13° CONGRESSO NAZIONALE AIOM GIOVANI

2019 NEWS IN ONCOLOGY

Sessione Educazionale
"Carcinoma Polmonare"

Caso Clinico
Saper Scegliere.
La malattia Oligometastatica ed il miglior approccio terapeutico

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Caso Clinico

Donna di 67 anni, fumatrice 30 pack-year
APR ndr

Esordio Patologia Oncologia Giugno 2018
Comparsa al risveglio di deviazione rima orale per cui accedeva c/o PS nostro Ospedale

***EON*: deficit del VII nervo cranico di tipo centrale, nella norma gli altri NNCC**

***Rm Encefalo c/s mdc:* In sede frontale sinistra presenza di lesione di 48x37x45 mm con estesa reazione edemigena. Ulteriore lesione in sede frontale di circa 27 mm Dmmax**

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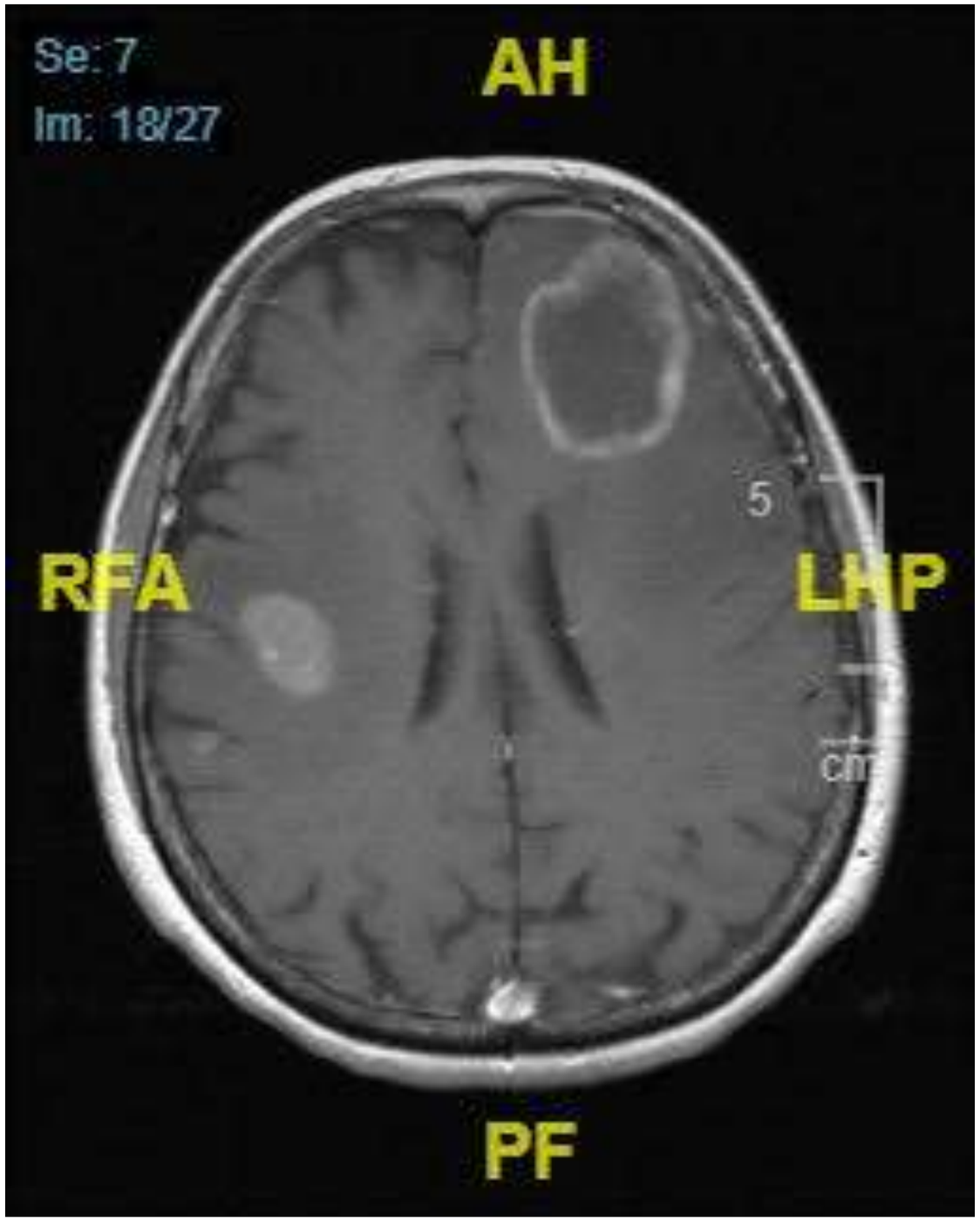

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- ***TcTb c/s mdc*: tessuto solido eteroformato di 42x 38mm a livello segmento apicale LSD, analogo reperto delle dm di 24x22 mm a livello del segmento postero-basale del LID.**

- ***Stadiazione Radiologica* T4 N0 M1b stadio IVa**

- ***Scintigrafia Ossea Tb*: negativa**

- ***Biopsia Polmonare TC-guidata*:**

Adenocarcinoma primitivo del polmone TTF-1+, NapsinA+, IHC negativa per Alk, Ros-1 e PD-L1, EGFR WT

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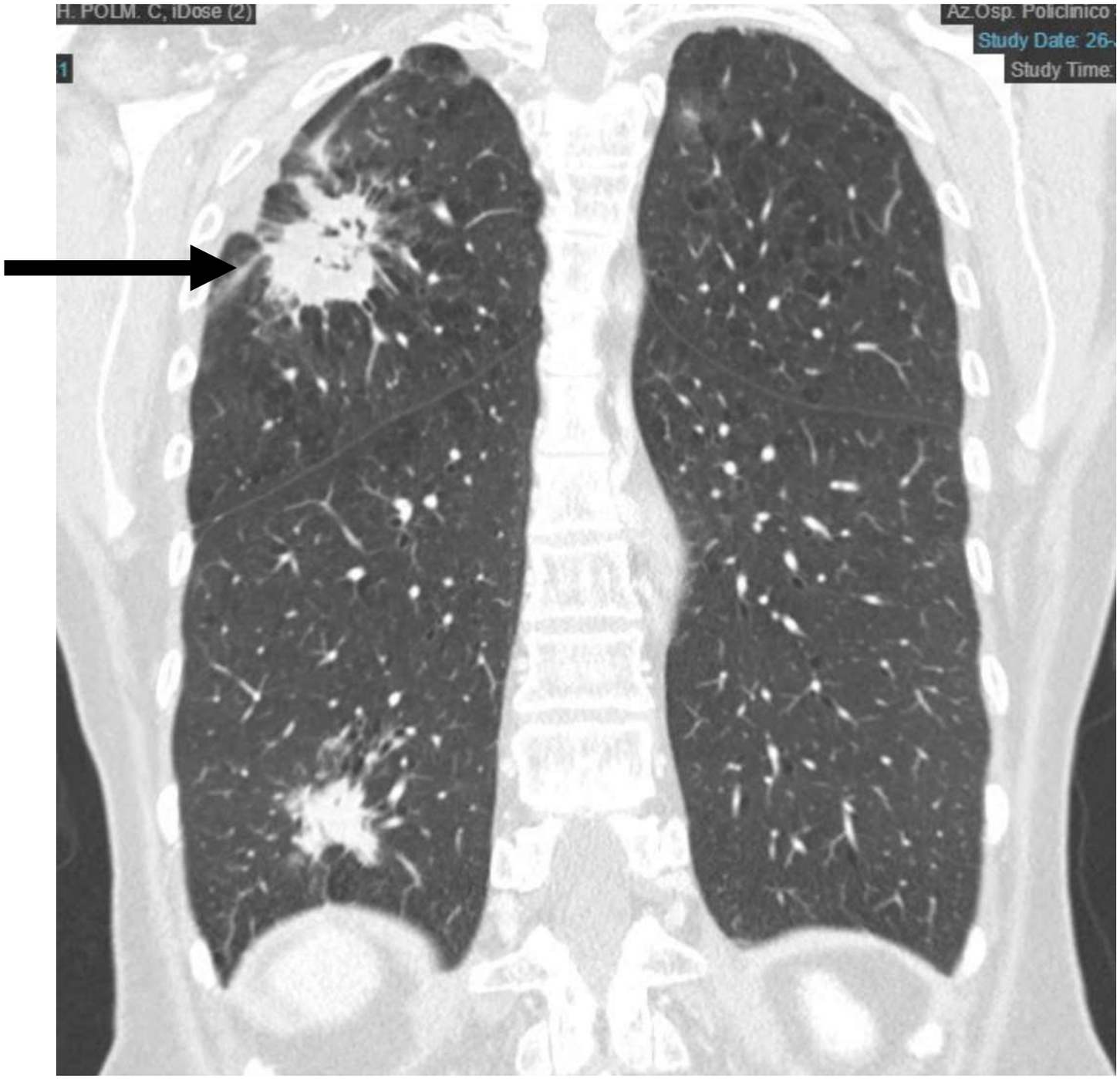

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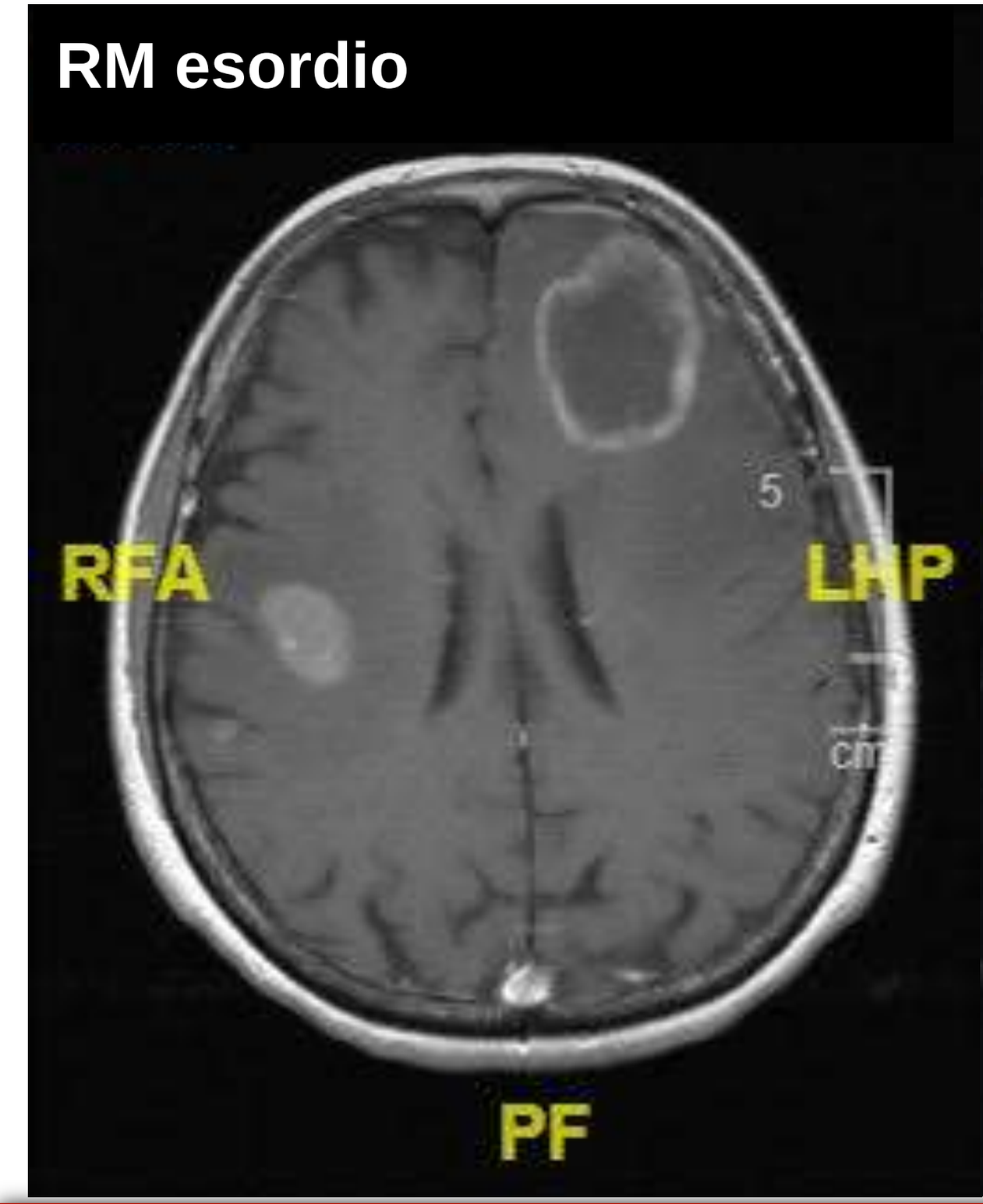
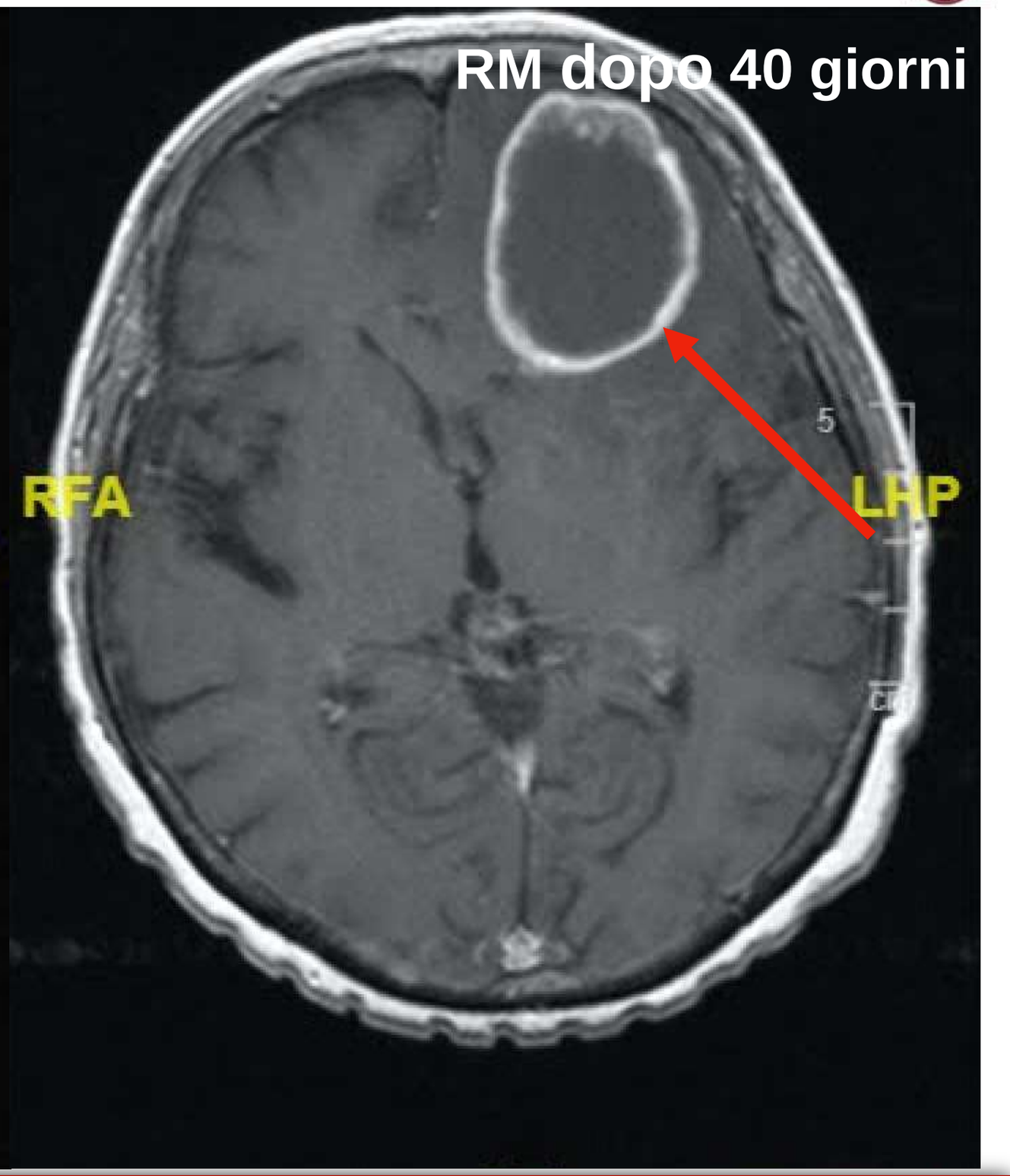
Luglio 2018 ricovero c/o Reparto Oncologia Medica.
Paziente in condizioni generali mediocri, PS2 ECOG
Peggioramento quadro Neurologico con afasia a prevalente contenuto motorio

***Valutazione Radioterapica*:**
Trattamento WBRT 5 fr da 4Gy, dose totale 20Gy

Inizio trattamento chemioterapico:
I linea CDDP 75 mg/mq-Pemetrexed 500 mg/mq q21

Caso Clinico





Caso Clinico

Paziente ha ottimo recupero funzionale dopo intervento.
A settembre ripresa trattamento chemioterapico in Dh con medesimo schema per ulteriori V cicli

TcTb di rivalutazione **PR cerebrale e SD toracica**

Ridiscusso il caso multidisciplinarmente veniva deciso:

- **Trattamento di mantenimento Pemetrexed 500 mq/mq q21**
- **Trattamento SBRT di consolidamento sui due noduli polmonari**

Caso Clinico

- ***Febbraio 2019*:**
  Trattamento SBRT LID 10 Gy in 5 fr, LSD 6.5 Gy in 8 fr

- ***Giugno 2019*:**
  RP polmonare ed encefalica

Malattia Oligometastatica

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

Both the contiguous and systemic theories of cancer pathogenesis are too restricting and do not consider what is now known about tumor progression during clinical evolution. A third paradigm, one that synthesizes the contiguous-systemic dialectic, has been suggested by one of us[6] to explain the natural history of breast cancer. This thesis argues that cancer comprises a biologic spectrum extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states. Metastases are a function of both tumor size and tumor progression.

While much tumor evolution occurs during the preclinmore about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding tumor cell number and characteristics as well as the receptivity of the host organ. The importance of ''seed and soil'' have been considered elsewhere[14,15] and will not be discussed further. Tumors early in the chain of progression may have metastases limited in number and location because the facility for metastatic growth has not been fully developed and the site for such growth is restricted (this is in contrast to micrometastases, which, although small in size, are extensive in number). With further progression, the tumor seeding efficiency increases and becomes less fastidious with regard to the location of metastatic growth. In addition to this progression of

Concetto di malattia oligometastatica

Proposto per la prima volta da Hellmann nel 1985 (J Clin Oncol 1985)

Definito come uno stadio intermedio tra il localmente avanzato e la malattia metastatica disseminata

Hellman and Weichselbaum, J Clin Oncol 1985

Malattia Oligometastatica: Criticità

Insufficienti evidenze dei dati scientifici

- ***Maggior parte studi osservazionali o case series***
- ***Solo due RCT pubblicati***

Malattia Oligometastatica: Criticità

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature

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ARTICLE INFO

Article history:
Received 30 April 2013
Received in revised form 17 July 2013
Accepted 29 July 2013

Keywords:
Lung cancer
Oligometastases
Stereotactic ablative radiotherapy

ABSTRACT

Objectives: Long-term survival has been observed in patients with oligometastatic non-small cell lung cancer (NSCLC) treated with locally ablative therapies to all sites of metastatic disease. We performed a systematic review of the evidence for the oligometastatic state in NSCLC.
Materials and Methods: A systematic review of MEDLINE, EMBASE and conference abstracts was undertaken to identify survival outcomes and prognostic factors for NSCLC patients with 1–5 metastases treated with surgical metastatectomy, Stereotactic Ablative Radiotherapy (SABR), or Stereotactic Radiosurgery (SRS), according to PRISMA guidelines.
Results: Forty-nine studies reporting on 2176 patients met eligibility criteria. The majority of patients

Malattia Oligometastatica: Criticità

- **Sono stati selezionati 49 lavori osservazionali che descrivono trattamenti ed outcomes di NSCLCs Oligometastatici**

- **Esiste una percentuale di Pazienti lungosopravviventi con malattia oligometastatica**

- **Sono stati identificati dei fattori prognostici di sopravvivenza significativi: controllo del tumore primario, lo status N intra-toracico, una DFI >6 mesi**

Malattia Oligometastatica: Criticità

Non uniformità nella definizione di malattia oligometastica

- **Malattia oligometastatica dall'esordio vs recidiva oligometastatica**

- **Numero di metastasi usate come Cut-off : 1, 1-2, 1-5?**

- **Numero di organi a distanza coinvolti: 1, 2, 3?**

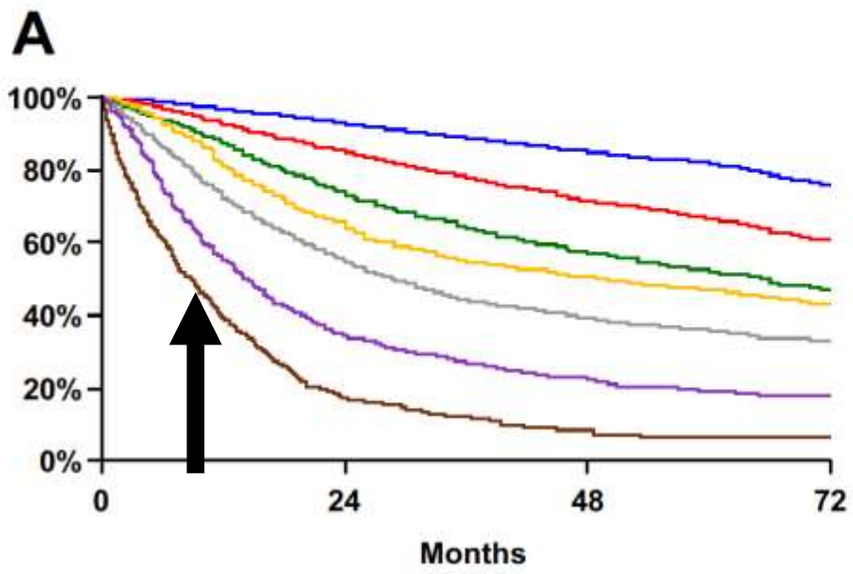
Malattia Oligometastatica: Criticità

Lung Cancer TNM 8th edition

T / M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Malattia Oligometastatica: Criticità

January 2016 *IASLC Staging Project: Stage Grouping Proposals*



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Malattia Oligometastatica: Criticità

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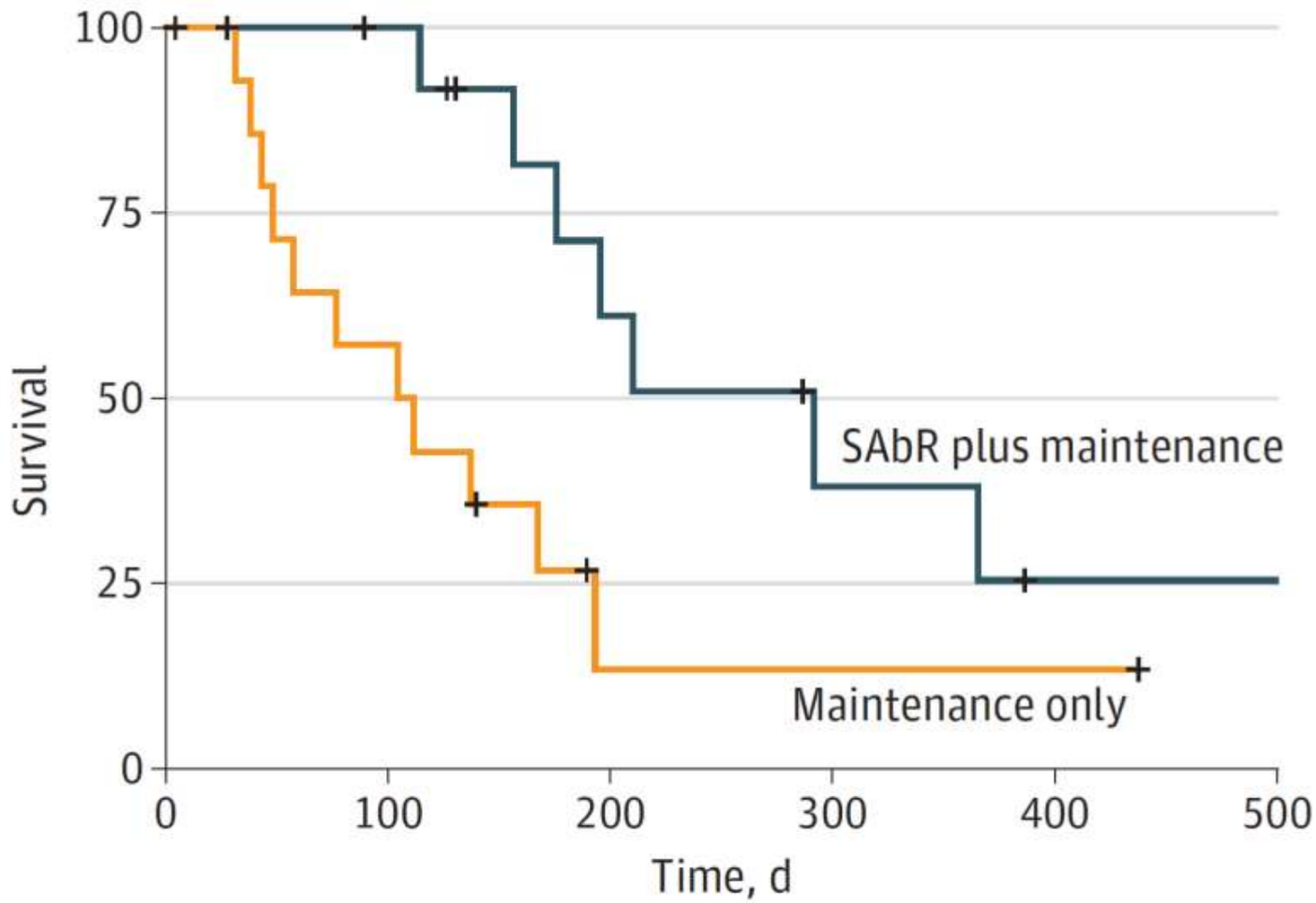
Malattia Oligometastatica: Criticità



No. at risk					
SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Yengar et al, JAMA Oncol. 2018

Malattia Oligometastatica: Criticità

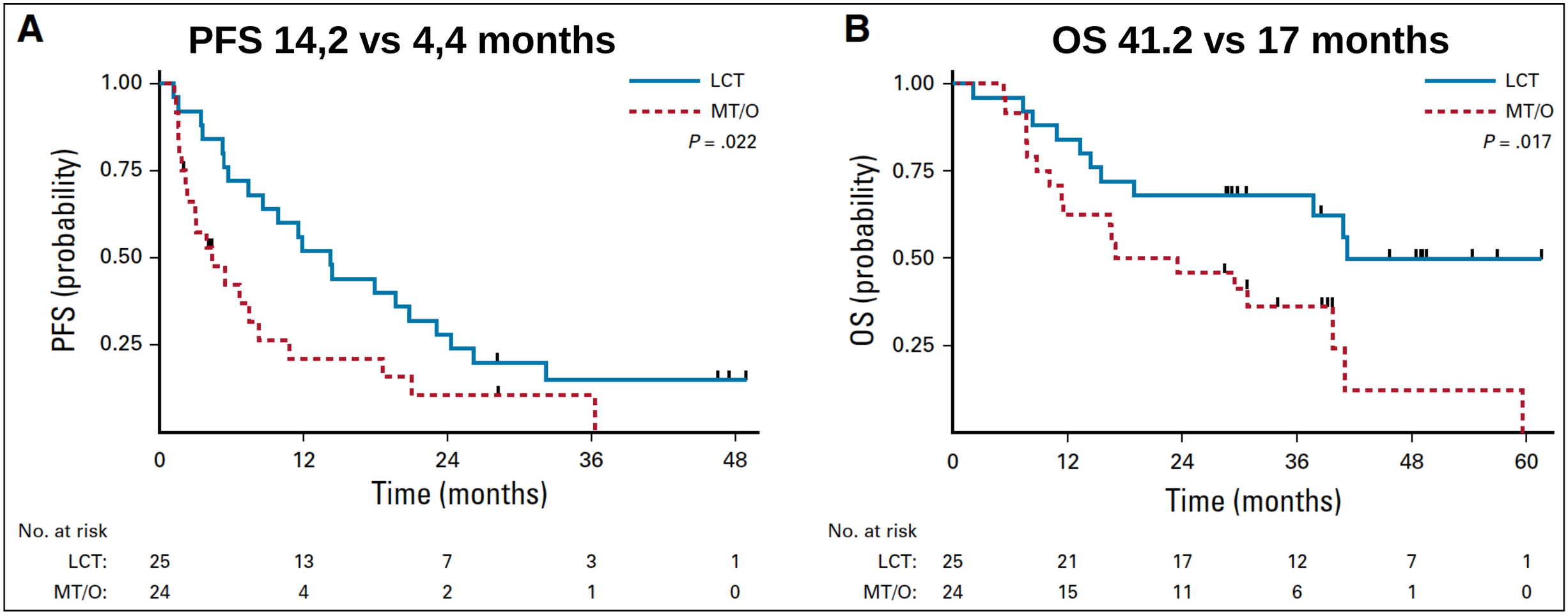


FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

Gomez et al, J Clin Oncol 2019

Malattia Oligometastatica: Criticità

Criteri di Inclusione studio

- NSCLC stadio IV
- N metastasi ≤3
- ECOG PS≤2
- Aver ricevuto almeno 4 cicli CHT standard platinum-based

Caso Clinico

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- N metastasi ≤3
- ECOG PS≤2
- Aver ricevuto almeno 4 cicli CHT standard platinum-based

Take home messages

- **Malattia oligometastatica polmonare: frequenza che varia 1-5% dei casi**

- **Il Caso clinico conferma i possibili benefici di un trattamento consolidativo locale (*Gomez e al, 2019*)**

- **L’approccio multidisciplinare (Oncologo, Radioterapista, Chirurgo Toracico, Anatomopatologo, Biologo Molecolare) in questo setting è fondamentale**

La Malattia Oligometastatica:

Dove dobbiamo migliorare?

- **Definizione concordemente accettata**
- **Caratteristiche inclusive più precise e più stringenti**
- **Definizione delle tecniche radiologiche necessarie per distinguere tra la vera malattia oligomestatica e la malattia metastatica diffusa occulta**
- **Caratterizzazione della biologia e dei meccanismi**
- **Necessità di nuovi RCT che includano le nuove terapie (RT+immunoterapia? RT+TKis?)**