

FAMILIAL SYNDROMES AND NEUROENDOCRINE TUMOURS

Ashley Grossman FMedSci

Oxford Centre for Diabetes, Endocrinology & Metabolism

University of Oxford



World ENETS Day
Newbury Nov. 10th 2011

PANCREATIC NETs

- **Functioning**
 - **Insulinomas**
 - **Gastrinomas**
 - **Glucagonomas**
 - **Somatostatinomas**
- **Non-functioning**

ARE NETS IN GENERAL FAMILIAL?

ARE NETS IN GENERAL FAMILIAL?

There is very little evidence in favour of a familial NET syndrome, but they may occur as part of other syndromes such as MEN1, TS, VHL and NF-1

MEN-1

MEN-1

- **Autosomal dominant**

MEN-1

- **Autosomal dominant**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**
- **Islet cell tumours in 40%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**
- **Islet cell tumours in 40%**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**
- **Islet cell tumours in 40%**
- **Collagenomas, fibromas, angiomas, adrenal adenomas, lipomas etc.**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**
- **Islet cell tumours in 40%**
- **Collagenomas, fibromas, angiomas, adrenal adenomas, lipomas etc.**

MEN-1

- **Autosomal dominant**
- **Hyperparathyroidism in 95%**
- **Pituitary tumours in 40%**
- **Islet cell tumours in 40%**
- **Collagenomas, fibromas, angiomas, adrenal adenomas, lipomas etc.**
- **No genotype-phenotype correlation**

ISLET CELL TUMOURS IN MEN1

ISLET CELL TUMOURS IN MEN1

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**
 - Usually benign (>90%)

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**
 - Usually benign (>90%)
 - Small (<2cm)

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**
 - Usually benign (>90%)
 - Small (<2cm)
 - Highly symptomatic and medically problematic

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**
 - Usually benign (>90%)
 - Small (<2cm)
 - Highly symptomatic and medically problematic
 - May be malignant in MEN1

ISLET CELL TUMOURS IN MEN1

- **Gastrinomas**
 - Often malignant
 - Multiple
 - Highly symptomatic but medically responsive
- **Insulinomas**
 - Usually benign (>90%)
 - Small (<2cm)
 - Highly symptomatic and medically problematic
 - May be malignant in MEN1

DIAGNOSIS OF INSULINOMA

DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L

DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L
- **Mixed meal**
 - 5% as only abnormality (Kar et al 2006)

DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L
- **Mixed meal**
 - 5% as only abnormality (Kar et al 2006)

DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L
- **Mixed meal**
 - 5% as only abnormality (Kar et al 2006)
- **Exclude sulphonylurea abuse etc.**

DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L
- **Mixed meal**
 - 5% as only abnormality (Kar et al 2006)
- **Exclude sulphonylurea abuse etc.**

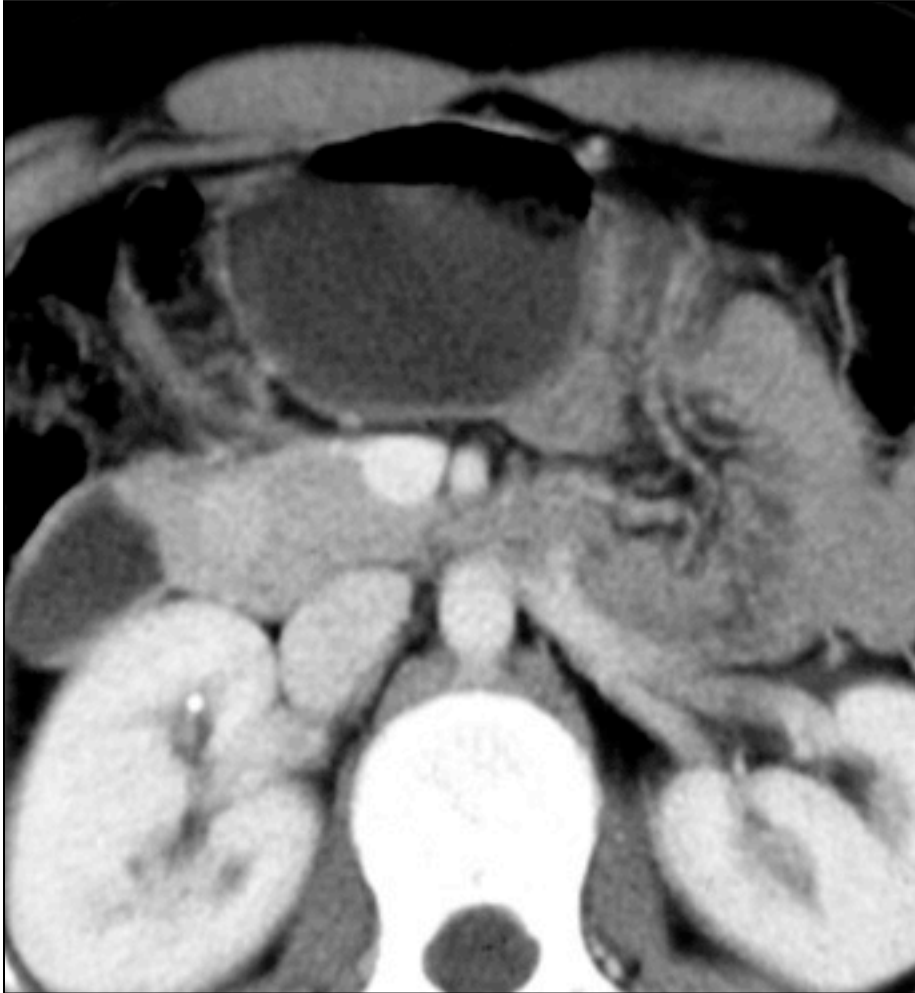
DIAGNOSIS OF INSULINOMA

- **Prolonged 72h fast**
 - Blood glucose <2.2 mmol/L
 - Insulin >3 mIU/L (care! Coelho et al 2009: 2.7mIU/L)
 - C-peptide >200 pmol/L
- **Mixed meal**
 - 5% as only abnormality (Kar et al 2006)
- **Exclude sulphonylurea abuse etc.**
- **See Endocrine Society Guidelines 2008**

IMAGING MODALITIES

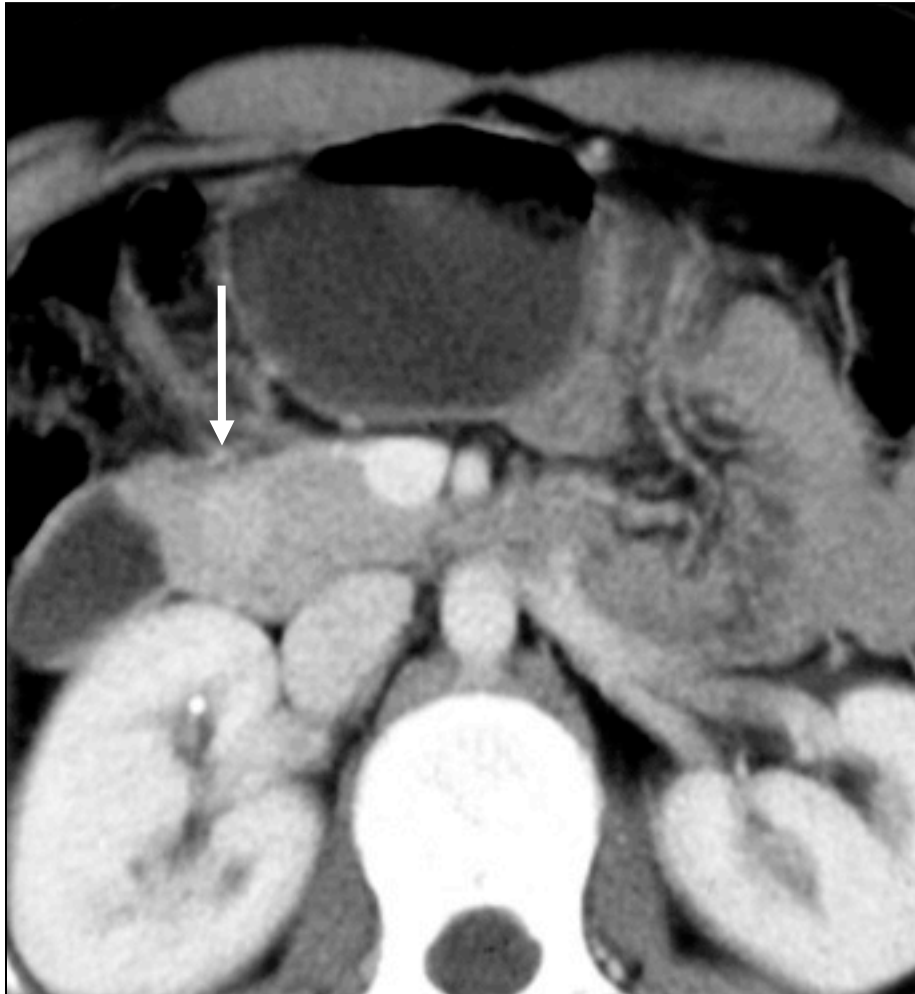
- **Ultrasound**
 - Transabdominal
 - Endoscopic with biopsy
 - Intra-operative
- **CT scanning**
- **MRI**
- **Radionuclide imaging**
- **Functional studies**

Insulinoma: CT



Stark DD, Radiology 1984; van Heerden JA, Surgery 1992;
Service FJ, Mayo Clin Proc 1976; Berends FJ, Surgery
2000

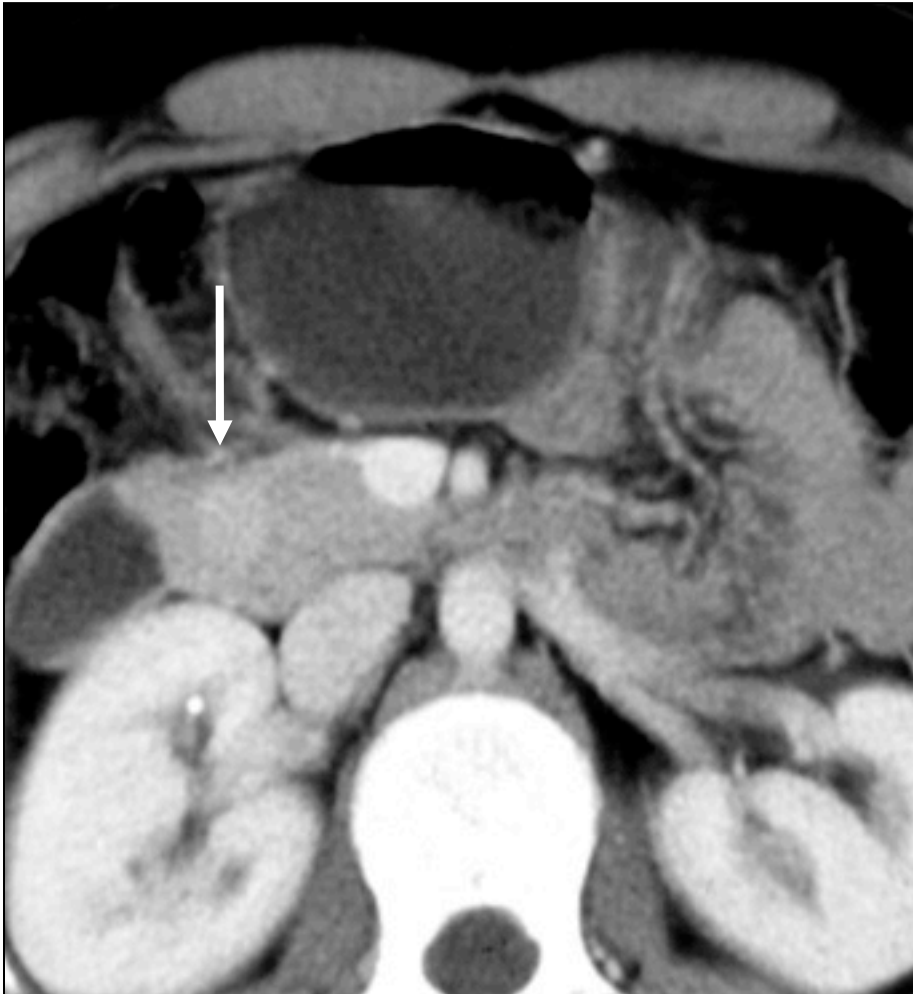
Insulinoma: CT



**Need precise
attention to imaging
protocol**

Stark DD, Radiology 1984; van Heerden JA, Surgery 1992;
Service FJ, Mayo Clin Proc 1976; Berends FJ, Surgery
2000

Insulinoma: CT



**Need precise
attention to imaging
protocol**

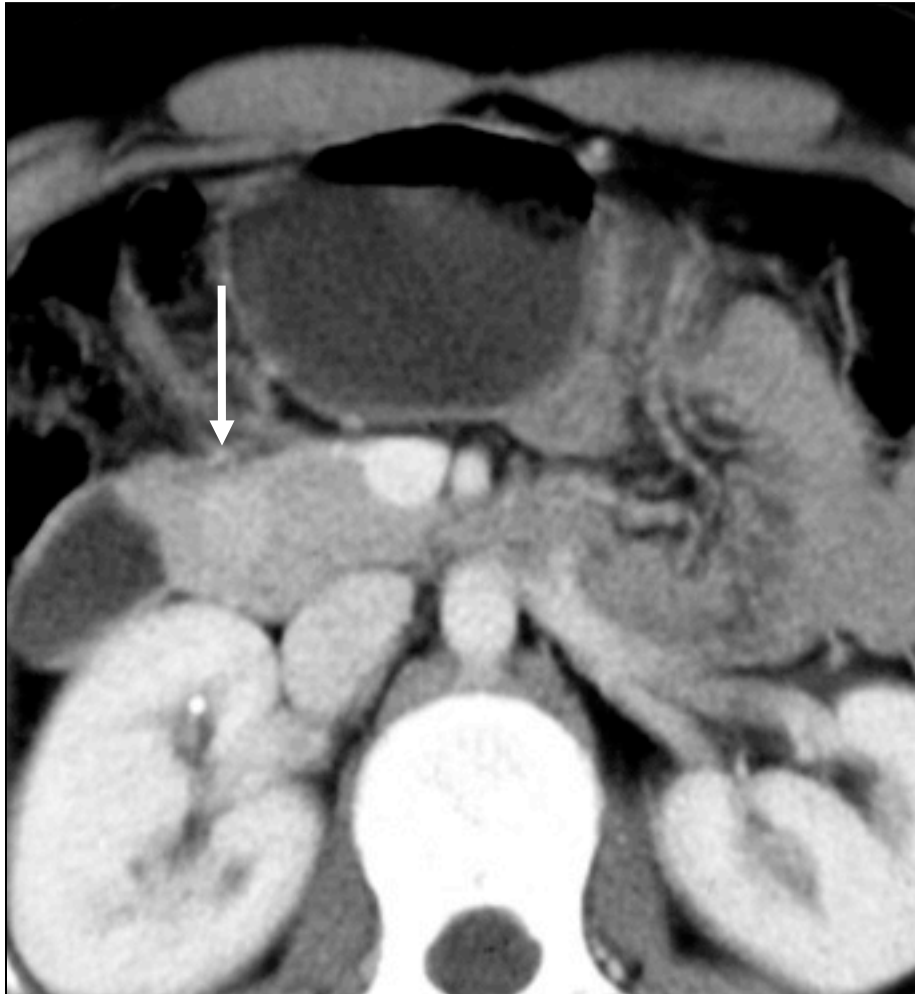
SMALL

90% <2cm

40% <1cm

Stark DD, Radiology 1984; van Heerden JA, Surgery 1992;
Service FJ, Mayo Clin Proc 1976; Berends FJ, Surgery
2000

Insulinoma: CT



**Need precise
attention to imaging
protocol**

SMALL

90% <2cm

40% <1cm

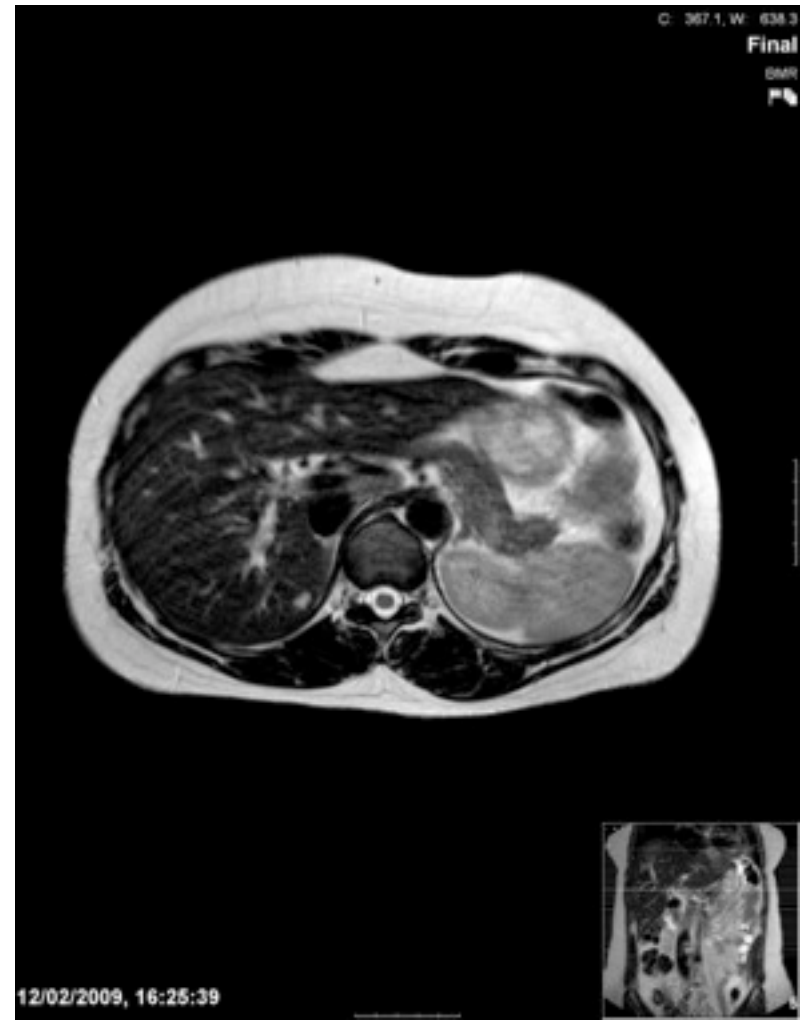
Benign in >90%

Stark DD, Radiology 1984; van Heerden JA, Surgery 1992;
Service FJ, Mayo Clin Proc 1976; Berends FJ, Surgery
2000

MRI IN INSULINOMA



T1

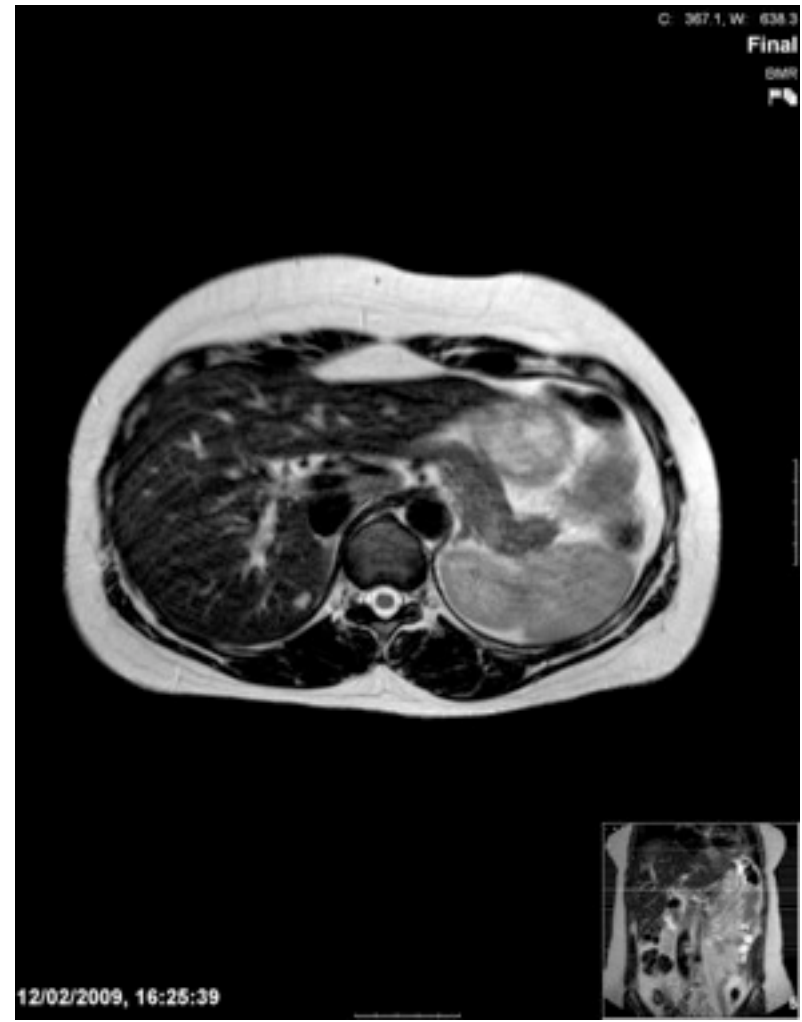


T2

MRI IN INSULINOMA



T1

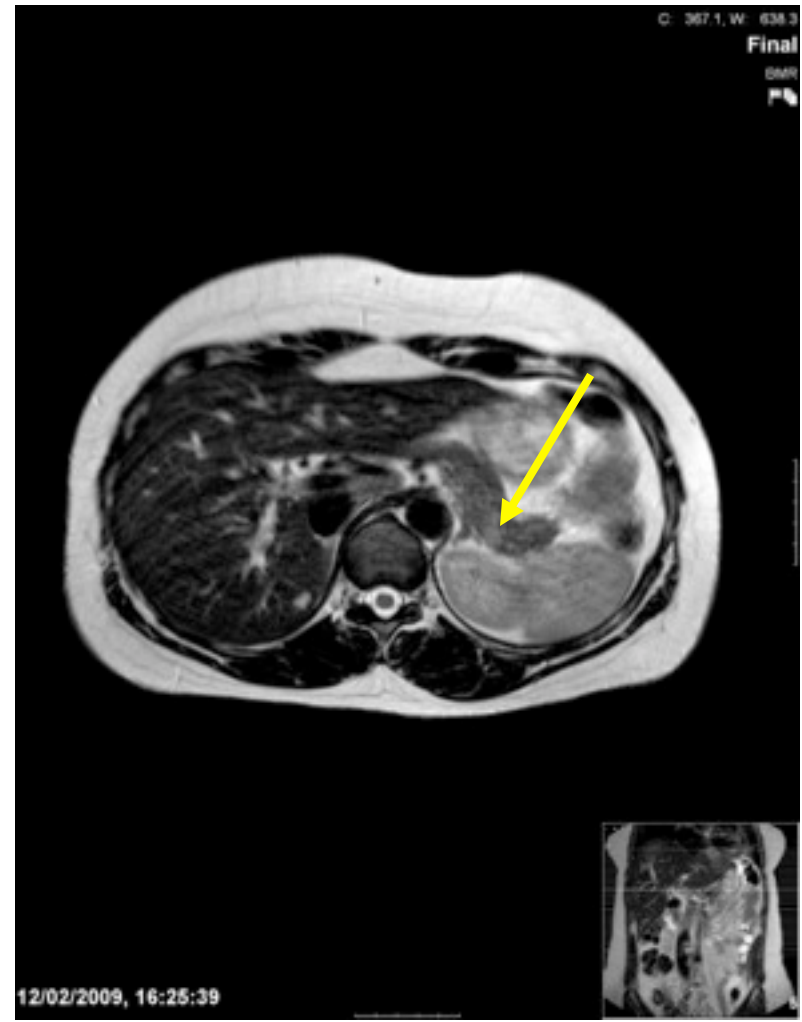


T2

MRI IN INSULINOMA

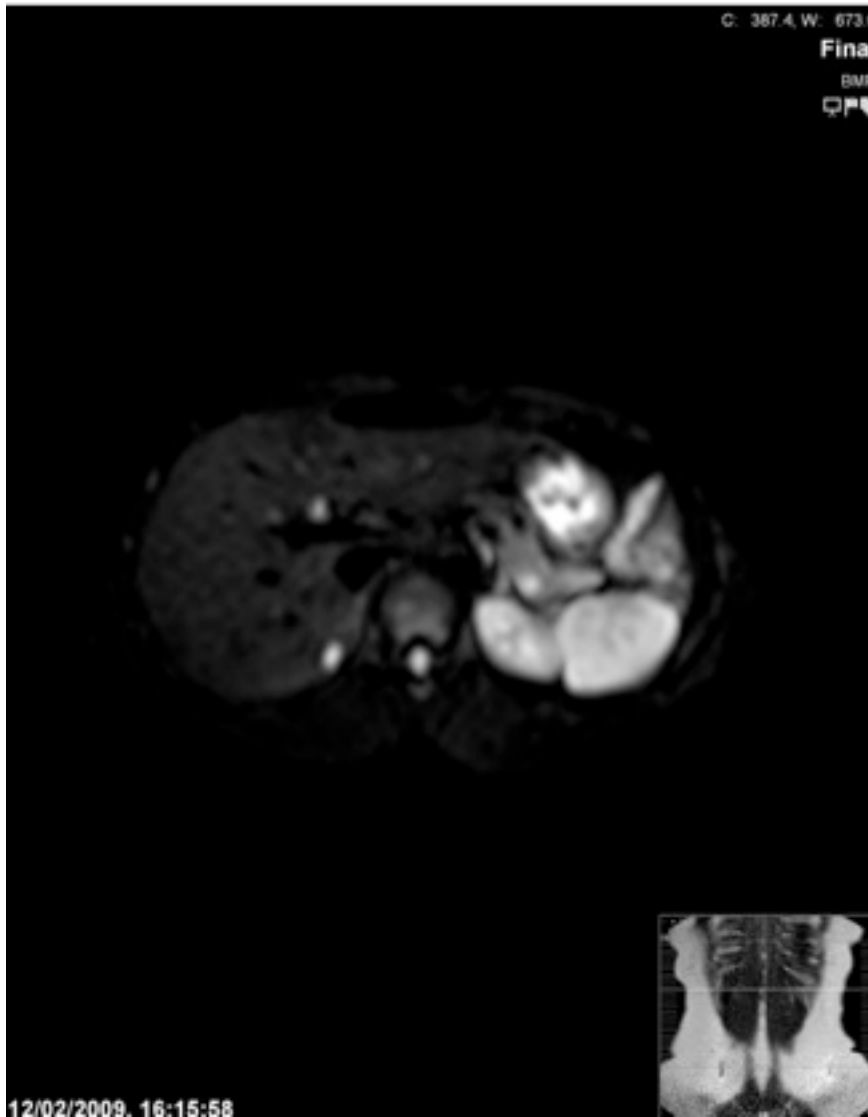


T1



T2

MRI IN INSULINOMA



DWI

MRI IN INSULINOMA



DWI

LOCALISATION OF INSULINOMAS

(Druce et al 2009)

LOCALISATION OF INSULINOMAS

- **Cross-sectional imaging 80% sensitivity and 100% specificity**

(Druce et al 2009)

LOCALISATION OF INSULINOMAS

- **Cross-sectional imaging 80% sensitivity and 100% specificity**

(Druce et al 2009)

LOCALISATION OF INSULINOMAS

- **Cross-sectional imaging 80% sensitivity and 100% specificity**
- **May improve to 90% or greater with DWI MRI**
- **Calcium stimulation catheters**
 - **63% correct**
 - **22% no lesion**
 - **15% discordant**

(Druce et al 2009)

MANAGEMENT STRATEGY

MANAGEMENT STRATEGY

- **INSULINOMAS**

MANAGEMENT STRATEGY

- **INSULINOMAS**
 - Locate and remove

MANAGEMENT STRATEGY

- **INSULINOMAS**
 - Locate and remove
 - Use MRI and calcium stimulation studies

MANAGEMENT STRATEGY

- **INSULINOMAS**
 - Locate and remove
 - Use MRI and calcium stimulation studies
 - ‘Hands of the surgeon’ plus intraoperative US

MANAGEMENT STRATEGY

- **INSULINOMAS**
 - Locate and remove
 - Use MRI and calcium stimulation studies
 - ‘Hands of the surgeon’ plus intraoperative US
 - Diazoxide \pm octreotide

MANAGEMENT STRATEGY

- **INSULINOMAS**
 - Locate and remove
 - Use MRI and calcium stimulation studies
 - ‘Hands of the surgeon’ plus intraoperative US
 - Diazoxide \pm octreotide

 - When malignant
 - Radiolabelled octreotide

MANAGEMENT STRATEGY

- **INSULINOMAS**

- Locate and remove
- Use MRI and calcium stimulation studies
- ‘Hands of the surgeon’ plus intraoperative US
- Diazoxide \pm octreotide

- When malignant
 - Radiolabelled octreotide
 - Everolimus (RAD001 – Novartis)

MANAGEMENT STRATEGY

- **INSULINOMAS**

- Locate and remove
- Use MRI and calcium stimulation studies
- ‘Hands of the surgeon’ plus intraoperative US
- Diazoxide \pm octreotide

- When malignant
 - Radiolabelled octreotide
 - Everolimus (RAD001 – Novartis)
 - Chemotherapy

PHYLLOID TUMORS

MANAGEMENT STRATEGY

• Locate and remove

• Use MRI and calcium stimulation studies

• Hands of the surgeon' plus intraoperative US

• Diazoxide \pm octreotide

• When malignant

• Radiolabelled octreotide

• Everolimus (RAD001 – Novartis)

• Chemotherapy

DIAGNOSIS OF GASTRINOMA

- **Recurrent or multiple peptic ulceration**
- **Diarrhoea**
- **Elevated plasma gastrin**
- **Elevated gastric acid (pH, secretin, acid output)**
- **Beware of PPIs and H2 antagonists**
- **Usually in gastrinoma triangle, often duodenal**

DIAGNOSIS OF GASTRINOMA

DIAGNOSIS OF GASTRINOMA

- **High gastrin levels in presence of gastric acidity**
 - No consensus as to assessment
 - N-g tube and pH meter
 - GI lab studies for acid output

DIAGNOSIS OF GASTRINOMA

- **High gastrin levels in presence of gastric acidity**
 - No consensus as to assessment
 - N-g tube and pH meter
 - GI lab studies for acid output
 - Secretin test

DIAGNOSIS OF GASTRINOMA

- **High gastrin levels in presence of gastric acidity**
 - No consensus as to assessment
 - N-g tube and pH meter
 - GI lab studies for acid output
 - Secretin test
- **Off H2 blockers for 3 days, PPIs for 2 weeks**
 - Switch to H2 blocker?

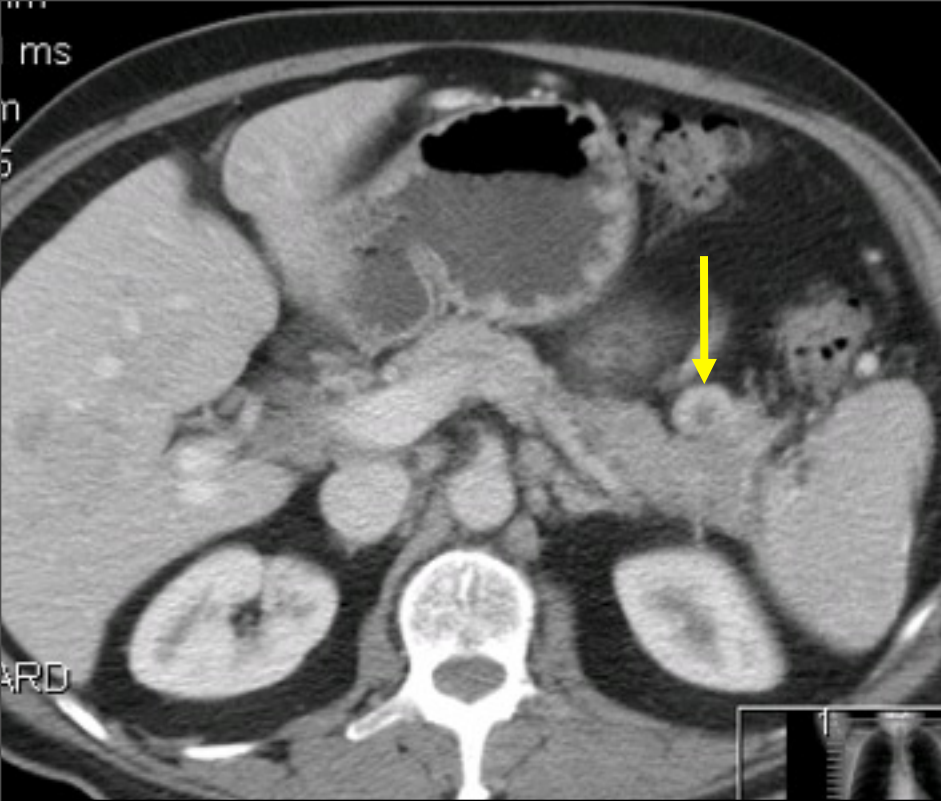
DIAGNOSIS OF GASTRINOMA

- **High gastrin levels in presence of gastric acidity**
 - No consensus as to assessment
 - N-g tube and pH meter
 - GI lab studies for acid output
 - Secretin test
- **Off H2 blockers for 3 days, PPIs for 2 weeks**
 - Switch to H2 blocker?
 - Admit and observe?

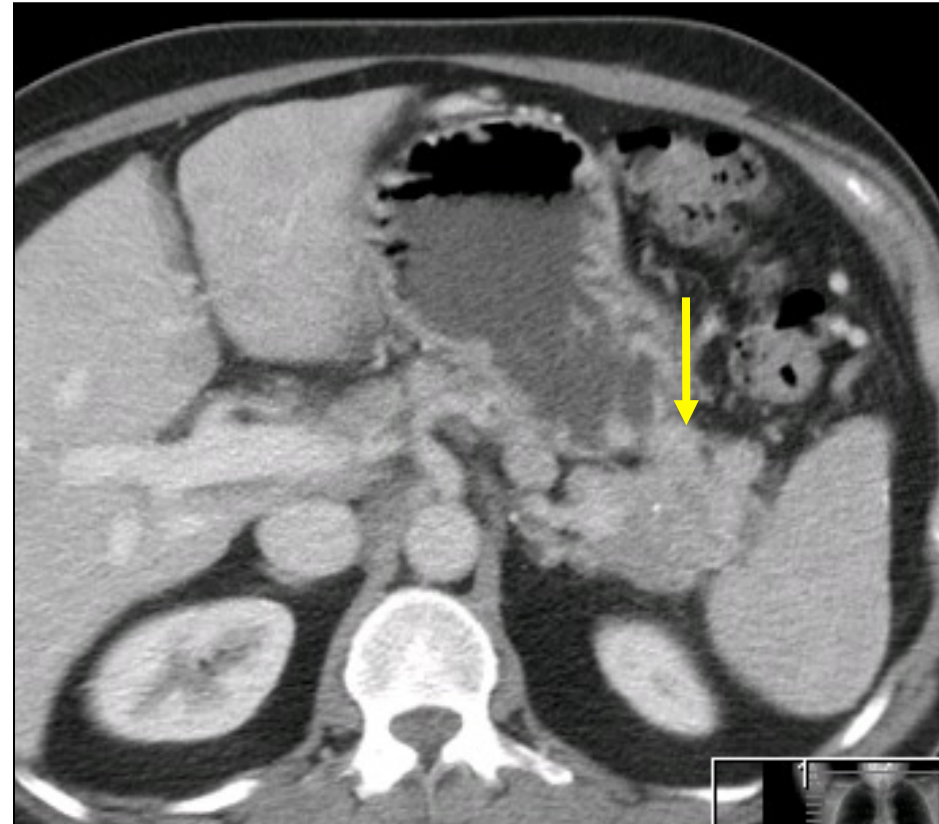
DIAGNOSIS OF GASTRINOMA

- **High gastrin levels in presence of gastric acidity**
 - No consensus as to assessment
 - N-g tube and pH meter
 - GI lab studies for acid output
 - Secretin test

- **Off H2 blockers for 3 days, PPIs for 2 weeks**
 - Switch to H2 blocker?
 - Admit and observe?
 - Use clinical 'judgement'?

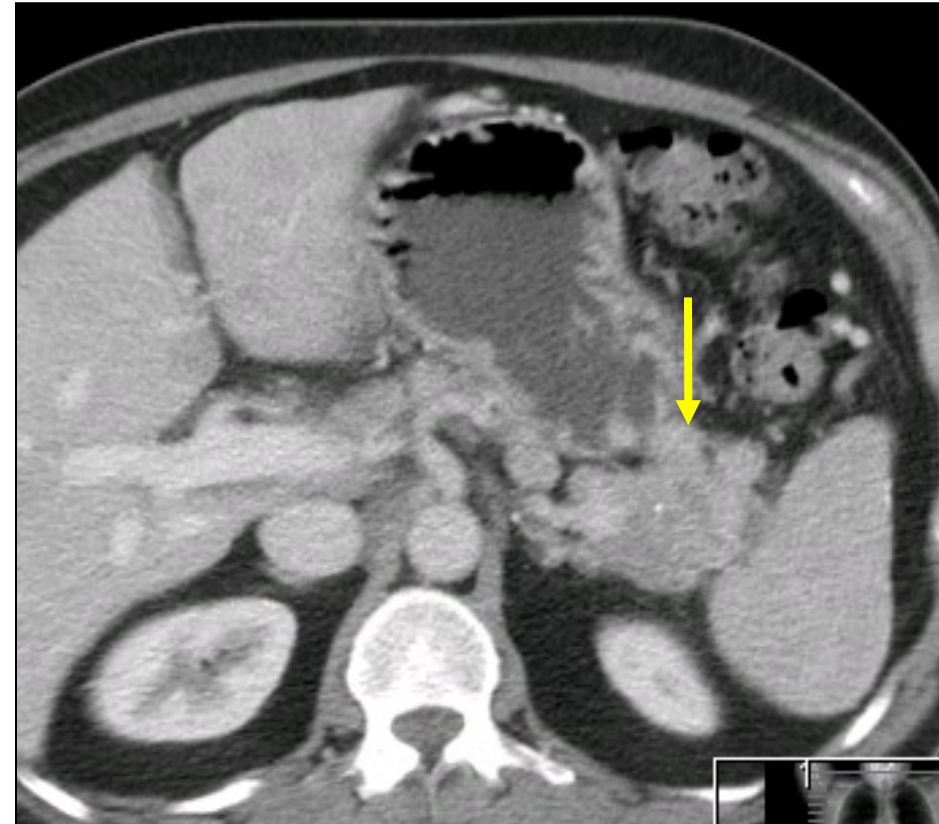
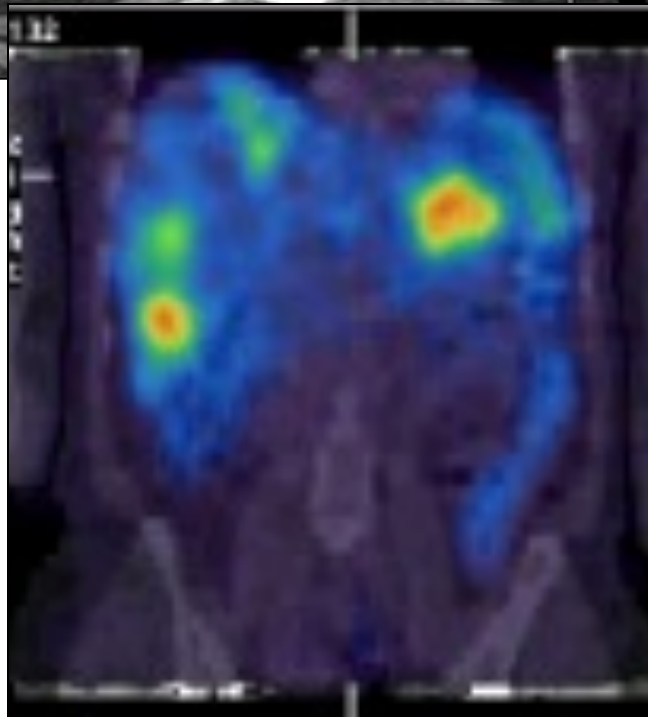


Malignant
gastrinoma in tail
of pancreas

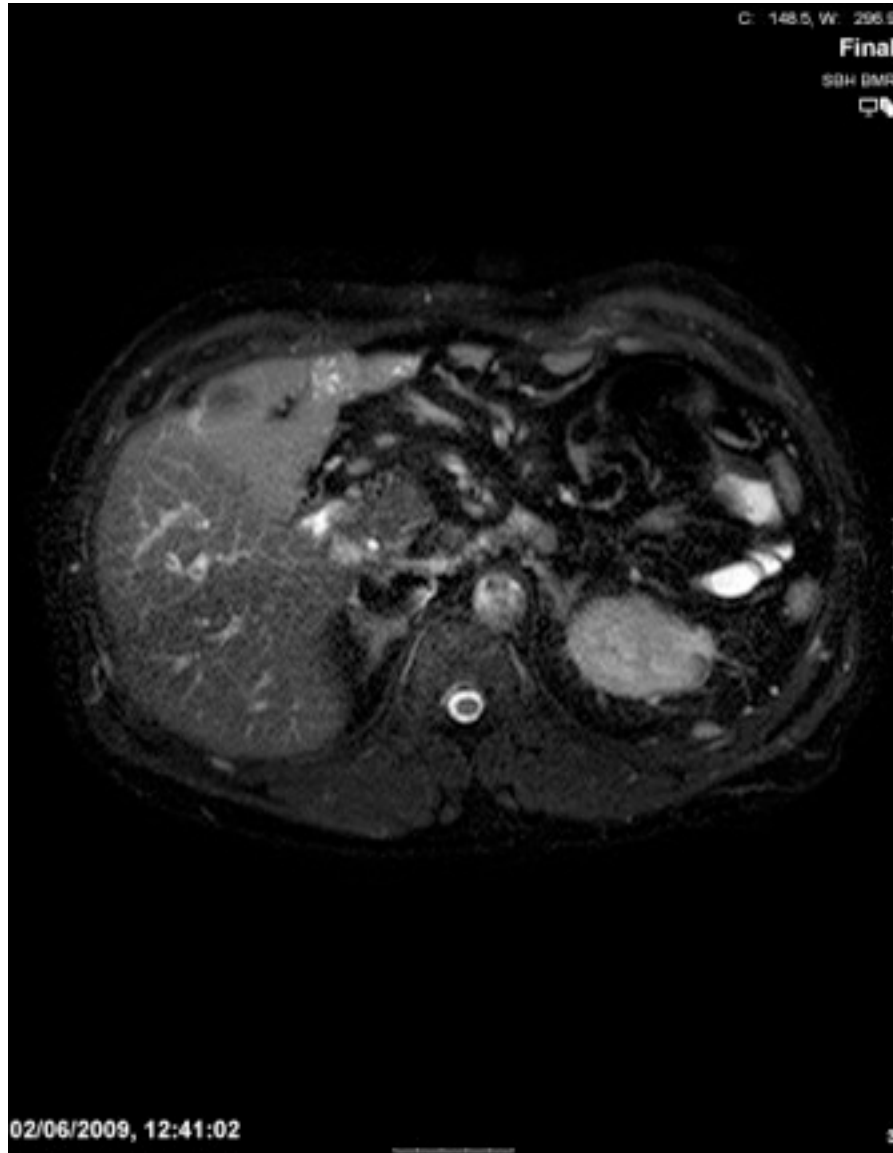




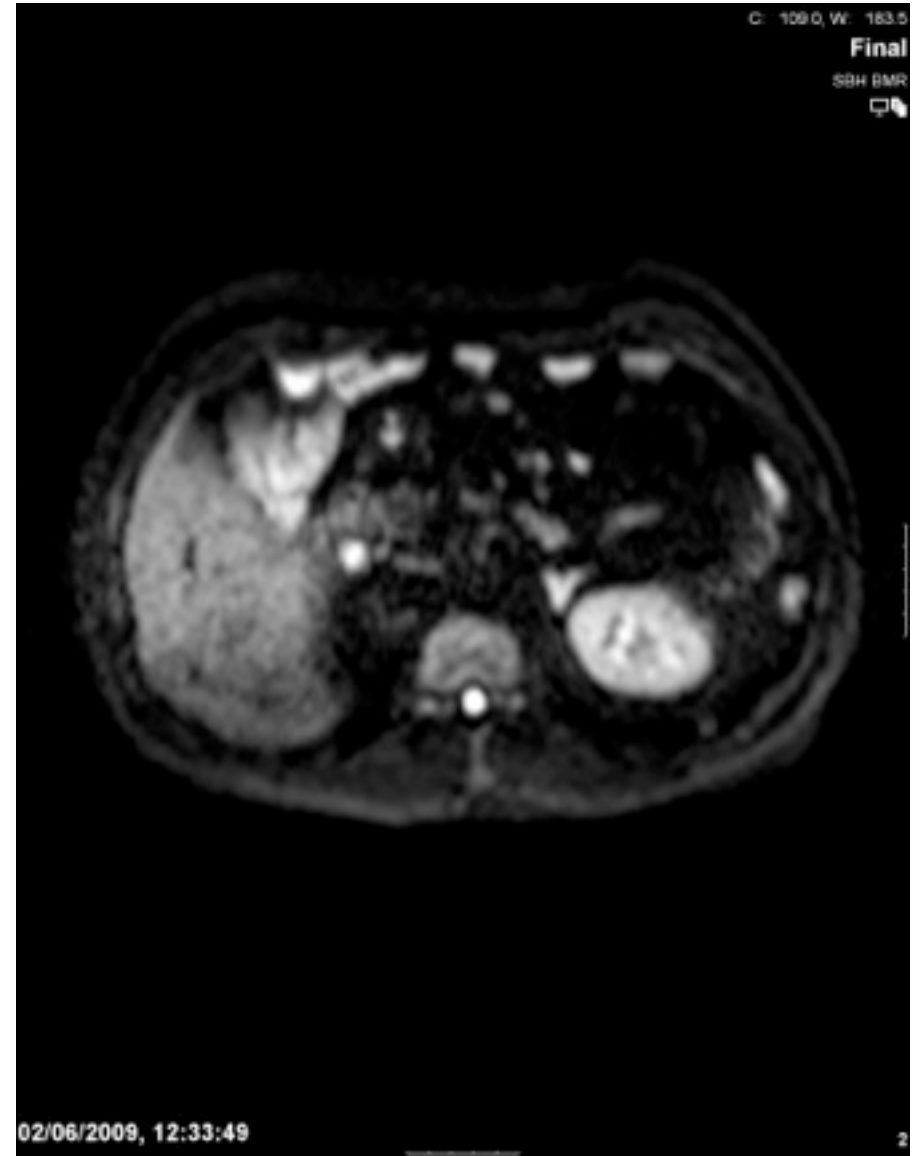
Malignant
gastrinoma in tail
of pancreas



GASTRINOMA

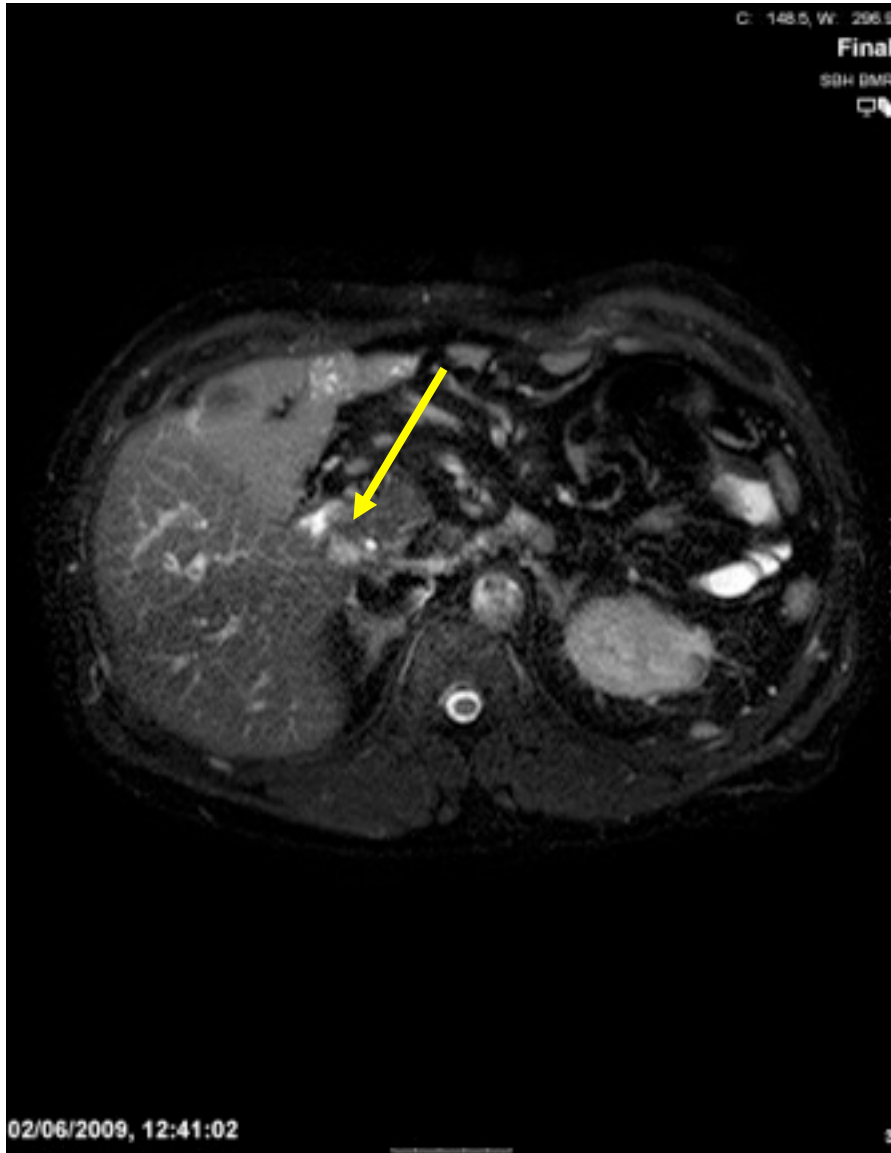


T2-FS

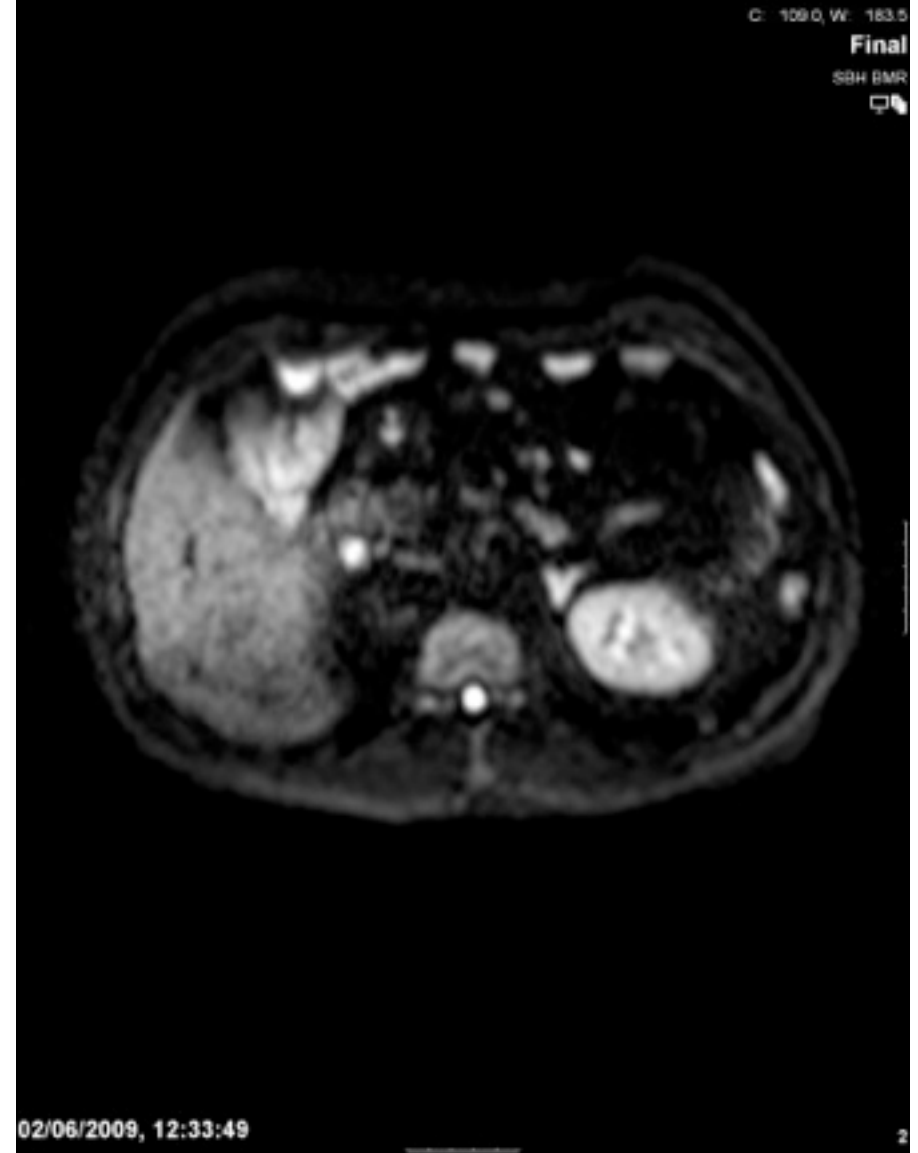


DWI

GASTRINOMA

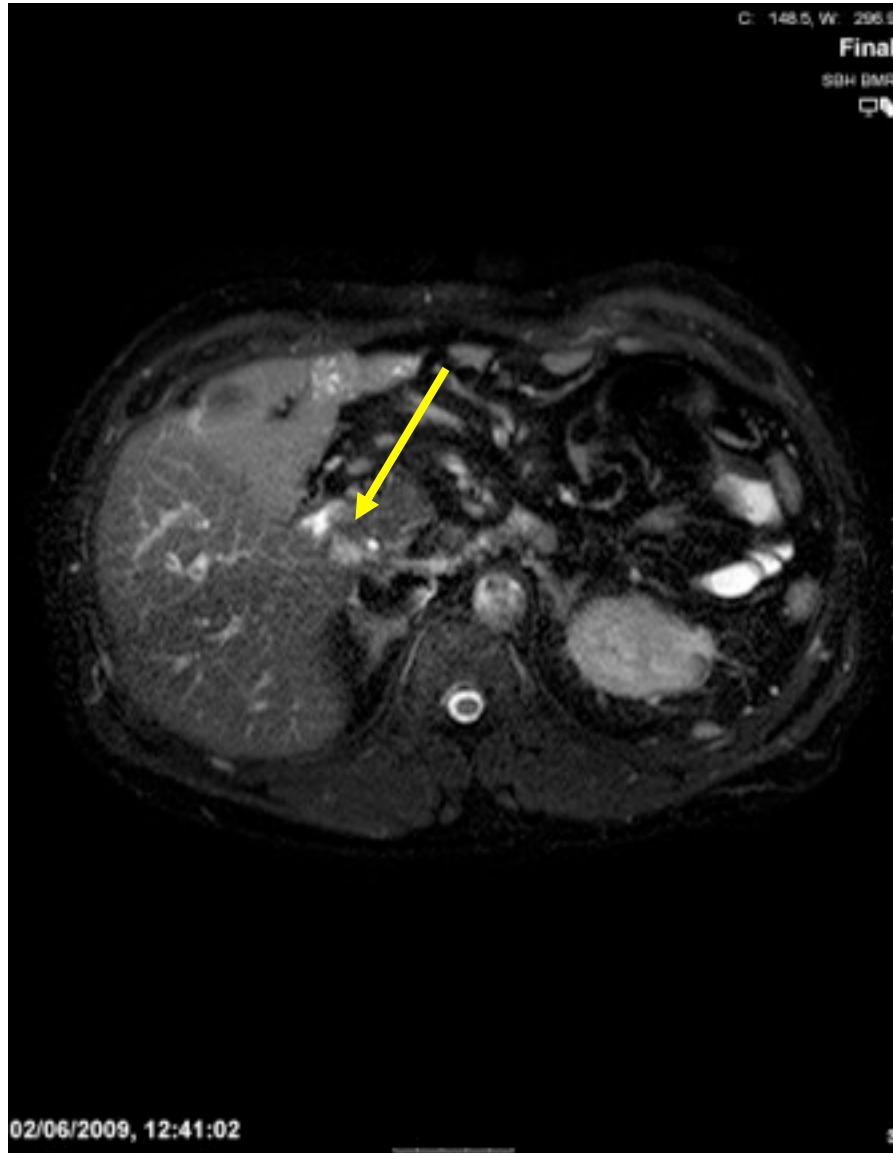


T2-FS

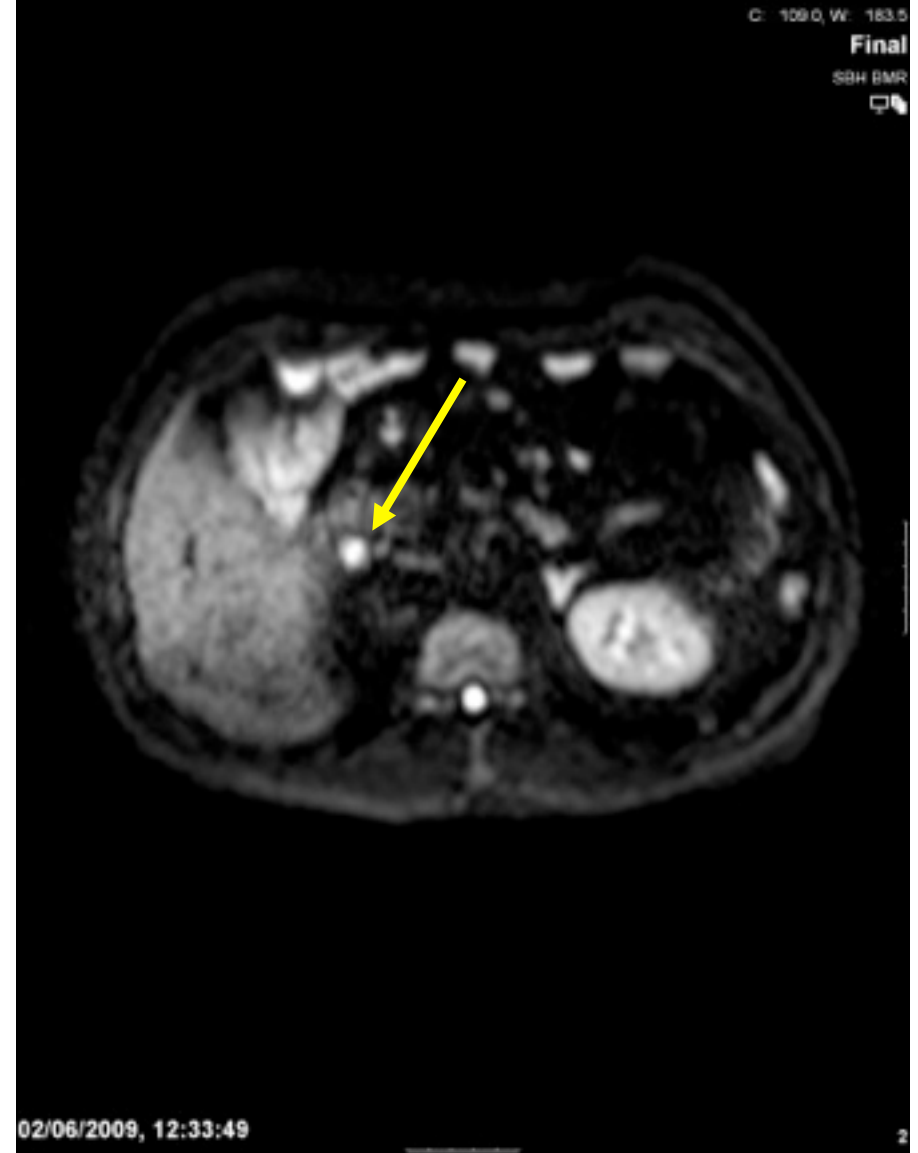


DWI

GASTRINOMA



T2-FS



DWI

MANAGEMENT STRATEGY

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide
 - Surgery as last resort (to debulk)

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide
 - Surgery as last resort (to debulk)

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide
 - Surgery as last resort (to debulk)

 - When malignant

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide
 - Surgery as last resort (to debulk)

 - **When malignant**
 - Radiolabelled octreotide

MANAGEMENT STRATEGY

- **Gastrinomas**
 - PPI at high doses
 - Octreotide/lanreotide
 - Surgery as last resort (to debulk)

 - **When malignant**
 - Radiolabelled octreotide
 - ?Everolimus

WHEN TO SUSPECT MEN1

WHEN TO SUSPECT MEN1

- **With family history of similar problems**

WHEN TO SUSPECT MEN1

- **With family history of similar problems**
- **In presence of hyperparathyroidism**
 - 4/5 gland hyperplasia

WHEN TO SUSPECT MEN1

- **With family history of similar problems**
- **In presence of hyperparathyroidism**
 - 4/5 gland hyperplasia
- **In presence of pituitary tumour**
 - Usually prolactinoma, but could be any type

WHEN TO SUSPECT MEN1

- **With family history of similar problems**
- **In presence of hyperparathyroidism**
 - 4/5 gland hyperplasia
- **In presence of pituitary tumour**
 - Usually prolactinoma, but could be any type

WHEN TO SUSPECT MEN1

- **With family history of similar problems**
- **In presence of hyperparathyroidism**
 - 4/5 gland hyperplasia
- **In presence of pituitary tumour**
 - Usually prolactinoma, but could be any type

Always check serum calcium and preferably prolactin in any patient with pancreatic islet cell tumour

MANAGEMENT STRATEGY

- **The asymptomatic pancreatic lesion in MEN-1**
- **Three considerations;**
 - They may become malignant so ‘get in early’
 - They are bound to be multiple and recur
 - **Total pancreatectomy is**
 - 1. A high morbidity procedure
 - 2. Produces permanent DM

PERSONAL RECOMMENDATIONS

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - **MRI every 1-3 years**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - **MRI every 1-3 years**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - MRI every 1-3 years
- **Treat symptomatically**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - MRI every 1-3 years
- **Treat symptomatically**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - MRI every 1-3 years
- **Treat symptomatically**
- **Remove enlarging nodules >2cm**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - MRI every 1-3 years
- **Treat symptomatically**
- **Remove enlarging nodules >2cm**

PERSONAL RECOMMENDATIONS

- **Regular monitoring mandatory**
 - MRI every 1-3 years
- **Treat symptomatically**
- **Remove enlarging nodules >2cm**
- **Consider use of endoscopic US with biopsy/
cytology**

OTHER NETs IN MEN1

- Occasional midgut carcinoids
- Thymic carcinoids
 - When sporadic often seen in elderly male smokers
 - May be associated with ectopic ACTH

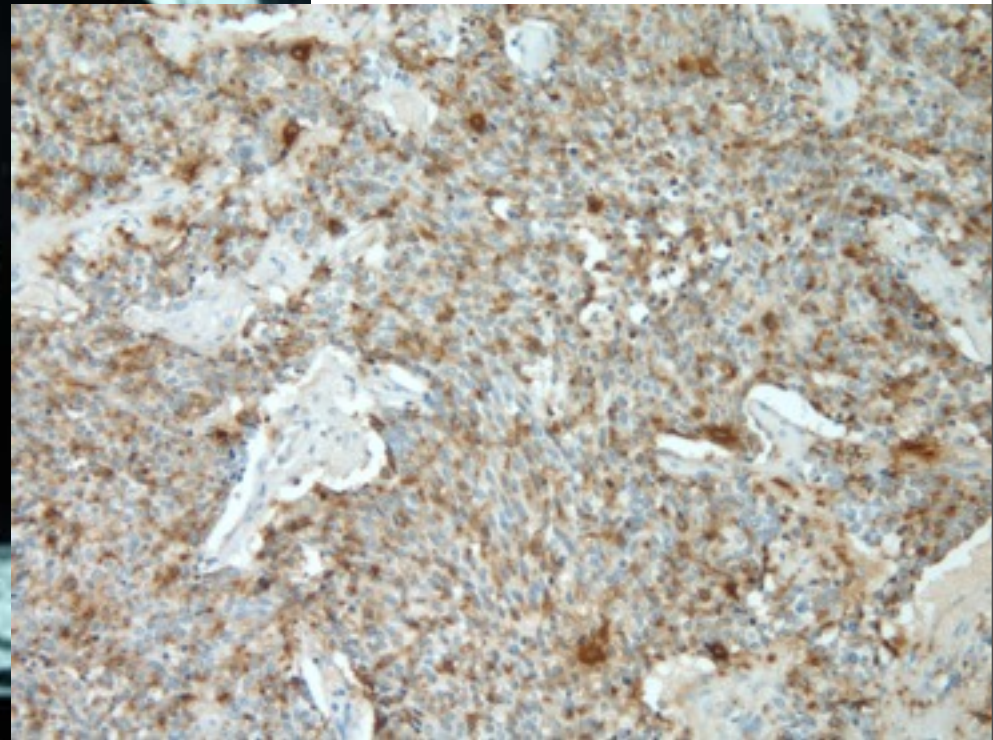
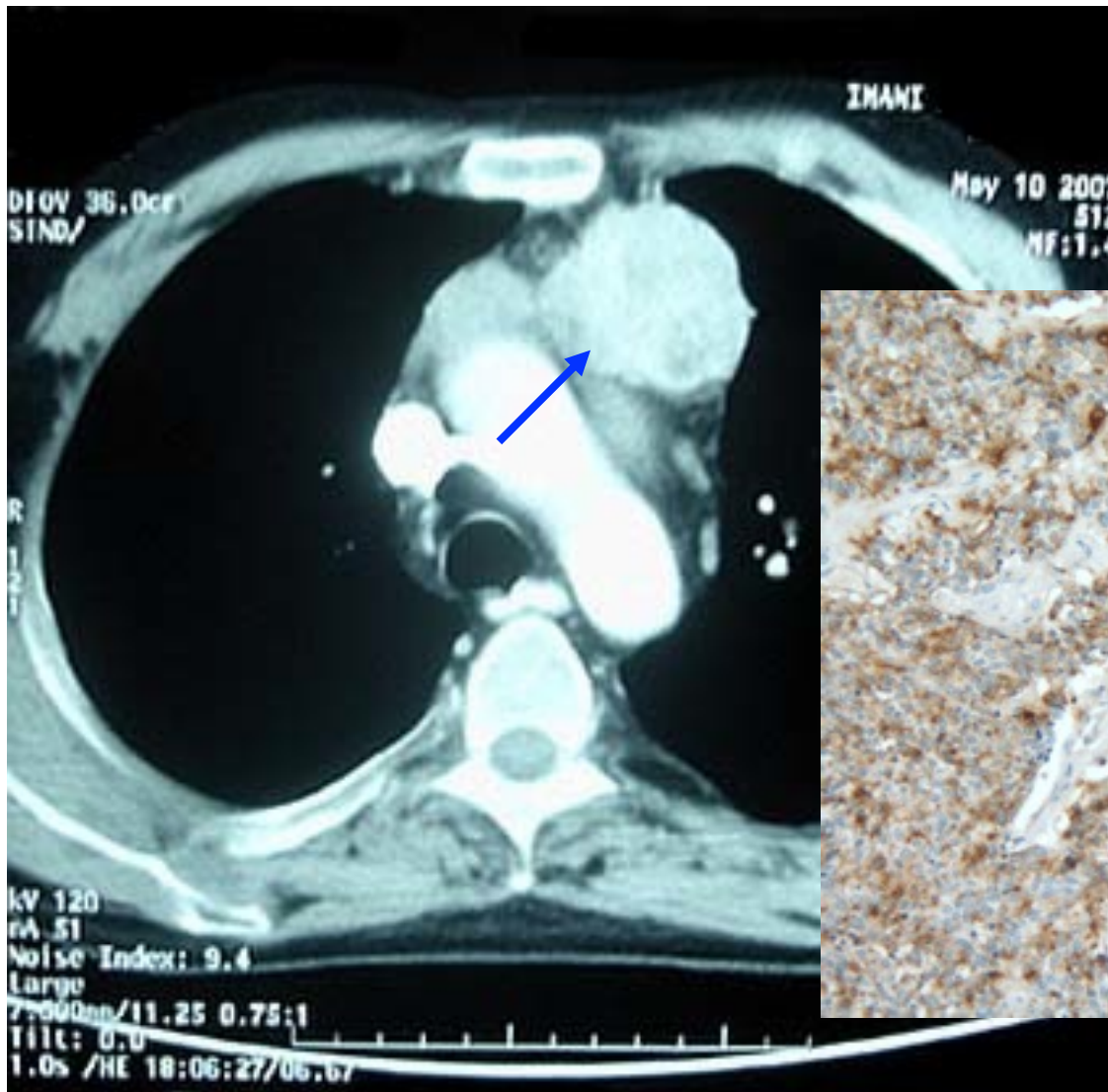
Always consider possibility of MEN1 in patients with thymic carcinoids

THYMIC CARCINOID IN MEN1



Ghazi et al 2011

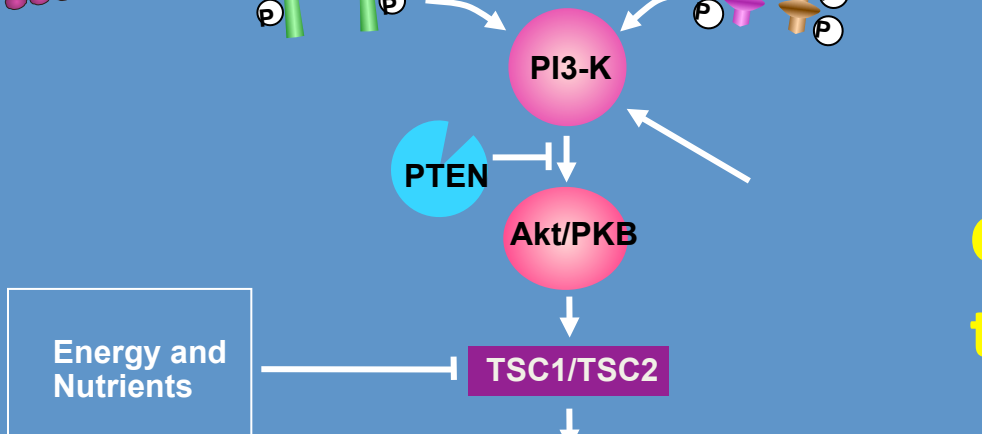
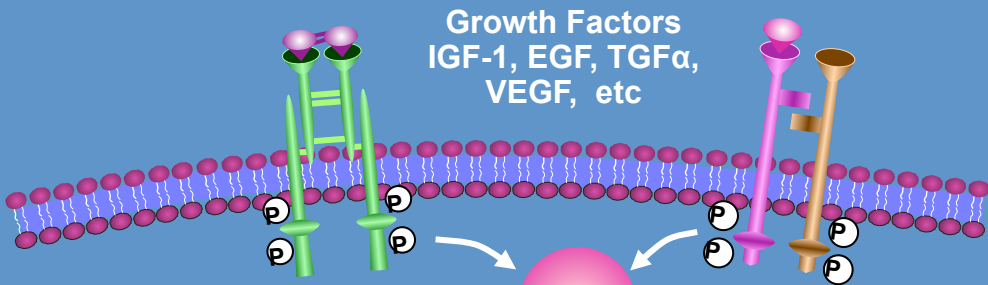
THYMIC CARCINOID IN MEN1



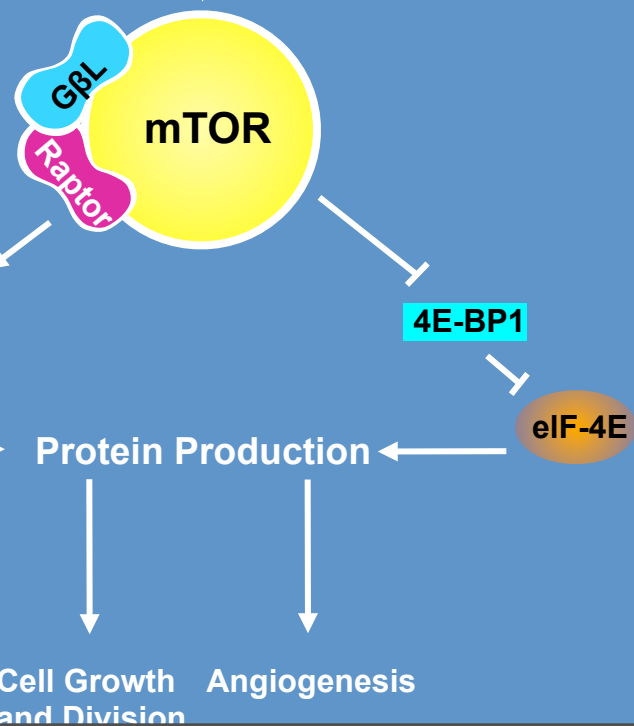
Ghazi et al 2011

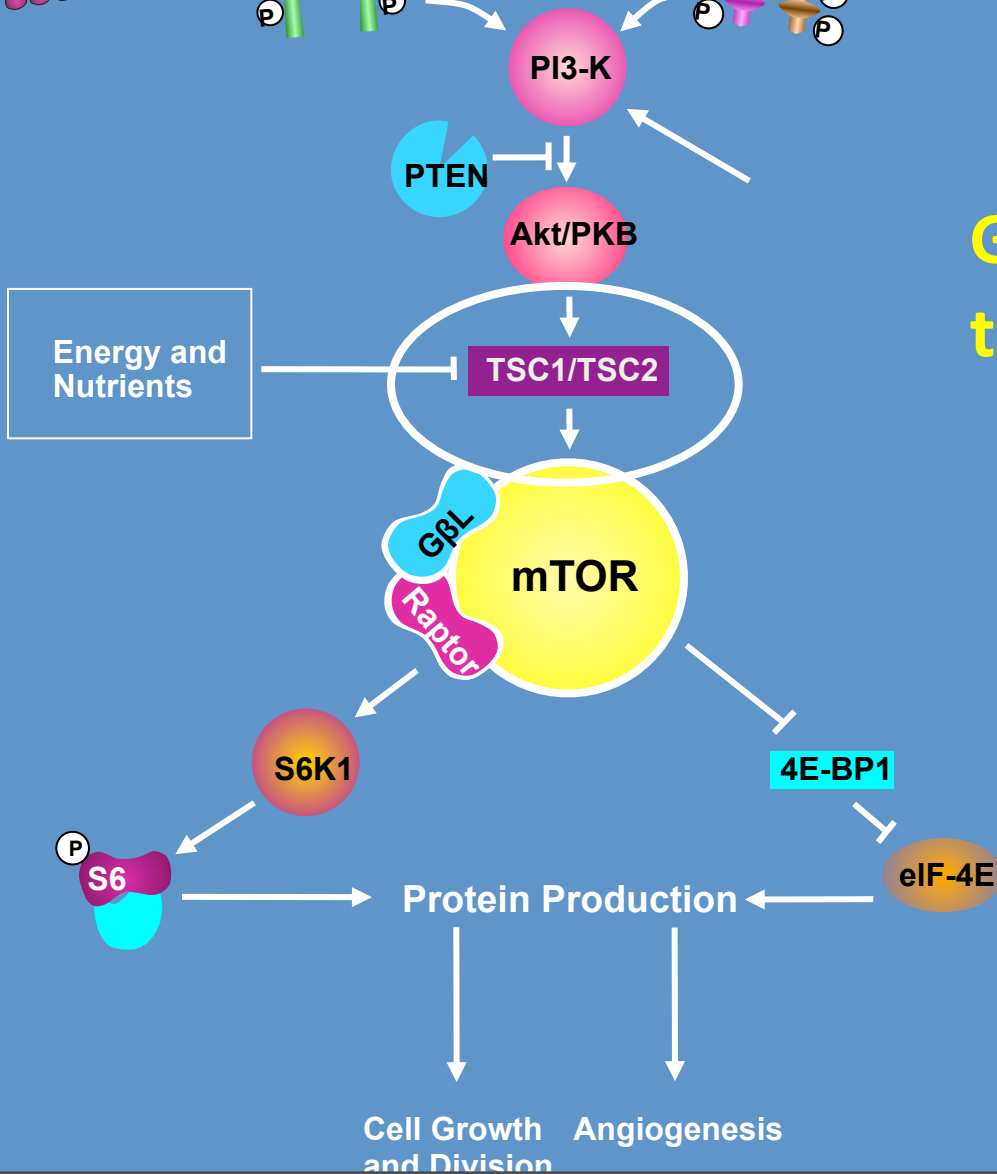
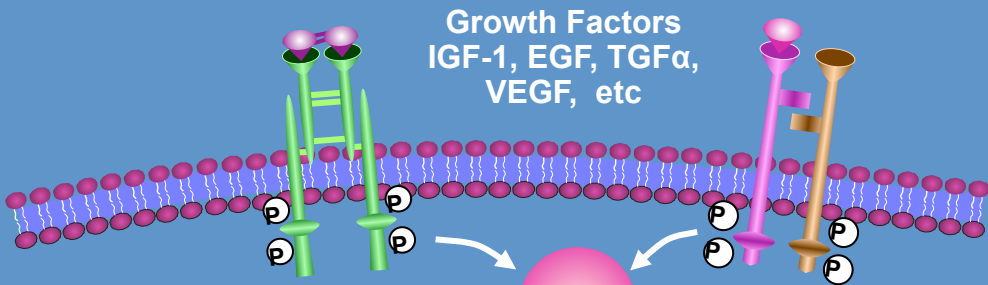
TUBEROUS SCLEROSIS

- **Autosomal dominant condition, high penetrance (80% new mutations)**
- **Prevalence 1/10,000**
- **Described by Bourneville (1880) and von Recklighausen (1865)**
- **EPILOIA**
 - **Epilepsy, Low IQ, Angiofibromas**
 - **Facial angiofibromas (adenoma sebaceum), cortical**



Growth Factors and the TSC1/2 & mTOR





Growth Factors and the TSC1/2 & mTOR

TS – MOLECULAR PATHOGENESIS

- **Loss of tumour suppressor tuberlin (TSC2) or hamartin (TSC1), intermediaries on Akt-mTOR pathway**
- **Occasional pancreatic islet cell tumours, especially insulinomas in young patients**
- **May be confused with underlying epilepsy**

(Dworakowska & Grossman, ERC, 2009)

VON HIPPEL-LINDAU SYNDROME

- Autosomal dominant inheritance
- Mutation of tumour suppressor gene coding for protein which ubiquitinates HIF-1 α
- Typical pheochromocytomas and renal cell carcinomas, but including:
 - Cerebellar and spinal cord haemangioblastomas
 - Endolymphatic sac tumours
 - Testicular tumours
- **May include** pancreatic islet cell tumours, often cystic, occasionally malignant

PANCREATIC LESIONS IN VHL

- **17 patients assessed**
 - Pancreatic lesions in **11 (65%)**, mostly cysts and microcystic adenomas
 - One possible islet cell tumor (Mukhopadhyay et al 2002)
- **389 patients assessed**
 - **44 islet cell tumours (11%)**, none metastatic if removed early (<3cm; Libutti et al 2000)

NEUROFIBROMATOSIS TYPE 1 (NF-1)

- Autosomal dominant condition
- One of largest genes sequenced
- Part of Ras-MAPK signalling pathway
- Tumour suppressor gene
- Multiple neurofibromas
- Other tumours
 - Pheochromocytomas in ~1%
 - Duodenal somatostatinomas
 - Insulinomas

NEUROFIBROMATOSIS TYPE 1 (NF-1)

- **Duodenal somatostatinomas (DS) in NF-1**
 - ~40 cases reported
 - Mean size 3.8cm
 - Unusual to be syndromic
 - 30% of DS are related to NF-1

Relles et al. 2010

CONCLUSIONS

CONCLUSIONS

NETs are rarely familial or have a known genetic cause

CONCLUSIONS

NETs are rarely familial or have a known genetic cause

CONCLUSIONS

NETs are rarely familial or have a known genetic cause

Pancreatic islet cell tumours may occur in the context of TS, VHL and NF-1, but the syndrome should be obvious

CONCLUSIONS

NETs are rarely familial or have a known genetic cause

Pancreatic islet cell tumours may occur in the context of TS, VHL and NF-1, but the syndrome should be obvious

CONCLUSIONS

NETs are rarely familial or have a known genetic cause

Pancreatic islet cell tumours may occur in the context of TS, VHL and NF-1, but the syndrome should be obvious

Always consider MEN1 with islet and thymic NETs



Tuesday, 22 November 11