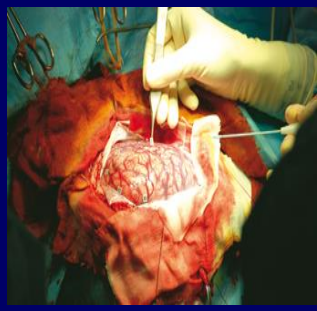
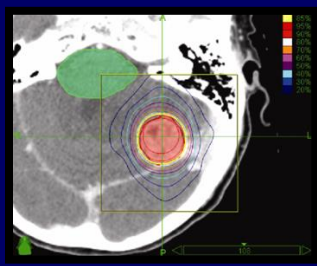


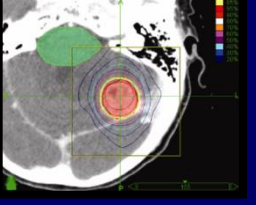
Métastases cérébrales

Quel traitement local optimal ?

David Azria, Agnès Tallet, Philippe Metellus

Montpellier - Marseille





Le(s) problème(s)

La(les) situation(s) clinique(s)

Patiente connue pour une pathologie mammaire

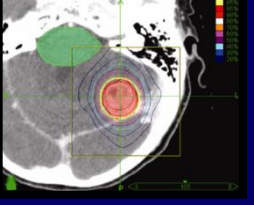
Métastase métachrone

- Soit en suivi d'adjuvant
- Soit en traitement pour une maladie extra cérébrale

Evènement cérébral de découverte initiale

Métastase synchrone

- Aucune notion de néoplasie mammaire



Le(s) problème(s)

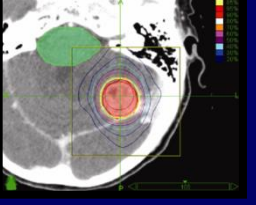
Le(les) signe(s) clinique(s)

Contexte d'urgence

- **HTIC: Céphalées, nausées, vomissements**
- **Déficit neurologique sévère**
- **Troubles de la conscience**

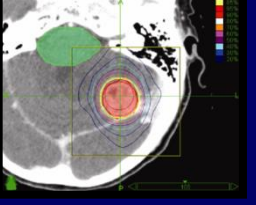
Contexte non urgent

- **Symptômes fonctionnels modérés** **(cognitifs, céphalées, asthénie, visuels)**
- **Signes déficitaires: moteurs ou visuels**



Les facteurs de risque d'apparition des métastases cérébrales

- **Caractéristiques cliniques**
  - Age < 40 ans
  - Charge tumorale
- **Caractéristiques biologiques de la tumeur**
  - Constamment retrouvées :
    - Statut RE -
    - Statut HER 2+
  - De plus en plus retrouvées:
    - Mutations BRCA1/Triples négatifs
    - Taux de LDH élevé au diagnostic de métastases viscérales



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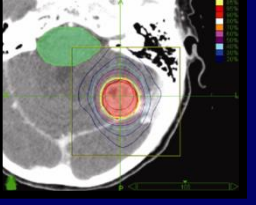


Mme A. C.

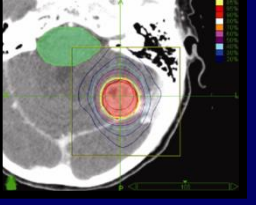
- **Née le 27/09/1973, enseignante, droitière**
- **Mère de 2 enfants**

  - Octobre 2010: T2 N3 M1
    - Union des quadrants inférieurs du sein gauche : tumeur de 2,5 cm
    - Une adénopathie creux axillaire gauche 2,5 cm
    - Une adénopathie sus-claviculaire gauche 2 cm

    } Cytoponctions positives

    - Ganglions médiastinaux fixants au TEP-FDG

  - Carcinome canalaire infiltrant grade 3, Index mitotique élevé,
    - Triple négative



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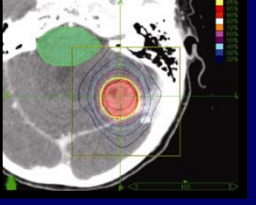
- **Née le 27/09/1973, enseignante, droitière**
- **Mère de 2 enfants**

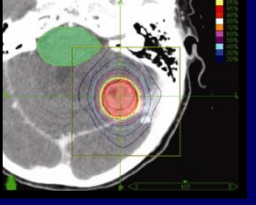
  - Marqueurs CA 15-3 initial 175 (normal < 23)
  - Scintigraphie osseuse: hyperfixation T11 mais en fait angiomes vertébraux multiples
  - Scanner cérébral initial normal

RCP : Chimiothérapie première (Epirubicine – Endoxan forte dose tous les 15j: 6 cures)



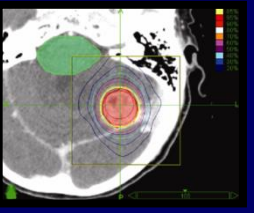
Mme A. C.

- **Rappel : 2010 T2N3M1 QI sein gauche**
  - Réponse clinique majeure
  - 08/02/2011
    - Tumorectomie – curage axillaire
    - Reliquat tumoral de 18 mm
    - Index mitotique nul – pas d'emboles – berges saines
    - 14 N+ / 15
  - RCP: Radiochimiothérapie par 5-FU + Navelbine
    - 4 cycles (dernier le 25/05/2011)
    - RT par modulation d'intensité du 30/03/2011 au 15/06/2011
  - Suivis réguliers fin 2011 et S1 2012: pas de symptômes, TEP normal, marqueur CA15-3 normal

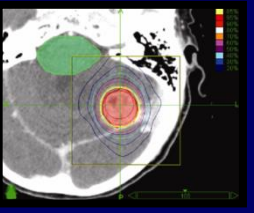


Mme A. C.

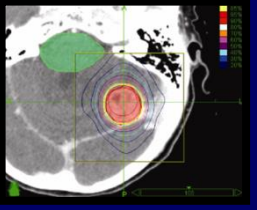
- **Rappel : 2010 T2N3M1 QI sein gauche**
  - Céphalées + scotomes en septembre 2012
  - IRM cérébrale le 13/09/2012
    - Lésion nodulaire de 17 mm occipitale droite
    - Une petite prise de contraste de 6 mm sous corticale
    - RCP : Radiothérapie cérébrale
  - Décision de déménager sur Montpellier
  - Vue en consultation initiale
    - IRM le jour même:
    - Lésion occipitale droite de 20 mm
    - Lésion de 6 mm temporo-pariétale paraventriculaire droite de 6 mm
    - Effet de masse sur la corne occipitale du ventricule latéral droit sans signe d'engagement



IRM Encéphalique initiale



IRM Encéphalique initiale

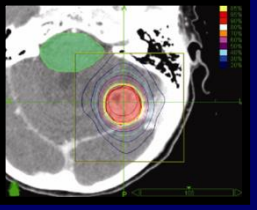


Mme A. C.

- **Rappel : 2010 T2N3M1 QI sein gauche**
  - RCP neurochirurgie : Indication d'exérèse chirurgicale sur la lésion occipitale droite
  - Après la chirurgie de la lésion occipitale, prise en charge de l'autre lésion par radiothérapie pan-encéphalique ou radiothérapie localisée

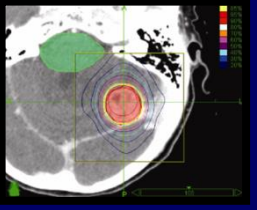
QUESTION 1:

Sur quels arguments faut-il opérer cette patiente ?



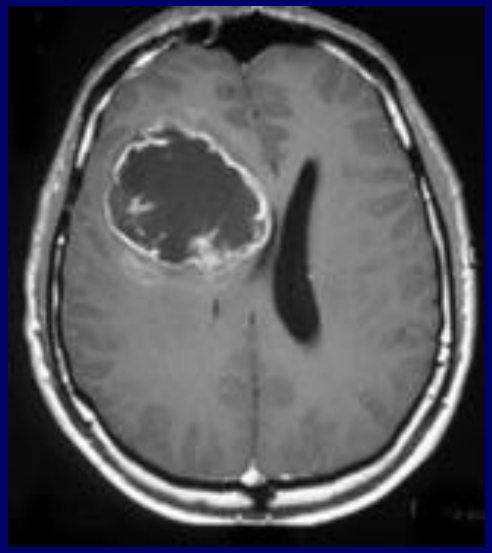
Sélection des patients pour la résection chirurgicale

- **Statut clinique et caractéristiques des patients**
  - Âge
  - KPS pré-op
  - Intervalle entre la tumeur primitive et la survenue d'une métastase cérébrale
- **Statut de la maladie systémique**
  - Active *vs* contrôlée
  - Métastases extra-crânienne
  - Survie estimée
- **Caractéristiques des tumeurs cérébrales**
  - Unique *vs* multiples
  - Kystique ou nécrotique
  - Effet de masse
  - Localisation / Aires fonctionnelles

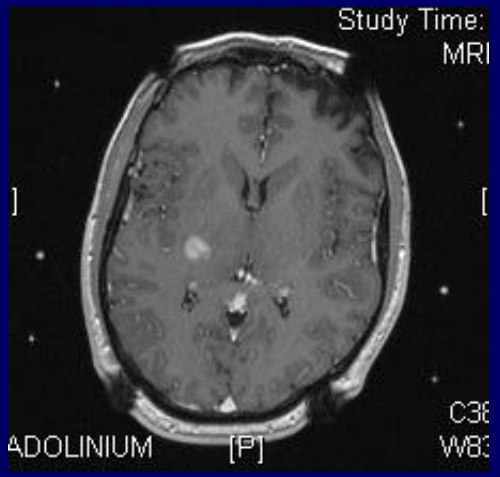


Rationel pour la Chirurgie *vs.* la Radiothérapie stéréotaxique dans les MC

- Taille > 3 cm
- Effet de masse
- Symtpomatique
- Localisation superficielle
- Oedème
- Aspect kystique/nécrotique
- Confirmation histol. nécess.

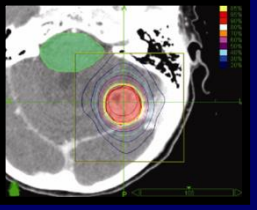


Candidat à la chirurgie



Candidat à la radio-chirurgie

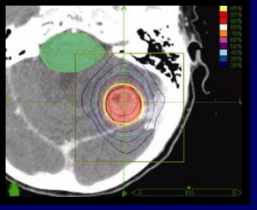
Bindal, JNS 1996; Schoggl, Acta Neurochir 2000, O'Neill, Int J Rad Oncol Biol Phys 2003



Surgical resection or stereotactic radiosurgery for BM ?

	Surgical resection	Stereotactic radiosurgery
Patient selection		
Tissue diagnosis	Confirms the lesion is a tumor	Can't confirm the lesion is a tumor
Lesion size	Large, ≥1.5 cm[a]; especially if there is mass effect	Small, ≤3.0 cm[a]; significant mass effect absent
Surgical candidate	Yes	No (or patient declines surgery)
Treatment outcome		
Tumor status	Removed (≥94% on average)[b]	Not removed
Local control	85% for >40 months (up to 5 years)[c]	85% at 12 months; 65% at 24 months[d]
Local recurrence rate	8[c] to 12%[b]	30[e] to 47%[f]
Median survival time	10[g] to 16.4[c] months	7.5[c] to 14[h] months
Complications		
Presentation	Usually immediate	Frequently delayed; necrosis may necessitate surgical resection
Major neurological	7% in eloquent brain; 6% overall[b]	25% in eloquent brain (RTOG[i] grade 3)[j]
Mortality (30-day)[k]	<2%	1.8%

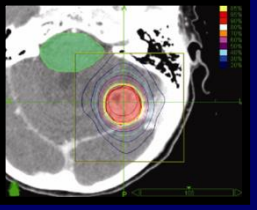
Al-Shamy G & Sawaya R, JNO 2009



Surgical resection or stereotactic radiosurgery for BM ?

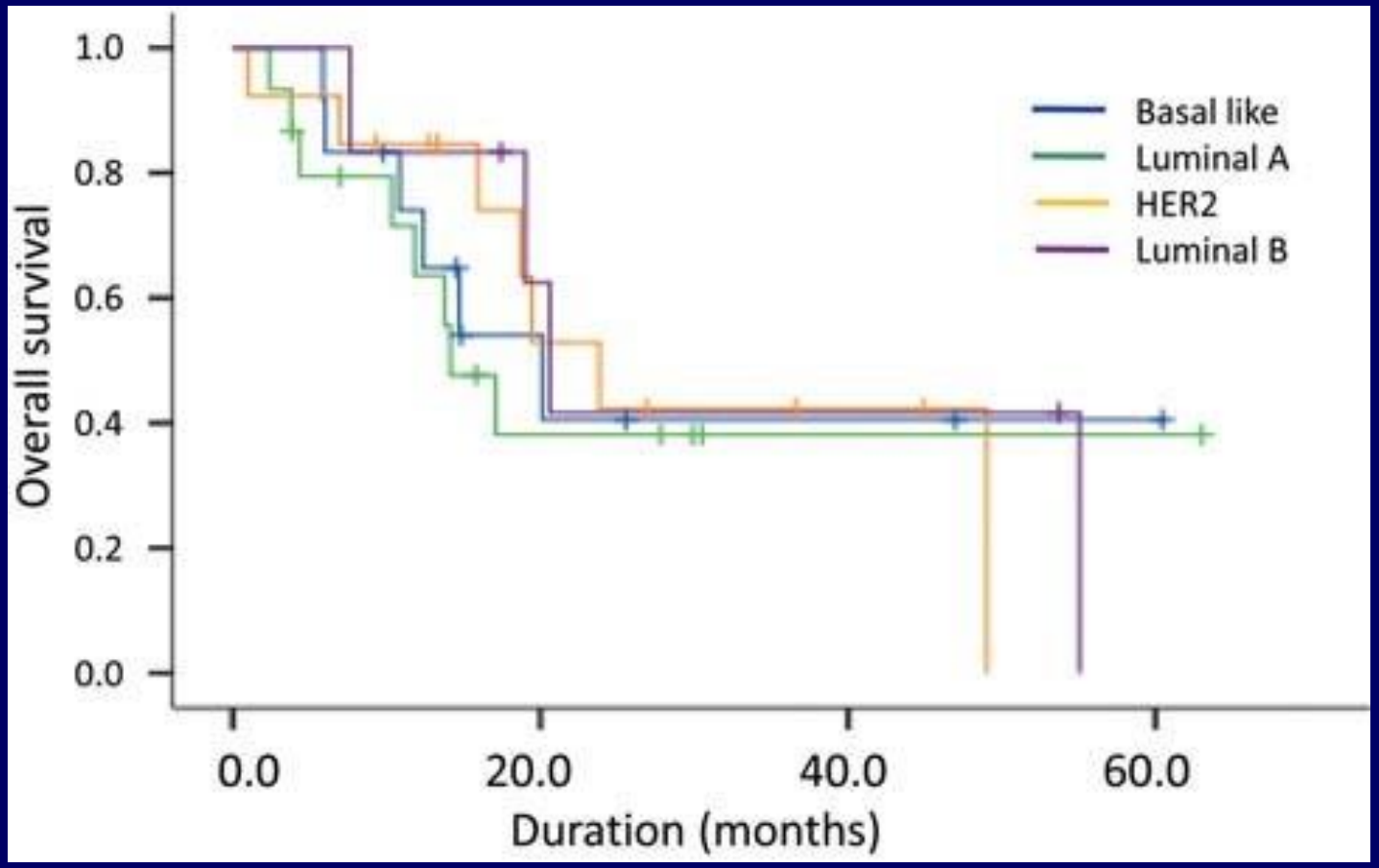
Cost-effectiveness	Based on 3-day hospital stay	Based on 1-day outpatient stay; includes no costs of maintenance steroids, follow-up office visits, or follow-up MR images
Quality of life		
Relief from mass effect	Immediate	Delayed
Steroid use	Tapered off over 2–4 weeks	Can last for months; may cause dependence
Follow-up visits	Few	Many
Patient debilitation	Not debilitated at home	Debilitated at home

Al-Shamy G & Sawaya R, JNO 2009

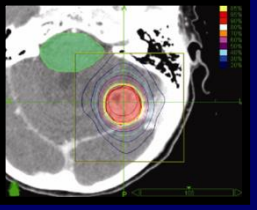


Surgical Resection of Brain Metastases from Breast Cancer in the Modern Era: Clinical Outcome and Prognostic Factors

EMELINE TABOURET[1,2], PHILIPPE METELLUS[2,4], AGNES TALLET-RICHARD[1], DOMINIQUE FIGARELLA-BRANGER[2,4], EMMANUELLE CHARAFFE-JAUFFRET[1,3,4], PATRICE VIENS[1,3,4] and ANTHONY GONÇALVES[1,3,4]



Tabouret, Metellus et al. Anticancer Res 2013



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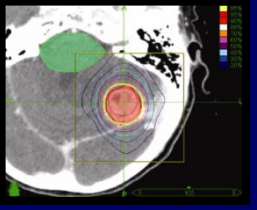
  - Patiente opérée
    - Craniotomie occipitale
    - Exérèse monobloc de la lésion
    - Anapath: carcinome d'origine mammaire – HER2 2+
      - CISH en attente

QUESTION 2:

Peut-il y avoir des modifications phénotypiques tumorales entre la tumeur primitive mammaire et les métastases cérébrales ?



Conversion of epidermal growth factor 2 and hormone receptor expression in breast cancer metastases to the brain

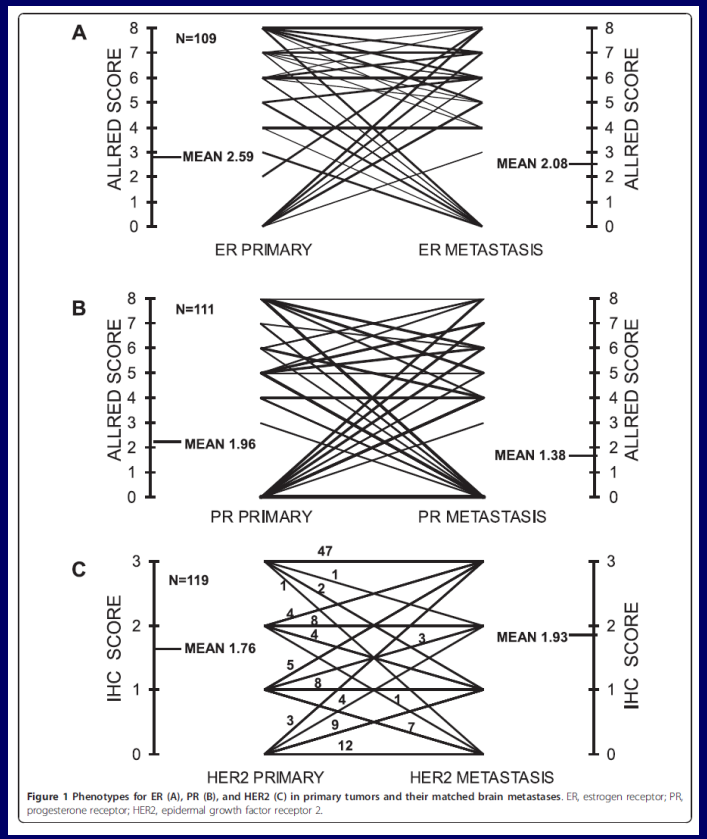


Figure 1 Phenotypes for ER (A), PR (B), and HER2 (C) in primary tumors and their matched brain metastases. ER, estrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor 2.

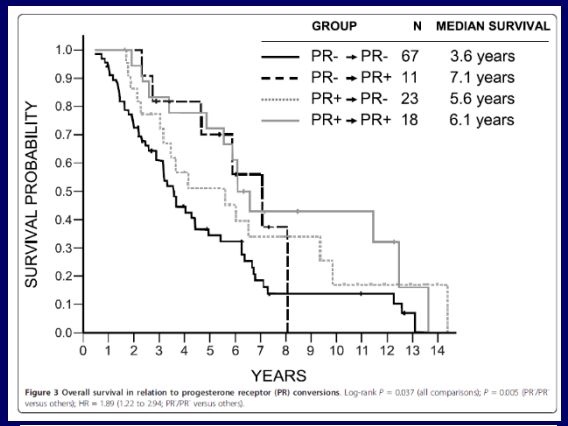


Figure 3 Overall survival in relation to progesterone receptor (PR) conversions. Log-rank $P = 0.037$ (all comparisons); $P = 0.005$ (PR-/PR- versus others); HR = 1.89 (1.22 to 2.94; PR-/PR- versus others).

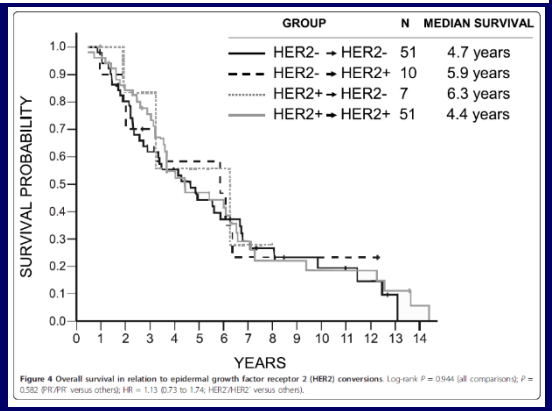
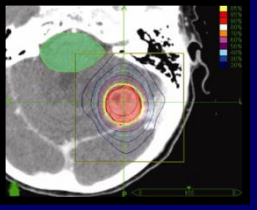


Figure 4 Overall survival in relation to epidermal growth factor receptor 2 (HER2) conversions. Log-rank $P = 0.944$ (all comparisons); $P = 0.582$ (PR-/PR- versus others); HR = 1.13 (0.73 to 1.74; HER2-/HER2- versus others).

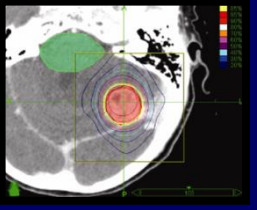
Duchnowska et al. **Breast Cancer Research 2012**



HER2 discordance between primary breast cancer and its paired metastasis: tumor biology or test artefact? Insights through meta-analysis

Study-level covariate used to examine between-study variability in HER2 discordant proportion (no. of studies providing data for covariate, no. of subjects)	Estimates for separate random-effects logistic regression models		Sensitivity analysis[a]	
	HER2 discordant % (95% CI)	*P* value	HER2 discordant % (95% CI)	*P* value
Overall pooled estimate	5.54 (3.56, 8.53)	–	5.23 (3.48, 7.77)	–
Test used to determine HER2 status (27 studies, 2520 subjects)		0.27		0.14
Immunohistochemistry (IHC)	5.15 (2.94, 8.87)		4.57 (2.78, 7.42)	
Immunohistochemistry/In situ hybridization (IHC/FISH)[b]	10.70 (4.13, 24.97)		10.91 (5.06, 21.97)	
In situ hybridization (ISH: FISH or CISH)[c]	4.34 (1.83, 9.93)		4.52 (2.17, 9.18)	
Type of metastasis included in paired testing of primary cancer and metastasis (27 studies, 2520 subjects)		0.0017		0.0006
Studies of nodes only	4.18 (2.45, 7.06)		4.46 (2.92, 6.74)	
Studies of nodes or local recurrence or distant metastases[d]	1.42 (0.40, 4.86)		1.59 (0.51, 4.82)	
Studies of distant metastases or local recurrence[e]	13.42 (7.16, 23.73)		13.62 (8.60, 20.90)	
Studies of distant metastases only	9.55 (4.94, 17.67)		6.03 (3.16, 11.19)	
Metastasis synchronous or metachronous to primary (27 studies, 2520 subjects)		0.0024		0.0043
Studies of synchronous metastases	4.52 (2.54, 7.92)		4.64 (2.81, 7.58)	
Studies of synchronous or metachronous metastases	1.86 (0.69, 4.92)		1.98 (0.80, 4.86)	
Studies of metachronous metastases	10.57 (6.67, 16.35)		9.26 (6.03, 13.98)	

***Houssami et al.* Breast Cancer Res Treat 2012**



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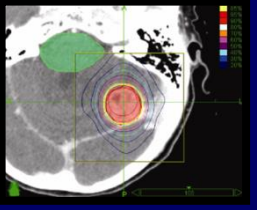
  - Patiente opérée
    - Craniotomie occipitale
    - Exérèse monobloc de la lésion
    - Anapath: carcinome d'origine mammaire – HER2 2+
      - **Pas d'amplification aux résultats définitifs**

QUESTION 3:

Quelle radiothérapie doit-on délivrer: in toto ou stéréotaxie ?



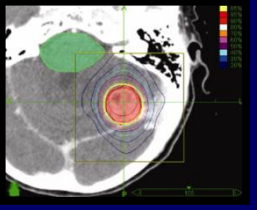
Traitement décidé au staff de radiothérapie

Radiothérapie pan-encépalique

en IMRT rotationnelle

Avec protection hippocampique

Et complément simultané de dose sur les zones à risque



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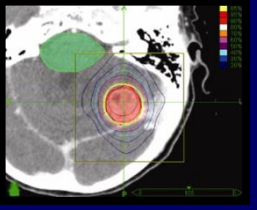
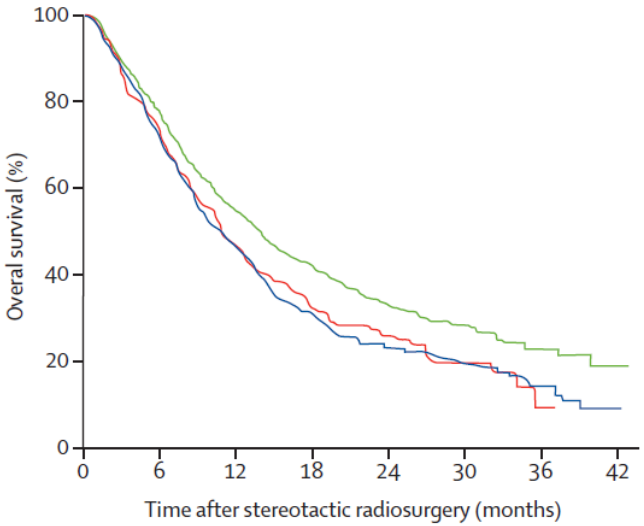


Les essais prospectifs SRS seul

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



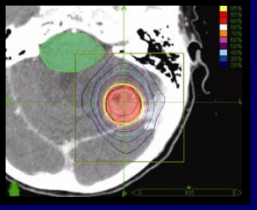
Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

10% sein

Primary cancer					0·35
Lung	912 (76%)	348 (76%)	400 (75%)	164 (79%)	..
Breast	123 (10%)	42 (9%)	57 (11%)	24 (12%)	..
GI tract	85 (7%)	35 (8%)	41 (8%)	9 (4%)	..
Kidney	36 (3%)	15 (3%)	19 (4%)	2 (1%)	..
Other	38 (3%)	15 (3%)	14 (3%)	9 (4%)	..

Yamamoto M et al., Lancet Oncol, 2014;15:387-95



In toto ou localisé ?

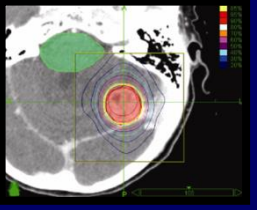
Essais prospectifs

2 essais prospectifs

Chougule PB (Proc ASTRO 2000): 12/73 cancers du sein (3 bras): aucune différence **mais jamais publié** !!

Ayoama H (JAMA, 2006, 295, 2483): 10/132 cancers du sein (2 bras):

- Aucune différence en survie
- Contrôle cérébral à 12 mois: 47% vs 76% ($p<0,001$)
- 2 leuco-encéphalites vs 7 ($p=0,09$)



Chirurgie ou SRS seules
vs
Chirurgie ou SRS + WBRT

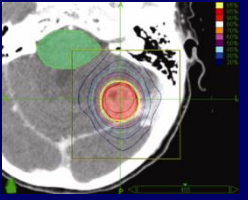
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

Kocher, 2010, *JCO*



Chirurgie ou SRS seules
vs
Chirurgie ou SRS + WBRT

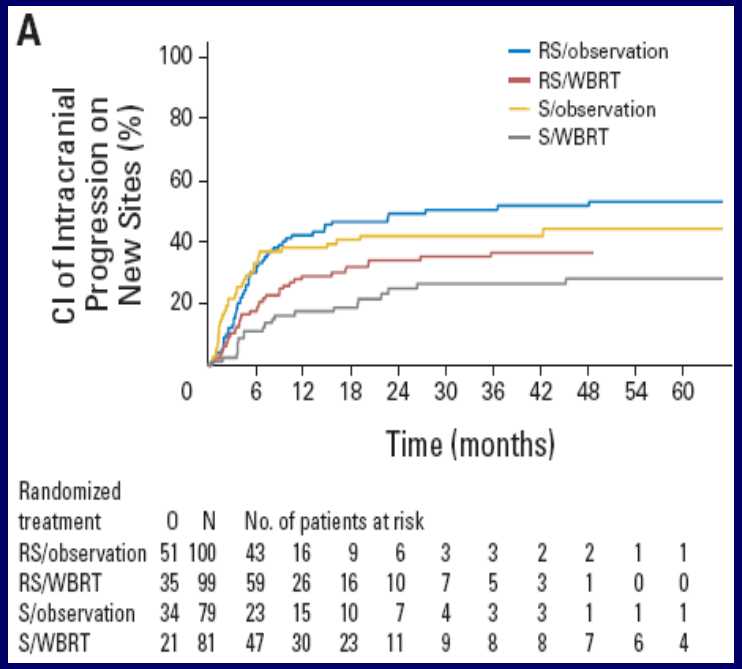
- Niveau de preuve 1
- Phase III EORTC – Méta C 1-3
- 359 patients inclus (60%)

- Endpoint principal
  - **Durée indépendance fonctionnelle**

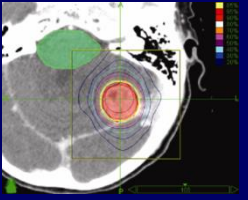
- Survie et état clinique
  - **Survie globale**
  - **Survie spécif. Neuro 48% vs 28% (*P*<.002)**

- Contrôle de la maladie intra-crânienne
  - **Contrôle local chir.: 59 vs 27% (*P*<.001)**
  - **Contrôle local SRS: 31% vs 19%(*P*.04)**

  - **Contrôle à dist. chir.: 42% vs 23% (*P*.008)**
  - **Contrôle à dist. SRS: 48% vs 23% (*P*.023)**

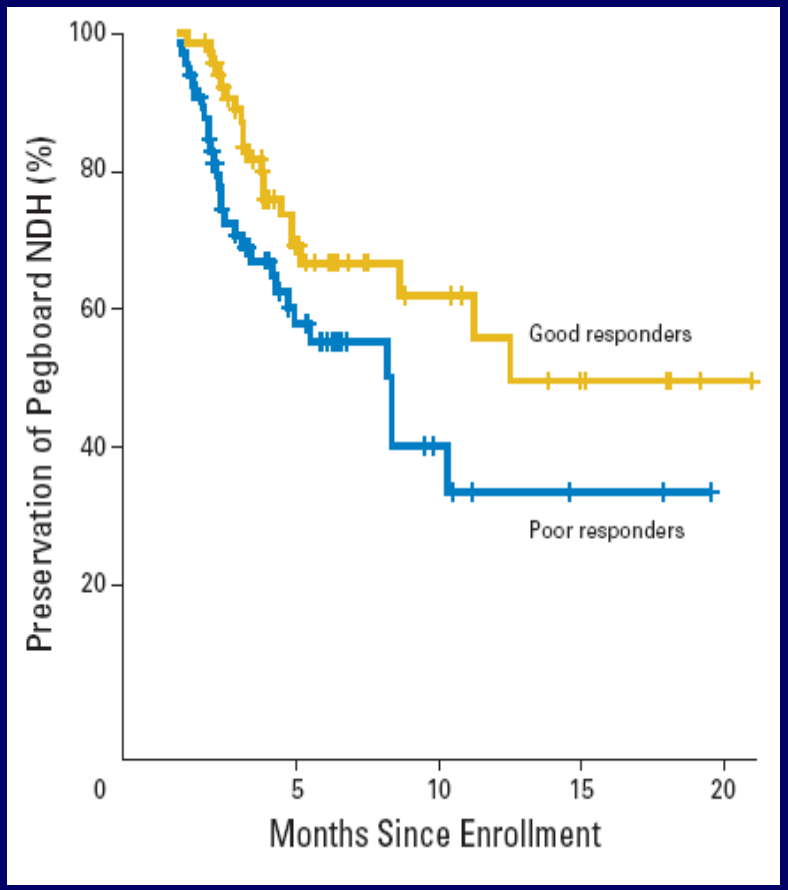


Progression intra-crânienne globale 78% (OBS) vs 48% (WBRT) *P*.002

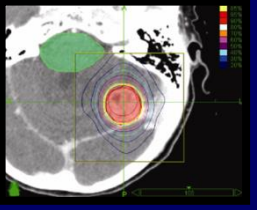


Neurocognitive function in patients treated with WBRT + MGd

- Phase III WBRT + MGd
- 208 patients – Métas non réséquables NSCLC
- Evaluation FNC: mémoire, fluence verbale, coordination motrice fine, fonctions exécutives
- MRI ts les 2 mois puis ts les 3 mois après 6 mois
- Schéma d'irradiation 30 Gy/10 (F=3 Gy)

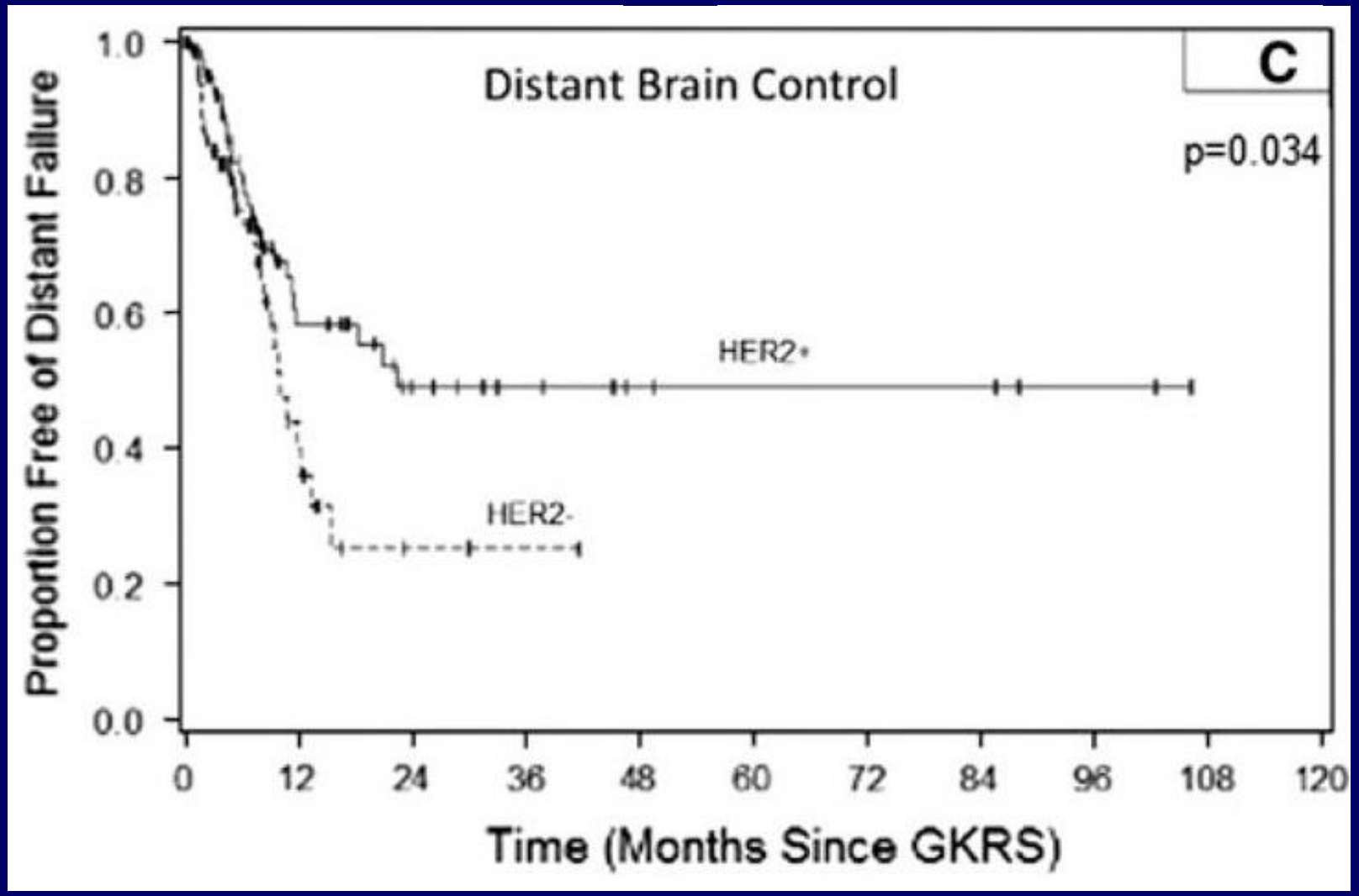


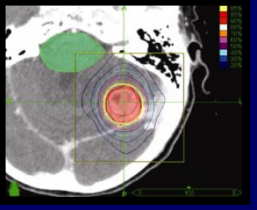
Li J, 2007, *JCO*



In toto ou localisé en fonction du sous-type tumoral ?

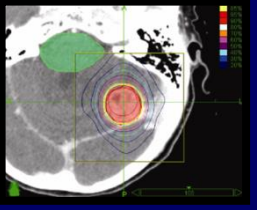
Vern-Gross et al., J Neurooncol, 2012;110:381-8





Traitement décidé au staff de radiothérapie

Et **complément simultané** de dose sur les zones à risque



Complément si RT in toto ?

Cochrane méta-analyse

Analysis 04.02. Comparison 04 WBRT and radiosurgery boost versus WBRT, Outcome 02 Local brain control at one year (includes single brain metastases from Andrews trial)

Review: Whole brain radiotherapy for the treatment of multiple brain metastases

Comparison: 04 WBRT and radiosurgery boost versus WBRT

Outcome: 02 Local brain control at one year (includes single brain metastases from Andrews trial)

Study	Radiosurgery boost n/N	WBRT n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Andrews 2004	131/164	117/167		99.6	1.14 [1.01, 1.29]
Kondziolka 1999	7/13	0/14		0.4	16.07 [1.01, 256.10]
Total (95% CI)	177	181		100.0	1.20 [1.06, 1.37]

Total events: 138 (Radiosurgery boost), 117 (WBRT)

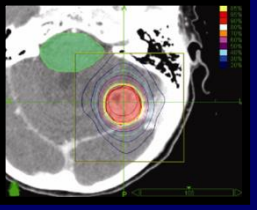
Test for heterogeneity chi-square=4.05 df=1 p=0.04 I^2 =75.3%

Test for overall effect z=2.80 p=0.005

0.001 0.01 0.1 1 10 100 1000

Favours WBRT Favours radiosurg

Patil CG et al., Cochrane Database Syst Rev, 2012 Sep 12;9:CD006121



Complément si RT in toto ?

Cochrane méta-analyse

Analysis 04.01. Comparison 04 WBRT and radiosurgery boost versus WBRT, Outcome 01 Mortality at six months (multiple brain metastases)

Review: Whole brain radiotherapy for the treatment of multiple brain metastases

Comparison: 04 WBRT and radiosurgery boost versus WBRT

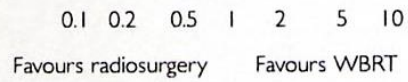
Outcome: 01 Mortality at six months (multiple brain metastases)

Study	Radiosurgery boost n/N	WBRT n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Andrews 2004	26/64	39/67		91.3	0.70 [0.49, 1.00]
Kondziolka 1999	4/13	4/14		8.7	1.08 [0.34, 3.44]
Total (95% CI)	77	81		100.0	0.72 [0.51, 1.02]

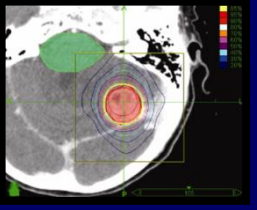
Total events: 30 (Radiosurgery boost), 43 (WBRT)

Test for heterogeneity chi-square=0.49 df=1 p=0.48 I^2 =0.0%

Test for overall effect z=1.84 p=0.07

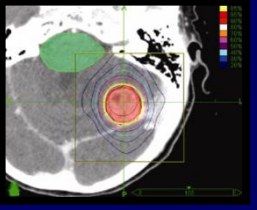


Patil CG et al., Cochrane Database Syst Rev, 2012 Sep 12;9:CD006121



Traitement décidé au staff de radiothérapie

Avec protection hippocampique



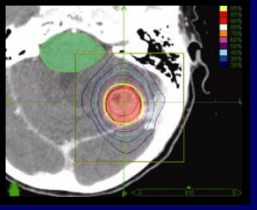
Neurocognitive function in patients with BM treated with SRS + WBRT vs WBRT

- Métas C 1 à 3
- Stratification: RPA, nb BM, histologie
- Primary endpoint: neurocognition
- Measurement: HVLT-R/mémoire verbale

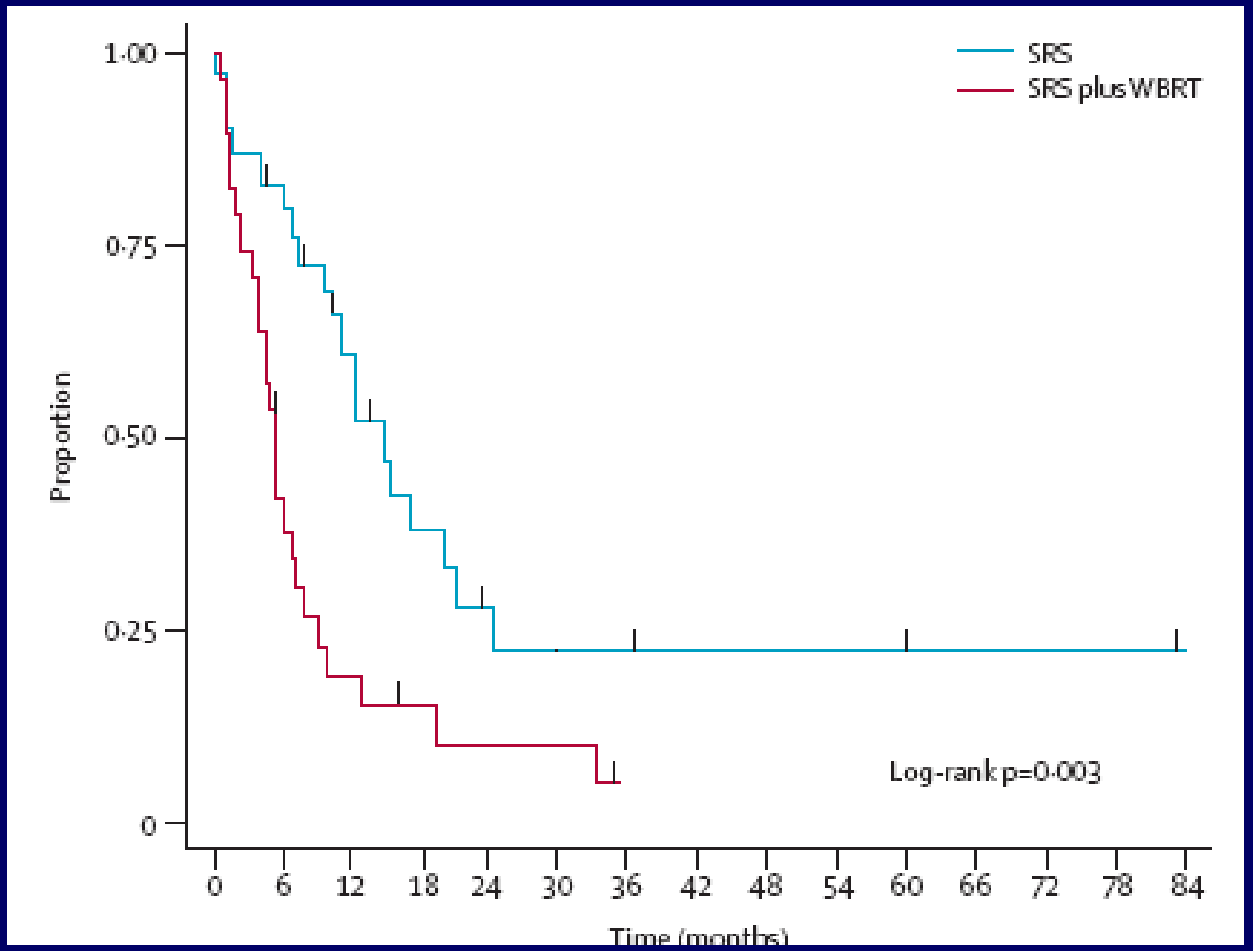
- Arrêt de l'étude à 4 mois
  - Drop de 5 points du HVLT-R
  - 52% (SRS+IPE) vs. 24% (SRS)

- Contrôle local 73% (SRS+IPE) vs. 27% (SRS)
- Toxicité de grade III 3% chaque groupe
- Recommandation: SRS à la demande et plus de WBRT !!!

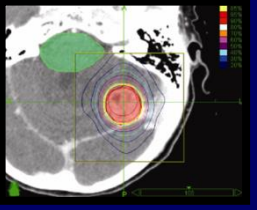
Chang E, 2009, *Lancet Oncol*



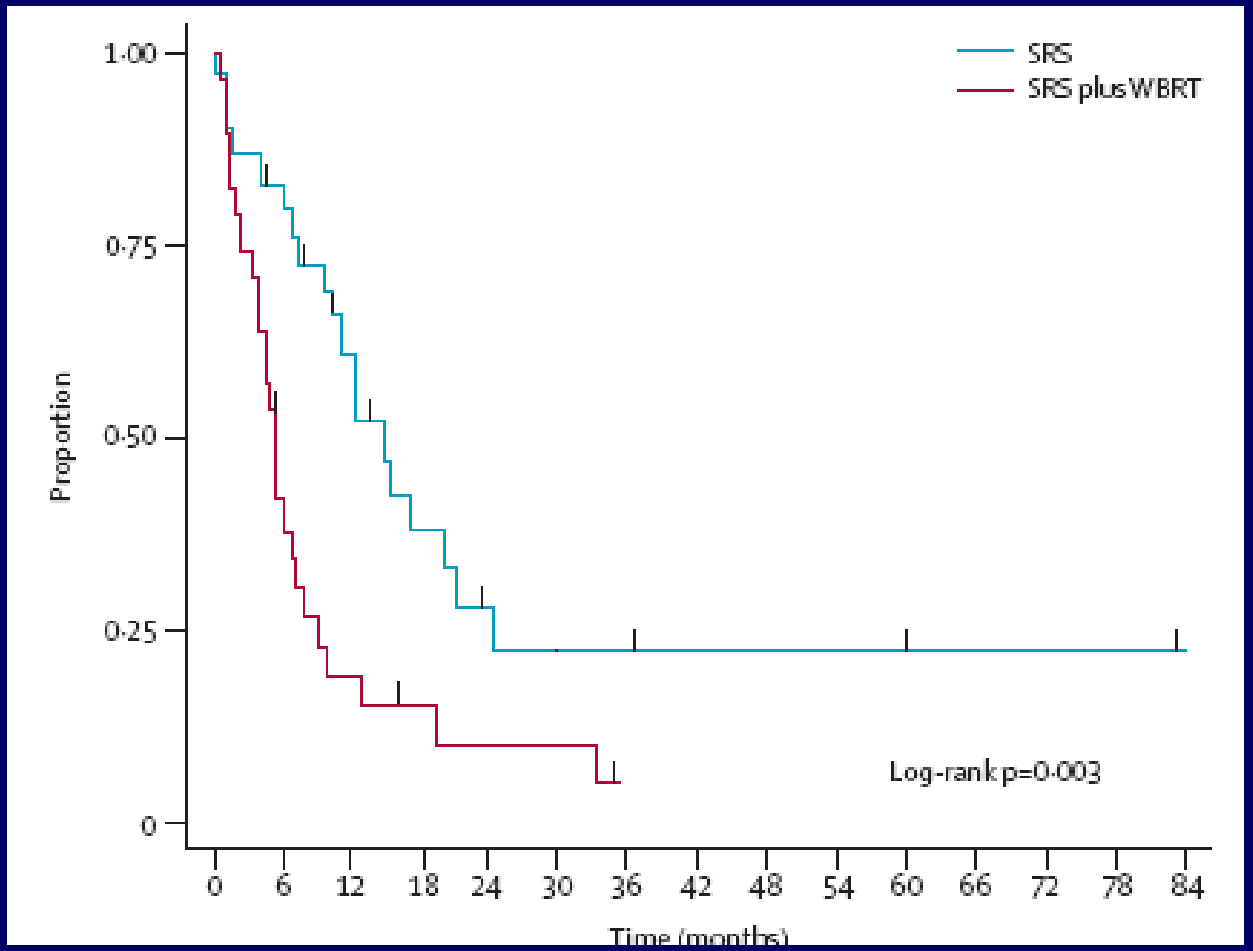
Neurocognitive function in patients with BM treated with SRS + WBRT vs WBRT



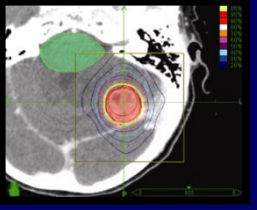
Chang E, 2009, *Lancet Oncol*



Neurocognitive function in patients with BM treated with SRS + WBRT vs WBRT

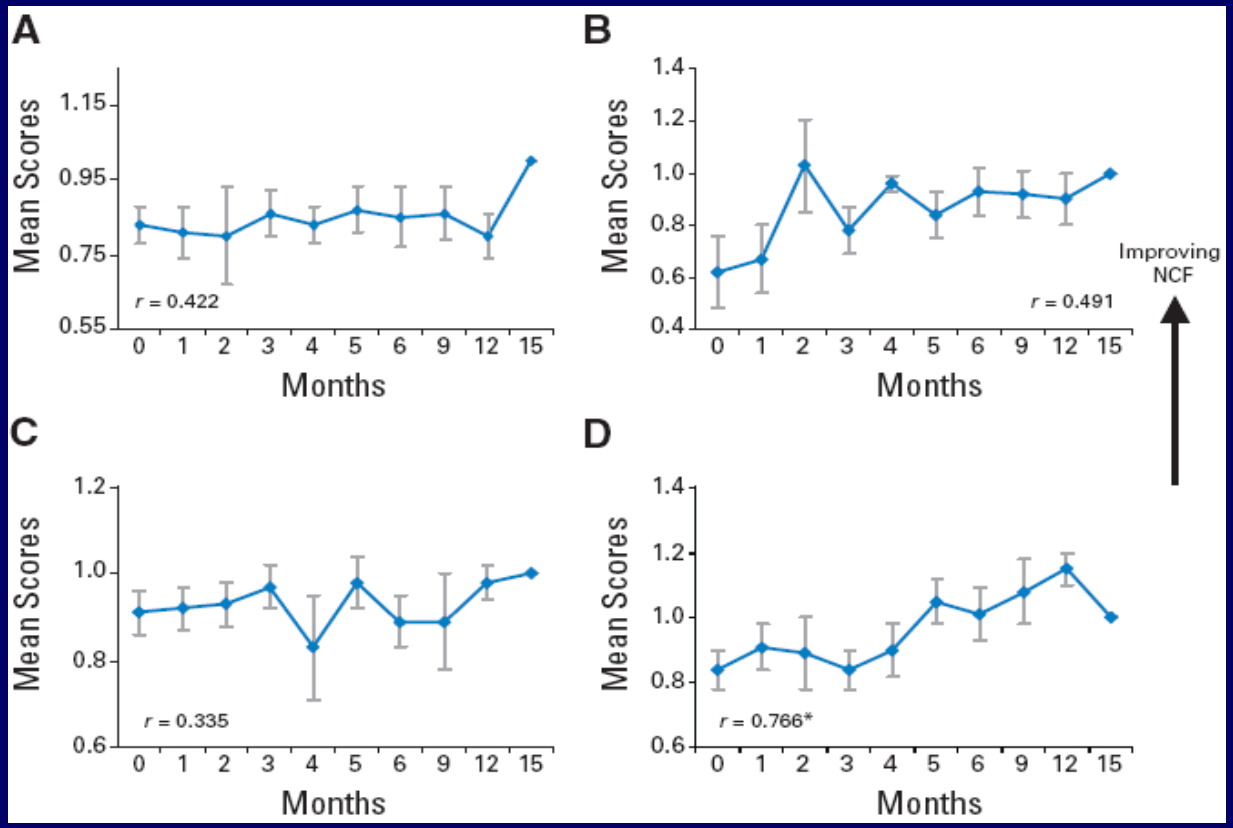


Chang E, 2009, *Lancet Oncol*

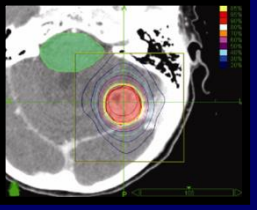


Neurocognitive function in patients treated with WBRT + MGd

Stabilité initiale et amélioration tardive des scores neurocognitifs chez les longs survivants (15 mois)



Li J, 2007, *JCO*



Protection hippocampique

- Basée sur la théorie des cellules souches
  - Processus de réparation des TNC induits par RPE (évolution biphasique)

Movsas, ASCO 2009, Li, JCO 2007

- Implication de l'hippocampe dans les troubles de la mémoire (rôle majeur, sensibilité à l'ischémie +++)

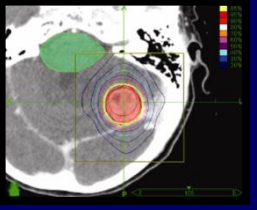
Abayomi, Acta Oncol 1996

- Sensibilité à l'irradiation: 2 Gy induit l'apoptose des cellules prolifératives de l'hippocampe avec diminution des capacités de repopulation

Peissner W Brain Res Mol Brain Res. 1999

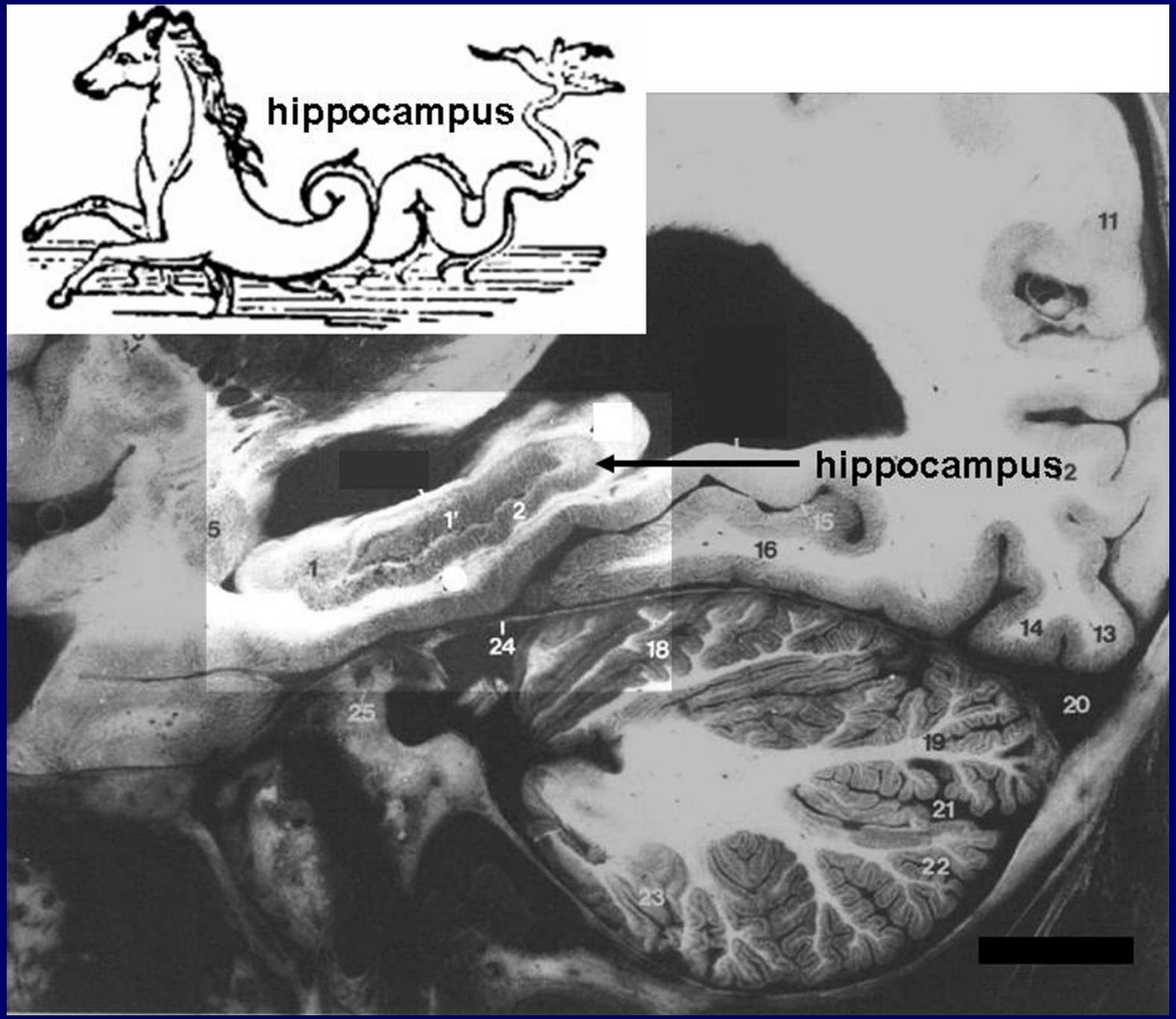
- Incidence des métas dans la région hippocampique ≈ 3%

Ghia et al., IJROBP 2007; Gondi et al., Radiother Oncol 2010; Marsch et al., IJROBP 2010



Essai phase II RTOG 0933

- ASTRO 2013 LBA; Gondi et al.
- Patients analysés par tests mémoriels à 4 et 6 mois
- Questionnaire du John Hopkins
- Diminution de seulement 1 à 3% des tests mémoriels à 4 mois et stables à 6 mois
- RTOG 1317 randomisé est en cours


hippocampus
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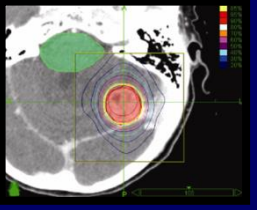
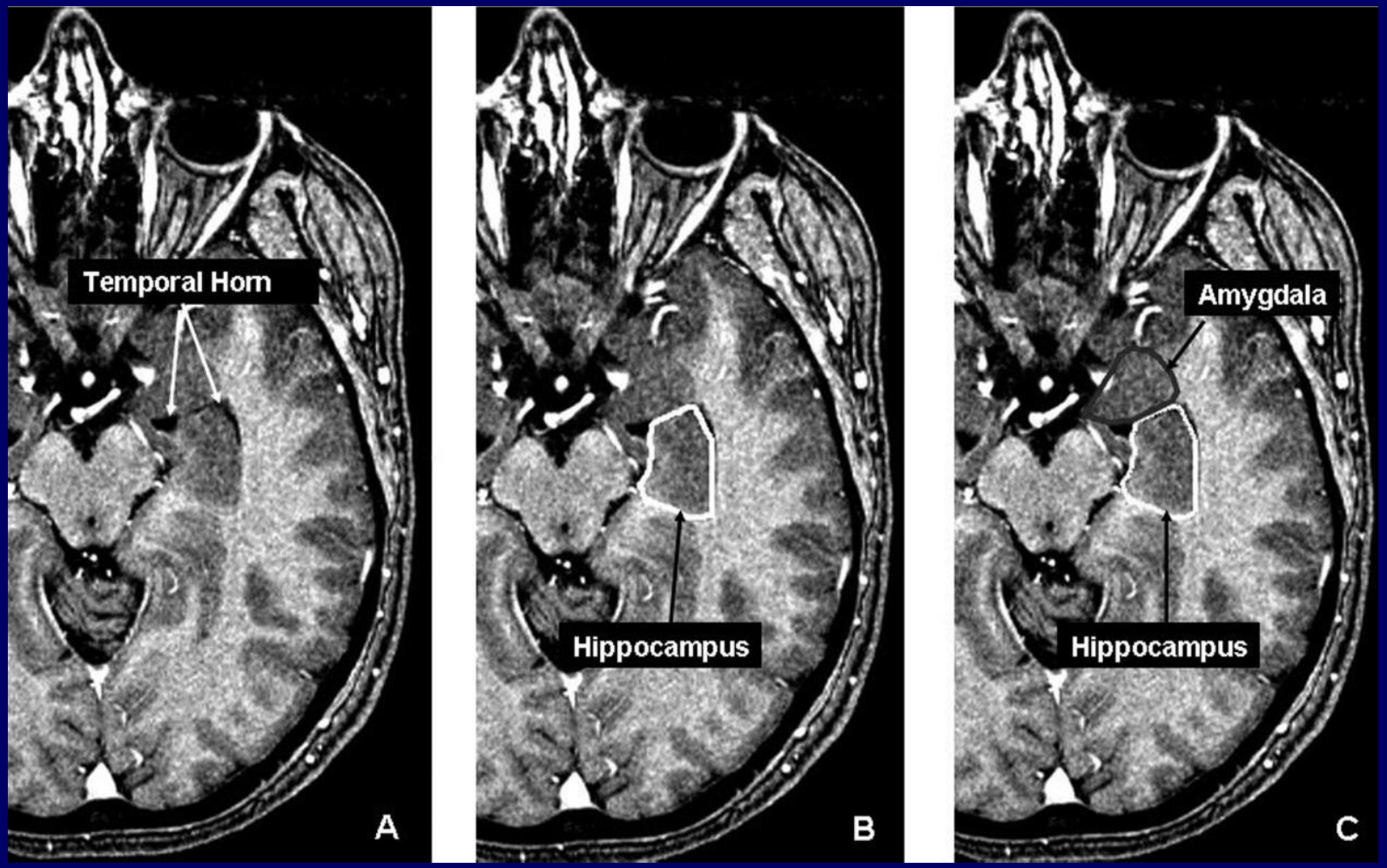
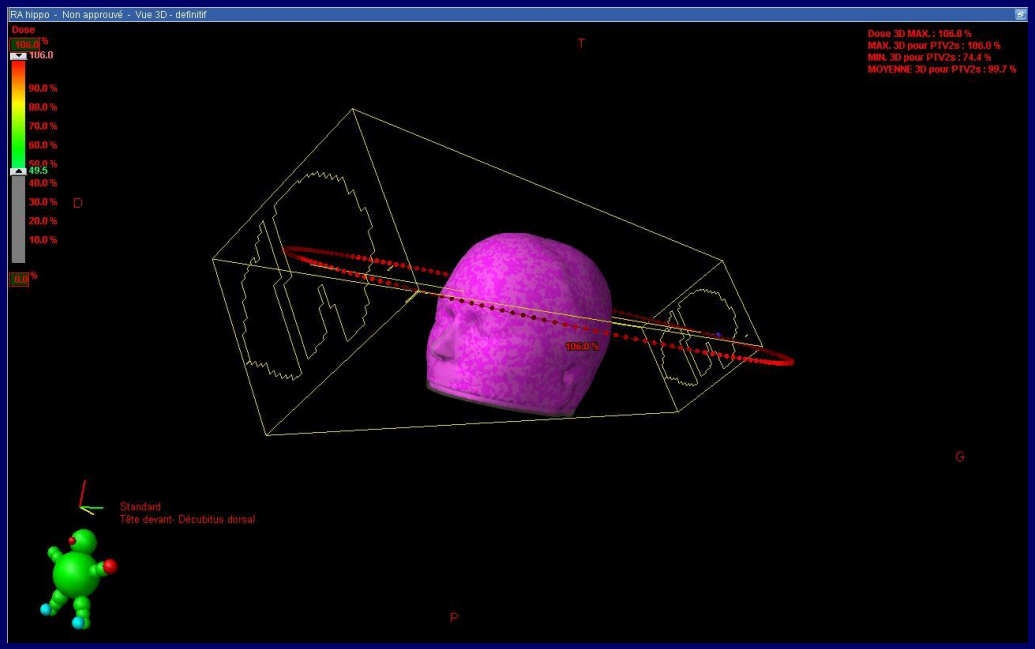
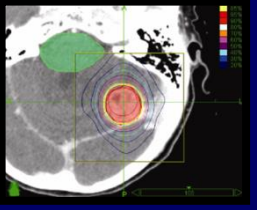


IRM puis fusion multimodalité



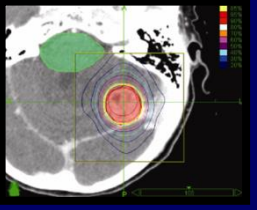
IMRT rotationnelle avec protection hippocampique





Suivi

- Revue en octobre 2014 (Deux ans après)
- Va parfaitement bien
- Troubles mnésiques très modérés apparus 18 mois la RT mais sans aggravation
- IRM cérébrale: normale
- TEP normal
- Marqueur CA 15-3 normal
- Aucun traitement en cours



Merci de votre attention