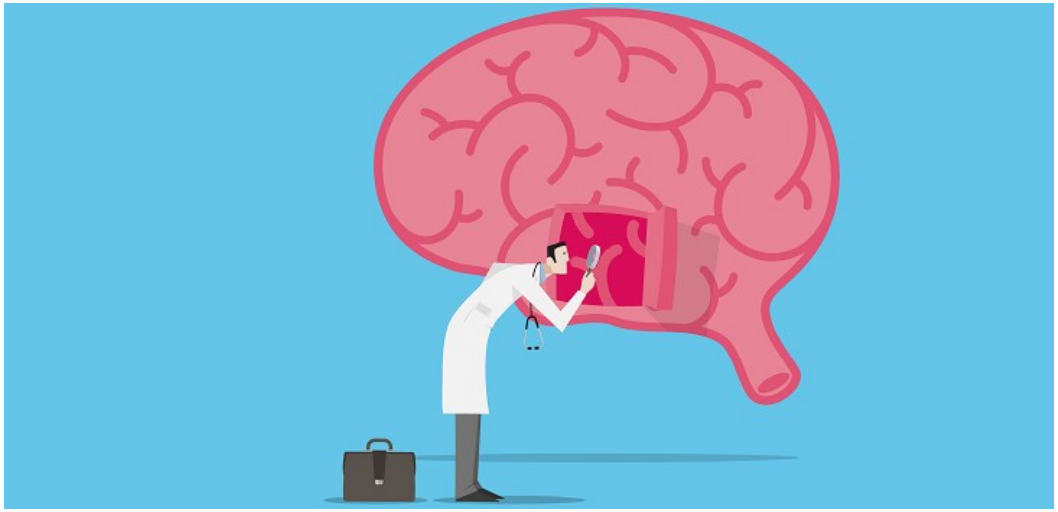
Li W, Jiang J, Huang L, Long F.

Future Oncol. 2022 Jan;18(3):403-412. doi: 10.2217/fon-2021-0795. Epub 2021 Nov 17.

PMID: 34787500

Background: The efficacy of PD-1 or PD-L1 inhibitors in patients with **brain metastases** of non-small-cell lung cancer (BM-NSCLC) is inconclusive. Materials & methods: An electronic search was performed. **Randomized** controlled trials RCTs that compared the e ...

Grazie per l'attenzione



silvia.scoccianti@uslcentro.toscana.it