IS SURGICAL CAVITY IRRADIATION NECESSARY FOR RESECTED BRAIN METASTASES : SPEAKER AGAINST

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CONFLICT OF INTEREST

- I have received grants and honoraria for Lectures and Advisory Boards from MSD, Roche, Merck Serono and Mundipharma.

OUTLINE

- Relevance of local control after irradiation of the surgical cavity.
- Risk of radionecrosis and other neurological complications.
- Risk of leptomeningeal relapse.
- Ongoing and future trials.

IS LOCAL CONTROL FOLLOWING POSTOPERATIVE LOCAL IRRADIATION RELEVANT?

- In terms of local control and failure at 1 and 2 years SRS to the resection cavity is not superior over WBRT.
- Similar numbers have been reported after single dose or multi-fractionated SRS (usually used for larger cavities).
- No dose response across the different fractionation-schemes → feasible a further increase of the efficacy?
- Few data regarding the value of involved field radiotherapy.

Soltys et al, 2008; Rwigema et al, 2011; Kelly et al, 2012; Connolly et al, 2013; Hartford et al, 2013 ; Hiesh et al, 2015;

SRS TO THE RESECTION CAVITY: UNSOLVED ISSUES

- Optimal margin around the resection cavity to be included in the treatment field.
- Optimal treatment of large (>3 cm) brain metastases.
- Relative efficacy in radiosensitive vs radioresistant tumors (in comparison with WBRT).
- Controversies on exclusion criteria: large tumors (>3 cm) with superficial dural / pial involvement (high risk for local failure?); specific molecular subgroups receiving targeted agents (EGFR and ALK mutated NSCLC; HER 2+ breast cancer?)

Choi et al, 2012; Minniti et al, 2013; Brennan et al, 2014

RISK OF RADIONECROSIS

- The reference value is 2.6% following WBRT (*EORTC study*, *Kocher et al, 2011*).
- The values following SRS range between 9% and 17.5% in recent papers (*Minniti et al, 2013; Brennan et al, 2014; Ling et al, 2015*).
- More often the reported values are based on both biopsy and MRI : thus, the distinction between true radiation necrosis and pseudoprogression is unknown.

RISK OF RADIONECROSIS

- Not always the clinical relevance of the so called “radionecrosis” is detailed.
- Some papers do not mention toxicity or simply state that “no toxicity was observed”.
- The actuarial risk increases over time: 7% at 1 year ; 16% at 2 years (*Minniti at al, 2013*).

RISKS OF NEUROLOGICAL COMPLICATIONS OTHER THAN RADIONECROSIS

- Seizures, headache and hemorrhage as acute complications in individual patients (*Minniti et al, 2013*).
- Increased T2 signal changes on MRI around the resection cavity (radiation-related edema) in 10.8% of patients (*Mathieu et al, 2008*).
- A steroid dependency can occur, and both frequency and duration have not been recorded.
- Overall, the incidence of both radionecrosis and other neurological complications is underestimated.

FOLLOW-UP IN THE SUSPICION OF RADIONECROSIS: PROBLEMS

- Need for additional neuroimaging investigations (MRS, MRI perfusion, PET with aminoacids or FDG), that often yield conflicting results (radionecrosis vs tumor growth vs both) (*see RANO papers, Lancet Oncol, 2013-2014-2015*).
- Potential usefulness of bevacizumab (*Boothe et al, 2013*).
- Last but not least increasing costs.

LEPTOMENINGEAL RELAPSE AFTER SURGERY OR POSTOPERATIVE SRS

Study Ref	Number of patients	Type of treatment	Risk of LMD
Suki et al, 2008	379	Surgery or SRS (infratentorial location)	Overall 19% Surgery 22% SRS 18%
Suki et al, 2009	827	Surgery or SRS (supratentorial location)	Overall 7% SRS 2% Surgery 12%
Hyong et al, 2012	242	Surgery	16%
Jensen et al, 2011	106	Resection cavity SRS	8%
Robbins et al, 2012	85	Resection cavity SRS	8%
Hashimoto et al, 2011	130	Resection cavity-local EBRT	9%
Atalar et al, 2013	165	Resection cavity SRS	11% at 1 year 13% at 2 years
Ling et al, 2015	99	Resection cavity SRS	6%
Hsieh et al, 2015	212	Resection cavity SRS	12%

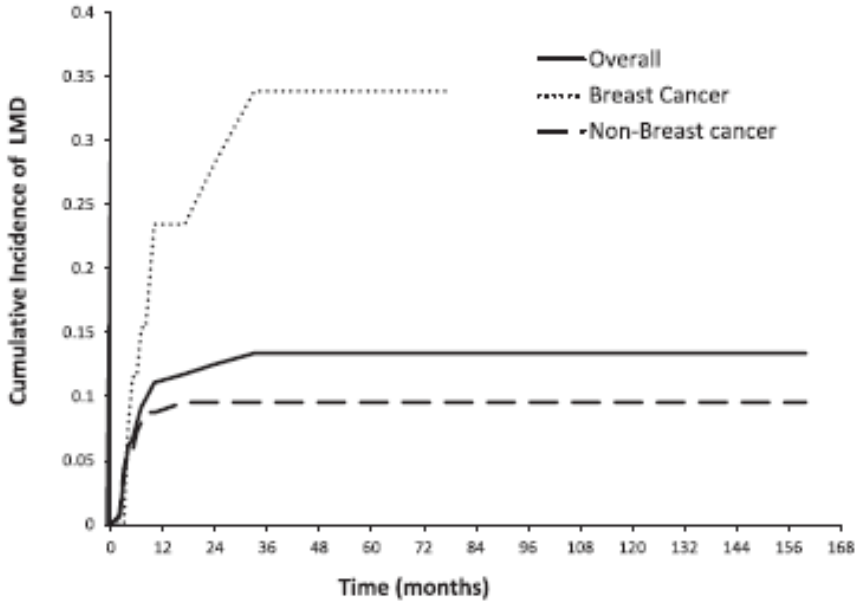

Fig. 2. Cumulative incidence of leptomeningeal disease (LMD), with death as a competing risk. Rates of LMD at 1 year were 11% overall, 24% for breast histology, and 9% for non-breast histology. The hazard ratio for breast cancer was 2.96 compared to non-breast histology.

Atalar et al, 2013

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Clinical Investigation: Thoracic Cancer

A New Treatment Paradigm: Neoadjuvant Radiosurgery Before Surgical Resection of Brain Metastases With Analysis of Local Tumor Recurrence

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NEOADJUVANT RADIOSURGERY WITHOUT WBRT : DISADVANTAGES

- Often the diagnosis is unknown preoperatively.
- The radiosurgery may lead to an increase of mass effect
- If visible tumor remains, the neoadjuvant treatment may not prevent seeding from piecemeal removal of metastasis.
- The impact on surgical complications (neurologic deficits, wound healing) is unknown.
- The ideal interval between radiosurgery and craniotomy has not been defined.
- The adjuvant approach allows dose-escalation to any residual tumor

Roberge et al, 2013

IRRADIATION OF THE SURGICAL CAVITY FOR RESECTED BRAIN METASTASES: GENERAL CONCERNS

- Lack of information on HRQOL to be compared with those after either observation or WBRT (*EORTC 22952-26001, Soffietti et al, 2012*).
- Lack of information on neurocognitive functions to be compared with those after SRS alone or SRS + WBRT (*Chang et al*, 2009).
- Lack of information on the role of salvage treatments → probably effective as in case of patients with initial observation after resection (*EORTC 22952-26001, Kocher et al, 2011*)

ONGOING / FUTURE STUDIES ON RESECTED BRAIN METASTASES

- Phase III Intergroup N107C trial (US) : SRS vs WBRT (in all histologies) (completed).
- Phase III MD Anderson trial (US) : SRS vs observation (in all histologies) (completed).
- Phase III EORTC trial : SRS vs observation (delayed SRT) in NSCLC (in preparation).

CONCLUSIONS

- The main limitations of available studies on postoperative local irradiation in resected brain metastases include relatively small sample size, short follow-up, heterogeneous primary histologies, unknown chemotherapy and disease stage.
- With the lack of clear risk / benefit data and increased financial costs, it is imperative SRS to the surgical cavity in brain metastases be studied in multi-institutional randomized trials before using in the routine clinical practice.