

Radioterapia stereotassica ablativa: quando è “standard of care”?

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WBRT

- ✓ *Standard palliative management for multiple brain metastases*
- ✓ *Short term relief of neurologic symptoms in > 70% patients*
- ✓ *Median survival 3-6 months*
- ✓ *Intracranial progression up to 40-50%*

➤ *Trials comparing WBRT schedules*

Study	Dose	Patients	Survival (months)
❖ RTOG Study 1	30 Gy in 10 fr 30 Gy in 15 fr 40 Gy in 15 fr 40 Gy in 20 fr	910	4.5
❖ RTOG Study 2	20 Gy in 5 fr 30 Gy in 10 fr 40 Gy in 15 fr	902	4
❖ RTOG Study 79-16	30 Gy in 10 fr 30 Gy in 15 fr	193 200	4.5 4.1
❖ RTOG Study 91-04	54.4 Gy in 34 fr 30 Gy in 10 fr	216 213	4.5 4.5

➤ *Recursive Partitioning Analysis (RPA)*

CLASS	PROGNOSTIC FACTORS	MEDIAN SURVIVAL (months)
CLASS I	KPS \geq 70 and age $<$ 65 controlled primary no extracranial metastases	7.1
CLASS II	All others	4.2
CLASS III	KPS $<$ 70	2.3

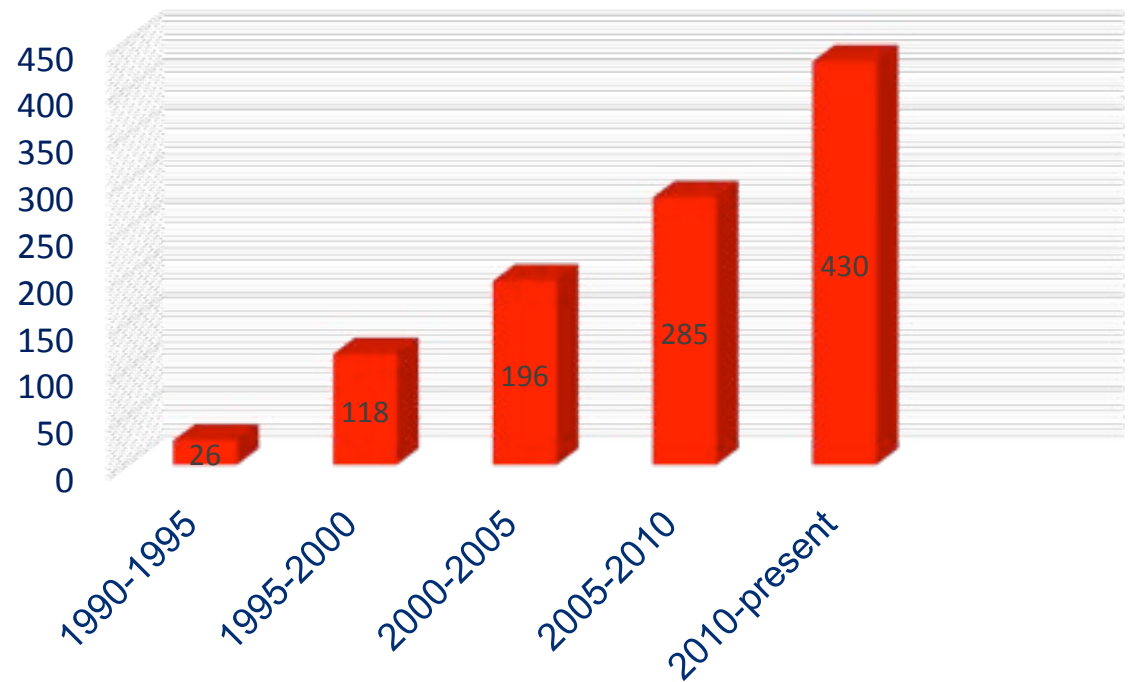
➤ *Solitary brain metastasis*

❖ Randomized trials (S+WBRT vs WBRT)

Authors	Patients	OS S + WBRT	OS WBRT	P
Patchell 1990	48	9.2	3.5	< 0.05
Noordijk 1994	63	10	6	< 0.05
Mints 1996	84	6.3	5.6	NS

➤ *Stereotactic Radiosurgery (SRS)*

- *Gamma Knife*
- *LINAC SRS*
- *Cyberknife*
- *Proton SRS*
- *Tomotherapy*

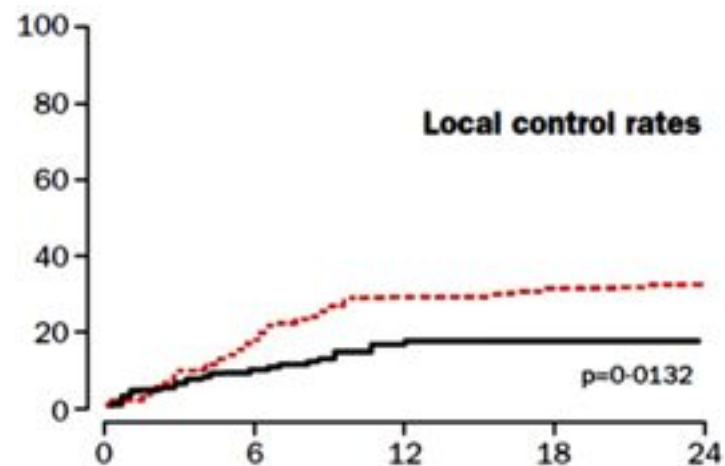
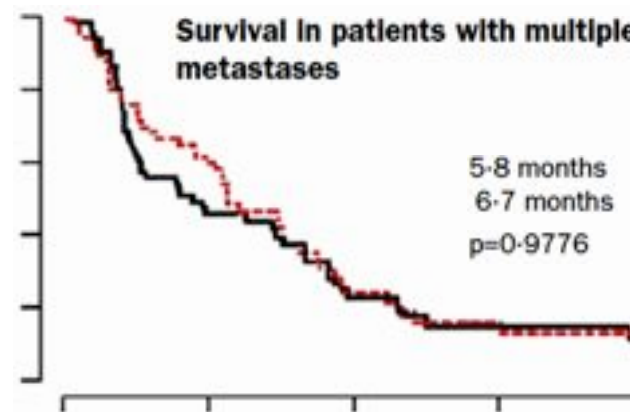
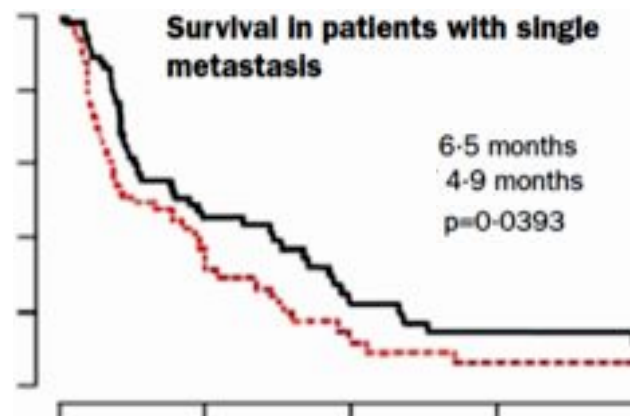
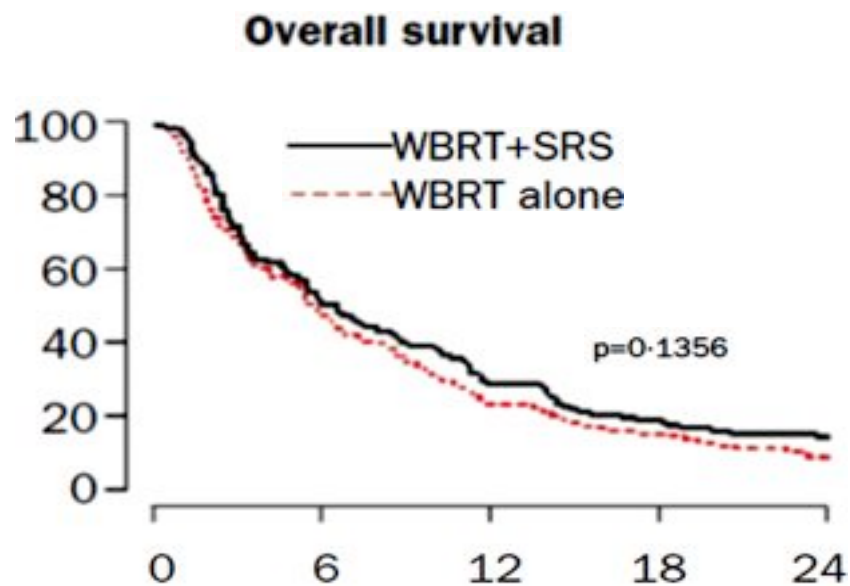


No of publications

With the establishment of the efficacy of SRS, new controversies have arisen

- ✓ *Does the addition of SRS to WBRT improve survival in patients with brain metastases?*

➤ RTOG 9508



➤ *RTOG 9508*

- ✓ *the advantage of SRS adding to WBRT was proven only for single brain metastasis*
- ✓ *The addition of SRS to should be the standard treatment for patients with a single unresectable brain metastasis and considered for patients with 2 or 3 metastases*

➤ controversial issue

*Is WBRT necessary after focal therapy
(surgery or SRS)?*

*SRS/S
vs
SRS/S + WBRT*

Kentucky study

- JAMA 1998,280:1485-9

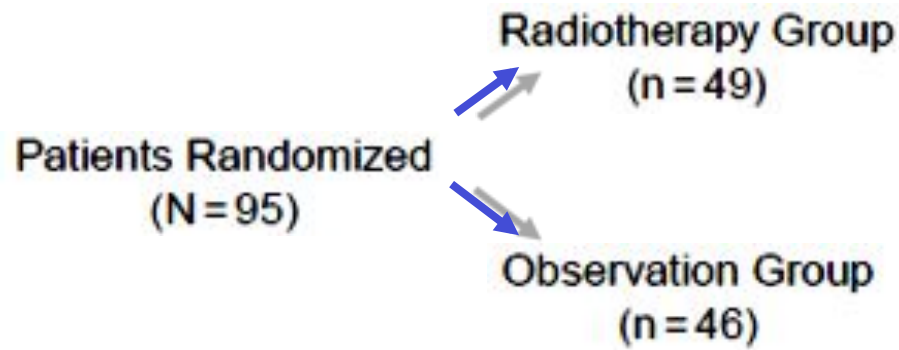
JROSG 99-1

JAMA 2006,295:2483-91

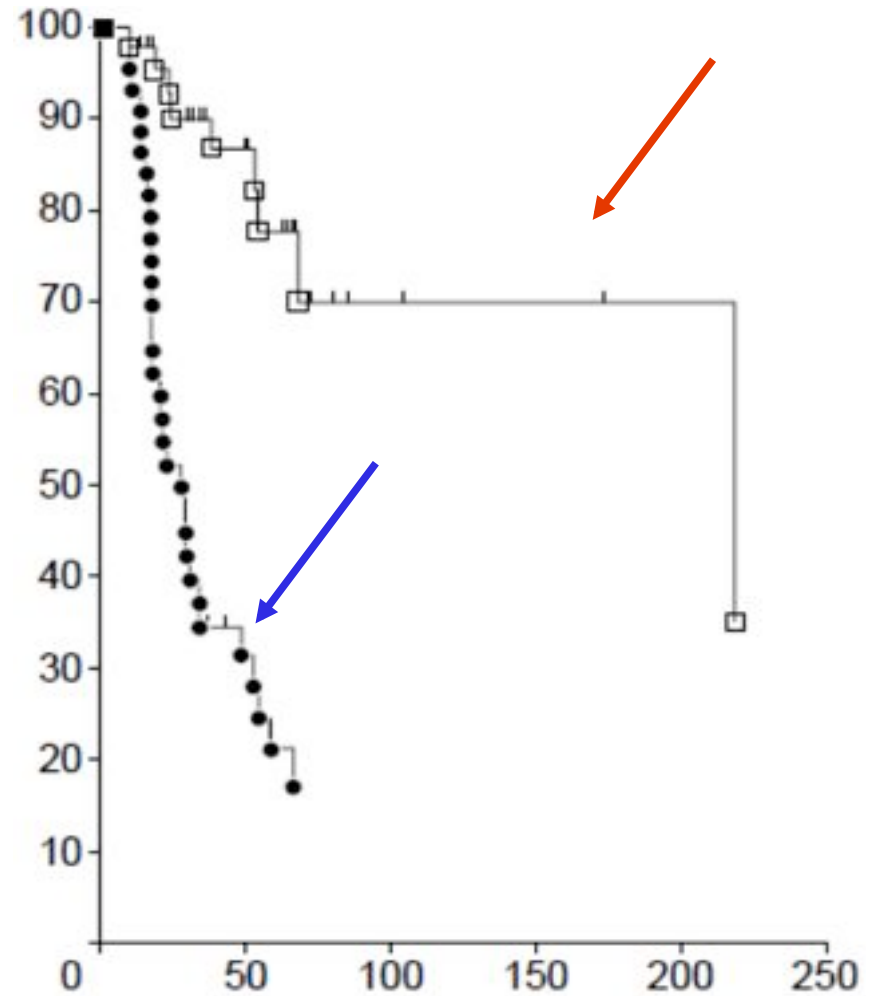
EORTC 22952-26001

JCO 2011,29:134-141

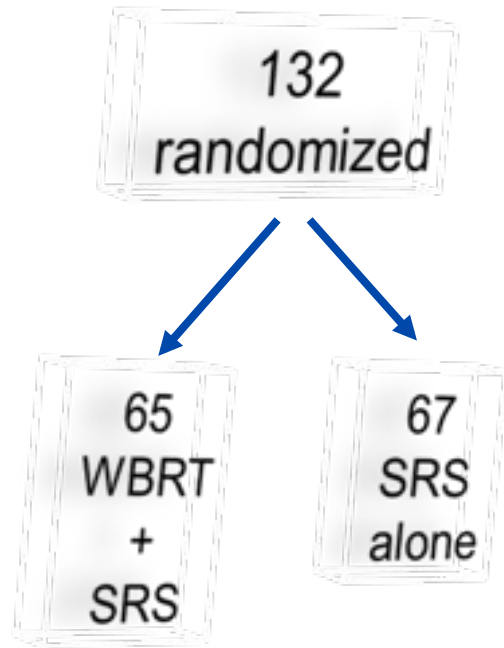
➤ *Kentucky study*



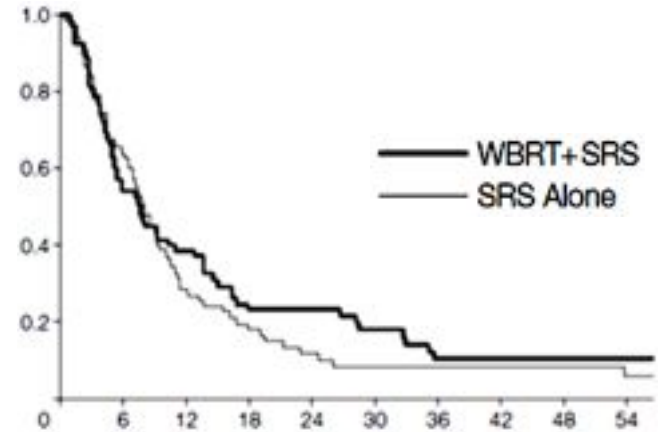
Recurrence Free, %



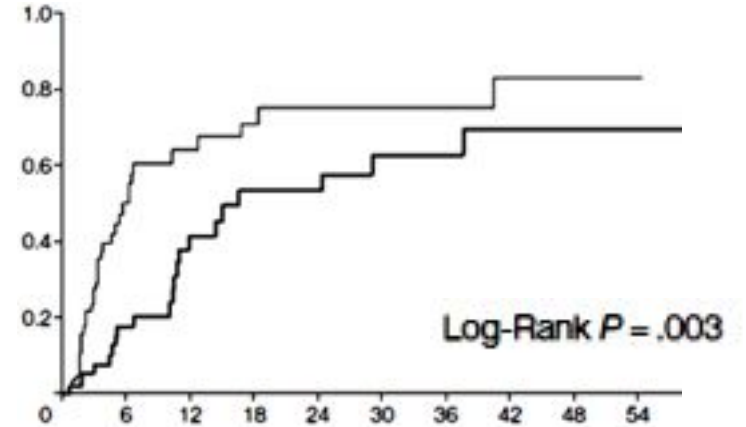
➤ *JROSG 99-1 study*



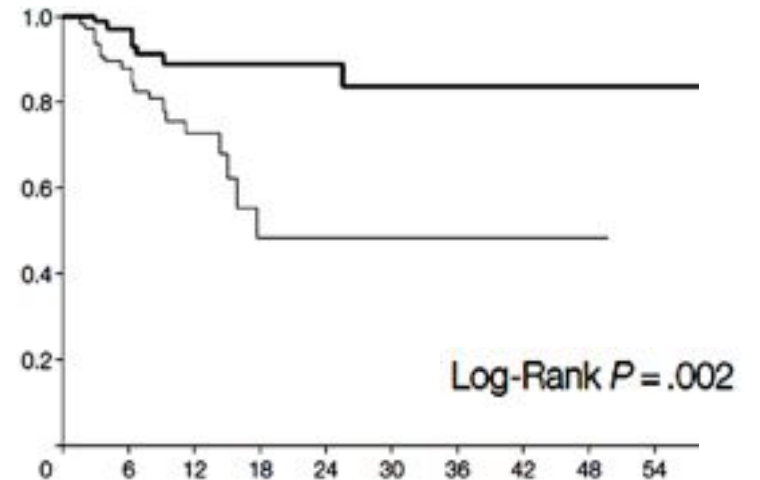
Overall survival



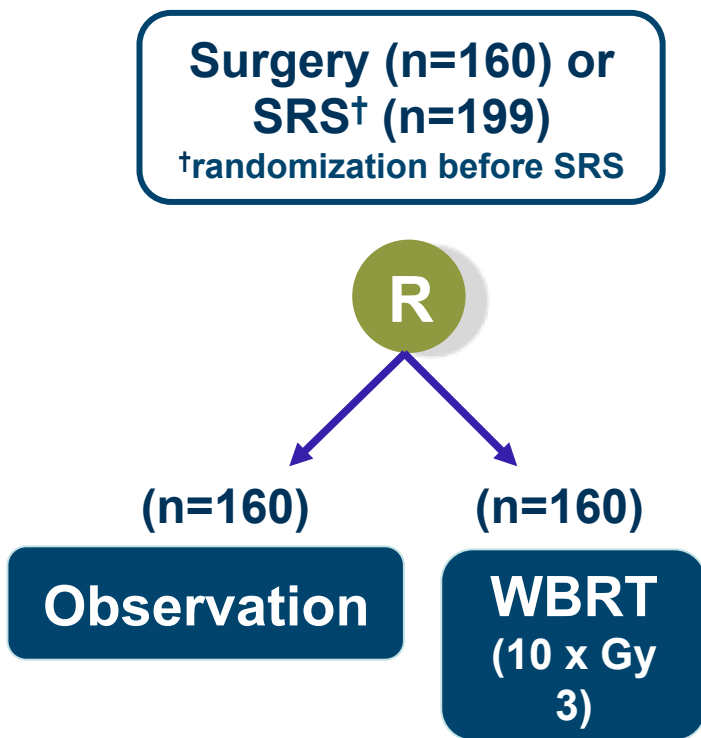
Brain tumor recurrence at distant sites



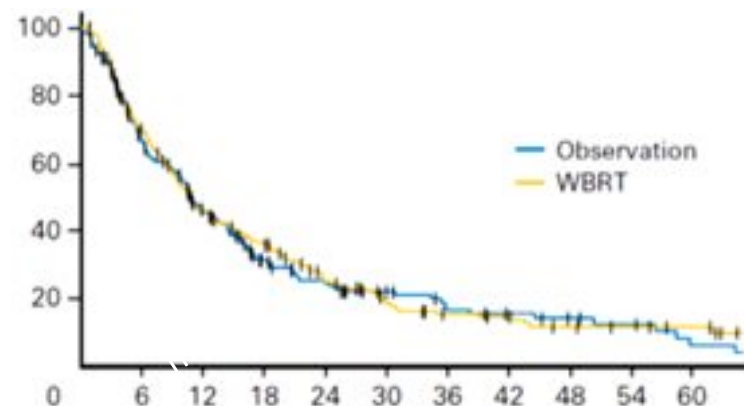
Local control of irradiated lesions



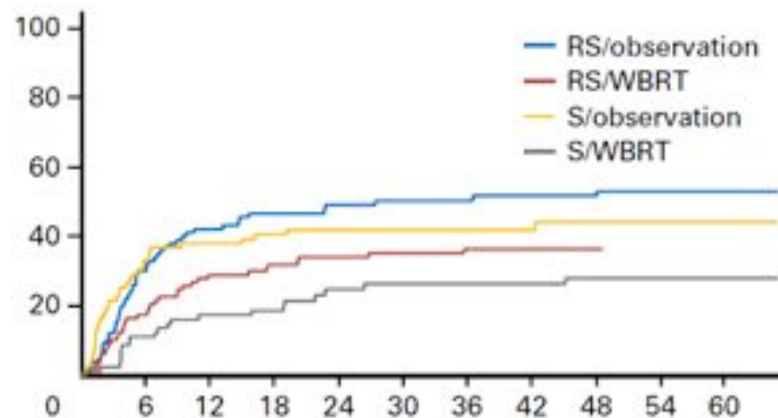
➤ EORTC 22952-26001



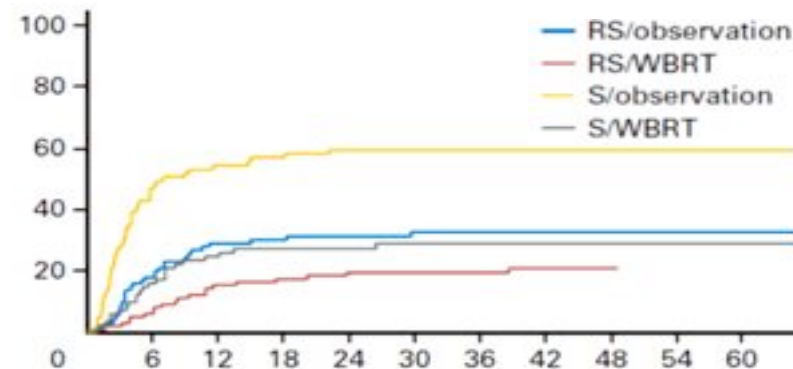
Overall survival



Brain tumor recurrence at distant sites



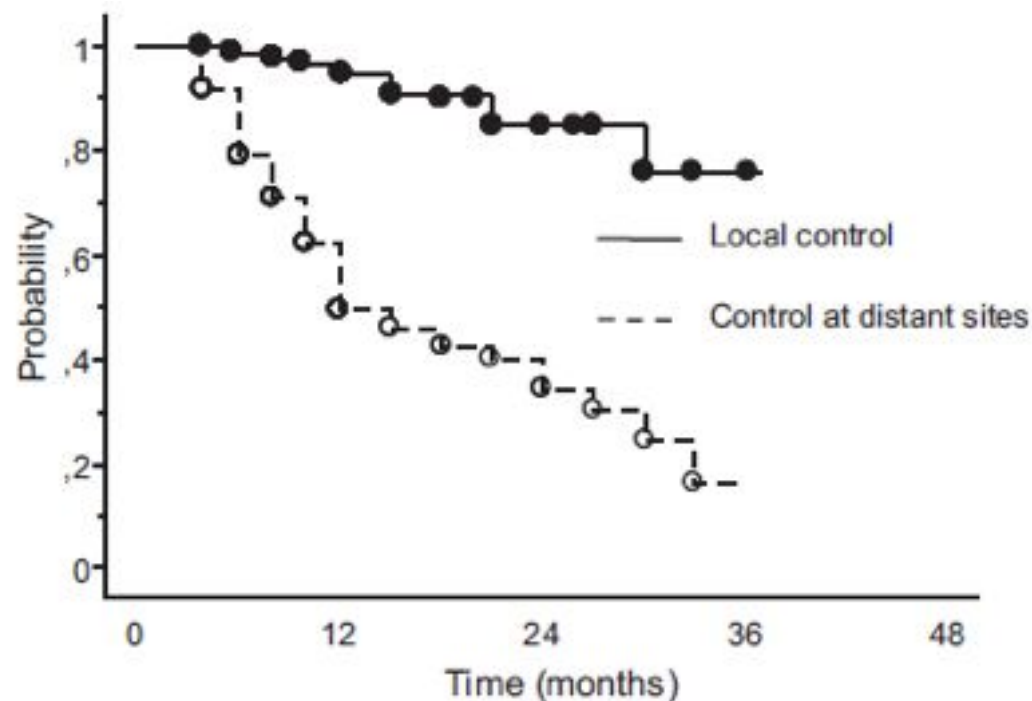
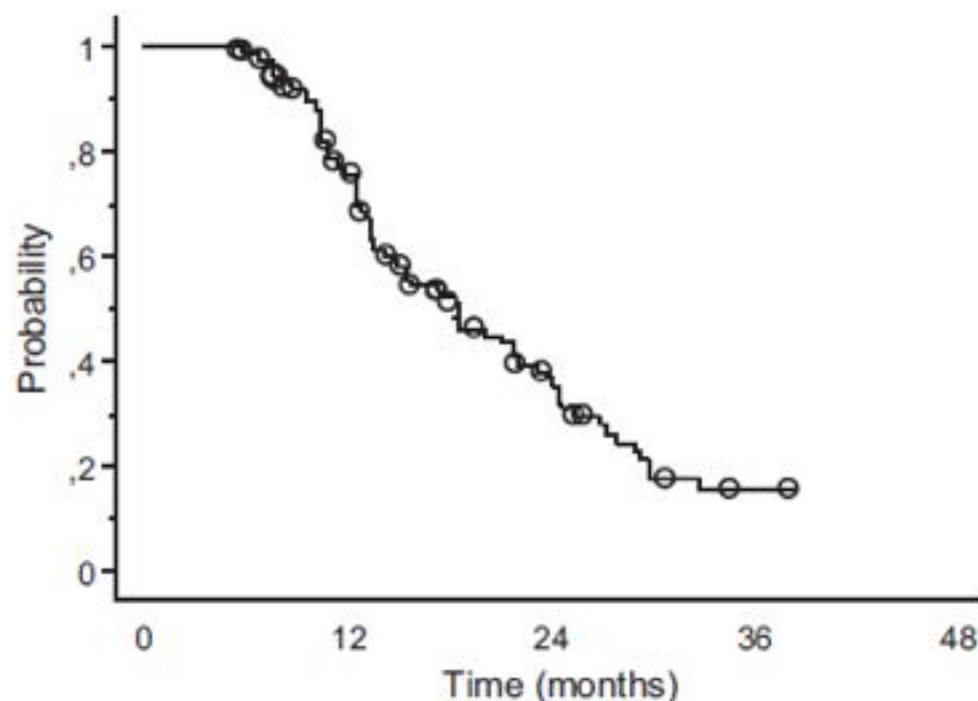
Brain tumor recurrence at initial sites



Multidose Stereotactic Radiosurgery (9 Gy × 3) of the Postoperative Resection Cavity for Treatment of Large Brain Metastases

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➤ *Summary*

- ✓ *In patients with multiple metastases SRS alone without WBRT is associated with increased intracranial tumor progression; however, it does not result in an increased risk of clinical deterioration or neurological death. Therefore, SRS alone could be a treatment option in selected patients with multiple brain metastases*
- ✓ *In patients with a single brain metastasis SRS and resection plus SRS are an effective treatment strategy*

➤ *controversial issue*

- ✓ *the impact of different treatments
SRS vs WBRT ± SRS on
neurocognitive function*

➤ *Neurocognitive function after WBRT*

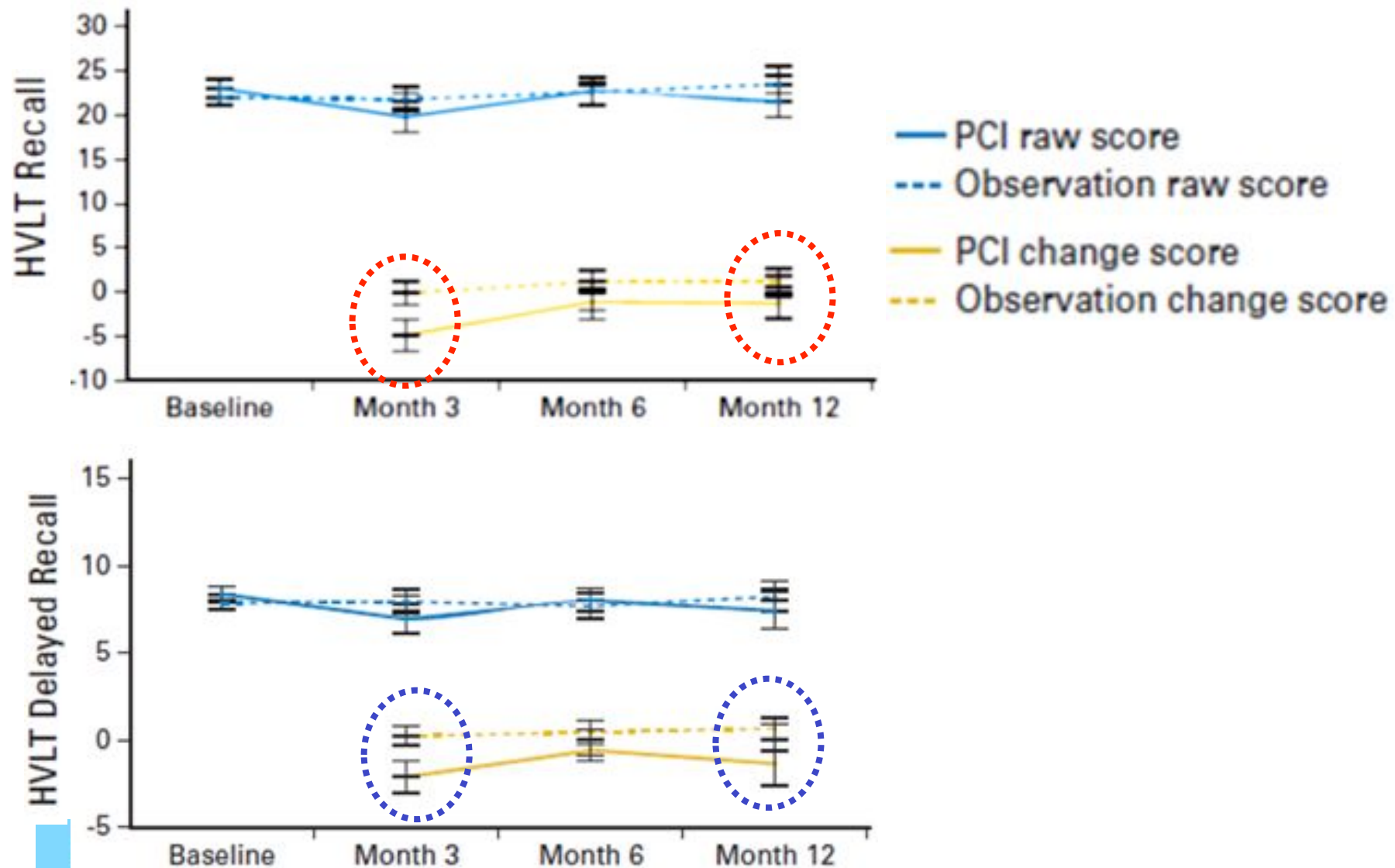
➤ *Murray et al 2000*

- ✓ *Improvement of MMSE score after WBRT 55%*

➤ *Regine et al 2001*

- ✓ *Decline of MMSE at 4 months (only in progressive patients)*

Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non-Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis

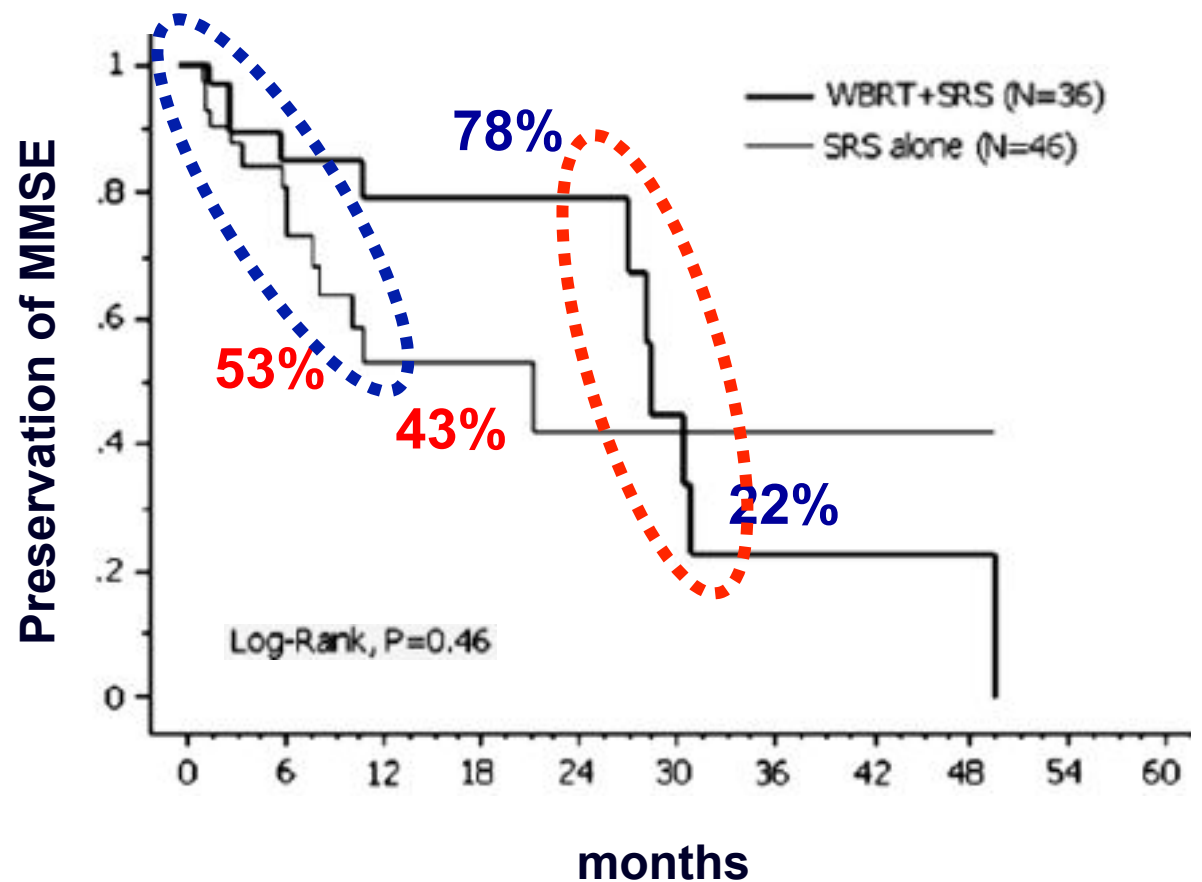


➤ JROSG 99-1 study

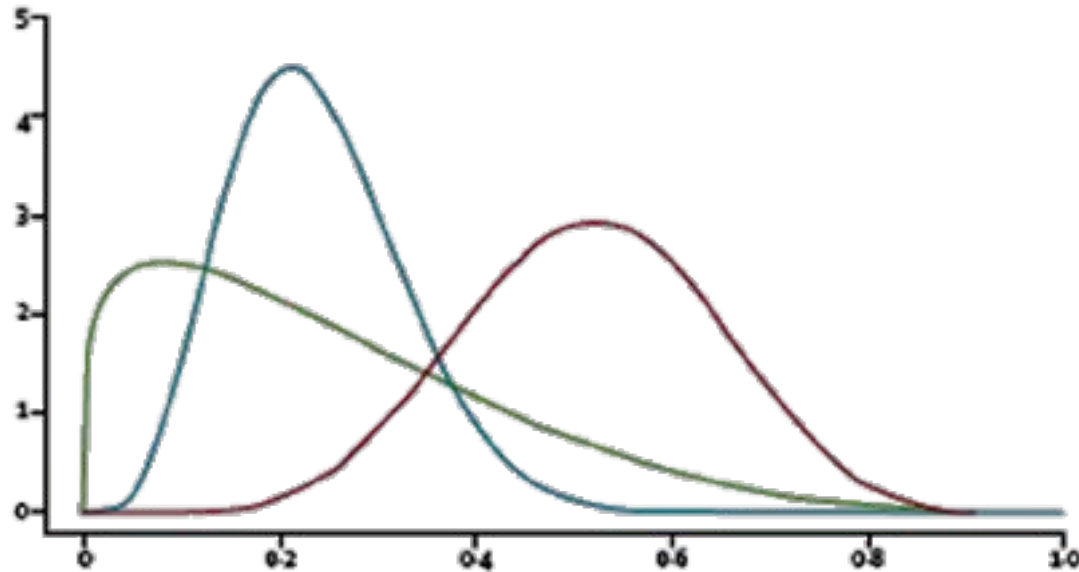
- ✓ Preservation of neurocognitive function (NCF)

Decline of NCF due to brain progression

Decline of NCF due to radiation toxicities



➤ *MDDCA study*



	SRS + WBRT N = 11	SRS N = 20
Total recall	52%	24%
Delayed recall	22%	6%
Delayed recognition	11%	0%

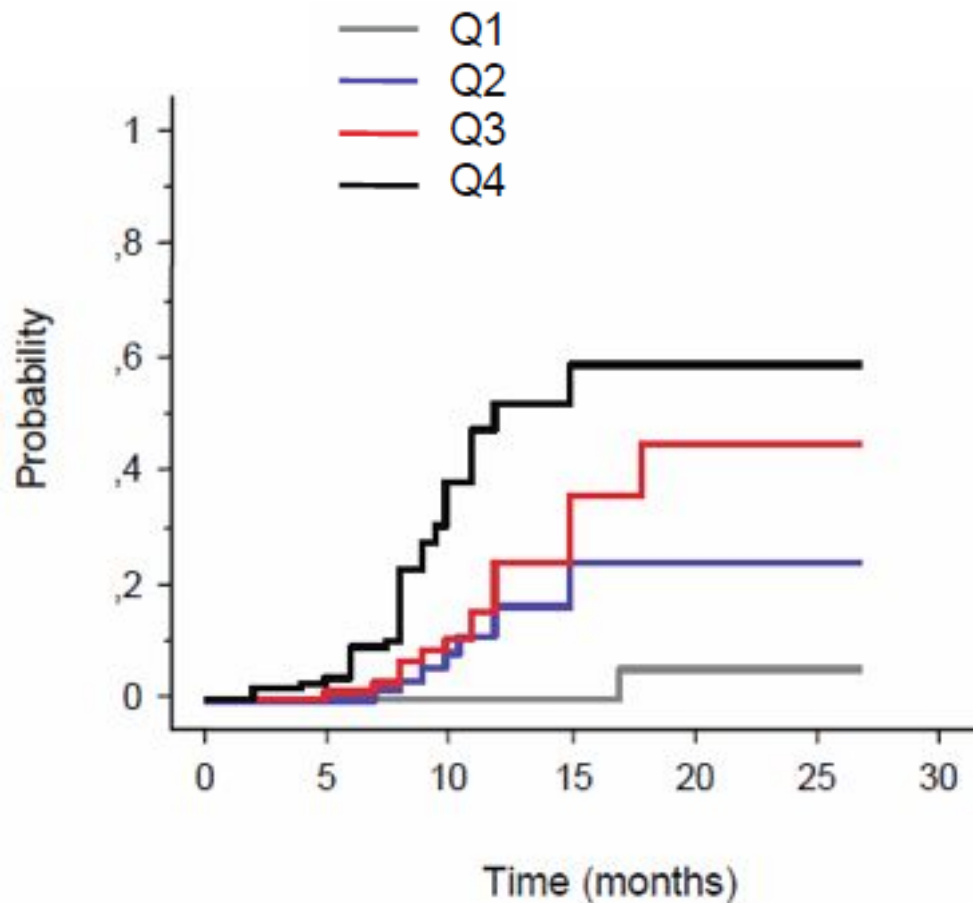
✓ initial SRS alone combined with close clinical monitoring should be the preferred treatment strategy for such patients

➤ *Neurocognitive function and quality of life*

- ✓ *Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with SRS alone.*
- ✓ *Adjuvant WBRT after surgery or SRS of brain metastases may negatively impact some aspects of HRQOL, even if these effects are transitory.*
- ✓ *Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve neurocognitive function and quality of life.*

➤ Toxicity of SRS

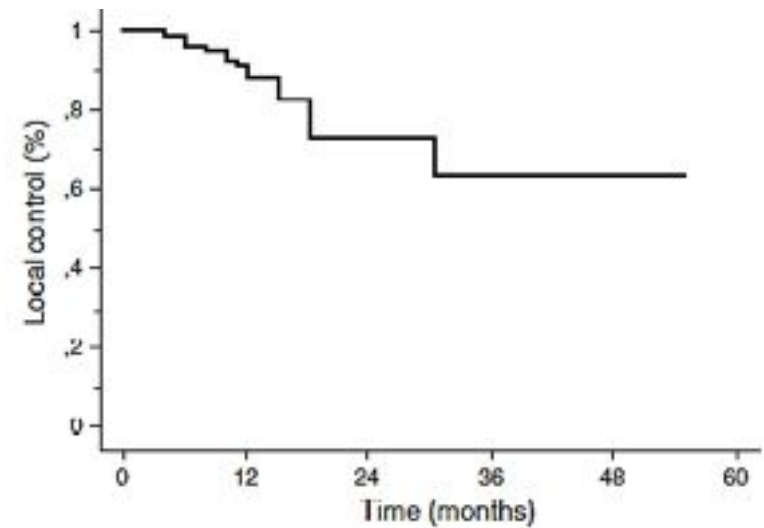
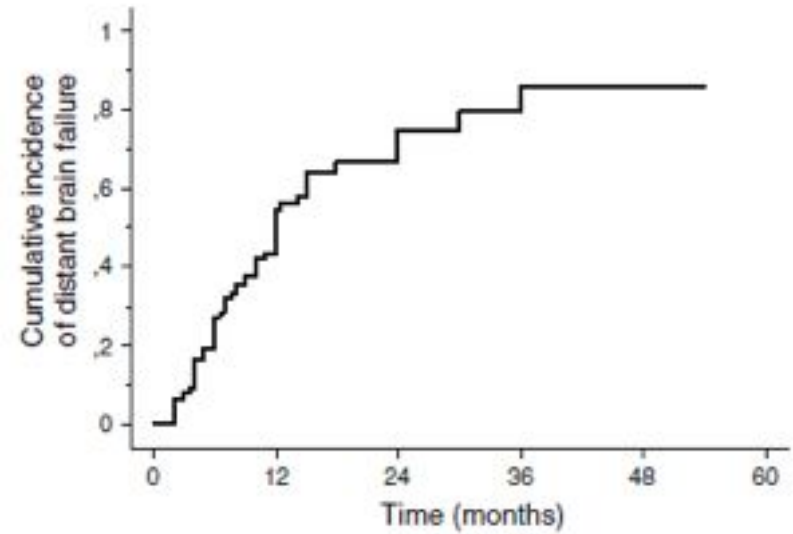
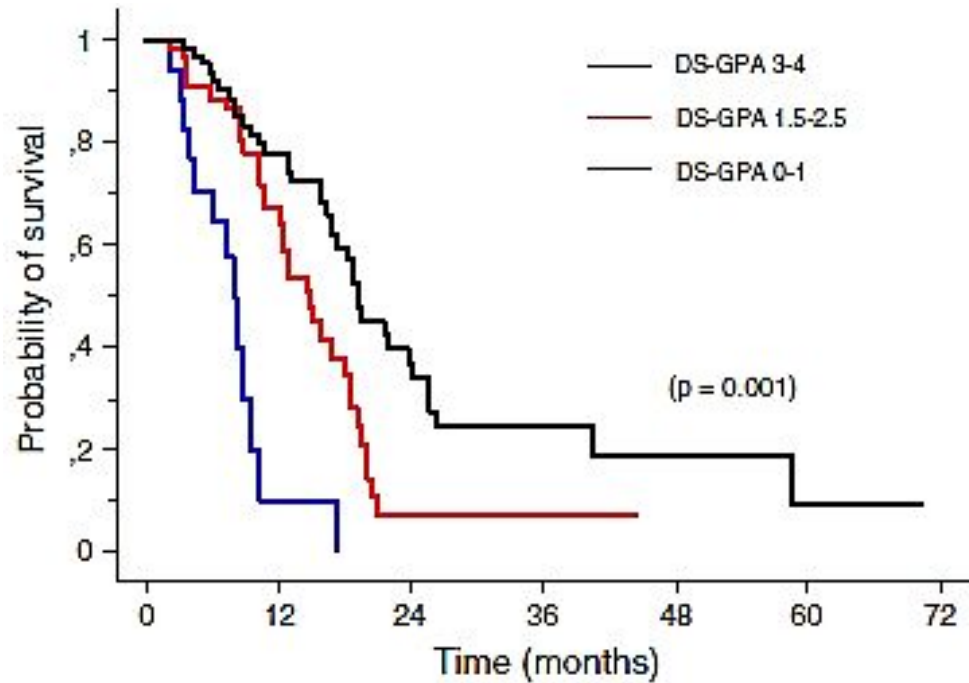
Radiation-induced brain necrosis



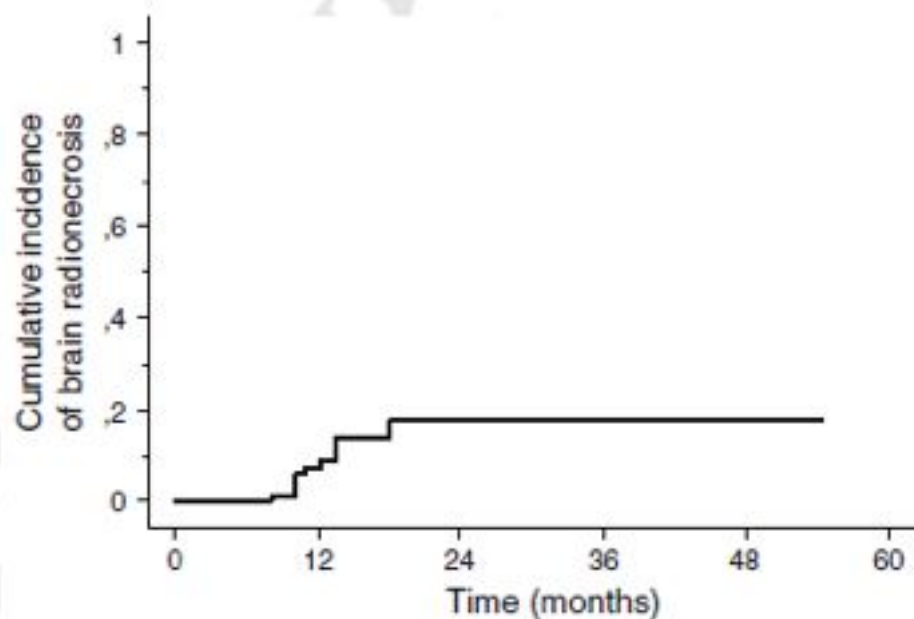
2.6% for V12 Gy < 3.3 cm³ (Q1),
11% for V12 Gy of 3.3-5.9 cm³ (Q2)
24% for V12 Gy of 6.0-10.9cm³ (Q3)
47% for V12 Gy of >10.9 cm³ (Q4)

The actuarial risk at 1 year for the development of brain radionecrosis was 0% in Q1, 16% in Q2, 24% in Q3, and 51% for V12

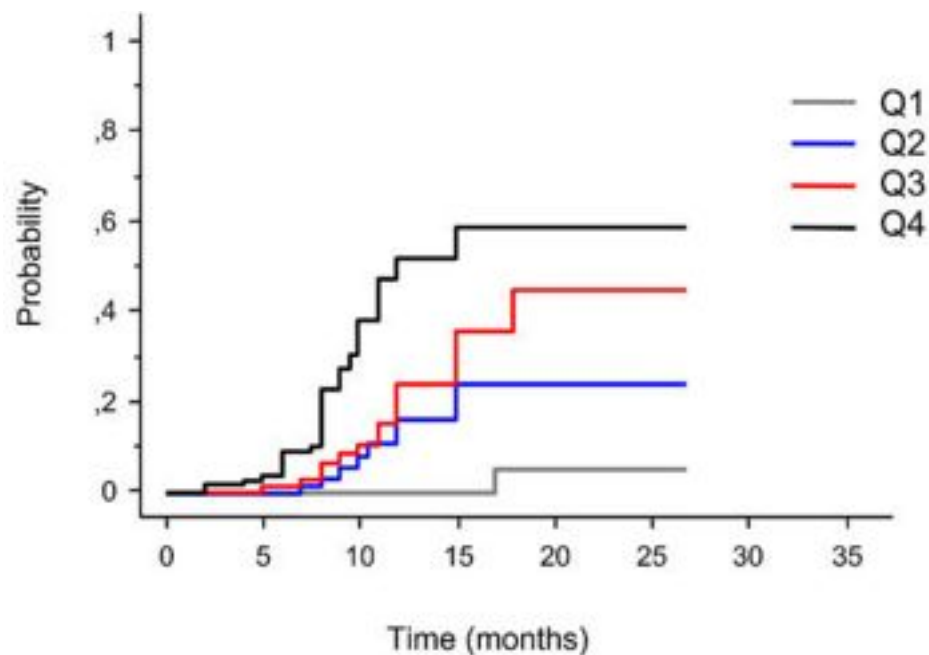
➤ Multi-fraction SRS



➤ Single-fraction SRS versus multi-fraction SRS



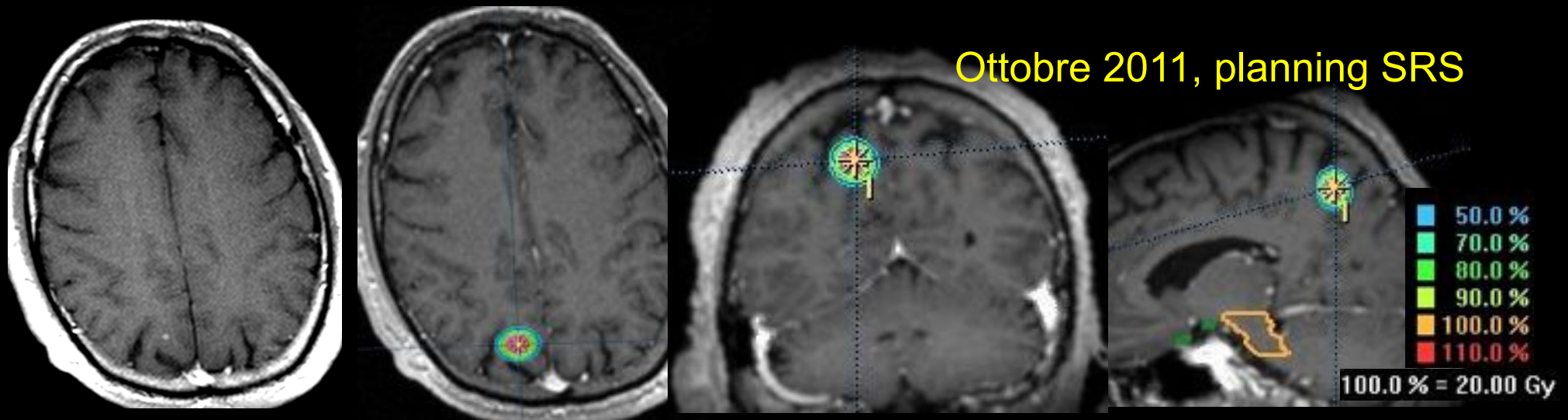
- 1-year risk of radionecrosis was 14% for $V18Gy \geq 26.2 \text{ cm}^3$, and 4% for $V18Gy < 26.2 \text{ cm}^3$, respectively.



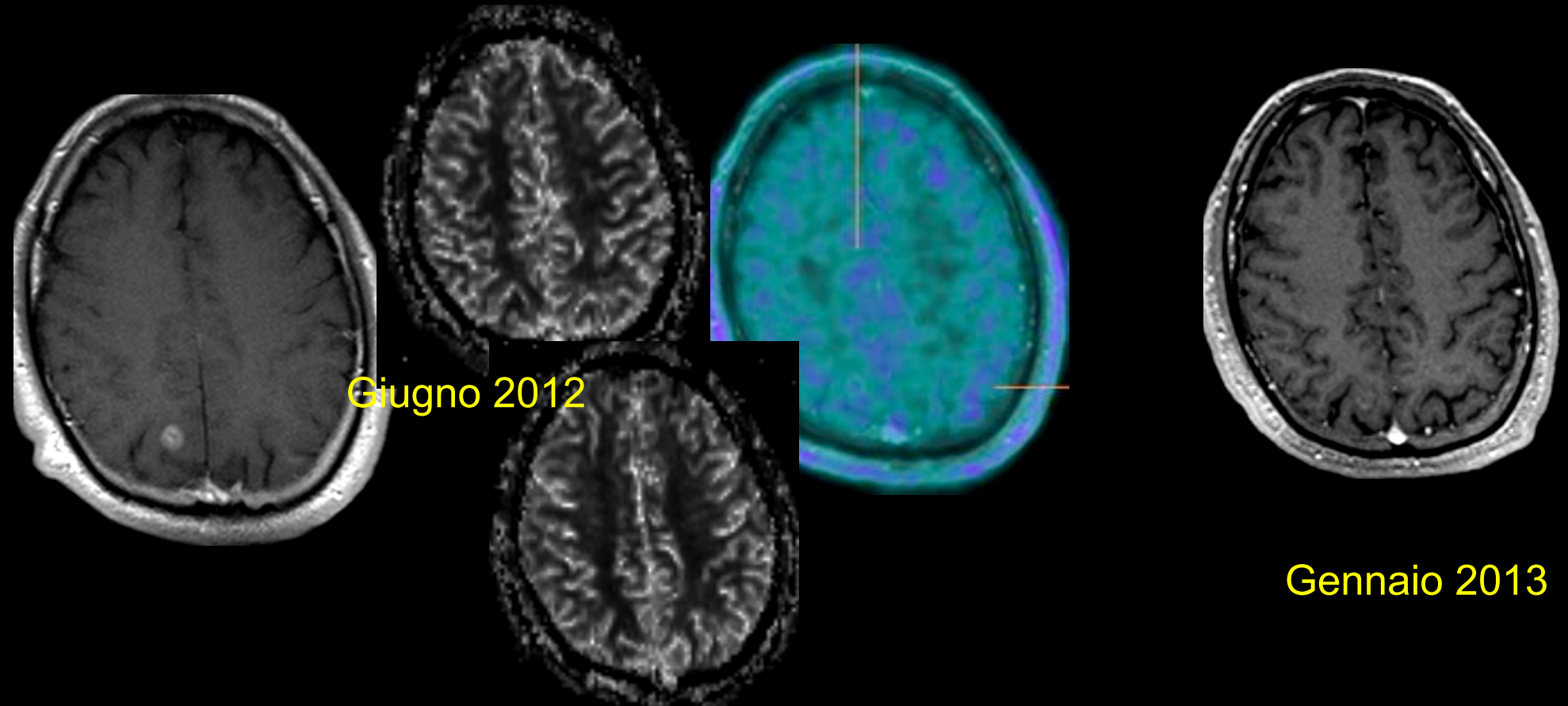
- 1-year risk of radionecrosis was 24% for $V12 \text{ Gy}$ of $6.0\text{-}10.9 \text{ cm}^3$ and 51% for $V12 \text{ Gy} > 10.9 \text{ cm}^3$, respectively.

Metastasi cerebrale da melanoma trattata con SRS

Ottobre 2011, planning SRS



Giugno 2012



Gennaio 2013

➤ *When SRS is standard care? Single brain metastasis*

- ✓ *For a single brain metastasis $\geq 3-4$ cm and amenable to safe complete resection, whole brain radiotherapy (WBRT) and surgery (**level 1**) should be considered. Alternative is surgery and SRS to the resection cavity (**level 3**).*
- ✓ *For single metastasis $< 3-4$ cm, SRS alone or WBRT and SRS or WBRT and surgery (all based on **level 1**) should be considered. Another alternative is surgery and SRS to the resection cavity (**level 3**). For single brain metastasis ($< 3-4$ cm) that is not resectable or incompletely resected, WBRT and SRS, or SRS alone should be considered (**level 1**).*
- ✓ *For nonresectable single brain metastasis ($\geq 3-4$ cm), WBRT should be considered (**level 3**).*

➤ *When SRS is standard care? Multiple brain metastases*

- ✓ *For selected patients with multiple brain metastases (all less than 3-4 cm) and good prognosis, SRS alone, WBRT and SRS, or WBRT alone should be considered (level 1). Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered (level 3).*
- ✓ *Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT (level 3).*
- ✓ *It should be recognized, however, that there are limitations in the ability of physicians to accurately predict patient survival. Prognostic systems such as recursive partitioning analysis, and diagnosis-specific graded prognostic assessment may be helpful.*

Thank you for your attention

