Radioterapia Stereotassica Ipofrazionata metastasi cerebrali

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Congresso Inter-regionale
AIRO Lombardia e AIRO Piemonte-Liguria-Valle d'Aosta

L'INNOVAZIONE TECNOLOGICA IN RADIOTERAPIA: NUOVI STANDARD CLINICI E PROBLEMATICHE GESTIONALI

Centro Congressi VILLA CAGNOLA
Via Cagnola, 19 - Gazzada Schianno (VA)

Sabato 29 novembre 2014

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Radiosurgery

Evidences

-Single dose stereotactic radiosurgery (SRS) + WBRT leads to a significantly longer overall survival compared to WBRT alone for the patients with good performance status (KPS >70) and single brain metastases (level 1 evidence)

- SRS + WBRT, seems to be more effective than WBRT alone in terms of local control in patients with one to four metastases and KPS >70 (level 2 evidence)

- SRS + WBRT may lead to significantly longer survival in patients with two to three metastases (level 3 evidence)

-The authors note that the incidence of distant recurrence is lower when WBRT is added

Lindsey ME et al. J Neurooncol Jan 96(1):45-68.

Radiosurgery
diffusion and limits

ASTRO guidelines

Practical Radiation Oncology (2012) **2**, 210–225

Table 1 Single brain metastasis—initial management

Prognostic category ([a])	Other features	Treatment options (evidence grade) references	Clinical benefit S	LC	WB control	Neurocognition
Good prognosis Expected survival 3 mo or more	Complete resection possible	If brain metastasis ≤3-4 cm: • Surgery and WBRT (level 1)[10,11,22,23,42,43,b]	✓	✓	✓	
		• Radiosurgery and WBRT (level 1)[51,53]	✓	✓	✓	
		• Radiosurgery alone (Level 1)[23,54]		✓		✓
		• Surgery with radiosurgery/radiation boost to the resection cavity with or without WBRT (level 3)[26-41,b]		✓	✓ (with WBRT)	
		If brain metastasis >3-4 cm: • Surgery and WBRT (level 1)[10,11,22,23,42,43,b]				
		• Surgery with radiosurgery/radiation boost to the resection cavity with or without WBRT (level 3)[26-41,b]				
Good prognosis Expected survival 3 mo or more	Not resectable	If brain metastasis ≤3-4 cm: • Radiosurgery and WBRT (level 1)[51,53]				
		• Radiosurgery alone (level 1)[23,54]				
		If brain metastasis >3-4 cm: • WBRT (level 3), with consideration of biopsy, if primary unknown[59,85,86]				
Poor prognosis Expected survival less than 3 mo		• WBRT (level 3)[59,85] • Palliative care without WBRT (level 3)[59,85]				

Table 2 Multiple brain metastases-initial management

Prognostic category ([a])	Other features	Treatment options (evidence grade) references	Clinical benefit S	LC	WB control	Neuroco
Good prognosis Expected survival 3 mo or more	All brain metastases ≤3-4 cm[b]	• Radiosurgery and WBRT (level 1)[51,53]		✓	✓	
		• Radiosurgery alone[23,54] (level 1)		✓		✓
		• WBRT (level 1)[59,85]		✓	✓	
Good prognosis	Brain metastasis/ metastases causing significant mass effect[c]	• Safe surgical resection of the brain metastasis/metastases causing significant mass effect and postoperative WBRT (level 3)[25,b]		✓	✓	
Expected survival 3 mo or more		• WBRT (level 3)[59,85]	✓	✓	✓	
Poor prognosis Expected survival less than 3 mo		• WBRT (level 3)[59,85] • Palliative care without WBRT (level 3)[59,85]		✓	✓	

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HSRT

limits and postulate

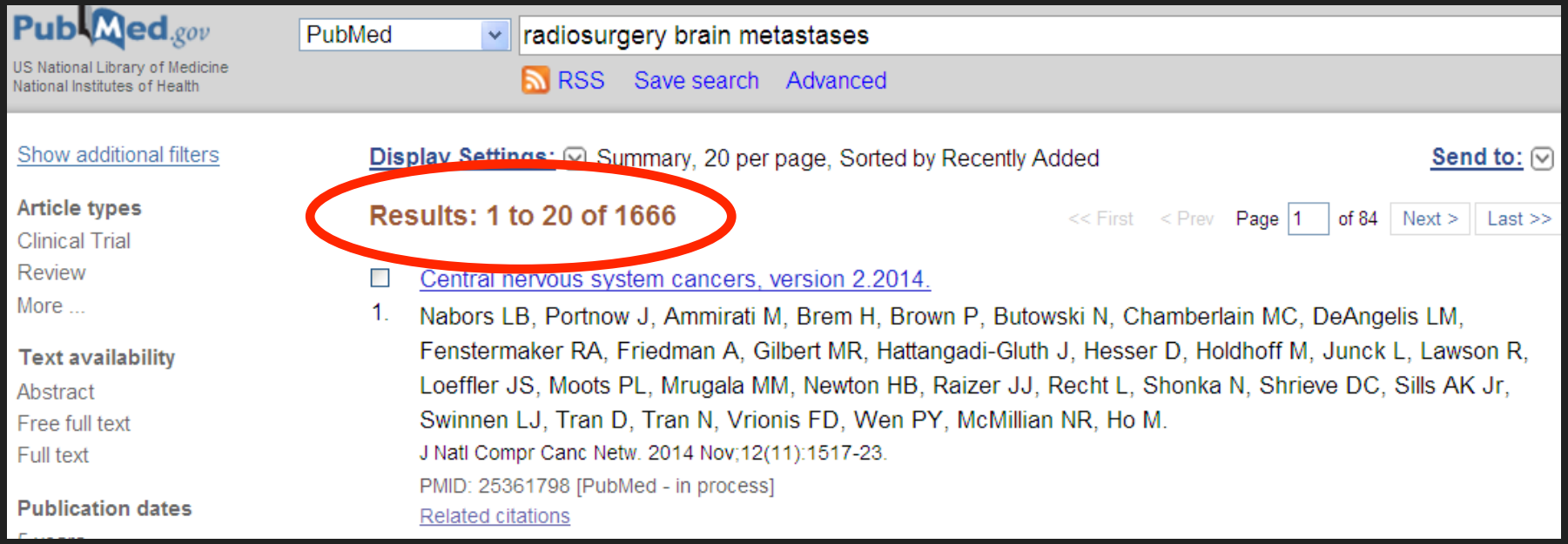
If the SRS has been limited traditionally by the lesion's dimensions and the proximity of critical structures

On the other hand the extent of late toxicity following WBRT is not well established, and so whether late toxicity is a major concern for clinicians is an open question (Hasegawa 2009, Soffietti 2013)

→HSRT could be the solution (??)

Indeed, Hypofractionated Stereotactic RadioTherapy (HSRT), by focusing the field of impact of the radiation, would theoretically improve the sparing of critical structures, and consequently may limit the long-term side effects of radiation therapy.

Lower dose per fraction may optimize the dose to the tumour and to the critical structures by increasing the BED to the tumour and at the same time by decreasing the BED to the OAR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J Natl Compr Canc Netw. 2014 Nov;12(11):1517-23.
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1. Optimal hypofractionated conformal radiotherapy for large brain metastases in patients with high risk factors: a single-institutional prospective study.
Inoue HK, Sato H, Suzuki Y, Saitoh JI, Noda SE, Seto KI, Torikai K, Sakurai H, Nakano T.
Radiat Oncol. 2014 Oct 17;9(1):231. [Epub ahead of print]
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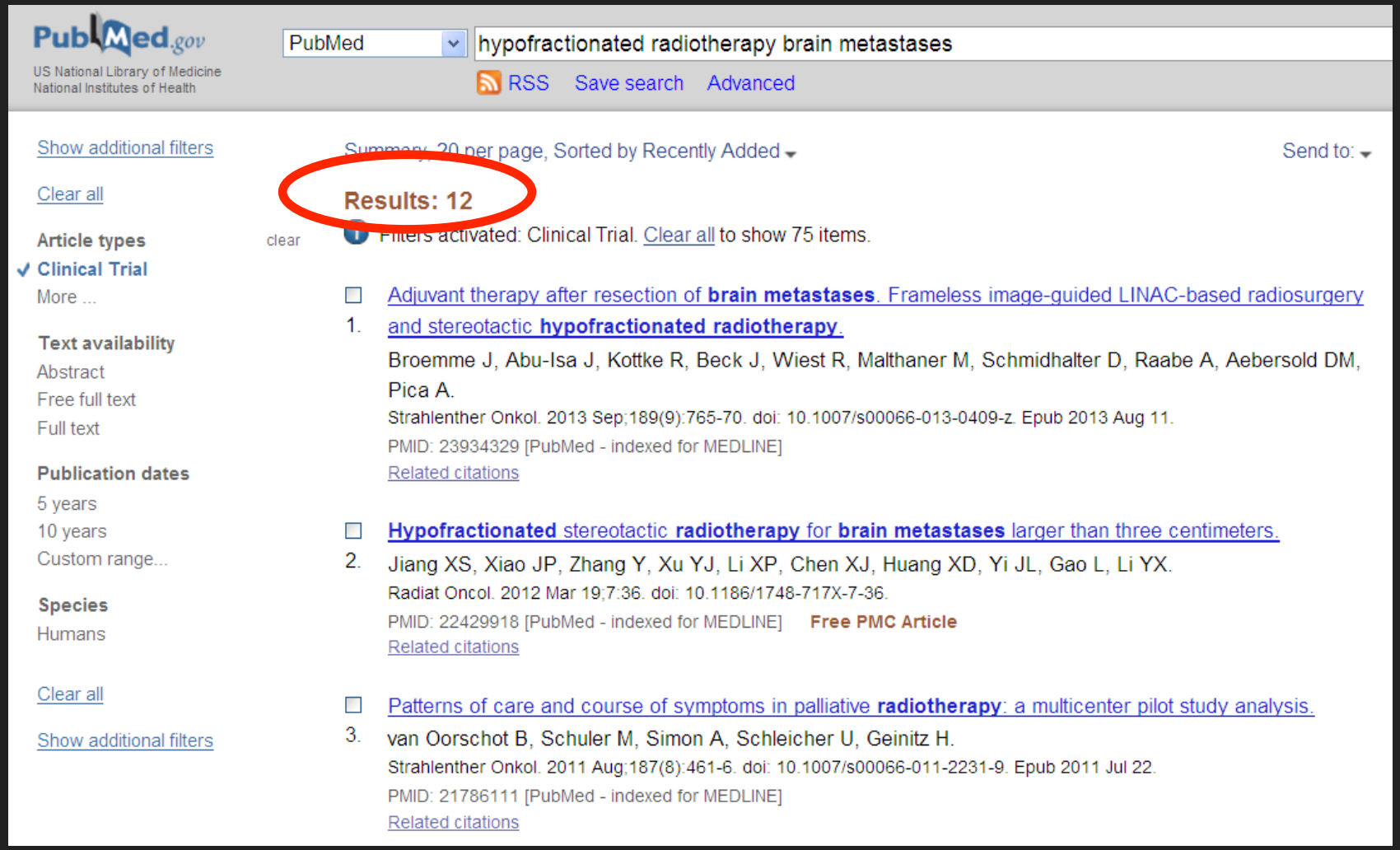

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Retrospective observational studies

Hypofractionated stereotactic radiotherapy as an alternative to radiosurgery for the treatment of patients with brain metastases.

Manning MA, Cardinale RM, Benedict SH, Kavanagh BD, Zwicker RD, Amir C, Broaddus WC.

Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):603-8.

- Pts — 32 (57 mets)
- Dose — 27Gy/3fr
- WBRT — all (30Gy)
- Median S — 12 mo

HSRT → Effective, more confortable and less expensive than SRS

Hypofractionated stereotactic radiotherapy for oligometastases in the brain: a single-institution experience.

Marchetti M, Milanesi I, Falcone C, De Santis M, Fumagalli L, Brait L, Bianchi L, Fariselli L.

Neurol Sci. 2011

- Pts: 65 (81 mets)
- Radioresistant: yes
- Dose: 21Gy/3fr; 24Gy/3fr
- WBRT: with or without

- OS: 69.3% (6mo); 51.7% (12 mo); 23.3% (36 mo)
- 1 yr LC: 58.6%

- Cause of Death:

Sistemic progression	68%
Intracerebral progression	19 %
Local Progression	10 %
Unrelated causes	3 %

- Toxicity: 1 pt surgery due to persistent oedema

- Significant Prognosic factors: RPA
- Not significant prognosic factors: volume; prev WBRT; hystology

Hypofractionated stereotactic radiotherapy of limited brain metastases: a single-centre individualized treatment approach.

Märtens B, Janssen S, Werner M, Frühauf J, Christiansen H, Bremer M, Steinmann D.

BMC Cancer. 2012

• Pts		75 (108 mets)
• Radioresistant		yes
• Dose		5Gy x 6-7fr; 6Gy x 5fr
	(Rec)	4Gy x 7-10fr; 5Gy x 5-6
• WBRT		with or without
• OS		59% (6mo)
		35% (12 mo)
• Median surv		9.1 mo
• Toxicity		mild (but higher if > 35Gy)
• Significant Prognosic factors:		EQD2 > 35Gy; vol; steroids uptake; primary tumor activity

Hypofractionated frameless stereotactic intensity-modulated radiotherapy with whole brain radiotherapy for the treatment of 1-3 brain metastases.

De Potter B, De Meerleer G, De Neve W, Boterberg T, Speleers B, Ost P.

Neurol Sci. 2013

• Pts	38
• Radioresistant	yes
• Dose	30Gy/5fr
• WBRT	with
• OS	65% (6mo)
	35% (12 mo)
• Median survival	7.6 mo
• 1 yr LC	66%
• Cause of Death:	Local Progression 5 %
• Toxicity	low/mild

Fractionated stereotactic radiosurgery for patients with brain metastases.

Minniti G, D'Angelillo RM, Scaringi C, Trodella LE, Clarke E, Matteucci P, Osti MF, Ramella S, Enrici RM, Trodella L.

J Neurooncol. 2014

- Pts: 135 (171 mets)
- Radioresistant: yes
- Dose: 9Gy x 3fr; 12 x 3 Gy/3fr
- WBRT: no

- OS: 57% (12 mo); 25% (24 mo)

- 1 yr LC: 88%
- 2 yr LC: 72%

- Cause of Death: Sistemic progression 78%; Intracerebral progression 22 %

- Toxicity: 5 pts RTOG 3-4 RMN related symptoms

- Significant Prognosic factors: melanoma histology; volume (univariate only)
- Not significant prognosic factors: KPS; DS-GPA; extracranial disease; dose
- Actuarial RN risk: 9% (1 yr); 18 % (2 yrs)

Fractionated stereotactic radiosurgery for patients with skull base metastases from systemic cancer involving the anterior visual pathway.

Minniti G, Esposito V, Clarke E, Scaringi C, Bozzao A, Falco T, De Sanctis V, Enrici MM, Valeriani M, Osti MF, Enrici RM.

Radiat Oncol. 2014

- Pts 34
- Radioresistant yes
- Dose 5Gy x 5fr
- WBRT no

- OS 63% (12 mo)
  32% (24 mo)

- 1 yr LC 89%
- 2 yr LC 72%

- Cause of Death: Sistemic progression 78%
  Intracerebral progression 22 %

- Toxicity mild, transient

- Significant Prognosic factors: extracranial disease; KPS

- Not significant prognosic factors: histology; mets #

Tollerance retrospective studies

Three-fraction CyberKnife radiotherapy for brain metastases in critical areas: referring to the risk evaluating radiation necrosis and the surrounding brain volumes circumscribed with a single dose equivalence of 14 Gy (V14).

Inoue HK, Seto K, Nozaki A, Torikai K, Suzuki Y, Saitoh J, Noda SE, Nakano T

J Radiat Res. 2013

- Pts 145
- Radioresistant yes
- Dose 27-30Gy/3fr
- WBRT no
- OS not reported
- 7 months LC 95.8%
- Toxicity 3 pt surgery (radiation necrosis/ persistent oedema)
- Recommendation to limit the V14 (sde)

Five-fraction CyberKnife radiotherapy for large brain metastases in critical areas: impact on the surrounding brain volumes circumscribed with a single dose equivalent of 14 Gy (V14) to avoid radiation necrosis.

Inoue HK, Sato H, Seto K, Torikai K, Suzuki Y, Saitoh J, Noda SE, Nakano T.

J Radiat Res. 2014

- Pts — 78 (85 mets)
- Radioresistant — yes
- Dose — 31-35Gy/5fr
- WBRT — no
- OS — not reported
- 7 months LC — 95.8%
- Toxicity — 2 pt surgery (radiation necrosis/persistent oedema)
- Recommendation — to limit the V14 (SDE), 28.8Gy

Prospective studies

Hypofractionated stereotactic radiotherapy for brain metastases larger than three centimeters.

Jiang XS, Xiao JP, Zhang Y, Xu YJ, Li XP, Chen XJ, Huang XD, Yi JL, Gao L, Li YX.

Radiat Oncol. 2012

Trial

- Pts — 40
  29 primary treatment
  11 after WBRT
- Dose — 20-53Gy/4-15fr
- boost after HSRT(23 pts) — 10-35Gy/2-10fr
- WBRT — with or without
- OS — 55.3% (12mo)
  23.8% (24 mo)
  15.9% (36 mo)
- Median survival — 15 mo (mean 17.8 mo)
- Cause of Death:
  - Sistemic progression — 37.5%
  - Intracranial progression — 28%
- Toxicity — 5 pts Edema CTCAE 3-5
- Significant prognosic factors (surv): — KPS>80, controlled primary
- Significant prognosic factors (LC): — Not significative: Mets #, primary tumor, extracrania mets, KPS, RPA

Treatment of single or multiple brain metastases by hypofractionated stereotactic radiotherapy using helical tomotherapy

Nagai A, Shibamoto Y, Yoshida M, Wakamatsu K, Kikuchi Y

Int J Mol Sci. 2014

Trial

• Pts	54 (128 mets)
• Dose	28-28.8 Gy/4fr
• OS	61% (6mo) 52% (12 mo)
• LC	96% (6mo) 91% (12 mo)
• Toxicity	no major complications
• Significant prognosic factors:	controlled primary; Vol (univariate only)
• Not significant prognosic factors:	# mets

Optimal hypofractionated conformal radiotherapy for large brain metastases in patients with high risk factors: a single-institutional prospective study.

Inoue HK, Sato H, Suzuki Y, Saitoh JI, Noda SE, Seto KI, Torikai K, Sakurai H, Nakano T.

Radiat Oncol. 2014

Trial

- Pts — 88 (92 mets)
- Dose — 27-30Gy/3fr (up to 19.9cc)
31-35Gy/5fr (up to 29.9 cc)
35-42Gy/8-10fr (> 30 cc)
- Radioresistant — yes
- Median S — 9 mo
- Toxicity — 10 pts osmo-steroid or steroid
- Significant prognosic factors: — # fractions; age
- Not significant prognosic factors: — Vol

V14 < 3cc or less if lesions are deeply located

Surgical cavities

Cyberknife hypofractionated stereotactic radiosurgery (HSRS) of resection cavity after excision of large cerebral metastasis: efficacy and safety of an 800 cGy × 3 daily fractions regimen.

Wang CC, Floyd SR, Chang CH, Warnke PC, Chio CC, Kasper EM, Mahadevan A, Wong ET, Chen CC. J Neurooncol. 2012

• Pts	37
• Radioresistant	yes
• Dose	24Gy/3fr
• WBRT	with or without
• OS	80% (6mo) 27-28% (12 mo) 18% (36 mo)
• Toxicity	seizures prolonged steroids
• Not significant prognosic factors:	prev WBRT; hystology

Adjuvant therapy after resection of brain metastases. Frameless image-guided LINAC-based radiosurgery and stereotactic hypofractionated radiotherapy.

Broemme J, Abu-Isa J, Kottke R, Beck J, Wiest R, Malthaner M, Schmidhalter D, Raabe A, Aebersold DM, Pica A.

Strahlenther Onkol. 2013

Trial

- Pts — 42 (44 surg cavity)
- Dose — SRS 17-18 Gy (< 10 cc) ->V12
  HSRT 6Gyx2 (<20cc);4Gyx6 ->V4
- OS — 87% (6mo)
  63.5% (12 mo)
- LC — 91% (6mo)
  77% (12 mo)
- Toxicity — 1 pt RN
- Prognostic factors — LC is not correlated to SRS or HSRT

Hypofractionated Stereotactic radiotherapy
Brain metastases
Summary

• OS	61-87% (6 months) 28-63 (12 months)
• Median survival	7.6-15 months
• Cause of death	37-78% systemic disease 22-30% intracerebral disease 5-10% local progression
• LC	59-91 months
• Toxicity	2-3% serious AE

Hypofractionated Stereotactic radiotherapy
Brain metastases
positive prognostic factors

Overall survival (6 studies)

- Age (6): none
- Gender (5): none
- KPS (4): 2
- RPA (3): 1
- dsGPA (1): none
- Volume (5): 1
- Histology (4): 1 (melanoma)
- Extracr Dis (5): 4
- Mets # (4): 1

Local control
NO significant prognostic factors, including WBRT (2 studies) [EQD2 > 35 Gy (1 study)]

Hypofractionated Stereotactic radiotherapy
Brain metastases
Conclusions

The literature lacks of strong evidences regarding HSRT despite this HSRT (or mRS) provides reasonable and comparable tumour control and survival in patients suffering for metastatic lesions of the brain.

The neurological toxicity rate was low, and because of the non-invasive nature of such treatments, the patient compliance is very high.

These considerations suggest that HSRT should be considered as an alternative approach in the treatment of larger lesion or when a critical area is involved

A specific schedule for HSRT has not yet been established,

Ongoing trials

- Exclusive Hypofractionated Stereotactic Radiotherapy in Non-resectable Single Brain Metastasis
- Phase I Dose Escalation in Patients With 1-3 Unresectable Brain Metastases


THANKYOU
GRAZIE