Teaching Module VII
ESUR guidelines on use of CM in certain clinical situations
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This slide deck was prepared by

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April 13th, 2010
Objectives

• Pregnancy and lactation
• Thyroid disease
• Diabetic patients on metformin
• Renal impairment
Pregnancy

Is it indicated to give CM?
Pregnancy

Is it indicated to give CM?

The radiation is more dangerous than the I-CM, e.g. abdominal CECT
No mutagenic or teratogenic effects were found in vivo with non-ionic I-CM or Gd-DTPA in animals.
Placental transfer

Current I-CM and Gd-CM which are water-soluble and have molecular weights in the range 500-850 Da are expected to transverse the placenta to some extent.
Pregnancy

No harmful effects of I-CM were reported with the exception of depression of the fetal thyroid. No prospective trials.

Fetal thyroid function is essential for the normal development of the CNS.
There are relatively few clinical reports of the effect on neonates of giving Gd-CM to the pregnant mother.

No adverse effects on the infants were detected in a total of 57 cases reported when the pregnant mother had been given Gd-DTPA in doses of 0.1-0.2 mmol/kg.
The ESUR guideline previously suggested that Gd-CM could be safely given to the pregnant female.

Recent data suggests potential for free gadolinium to be released from Gd-CM and to be deposited in bone and other tissues.

The potential harmful effect of slow excretion of CM in the neonate because of immature renal function, is important.

The use of Gd-CM in the pregnant female should be restrictive.
Gd-CM - Pregnancy

Recommendations:

Gd-CM should only be given to pregnant women when there is a very strong clinical indication.

One of the more stable, macrocyclic Gd-CM should be used in the lowest dose consistent with a diagnostic result.
Lactation

Is it indicated to give CM?

The baby gets very small amounts (< 0.5%) of I-CM – it may give a bad taste.
The amount of Gd-CM reaching the neonatal gut is less than 1% of the recommended intravenous dose for an infant after the lactating mother has received a Gd-CM intravenously.
The previous ESUR guideline indicated that when Gd-CM were given intravascularly to the pregnant woman, breastfeeding could continue normally.

However, the information about the potential harmful effects of free gadolinium combined with immature neonatal renal function indicate that despite the very tiny amounts of Gd-CM likely to be absorbed into the blood by the breastfeed infant, it may be prudent to recommend that breast feeding is discontinued for 24 hours if the lactating mother receives high risk intravascular Gd-CM.
### Guideline

#### 3.5. Pregnancy and lactation

<table>
<thead>
<tr>
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<td>Following administration of iodinated agents to the mother during pregnancy, thyroid function should be <strong>checked in the neonate during the first week</strong>.</td>
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<td>Breast feeding may be continued normally when iodinated agents are given to the mother.</td>
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<td><strong>Pregnant or lactating mother with renal impairment</strong></td>
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Thyrotoxicosis – a very late adverse reaction

Graves’ disease

- Stimulation of antibodies that stimulate iodine uptake and the synthesis of thyroid hormones.

Thyroid autonomy

- No TSH control. Large amounts of free iodine cause production and secretion of thyroid hormones.
Prevalence of iodine-induced hyperthyroidism

In iodine-deficient areas ~ 1.7%

In iodine-sufficient areas ~ very low
Iodine containing contrast media contains free iodine.

A 300 mgI/ml solution may contain < 50 µgI/ml right after production and < 90 µgI/ml after 3 to 5 years.

Normally, they contain less (1/5 - 1/10) than the previously mentioned figures.

A 200 ml bottle of 300 mgI/ml gives 7,000 µg free iodine ~ 45 times the recommended daily dose.
Thyrotoxicosis after CM

It is a very late reaction.

IT CAN BE SEEN UP TO 3 MONTHS AFTER THE INJECTION OF THE CONTRAST MEDIUM.

Then the patient is no longer in contact with the department of radiology – the possible link to the contrast application is often overlooked.
Recommendation

- Isotope imaging of the thyroid should be avoided for two months after iodinated contrast medium injection.

- No radioactive treatment of thyroid gland within the next 2 months and/or don’t give I-CM to patients planned for radioactive treatment within the next two months (*The iodine deposits are full*).
## Guideline

### 1.3. Very late adverse reactions

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**Recommendations**

- **Iodinated contrast media should not be given to patients with manifest hyperthyroidism.**
- Prophylaxis is generally not necessary.
- In selected high-risk patients, prophylactic treatment may be given by an endocrinologist; this is more relevant in areas of dietary iodine deficiency.
- Patients at risk should be closely monitored by endocrinologists after iodinated contrast medium injection.
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#### Thyrotoxicosis

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Metformin
The biguanides are used in non-insulin dependent diabetes mellitus in three ways:

- As primary treatment in obese patients inadequately controlled by diet
- As adjunct therapy when sulphonurea alone fails
- Sometimes in combination with insulin
- Now also available as a “retard” product
Renal handling

Biguanides differ in their routes of elimination.

- Phenformin and buformin undergo hepatic metabolism and renal excretion.
- Metformin is excreted unchanged in the urine.
Renal handling

Biguanides do not cause renal failure.

Metformin accumulation sufficient to produce lactic acidosis can occur only in the presence of renal failure (and rarely hepatic failure) and it occurs slowly.
In patients with renal failure, metformin may accumulate in body tissues and produce lactic acidosis.
Renal handling

Renal insufficiency with failure to clear metformin leads to accumulation of the drug and the potential for development for fatal lactic acidosis.
Lactic acidosis is generally defined as a metabolic acidosis due to the accumulation of lactic acid in the blood in excess of 5 mmol with an accompanying blood pH of less than 7.25.

Acute renal failure is a prominent causal factor.
About 20-25% of diabetics with serum creatinine less than 150 µmol/l (a common cutoff level for receiving metformin) have an eGFR between 30 and 59 ml/min/1.73 m² (chronic kidney disease, CKD, stage 3).

Webb et al., Letter to the Editor. Radiol. 2010
About 20-25% of diabetics with serum creatinine less than 150 µmol/l (a common cutoff level for receiving metformin) have an eGFR between 30 and 59 ml/min/1.73 m² (chronic kidney disease, CKD, stage 3).

The incidence of contrast-medium nephrotoxicity is higher in diabetics with renal impairment than in non-diabetics with the same degree of renal impairment.
Metformin

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The incidence of contrast-medium nephrotoxicity is higher in diabetics with renal impairment than in non-diabetics with the same degree of renal impairment.

Since metformin clearance is reduced by 74-78% in moderate or severe renal impairment, the potential for metformin retention and lactic acidosis is higher in CKD-3 patients.

Webb et al., Letter to the Editor. Radiol. 2010
Guideline

2.1 Renal adverse reactions to iodinated contrast media

<table>
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<th>Risk of iodinated contrast media in patients taking metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
</tr>
</tbody>
</table>

Note Metformin does not cause renal failure.
2.1.1. Time of referral

2) Identify diabetic patients taking metformin

Depending on eGFR/serum creatinine level, metformin will have to be stopped either before or at the time of contrast medium administration.
Guideline

2.1.1. Time of referral

1. Identify diabetic patients taking metformin

Measure eGFR (or serum creatinine) if the procedure can be deferred until the result is available without harm to the patient.

In extreme emergency, if eGFR (or serum creatinine) measurement cannot be obtained, follow the protocol for patients with eGFR less than 60 ml/min/1.73 m² (or raised serum creatinine) as closely as clinical circumstances permit.
Diabetic patients taking metformin

- Patients with eGFR equal to or greater than 60 ml/min/1.73 m² can continue to take metformin normally.
- Patients with eGFR is between 30 and 60 ml/min/1.73 m²:
  - A) Patients receiving intravenous contrast medium with eGFR equal to or greater than 45 ml/min/1.73 m² can continue to take metformin normally.
  - B) Patients receiving intraarterial contrast medium and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m² should stop metformin 48 h before contrast medium and should only restart metformin 48 h after contrast medium if renal function has not deteriorated.
- Patients with eGFR less than 30 ml/min/1.73 m² or with an intercurrent illness causing reduced liver function or hypoxia. Metformin is contraindicated and iodinated contrast should be avoided.
Guideline

2.1.2. Before the examination

<table>
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<th>Diabetic patients taking metformin</th>
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</thead>
<tbody>
<tr>
<td>• If eGFR is greater than 60 ml/min/1.73 m² (or serum creatinine is normal), follow instructions for elective patients.</td>
</tr>
<tr>
<td>• If eGFR is between 30 and 60 ml/min/1.73 m² (or serum creatinine is raised) or unknown, weigh the risks and benefits of contrast medium administration and consider an alternate imaging method. If contrast medium is deemed essential take the following precautions:</td>
</tr>
<tr>
<td>– Metformin therapy should be stopped.</td>
</tr>
<tr>
<td>– The patient should be hydrated (e.g. at least 1 ml per hour per kg b.w. of intravenous normal saline up to 6 hours after contrast medium administration – In warm areas more fluid should be given).</td>
</tr>
<tr>
<td>– Monitor renal function (eGFR/serum creatinine), serum lactic acid and pH of blood.</td>
</tr>
<tr>
<td>– Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnea, lethargy, diarrhea and thirst). Blood test results indicative of lactic acidosis: pH ≤ 7.25 with plasma lactate ≥ 5 mmol/l.</td>
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### Guideline

#### 2.1.3. Time of examination

| In patients at increased risk of contrast medium induced nephropathy | Use low- or iso-osmolar contrast media.  
Use the lowest dose of contrast medium consistent with a diagnostic result. |
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<td>Use the lowest dose of contrast medium consistent with a diagnostic result.</td>
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2.1.3. Time of examination

| In patients at increased risk of contrast medium induced nephropathy | • Use low- or iso-osmolar contrast media.  
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#### 2.1.4. After the examination

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<td>In patients with eGFR less than 60 ml/min/1.73 m² (or raised serum creatinine)</td>
<td>Continue hydration for at least 6 hours.</td>
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<td>In diabetic patients taking metformin who have eGFR less than 60 ml/min/1.73 m²</td>
<td>Measure eGFR (or serum creatinine) at 48 hours after contrast medium administration. If it is not worsened, metformin can be restarted. Metformin is not approved in most countries in patients with abnormal renal function.</td>
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Renal impairment
Your advice to the patient

Nephrogenic systemic fibrosis

and

Contrast medium induced nephropathy
We want to provide the patient with the best diagnostic service.
It is not only a question of the risk of CIN or NSF, but also the risk of missing an important diagnosis.
Factors which must be taken into consideration

1. The diagnostic consequences of an inferior diagnostic work-up

2. Radiation, in particular in young patients

3. Prevalence of acute reactions

4. Prevalence of NSF and CIN

5. Associated morbidity and mortality with NSF and CIN
Acute adverse reactions

I-CA >> Gd-CA
What is the prevalence?
Incidence after a high-risk agent

Among patients with reduced renal function or on dialysis

3 - 7 %*

University of Copenhagen
University of Linda Loma
University of Wisconsin
University of Glasgow
Connecticut

* Based on registries – excludes the lower stages of NSF
Incidence after a high-risk agent

Among patients with reduced renal function or on dialysis

18%

Based on inspection of skin and biopsy
All stages of NSF included
Prevalence:

- Macrocyclic agents
  - Only three published unconfounded cases in the peer-reviewed literature following a large dose of Gadovist – disagreement about whether the pathology is NSF
NSF – morbidity & mortality

• NSF is associated with marked morbidity in the majority of cases.

• 24-month mortality following examination was 48% and 20% in patients with and those without cutaneous changes of NSF, respectively.

Todd et al., Arthritis Rheum. 2007; 56(10):3433-41
What is the prevalence?
CIN with head-to-head comparisons of risk patients receiving I.V. contrast material

<table>
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<tr>
<th>Study</th>
<th>LOCM (monomers)</th>
<th>Iodixanol</th>
<th>Criteria</th>
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<td>Carraro et al. (1998)</td>
<td>0/32 (iopromide)</td>
<td>1/32</td>
<td>50% ↑ SCr</td>
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<tr>
<td>Nguyen et al. (2008)</td>
<td>10/65 (iopromide)</td>
<td>3/61</td>
<td>44 µmol/L ↑ SCr</td>
</tr>
<tr>
<td>Kolehmainen et al. (2003)</td>
<td>4/25 (iobiditrol)</td>
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<td>44 µmol/L ↑ SCr</td>
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<tr>
<td>Barrett et al. (2006)</td>
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<td>2/76</td>
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<td>Thomsen et al. (2008)</td>
<td>0/76 (iomeron)</td>
<td>5/72</td>
<td>44 µmol/L ↑ SCr</td>
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<tr>
<td>Kuhn et al. (2008)</td>
<td>7/125 (iopamidol)</td>
<td>6/123</td>
<td>25% ↑ SCr</td>
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<tr>
<td>Chuang (2009) (intravenous urography)</td>
<td>1/25 (iohexol)</td>
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<td>25% ↑ SCr</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>22/425</strong></td>
<td><strong>22/414</strong></td>
<td><strong>NO DIFFERENCE</strong></td>
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<td>(5.18%)</td>
<td>(5.31%)</td>
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Prevalence of CIN in CKD 5 after IV injection

Unknown

Best guess: 10 - 15 %

Very conservative guess
CIN is not only a temporary event

Adverse events in the follow-up period:
92 of 294 patients
CIN-group: 42%
Non-CIN-group: 26%

Major events
(death, stroke, myocardial infarction and ESRD requiring dialysis) in the follow-up period:
38 of 294 patients (13%)

Conclusion

• All ICM have the potential of inducing CIN in patients with renal impairment.

• For patients with advanced renal impairment, it is crucially important to protect residual GFR to delay dialysis dependence.

• Protecting residual GFR in dialysis patients is also important.

  • Enhanced MRI with a low-risk NSF agent seems safer for a patient with severely reduced renal function or on replacement therapy with urine output than an enhanced CT with a non-ionic agent.
• Only for dialysis patients with zero urine production, enhanced CT seems to be safer if it is diagnostically superior to MRI.
Conclusion

It does not seem appropriate to deny a patient with reduced renal function a clinically well indicated enhanced MRI.