Decennale di
HIGHLIGHTS in
RADIOTERAPIA

Update degli Studi Practice Changing 2024

Undicesima Edizione

In memoria di Renzo Corvò

ROMA
30-31 gennaio 2025
Starhotels Metropole

Brain metastases: update on Practice Changing studies published on 2024

Dott Silvia Scoccianti
SOC Radioterapia
Ospedale Santa Maria Annunzia
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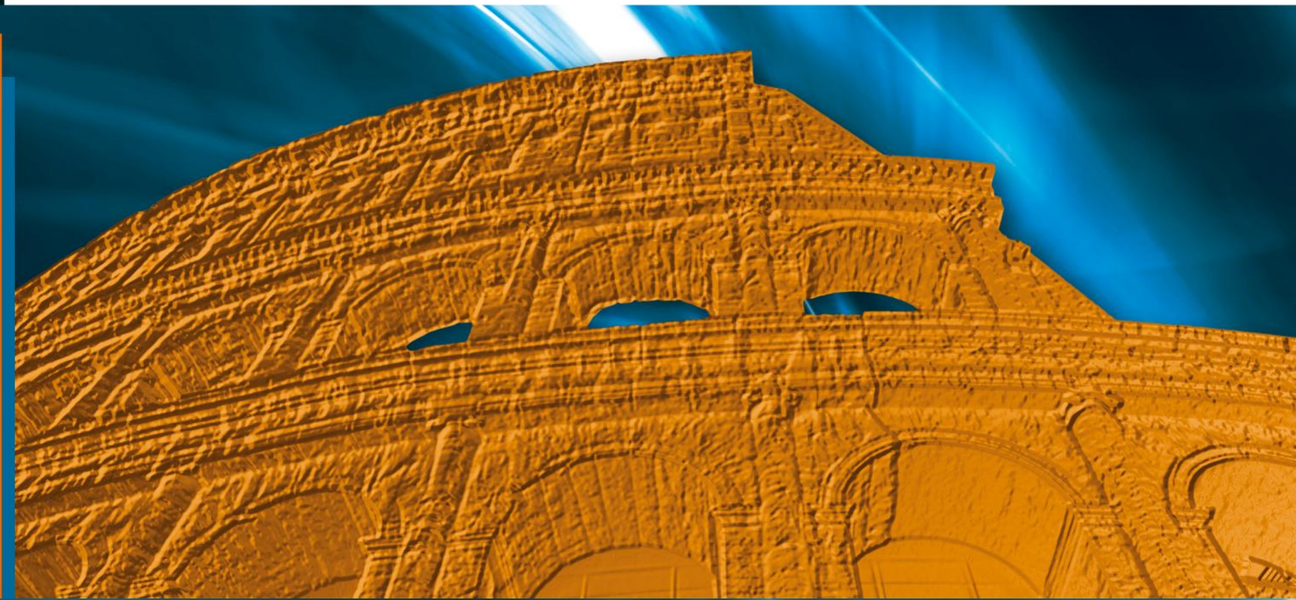

My outline

- SRS or SRT in the treatment of INTACT brain mets
- Indications
- Prognostic factors
- Brain mets from different primaries = Different diseases
- Radiotherapy withdrawal
- Radionecrosis
- Miscellanea

- PERIOPERATIVE SRS or SRT
- Indications
- Prognostic factors

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Guidelines for Brain mets published in 2024

Advances in Radiation Oncology (2024) 9, 101402

advances in radiation oncology
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Critical review

Stereotactic Radiosurgery in the Management of Brain Metastases: A Case-Based Radiosurgery Society Practice Guideline

Colton Ladbury, MD,[a] Michael Pennock, MD,[b] Tugba Yilmaz, MD,[c] Nii-Kwanchie Ankrah, MBBS,[d] Therese Andraos, MD,[e] Emile Gogineni, DO,[f] Grace Gwe-Ya Kim, PhD,[f] Iris Gibbs, MD,[g] Helen A. Shih, MD, MPH,[h] Jona Hattangadi-Gluth, MD,[f] Samuel T. Chao, MD,[i] Susan C. Pannullo, MD,[j] Ben Slotman, MD, PhD,[k] Kristin J. Redmond, MD, MPH,[l] Simon S. Lo, MB, ChB,[m] and Michael Schulder, MD[n,*]

1) What factors contribute to whether a patient might be a candidate for SRS treatment?

Suitable	Criteria
Number of lesions	1-15
Metastasis size	Diameter ≤3 cm, volume ≤14 cc

Cautionary	
Number of lesions	>15
Metastasis size	Diameter 3-6 cm, volume >14 cc (operative management preferred)
Specific scenarios	Small cell lung cancer, nodular lepto-meningeal disease

Unsuitable	
Metastasis size	>6 cm
Specific scenarios	Classical leptomeningeal disease

Guidelines

Advances in Radiation Oncology (2024) 9, 101402

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www.advancesradonc.org

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2) What fractionation schemes can be used in SRS?

Maximum diameter	Dose
<2 cm	20-24 Gy in single fraction
2-4 cm	27 in 3# or 30 in 5#
>4 cm	Surgery is recommended

3) What treatment volumes are used during SRS?

GTV = CTV
PTV = GTV + 0-2 mm (≤1 mm whenever is possible)

3) What technique can be used to treat multiple brain metastases using a linear accelerator?

When feasible, SIT (Single-isocenter techniques) plans can facilitate effective and efficient treatment planning and delivery for multiple metastases, allowing for time efficient clinical feasibility for initial and subsequent SRS courses

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4) What dose constraints are used for SRS?

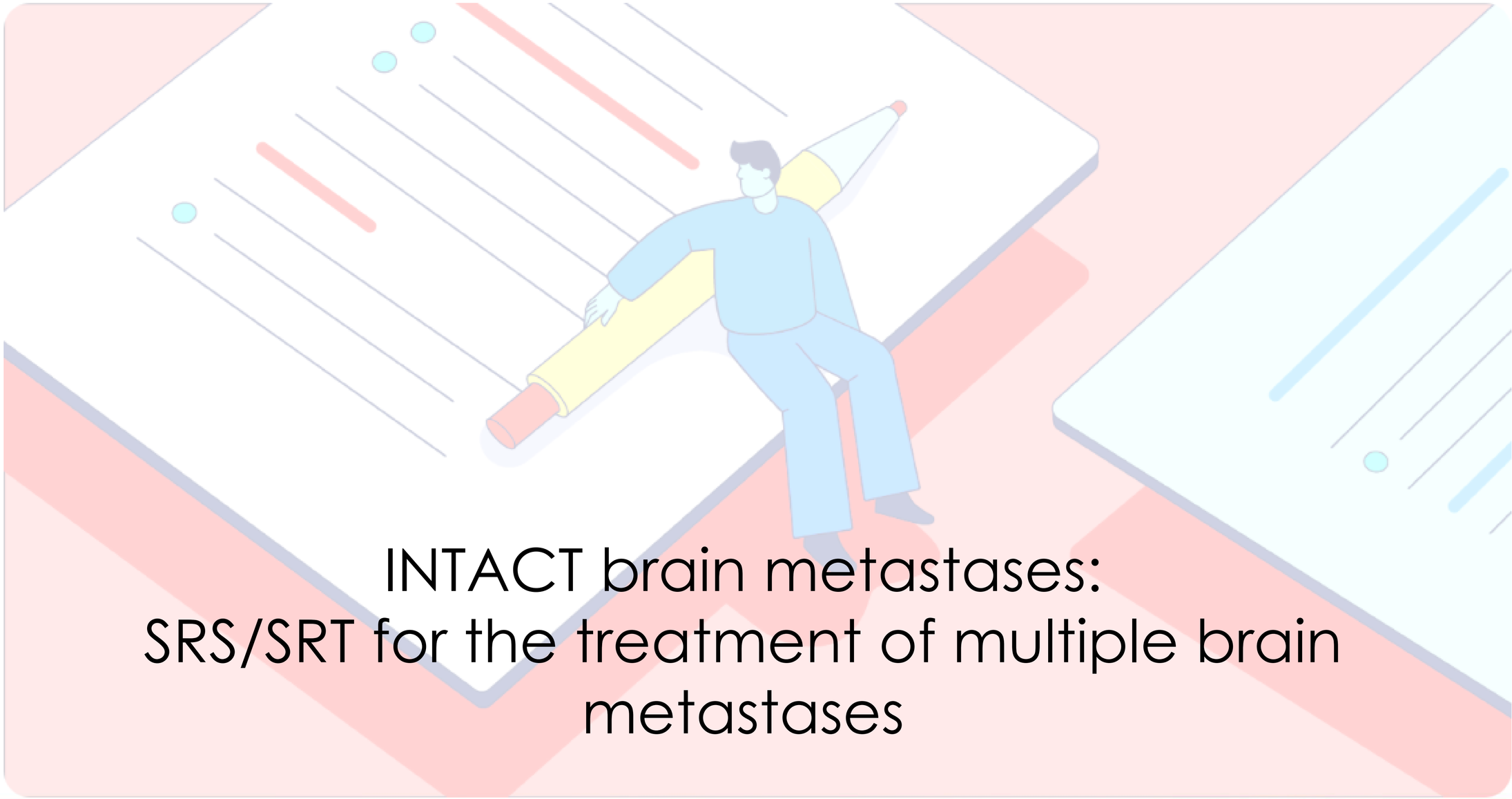
Table 2 Common dose constraints used in SRS planning

	Standard treatment		
Organ	**1 fx**	**3 fx**	**5 fx**
Brain	V12 <5-10 cc[13,53] V10 <12 cc[53]	V18 <26 cc[54] V21 <21 cc[54] V24 <16.8 cc[55]	V25 <16 cc[56] V28.8 <7 cc[57] V30 <10.5-30 cc[56]
Brain stem (not medulla)	Dmax <15 Gy[58] V10 <0.5 cc[58]	Dmax <23.1 Gy[58] V15.9 <0.5 cc[58]	Dmax <31 Gy[58] V23 <0.5 cc[58]
Spinal cord and medulla	Dmax <12.4-14 Gy[30,58] V10 <0.35 cc[58]	Dmax <20.3-22.5 Gy[30,58] V15.9 <0.35 cc[58]	Dmax <25.3-28 Gy[30,58] V22 <0.35 cc[58]
Cochlea	Dmax <9 Gy[58]	Dmax <14.4 Gy[58]	Dmax <22 Gy[58]
Optic pathway	Dmax <10 Gy[58,59] V8 <0.2 cc[58]	Dmax <17.4-20 Gy[58,59] V15.3 <0.2 cc[58]	Dmax <25 Gy[58,59] V23 <0.2 cc[58]

5) Can SRS be given concurrently with systemic therapies?

Currently, it appears most studies support concurrent systemic therapy + SRS with no need for a washout period

Single session Radiosurgery (SRS) and Fractionated Stereotactic Radiotherapy (SRT) in the treatment of INTACT brain metastases



INTACT brain metastases: SRS/SRT for the treatment of multiple brain metastases

Current Oncology
MDPI

Article

Survival after Stereotactic Radiosurgery in the Era of Targeted Therapy: Number of Metastases No Longer Matters

James de Boisanger [1,2,*], Martin Brewer [1], Matthew W. Fittall [3], Amina Tran [1], Karen Thomas [1], Sabine Dreibe [1], Antonia Creak [1], Francesca Solda [1], Jessica Konadu [1], Helen Taylor [1], Frank Saran [4], Liam Welsh [1] and Nicola Rosenfelder [1]

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2 The Institute of Cancer Research, London SM2 5NG, UK
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Cyberknife or Linac-based SRS/SRT

n= 1181

Retrospective study

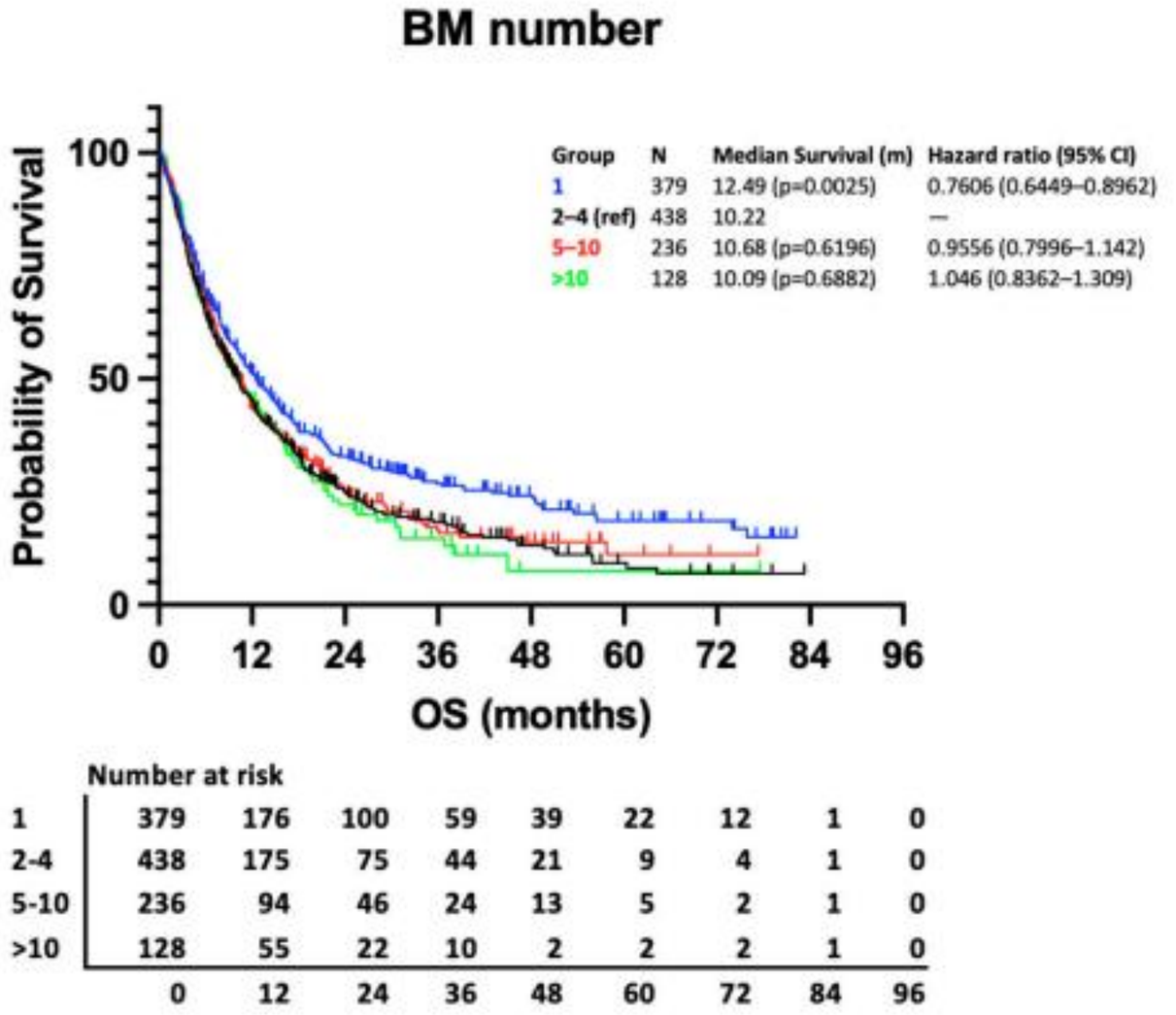


Figure 1. Kaplan–Meier curve presenting survival according to no. of BM groups.

Neuro-Oncology
XX(XX), 1–13, 2024 | https://doi.org/10.1093/neuonc/noae201 | Advance Access date 28 September 2024

Stereotactic radiosurgery for 1–10 brain metastases to avoid whole-brain radiotherapy: Results of the CYBER-SPACE randomized phase 2 trial

Rami A. El Shafie, Denise Bernhardt, Thomas Welzel, Annabella Schiele, Daniela Schmitt, Paul Thalmann, Sinem Erdem, Angela Paul, Simon Höne, Kristin Lang, Laila König, Fabian Weykamp, Sebastian Adeberg, Adriane Lentz-Hommertgen, Cornelia Jäkel, Farastuk Bozorgmehr, Ursula Nestle, Michael Thomas, Anja Sander, Meinhard Kieser, Jürgen Debus†, and Stefan Rieken†

- If subsequently new BM occurred, SRS was repeated.
- WBRT was indicated upon occurrence of >10 new BM, leptomeningeal disease, or exhausted SRS-radiotolerance.
- The primary outcome was freedom from WBRT indication (WBRTi).
- Secondary outcomes included overall survival (OS), safety, and quality of life.

Key Points

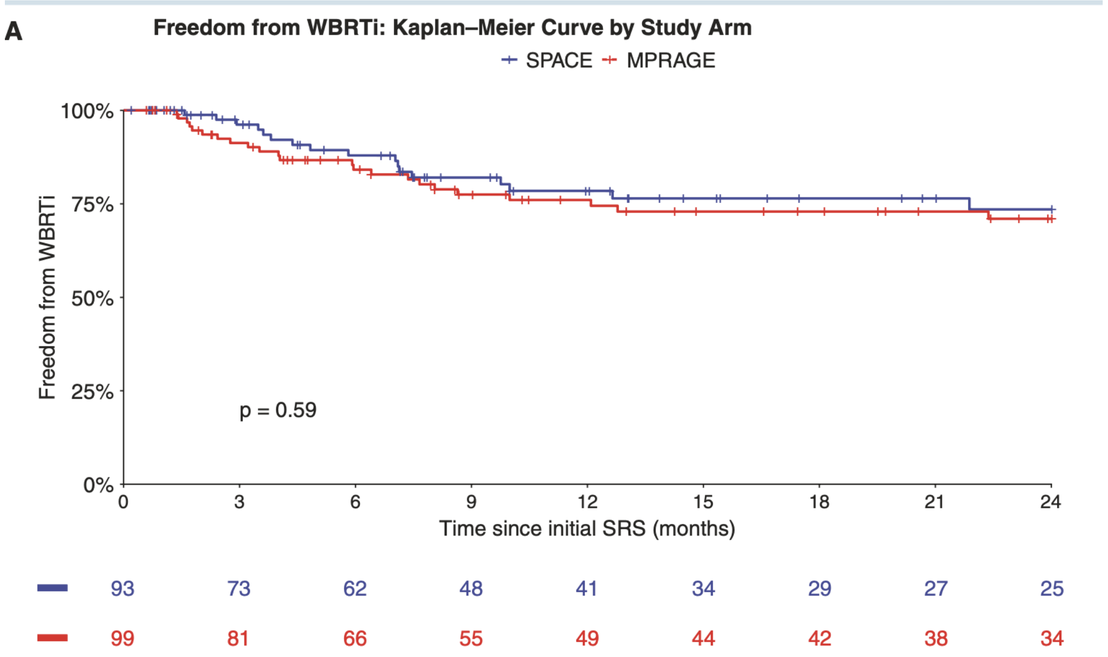
- Repeated stereotactic radiosurgery (SRS) for multiple brain metastases avoids whole-brain radiotherapy (WBRT) and neurologic death.
- The more sensitive SPACE MRI sequence did not improve outcomes over MPRAGE sequence.
- SRS with concurrent immuno-/targeted therapies is well tolerated and associated with favorable overall survival.

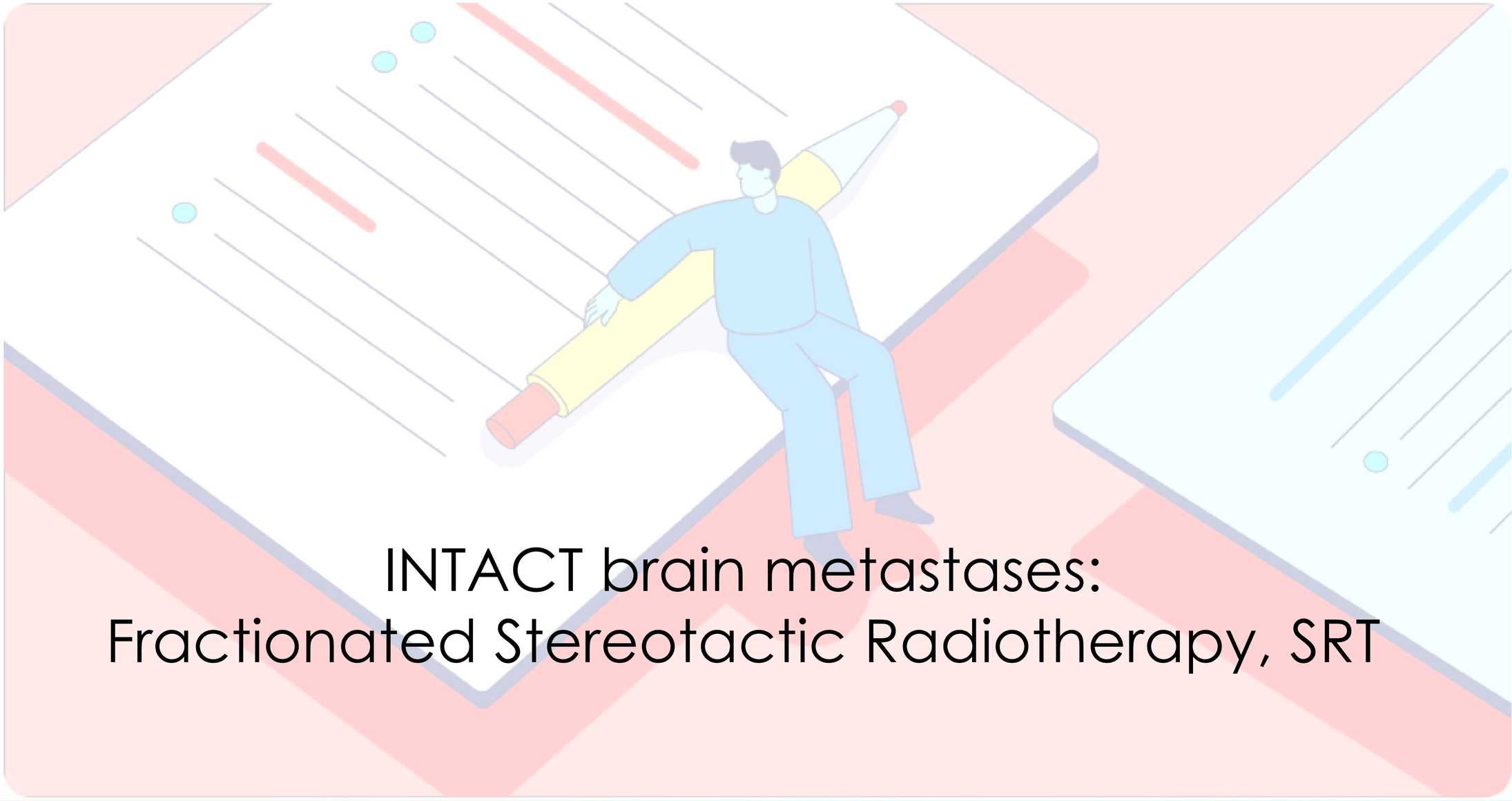
Phase 2 trial

Oncology

Table 2. Treatment and Outcome Parameters Over the Course of the Trial

	SPACE (*n* = 93)	MPRAGE (*n* = 99)	Total (*n* = 192)
Lesions treated with			
20 Gy	463 (88.9%)	445 (88.3%)	908 (88.6%)
18 Gy	35 (6.7%)	38 (7.5%)	73 (7.1%)
6 × 5 Gy	23 (4.4%)	21 (4.2%)	44 (4.3%)
SRS courses per patient before reaching WBRTi (including re-treatment of new lesions during follow-up)			
1	55 (59.1%)	53 (53.5%)	108 (56.3%)
2	18 (19.4%)	22 (22.2%)	40 (20.8%)
3	10 (10.8%)	9 (9.1%)	19 (9.9%)
≥4	10 (10.8%)	15 (15.2%)	25 (13.0%)
Total number of treated lesions before reaching WBRTi			
1	16 (17.2%)	17 (17.2%)	33 (17.2%)
2–4	36 (38.7%)	44 (44.4%)	80 (41.7%)
5–10	28 (30.1%)	27 (27.3%)	55 (28.6%)
>10	13 (14.0%)	11 (11.1%)	24 (12.5%)





INTACT brain metastases: Fractionated Stereotactic Radiotherapy, SRT

SECTION EDITOR REVIEW SERIES

Hypofractionated Stereotactic Radiosurgery in the Management of Brain Metastases

Eric J. Lehrer, MD, MS*, William G. Breen, MD*, Raj Singh, MD‡, Joshua D. Palmer, MD‡, Paul D. Brown, MD*, Daniel M. Trifiletti, MD§, Jason P. Sheehan, MD, PhD‖

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Neurosurgery 95:253–258, 2024 https://doi.org/10.1227/neu.0000000000002897

TABLE 2. Studies Using Hypofractionated Radiosurgery in the Postoperative Setting

Author	N	Median follow-up (mo)	Dose (Gy)	1-year LC (%)	1-year ARE/RN (%)
Minniti et al[15]	101	16.0	27 Gy in 3 fractions	93	9% (any grade) 5% (symptomatic)
Keller et al[41]	187	15.0	33 Gy in 3 fractions	88.2	19%
Soliman et al[43]	122	16.0	30 Gy in 5 fractions	84	7% (symptomatic)
Eitz et al[44]	558	12.3	30 Gy in 5 fractions	84	8.6%

ARE, adverse radiation events; Gy, gray; n, number of patients; RN, radiation necrosis.

TABLE 3. Studies Using Hypofractionated Radiosurgery in the Upfront Setting

Author	n	Median follow-up (mo)	Dose (Gy)	1-year LC (%)	1-year ARE/RN (%)
Minniti et al[16]	138[a]	29	27 Gy in 3 fractions	91	8%
Wegner et al[45]	36	24 (surviving patients)	24 Gy in 2–5 fractions	63	0%
Navarria et al[46]	102	14	27 Gy in 3 fractions and 32 Gy in 4 fractions	96	5.8% (required surgical resection)

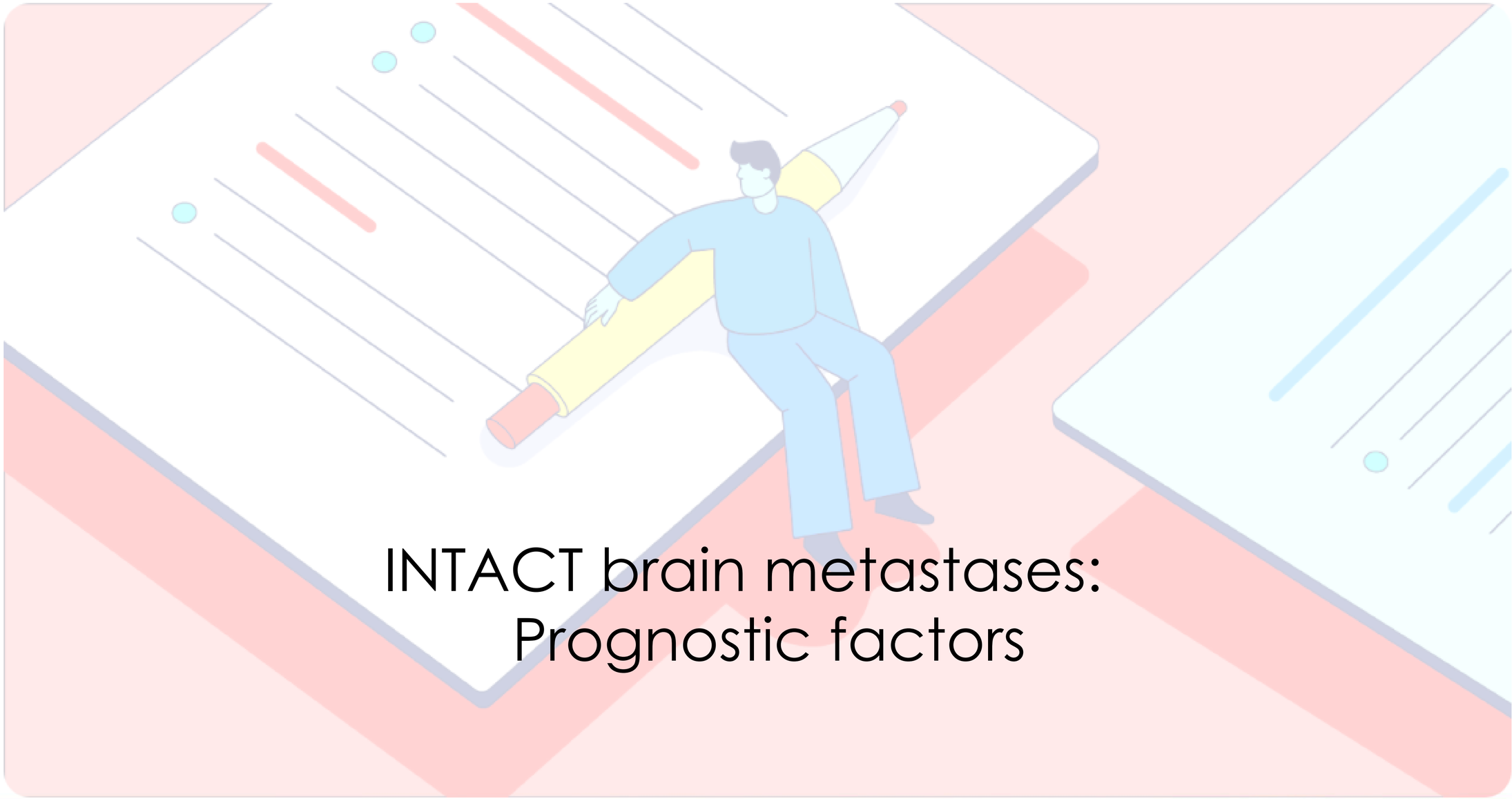
ARE, adverse radiation events; Gy, gray; n, number of patients; RN, radiation necrosis.
[a]Fractionated stereotactic radiosurgery group only.

TABLE 1. Normal Brain Dose Constraints to Minimize Risk of Adverse Radiation Events/Radiation Necrosis

Study	Constraint	ARE/RN risk and notes
Single-fraction SRS		
Flickinger et al[19]	V_{12} < 10 cm^3[a]	Symptomatic ARE/RN risk markedly increases above 10 cm^3 Risk dependent on the intracranial location, where the greatest risk was associated with pontine/midbrain lesions Study analyzed AVMs only
Milano et al[29] (HyTEC)	V_{12} < 5 cm^3[a]	<10% symptomatic ARE/RN risk
	V_{12} < 10 cm^3[a]	<15% symptomatic ARE/RN risk
	V_{12} < 15 cm^3[a]	<20% symptomatic ARE/RN risk
Blonigen et al[30]	V_{10} > 10.5 cm^3[b] V_{12} > 7.9 cm^3	Recommended consideration of HSRS to minimize risk of ARE/RN when these constraints are exceeded
Minniti et al[13]	V_{12} < 8.5 cm^3[b] V_{12} < 10.9 cm^3[b]	Symptomatic ARE/RN risk >10% and >50% for V12 Gy > 8.5 cm^3 and >10.9 cm^3, respectively Correlation with any grade and symptomatic ARE/RN with these dosimetric variables although correlation was notably higher for symptomatic ARE/RN
Hanna et al[31]	V_{12} < 10 cm^3[b]	Not reported
3-fraction HSRS		
Milano et al[29] (HyTEC)	V_{20} < 20 cm^3[a]	<10% risk of any ARE/RN
Minniti et al[16]	V_{18} < 30 cm^3[b]	≤10% risk of any ARE/RN Study only included intact brain metastases
Minniti et al[15]	V_{24} < 16.8 cm^3[b]	<10% risk of any ARE/RN Study only included postoperative cavities
5-fraction HSRS		
Milano et al (HyTEC)[29,a]	V_{24} < 20 cm^3	<10% risk of any ARE/RN
Tanenbaum et al[32]	PTV D_{max} < 33.5 Gy	PTV hotspots of 33.5 Gy or higher were significantly associated with radiographic ARE/RN CTV hotspots were not predictive of radiographic ARE/RN

ARE, adverse radiation effects; AVM, arteriovenous malformation; CTV, clinical target volume; D_{max}, maximum point dose; HSRS, hypofractionated stereotactic radiosurgery; Gy, gray; HyTEC, hypofractionated treatment effects in the clinic; PTV, planning target volume; RN, radiation necrosis; SRS, stereotactic radiosurgery; V_x, volume of brain receiving x of radiation.

Review



INTACT brain metastases: Prognostic factors

Kanakarajan *et al.*
BMC Medical Informatics and Decision Making (2024) 24:177
https://doi.org/10.1186/s12911-024-02579-z

BMC Medical Informatics and Decision Making

SYSTEMATIC REVIEW Open Access

Factors associated with the local control of brain metastases: a systematic search and machine learning application

Hemalatha Kanakarajan[1*], Wouter De Baene[1], Karin Gehring[1,3], Daniëlle B. P. Eekers[4], Patrick Hanssens[2,3] and Margriet Sitskoorn[1*]

Review

SRS

Factors associated with better LC:

- Breast cancer primary type [88, 89, 90]
- Selectivity index [91]
- Uterine cervical carcinoma histology [92]
- Absolute neutrophil count [93]
- Serum albumin concentration [94]
- Lymphocyte percentage [94]

- Higher radiation dose [8, 88, 90, 91, 95, 96, 97, 98, 99, 100,101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120]
- Higher volume coverage[97, 121]
- Addition of WBRT [113]
- Intensity modulated radiosurgery [102]
- Single fraction [102]
- Tyrosine kinase inhibitor [118]
- Previous craniotomy [107]
- Upfront SRT [89]
- Higher number of radiation shots [115]

- RCC specific GPA score [122]

Factors associated with worse LC:

- Higher tumor volume [12, 88, 89, 91, 95, 97, 99, 101, 102,103, 105, 106, 107, 109, 112, 113, 114, 115, 118, 119, 121, 123, 124, 125, 126, 127,128, 129, 130, 131, 132, 133]
- Larger tumor size [89, 97, 103, 113, 114, 116, 117, 118,120, 125, 130, 134, 135]
- Brainstem location [116]
- Higher relative cerebral blood volume [101]
- Active systemic metastases [98]
- Pre-treatment neutrophil percentage [94]
- Higher PLR [94]
- Pre-SRT neutrophil-to-lymphocyte ratio [99]
- Extracranial progression [100]
- Increase in Ktrans ratio [136]
- Cystic lesions [137]
- Absolute neutrophil count-absolute lymphocyte count ratio [93]
- Renal cell histology [112]
- Radioresistant tumor histology [114]
- Colorectal histology [89]

- SRT for progressive lesion [89]
- Previous resection [138]

- Higher RPA class [102]
- Neurological symptoms [139]
- DS-GPA [132]
- Extracerebral metastases [139]

SRT

Factors associated with better LC:

- Higher radiation dose [140, 141, 142]
- Prior surgery [143]

- Adenocarcinoma as the histological type [140]
- Tumor volume decrease after first SRT [144]

- Higher KPS [144]

Factors associated with worse LC:

- Larger tumor size [143,145, 146]
- Melanoma histology [146,147]
- Higher tumor volume [144]
- Larger number of metastases [144]

Clinical Oncology 36 (2024) 307–317

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journal homepage: www.clinicaloncologyonline.net

Original Article

Predicting Survival with Brain Metastases in the Stereotactic Radiosurgery Era: are Existing Prognostic Scores Still Relevant? Or Can we do Better?

M.W. Fittall *, M. Brewer †, J. de Boisanger †, L. Kviat †, A. Babiker †, H. Taylor †, F. Saran ‡, J. Konadu †, F. Solda †, A. Creak †, L.C. Welsh †, N. Rosenfelder †

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‡ Cancer and Blood Service, Auckland City Hospital, Auckland, New Zealand

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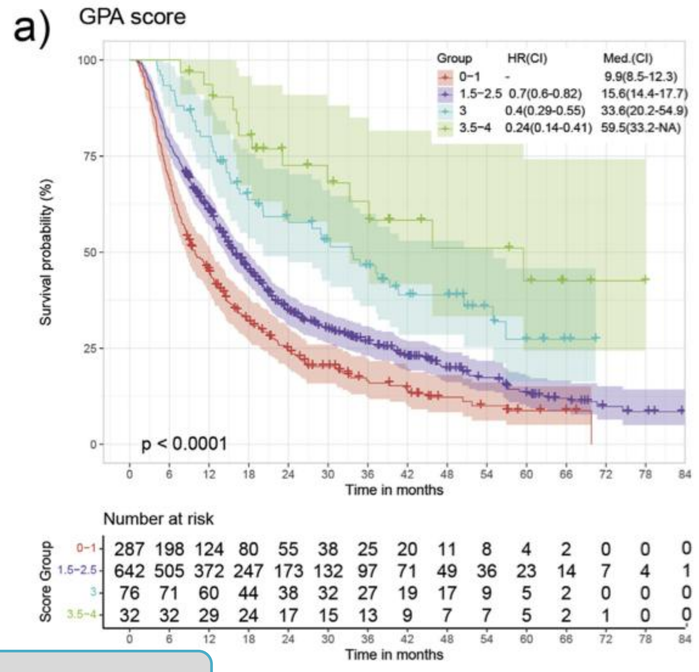
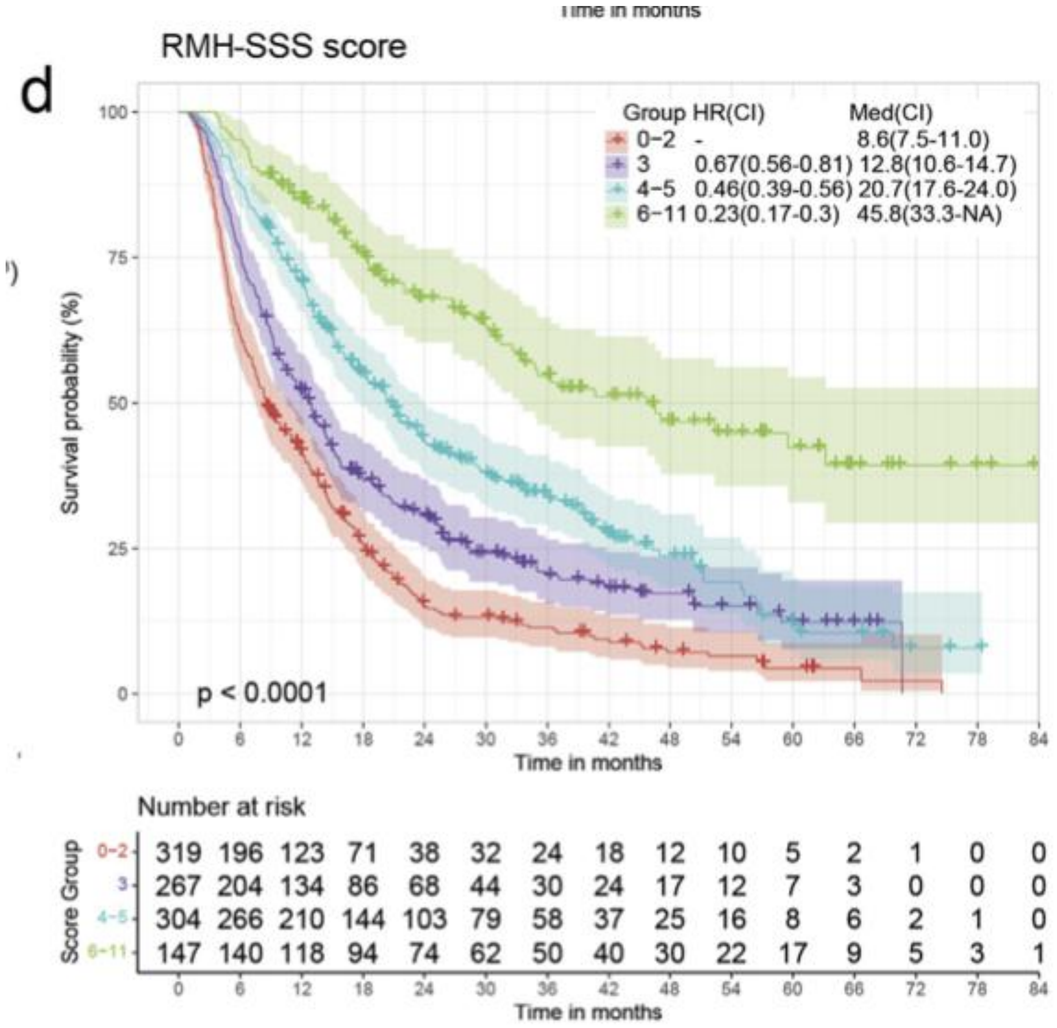


Inclusion of Total Brain Tumor Volume



Retrospective study

Ocaña-Tienda *et al. Cancer Imaging* (2024) 24:111
https://doi.org/10.1186/s40644-024-00753-0

Cancer Imaging

RESEARCH Open Access

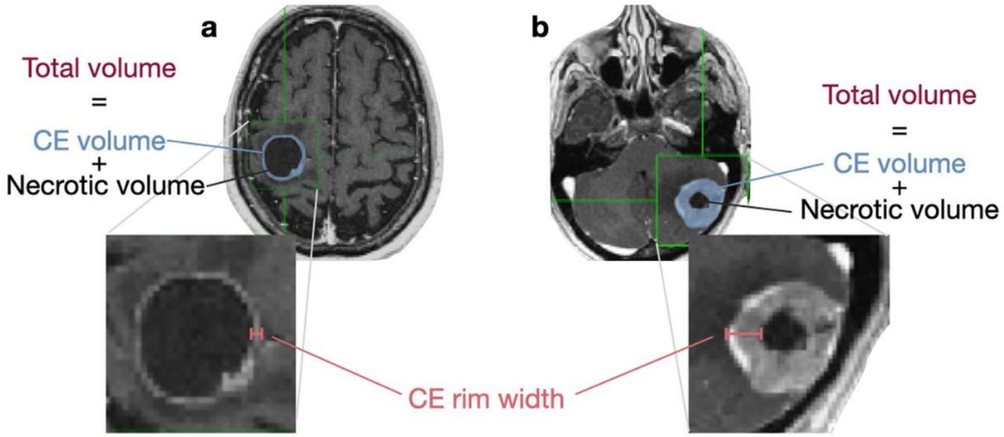
Morphological MRI features as prognostic indicators in brain metastases

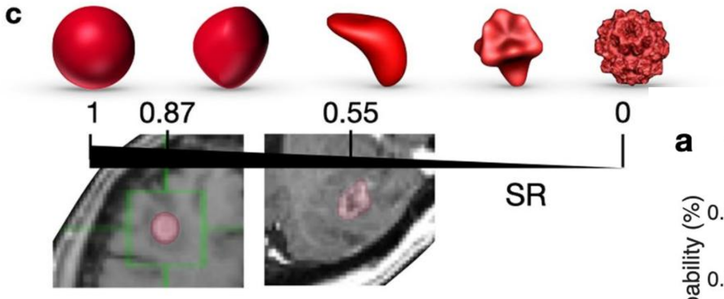
Beatriz Ocaña-Tienda[1*], Julián Pérez-Beteta[1], Ana Ortiz de Mendivil[2], Beatriz Asenjo[3], David Albillo[4], Luís A. Pérez-Romasanta[5], Manuel LLorente[4], Natalia Carballo[4], Estanislao Arana[6†] and Víctor M. Pérez-García[1†]

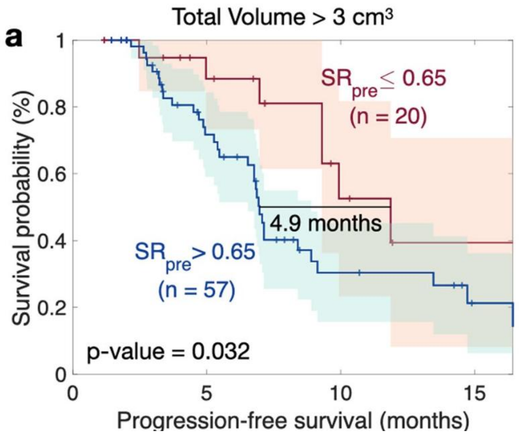
Table 3 Results of univariate Cox and Kaplan–Meier analyses of imaging biomarkers obtained from pre-treatment and post-treatment RM images

	Median difference (months)	Best threshold	*p* value	HR
Pre-treatment				
Total Volume (cm^3)	3.3	8.30	0.051	1.009 (0.984, 1.035)
Necrotic Volume (cm^3)	3.3	0.10	0.097	1.622 (0.909, 2.896)
Necrosis yes/no	-	-	0.682	0.896 (0.528, 1.520)
Surface Regularity	-	0.64	0.110	6.91 (0.257, 185.64)
Surface Regularity (> 3 cm^3)	4.9	0.65	0.032	2.384 (1.049, 5.422)
CE rim width (cm)	3.6	0.60	0.234	0.759 (0.481, 1.198)
Post-treatment				
Total Volume (cm^3)	8.6	1.17	$p < 0.001$	3.510 (2.199, 5.603)
Necrotic Volume (cm^3)	7.3	0.09	0.004	3.039 (1.932, 4.779)
Necrosis yes/no	6.4	-	0.021	1.919 (1.090, 3.379)
Surface Regularity	5.5	0.65	0.068	1.525 (0.965, 2.408)
CE rim width (cm)	5.1	0.49	$p < 0.001$	2.609 (1.661, 4.098)
Total Volume (post/pre)	7.4	0.50	$p < 0.001$	3.610 (2.268, 5.747)

HR Hazard Ratio, *CE* Contrast enhanced. *P* values correspond to the log rank test and data in parenthesis are 95% confidence intervals for the HR







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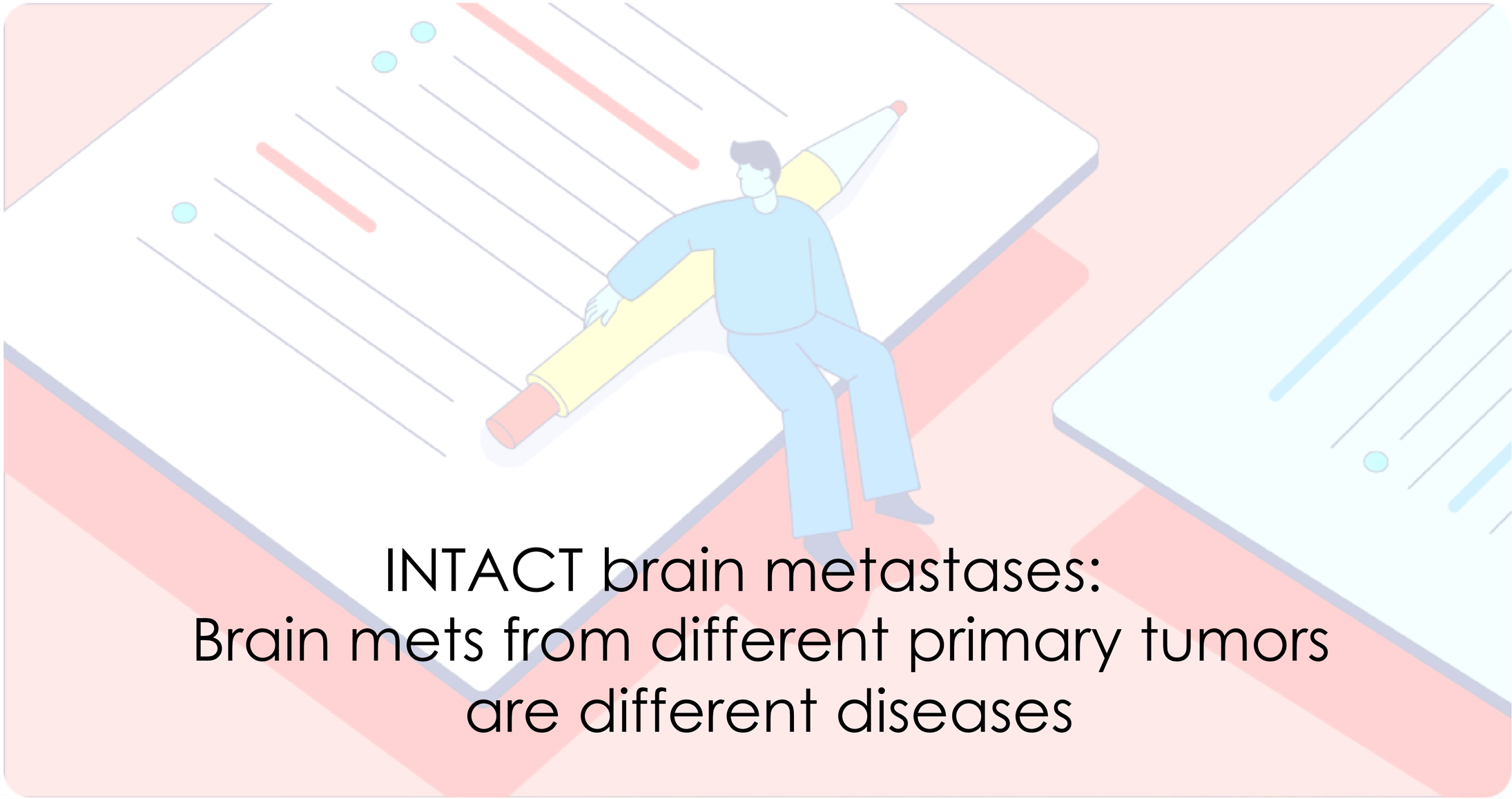
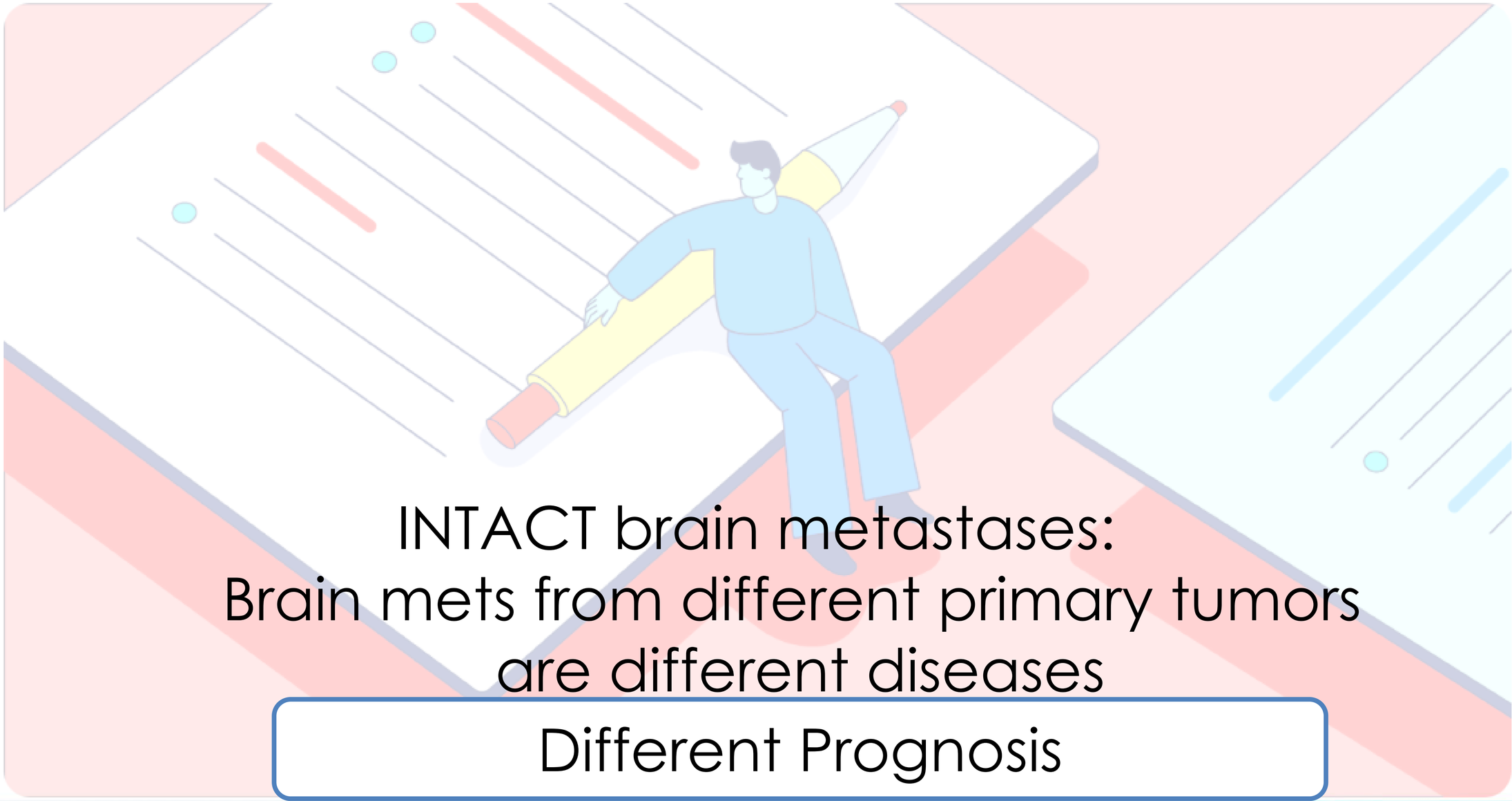
Retrospective study



INTACT brain metastases: Brain mets from different primary tumors are different diseases



INTACT brain metastases: Brain mets from different primary tumors are different diseases

Different Prognosis

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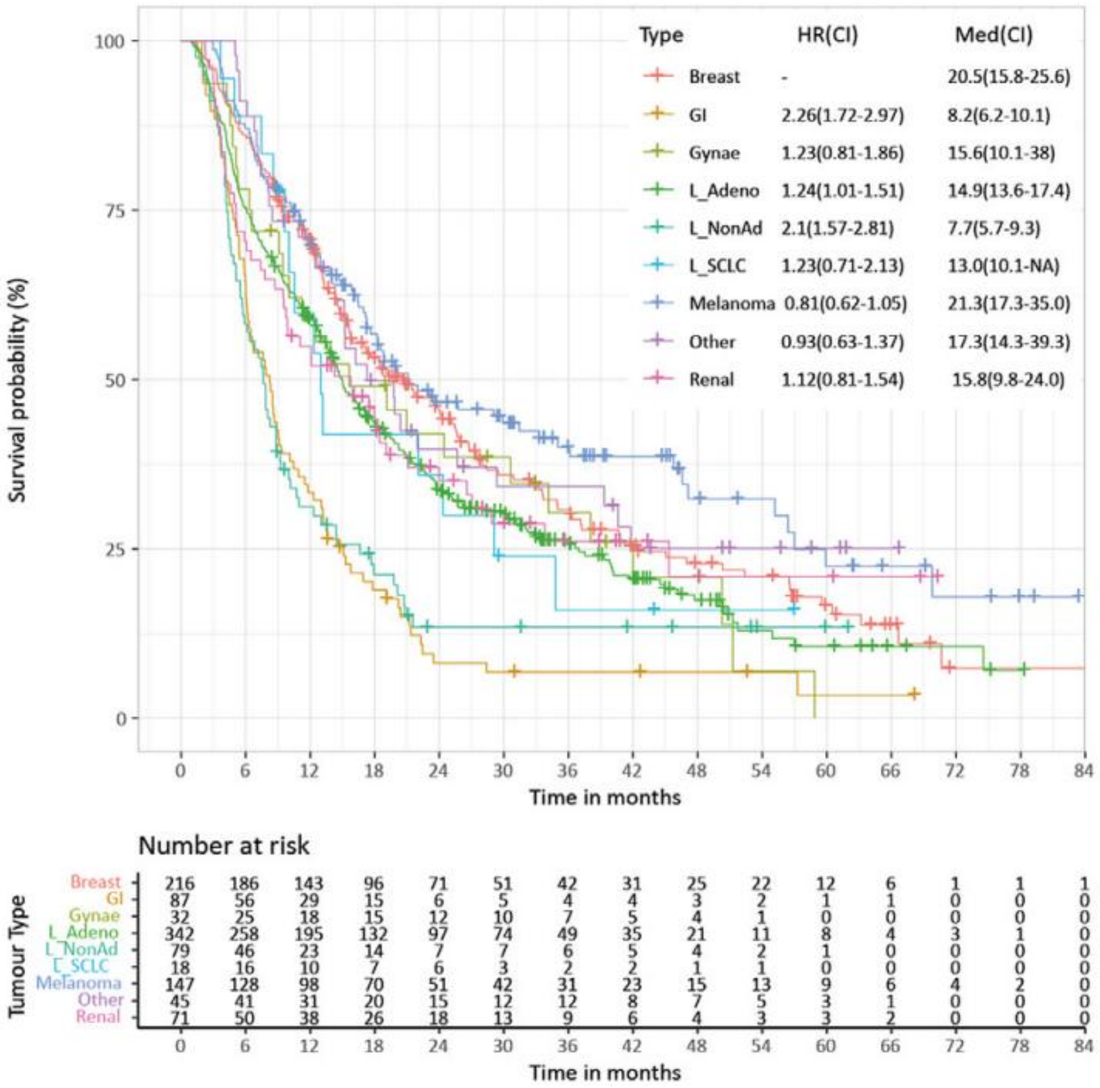
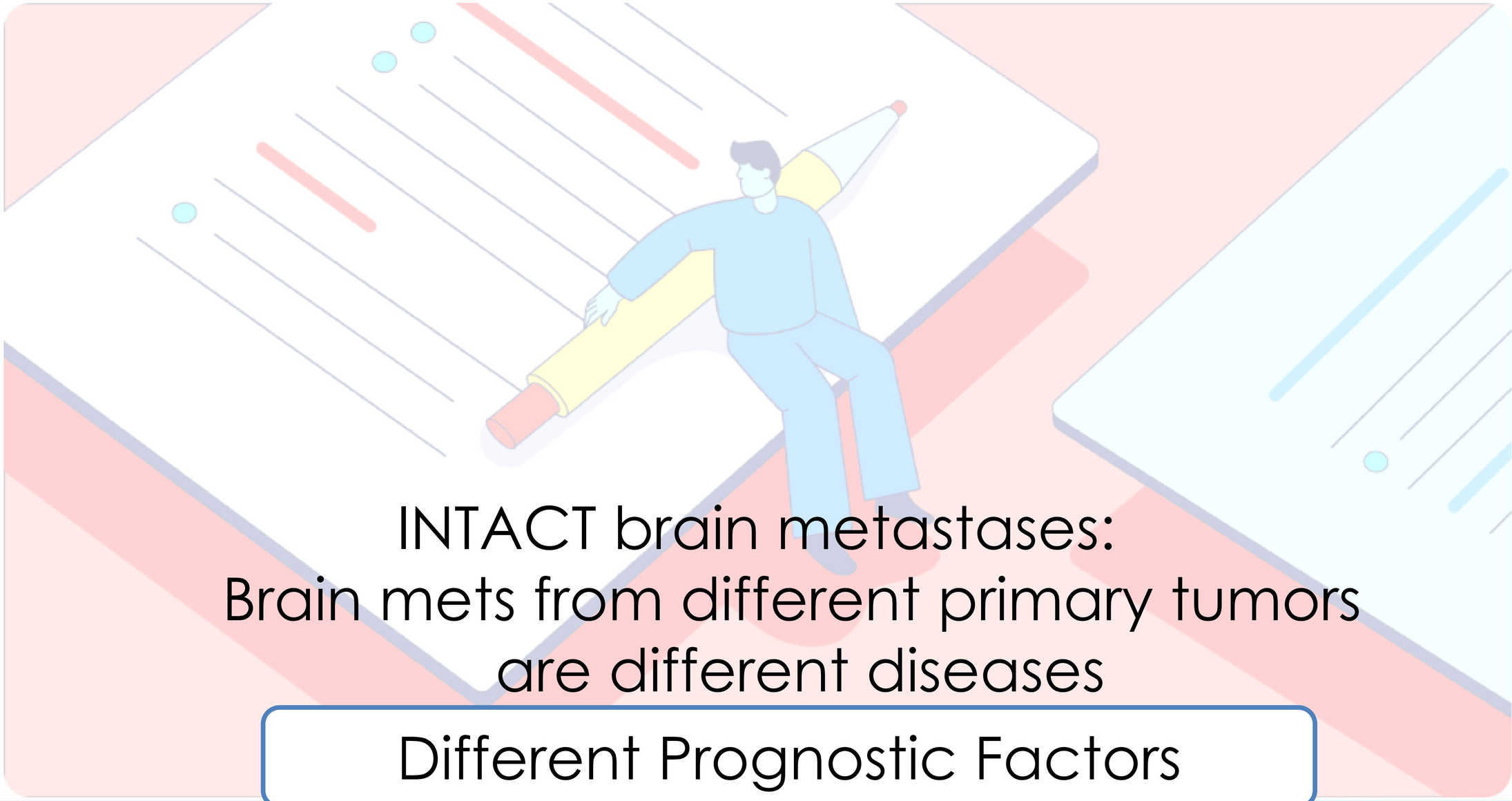


Retrospective study



INTACT brain metastases: Brain mets from different primary tumors are different diseases

Different Prognostic Factors

Kanakarajan *et al.*
BMC Medical Informatics and Decision Making (2024) 24:177
https://doi.org/10.1186/s12911-024-02579-z

BMC Medical Informatics and Decision Making

SYSTEMATIC REVIEW Open Access

Factors associated with the local control of brain metastases: a systematic search and machine learning application

Hemalatha Kanakarajan[1*], Wouter De Baene[1], Karin Gehring[1,3], Daniëlle B. P. Eekers[4], Patrick Hanssens[2,3] and Margriet Sitskoorn[1*]

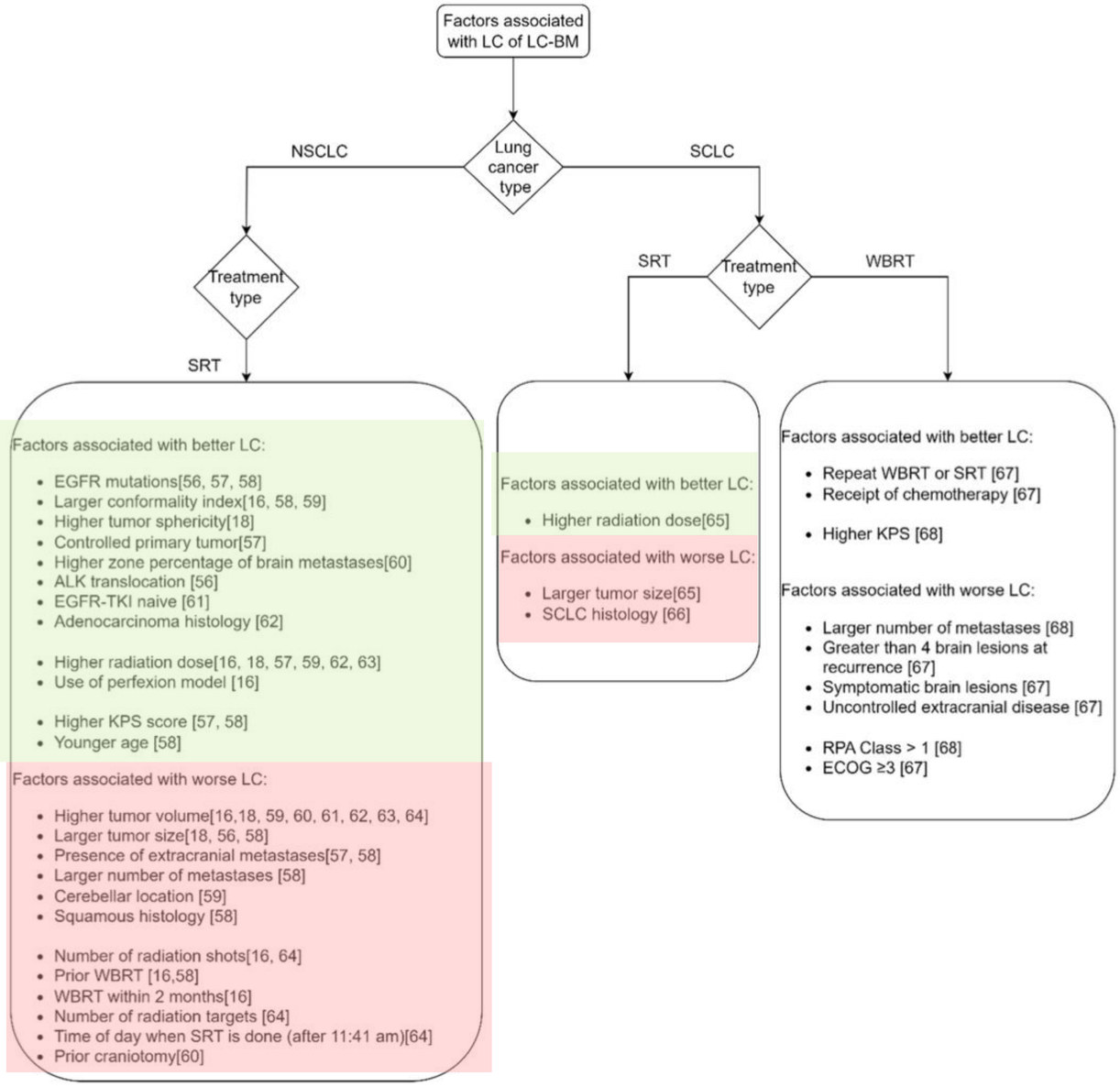


Fig. 2 The factors associated with LC of Lung cancer brain metastases

Review

Kanakarajan *et al.*
BMC Medical Informatics and Decision Making (2024) 24:177
https://doi.org/10.1186/s12911-024-02579-z

BMC Medical Informatics and Decision Making

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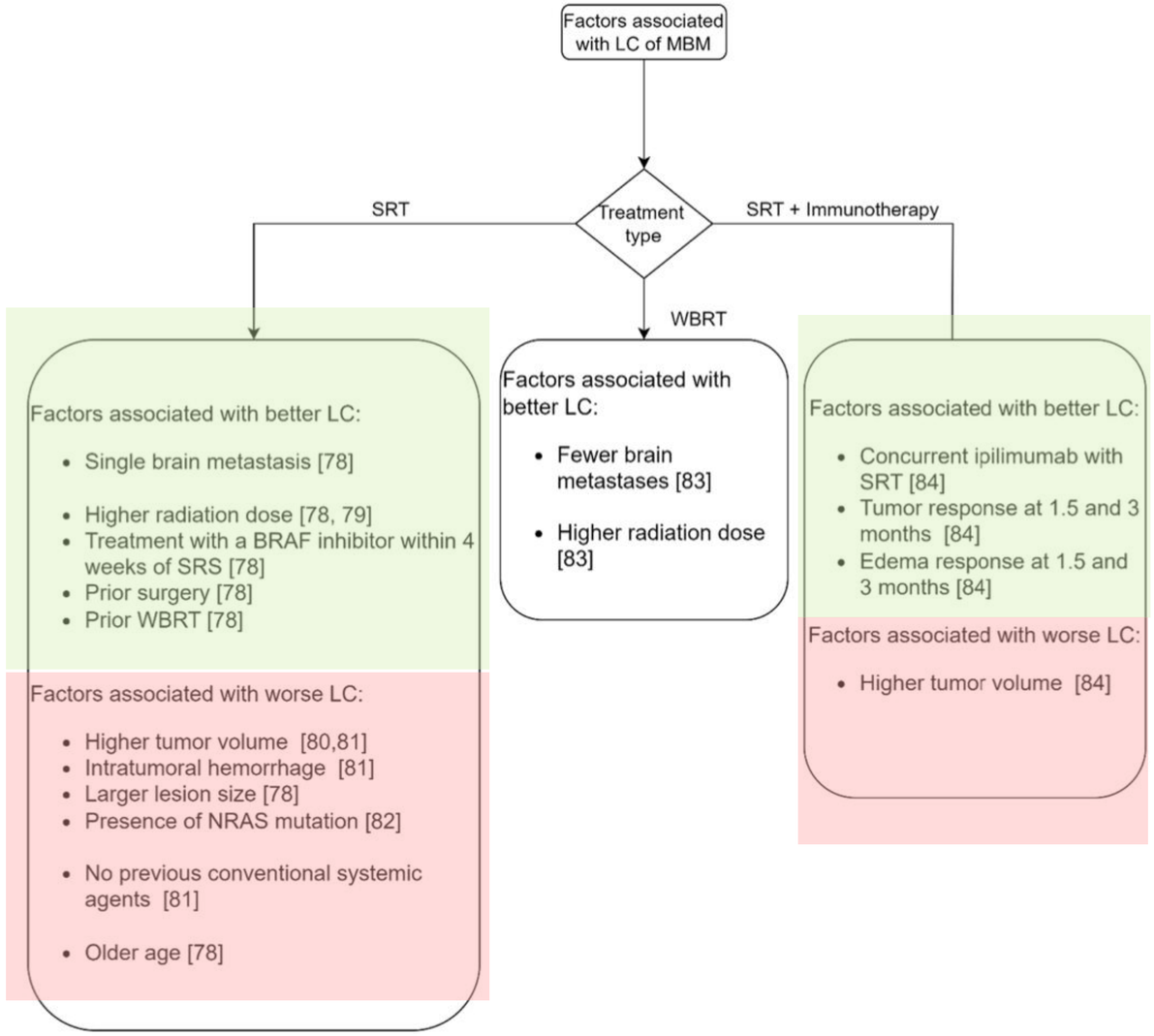


Fig. 4 The factors associated with LC of melanoma brain metastases

Kanakarajan *et al.*
BMC Medical Informatics and Decision Making (2024) 24:177
https://doi.org/10.1186/s12911-024-02579-z

BMC Medical Informatics and Decision Making

SYSTEMATIC REVIEW Open Access

Factors associated with the local control of brain metastases: a systematic search and machine learning application

Hemalatha Kanakarajan[1*], Wouter De Baene[1], Karin Gehring[1,3], Daniëlle B. P. Eekers[4], Patrick Hanssens[2,3] and Margriet Sitskoorn[1*]

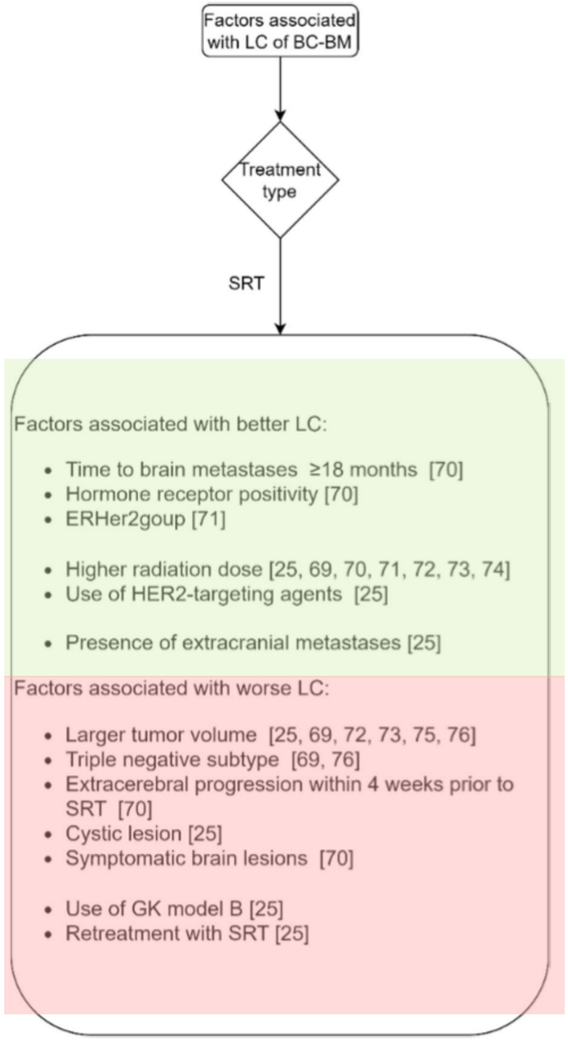
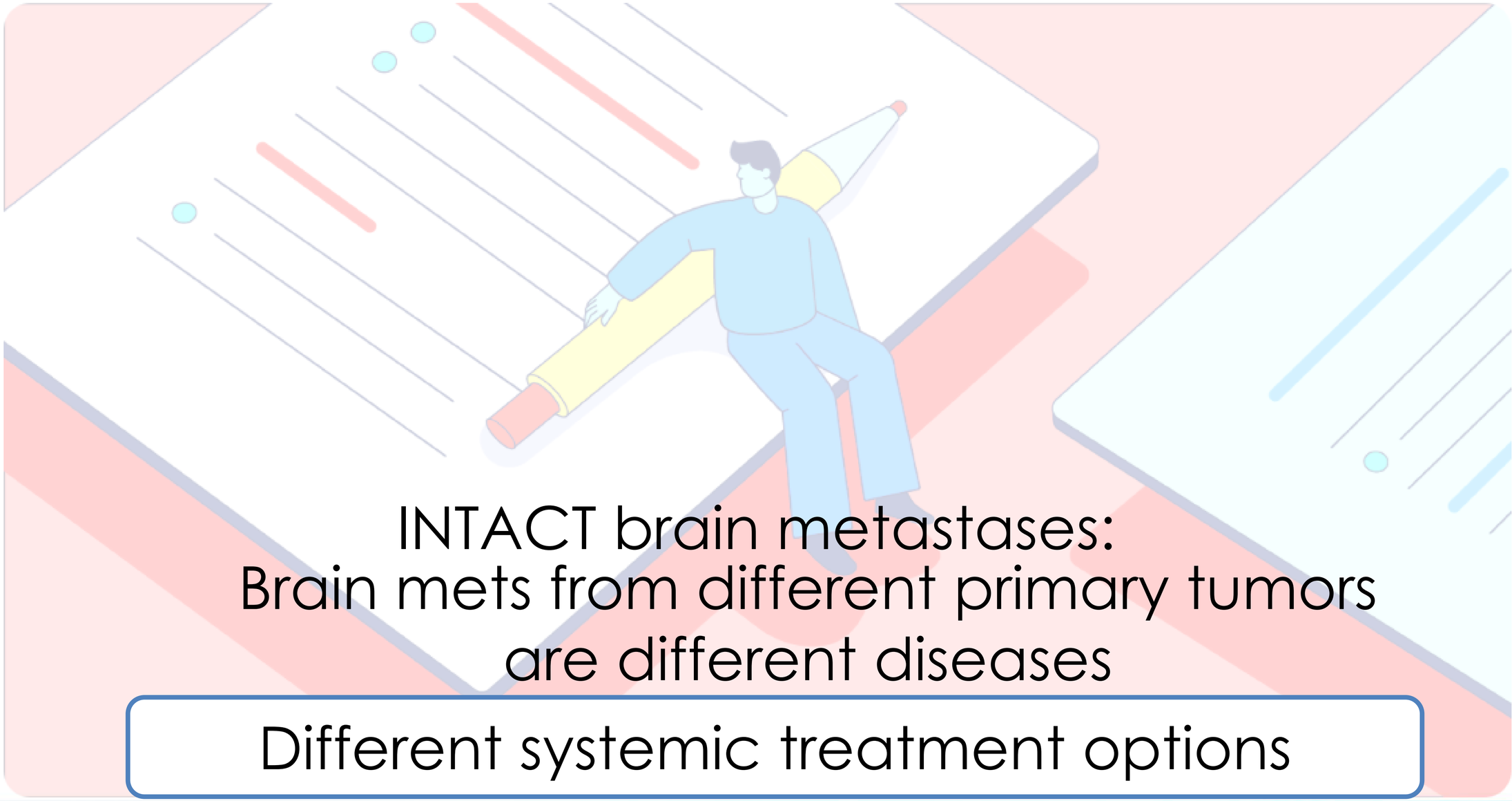


Fig. 3 The factors associated with LC of breast cancer brain metastases



INTACT brain metastases: Brain mets from different primary tumors are different diseases

Different systemic treatment options

Brain mets from Breast Cancer

CLINICAL RESEARCH: TUMOR

Long-term Survival From Breast Cancer Brain Metastases in the Era of Modern Systemic Therapies

Mashiach, Elad MS*; Alzate, Juan Diego MS, MD*; De Nigris Vasconcellos, Fernando MD*; Bernstein, Kenneth MS, DABR‡; Donahue, Bernadine R. MD‡; Schnurman, Zane MD, MBA*; Gurewitz, Jason DO‡; Rotman, Lauren E. MD*; Adams, Sylvia MD§,¶; Meyers, Marleen MD§,¶; Oratz, Ruth MD§,¶; Novik, Yelena MD§,¶; Kwa, Maryann J. MD§,¶; Silverman, Joshua S. MD, PhD‡; Sulman, Erik P. MD, PhD‡; Golfinos, John G. MD*; Kondziolka, Douglas MD, MSc, FRCS(C), FACS*

Author Information

Neurosurgery 94(1):p 154-164, January 2024. | *DOI:* 10.1227/neu.0000000000002640

n=190

OS: 17% @ 5y after SRS

Retrospective study

Long-term Survival from Breast Cancer Brain Metastases in the Era of Modern Systemic Therapies

Study Objective

- To characterize breast cancer patients with brain metastases (BCBM) that achieved long-term survival
- To find predictors of the causes of death of BCBM patients

Methods

We reviewed prospectively collected records of patients treated with SRS at our institution between 2012-2022.

190 Patients | 931 Tumors | 429 SRS Treatments

Outcomes

25 months median OS from initial SRS

130 months median OS from primary breast cancer

17% of patients achieved survival ≥ 5 years from SRS

Predictors of long-term survival

- Use of targeted therapy
- HER2+ receptor status

Cause of death

11% CNS-related mortality

0% CNS-related mortality in patients surviving ≥5 years

Predictor of CNS mortality

Leptomeningeal disease

Predictors of non-CNS mortality

Triple negative | KPS <80

Active systemic disease | Extracranial metastases

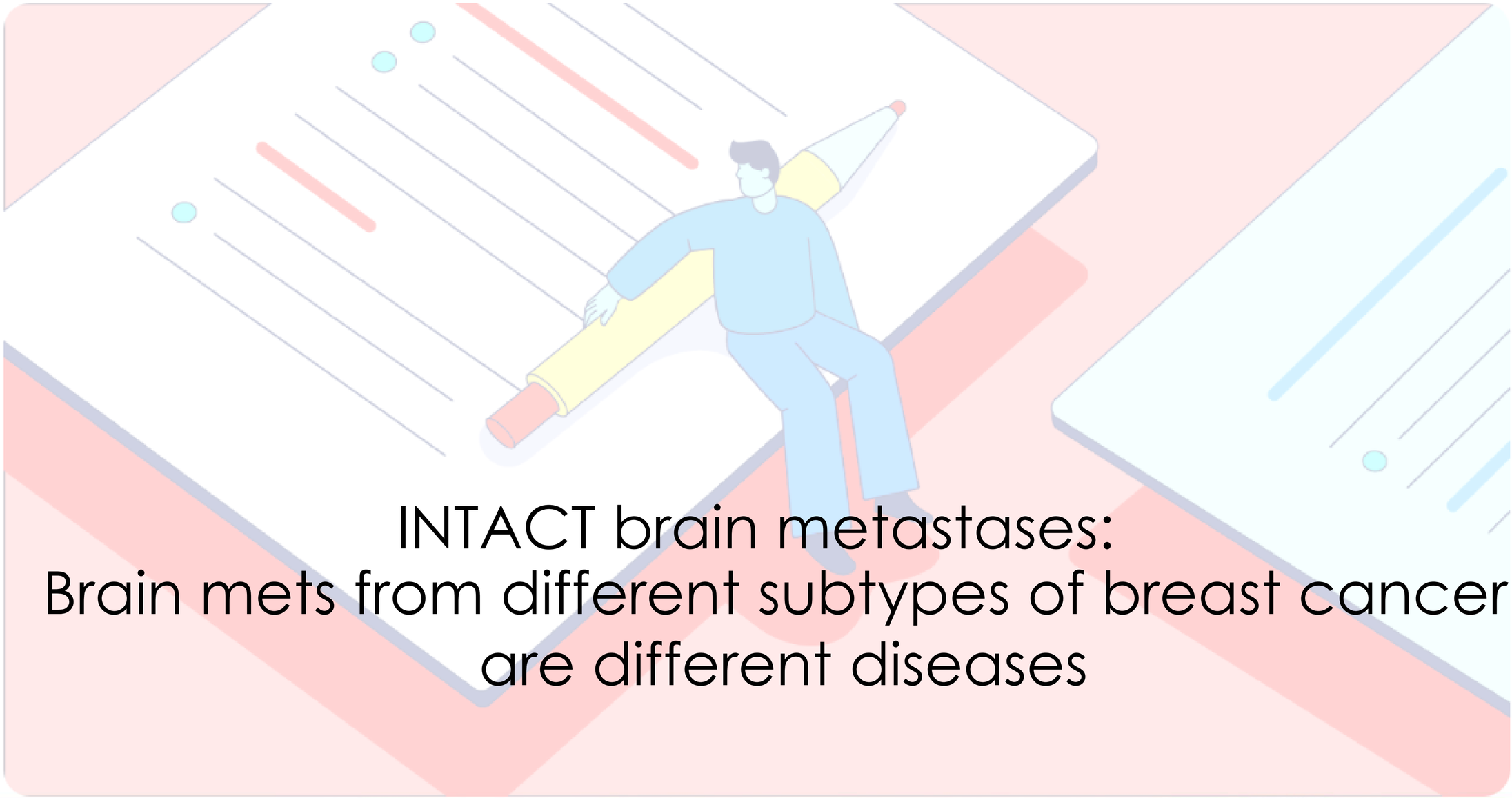
Conclusion

The use of targeted therapy and HER2+ status are associated with long-term survival. The primary causes of death were non-CNS related and none of the patients living ≥5 years died from CNS-related disease.

Neurosurgery

Mashiach et al.

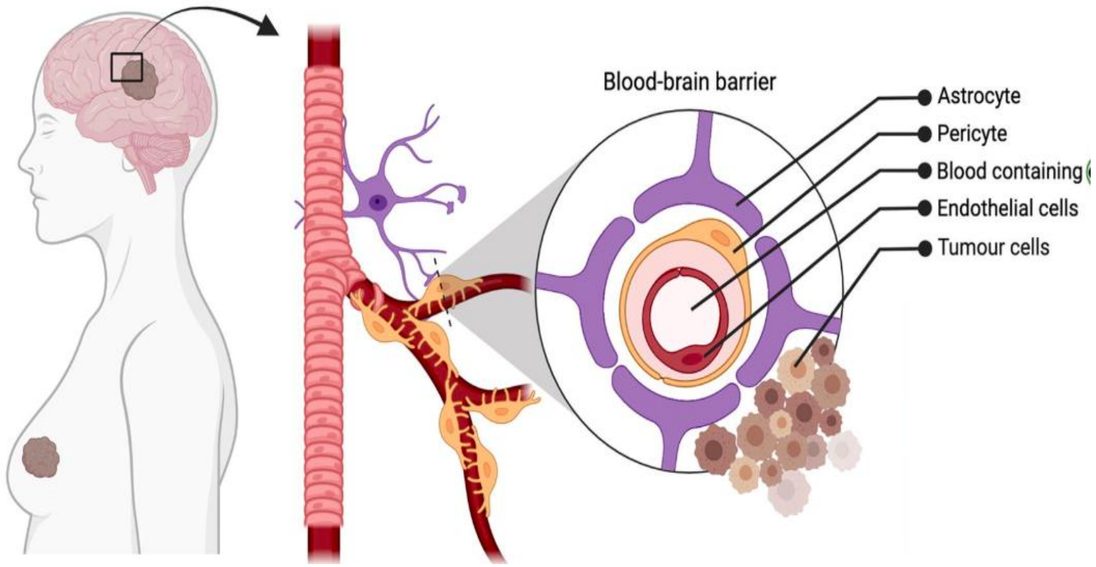
CONGRESS OF NEUROLOGICAL SURGEONS 1951 CNS



INTACT brain metastases: Brain mets from different subtypes of breast cancer are different diseases

Brain mets from different subtypes of breast cancer are different diseases

	HER2 +	TN	Luminal
BM diagnosis	Continuous over time	Early	Late
Control of extracranial disease at the time of diagnosis of BMs	Frequent	Uncommon	Variable
Leptomeningeal involvement	Less common	More frequent and early	Frequent but late
Posterior fossa	More common site	Less common	Less common
Median OS after BMs diagnosis	12 m	4 m	6 m



Survival analysis of patients with brain metastases at initial breast cancer diagnosis over the last decade

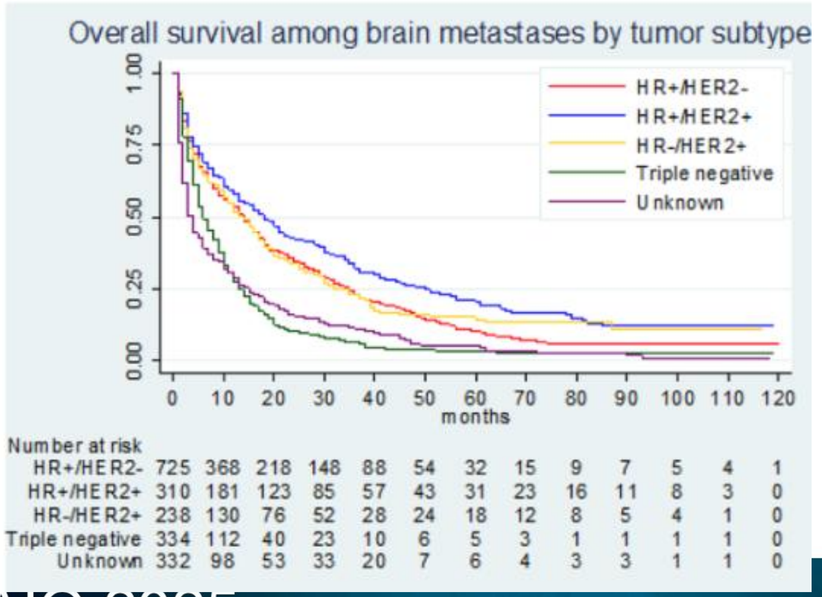
Research | Published: 07 March 2024

Volume 205, pages 579–587, (2024) Cite this article

Jorge Avila ✉, Julieta Leone, Carlos T. Vallejo, Nancy U. Lin & José P. Leone

n=1939

Retrospective study



HR+/HER2+

OS: 12,2% @ 8y

Results

1,939 patients with brain metastases at initial breast cancer diagnosis were included. Factors associated with this presentation were grade III/IV tumors, ductal histology, hormone receptor (HR)-negative/human epidermal growth factor receptor 2 (HER2)-positive subtype, and extracranial metastases. Patients with HR-positive/HER2-positive disease had the longest OS (median 18 months) and 12.2% were alive at 8 years. Factors associated with shorter OS included older age, lower income, triple-negative subtype, higher grade, and visceral metastases.

Conclusion

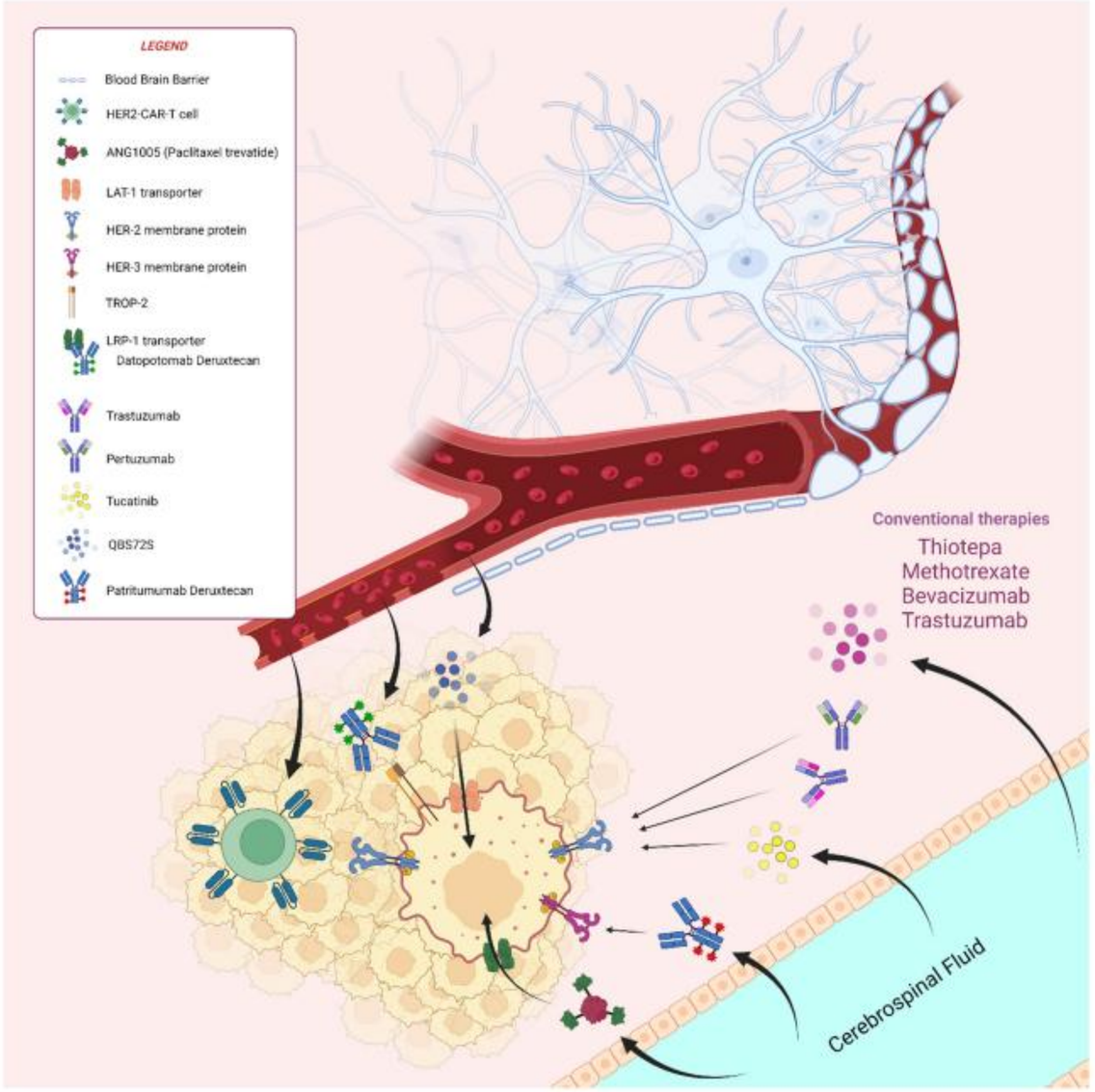
Over the last decade, the median OS of patients with brain metastases at initial breast cancer diagnosis remained poor; however, a substantial minority survive 5 or more years, with rates higher in patients with HER2-positive tumors. In addition to tumor subtype, OS varied according to age, extracranial metastases, and sociodemographic factors.

Review

Current Evidence in the Systemic Treatment of Brain Metastases from Breast Cancer and Future Perspectives on New Drugs, Combinations and Administration Routes: A Narrative Review

Ornella Garrone [1,*], Fiorella Ruatta [1], Carmen Giusy Rea [1], Nerina Denaro [1], Michele Ghidini [1], Carolina Cauchi [1], Claudia Bareggi [1], Barbara Galassi [1], Marco C. Merlano [2,†] and Roberto Rosenfeld [1,†]

Cancers **2024**, *16*, 4164. https://doi.org/10.3390/cancers16244164



Review

Brain metastases from HER2+ Breast Cancer

Nearly 50% of patients with advanced HER2-positive BC will eventually develop BMs, even in cases of absent or stable extracranial disease

Cancer Treatment Reviews 132 (2025) 102853

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

Expert recommendations on treatment sequencing and challenging clinical scenarios in human epidermal growth factor receptor 2-positive (HER2-positive) metastatic breast cancer

Rupert Bartsch [a], David Cameron [b], Eva Ciruelos [c,d], Carmen Criscitiello [e,f], Giuseppe Curigliano [e,f], Francois P Duhoux [g], Theodoros Foukakis [h,i], Joseph Gligorov [j], Nadia Harbeck [k], Nathalie LeVasseur [l], Alicia Okines [m,n], Frederique Penault-Llorca [o], Volkmar Müller [p,*]

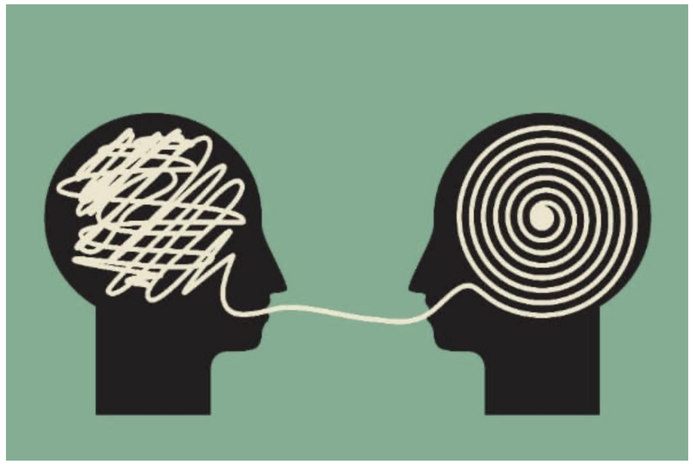
First	HR+	ChT contraindication	Trastuzumab (± pertuzumab) + ET
		No ChT contraindication	Trastuzumab + pertuzumab + taxane for ≥ 6 cycles followed by trastuzumab + pertuzumab + ET until progression
	HR–	ChT contraindication	Trastuzumab + pertuzumab until progression
		No ChT contraindication	Trastuzumab + pertuzumab + taxane for ≥ 6 cycles followed by trastuzumab + pertuzumab until progression
Second	No, unknown or stable brain metastases		T-DXd (preferred) T-DM1
	Active brain metastases†		Tucatinib + trastuzumab + capecitabine (preferred) T-DXd
Third	No, unknown or stable brain metastases		Tucatinib + trastuzumab + capecitabine T-DXd T-DM1
	Active brain metastases†		Tucatinib + trastuzumab + capecitabine
Later	No, unknown or stable brain metastases		Lapatinib + trastuzumab Trastuzumab + ChT Margetuximab + ChT‡ Neratinib + ChT‡
	Active brain metastases†		T-DXd Lapatinib + trastuzumab Trastuzumab + ChT Margetuximab + ChT‡ Neratinib + ChT‡

Expert recommendations

Systemic treatmente for BM from HER2+ Breast Cancer

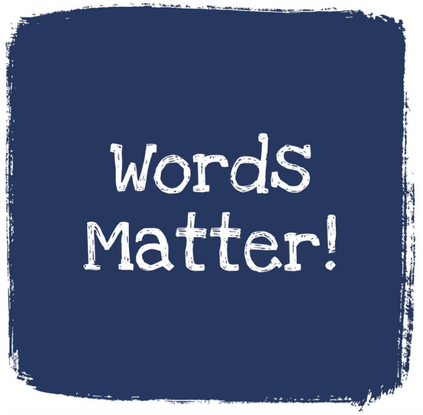
			RT-treated
Emilia trial	T-DM1	Retrospective analysis of BM pts	70%
Kamilla trial	T-DM1	Exploratory final analysis	38%
Tuxedo-1 trial	T-Dxd	Single arm phase II	60%
Roset-BM	T-Dxd	Retrospective	95%
HER2CLIMB Trial	Tucatinib Trastuzumab Capecitabine	Ph III	77.8%
Debbrah trial	T-Dxd	Single arm phase II	36%

Untreated or treated BM
SRS/SRT or WBRT
Active or Stable BM

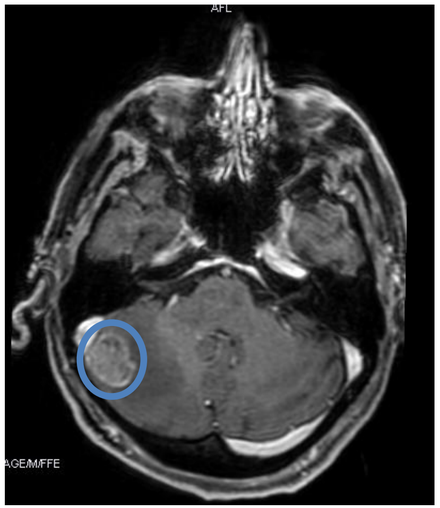


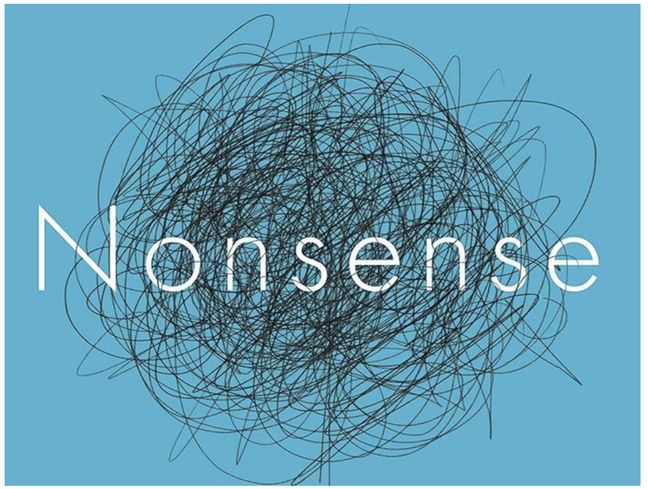
BMs are classified as **stable**

- if stabilized at least 14 days after local therapy
- if the patient does not need anti-convulsive or corticosteroid therapy

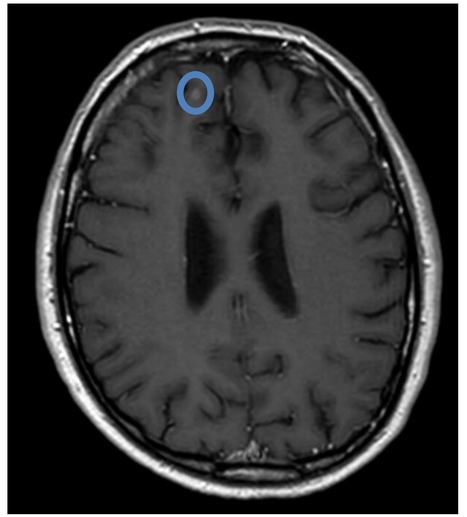


This BM, if treated with SRS, may be classified as **stable**





This BM may be classified as **active**



GENERAL SESSION ABSTRACTS | MAY 02 2024

Abstract GS01-10: HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer FREE

Sara Hurvitz; Sherene Loi; Joyce O'Shaughnessy; Alicia Okines; Sara Tolaney; Joo Hyuk Sohn; Cristina Saura; Xiaofu Zhu; David Cameron; Thomas Bachelot; Erika Hamilton; Giuseppe Curigliano; Antonio Wolff; Nadia Harbeck; Norikazu Masuda; Linda Vahdat; Khalil Zaman; Frances Valdes-Albini; Margaret Block; Timothy Pluard; Tira Tan; Chelsea Gawryletz; Arlene Chan; Philippe Bedard; Rinat Yerushalmi; Binghe Xu; Konstantinos Tryfonidis; Michael Schmitt; Joan Xie; Virginia Borges

n=463

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)
Stage at initial diagnosis, n (%)[b]		
0-III	120 (52.6)	130 (55.3)
IV	103 (45.2)	98 (41.7)

Total	463
Brain mets	44%
Treated/Stable Brain mets	20.9%

HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy were allowed on study

N=460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

T-DM1 + Tucatinib
T-DM1 3.6 mg/kg IV and Tucatinib 300 mg PO BID

T-DM1 + Placebo
T-DM1 3.6 mg/kg IV and Placebo PO BID

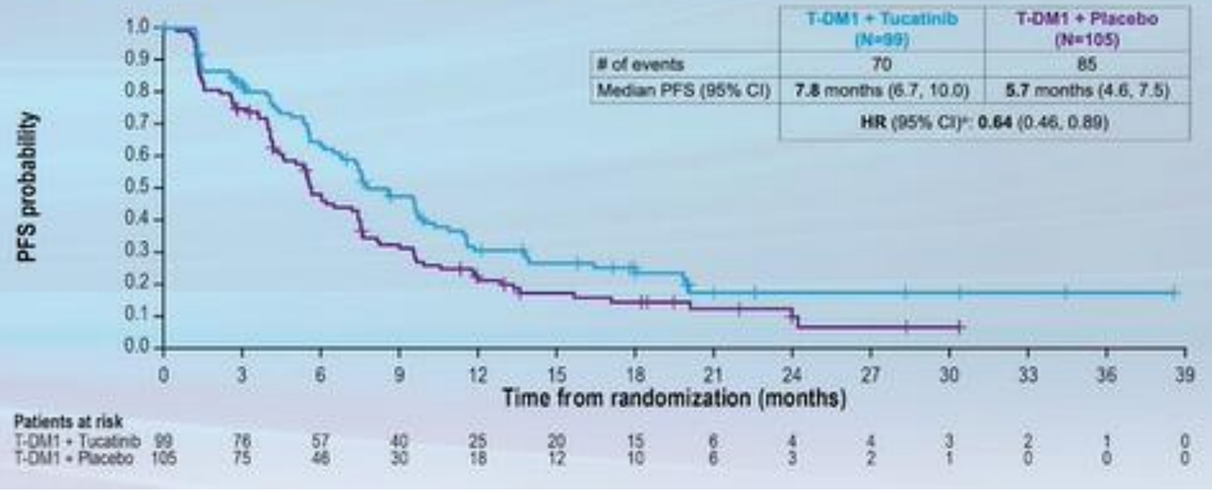
Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

The primary analysis for PFS was planned after ~331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.[b]

PFS in Patients with Brain Metastases



	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	7.8 months (6.7, 10.0)	5.7 months (4.6, 7.5)
HR (95% CI)[a]: 0.64 (0.46, 0.89)		

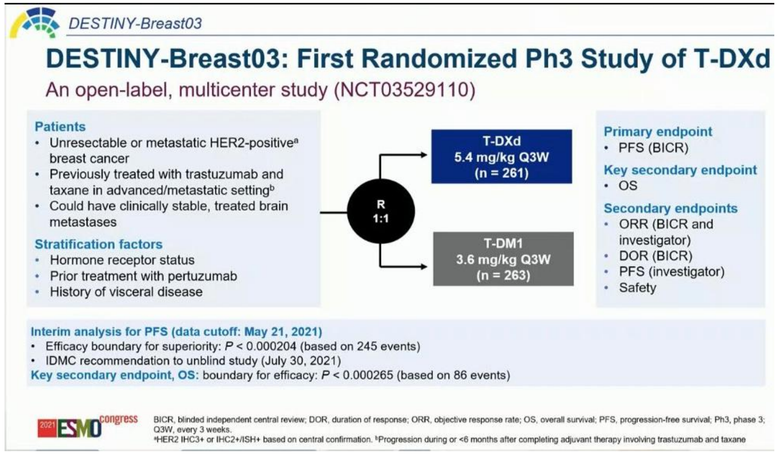
- This is the second randomized study which included patients with brain metastases to demonstrate that a tucatinib-containing regimen delays disease progression in HER2+ LA/MBC

Phase III trial

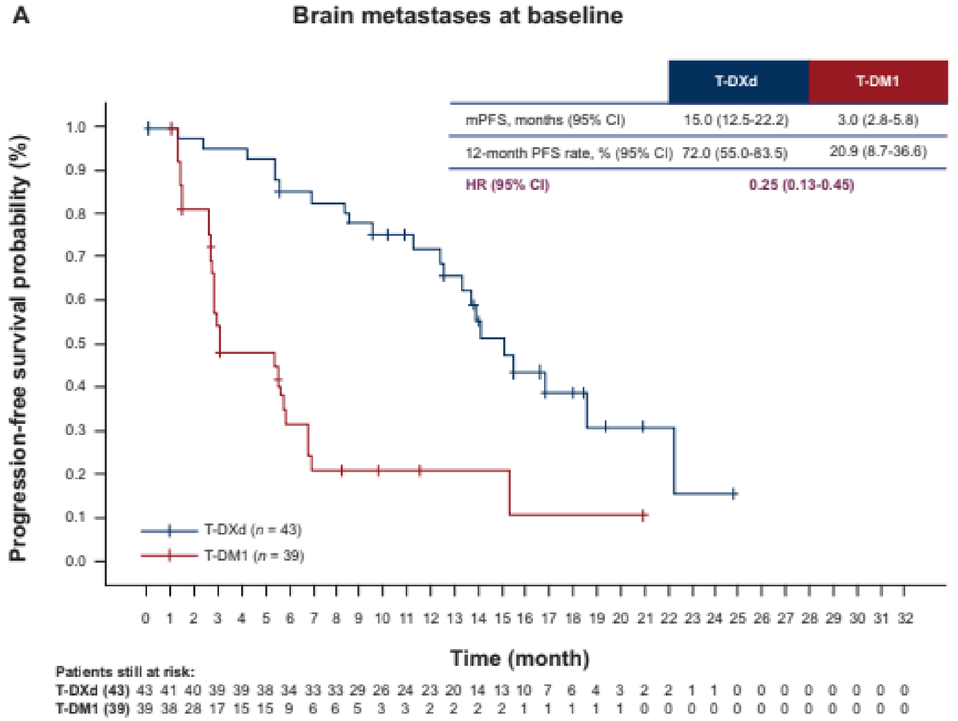
Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial

S. A. Hurvitz[1,†], S.-B. Kim[2], W.-P. Chung[3], S.-A. Im[4], Y. H. Park[5], R. Hegg[6], M.-H. Kim[7], L.-M. Tseng[8], V. Petry[9], C.-F. Chung[10], H. Iwata[11], E. Hamilton[12], G. Curigliano[13,14], B. Xu[15], A. Egorov[16], Y. Liu[17], J. Cathcart[16], E. Bako[18], K. Tecson[17], S. Verma[19] & J. Cortés[20,21,22]

BM from HER2 + BC



n=82



n=82

Prior treatment for BMs:
T-DXd group: 53,5%
T-DM1 group: 51.3%

Time since prior RT to the brain:
T-DXd group: 1.6 m
T-DM1 group: 3.4 m

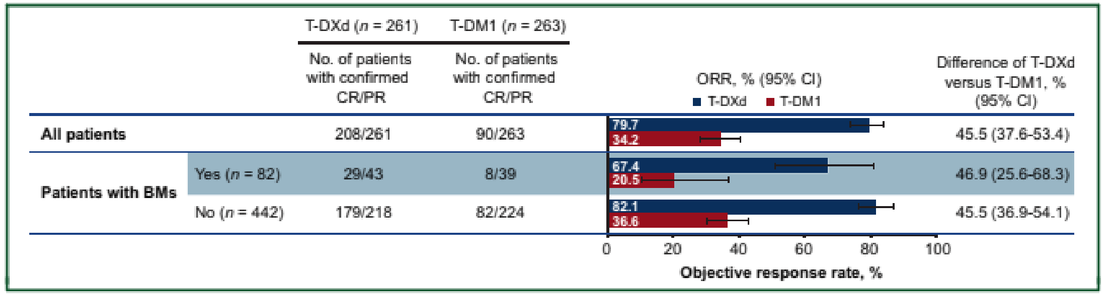


Figure 2. Confirmed systemic ORR in patients with and without BMs.
BMs, brain metastases; CR, complete response; ORR, objective response rate; PR, partial response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Phase III trial

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

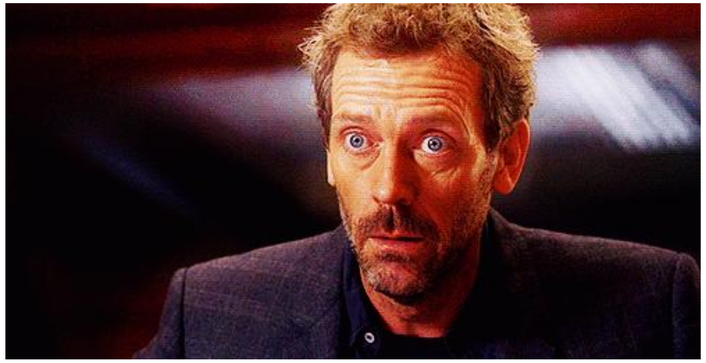
The efficacy of sacituzumab govitecan and trastuzumab deruxtecan on stable and active brain metastases in metastatic breast cancer patients—a multicenter real-world analysis

D. Dannehl[1*], D. Jakob[2], F. Mergel[3], A. Estler[4], T. Engler[1], L. Volmer[1], M.-L. Frevert[2], S. Matovina[1], A. Englisch[1], C. M. Tegeler[1], A. Rohner[1], A. Seller[1], M. Hahn[1], K. Pfister[3], A. Fink[3], I. Popp[5], S. Lorenz[6], G. Tabatabai[7], I. Juhasz-Böss[2], W. Janni[3], S. Brucker[1], F.-A. Taran[2], A. Hartkopf[1,3] & H. Schäffler[3]

Volume 9 ■ Issue 5 ■ 2024 https://doi.org/10.1016/j.esmoop.2024.102995

n=26;
Sacituzumab Govitecan: n=12;
Trastuzumab Deruxtecan: n=16
Active BM: 10 out of 26

Median intracranial PFS:
SG = 2.7 months
T-DXd =11.2 months



Retrospective study

SG and T-DXd showed promising clinical activity in both stable and active BCBMs

EDITORIAL

ESMO Open Volume 9 ■ Issue 5 ■ 2024

Antibody–drug conjugates are active in patients with HER2-positive breast cancer brain metastases: where do we go from here?

S. Sammons[1,2,3] & N. U. Lin[1,2,3]*

T-DXd in the second line for patients with extracranial progression who have stable BrMs with **low brain metastasis velocity**, or those with small asymptomatic/untreated lesions.

Tucatinib/capecitabine/trastuzumab for patients with previously treated but progressive lesions and those with **high brain metastasis velocity**

Editorial

The Breast 76 (2024) 103742

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

"Positioning of tucatinib in the new clinical scenario of HER2-positive metastatic breast cancer: An Italian and Spanish consensus paper"

Pierfranco Conte [a], Eva Ciruelos [b,c,d], Giuseppe Curigliano [e,f], Michelino De Laurentiis [g], Lucia Del Mastro [h,i], Alessandra Gennari [j], Antonio Llombart [k,l], Miguel Martìn [m], Francesca Poggio [h,*], Aleix Prat [n,o,p,q,r], Fabio Puglisi [s,t], Cristina Saura [u]

Expert recommendations

3.2 - Currently, from a sequencing perspective, the standard of treatment in the metastatic setting is: taxane/trastuzumab/pertuzumab -> T-Dxd -> trastuzumab/tucatinib/capecitabine	0	2	22	30	26	80
	3%		**98%**			100%
2.4 - Tucatinib has the most robust data from the registration trial regarding treatment efficacy of patients with active brain metastases	1	1	24	30	24	80
	3%		**98%**			100%

Home > Journal of Neuro-Oncology > Article

Impact of concurrent antibody–drug conjugates and radiotherapy on symptomatic radiation necrosis in breast cancer patients with brain metastases: a multicenter retrospective study

Research | Published: 22 April 2024
Volume 168, pages 415–423, (2024) Cite this article

n=67

Koide et al JNO 2024	ADC (T-DM1 or T-DXd)	RT within 4 w before or after systemic treatment	2y-Symptomatic RN 27% vs 7%

Among the 168 pts,
48 received ADC,
19 had concurrent ADC
33% had previous BM radiation

The groups with and without concurrent ADC had 5 SRNs in 19 patients and 13 SRNs in 149

Radionecrosis: G2 n=11; G3 n=7

Retrospective study

Brain metastases from HER2 LOW Breast Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Incidence and outcome of brain and/or leptomeningeal metastases in HER2-low metastatic breast cancer in the French ESME cohort

N. Epaillard[1,*], A. Lusque[2], W. Jacot[3], A. Mailliez[4], T. Bachelot[5], M. Arnedos[6], F. Le Du[7], E. Brain[8], J. M. Ferrero[9], V. Massard[10], I. Desmoulins[11], M. A. Mouret-Reynier[12], C. Levy[13], A. Gonçalves[14], M. Leheurteur[15], T. Petit[16], T. Filleron[2], L. Bosquet[17], B. Pistilli[1,18] & J. S. Frenel[19]

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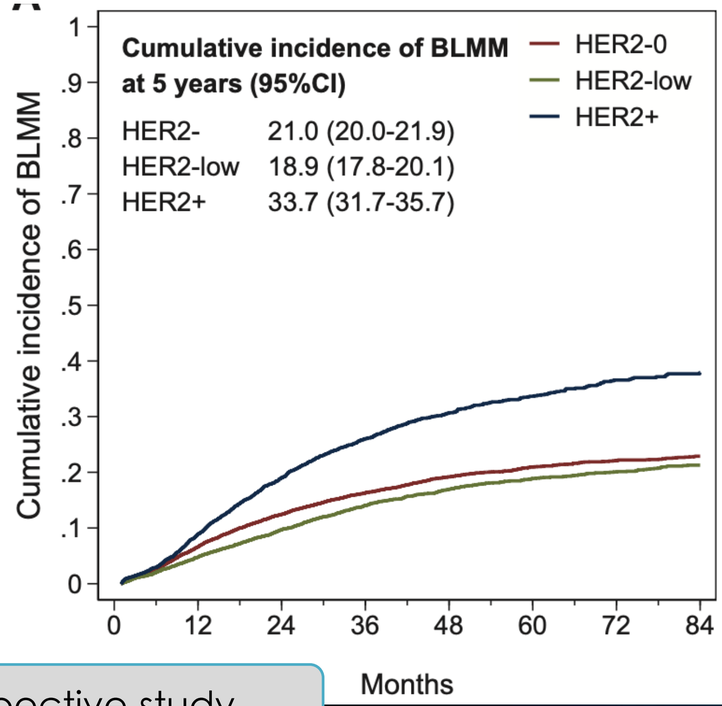


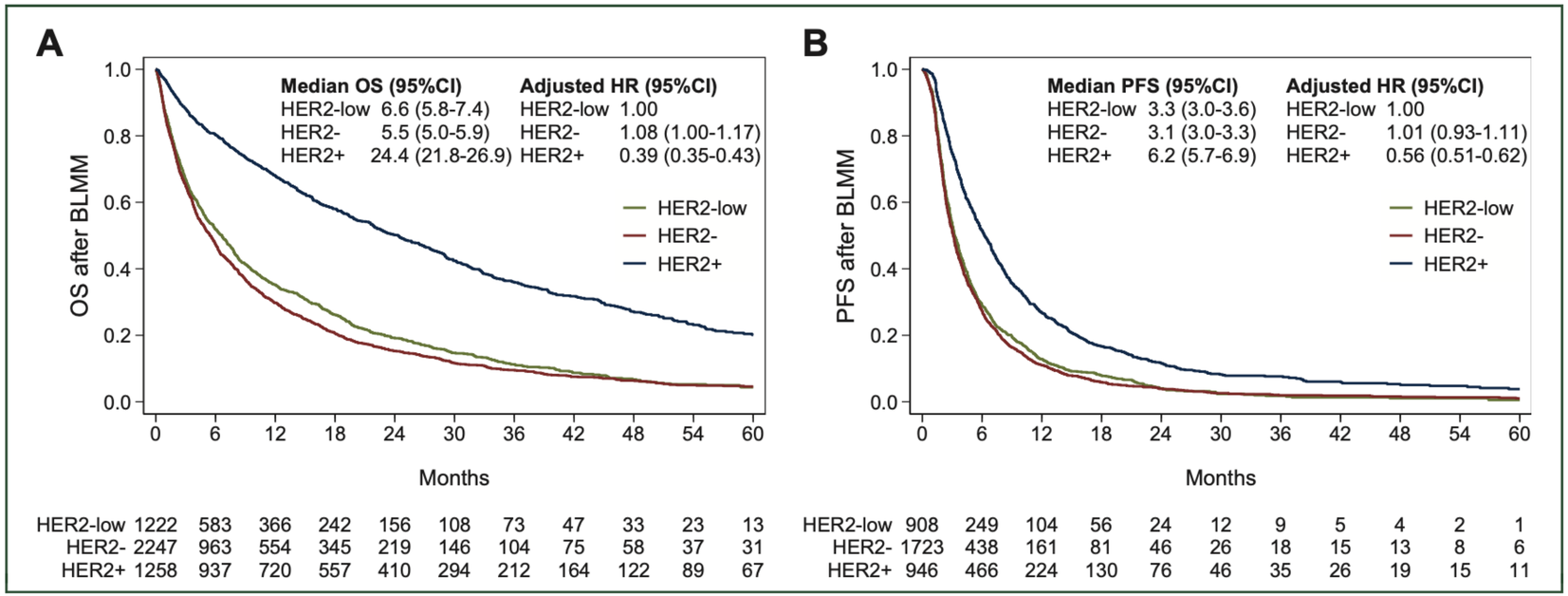


Figure 2. Progression-free survival and overall survival after dBLMM by HER2 status. (A) Overall survival and (B) progression-free survival after BLMM by HER2 status.

CI, confidence interval; dBLMM, diagnosis of brain and leptomeningeal metastases; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

19585 patients

Retrospective study

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

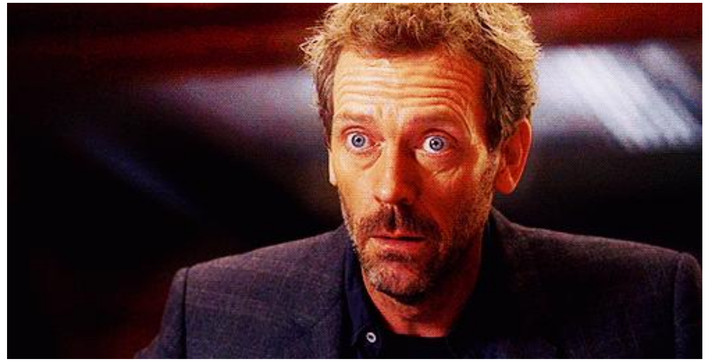
Trastuzumab deruxtecan in patients with previously treated HER2-low advanced breast cancer and active brain metastases: the DEBBRAH trial

M. Vaz Batista[1,2†], J. M. Pérez-García[2,3†], P. Cortez[4], L. Garrigós[3,5], M. Fernández-Abad[6,7], M. Gion[6], A. Martínez-Bueno[5], C. Saavedra[6], I. Teruel[8], A. Fernandez-Ortega[8], S. Servitja[10], M. Ruiz-Borrego[11], J. de la Haba-Rodríguez[12], G. Martrat[2], J. Pérez-Escuredo[2], D. Alcalá-López[2], M. Sampayo-Cordero[2], S. Braga[1], J. Cortés[2,3,13*] & A. Llombart-Cussac[2,14,15*]

[1]Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal; [2]Medica Scientia Innovation Research (MEDSIR) — Oncoclínicas & Co, Jersey City, USA, Sao Paulo, Brazil; [3]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona; [4]IOB Institute of Oncology, Hospital Ruber Internacional, Quiron Group, Madrid; [5]Hospital Universitari Dexeus, Barcelona; [6]Medical Oncology Department, Hospital Ramon y Cajal, Madrid; [7]Alcalá de Henares University, Faculty of Medicine, Madrid; [8]Institut Català d'Oncologia Badalona (ICO), Badalona, Barcelona; [9]Institut Català d'Oncologia L'Hospitalet (ICO), L'Hospitalet de Llobregat, Barcelona; [10]Hospital del Mar, Barcelona; [11]Hospital Universitario Virgen del Rocío, Seville; [12]Instituto Maimonides de Investigacion Biomedica, Hospital Reina Sofia, Universidad de Córdoba, Córdoba; [13]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid; [14]Hospital Arnau de Vilanova, FISABIO, Valencia; [15]Universidad Católica de Valencia, Valencia, Spain

Volume 9 ■ Issue 9 ■ 2024

https://doi.org/10.1016/j.esmoop.2024.103699

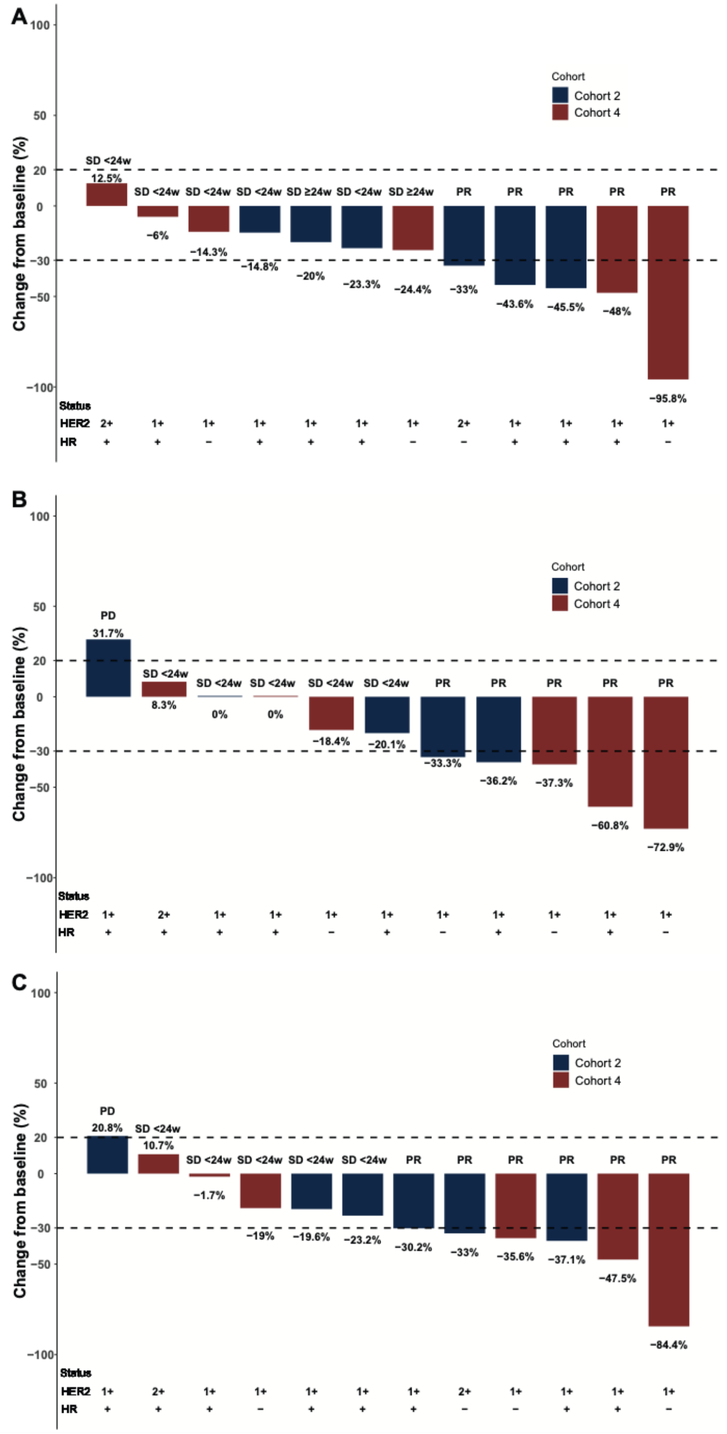


Phase II study HER2 + and HER2 low patients

n=12 HER2 low pts
(n=6 asymptomatic and untreated
and n=6 progressing BM after local treatment)

T-DXd demonstrated promising intracranial activity in pretreated HER2-low BC patients with active BMs

Phase II Study



Brain metastases from TN Breast Cancer

Breast Cancer (2024) 31:572–580
https://doi.org/10.1007/s12282-024-01565-7

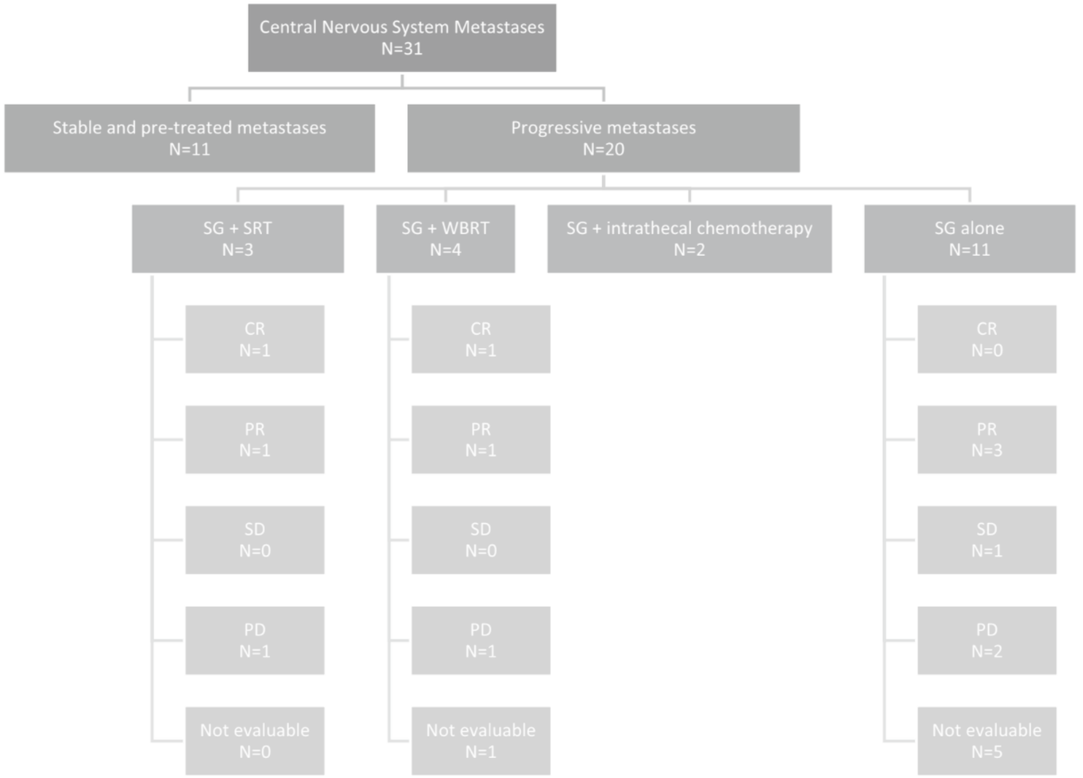
ORIGINAL ARTICLE

Check for updates

Sacituzumab govitecan in metastatic triple-negative breast cancer patients treated at Institut Curie Hospitals: efficacy, safety, and impact of brain metastases

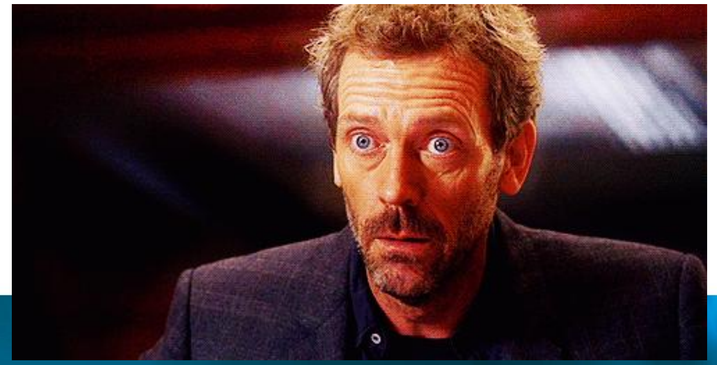
Alexandre De Moura[1] · Delphine Loirat[1] · Sarah Vaillant[2] · Sinen Korbi[1] · Nicolas Kiavue[1,3] · Diana Bello Roufai[1] · Laurence Escalup[2] · Romain Desmaris[2] · Pauline Vaflard[1] · Paul Cottu[1] · Jean-Yves Pierga[1,4] · François-Clément Bidard[1,3] · Luc Cabel[1] · Alexandre Acramel[2,5]

n=31



Among patients with brain metastases,
- median PFS 3.7 months (95%CI[2.6–6.2])
- median OS 6.7 months (95%CI[6.3–NR])

The observed response rate and safety of SG are consistent with the results of the ASCENT trial, with efficacy observed in patients with brain metastases



Retrospective study

The Breast 76 (2024) 103757

Contents lists available at ScienceDirect

The Breast

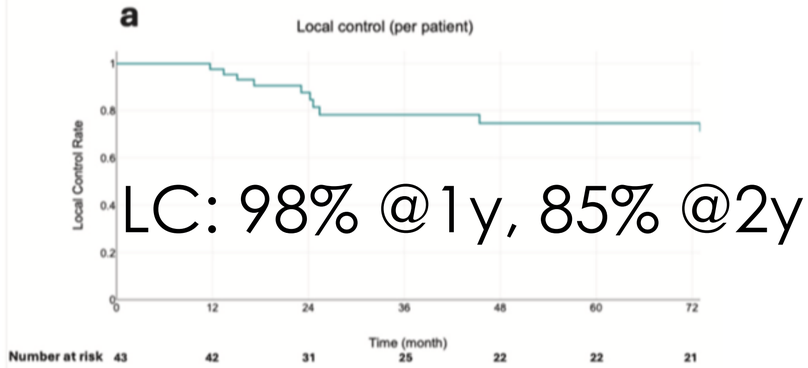
journal homepage: www.journals.elsevier.com/the-breast

Comprehensive analysis of stereotactic Radiosurgery outcomes in triple-negative breast cancer patients with brain metastases: The influence of immunotherapy and prognostic factors☆

Menekse Turna [a,*], Berna Akkus Yıldırım [b], Çakır Numanoglu [b], Mustafa Halil Akboru [b], Rashad Rzazade [a], Hale Başak Çağlar [a]

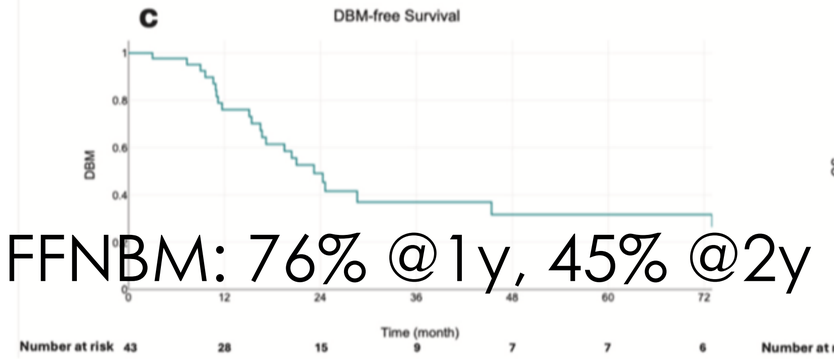
[a] Anadolu Medical Center, Department of Radiation Oncology, Gebze, KOCAELI, Turkey
[b] Cemil Taşcıoğlu Şehir Hastanesi, Radyasyon Onkolojisi Kliniği, İstanbul, Turkey

Retrospective Study
n=43, 129 lesions

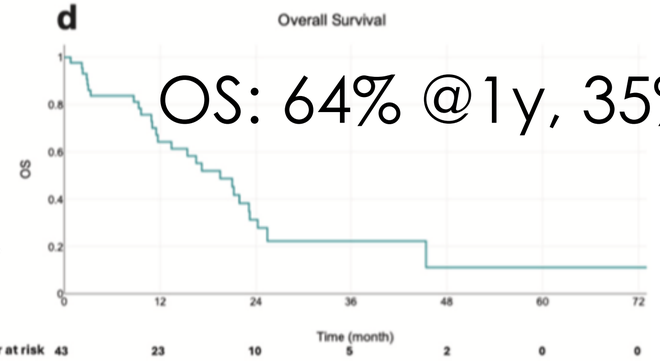


LC: 98% @1y, 85% @2y

median local PFS = 17.9 months
median distant PFS = 10 months
Median OS = 19.5 months

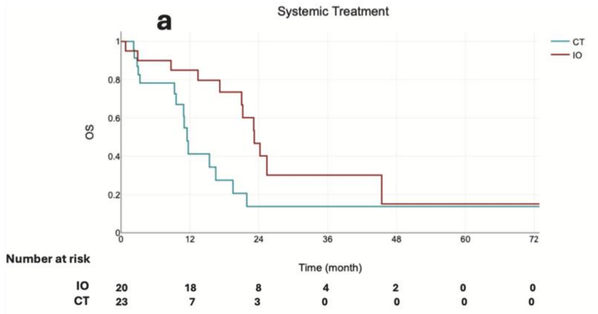


FFNBM: 76% @1y, 45% @2y



OS: 64% @1y, 35% @2y

Kaplan–Meier curves depicting **a** local control (per patient), **b** local control (per lesion) **c** distant brain control, **d** overall survival from the date ofster-radiation.



Retrospective study

FFNBM= Freedom from New Brain Mets

Studio AIRO GdS Neuro-oncologico

Raccolta retrospettiva di pazienti affette da metastasi encefaliche da tumore mammario trattate con SRT in associazione alle nuove terapie farmacologiche

RaBBIT-NEW study

Radiosurgery for
Breast cancer
Braln Me**T**astases
+ **NEW** drugs

Centro coordinatore
SOC Radioterapia
OSMA, Firenze

Strahlentherapie und Onkologie (2024) 200:259–275
https://doi.org/10.1007/s00066-024-02202-0

REVIEW ARTICLE

DEGRO guideline for personalized radiotherapy of brain metastases and leptomeningeal carcinomatosis in patients with breast cancer

Kai J. Borm[1] · Sophie T. Behzadi[1] · Juliane Hörner-Rieber[2] · David Krug[3] · Rene Baumann[4] · Stefanie Corradini[5] · Marciana Nona Duma[6,7] · Jürgen Dunst[3] · Gerd Fastner[8] · Petra Feyer[9] · Rainer Fietkau[10] · Wulf Haase[11] · Wolfgang Harms[12] · Thomas Hehr[13] · Christiane Matuschek[14] · Marc D. Piroth[15] · Leonard Christopher Schmeel[16] · Rainer Souchon[17] · Vratislav Strnad[10] · Wilfried Budach[14] · Stephanie E. Combs[1,18,19] on behalf of Breast Cancer Expert Panel of the German Society of Radiation Oncology DEGRO

Received: 3 January 2024 / Accepted: 7 January 2024 / Published online: 15 March 2024

- Limited brain metastases ($n = \leq 4$):
  - Local therapy including SRS/SRT is generally recommended irrespective of molecular subtype and systemic therapy.
  - In case of limited intact BCBM ($n = \leq 4$), SRS/SRT should be used.
  - After resection with a limited number of remaining BCBM ($n = \leq 4$), SRS/SRT to the resection cavity should be used as postoperative treatment with additional SRS/SRT of the intact BCBM.

- Multiple brain metastases:
  - SRS should be considered in case of $n = 5–10$ intact BCBM (cumulative volume < 15 ml); alternatively, WBRT can be applied.
  - After resection of BCBM and limited further BCBM ($n = 5–10$ and < 15 ml), SRS/SRT to the resection cavity and remaining intact BCBM is a possible option. Alternatively, WBRT can be applied.
  - In disseminated brain metastases ($n = > 10$), WBRT is generally recommended.
  - After interdisciplinary discussion, in cases of asymptomatic disseminated brain metastases ($n = > 10$) or in multiple BCBM if SRS/SRT is not feasible, WBRT can be postponed with early reassessment and reevaluation of local treatment options (8–12 weeks) if HER2-targeted systemic therapy with significant response rates in the CNS (tucatinib/trastuzumab/capecitabine, trastuzumab deruxtecan) is being used.

- Leptomeningeal carcinomatosis:
  - In symptomatic leptomeningeal carcinomatosis, local radiotherapy (WBRT/involved-field SRS/SRT or local spinal irradiation) should be administered to symptomatic lesions in addition to systemic therapy.
  - In case of patients with disseminated leptomeningeal carcinomatosis in good clinical condition and with limited, stable extra-CNS disease, CSI may be considered.

- Concurrent systemic therapy:
  - There is a general lack of data regarding the combination of systemic therapy and SRS/SRT for brain metastases.
  - Each case should be discussed individually in an interdisciplinary setting based on the type of systemic therapy, size and location of the metastases, as well as planned dose and fractionation.
  - Particular caution should be taken when administering SRS/SRT concurrently (≤ 7 days before or ≤ 21 days after) with antibody drug–conjugates.

Guidelines

Brain mets from different subtypes of breast cancer have different systemic treatment options but data for radiotherapy withdrawal are still immature

Reviews

Breast Cancer Brain Metastasis: A Comprehensive Review

Akshara S. Raghavendra, MD, MS[1] and Nuhad K. Ibrahim, MD, FACP[1]

DOI https://doi.org/10.1200/OP.23.00794

JCO Oncol Pract 20:1348-1359

All subtypes:
8 out of 12 trials include SRS/SRT

HR+ HER2-:
0 out of 2 trials include SRS/SRT

Review

TABLE 3. Ongoing Clinical Trials Focused on Breast Cancer Brain Metastasis Including Various Subpopulations

NCT Identifier	Phase	Treatment	Biomarkers
All subtypes			
NCT03807765	I	SBRT + nivolumab	All subtypes
NCT03449238	I/II	SRS + pembrolizumab	All subtypes
NCT03697343	III	FSRT *v* comparison with single session radiosurgery in patients with larger brain metastases (2-4 cm)	All subtypes
NCT05703269	III	SSRS *v* FSRS	All subtypes
NCT03075072	III	Hippocampal sparing WBRT *v* SRS with 5-20 BMs	All subtypes
NCT04899908	II	SRS ± AGuIX gadolinium-based nanoparticles	All subtypes
NCT05222620	II	SRS *v* FSRS—FRACTIONATE trial	All subtypes
NCT03550391	III	SRS *v* HA-WBRT plus memantine for ≥5 more BMS	All subtypes
NCT04030507	II	Preventive: Screening MRI of the brain in MBCs	All subtypes
NCT05115474	II	Screening brain MRIs in stage IV breast cancer	All subtypes
NCT04420598	II	T-DXd	All subtypes
NCT03994796	II	Genetic testing in guiding treatment for patients with BMs	All subtypes
HR+ HER2−			
NCT04791384	Ib/II	Elacestrant and abemaciclib	HR+/HER2−
NCT05293964	I	SCR-6852, palbociclib	HR+/HER2−

Reviews

Breast Cancer Brain Metastasis: A Comprehensive Review

Akshara S. Raghavendra, MD, MS[1] and Nuhad K. Ibrahim, MD, FACP[1]

DOI https://doi.org/10.1200/OP.23.00794

JCO Oncol Pract 20:1348-1359

HER2+:
1 out of 19 trials include SRS/SRT

HER2-:
1 out of 5 trials include SRS/SRT

HER2+			
NCT03933982	II	Pyrotinib + vinorelbine	HER2+
NCT04639271	II	Pyrotinib + trastuzumab + Nab paclitaxel	HER2+
NCT05042791	II	Concomitant SBRT pyrotinib + capecitabine	HER2+
NCT01494662	II	Preoperative neratinib with or without capecitabine or T-DM1	HER2+
NCT04760431	II	THP *v* TH + TKI (neratinib or tucatinib; HER2BRAIN)	HER2+
NCT05323955	II	HP or T-DM1 + tucatinib	HER2+
NCT05593094	I	ZN-A-1041 or ZN-A-1041 combination	HER2+
NCT04512261	II	Tucatinib + trastuzumab + pembrolizumab (TOPAZ)	HER2+
NCT04739761	III	T-DXd	HER2+
NCT04760431	II	THP *v* TH-pyrotinib	HER2+
NCT04509596	I	DZD1516 with capecitabine or T-DM1	HER2+
NCT05018702	II	ARX788	HER2+
NCT04539938	II	T-DXd, tucatinib	HER2+
NCT03190967	I/II	Metronomic temozolomide and T-DM1	HER2+
NCT03765983	II	Paxalisib (GDC-0084) + trastuzumab	HER2+
NCT04348747	II	Anti-HER2/HER3 dendritic cell vaccine ID, celecoxib, interferon alfa-2b followed by pembrolizumab	HER2+
NCT03714243	NA	HIFU (ExAblate BBBD)	HER2+
NCT04582968	I/II	SRS or WBRT and pyrotinib + capecitabine	HER2+
NCT04158947	II	Afatinib, T-DM1	HER2+
HER2−			
NCT03328884	II	MM-39 (phenomenal)	HER2−
NCT04965064	II	Pyrotinib, capecitabine	HER2−
NCT04647916	II	Sacituzumab govitecan	HER2−

Reviews

Breast Cancer Brain Metastasis: A Comprehensive Review

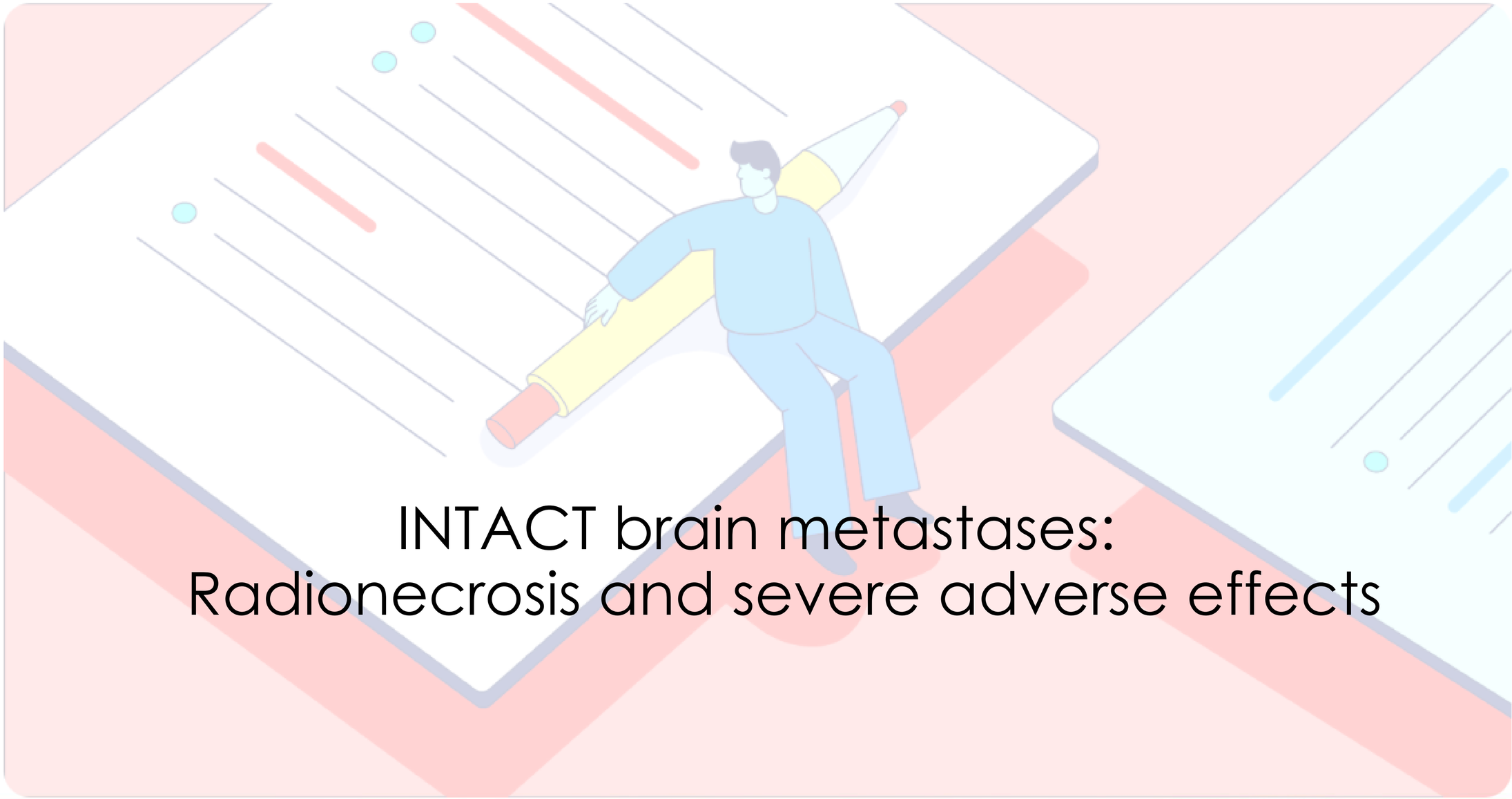
Akshara S. Raghavendra, MD, MS[1] and Nuhad K. Ibrahim, MD, FACP[1]

DOI https://doi.org/10.1200/OP.23.00794

JCO Oncol Pract 20:1348-1359

TN:
3 out of 12 trials include SRS/SRT

NCT Identifier	Phase	Treatment	Biomarkers
NCT04923542	II	SRS + abemaciclib/ET	HER2−
NCT01770353	I	MM-398 (nanoliposomal irinotecan)	HER2−
TNBC			
NCT04348747	II	Anti-HER2/HER3 dendritic cell vaccine ID, celecoxib, interferon alfa-2b followed by pembrolizumab	TNBC
NCT03995706	I	Sacituzumab govitecan	TNBC
NCT02574455	III	ASCENT study, sacituzumab govitecan	TNBC
NCT05255666	II	Nal-IRI, pembrolizumab	TNBC
NCT03483012	II	SBRT + atezolizumab	TNBC
NCT04434560	II	Nivolumab + ipilimumab	TNBC
NCT03483012	II	Atezolizumab + stereotactic radiation	TNBC
NCT03761914	I/II	Galinpepimut-S + pembrolizumab	TNBC
NCT04303988	II	SHR-1316 + bevacizumab + cisplatin/carboplatin	TNBC
NCT04789668	I/II	Bintrafusp alfa + pimasertib	TNBC
NCT05305365	II	QBS72S	TNBC
NCT04711824	I/II	Olaparib + SRS → pembrolizumab	TNBC or BRCA-mutated BC



INTACT brain metastases: Radionecrosis and severe adverse effects

Radiología 66 (2024) 166–180

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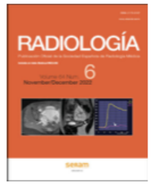

UPDATE IN RADIOLOGY

Challenges in radiological evaluation of brain metastases, beyond progression

A. Ortiz de Mendivil[a,*], P. Martín-Medina[a], L. García-Cañamaque[b], B. Jiménez-Munarriz[c], R. Ciérvide[d], J. Diamantopoulos[e]

[a] Servicio de Radiodiagnóstico, Sección de Neurorradiología, Hospital Universitario HM Sanchinarro, Madrid, Spain
[b] Servicio de Medicina Nuclear, HM Hospitales, Madrid, Spain
[c] Servicio de Oncología Médica, Hospital Universitario HM Sanchinarro, Madrid, Spain
[d] Servicio de Oncología Radioterápica, Hospital Universitario HM Sanchinarro, Madrid, Spain
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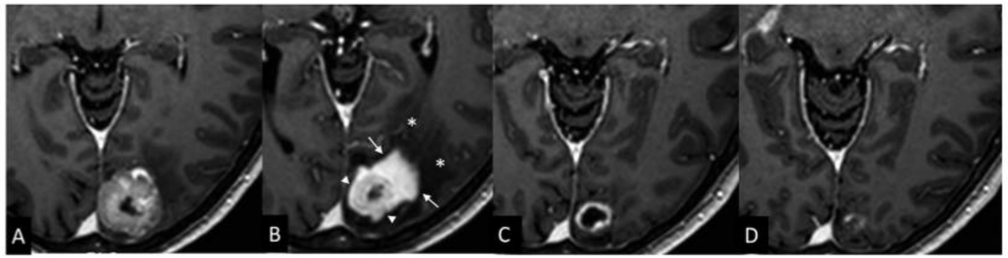
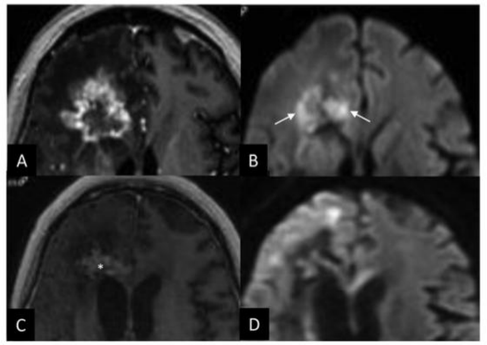
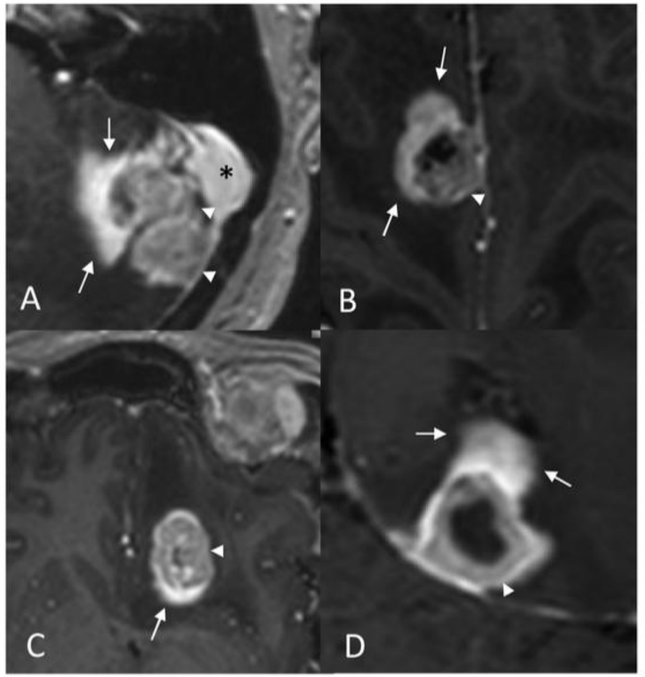
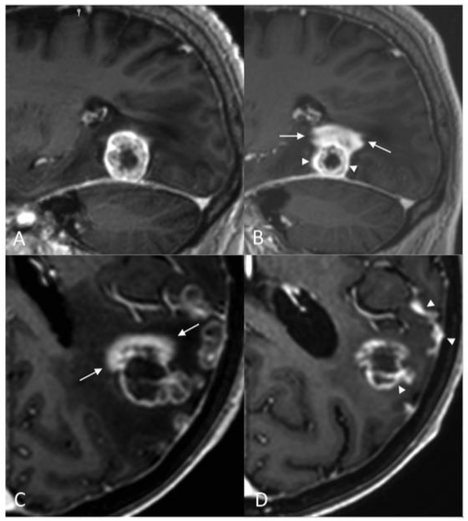
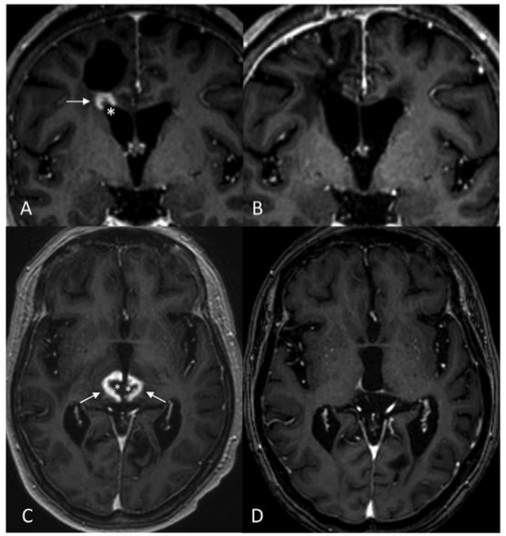










- inflammatory cloud
- incomplete ring enhancement

Journal of Neuro-Oncology (2024) 166:535–546
https://doi.org/10.1007/s11060-024-04578-6

RESEARCH

Check for updates

Adverse radiation effect versus tumor progression following stereotactic radiosurgery for brain metastases: Implications of radiologic uncertainty

Mia Salans[1] · Lisa Ni[1] · Olivier Morin[1] · Benjamin Ziemer[1] · Dante P. I. Capaldi[1] · David R. Raleigh[1,2,3] · Harish N. Vasudevan[1,2] · Jessica Chew[1] · Jean Nakamura[1] · Penny K. Sneed[1] · Lauren Boreta[1] · Javier E. Villanueva-Meyer[2,4] · Philip Theodosopoulos[2] · Steve Braunstein[1]

Received: 22 December 2023 / Accepted: 17 January 2024 / Published online: 5 February 2024

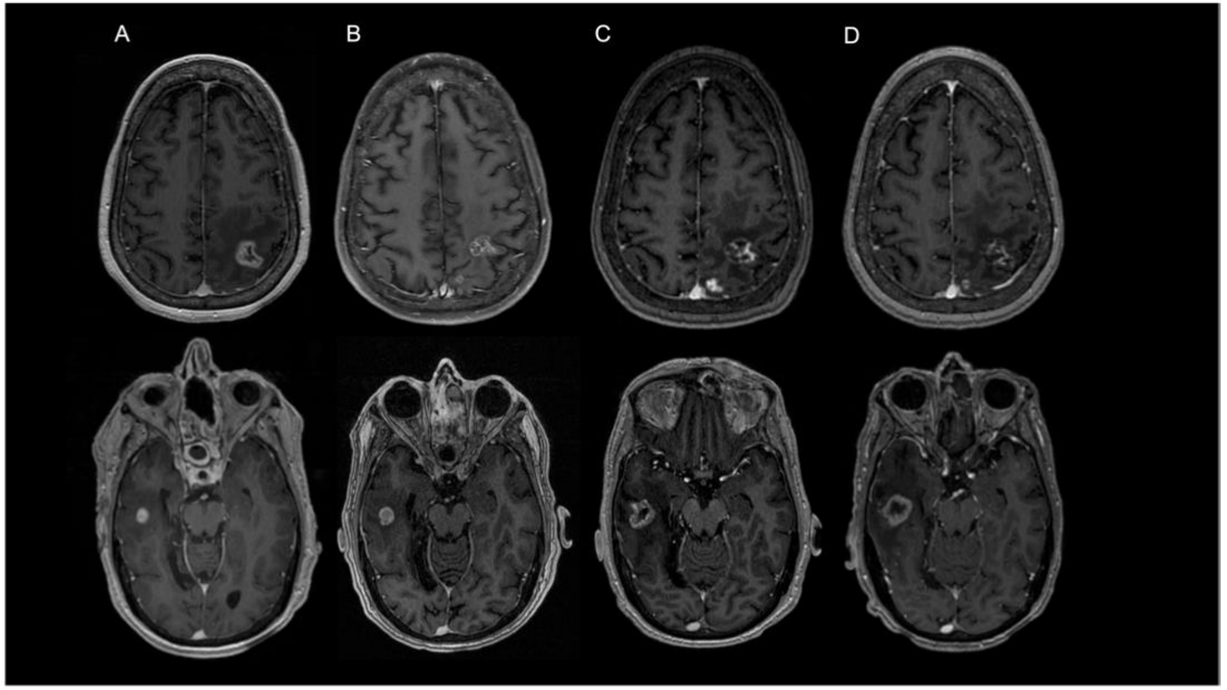


Fig. 1 Lesions with RU for representative patients diagnosed with ARE and tumor progression. Lesions with RU on T1 post-gadolinium MRI at **A**) RU onset, **B**) 18 months after RU onset, **C**) 30 months after RU onset, and **D**) RU resolution for representative patients diagnosed with ARE (top panel) and tumor progression (bottom panel)

Radiologic uncertainty (RU) is often resolved with monitoring of serial MRIs before a diagnosis is reached or a definitive intervention is performed
RU resolution took > 6 months in > 25% of cases

A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations

Balamurugan Vellayappan, MBBS, FRANZCR,* Mary Jane Lim-Fat, MD, MSc, FRCPC,† Rupesh Kotecha, MD,‡ Antonio De Salles, MD, PhD,§,‖ Laura Fariselli, MD,¶ Marc Levivier, MD, PhD,# Lijun Ma, PhD,** Ian Paddick, MSc,†† Bruce E. Pollock, MD,‡‡ Jean Regis, MD,§§ Jason P. Sheehan, MD, PhD,‖‖ John H. Suh, MD,¶¶ Shoji Yomo, MD, PhD,## and Arjun Sahgal, MD, FRCPC***

ISRS

- To provide consensus guidelines for grading and management of RN on behalf of the International Stereotactic Radiosurgery Society
- To summarize the literature specific to efficacy and toxicity of treatment paradigms for patients with symptomatic corticosteroid-refractory RN

Guidelines

ISRS grade	Description of severity	Recommended management and follow-up	Supporting level of evidence/strength of recommendation based on author consensus
1	Asymptomatic and no prior corticosteroid administration	• Close surveillance with repeat imaging at 6-12 wk intervals • Consider a short-course of corticosteroids (e.g. dexamethasone). • Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.	Not assessable based on this review
2	Symptomatic and no prior corticosteroid administration	• Dexamethasone can be started as 4-8 mg/d, with or without an initial bolus, and tapered gradually. Generally, a 3-6 wk course of steroids may be required. • Repeat imaging should be considered at 6-12 wk intervals. • Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.	Not assessable based on this review
3	Symptomatic and corticosteroid-refractory	• Bevacizumab at doses ranging between 5-10 mg/kg every 2-3 wk for 2-4 cycles • Repeat imaging after 2 cycles and after the 4th cycle for response assessment and to guide corticosteroid tapering as required. • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Moderate/strong
		• LITT/surgery • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Low/weak
		• HBOT • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Insufficient/weak
4	Symptomatic with neurologic impairment, progressive RN despite a trial of noninvasive treatments, dependency on high doses of corticosteroid	• Surgical resection • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Low/strong

Abbreviations: HBOT = hyperbaric oxygen therapy; ISRS = International Stereotactic Radiosurgery Society; LITT = laser interstitial thermal therapy; RN = radiation necrosis.

A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations

Balamurugan Vellayappan, MBBS, FRANZCR,* Mary Jane Lim-Fat, MD, MSc, FRCPC,† Rupesh Kotecha, MD,‡ Antonio De Salles, MD, PhD,§,‖ Laura Fariselli, MD,¶ Marc Levivier, MD, PhD,# Lijun Ma, PhD,** Ian Paddick, MSc,†† Bruce E. Pollock, MD,‡‡ Jean Regis, MD,§§ Jason P. Sheehan, MD, PhD,‖‖ John H. Suh, MD,¶¶ Shoji Yomo, MD, PhD,## and Arjun Sahgal, MD, FRCPC***

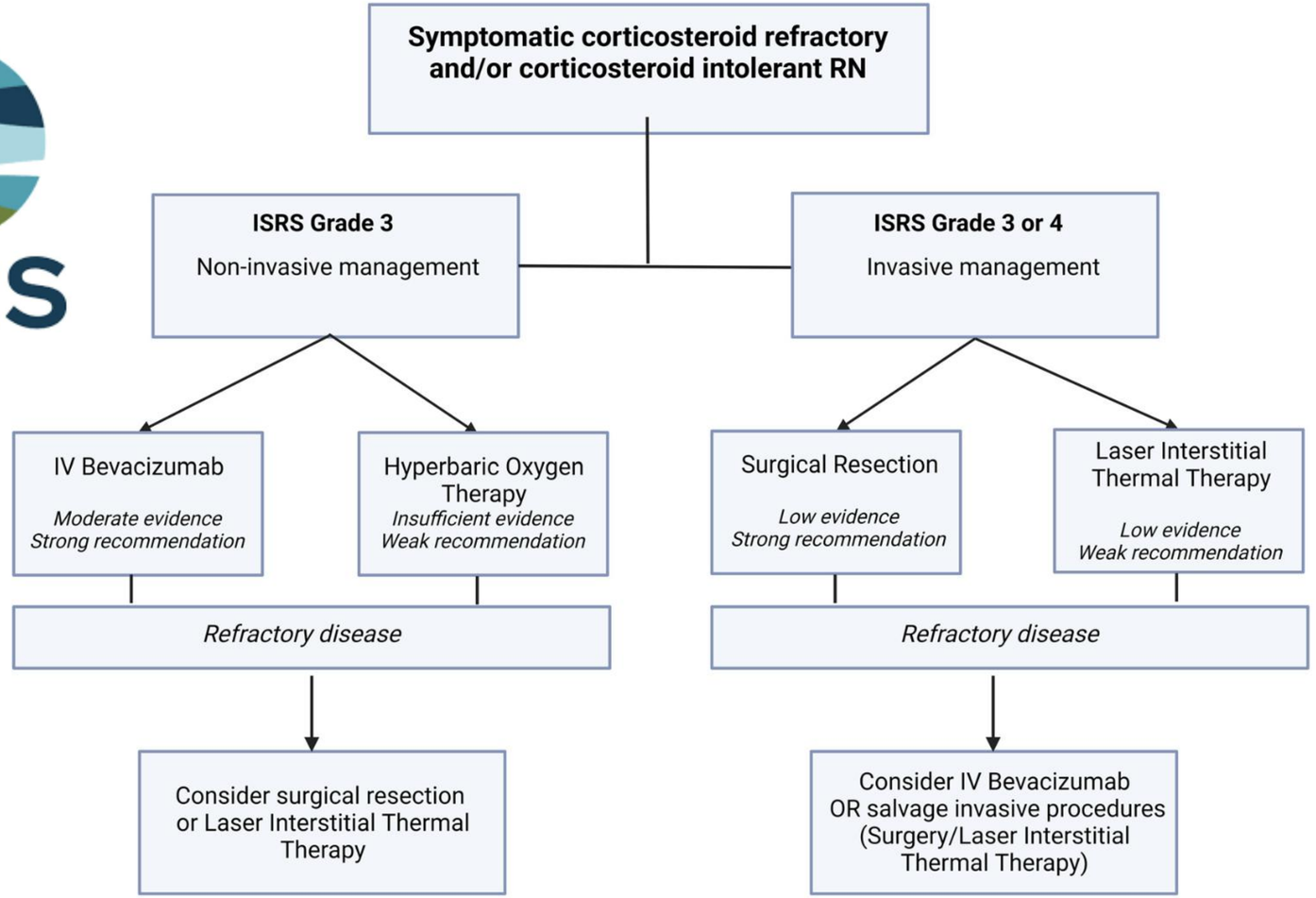


Fig. 5. Suggested management flowchart for symptomatic corticosteroid-refractory and/or corticosteroid-intolerant radiation necrosis.

CLINICAL RESEARCH: RADIOSURGERY AND RADIATION ONCOLOGY

Outcomes of Gamma Knife Radiosurgery for Brain Metastases in the Motor Cortex

Prasad, Shefalika BA[*,§,||]; Alzate, Juan Diego MD[*,§]; Mullen, Reed BS[*,§]; Bernstein, Kenneth MS[‡,§]; Qu, Tanxia PhD[‡,§]; Silverman, Joshua MD, PhD[*,‡,§]; Kondziolka, Douglas MD[*,‡,§]

Author Information

Neurosurgery 94(3):p 606-613, March 2024. | **DOI:** 10.1227/neu.0000000000002716

n=208

The SRS margin dose varied from 10 to 20 Gy (mean 16.9 Gy)

Adverse radiation effects (ARE) were noted in 6% of all tumors but were symptomatic in only 1.4%.
Median time to appearance of symptomatic ARE was 8 months. Edema without ARE was observed in 13%.

Absence of a neurological deficit, recursive partitioning analysis Class I and II, and dose >18 Gy were each associated with a significant survival advantage.

Patients treated before neurological deficits develop show better outcome.

Retrospective study

Association between tumor location and toxicity outcomes after stereotactic radiosurgery for brain metastases

Case Study | Published: 15 November 2024

Volume 171, pages 473–483, (2025) Cite this article

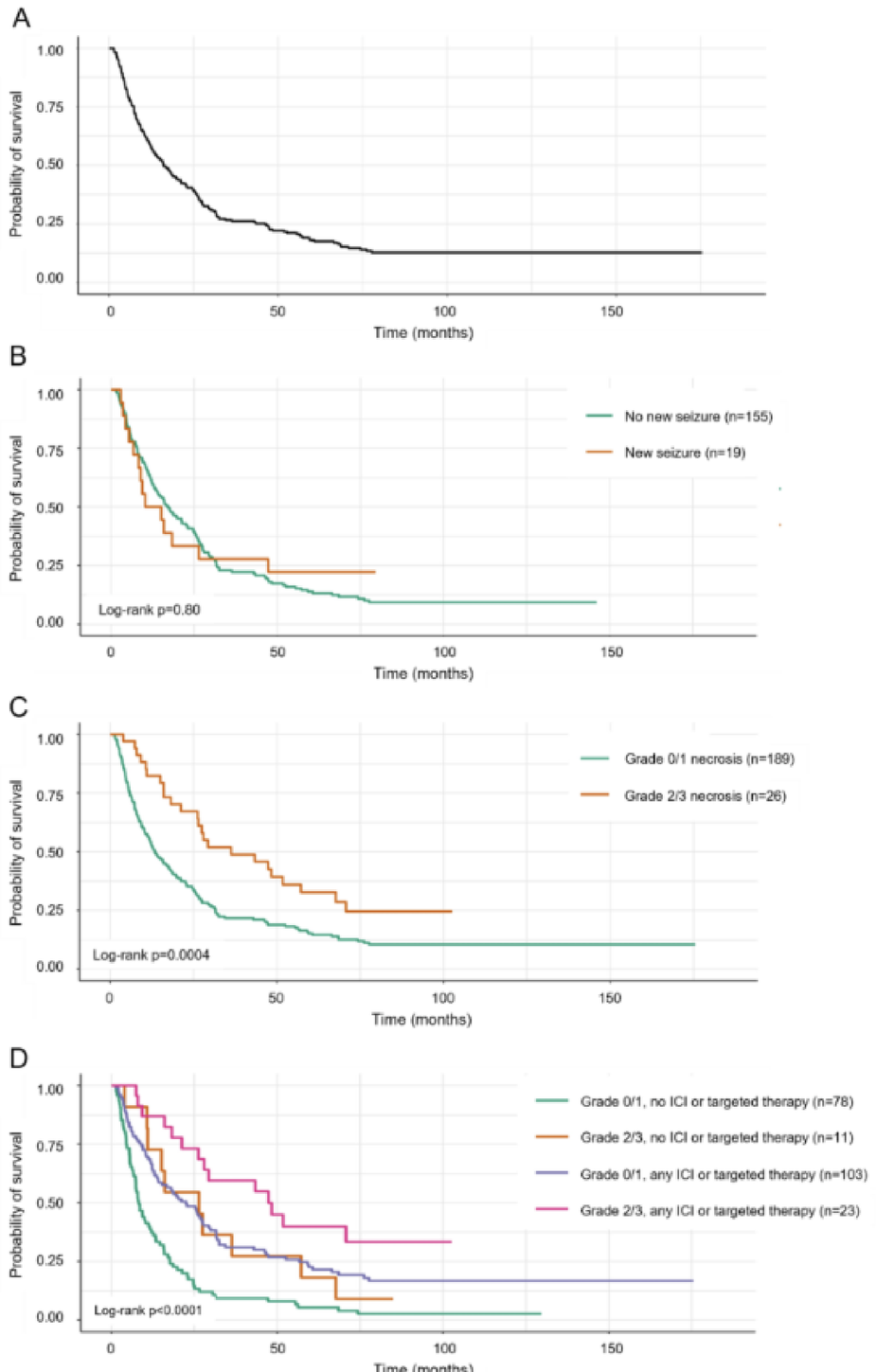
Boya Wang, Alexandra Bukowski, Orit Kaidar-Person, James M. Choi, Deanna M. Sasaki-Adams, Sivakumar Jaikumar, Dominique M. Higgins, Matthew G. Ewend, Soma Sengupta, Timothy M. Zagar, Theodore K. Yanagihara, Joel E. Tepper, Lawrence B. Marks & Colette J. Shen Show fewer authors

N=215, 605 lesions

Brain metastasis location in the motor or sensory cortex is associated with increased risk of new-onset seizure following SRS and may warrant consideration of steroid and/or anti-epileptic prophylaxis.

Symptomatic radiation necrosis is uncommon in the cerebellum

Retrospective study



Radiotherapy and Oncology 197 (2024) 110330

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

The effect of time-delayed contrast-enhanced scanning in determining the gross tumor target volume of large-volume brain metastases

Shanshan Du [a,b], Guanzhong Gong [b], Mingming Chen [c], Rui Liu [b], Kangning Meng [b], Yong Yin [b,*]

[a] Department of Oncology, Afliated Hospital of Southwest Medical University, No.25 Taiping Street, Jiangyang District, Luzhou 646000, Sichuan, China
[b] Department of Radiation Oncology Physics and Technology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Ji Yan Road No.440, 250117 Jinan, China
[c] Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

n= 155 pts for 561 lesions

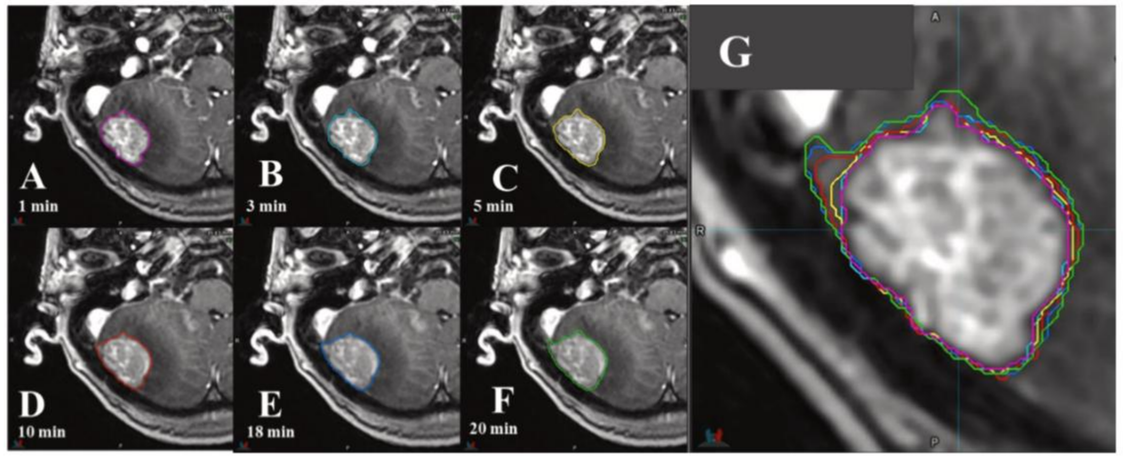


Fig. 2. Changes of the BMs boundary in a patient at different delay times. A–F show the gross tumor target volume (GTV) determination of the BMs at different delay times. G shows that all six determined GTVs are on the 1-min image, which suggests a significant change in tumor boundaries at different delay times.

Enhanced MR scans with different delay times show significant differences in the boundaries and shapes of large-volume BMs, and time-delayed multi-phase CE scanning should be used in GTV determination, with time phases ≥10 min being mandatory.

Prospective study

CHALLENGES IN CANCER-ASSOCIATED THROMBOSIS

Management of anticoagulation in patients with brain metastasis

Eva. N. Hamulyák,[1] Shlomit Yust-Katz,[2] and Avi Leader[3]

DVT: Deep Venous Thrombosis
PE: Pulmonary Embolism
ICH: Intracranial Hemorrhage
VTE: Venous Thromboembolism

Low Intermediate Thrombotic Risk	Isolated distal DVT Isolated subsegmental PE	Despite of a clinically relevant risk of progression, the sites and the nature of recurrence are less commonly life threatening	Consider to hold anticoagulation or recommend dose-reduced anticoagulation IVC filter is not usually placed Surveillance Lower-extremity ultrasound dopplers to assess for proximal DVT
Standard High Thrombotic Risk	Acute proximal lower-extremity DVT or PE with or without concomitant lower-extremity DVT (excluding isoalted subsegmental PE)		Consider placement of an IVC filter for patients who have a very high risk of anticoagulant-associated ICH or recent ICH precluding full-dose anticoagulation

Clinical recommendations

Single session Radiosurgery (SRS) and Fractionated Stereotactic Radiotherapy (SRT) in the PERIOPERATIVE treatment of brain metastases

Kanakarajan *et al.*
BMC Medical Informatics and Decision Making (2024) 24:177
https://doi.org/10.1186/s12911-024-02579-z

BMC Medical Informatics and Decision Making

SYSTEMATIC REVIEW Open Access

Factors associated with the local control of brain metastases: a systematic search and machine learning application

Hemalatha Kanakarajan[1*], Wouter De Baene[1], Karin Gehring[1,3], Daniëlle B. P. Eekers[4], Patrick Hanssens[2,3] and Margriet Sitskoorn[1*]

Postoperative SRT

Factors associated with better LC:

- Higher radiation dose [148, 149, 150]
- Post-surgical SRT [151, 152]
- Larger cavity volume [148]
- Number of fractions [153]

- Lung cancer primary tumor type [154]
- NSCLC histology [152]

- Higher RPA [155]

Factors associated with worse LC:

- Higher tumor volume [150, 153, 155,156, 157, 158, 159, 160, 161, 162]
- Larger tumor size [152, 155, 157, 158, 163, 164,165]
- Presence of meningeal contact [155]
- Residual/recurrent tumor at GK [165]
- Cavity enhancement on MRI before irradiation [156]
- Superficial tumors with dural/pial involvement [152]

- Prior radiation treatment [154]
- Surgery-to-SRT delay [163]
- Incomplete resection [159]

- Older age[155]
- Lower ECOG score [162]
- Presence of more than one brain metastasis [164]

Review

Advances in Radiation Oncology (2024) 9, 101402

advances in radiation oncology
www.advancesradonc.org

Critical review

Stereotactic Radiosurgery in the Management of Brain Metastases: A Case-Based Radiosurgery Society Practice Guideline

Colton Ladbury, MD,[a] Michael Pennock, MD,[b] Tugba Yilmaz, MD,[c] Nii-Kwanchie Ankrah, MBBS,[d] Therese Andraos, MD,[e] Emile Gogineni, DO,[e] Grace Gwe-Ya Kim, PhD,[f] Iris Gibbs, MD,[g] Helen A. Shih, MD, MPH,[h] Jona Hattangadi-Gluth, MD,[f] Samuel T. Chao, MD,[i] Susan C. Pannullo, MD,[j] Ben Slotman, MD, PhD,[k] Kristin J. Redmond, MD, MPH,[l] Simon S. Lo, MB, ChB,[m] and Michael Schulder, MD[n,*]

1) What fractionations are used during postoperative SRS?

When selecting dose fractionation, similar principles to treatment of intact metastases may be applied, though a fractionated approach is often preferred as a means of potentially minimizing risk of toxicity

Guidelines

Advances in Radiation Oncology (2024) 9, 101402

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Critical review

Stereotactic Radiosurgery in the Management of Brain Metastases: A Case-Based Radiosurgery Society Practice Guideline

Colton Ladbury, MD,[a] Michael Pennock, MD,[b] Tugba Yilmaz, MD,[c] Nii-Kwanchie Ankrah, MBBS,[d] Therese Andraos, MD,[e] Emile Gogineni, DO,[e] Grace Gwe-Ya Kim, PhD,[f] Iris Gibbs, MD,[g] Helen A. Shih, MD, MPH,[h] Jona Hattangadi-Gluth, MD,[f] Samuel T. Chao, MD,[i] Susan C. Pannullo, MD,[j] Ben Slotman, MD, PhD,[k] Kristin J. Redmond, MD, MPH,[l] Simon S. Lo, MB, ChB,[m] and Michael Schulder, MD[n,*]

Table 3 Comparison between potential benefits of preoperative and postoperative SRS

Preoperative SRS	Postoperative SRS
• Improved target delineation	• Pathologic confirmation before treatment
• Improved local control	• Compatible with cases with mass effect
• Higher oxygenation	• Immediate treatment of neurologic symptoms†
• Decreased risk of subsequent leptomeningeal disease	• Abundant data including level 1 evidence
• Decreased risk of radionecrosis	
• Smaller treatment volumes*	

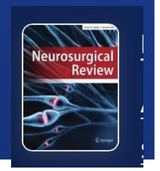
* May not apply if surgical cavity shrinks significantly postoperatively, but is related to improved target delineation, not needing to cover elective volumes such as surgical tract, and in some cases allowing smaller treatment margins.

† Can be due to either needing urgent decompression to prevent further neurologic decline/damage, or due to logistical challenges of stabilizing and discharging patients with symptomatic disease to allow for outpatient preoperative treatment.

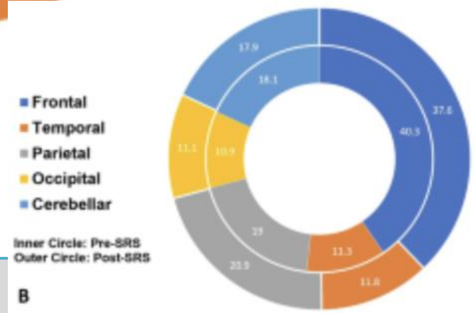
Home > Neurosurgical Review > Article

Preoperative versus postoperative stereotactic radiosurgery for brain metastases: a systematic review and meta-analysis of comparative studies

Review | Published: 02 January 2025
Volume 48, article number 16, (2025) Cite this article



S. Farzad Maroufi, Mohammad Sadegh Fallahi, S. Parmis Maroufi, Vida Kassaeyan, Paolo Palmisciano & Jason P. Sheehan
Show fewer authors



Meta-Analysis

LINAC RS and Gamma Knife RS

- hypofractionated treatments more common postoperatively

Preoperative and Postoperative SRS showed comparable

- overall survival ($p = 0.07$)
- local failure ($p = 0.26$)
- distant failure rates ($p = 0.84$)
- wound issues ($p = 0.98$)

Preoperative SRS group had

- lower risks of radiation necrosis ($p = 0.02$)
- lower risks of leptomeningeal disease ($p = 0.03$)

Single-Fraction Versus Fractionated Preoperative Radiosurgery for Resected Brain Metastases: A PROPS-BM International Multicenter Cohort Study

Roshan S. Prabhu, MD, MS *,† · Tobi Akinyelu, BS * · Zachary K. Vaslow, MD ‡ · ... · Samuel T. Chao, MD †† · Anthony L. Asher, MD *,‡‡ · Stuart H. Burri, MD *,†... Show more

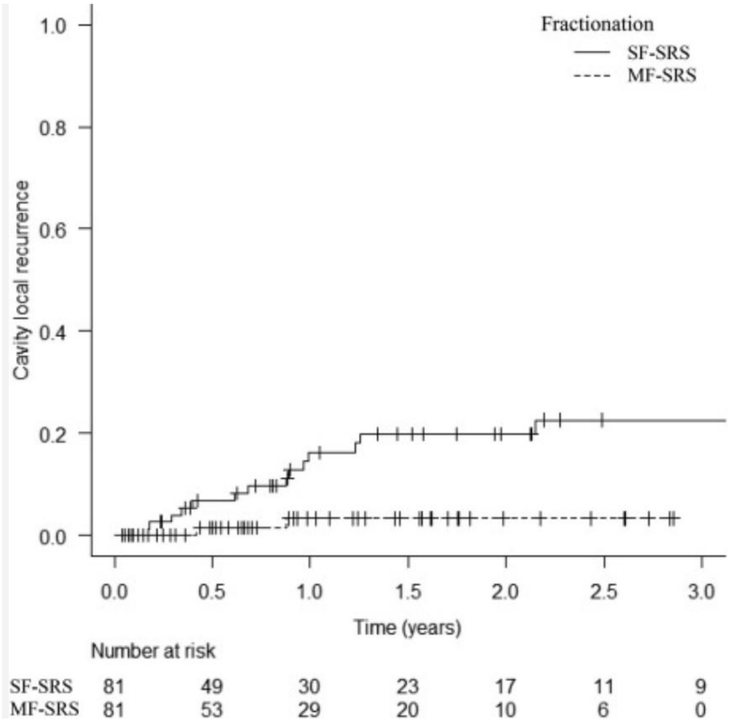
n=404

SRS: 15 Gy
SRT: 24 Gy in 3#

There was no difference in adverse radiation effect, meningeal disease, or overall survival based on fractionation.

SRT was associated with significantly reduced risk of cavity Local relapse

SRT may be a preferred option for neoadjuvant radiation therapy of resected BMs.



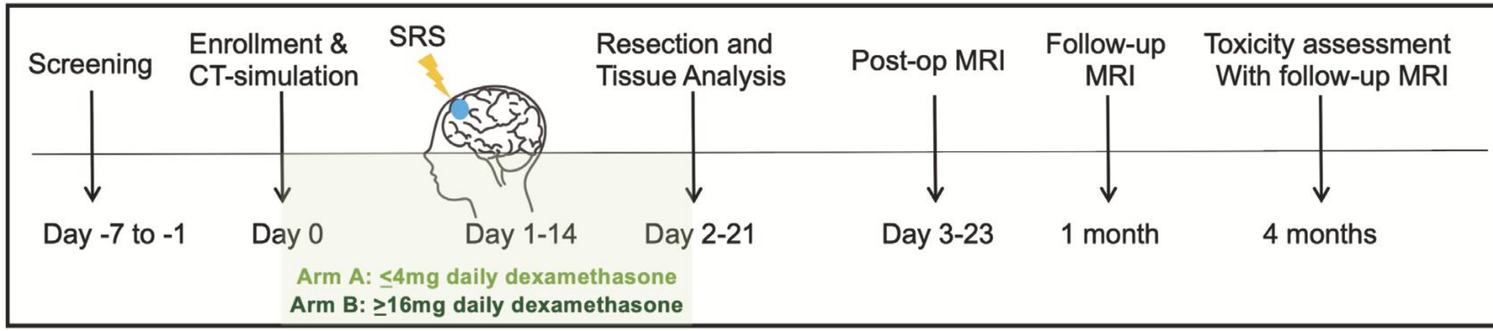
Retrospective study

nature communications

Article https://doi.org/10.1038/s41467-024-53034-6

Pre-operative stereotactic radiosurgery and peri-operative dexamethasone for resectable brain metastases: a two-arm pilot study evaluating clinical outcomes and immunological correlates

n=26



- safety at 4 months
- overall survival at 12-months 66%
- distant brain failure at 12-months 37.3%
- leptomeningeal disease at 12-months 6%
- local recurrence at 12-months 0%

No signicantly differences between the two arms

Prospective trial

Table 2 | Adverse Events within 4 months

Adverse Event	Arm A (*n* = 10)		Arm B (*n* = 11)	
	Grade 1-2 (%)	Grade 3-4 (%)	Grade 1-2 (%)	Grade 3-4 (%)
Altered Mental Status	0	0	0	1 (9.1)
Cerebral Edema	0	0	0	1 (9.1)
Cognitive Disturbance	1 (10.0)	0	0	0
Confusion	5 (50.0)	0	1 (9.1)	0
Dysarthria	1 (10.0)	0	0	0
Dysphasia	0	0	1 (9.1)	0
Facial Muscle Weakness	1 (10.0)	0	0	0
Fatigue	2 (20.0)	0	3 (27.3)	0
Gait Abnormality	0	0	1 (9.1)	0
Generalized Muscle Weakness	1 (10.0)	0	1 (9.1)	0
Headache	3 (30.0)	0	2 (18.2)	0
Paresthesia	0	0	1 (9.1)	0
Radiation Necrosis	0	0	1 (9.1)	0
Scalp Pain	1 (10.0)	0	0	0
Somnolence	2 (20.0)	0	0	0
Symptomatic	0	0	1 (9.1)	0
Tremor	0	0	1 (9.1)	0
Vision Changes	1 (10.0)	0	3 (27.3)	0

Routman et al. BMC Cancer (2024) 24:332
https://doi.org/10.1186/s12885-024-12060-9

BMC Cancer

STUDY PROTOCOL Open Access

Pre-operative vs. post-operative stereotactic radiosurgery for operative metastatic brain tumors: study protocol for a phase III clinical trial

David M. Routman[1], Ignacio Jusue-Torres[2], Paul D. Brown[1], Daniel M. Trifiletti[3], Sujay A. Vora[1,4], Desmond A. Brown[5], Ian F. Parney[2], Terry C. Burns[2] and Elizabeth Yan[1*]

- Age: less than 60 versus those 60 or older
- Number of brain metastases: 1 vs. 2–4 vs. 5–10
- Tumor Size: Planned resection of metastasis < 3.0 cm vs. > 3.0 cm (but < 5.0 cm)
- Primary Malignancy: Lung vs. Radioresistant (melanoma, renal cell carcinoma, sarcoma) vs. Other
- Dural Contact: Yes, versus No, with dural contact defined radiologically as suspicion of loss of a plane between the tumor and dura or within 1 mm.
- RT modality: SRS planned as LINAC vs. Gamma knife

Arm A: Pre-op SRS followed by surgery (within two weeks post-SRS).
Arm B: Surgery followed by post-op SRS (within four weeks of surgery).

Radiation therapy dosing:

Lesions < 4.2 ccs receive 20 Gy (22 Gy is allowed for subcentimeter metastases)
Lesions ≥ 4.2c to <8.0 cc receive 18Gy
Lesions ≥ 8.0 to <14.4 cc receive 17Gy
Lesions ≥ 14.4 to <20cc receive 15Gy
Lesions ≥ 20 to <30cc receive 14Gy
Lesions ≥ 30cc max 12Gy

ISRS
Certified Center

CERTIFICATE OF QUALITY IN STEREOTACTIC RADIOSURGERY

Presented to

Ospedale Santa Maria Annunziata

To acknowledge their demonstration during an audit on September 30th-October 1st 2024 to operate at a level that meets the ISRS Certification Standards for the treatment of malignant intracranial lesions on Versa HD

Marc LEVIVIER
Co-chair | Past President of ISRS Certification Committee

Ian PADDICK
Co-chair ISRS Certification Committee

*This certificate is valid for three years from the date of audit

Grazie dell'attenzione

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