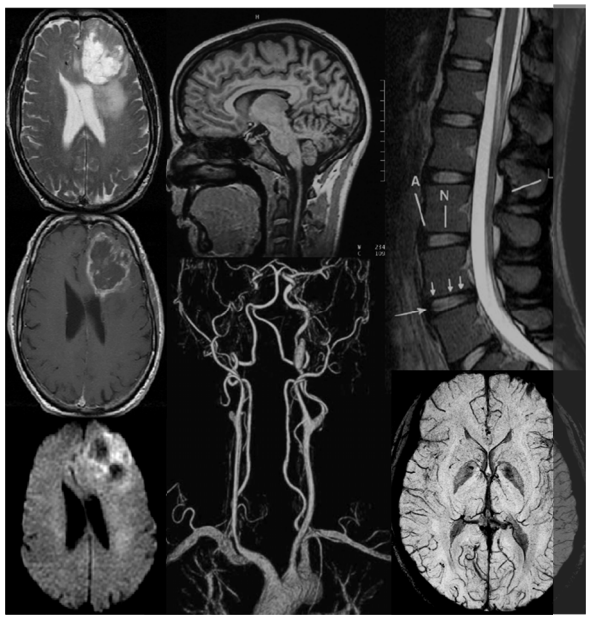
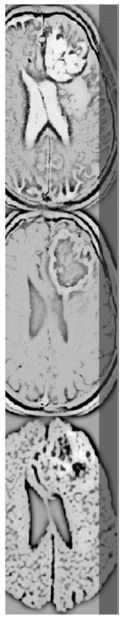


Magnetic Resonance in Medicine
MR Contrast Agent

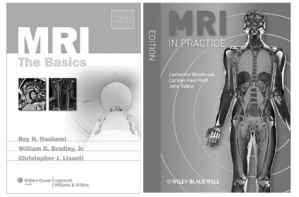
Chia-Feng Lu (盧家鋒), Ph.D.
Department of Biomedical Imaging and Radiological Sciences, NYCU
alvin4016@nycu.edu.tw



Content http://cflu.lab.nycu.edu.tw/

- **Mechanism and Safety of MR Contrast Agents**
  磁振對比劑原理與安全性
- **Applications of Gd Contrast Agents**
  Gd對比劑應用

- **MRI The Basics (3rd edition)**
  - Chapter --: --
- **MRI in Practice, (4th edition)**
  - Chapter 11: Contrast Agent in MRI



Mechanism and Safety of MR Contrast Agents

磁振對比劑原理與安全性

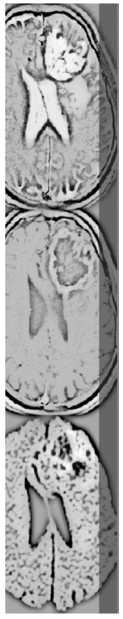
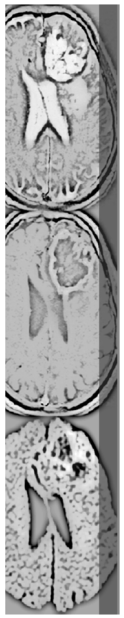


Image Contrast Parameters

- Intrinsic contrast parameters
  - T1 relaxation time
  - T2 relaxation time
  - Relative proton density

Contrast agent (with varying magnetic susceptibility) can affect local magnetic field and hence T1 and T2 relaxation times.

- Extrinsic contrast parameters (can be controlled)
  - TR (repetition time)
  - TE (echo time)
  - TI (inversion time)
  - Flip angle

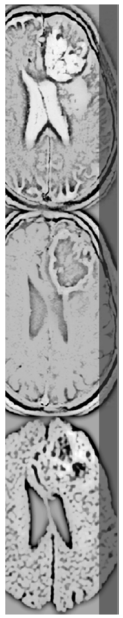


Gadolinium (Gd) 釓

64
Gd
Gadolinium
157.25

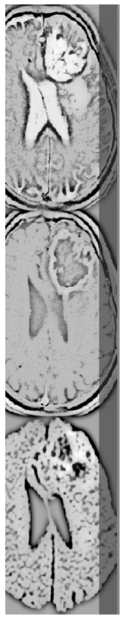
- The most commonly used MR contrast agents are Gadolinium based.
- As an element, Gd is ferromagnetic and highly toxic.
- Metal ions (Gd^{3+}) with free electrons tend to accumulate in tissues with a natural affinity for metals (compete with Ca^{2+}).
  - Membranes
  - Transport proteins
  - Enzymes
  - Osseous matrix
  - Renticuloendothelial system: lungs, liver, spleen, and bone

A cumulative poison !



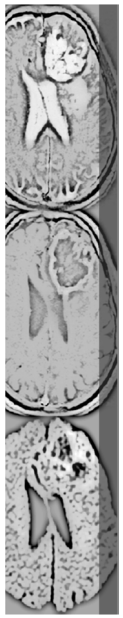
Gadolinium Chelates (螯合物)

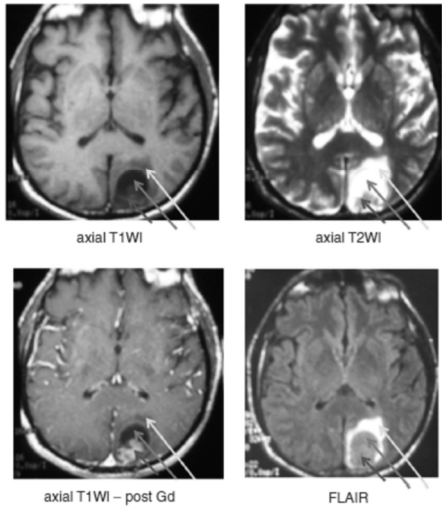
- Chelates have a high affinity for metal ions.
- Gd chelates are paramagnetic and relatively safe.
  - Shorten T1 relaxation time
- In a patient with normal renal function, the biological half-life of Gd chelates is 2 hours.
- Majorly excreted by the renal system.



Magnetic Susceptibility

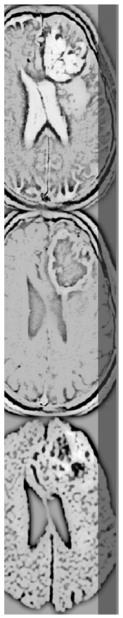
- Diamagnetic substances
  - Mild negative effects on the local magnetic field
  - Gold, silver, and oxyhemoglobin
- **Paramagnetic substances**
  - Low but positive effect on the local magnetic field
  - Gd chelate, deoxyhemoglobin
- **Superparamagnetic substances**
  - Higher positive susceptibility, create large disruptive changes in local magnetic field
  - Iron oxide
- Ferromagnetic substances
  - Very high positive susceptibility
  - iron





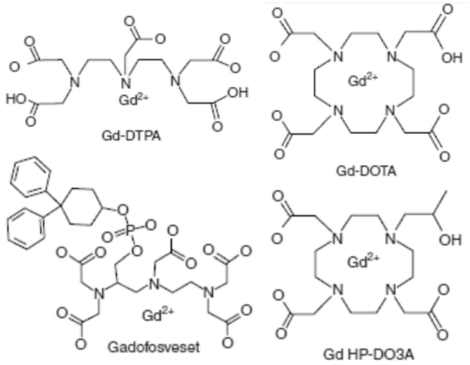
Effects of Contrast agents

Edema
Cyst
Tumor

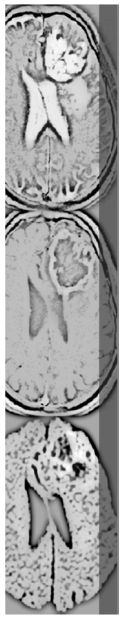


Paramagnetic Gd contrast agent

The first chelate that proved effective for MR contrast media was diethylene triaminepentaacetic acid (DTPA)



Linear molecules Macrocyclic molecules



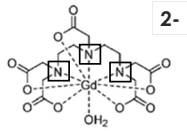
Development of Contrast Agent

1st generation **Linear ionic** → **2nd generation** **Linear nonionic** → **3rd generation** **Macrocyclic ionic/nonionic**

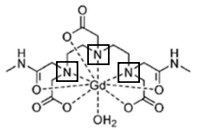
Products: **Magnevist** (Gd-DTPA)

Products: **Omniscan** (Gd-DTPA-BMA)

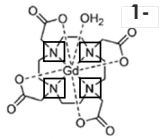
Products: **Dotarem** (Gd-DOTA) **ProHance** (Gd-HP-DO3A)



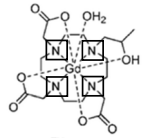
Magnevist™ (Berlex, NJ, USA) Gadopentetate dimeglumine Gd-DTPA^{2-}



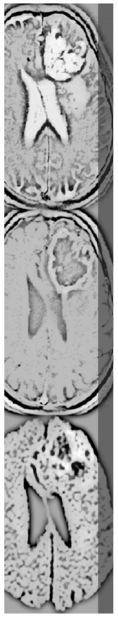
Omniscan™ (GE Healthcare, NJ, USA) Gadodiamide Gd-DTPA-BMA



Dotarem™ (Guerbet, France) Gadoterate meglumine Gd-DOTA^{1-}



ProHance™ (Bracco Diagnostics NJ, USA) Gadoteridol Gd-HP-DO3A



7 July 2017
EMA/424715/2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRAC confirms restrictions on the use of linear gadolinium agents

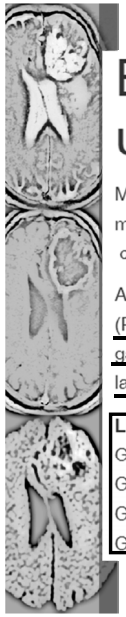
Benefit-risk balance of certain linear gadolinium agents no longer favourable

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed its previous conclusion from March 2017 that there is convincing evidence of gadolinium deposition in brain tissues following use of gadolinium contrast agents.

No specific conditions linked to gadolinium deposition in the brain have been identified, but the clinical consequences are unknown.

As a result of the review, the PRAC recommends that the intravenous linear agents gadoxetic acid and gadobenic acid should only be used for liver scans in the situations where they meet an important diagnostic need. In addition, gadopentetic acid should only be used for joint scans as the gadolinium concentration in the formulation used for joint injections is very low.

All other intravenous linear agents (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in line with the PRAC's March 2017 recommendation.



European group recommends to stop using 4 linear GBCAs

March 10, 2017 – A committee of the European Medicines Agency (EMA) has recommended the suspension of the marketing authorizations for four linear gadolinium-based contrast agents (GBCAs) used for MRI scans because of concerns about small amounts of gadolinium from administered GBCAs being deposited in the brain.

At the completion of its year-long review of GBCAs, the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) "found convincing evidence of accumulation of gadolinium in the brain from studies directly measuring gadolinium in brain tissues and areas of increased signal intensity seen on MRI scan images many months after the last injection of a gadolinium contrast agent".

Linear agents recommended for suspension by the PRAC are:
Gadobenic acid, marketed as MultiHance by Bracco Diagnostics Inc.
Gadodiamide, marketed as Omniscan by GE Healthcare
Gadopentetic acid, marketed as Magnevist by Bayer HealthCare Pharmaceuticals
Gadoversetamide, marketed as OptiMARK by Mallinckrodt Inc.

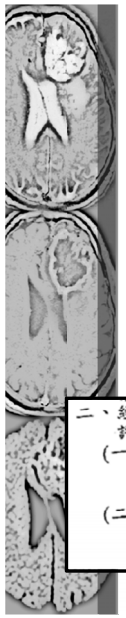
Brand name	Chemical name	Structure	Comments
Magnevist®	gadopentetate (Gd-DTPA)	linear ionic	Oldest agent (FDA approved 1988) with historically largest world-wide market share and clinical experience; below average relaxivity; probable ↑risk NSF
MultiHance®	gadobenate (Gd-BOPTA)	linear ionic	Highest relaxivity of all extracellular gadolinium agents due to transient protein binding; 3-5% hepatocyte uptake; competitive inhibitor for cMOAT drugs (tamoxifen, methotrexate, cisplatin); QT prolongation
Omniscan™	gadodiamide (Gd-DTPA-BMA)	linear nonionic	Low thermodynamic stability; disproportionately ↑risk NSF; may interfere with serum Ca^{++} measurements
Optimark™	gadoversetamide (Gd-DTPA-BMEA)	linear nonionic	Low thermodynamic stability; probable ↑risk NSF; may interfere with measurements of serum Ca, Fe, Cu, and Zn
Dotarem®	gadoterate (Gd-DOTA)	macrocyclic ionic	One of oldest agents with largest market share in Europe; most recent entry (2013) into US market
ProHance®	gadoteridol (Gd-HP-DO3A)	macrocyclic nonionic	Lowest osmolality and viscosity of all agents; below average relaxivity
Gadavist®	gadobutrol (Gd-BT-DO3A)	macrocyclic nonionic	Highest viscosity due to 1.0M formulation (all others 0.5M); above average relaxivity; marketed as Gadovist® outside the US
Eovist® (USA) Primovist®	gadoxetate (Gd-EOB-DTPA)	linear ionic	Designed for liver imaging; ~50% uptake by hepatocytes after initial extracellular phase; joint renal & biliary excretion; very high relaxivity due to size and transient protein binding; may interfere with serum Fe measurements; QT prolongation
Ablavar®	gadofosveset (Gd-DTPA-DCHP) (MS-325)	linear ionic	Highest relaxivity of any agent due to reversible albumin binding; intended for MRA; steady-state blood pool imaging 20 min – 4 hrs after injection; long elimination half-life (16+ hrs); QT prolongation

extracellular interstitial space

hepatic

vascular

http://mri-q.com/so-many-gd-agents.html



Gd Deposition

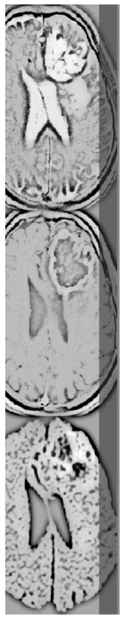
衛生福利部 公告

發文日期：中華民國106年11月23日
發文字號：衛授食字第10614103891號
附件：

主旨：公告含gadolinium類成分顯影劑藥品可能會蓄積於腦部之安全性再評估結果相關事宜。
依據：藥事法第48條。
公告事項：
一、含gadolinium成分顯影劑可能會蓄積於腦部，故本部依據藥事法第48條重新評估其使用之臨床效益及風險。
二、經本部彙整國內外相關資料及臨床相關文獻進行整體性評估，評估結果如下：
(一)依現有資料尚無法認定該類藥品蓄積於腦部具有危害情形，且臨床仍有使用之必要，故暫不限縮該類藥品之使用。
(二)惟該類藥品，不論線性或環狀結構成分皆可能會蓄積於腦部，故使用前應審慎評估病人使用之臨床效益及風險，並使用最低有效劑量。

二、經本部彙整國內外相關資料及臨床相關文獻進行整體性評估，評估結果如下：
(一)依現有資料尚無法認定該類藥品蓄積於腦部具有危害情形，且臨床仍有使用之必要，故暫不限縮該類藥品之使用。
(二)惟該類藥品，不論線性或環狀結構成分皆可能會蓄積於腦部，故使用前應審慎評估病人使用之臨床效益及風險，並使用最低有效劑量。

部長陳時中

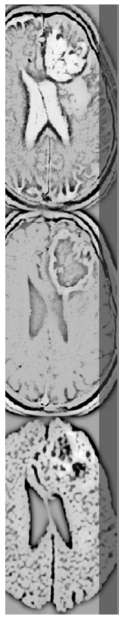


Ionicity離子性 (renal safety and adverse reactions)

- **Osmolality滲透壓**: The number of dissolved particles per kg of water.
- A close tracking between ionicity and high osmolality is noted (may affected by the manufacturer's decision).
- When the concentration is low, the effect of ionicity on osmolality of human body is quite small.

http://mri-q.com/ionic-v-non-ionic.html

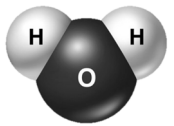
Brand Name	Ionicity	Osmolality (mOsm/kg)
Magnevist®	ionic	1960
MultiHance®	ionic	1970
Omniscan™	non-ionic	789
Optimark™	non-ionic	1110
Dotarem®	ionic	1350
ProHance®	non-ionic	630
Gadavist®	non-ionic	1603
Eovist®	ionic	688
Ablavar®	ionic	825



Gd contrast agent

- Has seven unpaired electrons and the ability to allow rapid exchange of bulk water.
- Unpaired electrons have a magnetic moment that is 500,000 times that of a hydrogen proton.
- This large magnetic moment creates fluctuations in the local magnetic fields.

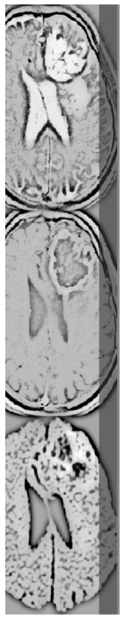
Low relaxation efficiency!!



Tumbles much faster than Larmor frequency

Creates fluctuations in a magnetic field near the Larmor frequency

Reduce the T1 relaxation time of nearby water spins !!

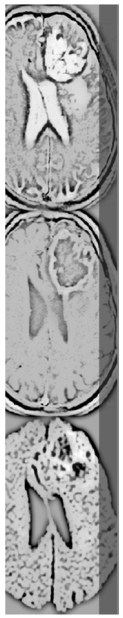


Relaxivity (弛緩率: 縮短組織弛緩時間的能力)

- The effect of a substance on relaxation rate is known as its relaxivity.

Relaxivity (L/mmol*s) Concentration(mol/L)

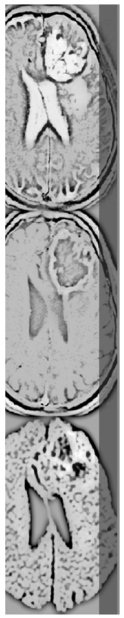
- $\frac{1}{T1_{w.contrast}} = r*[C]$
- $\frac{1}{T1_{observed}} = \frac{1}{T1_{\text{w. contrast}}} + \frac{1}{T1_{\text{w/o contrast}}}$



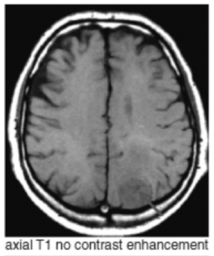
Gadolinium Administration/Dose

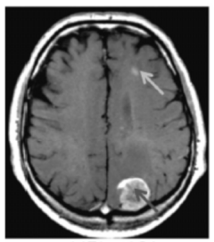
- The recommended dosage of gadolinium is 0.1 millimoles per kilogram (mmol/kg) of body weight (0.2 mL/kg).
- The lethal dose, (LD_{50} – the dose required to kill half of the study population) determined in rat studies is between 6 and 20 mmol/kg.
- As dose increases (to a point), the ability to visualize structures and lesions also increases. With standard gadolinium the optimal dose is weight-based.

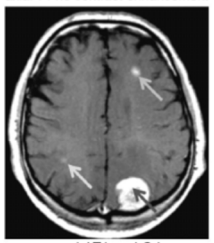
A standard (fix) dose of contrast agent is unacceptable!

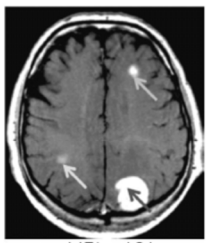


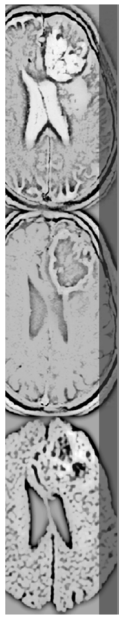
Dose effects


axial T1 no contrast enhancement


axial T1 post Gd
single dose


axial T1 post Gd
double dose

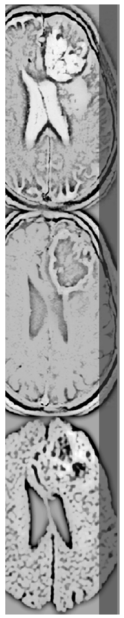

axial T1 post Gd
triple dose



ACR White Paper on MRI Safety

- The ACR approves of the injection of contrast material and diagnostic levels of radiopharmaceuticals by certified and/or licensed radiologic technologists and radiologic nurses under the direction of a radiologist or his or her physician designee who is personally and immediately available, if the practice is in compliance with institutional and state regulations.

ACR: American College of Radiology.

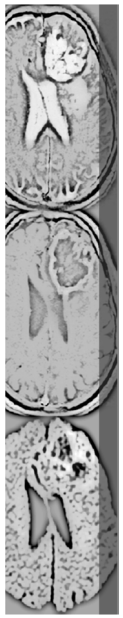


Clinical Consideration

- Three clinical scenarios must be considered…
  - **subcutaneous extravasation of contrast**
    - slightly better performance of low osmolar/non-ionic agents
  - **potential nephrotoxicity**
    - the difference between ionic and nonionic formulations is minimal.
  - **problems related to acute increase in serum osmolality**
    - The osmolar effect of a contrast agent is determined by its concentration in the blood.

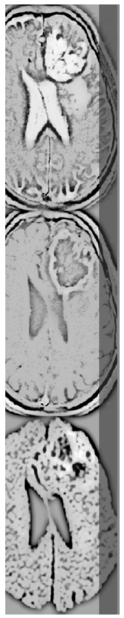
Contrast media (by IV injection) has circulated through the heart and aorta, its concentration has been significantly diluted.

http://mri-q.com/ionic-v-non-ionic.html



Nephrogenic Systemic Fibrosis

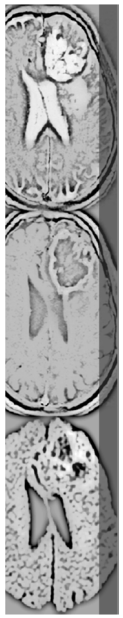
- **Nephrogenic systemic fibrosis (NSF)腎因性全身性纖維化**: patients who suffered from renal insufficiency.
- Normally, approximately 80% of gadolinium is excreted by the kidneys in 3 h and 98% is recovered by feces and urine in one week.
- But it may take longer for patients with NSF.
- Gadolinium is a contraindication and a relative precaution for patients in renal failure.



台灣衛生署 2011 年 8 月 4 日公告

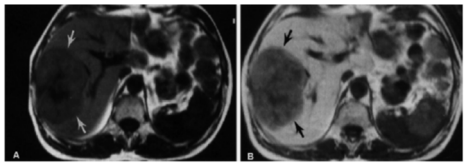
- 需至少檢視病人三個月內之 serum creatinine 檢測結果」，以了解受檢者之腎功能及是否有急性腎衰竭。
- 不可用於慢性嚴重腎臟疾病或急性腎衰竭之受檢者。
- 必要施行顯影性磁振造影時，謹慎的使用不超過標準劑量(0.1 mmol/kg) 之中或低風險含釓對比劑。
- 兩次顯影性磁振造影需間隔 7 天以上。

2017 中華民國放射線醫學會對比劑手冊

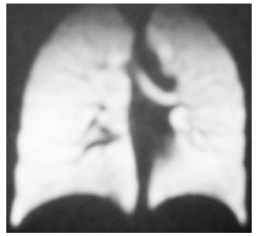


Other T1 agents

- Manganese
  - For liver imaging
  - Be taken up by the Kupffer cells in the liver.
- Hyperpolarized helium gas
  - For inhalation imaging for the lungs
- Superparamagnetic iron oxide (SPIO) agents

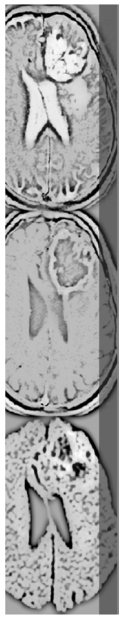


before after



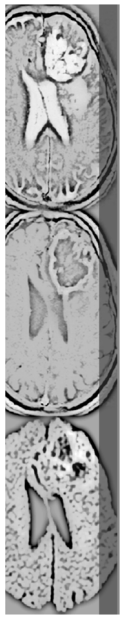
Applications of Gd contrast agents

Gd對比劑應用

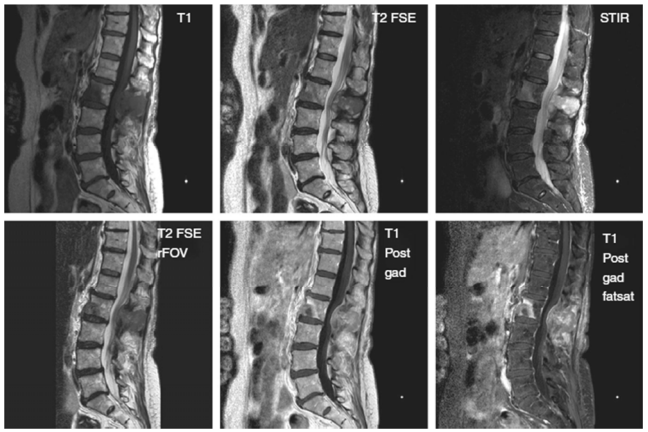


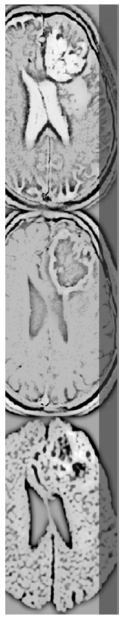
Clinical Applications

- Tumors pre- and post- operation
- Pre- and post- radiotherapy
- Infection
- Infarction
- Inflammation
- Post-traumatic lesions
- Post-operation lumbar disc
- Contrast- enhanced MRA

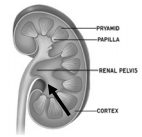


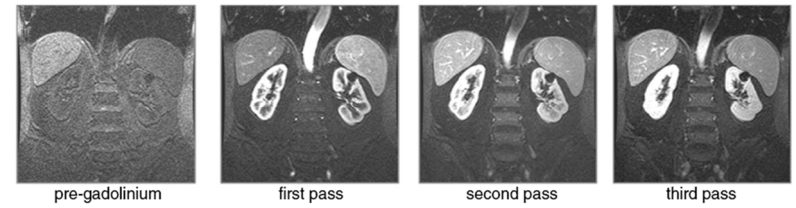
Lumbar Spine with bone metastases

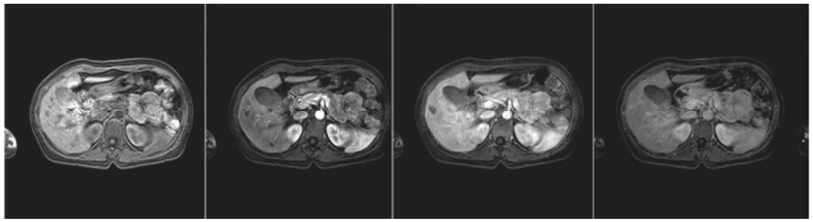




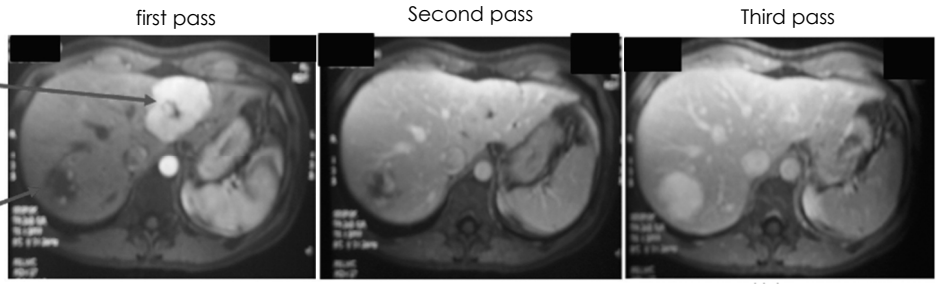
Timing for abdominal imaging



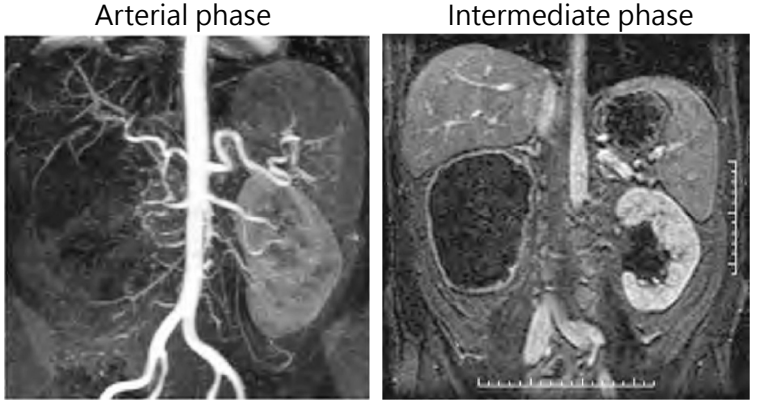




Enhancement and phase



Abdominal vessels



放射師打顯影劑!?

https://youtu.be/nTjw2NqtwoE

THE END

alvin4016@nycu.edu.tw