BRAIN AND LEPTOMENINGEAL METASTASES

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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.

LEARNING OBJECTIVES

- To describe diagnostic tools
- To discuss a prognostic factors-based management
- To review treatment options and future developments

KEY MESSAGE

- The incidence of brain and leptomeningeal metastases is increasing

- The choice of therapeutic options must be based on prognostic factors

BRAIN METASTASES: EPIDEMIOLOGY

- The most common intracranial tumors, outnumbering primary brain tumors
- Frequency: 20-40% of patients with cancer, being symptomatic during life in 60-75%
- Increasing incidence over time due to improved detection by MRI in asymptomatic patients, better treatment of systemic disease, and aging population

Soffietti et al, Handbook of Clinical Neurology , Elsevier, 2012;105:747-55

BRAIN METASTASES: DIAGNOSIS

- MRI with contrast medium is more sensitive than CT (especially for lesions in the posterior fossa or multiple punctate).
- A peripheral location,spherical shape, ring enhancement, prominent peritumoral edema and multiple lesions on CT/MRI all suggest metastatic disease. These characteristics are helpful but not diagnostic, even in patients with a history of cancer.
- Depending on the clinical setting, the differential diagnosis includes primary brain tumors (especially malignant glioma, PCNSL, meningioma) or nonneoplastic conditions (absess, infection, hemorrhage, stroke).

Table 1 Prognostication of patients with brain metastases

(a) Recursive partitioning analysis (RPA) classification [2]

RPA class	Characteristics	Incidence	Median survival after WBRT alone[a] (months)	Median survival after WBRT + SRS (months)[c]	Median survival after WBRT + surgery (months)[d]
I	KPS ≥70 Age <65 Controlled primary site No extracranial metastases	20%	7.1	16.1	14.8
II	Not class I or III	65%	4.2	10.3	9.9
III	KPS <70	15%	2.3	8.7	6.0

(b) Graded prognostic assessment (GPA) [3]

GPA score	0	0.5	1.0	Sum GPA score	Median survival (months)[b]
Age	>60	50–59	<50	3.5–4.0	11.0
KPS	<70	70–80	90–100	3.0	6.9
No. of brain metastases	>3	2–3	1	1.5–2.5	3.8
Extracranial metastases	Present	–	None	0–1.0	2.6

KPS, Karnofsky performance score; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.
[a] Median survival after WBRT alone provided by RTOG phase III trials [2] and independently validated in a separate RTOG trial [4].
[b] Median survival after WBRT alone provided by RTOG phase III trials [3].
[c] Median survival after WBRT + SRS provided by Sanghavi *et al.* [5].
[d] Median survival after WBRT + surgery provided by Agboola *et al.* [6].

Gondi and Mehta, Current Opinion in Neurology, 2010;23:556-562

SURGERY FOR SINGLE BRAIN METASTASIS

- Three phase III studies have compared surgical resection + WBRT to WBRT alone.
- The American (***Patchell et al, 1990***) and the Dutch (***Vecht et al, 1993***) studies, including mainly patients with controlled or limited systemic disease, have reported a significant survival advantage for surgery + WBRT over WBRT alone (7-10 versus 3-6 mos).
- The Canadian study (***Mintz et al, 1996***), including mainly patients with active systemic disease and lower perfomance status, did not show any difference between the two treatment arms.
- In selected patients with recurrent metastasis surgery allows palliation of symptoms and improvement of survival

STEREOTACTIC RADIOSURGERY (SRS) FOR SINGLE BRAIN METASTASIS

- Local tumor control (shrinkage or no growth) in 80-90% of patients, with median survival of 7-12 months.
- Results after SRS comparable to those after surgery, but lack of randomized studies.
- Improvement of survival (6.9 vs 4.9 months) with the addition of SRS to WBRT (“boost”).

Andrews et al, 2004 ; Linskey et al, 2010; Jenkinson et al, 2011

STEREOTACTIC RADIOSURGERY OR SURGERY FOR MULTIPLE BRAIN METASTASES

- In patients with limited number of brain metastases (2-3) and good prognostic factors, radiosurgery or surgery yield similar results as in single lesions.

- SRS combined with WBRT ("radiosurgical boost") is not superior to WBRT alone in improving survival.

Andrews et al, 2004; Linskey et al, 2010; Jenkinson et al, 2011

WBRT ALONE

- Treatment of choice for patients with single or multiple lesions not amenable to surgery or radiosurgery and/or those with an active systemic disease.
- Survival between 3 and 6 months in two thirds of patients with a neurological improvement after steroids and WBRT.
- Tumor volume reduction associated with improved cognitive function and survival.
- Different fractionation schedules comparable → standard treatment 30 Gy in 10 fractions.
- Supportive care alone as an alternative (especially for non-ambulatory patients) : ongoing phase III MRC QUARTZ trial

Barnes et al, 2010; Gondi and Mehta, 2010

Adjuvant Whole Brain Radiotherapy versus Observation after Radiosurgery or Surgical Resection of 1-3 Cerebral Metastases: Results of the EORTC 22952-26001 Study

M. Kocher[2], R. Soffietti[1], M.U. Abacioglu[3], S. Villa[4], F. Fauchon[5], B.G. Baumert[6], L. Fariselli[7], T. Tzuk-Shina[8], L. Collette[9], R.P. Mueller[2]

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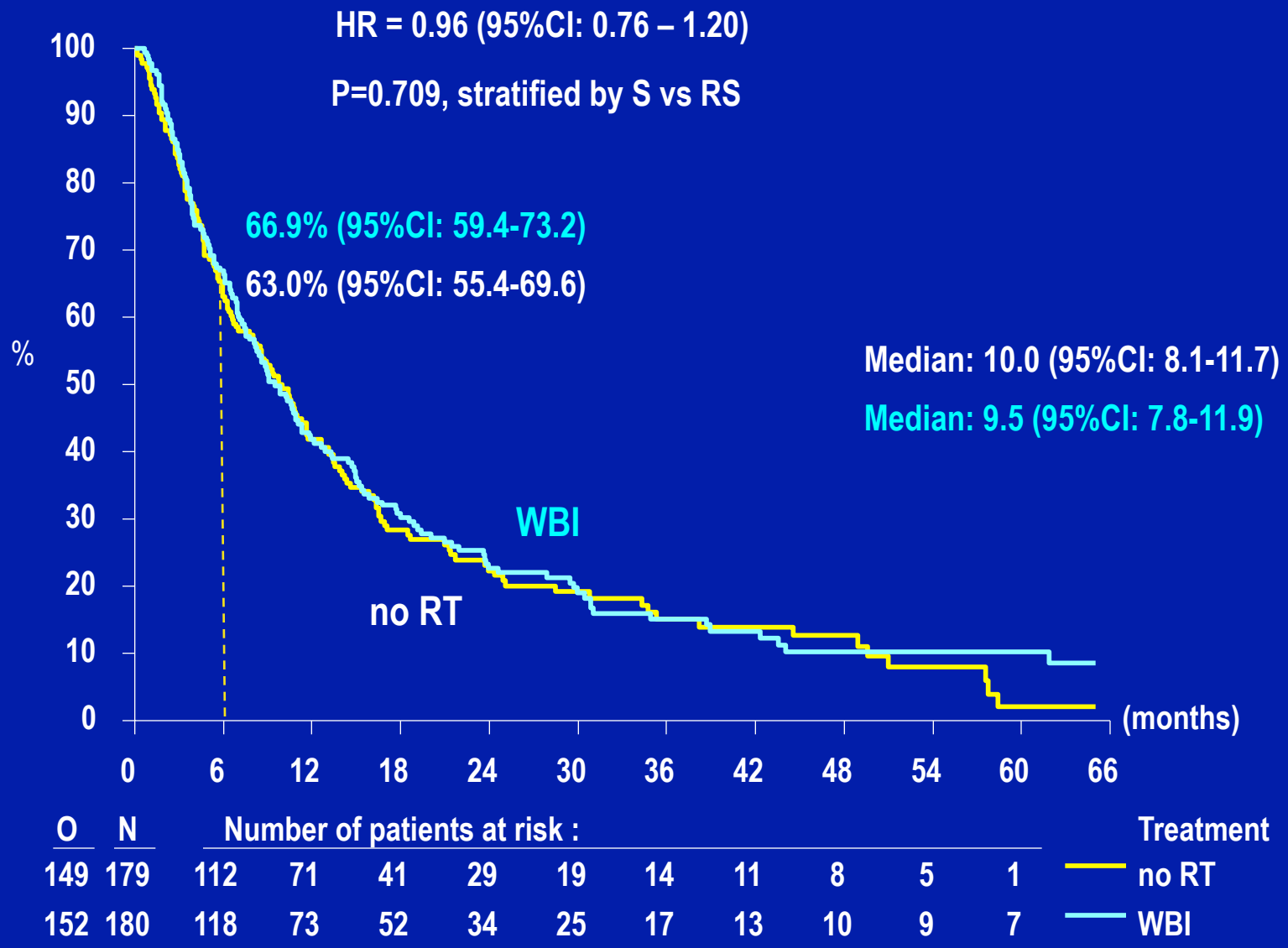
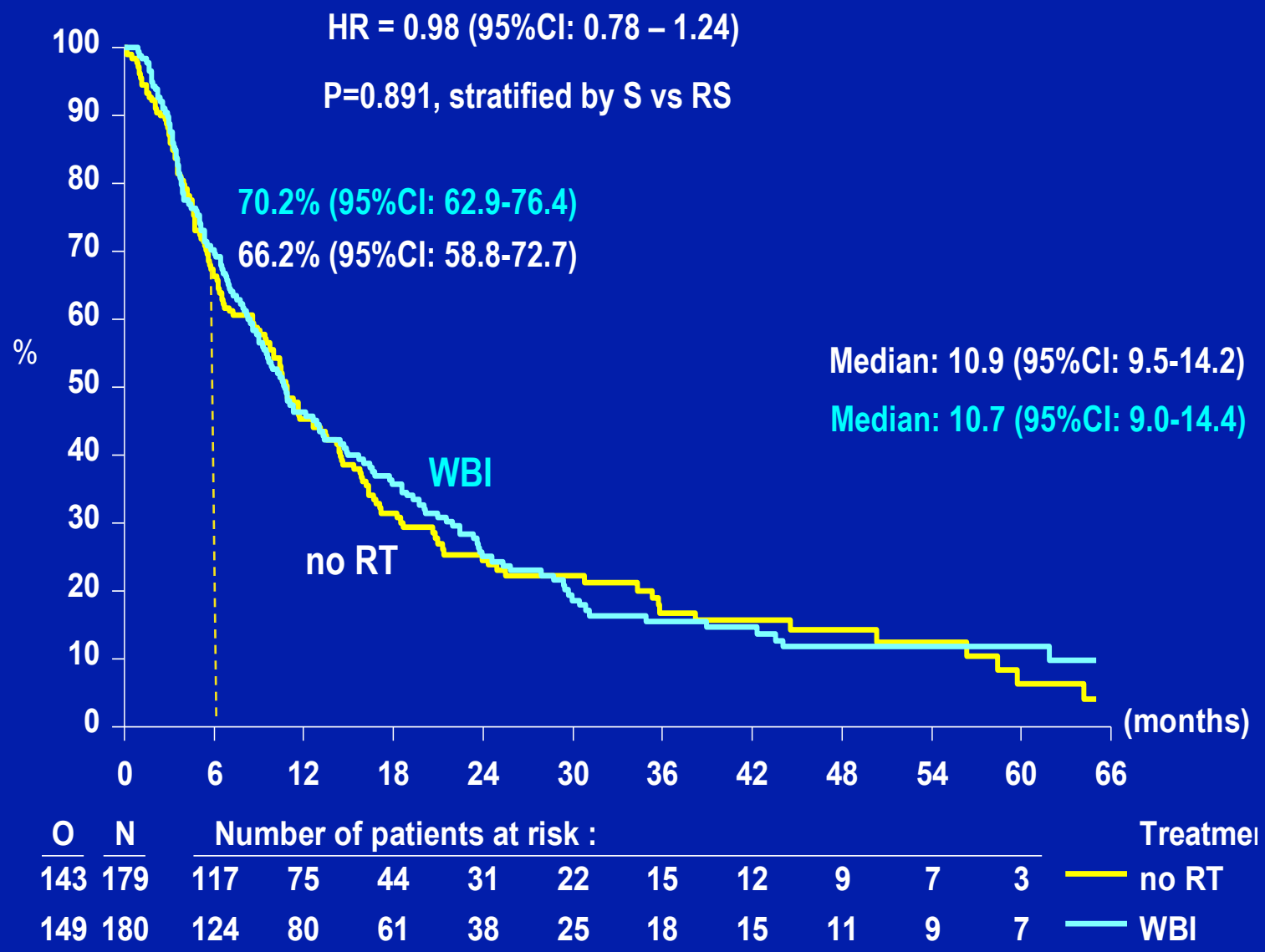
J Clin Oncol 29/2, 134-141, 2011

Primary endpoint: Survival with PS ≤ 2 (ITT)



Overall Survival (ITT)



WBRT MAY NEGATIVELY AFFECT COGNITIVE FUNCTIONS

- Dementia occurs predominantly with large size fractions (4-6 Gy) that are not used anymore

- The true incidence of subtle cognitive deficits in long-term survivors (>1 year), when using conventional regimens (30 Gy, 10 fractions), is unknown.

- Long-term survivors frequently develop overtime changes on MRI, such as cortical atrophy, hyperintensity of the white matter in T_2/FLAIR images, hydrocephalus, but the incidence of clinical concomitants has not been studied.

Soffietti et al, 2008; Witgert and Myers, 2011

EARLY COGNITIVE DECLINE AFTER WBRT

- Early neurocognitive decline can occur within the first 1-4 months (*Li et al, 2007; Welzel et al, 2008; Chang et al, 2009*)
- Verbal and short-term memory recall (mediated by hippocampus) are affected (*Chang et al, 2009; Sun et al, 2010*)
- Unknown whether this early decline in memory is associated with long-term and/or permanent decline (*Aoyama et al, 2007; Sun et al, 2010*)

NEW APPROACHES TO AVOID COGNITIVE DYSFUNCTIONS AFTER WBRT

- Hippocampus avoidance with intensity modulated radiotherapy (ongoing RTOG 0933)
- Use of “protective” drugs (memantine) (RTOG 0614)
- Anti-inflammatory compounds (pioglitazone, fenofibrate, angiotensin type 1 receptor antagonists)
- Identification of subgroups of patients at higher risk of developing cognitive deficits

Gondi and Mehta, 2010; Steeg et al, 2011

Chemotherapy and targted therapies for brain metastases

- Sensitivity of neoplastic cells
- Drug exposure
  - Drug properties
    (liposolubility, molecular weight)
  - blood-brain barrier
    (including P-glycoprotein)

LEPTOMENINGEAL METASTASES

- Leptomeningeal metastases represent a disease of the entire neuraxis, characterized by invasion of the leptomeninges/ cerebrospinal fluid (CSF) by cancer cells

- Increasing incidence due to improvements in diagnosis (MRI) and outcome of cancer patients because of more effective treatment of the systemic disease

- Still understimated

CLINICAL FEATURES

- Clinically, neoplastic meningitis (NM) is a multifocal disease that may involve the entire neuraxis at different levels: brain, cranial nerves, spinal cord and spinal roots.

- The key feature is therefore the coexistence of multifocal signs and symptoms.

- At an early stage, when isolated neurological symptoms develop, the diagnosis is difficult.

- Conversely, due to the dramatic evolution of signs and symptoms, when the clinical picture is clear, many patients are not candidate for treatment.

CSF ANALYSIS

- Single most useful test for diagnosing NM and monitoring treatment.
- Abnormal CSF in nearly all patients with NM, regardless of the results of CSF cytology.
- Initial lumbar CSF citology positive in 55% of patients, increasing to 80% after a second CFS examination.
- Overall, at least 20% of patients with ultimately negative cytology.

DIAGNOSIS OF NEOPLASTIC MENINGITIS (NM)

- Pathologically defined NM: Patients with positive CSF cytology regardless of neuroimaging findings

- Clinically defined NM: Patients with negative CSF cytology, but pathologically proven cancer in the history and a clinical syndrome suggesting NM with corroborating neuroimaging findings

Chamberlain, 2000

TREATMENT AND PROGNOSIS OF NEOPLASTIC MENINGITIS: GENERAL CONCEPTS

- The majority of patients are not candidates for aggressive therapy, as NM presents at an advanced stage of the cancer history: these patients are best offered supportive care only.

- A subset of patients may benefit from aggressive therapy, such as intrathecal or systemic chemotherapy .

- Overall survival after treatments is 2-6 months.

- The main objective of treatment is to palliate CNS symptoms/ signs, thereby improving the patient's quality of life.

NEOPLASTIC MENINGITIS: INTRATHECAL CHEMOTHERAPY

- Intrathecal chemotherapy is still the mainstay of treatment for leptomeningeal disease. The 3 agents most commonly used are methotrexate, cytarabine and thio-TEPA.

- Methotrexate and cytarabine are active against leukemia and lymphoma. Methotrexate and thiotepa are active against breast cancer, but none of these agents have intrinsic activity against lung cancer or melanoma.

- A modest advantage of Depocyt (liposomal encapsulated cytarabine) over standard cytarabine and methotrexate has been reported.

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