Intra-CSF pharmacotherapy for leptomeningeal metastasis?

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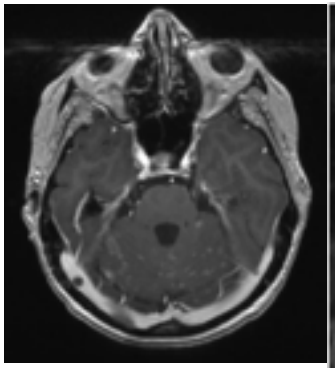
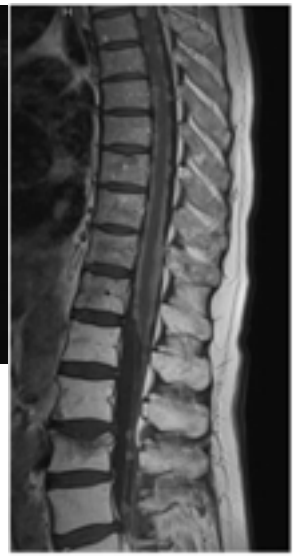
Definition of leptomeningeal metastasis

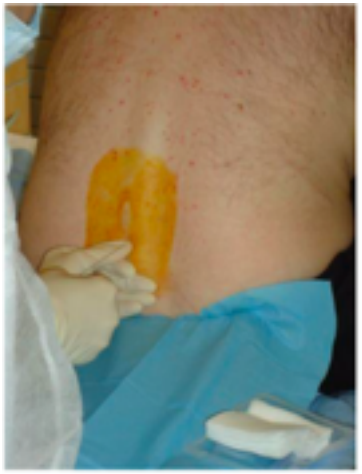
- **LM is defined as the spread of tumor cells within the leptomeninges and the subarachnoid space**
- **LM is synonymous with neoplastic meningitis and can be further denoted by primary tumor as leptomeningeal carcinomatosis, gliomatosis or lymphomatosis**



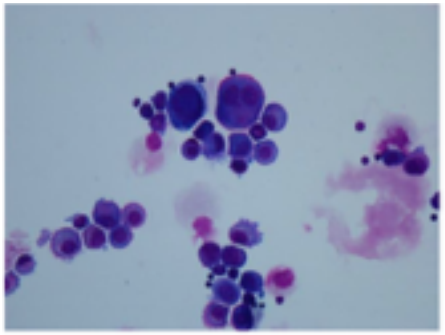
Axial brain gadolinium enhanced MRI



Sagittal spinal gadolinium enhanced MRI



Lumbar puncture



Invasive lobular carcinoma (x40)

Leptomeningeal metastasis

- Leptomeningeal metastasis affects up to 10% of patients with solid tumors
- Median survival limited to 2-3 months, 1-year survival rate below 10%
- Only a few prospective clinical trials are available
- Treatment strategies include intra-CSF chemotherapy, systemic pharmacotherapy, and focal or large volume radiotherapy

Diagnosis and treatment of leptomeningeal metastasis: Levels of evidence

No standards for:

- Neurological examination
- Neuro-imaging assessment
- CSF diagnosis

- No trial on systemic treatment
- No trial on radiotherapy
- Only 5 trials on intra-CSF therapy….

Randomized trials of intra-CSF chemotherapy for leptomeningeal metastasis

Trial	Design	Population	Primary endpoint	Efficacy	Safety
Grossman 1993	IT MTX versus IT thiotepa	Solid tumors (n=40), CUPS (n=1) and lymphomas (n=10)	Neurological response rate	IT MTX vs. IT thiotepa Neurological response rate: none Neurological stabilization: 32% vs. 12.5% Survival: 15.9 weeks vs. 14.1 weeks	IT MTX vs. IT thiotepa Serious toxicities similar in both group Mucositis (p=0.04) and neurological complications (p=0.008) more frequent in MTX arm
Hitchins 1997	IT MTX versus IT MTX + cytarabine	Solid tumors (n= 30), cancers of unknown primaries (n=7) and lymphomas (n=7)	Response rate	IT MTX vs. MTX + cytarabine Response rate : 61 vs. 45% (p<0.05) Median survival : 12 vs. 7 weeks (p<0.05)	IT MTX vs. MTX + cytarabine Nausea and vomiting : 36% vs. 50% Septicemia, neutropenia : 9% vs. 15% Mucositis : 14% vs. 10% Pancytopenia : 9% vs. 10%
Glantz 1999	IT liposomal cytarabine versus IT MTX	Solid tumors (n=61)	Response rate at the end of the induction period	IT liposomal cytarabine vs. IT MTX Responses rate : 26% vs. 20% (p = 0.76) Median survival : 105 days vs. 78 days (p *P* = 0.15) Time to neurological progression : 58 vs. 30 days (p = 0.007) Neoplastic meningitis-specific survival : 343 *vs.* 98 days (p = 0.074)	IT liposomal cytarabine vs. IT MTX Sensory/motor dysfunction : 4% vs. 10% (p = 0.021) Visual impairment 0% vs. 13% (p = 0.066) Chemical meningitis of any grade : 23% vs. 19% *(p*=0.57)
Boogerd 2004	IT MTX versus no IT	Breast cancers (n=35)	Overall survival: time from randomization until death	IT MTX vs. no IT Overall survival :18.3 weeks vs. 30.3 weeks (p = 0.32) Neurological improvement or stabilisation : 59% vs. 67% (p = NR) Median time to progression of 23 weeks and 24 weeks (p = NR)	IT MTX vs. no IT Neurological complications : 47% vs 6% (p = 0.0072)
Shapiro 2006	solid tumors: IT liposomal cytarabine versus IT MTX (lymphomas: IT liposomal cytarabine versus IT aracytine)	Solid tumors (n=103) and lymphomas (n=25)	Progression free survival: randomized to neurological progression or death	IT liposomal cytarabine versus IT MTX or aracytine Median progression free survival: 35 vs. 43 days (p=0.7321)	IT liposomal cytarabine versus IT control Drug related AE: 48% vs. 60% of the serious AE: 86 vs. 77%

ELSEVIER
European Journal of Cancer
UniversitätsSpital Zürich

The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study☆

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Breast cancer patients; diagnosis of LM based on CSF cytology or MRI, no progressive or untreated brain metastases

- Intraventricular MTX, appropriate systemic therapy, and if necessary RT to clinically relevant sites
- Appropriate systemic therapy, and if necessary RT to clinically relevant sites – No intraCSF therapy

Table 2
Applied therapy within 4 weeks after randomisation

	Group 1 (IT)	Group 2 (non-IT)
Intraventricular chemotherapy	17 (100%)	–
Systemic chemotherapy	7 (41%)	9 (50%)
Hormonal therapy	7 (41%)	6 (33%)
Systemic chemotherapy and hormonal therapy	–	1 (6%)
No systemic therapy	3 (18%)	2 (11%)
Involved field radiotherapy	6 (35%)	9 (50%)

IT, intraventricular treatment.

Table 5
Toxicity and complications of treatment

	Group 1 (IT)	Group 2 (non-IT)
Treated for vomiting	6 (35%)	6 (33%)
Intractable vomiting	1 (6%)	1 (6%)
Permanent myelosuppression (grade 4)	–	1 (6%)
Headache		
Mild	3 (18%)	2 (11%)
Moderate	7 (41%)	4 (22%)
Serious	2 (12%)	3 (17%)
Intractable	1 (6%)	1 (6%)
Gait disturbances		
Moderate	3 (18%)	9 (50%)
Serious/bedridden	11 (65%)	5 (28%)
Lethargy		
Moderate	7 (41%)	6 (33%)
Serious	2 (12%)	1 (6%)
Cognitive impairment		
Moderate	9 (53%)	4 (22%)
Serious	3 (18%)	2 (11%)
MTX meningitis	2 (12%)	–
Infectious meningitis	2 (12%)	–
Ommaya reservoir revision	3 (18%)	–
Intracerebral haemorrhage	1 (6%)	–
Subdural haematoma	1 (6%)	–
Acute fatal encephalopathy	1 (6%)	–
Subacute transient encephalopathy	1 (6%)	–
Delayed leucoencephalopathy	3 (18%)	1 (6%)

Median survival:
18.3 weeks in the intra-CSF arm vs. 30.3 weeks in the control arm

Neuroimaging was not used to evaluate the neurological response; trial stopped after 35 patients enrolled between 1991 and 1998 (instead of 50 initially expected)

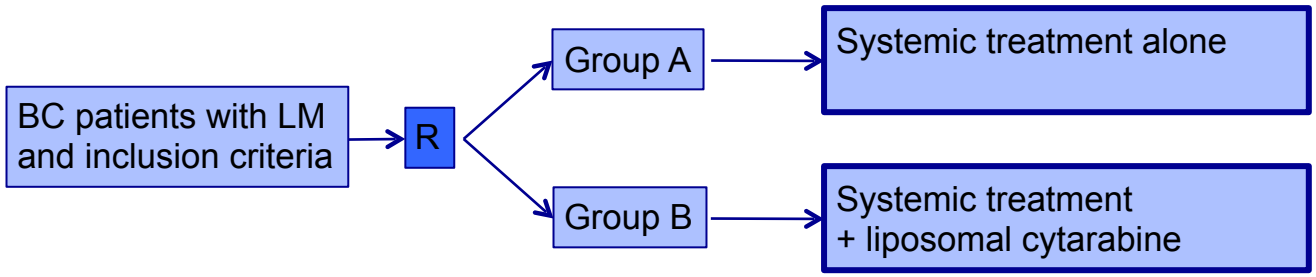
DEPO-SEIN
NCT01645839

Main inclusion criteria

- Adult breast cancer patients requiring a systemic treatment at inclusion, ECOG PS: 0-2
- Diagnosed with LM (CSF positive cytology; combination of typical clinical and MRI findings)
- Meningeal metastases <0.5 cm (or >0.5 if treated by SRS/SRT)
- Asymptomatic brain metastases permitted
- WBRT not allowed
- Untreated CSF blockade not allowed

Main objective

- To compare the neurological progression free survival (clinical and imaging criteria) between the 2 groups



- **Liposomal cytarabine until unacceptable toxicity, neurological progression or a maximum of 12 months**
- **Systemic treatment at the discretion of the investigator**

J Neurooncol (2017) 133:419–427
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CLINICAL STUDY

Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe

Emilie Le Rhun[1,2,3,4] · Roberta Rudà[5] · Patrick Devos[6] · Khê Hoang-Xuan[7] · Dieta Brandsma[8] · Pedro Pérez Segura[9] · Riccardo Soffietti[5] · Michael Weller[4]

Table 1 (continued)

Treatment—follow up	Number (%)
At your institution, intra-CSF treatment for LM is administered:[a]	Always: 8 (3.5) Never: 23 (10.5) Depending on CSF and MRI findings: 81 (36) Depending on the primary cancer: 126 (56) Depending on molecular data of the primary cancer: 28 (12.5) Depending on the systemic treatment: 68 (30.5) Only in combination with a systemic treatment: 12 (5.5) No response: 25 (10.5)

Intra-CSF therapy

Agent	Description	Half-life in the CSF	Recommended schedules of administration	Prophylaxis of adverse events
Methotrexate	folate anti-metabolite, cell cycle specific drug	4.5-8 hours	10-15 mg twice weekly (total, 4 weeks), then 10-15 mg once weekly (total, 4 weeks) then 10-15 mg once monthly	folinic acid rescue, 25 mg x 6 h for 24 h starting 6 h after administration
Cytarabine	pyrimidine nucleoside analogue, cell cycle specific	<1 hour	10 mg twice weekly (total, 4 weeks) then 10 mg once weekly (total, 4 weeks) then 10 mg once a month	none
Liposomal cytarabine	pyrimidine nucleoside analogue, cell cycle specific	14-21 days	50 mg every 2 weeks (total, 8 weeks) then 50 mg once a month	Oral steroids, e.g., 6 mg dexamethasone equivalent daily, (d-1 to d4
Thiotepa	alkylating ethyleneimine compound, cell cycle non-specific drug	3-4 hours	10 mg twice weekly (total, 4 weeks) then 10 mg once weekly (total, 4 wks) then 10 mg once a month	None

Pros & Cons

Limits of intra-CSF therapy	In favor of intra-CSF therapy
No randomized trial has demonstrated that intra-CSF therapy prolongs survival in LM patients	Used by a large majority of physicians in addition to systemic treatments across Europe (only 11% of physicians never use intra-CSF therapy) Recent prospective safety data have shown a good tolerance of liposomal cytarabine
The compounds routinely used for intra-CSF treatment do not have a key role as single agents for systemic treatment of common cancers causing LM	Compounds with systemic efficacy are currently under evaluation as intra-CSF agents in clinical trials
Intra-CSF therapy has only a limited penetration (1-3 mm) into solid tumor lesions Intra-CSF therapy may be inefficient and toxic in case of CSF flow blocks	Rationale for the treatment of floating tumor cells in the CSF in the setting of little or no blood CSF barrier dysfunction Rationale for the treatment of linear diffuse or ependymal spread not yet accompanied by blood brain barrier dysfunction

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv84–iv99, 2017
doi:10.1093/annonc/mdx221

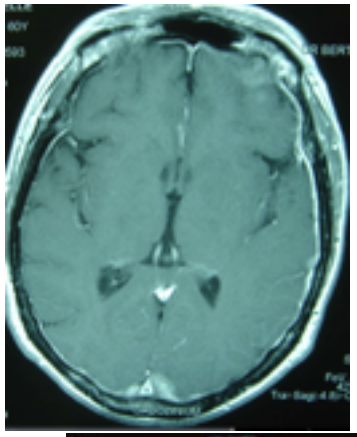
CLINICAL PRACTICE GUIDELINES

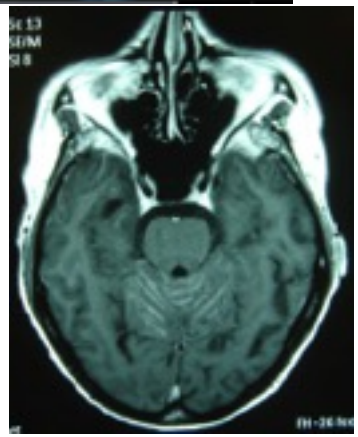
EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours†

E. Le Rhun[1,2,3], M. Weller[4], D. Brandsma[5], M. Van den Bent[6], E. de Azambuja[7], R. Henriksson[8,9], T. Boulanger[10], S. Peters[11], C. Watts[12], W. Wick[13,14], P. Wesseling[15,16], R. Rudà[17] & M. Preusser[18], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

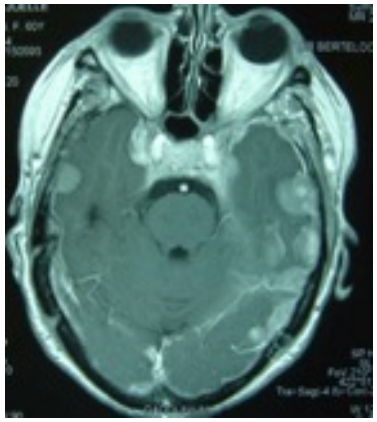
Imaging-based classification?

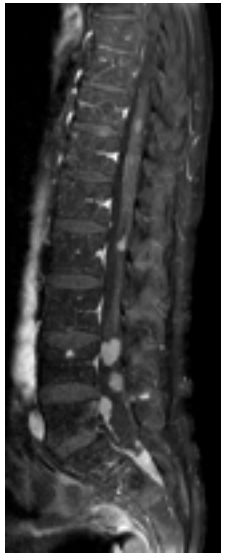
Type A: LM with typical linear MRI abnormalities



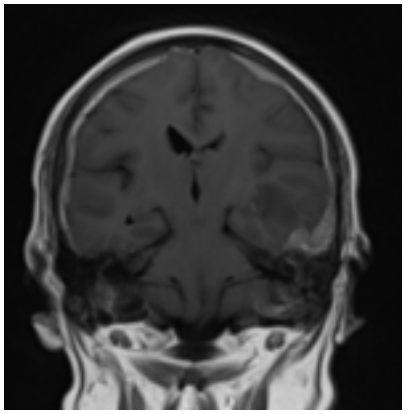


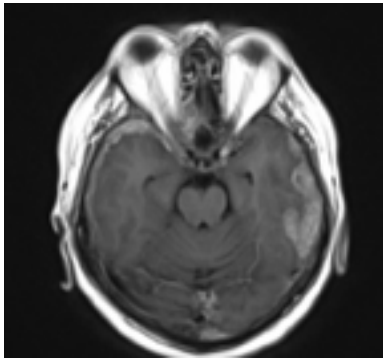
Type B: LM with nodular disease only as type B



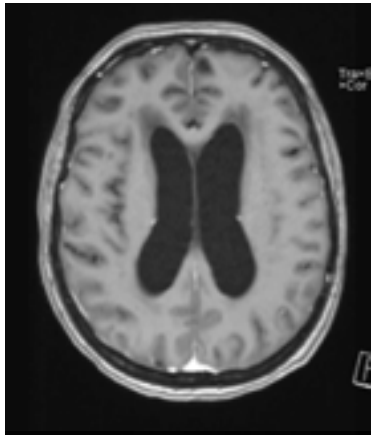


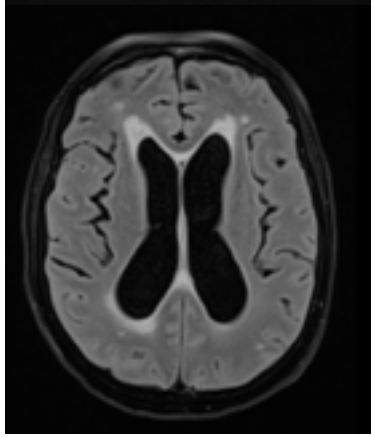
Type C: LM with both linear and nodular disease





Type D: LM without MRI abnormalities, except possibly hydrocephalus





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Is there a role for intra-CSF treatment?

→ **in selected patients:**

In the presence of:

- **floating tumor cells in the CSF in the setting of little or no blood CSF barrier dysfunction**
- **linear diffuse or ependymal spread not yet accompanied by blood brain barrier dysfunction**

Not as first option in patients with symptomatic hydrocephalus who require ventriculoperitoneal shunt placement or with a ventricular device without on/off option

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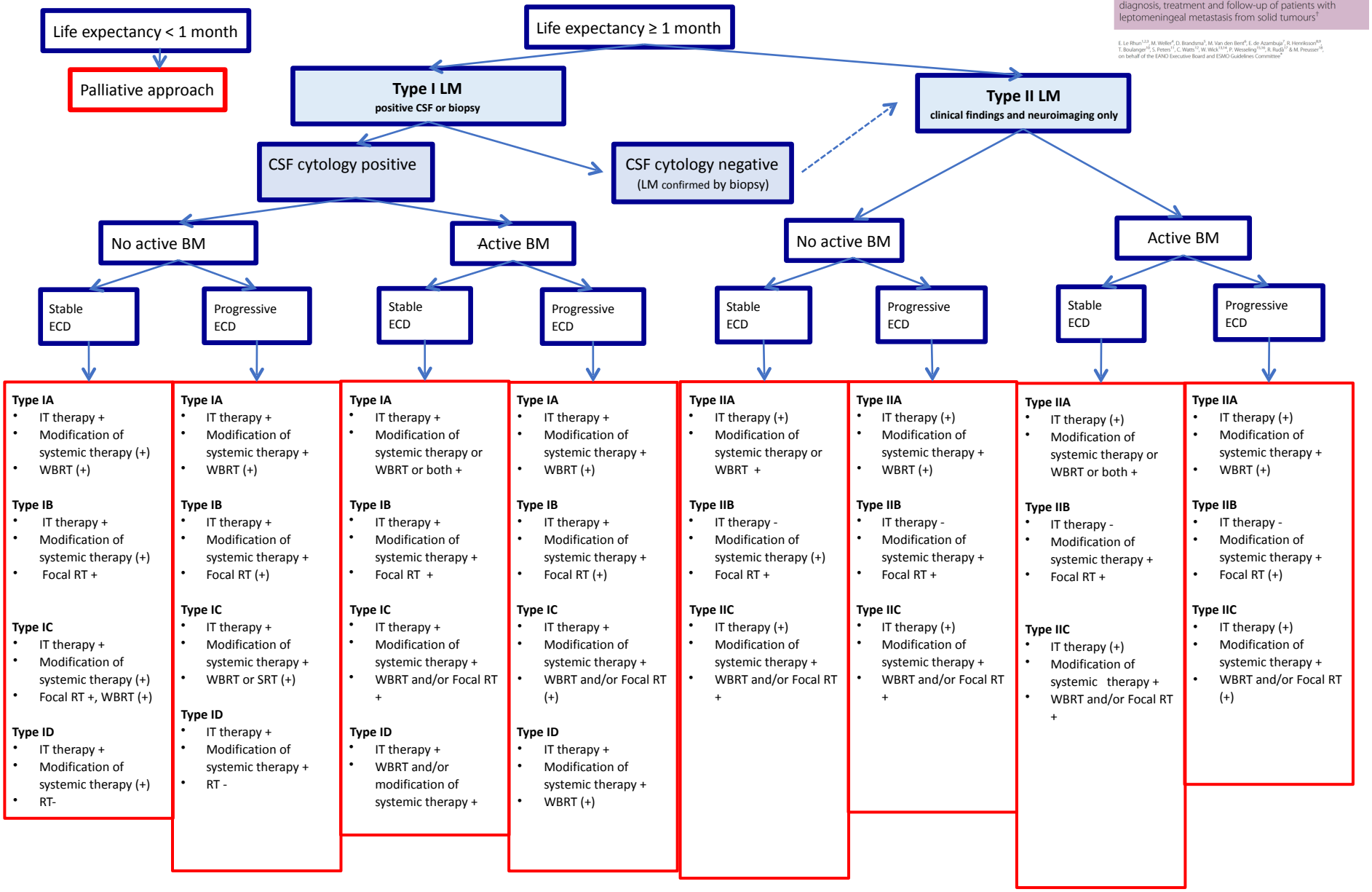

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