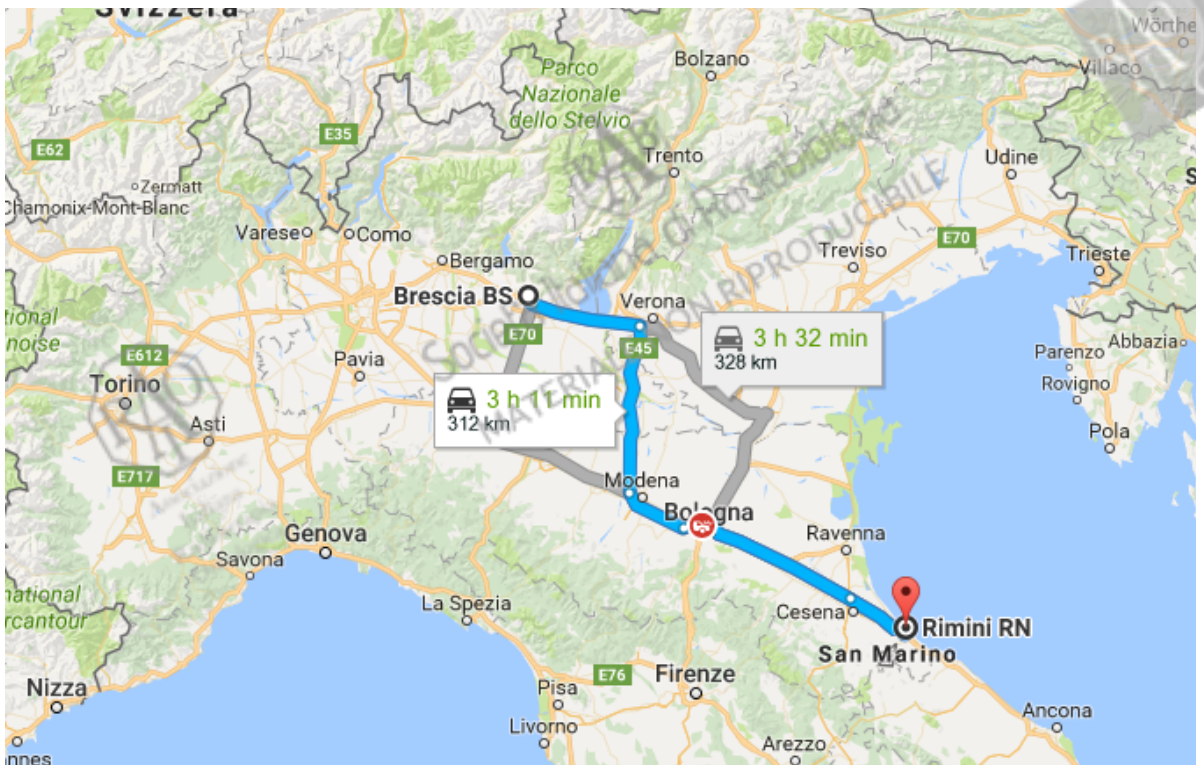
Encefalo: metastasi cerebrali

Frazionamenti e dosi nella radioterapia delle metastasi cerebrali

Michela Buglione
Università e Spedali Civili – Brescia

- Radiotherapy?
- Radiotherapy --> solid results
- SRS or FSRT ?--> from radiobiology to clinic



- Radiotherapy?
- Radiotherapy in the past --> solid results
- Stereotactic radiotherapy --> from radiobiology to clinic

Why radiotherapy?

In the past → the standard WBRT

rapid treatment
feasible everywhere
treatment of visible and occult mets

Obj → short-term symptomatic palliative treatment (OS 6 months)

Why radiotherapy?

Study		Number of patients	Randomization Gy/# fractions	Median survival (months)
Harwood and Simpson [18]	1977	101	30/10 versus 10/1	4.0–4.3
Kurtz et al. [19]	1981	255	30/10 versus 50/20	3.9–4.2
Borgelt et al. [17, 20]	1981 1980	138	10/1 versus 30/10 versus 40/20	4.2–4.8
Borgelt et al. [17, 20]	1981 1980	64	12/2 versus 20/5	2.8–3.0
Chatani et al. [21]	1986	70	30/10 versus 50/20	3.0–4.0
Haie-Meder et al. [22]	1993	216	18/3 versus 36/6 or 43/13	4.2–5.3
Chatani et al. [23]	1994	72	30/10 versus 50/20 or 20/5	2.4–4.3
Murray et al. [24]	1997	445	54.4/34 versus 30/10	4.5

* Adapted from Khuntia et al. [25].

Why radiotherapy?

In the last 15 years

from WBRT alone to other therapeutic options

- Surgery
- Surgery plus RT

WBRT

Only surgical bed

- SRS
- FSRT
- WBRT + SRS

Better survival → more attention to side effects of the treatments

- Why radiotherapy?
- Radiotherapy --> solid results
- Stereotactic radiotherapy --> from radiobiology to clinic

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- **Radiotherapy --> solid results**
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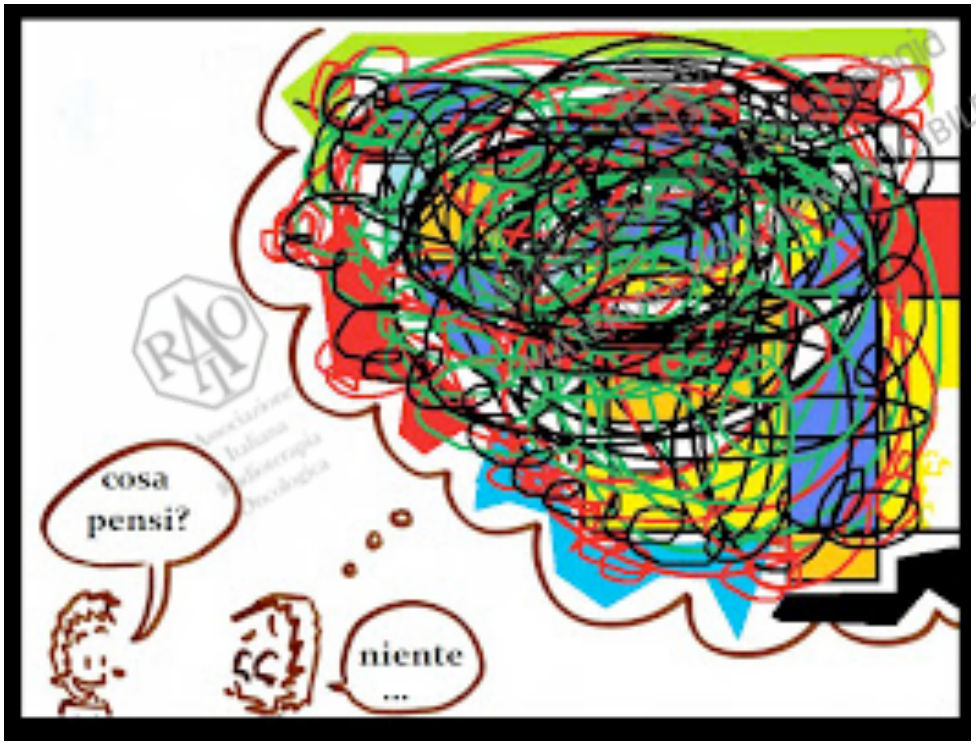
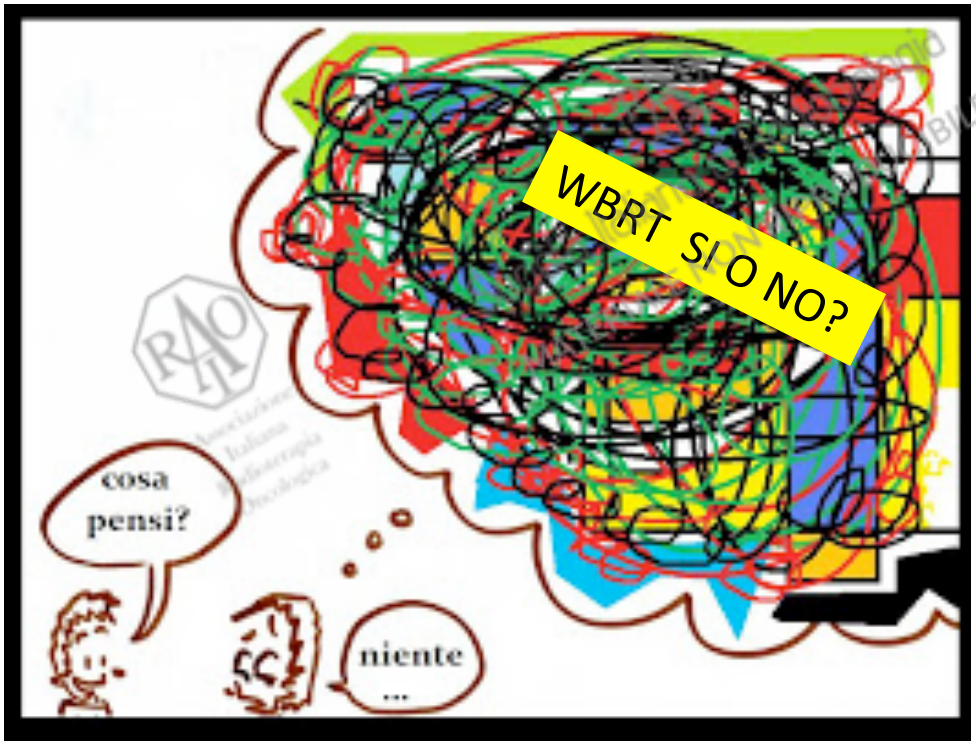


- Why radiotherapy?
- **Radiotherapy --> solid results**
- Stereotactic radiotherapy --> from radiobiology to clinic



Radiotherapy --> solid results

2006 – 2011: SRS ± WBRT

3 TRC showed, in patients with ≤ 4 BM:

- no OS reduction without WBRT
- optimal local control with SRS, better with SRS + WBRT
- higher brain relapse in SRS group (even if also 25% of pts in WBRT had brain progression)
- worse neurocognitive outcome with WBRT

Radiotherapy --> solid results

	JROSG 2006* 132 pt, SRS ± WBRT 1-4 BM	MDACC 2009** 58 pz, SRS ± WBRT 1-3 BM	EORTC 22952-26001 2011*** 199 pz, SRS ± WBRT 1-3 BM
Dose	≤ 2 cm→ 22-25 Gy > 2 cm→ 18-20 Gy	≤ 2 cm→ 22-25 Gy > 2 cm→ 18-20 Gy	Single ≤ 3.5 cm → 25 Gy Multiple ≤ 2.5 cm →25 Gy
Local control (SRS +WBRT vs SRS)	12 m Brain Recurrence: 46.8% vs 76.4% (p <0.001); 12 mm distant brain rec: 41.5% vs 63.7 (p<0.003)	1 year distant brain control: 73% vs 45% (p .02)	Local control (2 years) 33 vs 48% (p 0.023) Distant brain control a 2 anno: 28 vs 44% (p .<0.002)
Median overall survival	OS (SRS+WBRT vs SRS): 7.5m vs 8.0 m (ns)	OS (SRS+WBRT vs SRS): 5.7 m vs 15.2 m (p .003)	Neurologic death (SRS +WBRT vs SRS): 10.7 m vs 10.9 m (ns)
Toxicity (SRS +WBRT vs SRS)	Neuro cognitive worsening at 12 m: 28% vs 30% (ns)	4 m neurocognitive worsening: 52% vs 24% (statistically significant)	No neurocognitive assessment

*Aoyama H et al Jama 2006; 265 (21), 2483; IJROBP 2007; 68, 1388;
**EE Chang et al Lancet Oncol 2009; 10: 1037
*** Kocher M et al JCO 2011; 29(2): 134

Radiotherapy --> solid results

Choosing Wisely®

An initiative of the ABIM Foundation

American Society for Radiation Oncology

ASTRO

TARGETING CANCER CARE

Five Things Physicians and Patients Should Question

10

Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

- Primary analyses of randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors.
- The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small-cell lung cancer.
- Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the highest quality of life without a detriment in overall survival. Patients should discuss these options with their radiation oncologist.

September 15, 2014

Radiotherapy --> solid results

Is the game over? → probably not

RTOG 95-08 PHASE III; 331 patients WBRT ± SRS
WBRT could improve OS in patients with good prognostic factors (RPA class 2) or NSCLC; and in patients with RPA 3.5-4 and NSCLC (Andrews DW et al lancet 2004, 363: 1665; Sperduto PW et al IJROBP 2014, 90:526)

Doses*: prescribed to the tumour margin in relation with diameter;

- RTOG 90-05
- WBRT 2,5 Gy fr→ 37·5 Gy in 3 weeks.

Radiotherapy --> solid results

Is the game over? → probably no

RTOG 95-08 PHASE III; 331 pati
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2004, 363: 1665; Sperduto PW

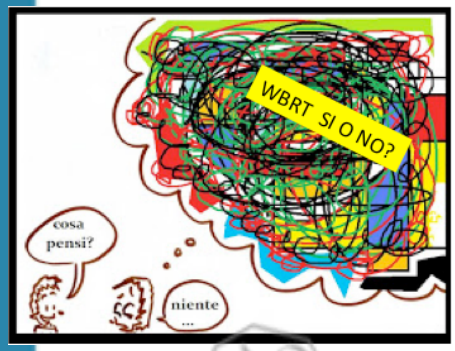
Modern techniques consent us to perform WBRT with hippocampal sparing

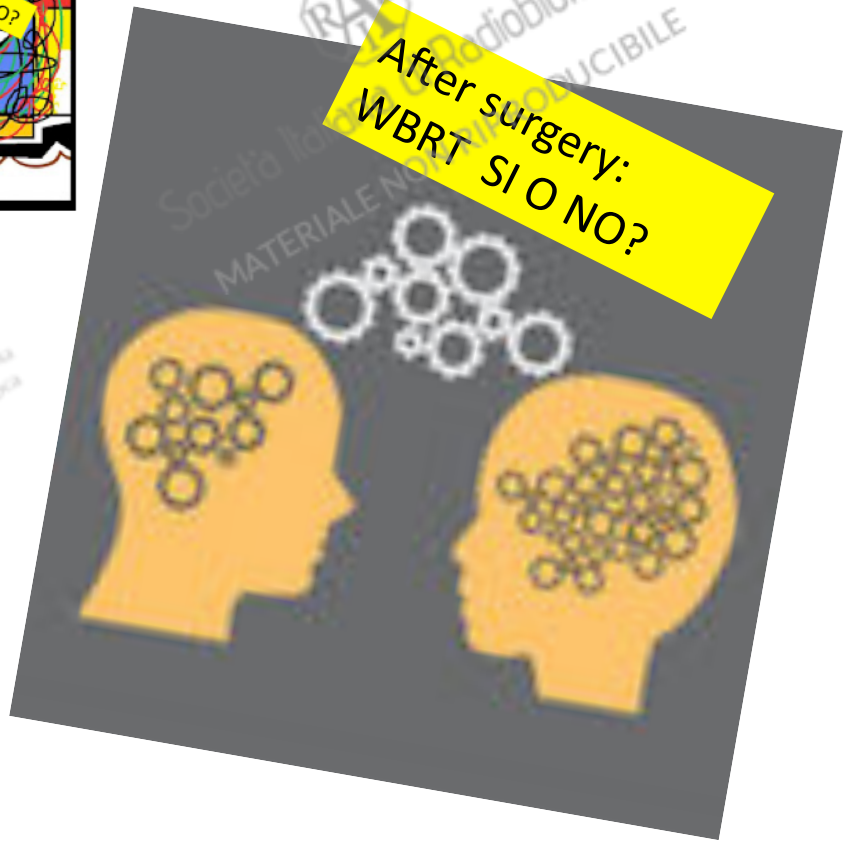
Ongoing NRG-CC001 WB ± HS

Doses*: prescribed to the tumour margin in relation with diameter;

- RTOG 90-05
- WBRT 2,5 Gy fr→ 37·5 Gy in 3 weeks.

- Why radiotherapy?
- **Radiotherapy --> solid results**
- Stereotactic radiotherapy --> from radiobiology to clinic
- Which dose?
- The future





Radiotherapy --> solid results

Post surgery → WBRT

Data from the literature confirm the utility of WBRT after surgery

- WBRT 1,8 Gy Fr→ 50,4 Gy
- Local and distant intracranial control
- Freedom from neurologic death;
- Failure on the tumor bed (46 vs 10% p<0.001) Patchell RA at al JAMA 1998; 280(17): 1485

EORTC 22952-26001

- WBRT 30 Gy in 10 fr
- Reduced local relapse (59 vs 27% p<0.001)
- Reduced distant intracranial mets (42 vs 23 p= 0,008)
- No difference in OS Kocher M et al JCO 2011; 29(2): 134

Radiotherapy --> solid results

Post surgery → from WBRT to SRS and FSRT

Speedest evolution towards SRS

- Post-operative SRS is now commonly administered as an alternative to post-operative WBRT
- Obj → reduce the very high risk of recurrence in the operative bed.
- No randomized trials; the approach is supported by the evidence of higher recurrence rate in the surgical site
- The omission of WBRT produces pattern of relapse similar to those showed in the SRS alone trials and no detrimental OS
- Better neuro-cognition

Radiotherapy --> solid results

Post surgery → from WBRT to SRS and FSRT

Quicker evolution toward SRS (FSRT?)

- Mostly retrospective trials (8; 2010-2016)
- N° of patients: range 39-165
- Dose: between 16 and 18 Gy; 27-30 in 3 fr Gy
- CTV: surgical cavity; PTV: CTV + 2mm
- Median OS: 10,9-24 months (better in FSRT)
- Local recurrence: 7-19% (better in FSRT)
- Distant failure: 33-64%

Brennan C et al IJROBP 2014; (88)130
Hwang SW et al. J Neuro-Oncol. 2010;98(1):77
Jensen CA et al. J Neurosurg. 2011;114(6):1585
Prabhu R, et al IJROBP Int J Radiat Oncol Biol Phys. 2012;83(1):e61–6
Minniti G et al IJROBP 2013;86:623
Atalar B, et al. IJROBP 2013;87(4):713
Choi CY, et al. IJROBP 2012;84:336
Pessina F et al. PloseOne 2016; June 27

SRS or FSRT ?--> from radiobiology to clinic

Yes → LOCAL TREATMENT

SRS or FSRT ?--> from radiobiology to clinic

Radio-biologic effect of SRS and FSRT

	SRS	FSRT
α/β ratio and LQ model	✗	✗

Radiobiological basis of SBRT and SRS

Chang W. Song · Mi-Sook Kim · L. Chinsoo Cho · Kathryn Dusenbery · Paul W. Sperduto

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Critical Review

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Immunomodulation	✓	✓

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Repair intra-fraction	✓	✓
Redistribution	✗	✗
Repopulation	✗	✗
Immunomodulation	✓	✓

Better for OAR

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SRS or FSRT ?--> from radiobiology to clinic

* RTOG 90-05

Obj: to search the MTD in patients with BM already treated with WB

≤ 2 cm → 18 Gy
21 - 30 mm → 15 Gy
31 - 40 mm → 12 Gy

MTD
24 Gy → ≤ 2 cm
18 Gy → 21-30 mm
15 Gy → 31-40 mm

Shaw e et al IJROBP, 1996, 34: 647; IJROBP 2000; 47: 291

SRS or FSRT ?--> from radiobiology to clinic

2014 Japan→ is there a limit in terms of mets number?

Observational prospective study; 1200 pz (1/6 con 5-10 BM) → unico vincolo: no BM>3 cm

- comparison: 2-4 BM vs 5-10 BM
- median peripheral dose: 21 (10-32) Gy vs 20,33 (10-27)
- no difference → OS (0.9 month; ns), neurological death, brain disease progression (66% vs 72%), WBRT; MMSE outcome
- Higher lepto-meningeal spread R in the 5-10 BM group

Yamamoto M et al, J neurosurg, 2013; 118: 1258

- comparison: 2-9 BM vs >10 BM
- "……carefully selected patients with 10 or more tumors are not unfavourable candidates for SRS alone……"

Yamamoto M et al, J Neurosurg, 2014; Suppl 2) 121: 16

SRS or FSRT ?--> from radiobiology to clinic

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J Cancer Res Ther. 2014 Jan-Mar;10(1):79-83. doi: 10.4103/0973-1482.131390.

Surgery in cerebral metastases: are numbers so important?

Agnoletti A, Mencarani C, Panciani PP[1], Buffoni L, Ronchetti G, Spena G, Tartara F, Buglione M, Pagano M, Ducati A, Fontanella M, Garbossa D.

Yamamoto M et al, J Neurosurg, 2014; Suppl 2) 121: 16

SRS or FSRT ?--> from radiobiology to clinic

How the better treatment has to be to choosen?

- disease characteristics?
- histology?
- prognosis?
- toxicity?
- others?

SRS or FSRT ?--> from radiobiology to clinic

	FSRT (2000-2009) n° 448	SRS (1994-2005) n° 2157
dose	24-40 Gy in 3-5 fr	10-25 Gy
margin	2-10 mm	no margin
median GTV	0,52–4,47cm^3 (median 2,8 cm^3)	1,3 to 5,5cm^3 (median 2 cm^3)
median survival	5–16 months (median 8,7 m)	5,5 to 22 months (median 11 months)
1-year survival rate	68,2–93% (median 82,5%)	71 to 95% (median 85%)
necrosis	3,1%	0,5 to 6% (median 2,4%)
+WBRT rates	30%	58%

M. Schlienger et al. Cancer Radiothérapie 2010; 14: 119

SRS or FSRT ?--> from radiobiology to clinic

GTV> 500 mm^3 and ≤4200 mm^3 (Ø 20mm) → both

GTV< 500 mm^3 (Ø 10 mm) → SRS.

GTV> 4200 mm^3 (Ø 20 mm) → FSRT 4 to 6 Gy fractions in 10–12 days (margin of 2 mm)

M. Schlienger et al. Cancer Radiothérapie 2010; 14: 119

SRS or FSRT ?--> from radiobiology to clinic

- Retrospective analysis 214 pts; SRS vs FSRT in radio-resistant vs radiosensitive tumours
- The decision was guided by GTV dimension, adjacent critical structures (brainstem, optic chiasm)
- Median peripheral dose 20 Gy
- Statistical analysis: Radiosensitive vs radio-resistant

Oermann EK et al J neurosurg 2013; 119: 1131

SRS or FSRT ?--> from radiobiology to clinic

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- The decision was guided by GTV dimension, adjacent critical structures (brainstem, optic chiasm)
- Median peripheral dose 20 Gy
- Statistical analysis: Radiosensitive vs radio-resistant

- Equivalent rates of local control
- TTLF p=0.46
- The analysis within the SRS and FSRT groups → worse local control in pts with radio-resistant t. in the FSRT group (14.4 vs 41.5 months) --> maintained at multivariate analysis
- No different toxicities

Oermann EK et al J neurosurg 2013; 119: 1131

SRS or FSRT ?--> from radiobiology to clinic

- Retrospective analysis 98 pts; FSRT 36 Gy in 6 fr (large lesions and near OAR) vs SRS 20 Gy
- Median follow-up 7 months
- 1 y Local PFS: 69% vs 71% (p=0.31)
- FSRT not inferior to SRS
- Higher tox in SRS group (5% vs 17% --> p=0.05)

Yeon-Joo K et al IJROBO 2011; 81(2): 483

SRS or FSRT ?--> from radiobiology to clinic

Treatment	Patients (*n*)	Median survival (months) by RPA class: Class 1 (Primary controlled, age <65, no extracranial metastases, KPS ≥ 70)	Class 2 (primary uncontrolled OR age ≥65, OR extracranial metastases)	Class 3 (KPS < 70)
WBRT (RTOG phase III trials)	1176	7.1	4.2	2.3

(b)

Score	0	0.5	1	Sum GPA score	RTOG MS	WBRT and/or SRS MS**
Age	>60	50–59	<50	3.5–4	11.0	21.7
KPS	<70	70–80	90–100	3	6.9	17.5
Number brain mets	>3	2-3	1	1.5–2.5	3.8	5.9
ExtraCNS mets	Present	—	None	0-1	2.6	3.0

MS = median survival (months).

(c)

Primary	Median survival (Months)	95% CI
Non-small-cell lung cancer	7.00	6.53–7.50
Small cell lung cancer	4.90	4.30–6.20
Melanoma	6.74	5.90–7.57
Renal cell carcinoma	9.63	7.66–10.91
Breast cancer	11.93	9.69–12.85
Gastrointestinal cancer	5.36	4.30–6.30
Unknown	6.37	5.22–7.49

The role of prognostic factors

The role of prognostic factors !!

The accuracy of predicting survival in individual patients with cancer.

Kondziolka D[1], Parry PV, Lunsford LD, Kano H, Flickinger JC, Rakfal S, Arai Y, Loeffler JS, Rush S, Knisely JP, Sheehan J, Friedman W, Tarhini AA, Francis L, Lieberman F, Ahluwalia MS, Linskey ME, McDermott M, Sperduto P, Stupp R.

METHODS: The authors prospectively estimated survival in 150 consecutive cancer patients (median age 62 years) with brain metastases undergoing radiosurgery. They recorded cancer type, number of brain metastases, neurological presentation, extracranial disease status, Karnofsky Performance Scale score, Recursive Partitioning Analysis class, prior whole-brain radiotherapy, and synchronous or metachronous presentation. Finally, the authors asked 18 medical, radiation, or surgical oncologists to predict survival from the time of treatment.

RESULTS: The actual median patient survival was 10.3 months (95% CI 6.4-14). The median physician-predicted survival was 9.7 months (neurosurgeons = 11.8 months, radiation oncologists = 11.0 months, and medical oncologist = 7.2 months). For patients who died before 10 months, both neurosurgeons and radiation oncologists generally predicted survivals that were more optimistic and medical oncologists that were less so, although no group could accurately predict survivors alive at 14 months. All physicians had individual patient survival predictions that were incorrect by as much as 12-18 months, and 14 of 18 physicians had individual predictions that were in error by more than 18 months. Of the 2700 predictions, 1226 (45%) were off by more than 6 months and 488 (18%) were off by more than 12 months.

SRS or FSRT ?--> from radiobiology to clinic

	Dana Farber 2014 n°70	Couper univ; New Jersey 2009 n°27 (52 BM)	Hannover 2012 n° 75 (108 BM)
Dose	5 x 5 Gy; 7 x 3 Gy	20-36 Gy in 4-6 Fr	6 -7x5 Gy, 5x6 Gy, 7-10x4 Gy, 5-6x5 Gy
Local control	68% (6m); 54%(1y)	93.9% (6m); 68.2% (1 year)	EQD2 35 Gy: (if EQD2>35 Gy 14.9 m vs 3.4 m if EQD2<35 Gy
Median overall survival	10.7 months	10.8 months	9.1 months related to GTV, BED >39Gy, extracranial disease
Toxicity	G1-2 acute tox in 11 pt (16%) 3 RMN alterations no sympt	1 pts had G3 toxicity	Higher acute tox if EQD2>35 (31% vs 8% p=0,026)

Rajakesari S et al J Neurooncol. 2014;120(2):339-346
Kwon AK et al Cancer 2009;115(4):890-898
Martens et al, BMC Cancer 2012, 12:497

SRS or FSRT ?--> from radiobiology to clinic

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Cancer Treatment Reviews 37 (2011) 567–578

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Complications of Treatment

Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy: Normal tissue dose constraints of the central nervous system

Michael T. Milano [a,*], Kenneth Y. Usuki [a,1], Kevin A. Walter [b,2], Douglas Clark [a,1], Michael C. Schell [a,1]

[a] Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY, United States
[b] Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, United States

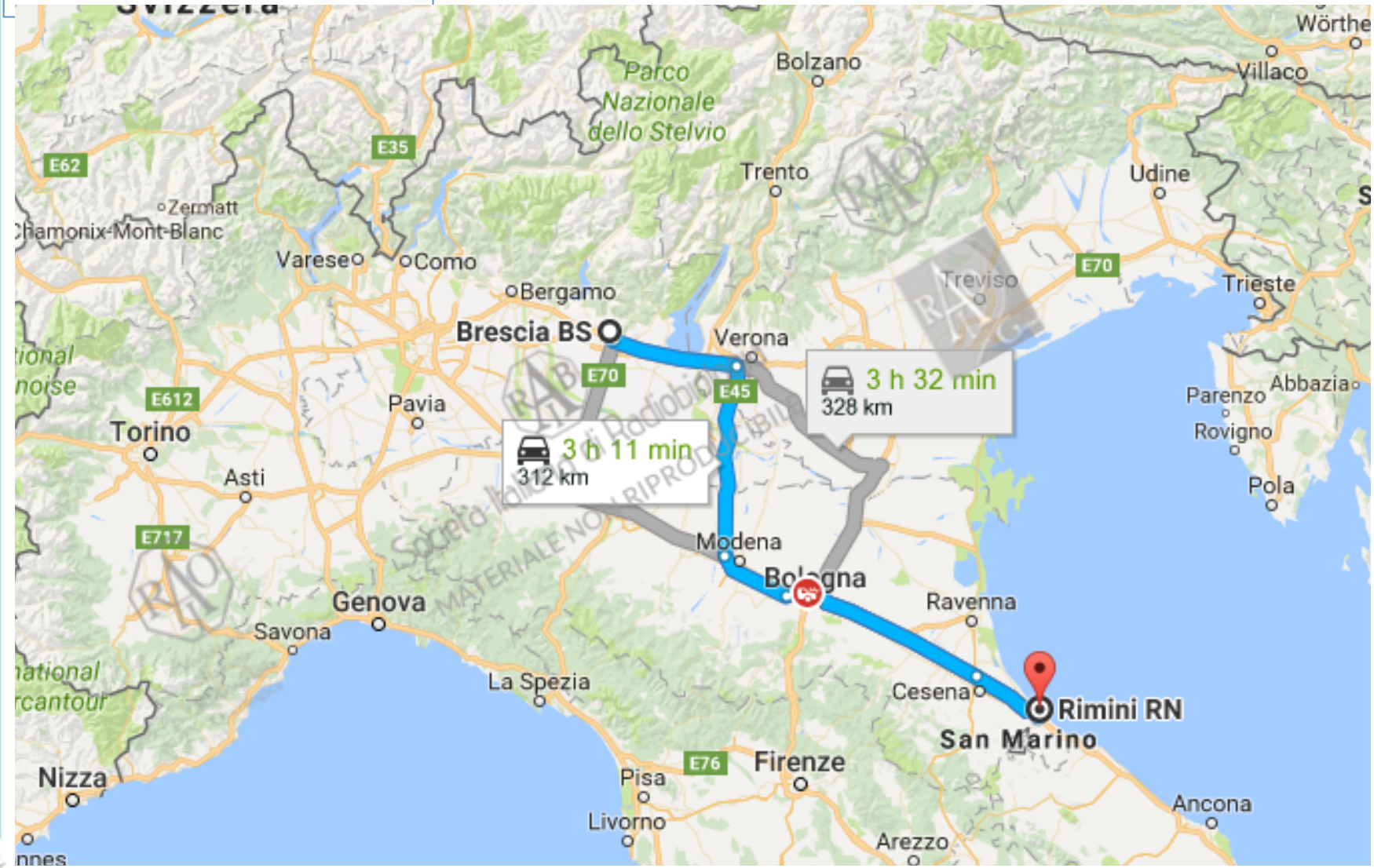
SRS or FSRT ?--> from radiobiology to clinic

OAR

Table 2
Summary of central nervous system dose expected to yield acceptable toxicity outcomes after single fraction SRS.

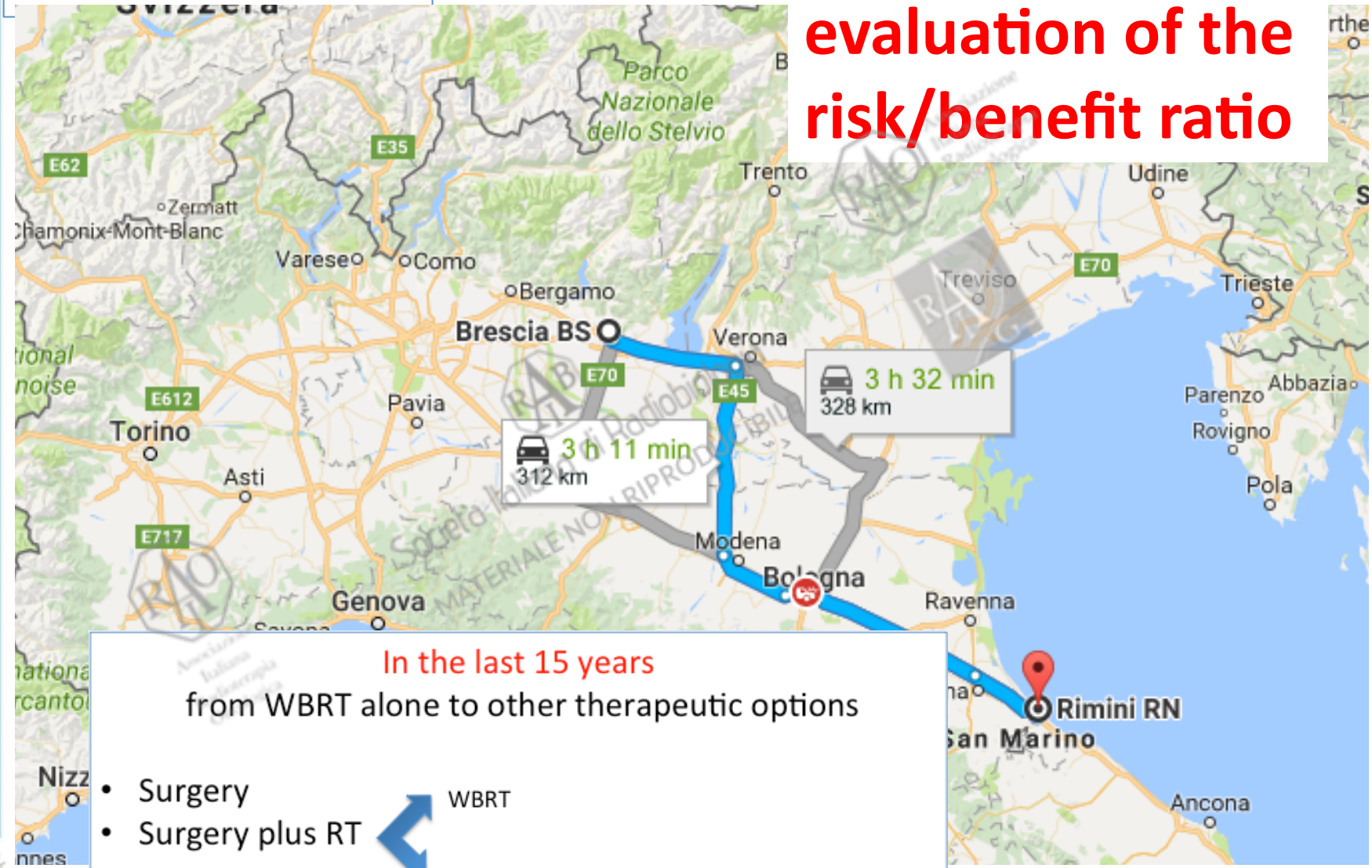
Structure	Outcome	Constraint
Brain parenchyma[a]	Necrosis	Tissue V12 <5–10 ml Tissue V10 <10 ml
Brainstem	Necrosis or neurologic deficits	<10–12 Gy maximum
Optic nerve/optic chiasm	Vision loss, anopsia, decreased visual acuity	<10–12 Gy maximum
Carotid artery	Occlusion	<20–23 Gy maximum
Acoustic neuroma	Symptomatic cranial nerve V and/or VII neuropathy	<12–13 Gy at tumor margin
	Hearing preservation	<12–13 Gy at tumor margin
Modiolus of cochlea	Hearing preservation	<4–5 Gy maximum
Cochlea	Hearing preservation	<6 Gy maximum
Spinal cord (RTOG 06-31)	Symptomatic myelopathy	0.35 ml <10 Gy[b] 0.035 ml <14 Gy[b]
Cauda equina (RTOG 06-31)	Symptomatic neuritis	<16 Gy maximum[b] 5 ml <14 Gy[b]
Spinal cord (conservative)	Symptomatic myelopathy	<8–10 Gy maximum
Thecal sac (conservative)	Symptomatic myelopathy	<10–14 Gy maximum

Conclusions



Conclusions

Patient to patient
evaluation of the risk/benefit ratio



In the last 15 years

from WBRT alone to other therapeutic options

- Surgery
- Surgery plus RT

WBRT

Only surgical bed

- SRS
- FSRT
- WBRT + SRS

Conclusions

Rimuovi

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Rimuovi

Grazie dell'attenzione