Treatment-Induced Neurotoxicity after Chemotherapy & Immunotherapy: *Part 1*

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Disclosures

None of us or our immediate family members have a financial relationship with a commercial organization that may have a direct or indirect interest in the content.

Objectives

After completing this exhibit, participants will be able to:

- *Recognize imaging abnormalities found during & after chemotherapy & immunotherapy of the CNS.*

- *Classify side effects of these oncologic therapies into acute, subacute & chronic stages.*

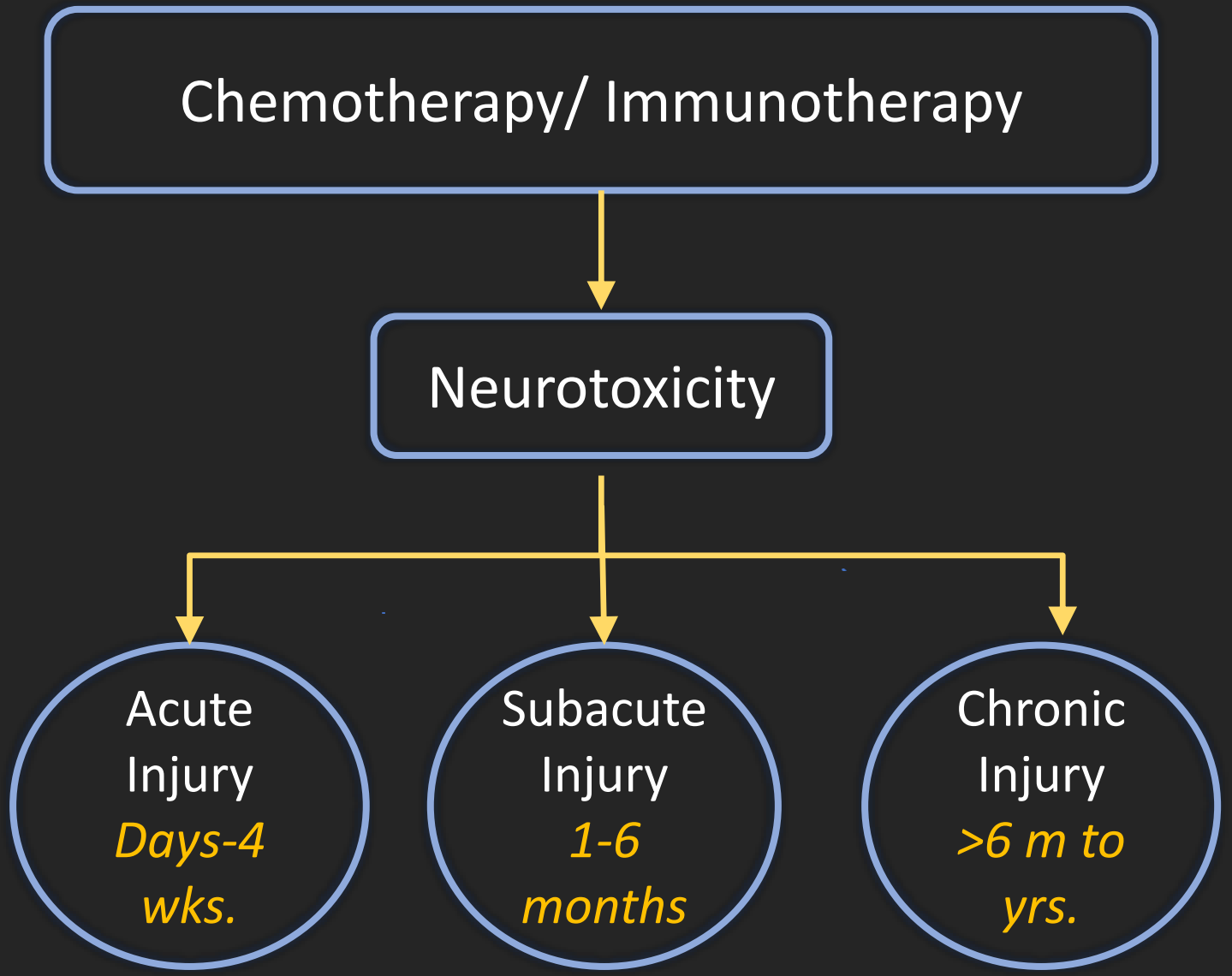
Target Audience

- *This exhibit is primary intended for diagnostic radiologists and neuroradiologist. Internists and oncologists may also find it useful.*

Interesting and Common Facts

- An adverse drug reaction (ADG) is defined by the WHO as “one that is noxious, unintended & occurs at doses normally used in humans”.
- Treatment-induced neurotoxicity is a significant cause of morbidity in 30-50% of cancer patients.
- *New patterns* of neurotoxicity have emerged due to development of new anticancer drugs.
- Neurotoxicity is the *second most common* dose-limiting factor after myelosuppression & is a diagnosis of exclusion.

Timing of Neurotoxicity



Chemotherapy-Induced Neurotoxicity

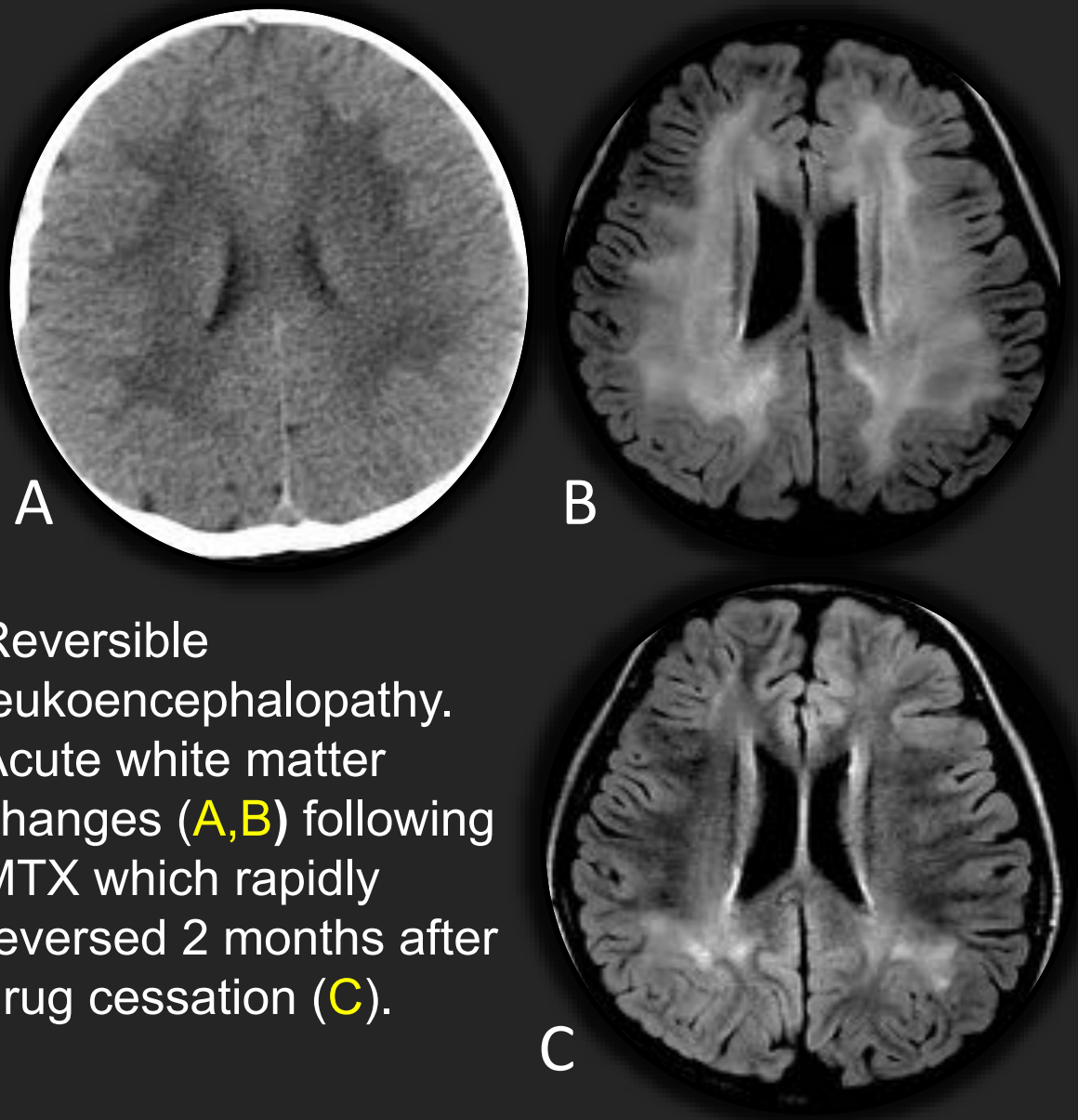
Chemotherapy & the war on cancer…

- *Primary aim* of chemotherapy is to reduce tumor burden.
- Not curative in majority of cancers, mainly given as palliative Tx.
- 5-year survival benefit attributable solely to chemo in adult malignancies is 2.1% in the USA.
- *"Top-five"* chemo-sensitive cancers: testicular cancer, Hodgkin's and non-Hodgkin's lymphoma, cervical & ovarian cancer.
- It is associated with numerous severe side effects & affect all organs.
- Given its relatively low tumor specificity & high toxicity, biological therapy (immunotherapy) as shows promising results in cancer control with better tolerance.

Acute Injury

Chemo-Induced Reversible Leukoencephalopathy

- Reversible acute white matter changes after chemo or immunotherapy.
- Non-fatal condition.
- Acute reactions are usually mild & of little consequence but severe reactions may occur.
- White matter changes reverse rapidly after cessation of therapy, within 1- 4 weeks.



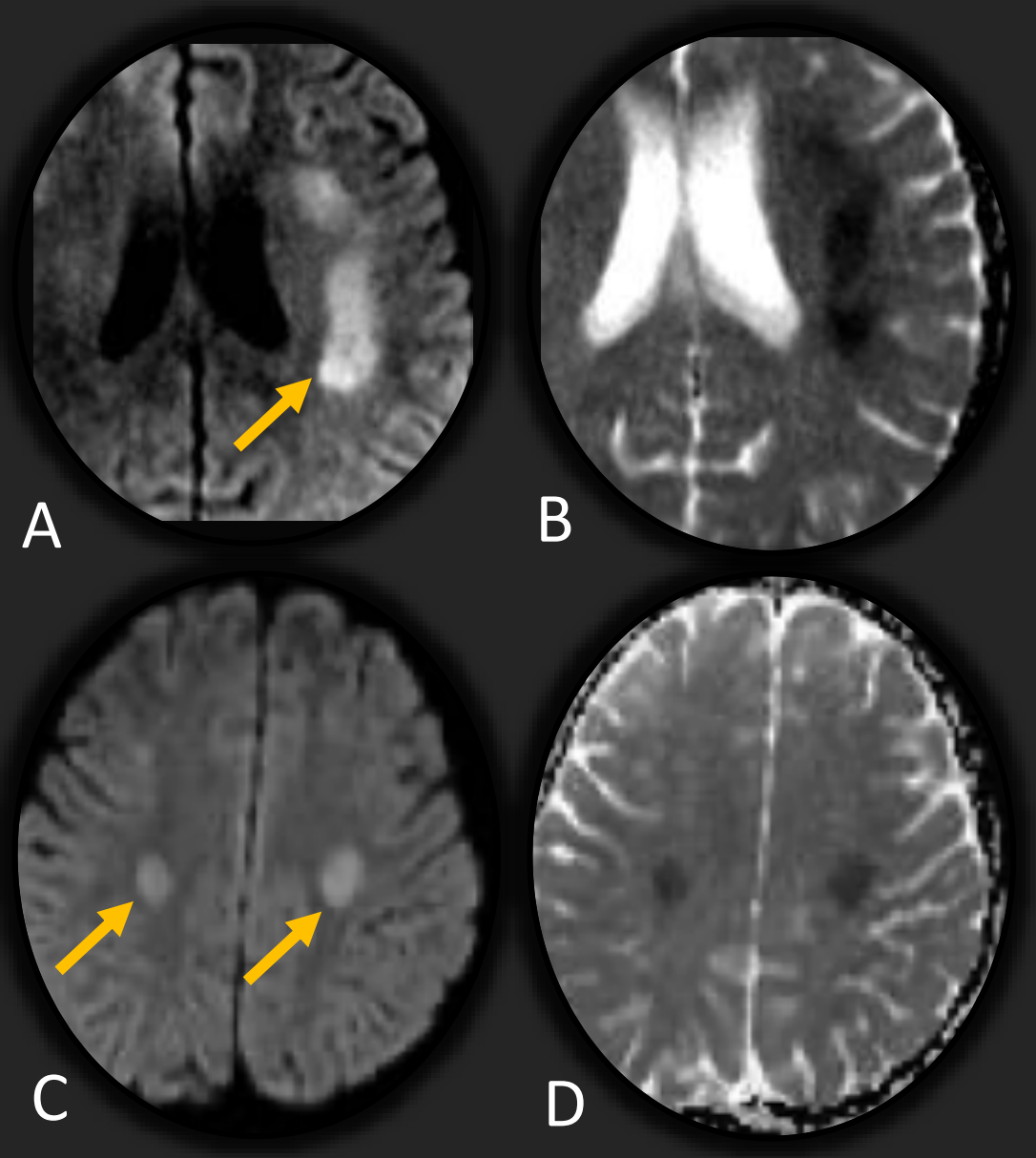
Reversible leukoencephalopathy. Acute white matter changes (A,B) following MTX which rapidly reversed 2 months after drug cessation (C).

Acute Injury

Acute Methotrexate (MTX) Neurotoxicity

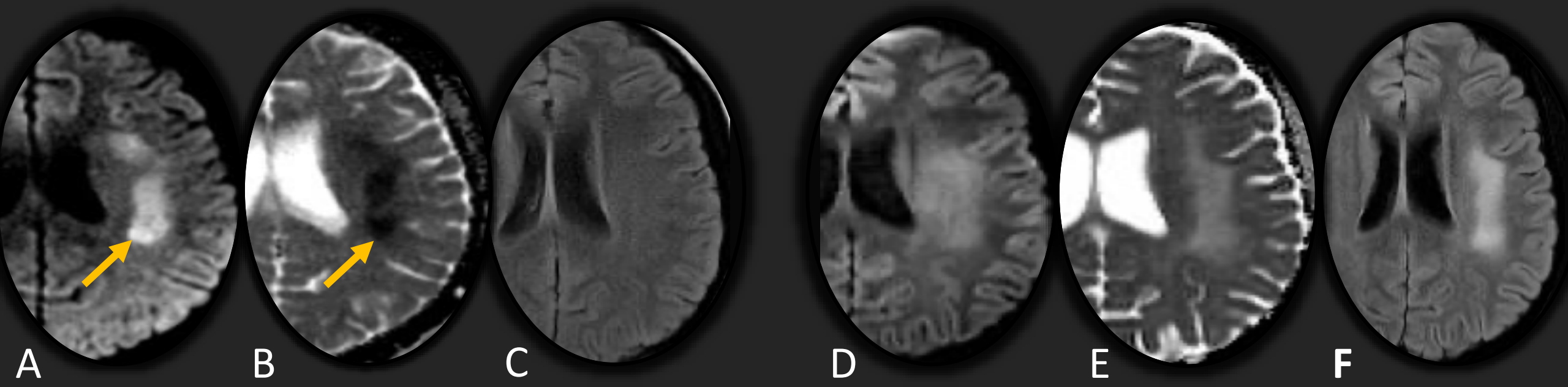
- Usually 5-14 days after 3rd course of MTX.
- *Findings:*
  - Uni (top row) or bilateral (bottom row) restricted diffusion on DWI (arrows) in periventricular white matter, without T2/FLAIR abnormality (acute stage).
  - Restricted diffusion *resolves within 2-3 weeks* while T2/FLAIR start to show signal abnormality.

Most patients can resume MTX without permanent neurological sequelae.



Signal Changes on DWI vs. FLAIR

Onset *14 days later*



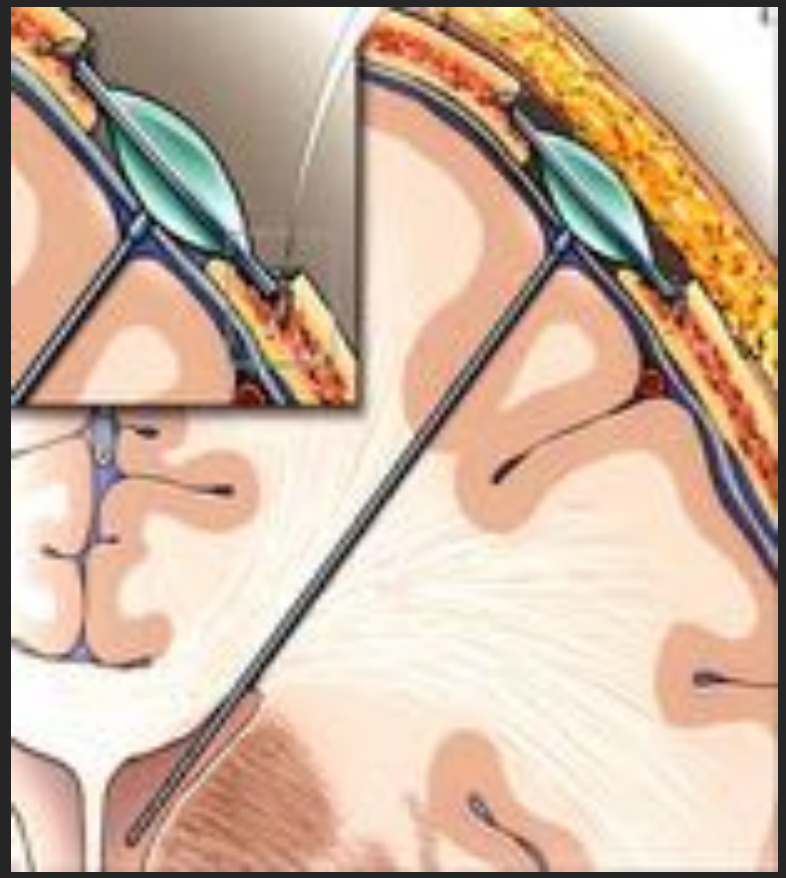
MTX neurotoxicity. In the acute onset, DWI (A,B) shows restricted diffusion in the white matter (arrow) w/o changes on FLAIR (C). 2 weeks later, ADC signal changes start to decrease while signal changes on FLAIR are present.

Acute Injury

MTX-Induced Focal Cerebral Necrosis

- Associated with ventricular access devices (e.g. ommaya reservoir) for administration of chemo.
- Rare complication (0.6%).
- 2ry to catheter malposition, malfunction or disconnection with chemo release into the brain parenchyma inducing focal necrosis.

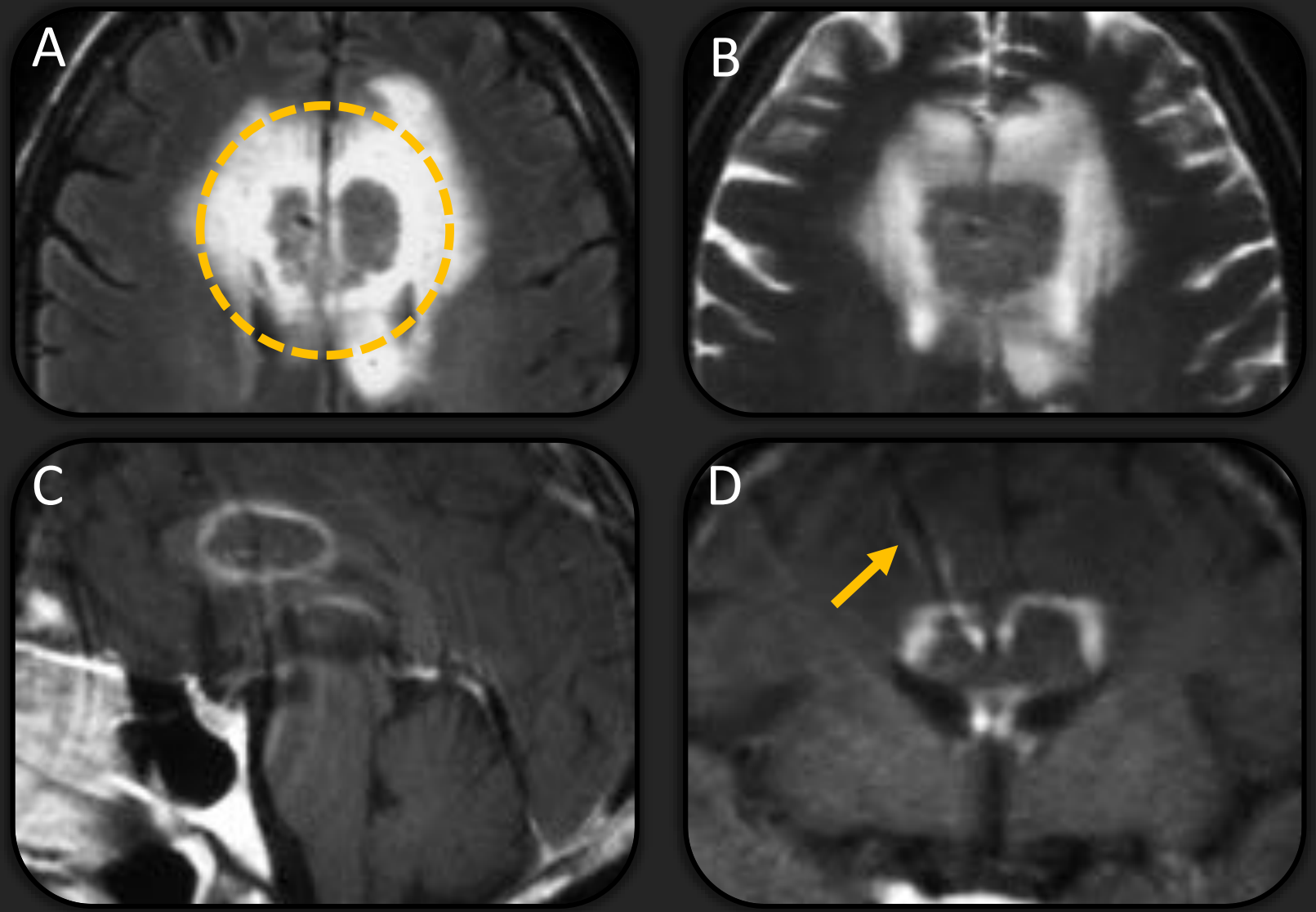
No benefit of ventricular vs. intrathecal route has been demonstrated; however, a longer progression-free survival has been seen with intraventricular MTX.



Ommaya Reservoir

Le Rhun et al. Annals of Oncology 28: iv84–iv99, 2017.

Focal Cerebral Necrosis after Ommaya Reservoir Malposition

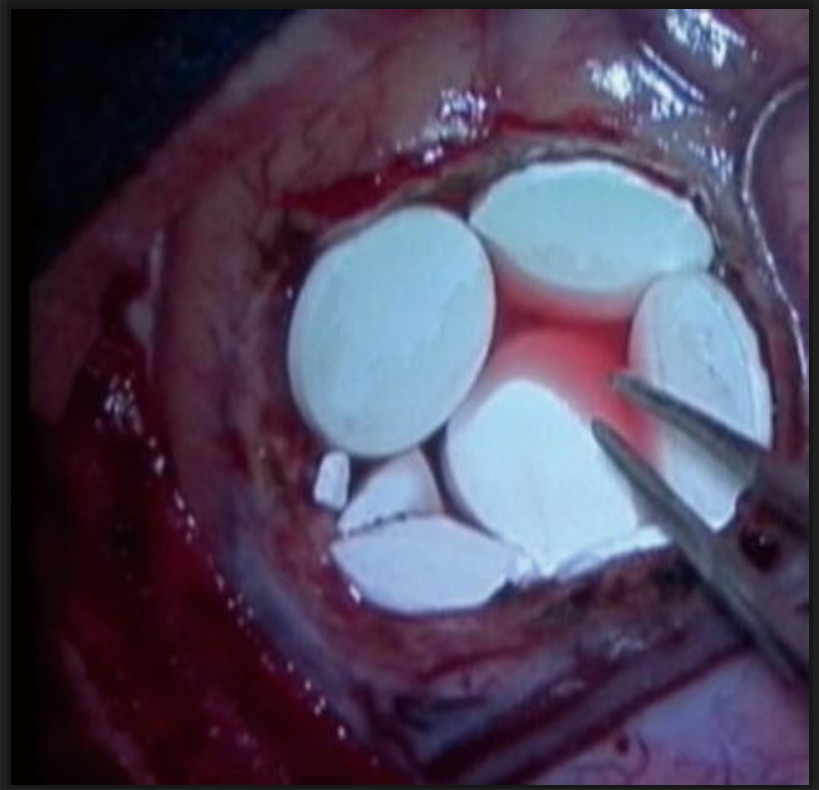


Focal cerebral necrosis (dotted circle) demonstrating hypointense signal on FLAIR (A) & T2 (B) with ring enhancement (C ,D) involving the anterior body of corpus callosum & previous catheter tract (arrow).

Subacute Injury

Chemo-Wafers Induced Focal Inflammatory Response

- Chemo-impregnated (carmustine) wafers placed in the resection cavity for treatment of 1ry high-grade brain tumors.
- Provide controlled release of chemo over a period of 2-3 wks.
- Increased *wound healing & infections complications* are reported.
- Increase enhancement & pericavitary T2/FLAIR signal changes within *first 2 months* with subsequent decrease of inflammatory response are reported on MRI.

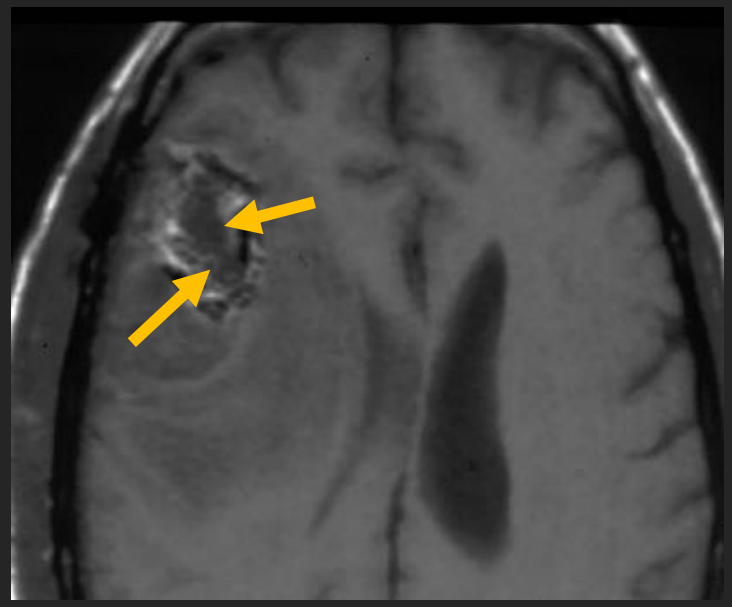


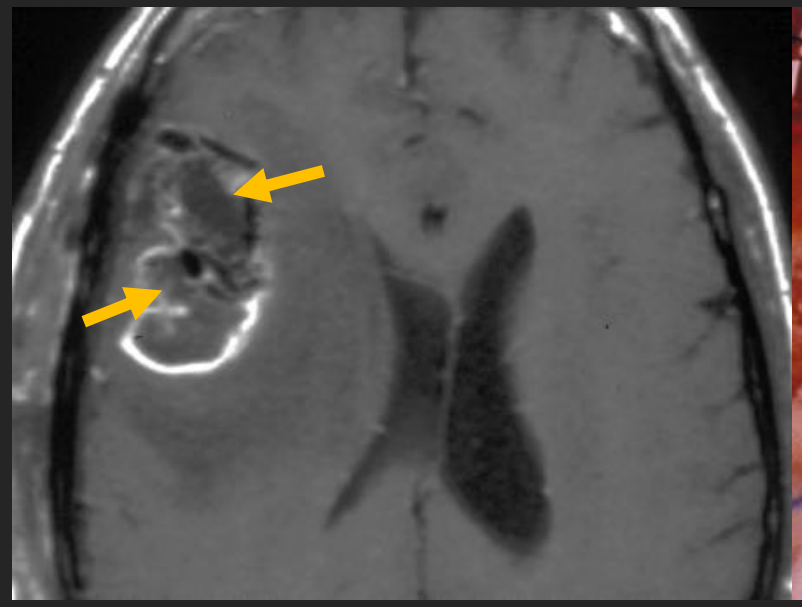
Intracavitary wafers (white round structures) along walls of surgical cavity. *World J Radiol. 2011 Nov 28; 3(11): 266–272.*

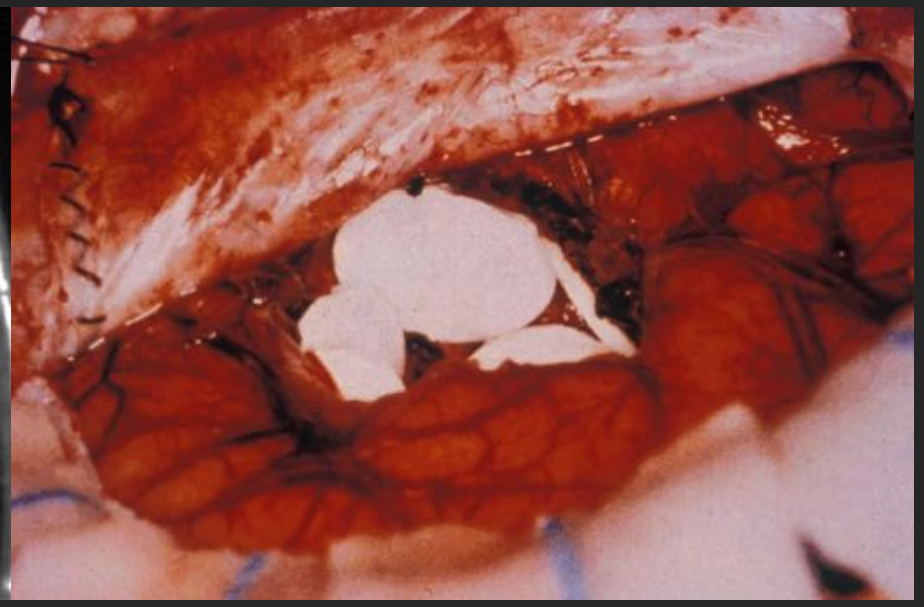
Le Rhun et al. Annals of Oncology 28: iv84–iv99, 2017.

Subacute Injury

MRI Appearance of Chemo Wafers







Chemo wafers are seen as linear non enhancing areas (arrows in A & B) placed in surgical bed (C).

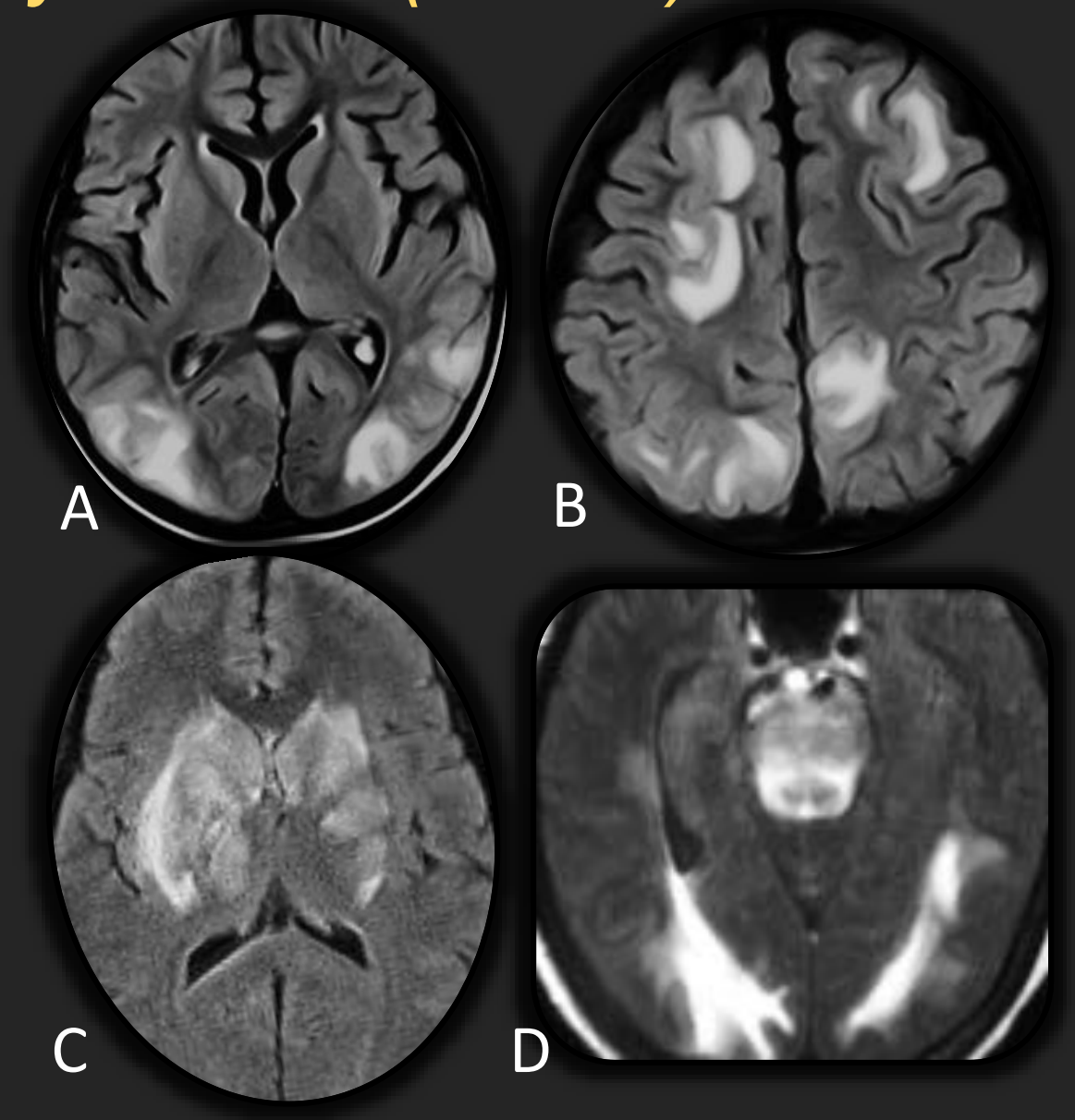
Wafers have shown a marginally improve median survival compared with RT alone; however, no prospective data is available when compared with current standard TMZ/RT.

Subacute Injury

Chemo-associated Posterior Reversible Encephalopathy Syndrome (PRES)

- Multidrug chemotherapy more frequently results in PRES than single-agent therapy.
- Occurs 1- 4 weeks after Tx, > women.
- *Findings*:
  - *Classic PRES*: bilateral symmetric hemispheric subcortical edema on T2/FLAIR involving anterior & posterior circulation (A,B).
  - *Central PRES*: High signal on T2/FLAIR within basal ganglia & brainstem (C,D).

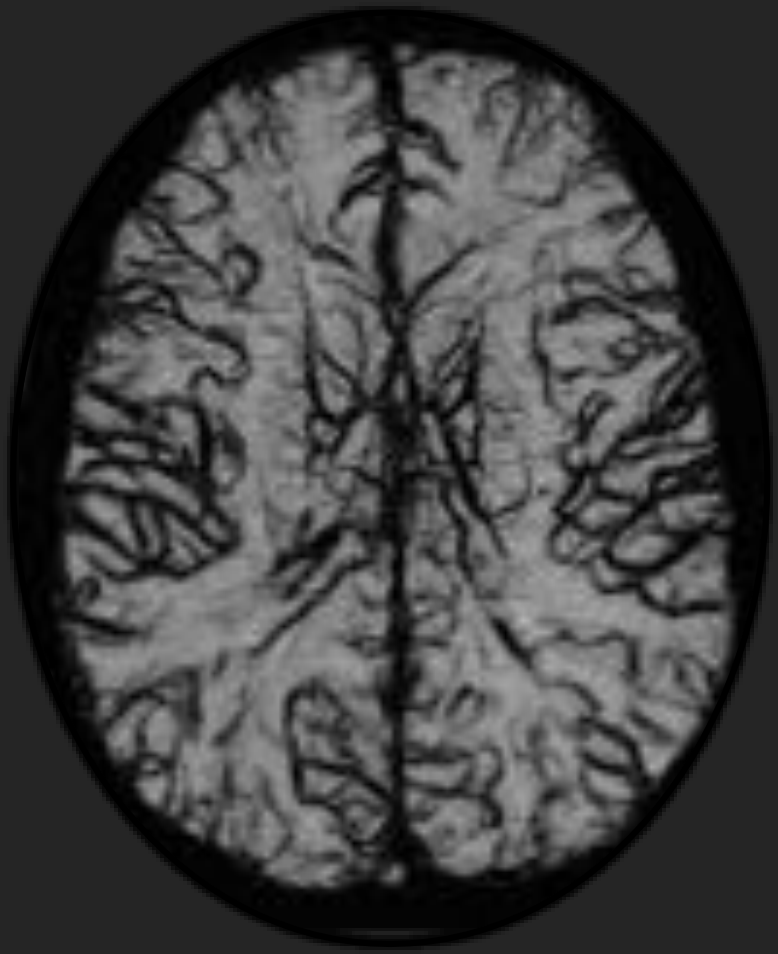
Symptoms resolve within 7-10 days whereas MRI findings in 20-30 days.



Subacute effect

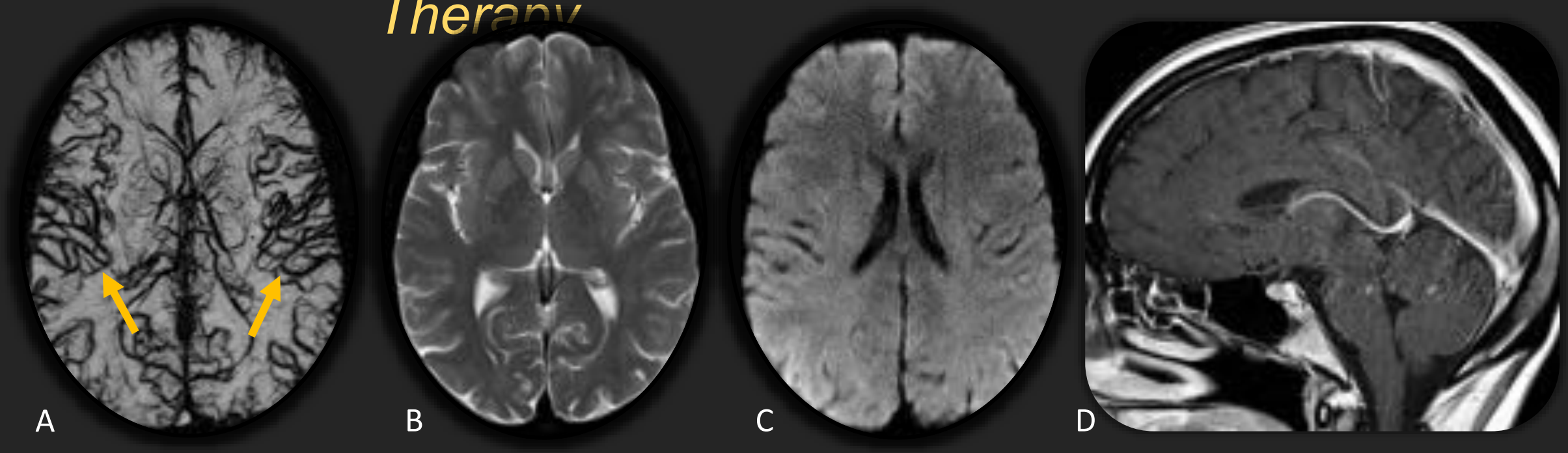
Chemo-Induced Anemia & Iron Deficiency (ID)

- Frequent complications in patients treated with chemo.
- Anemia may decrease the response to treatment & reduce overall survival (OS).
- *Treatment*: erythropoiesis-stimulating agents (ESAs), iron preparations & red blood cells transfusions.
- ID is treated when serum ferritin <100 ng/ml & before initiation of ESA therapy.
- No neurotoxicity is associated with I.V. iron therapy; however, it causes increased susceptibility on MRI due to paramagnetic properties of iron in blood vessels (image) *of no clinical significance*.



SWI

Imaging Changes after I.V. Iron Therapy



SWI (A) shows an increase susceptibility in blood vessels, both arterial & venous (A, arrows), without parenchymal abnormalities on T2-WI & DWI (B & C, respectively), nor signs of venous thrombosis on T1 post-Gd (D).

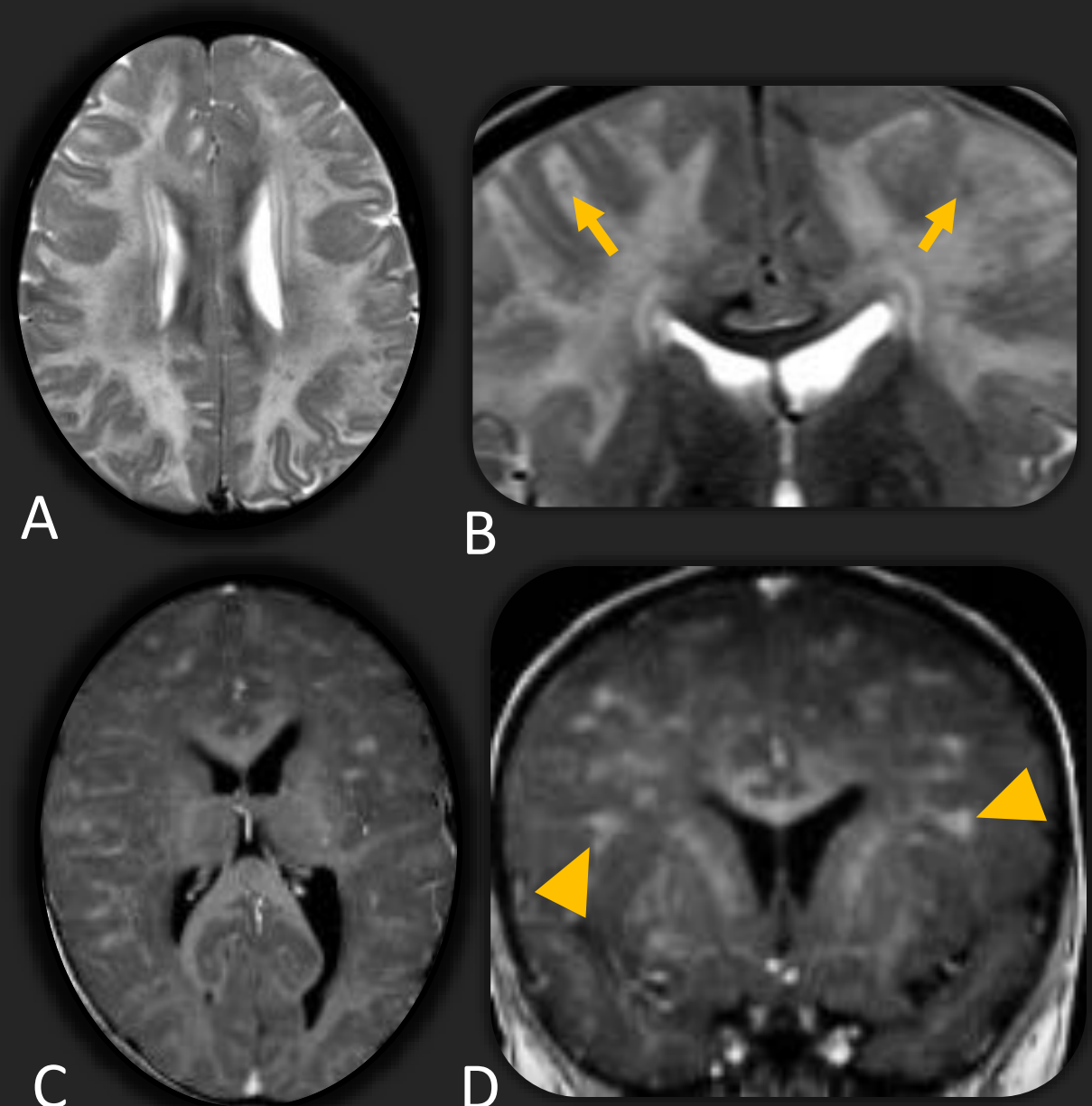
Degree of signal loss is proportional to iron concentration.

Disseminated Necrotizing Leukoencephalopathy (DNL)

Subacute Injury

- Severe, progressive, fatal leukoencephalopathy (1-3 months after Tx).
- Rare condition (2%) usually after MTX for hematological diseases or lymphoma.
- Greater risk when combined with RT.
- *Findings*:
  - Extensive white matter involvement (A,B).
  - Multiple low signal foci in white matter on T2/FLAIR (*arrows*) with nodular enhancement (*arrowheads*).

Main differential diagnosis is progression or recurrence of 1ry disease



Immunotherapy-Induced Neurotoxicity

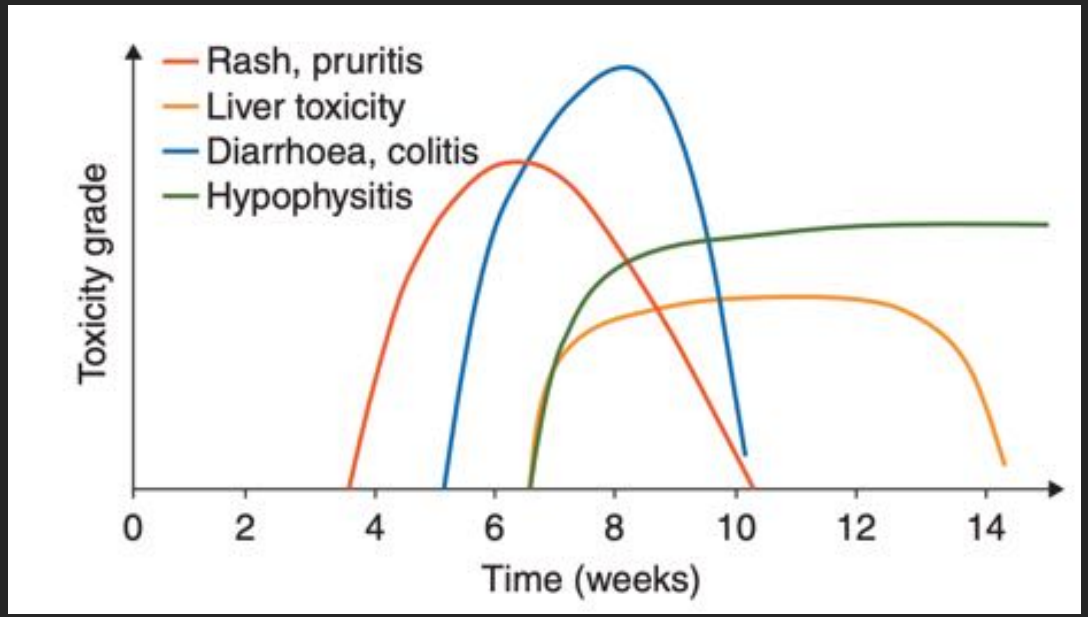
Cancer Immunotherapy

- *Goal*: treat cancer by generating or augmenting an immune response against it.
  - Clinical trials have demonstrated improved OS of patients with advanced-stage cancer.
- *Two types*
  - Immune-cell-targeted monoclonal antibody (mAb) therapy
    - T-Cell function stimulated with mAb that either block or target their inhibitory/stimulatory receptors, respectively. (e.g. rituximab, ipilimumab).
  - Adoptive cellular therapy (ACR)
    - Robust immune-mediated response through ex vivo manipulation of T cells. (e.g. chimeric antigen receptor [CAR] into T cells).

Subacute Injury

Ipilimumab-Induced hypophysitis (IH)

- MoAb for treatment of metastatic or stage III melanoma.
- Adverse events occur in 60-85% of patients; IH has an incidence of 0-17% >6 wks-3 mo after Tx.
- *Incidence is dose-dependent*: 3 mg/kg, 10 mg/kg reported to be 1% & 16%, respectively.
- Etiology remains unknown: ? mononuclear cell infiltration of pituitary gland.



Timing of occurrence of adverse events following Ipilimumab treatment.

Annals of Oncology 28 (Supplement 4): i119–i142, 2017

IH, Imaging Findings

MRI Findings:

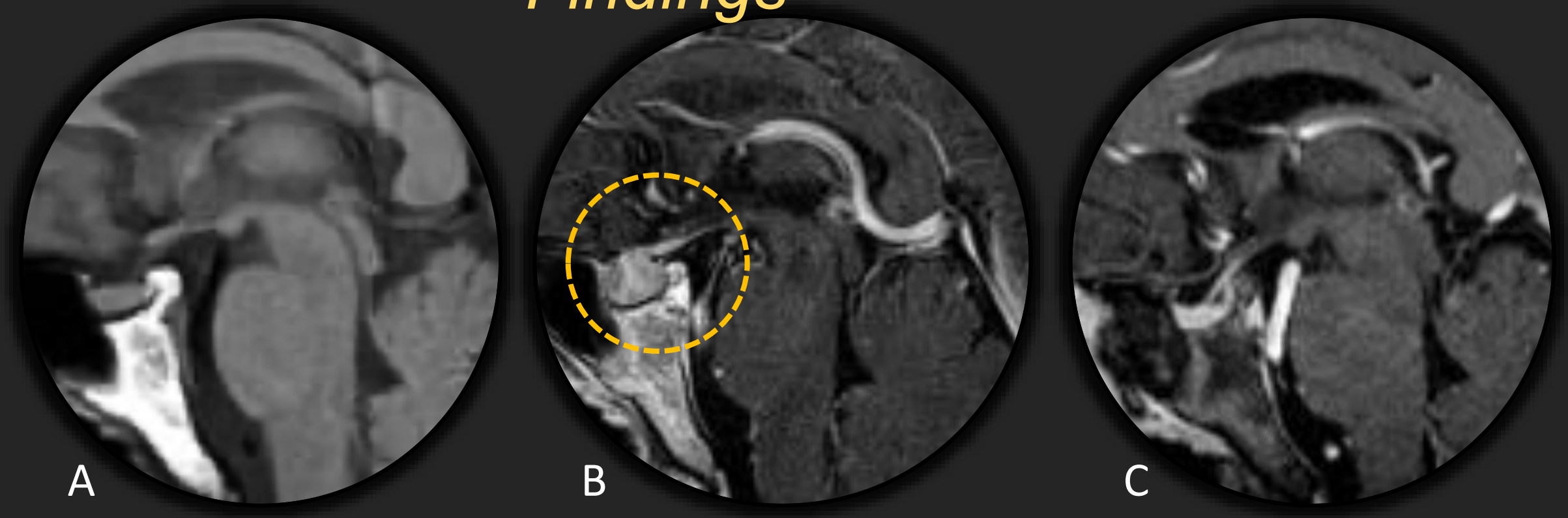
- Enlargement of the infundibulum & pituitary gland.
- Uniform or heterogeneous enhancement.
- Pituitary gland returns to normal size within 4-6 weeks after steroids in all patients (table).

Table 1 Longitudinal case cohorts of ipilimumab-induced hypophysitis

	Faje et al. [17]	Min et al. [18]	Albarel et al. [16]	Total
Cohort size (male/female)	154 (99/55)	187 (118/69)	87–131[a] (–)	428–472
Hypophysitis (n, %)	17, 11.0 %	25, 13.3 %	15, 11.4–17.2 %	57, 12.0–13.3 %
Hypophysitis (male/female)	15/2	19/6	10/5	44/13
Hypophysitis mean age (y)	68.2	–	55.5	–
Dosage (3, 10 mg/kg)	13, 4	17, 8	2–4, 11–13[a]	32–34, 23–25
Median time to diagnosis after Ipi initiation (wks)	8.4	9	9.5	–
Radiographic pituitary enlargement	17/17	15/25[b]	12/14[b]	44/56[b]
Visual defects	0/17	0/25	0/15	0/57
Hyponatremia	8/14	14/25	–	22/39
Most common presenting symptoms	HA (14/17), fatigue (10/17)	–	HA (13/15), fatigue (11/15)	HA (27/32), Fatigue (21/32)
Hypopituitarism at diagnosis				
Thyroid	17/17	22/25	13/15	52/56
Adrenal	7/14	22/25	11/15	40/54
Gonadal	15/15	15/20	12/14	42/49
Growth hormone (IGF-1)	1/6	3/7	2/8	6/21
Prolactin (elevated, low)	0/13, 12/13	1/9, 4/9	1/9, 3/9	2/31, 19/31
Diabetes Insipidus	0/17	0/25	0/15	0/57
Resolution of pituitary enlargement	17/17	11/11	12/12	40/40
Hypopituitarism at most recent followup				
Thyroid	13/17[c]	8/25	2/15	23/57
Adrenal	14/17[c]	22/25	13/15	49/57
Gonadal	13/15	8/25	2/15	23/57
Growth hormone (IGF-1)	–	–	1/11	1/11
Prolactin (elevated, low)	–	–	1/11, 1/11	1/11, 1/11

Pituitary.2016 Feb;19(1):82-92.

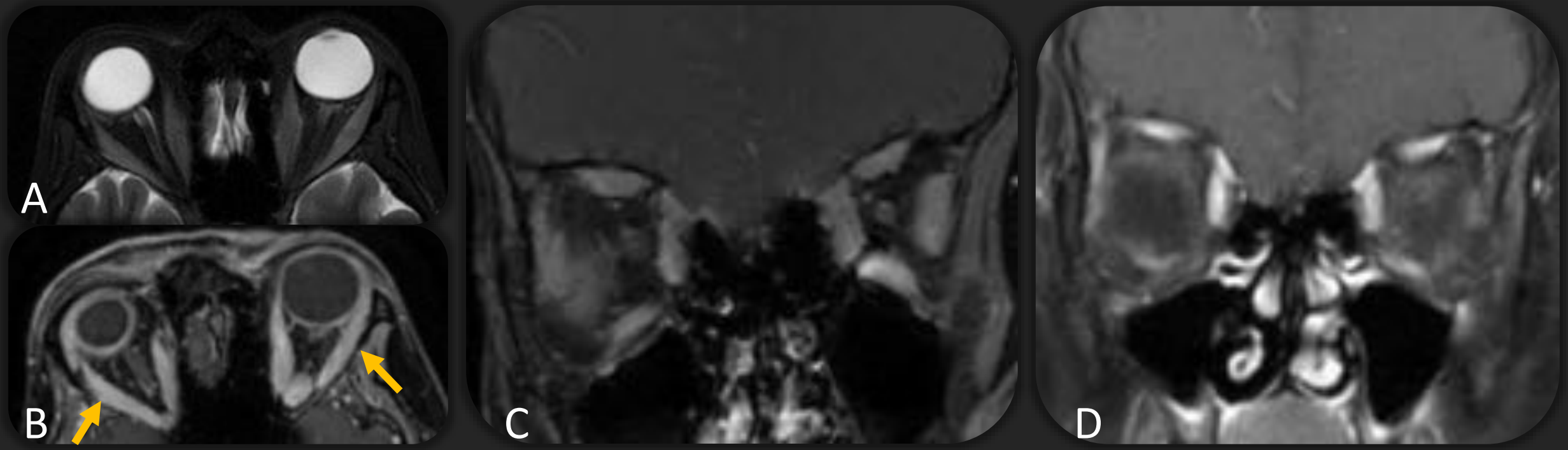
IH, Imaging Findings



IH in a patient treated for metastatic melanoma. A) baseline study, B) 2 months after ipilimumab there is diffuse enlargement & enhancement of pituitary gland & infundibulum (B, dotted circle). C) resolution 1 month after steroids & cessation of immunotherapy.

MRI findings can precede clinical diagnosis in some cases

Companion Case: Immunotherapy-Induced Ocular Myositis



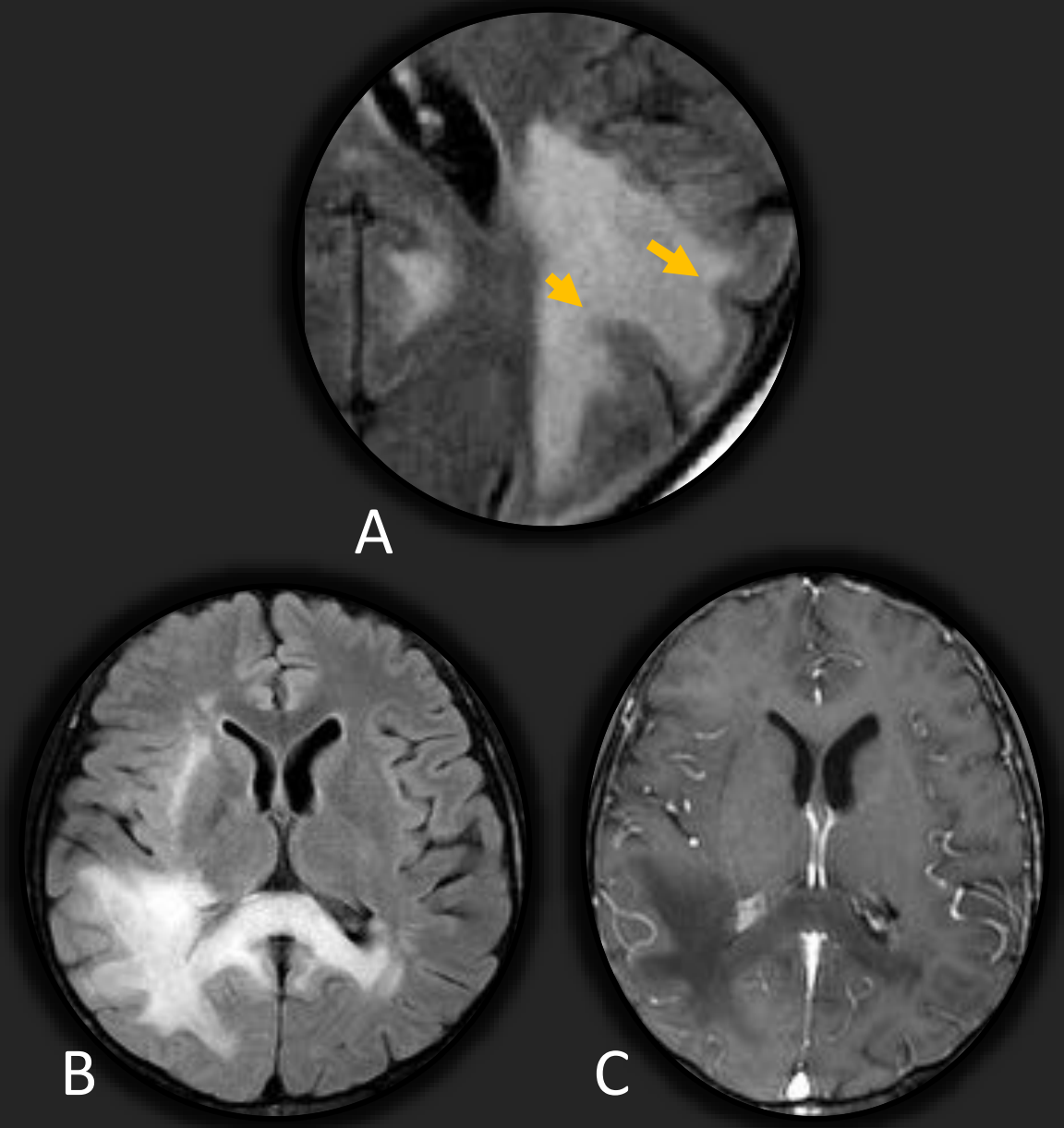
Patient with metastatic RCC & combined, nivolumab + ipilimumab, immunotherapy. Axial T2-WI (A) & T1 post-Gd (B&C) demonstrate diffuse thickening & enhancement of bilateral extraocular muscles (arrows) that resolved after therapy interruption & steroids (D).

Chronic Injury

Rituximab-associated PML

- Immunotherapy affects mainly anti-JCV antibody positive patients 0-12 months after Tx initiation.
- *Findings:*
  - Asymmetric multifocal involvement of supra (subcortical U fibers, arrows in A) or infratentorial (cerebellar peduncles) white matter structures; usually without mass effect (B) or enhancement (C).
  - PML-IRIS is observed in up to 70% of cases after discontinuation of immunotherapy.

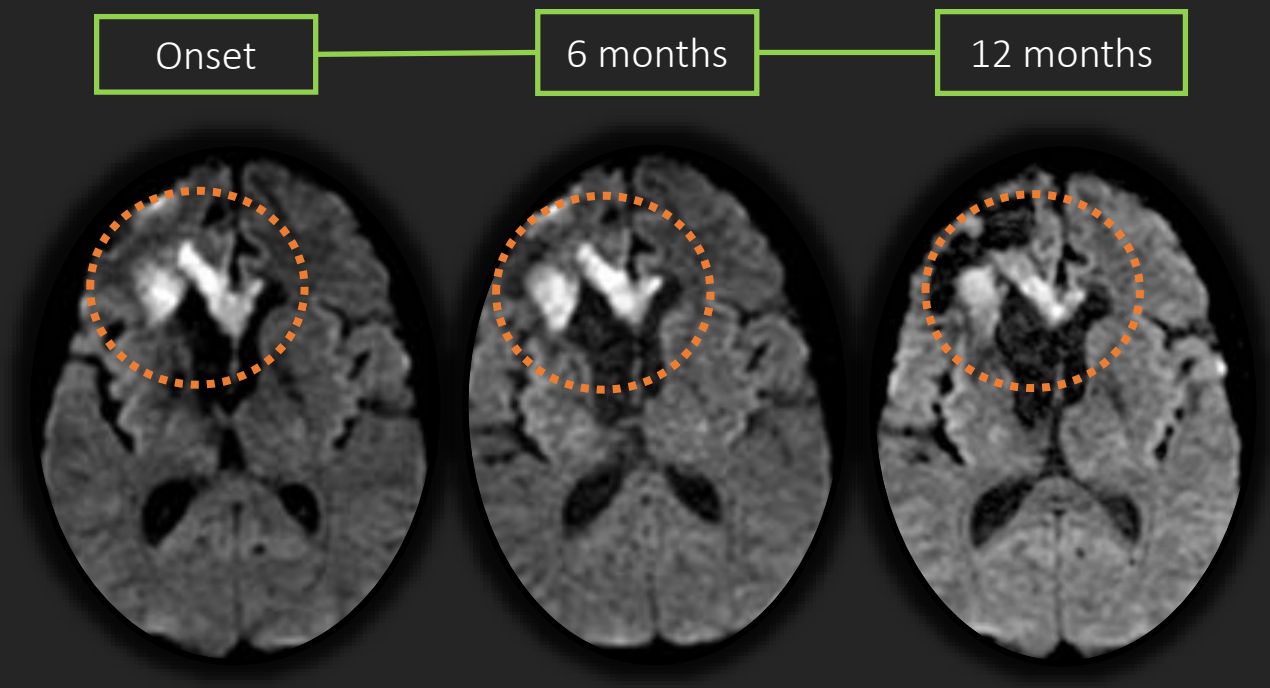
PML-immunotherapy has better survival rates than PML-AIDS, 80% vs 50% at 1 year, respectively.



Chronic Injury

Bevacizumab-Induced Diffusion Restricted (DR) in Malignant Gliomas

- Regions of DR represent coagulative necrosis surrounded by viable tumor.
- Time to develop DR regions after Bevacizumab: 30-700 days.
- Predisposition in unmethylated MGMT gliomas.
- *Findings:*
  - Progressive or stable areas of DR in postop region, along ventricles or corpus callosum.
  - Progressive areas likely to represent tumor progression.

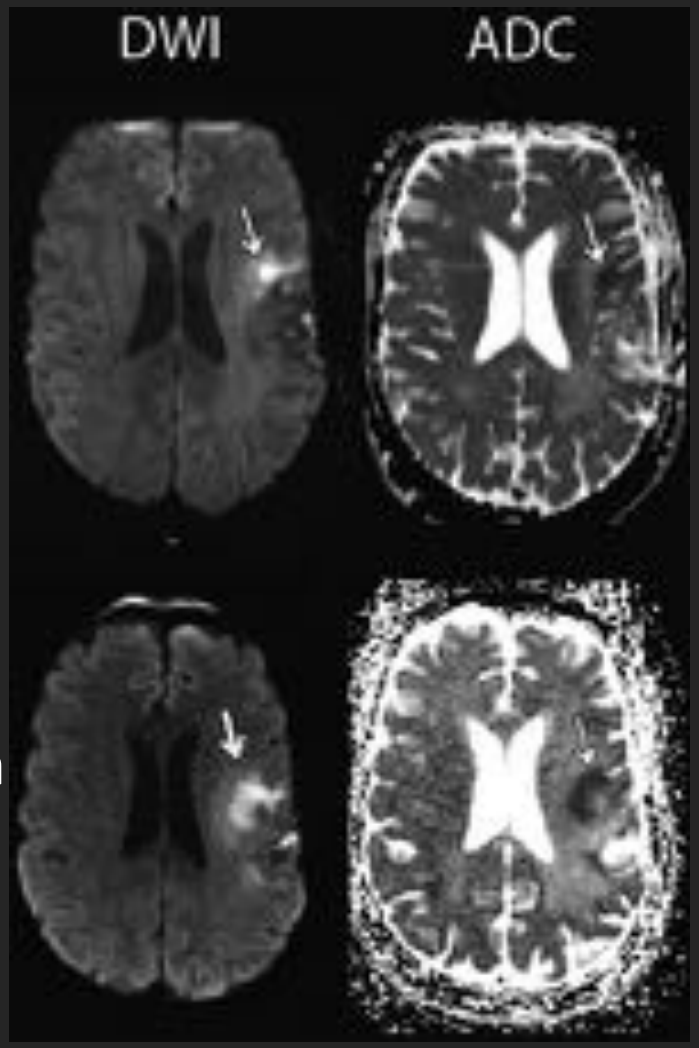


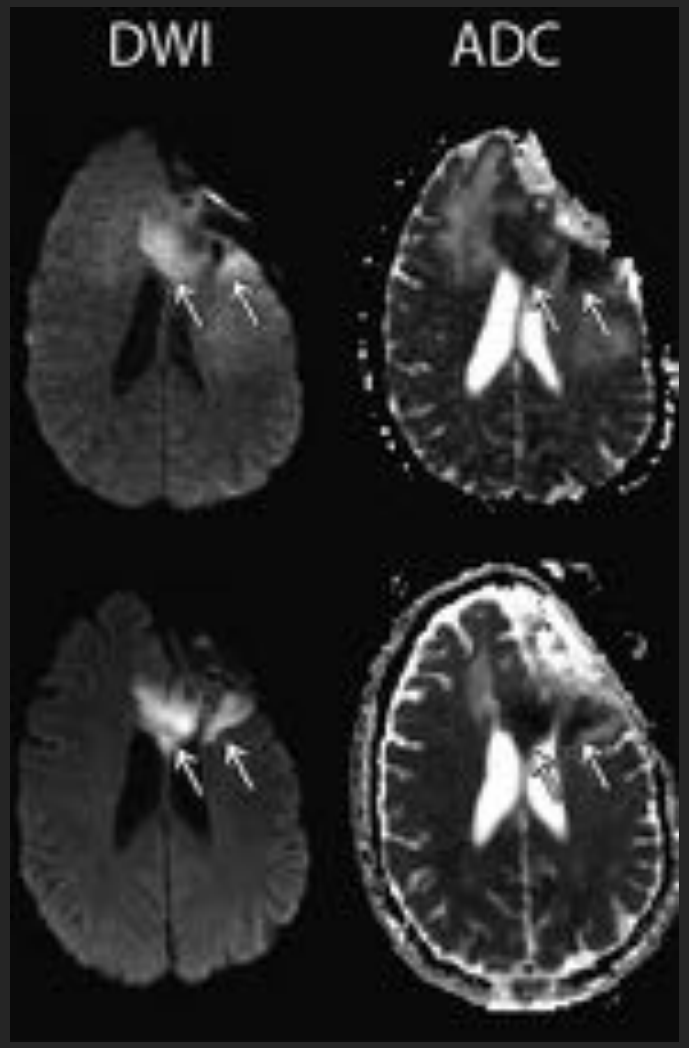
Stable region of DR over 12 months (dotted circles) involving right frontal lobe & corpus callosum in a patient treated for GB. Onset was 1 month after initiation of Bevacizumab.

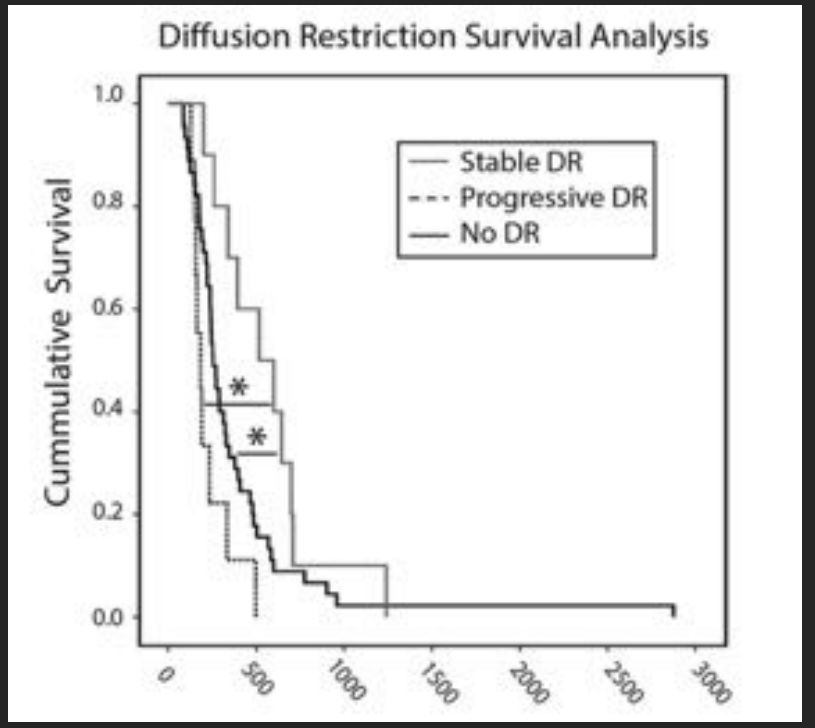
Progressive DR *Stable DR*

Initial

3 month F/U







Survival analysis. OS is significantly lower in patients with progressive DR compared with those with stable DR.

Progressive DR lesions - decreased overall survival (OS).

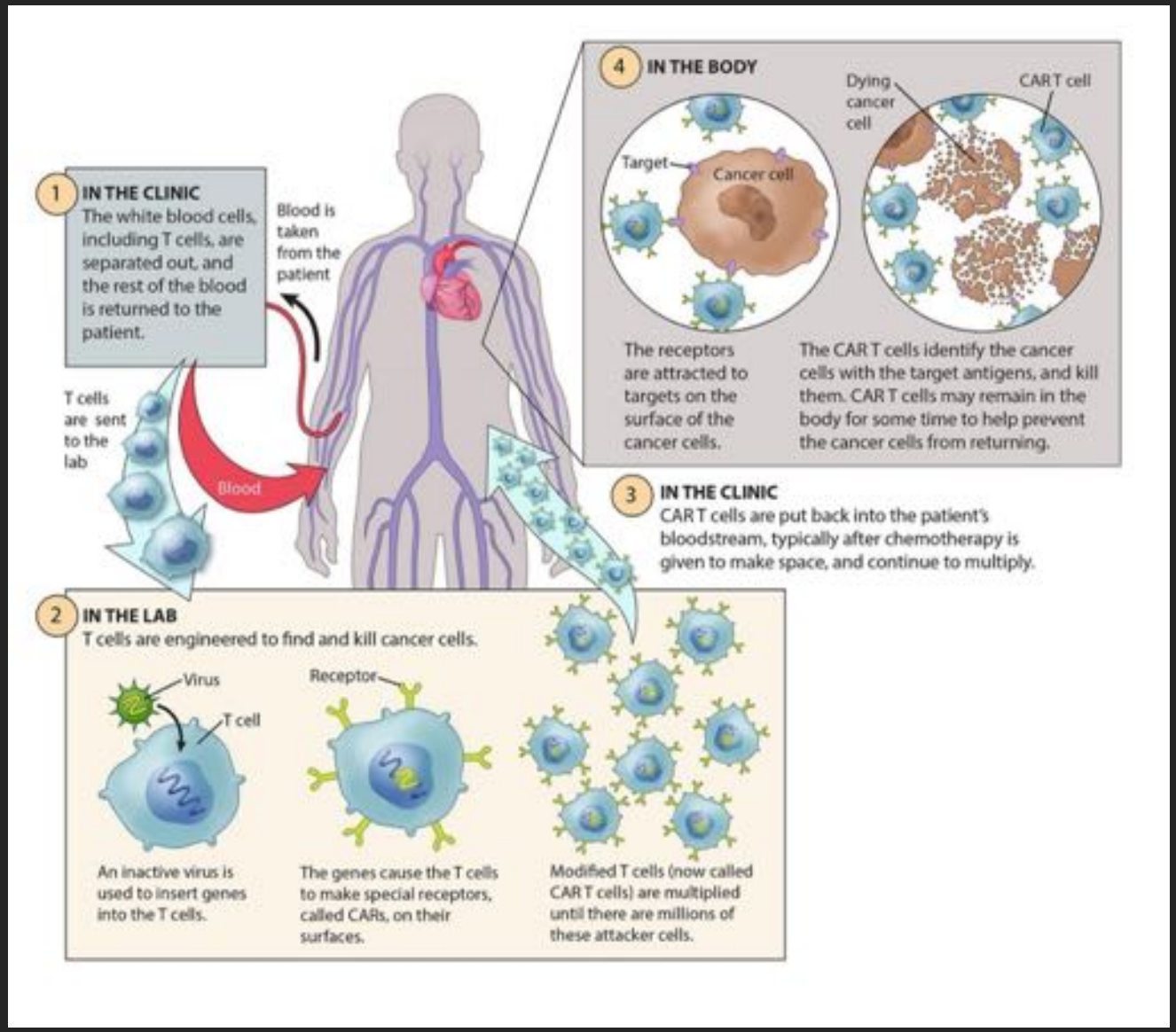
Stable DR lesions - increased OS

AJNR Am J Neuroradiol 37:2201– 08

CAR T-cell Therapy Induced Neurotoxicity

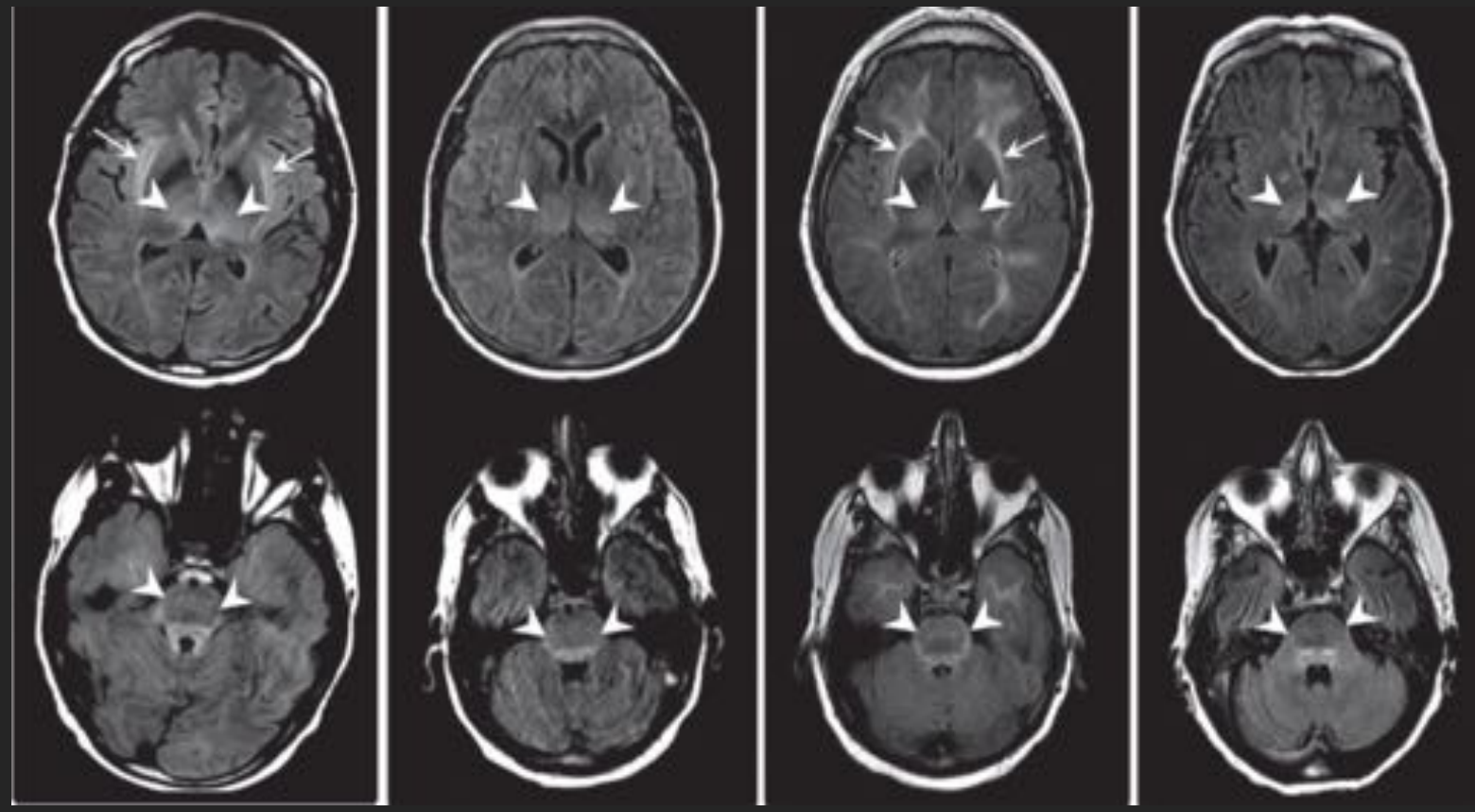
- Chimeric antigen receptor (CAR) T-cell therapy.
- "fifth pillar" treatment for hematologic cancers.
- *Indications*
  - Diffuse large B-cell lymphoma
  - Young adult leukemia
  - Adult non-Hodgkin lymphoma
- *Toxicities*
  - Cytokine release syndrome (CRS).
  - CAR-T-cell-related encephalopathy syndrome (CRES).
    - Typically occurs after start of CRS.

CAR T-cell Therapy, how does it work?



CAR T-cell Therapy Induced Neurotoxicity

- Incidence of neurotoxicity in pediatric & adult population: 40-45%
- *2 forms of neurotoxicity*:
  - Mild (no imaging findings)
  - Severe
    - White matter involvement (arrows)
    - Thalami (arrowheads)
    - Brainstem (arrowheads)



Cancer Discov; 8(8); 958–71. 2018 AACR.

Conclusions

- 1ry aim of chemotherapy is to reduce tumor burden whereas aim of immunotherapy is to generate systemic protective anticancer immunity.
- Recognition of patterns of neurotoxicity after oncologic treatment is important because drug discontinuation or dose adjustment may prevent further neurological injury & change outcome.
- Radiologists need to be familiar with side effects of cancer therapy in CNS in order to accelerate the correct diagnosis & minimize as much as possible associated morbidity.

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